



REVIEW

Autoimmunity and Inflammation Link to Cardiovascular Disease Risk in Rheumatoid Arthritis

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Received: October 29, 2019 / Published online: December 18, 2019
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ABSTRACT

Rheumatoid arthritis (RA) patients have a 50% increased risk of cardiovascular (CV)-related morbidity and mortality. This excess CV risk is closely linked to RA disease severity and chronic inflammation, hence is largely underestimated by traditional risk calculators such as the Framingham Risk Score. Epidemiological studies have shown that patients with RA are more likely to have silent ischemic heart disease, develop heart failure, and experience sudden death compared with controls. Elevations in pro-inflammatory cytokines, circulating autoantibodies, and specific T cell subsets, are believed to drive these findings by promoting atherosclerotic plaque formation and cardiac

remodeling. Current European League Against Rheumatism (EULAR) guidelines state that rheumatologists are responsible for the assessment and coordination of CV disease (CVD) risk management in patients with RA, yet the optimal means to do so remain unclear. While these guidelines focus on disease activity control to mitigate excess CV risk, rather than providing a precise algorithm for choice of therapy, studies suggest a differential impact on CV risk of non-biologic disease-modifying anti-rheumatic drugs (DMARDs), biologic DMARDs, and small molecule-based therapy. In this review, we explore the mechanisms linking the pathophysiologic intrinsic features of RA with the increased CVD risk in this population, and the impact of different RA therapies on CV outcomes.

Keywords: Atherosclerosis; Cardiovascular disease; Cardiovascular risk assessment
Inflammation; Rheumatoid arthritis

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Key Summary Points

Patients with rheumatoid arthritis (RA) have a 50% increased risk of cardiovascular-related (CV-related) morbidity and mortality. CV risk assessment tools used in the general population, such as the Framingham and Reynolds Risk Scores, largely underestimate the CV risk in patients with RA.

CV risk is closely linked to the severity of RA. Chronic inflammation is hypothesized to exert direct and indirect effects on the vasculature and myocardium, with mechanistic evidence implicating elevated acute phase reactants, pro-inflammatory cytokines, autoantibodies, and specific T cell subsets.

The presence of anti-citrullinated peptide antibodies (ACPAs), anti-malondialdehyde-acetaldehyde adducts (anti-MAA), and anti-carbamylated proteins (anti-CarP) antibodies have been associated with an increased risk of CV death in RA patients by potentially promoting atherosclerotic plaque formation and cardiac remodeling.

Current EULAR guidelines recommend rheumatologists play an active role in the assessment and coordination of cardiovascular disease (CVD) risk management in patients with RA.

RA treatment may lower the risk of CVD by decreasing chronic inflammation. Aggressive RA control with disease-modifying anti-rheumatic drugs (DMARD) therapy is recommended. Current guidelines prioritize disease control over precise treatment choice; however, data suggests a differential impact on CVD amongst treatment classes.

INTRODUCTION

Population-based studies and meta-analyses have shown a 1.5 times higher mortality in RA patients compared with the general population [1, 2]. While this excess death is, in part, due to increased infectious complications and respiratory diseases, cardiovascular disease (CVD) accounts for 30–40% of deaths, representing the leading cause of mortality in RA [2–5]. Despite early intervention with treat-to-target strategies and rapidly increasing treatment options, CVD mortality rates remain 1.5–3-fold higher than matched controls, on par with the CVD risk imparted by diabetes mellitus [6–8].

Rheumatologists are becoming increasingly aware of the association between CVD and RA supported by the publication of official EULAR recommendations for increased surveillance of CV risk in RA patients [9]. An observational study by Gossec et al. [10], however, suggests that sufficient CV assessment by physicians does not often occur. Several studies have shown that primary lipid screening is performed in less than half of RA patients [10, 11]. A systemic literature review by Ghosh-Swaby et al. [12] found this area also remains a major knowledge gap for patients, with approximately 70–90% of RA patients being unaware of their increased risk of developing CVD. In this review, we attempt to bridge these knowledge gaps by summarizing fundamental data evaluating potential mechanisms that link the pathophysiology of RA to its increased CVD risk, and provide insight into the interplay between RA treatments and subsequent risk of CVD-related events.

Literature review was performed via PUBMED search for key phrases that included: rheumatoid arthritis, cardiovascular disease, and cardiovascular risk assessment. Articles were individually reviewed and selected for inclusion in this review on the basis of their perceived merit and relevance.

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

MANIFESTATIONS AND RISK FACTORS

Both traditional CV risk factors and intrinsic RA features contribute to the overall excess CVD-related morbidity and mortality in these patients. Pericarditis, though usually asymptomatic, is the most common “cardiac” manifestation of RA and has been found on random electrocardiographic evaluation and autopsy studies in up to 50% of RA patients, yet it is not associated with an increased CVD risk [13]. However, Solomon et al. [6] illustrate that the risk for myocardial infarction (MI), when adjusted for traditional CV risk factors, is increased by twofold when compared with matched controls. Furthermore, RA patients are more likely to have silent ischemic heart disease, develop heart failure, and experience sudden death [14]. Similar trends have been identified with respect to cerebrovascular accidents and venous thromboembolism, each with an approximately twofold increased risk in RA compared with the general population [15, 16].

Traditional CV risk factors, such as hypertension, smoking, type 2 diabetes mellitus, and hyperlipidemia are well defined in the general population and in RA subjects, yet CV risk assessment tools such as the Framingham Risk Score (FRS), the Reynolds Risk Score (RSS), or the Systemic Coronary Risk Evaluation (SCORE) largely underperform in RA [17–19]. RA is an independent risk factor for CV-related mortality. RA patients have a higher atherosclerotic burden, with up to a 2.5-fold increase in coronary artery calcifications (CAC) measured by cardiac computed tomography (CT) and CT angiography [20–22]. Similarly, in a meta-analysis by Boyer et al. [23] of 15 case-control studies including 2956 RA patients and 3713 controls, RA patients had a statistically higher prevalence of traditional CV factors including smoking (odds ratio [OR] 1.56, 95% confidence interval [CI] 1.35–1.80, $p < 0.00001$), diabetes mellitus (OR 1.74, 95% CI 1.22–2.50, $p = 0.003$), and lower HDL cholesterol levels (mean weighted difference, -17.72 mg/dl, 95% CI -18.35 to -17.08 , $p < 0.00001$). An increased incidence of metabolic syndrome, a complex

cluster of metabolic abnormalities including abdominal obesity, hypertension, insulin resistance, and pro-thrombotic states, has also been recognized in RA patients, and is associated with a twofold increase in the risk of developing CVD [24]. It is hypothesized, however, that chronic inflammation is the key determinant to explain underestimations of CV risk by FRS, SCORE, and RSS.

PATHOPHYSIOLOGY OF CVD IN RA

CV risk is closely linked to the severity of RA, with higher CV risk seen in patients with more aggressive disease [25]. Chronic systemic inflammation, involving both the innate and the adaptive immune system, exerts direct and indirect effects on the vasculature and myocardium, with potential mechanistic contributions from elevated acute phase reactants, pro-inflammatory cytokines, autoantibodies, and specific T cell subsets (Fig. 1) [26–29].

Inflammation and Atherosclerotic Burden

Atherosclerosis is an inflammatory process, reflected directly in plaque by the presence of infiltrating macrophages and T cells, and systemically, by mildly elevated levels of inflammatory cytokines such as tumor necrosis factor (TNF), interleukins-1 and -6 (IL-1, IL-6), and metalloproteases (MMPs). Various epidemiologic studies in the general population have associated high levels of MMPs, acute phase reactants, and inflammatory cytokines with an increased risk for CV events [27, 28, 30]. Mild elevation in the acute phase reactant C-reactive protein (CRP) is an independent risk factor for CVD, particularly MI, presumably through promotion of plaque rupture [31]. In RA, levels of high sensitivity (hs) CRP ≥ 5 mg/dl independently predict CVD-related mortality (HR 3.3, 95% CI 1.4–7.6), after adjusting for age, sex, smoking status, HAQ score, RF positivity, and swollen joint counts [32]. Similarly, elevated levels of IL-6 have been associated with CVD in both the general population and in RA [27]. A genome-wide association study by the IL-6 Receptor (IL-6R) Mendelian Randomization

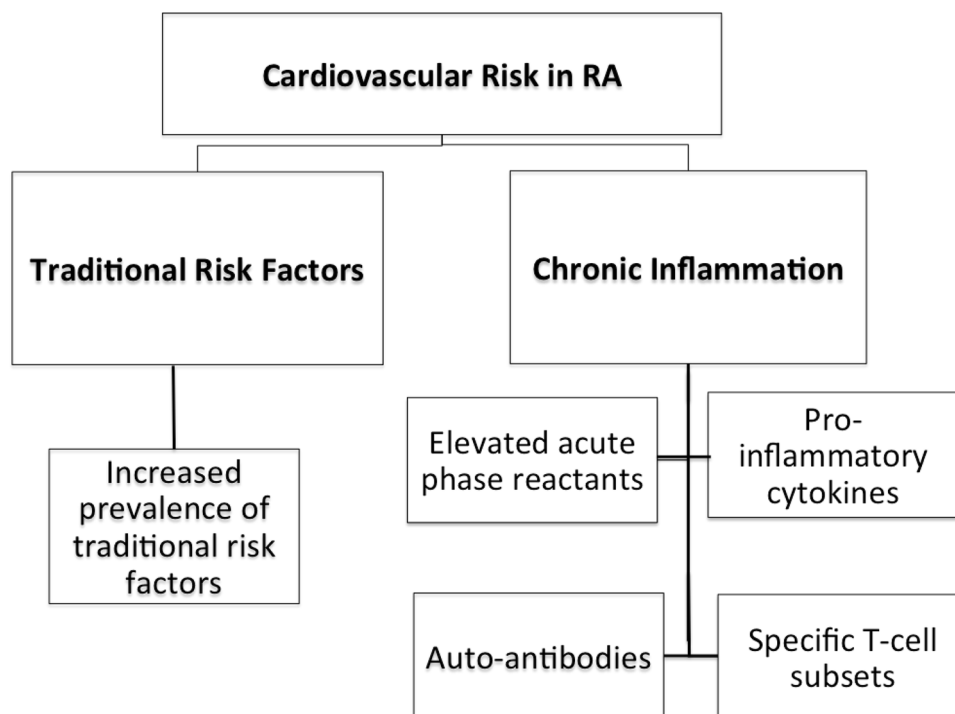


Fig. 1 The increased risk for CVD in RA is not only due to a high prevalence of traditional risk factors but also due to the effects of chronic inflammation. Elevated acute phase reactants, pro-inflammatory cytokines, specific T cell

subsets, and the presence of auto-antibodies, are thought to exert direct and indirect effects on the vasculature and myocardium

Analysis Consortium further supported this finding, revealing that specific single nucleotide polymorphisms (SNPs) involving the interleukin 6 receptor gene leading to decreases in fibrinogen and CRP, were associated with a decreased odds of CV events (per allele odds ratio 0.95, 95% CI 0.93–0.97, $p = 0.0001$) [33].

In both RA patients and the general population, a linear association between elevated erythrocyte sedimentation rate (ESR) and CRP with carotid intima-media thickness (cIMT) has been described, independent of traditional CV risk factors and disease status [34]. In RA, median serum concentrations of inflammatory molecules such as IL-6, TNF alpha, and myeloperoxidase are significantly higher compared with controls. Importantly, IL-6 (OR 1.72, 95% CI 1.12–2.66) and TNF alpha (OR 1.49, 95% CI 1.16–1.90) are associated with higher CAC independent of the Framingham Risk Score and diabetes mellitus status [35]. These associations have led to the favored hypothesis that higher

levels of pro-inflammatory cytokines in RA accelerate atherosclerosis by inducing a pro-thrombotic environment characterized by endothelial dysfunction, insulin resistance, dyslipidemia, and aberrant activation of the coagulation cascade that ultimately leads to plaque rupture and CV-related events [36].

The Role of Autoantibodies in RA-Associated CVD

Citrullination is an irreversible post-translational modification of arginine to citrulline by a family of peptidyl-arginine deiminase (PAD) enzymes. While implicated in aging and disease states such as malignancy, inflammatory bowel disease, Alzheimer's disease, and multiple sclerosis [37–39], the development of anti-citrullinated peptide antibodies (ACPAs) is relatively specific to RA. Citrullinated synovial proteins such as vimentin, fibrinogen, biglycan, enolase,

and fibronectin have been identified as targets for ACPAs, and the presence of such autoantibodies in RA predicts erosive disease and overall poor clinical outcomes [40, 41]. A retrospective cohort analysis by López-Longo et al. [26] of 937 RA patients showed that those with an anti-cyclic citrullinated peptide (anti-CCP) titer of > 25 units/ml had a higher risk of ischemic heart disease (6.5 vs. 2.6%, OR 2.58, 95% CI 1.17–5.65) and death (11.2 vs. 6.8%, OR 1.72, 95% CI 1.01–2.91) compared with RA patients with anti-CCP titers < 25 units/ml. Importantly, after adjusting for confounders, anti-CCP antibody positivity was independently associated with ischemic heart disease (OR 2.8, 95% CI 1.19–6.56, $P = 0.009$), though the association with increased mortality was no longer seen.

Sokolove et al. [42] described the presence of citrullinated proteins, such as fibrinogen and vimentin, co-localizing with PAD type 4 within the atherosclerotic plaques of non-RA patients. In subsequently analyzed serum ACPA levels from 134 seropositive RA women previously diagnosed with subclinical atherosclerosis, levels of anti-citrullinated fibrinogen ($p < 0.001$) and anti-citrullinated vimentin ($p = 0.034$), were associated with greater subclinical atherosclerosis as measured by increases in aortic calcium score; an association not seen with conventional anti-CCP testing [42]. In addition, prior *in vitro* human models have illustrated the inflammatory potential of citrullinated-fibrinogen immune complexes, mediated by engagement of Fc-gamma receptor IIa and the subsequent release of TNF alpha [43]. Though no direct ACPA immune complexes were noted within the plaques of these patients, RA patient-derived ACPAs were able to directly immunoprecipitate citrullinated proteins from the plaque tissue of non-RA subjects. It is therefore hypothesized that such citrullinated epitopes present within the atherosclerotic plaque are targeted by ACPAs and can promote plaque formation through an exuberant inflammatory response. This is further supported by a cross-sectional study performing ^{18}F -fluorodeoxyglucose positron emission tomography (FDG-PET) in 91 RA patients to directly assess vascular inflammation, in which

for patients with active RA, anti-CCP levels ≥ 60 units were positively associated with higher aortic uptake compared with those with lower CCP levels [44].

The presence of ACPAs is also thought to convey an increased CV risk through interactions directly at the level of the myocardium. Heart failure-related mortality rates are notably higher in RA patients, independent of coronary artery disease (CAD) [45]. The phenotype of heart failure seen in RA differs from that of non-RA patients, primarily characterized by diastolic dysfunction, low blood pressure, and higher ejection fraction at presentation, suggesting different mechanisms for the development of myocardial impairment in RA compared with controls [46, 47]. Proteomic and histopathologic studies have shown that many of the citrullinated proteins present in the RA synovium are also expressed in the myocardium, with a significantly higher amount of citrullination occurring in the myocardia of patients with RA compared with controls that is not accounted for by demographics or the presence of atherosclerosis [47, 48]. Importantly, citrullination of sarcomeric proteins diminishes the sensitivity to calcium release, essential for a robust cardiac contraction [48]. Though the precise pathophysiologic implications of this finding remain unclear, in two independent RA cohorts without clinical CVD, higher levels of autoantibodies targeting citrullinated fibrinogen and citrullinated vimentin, were associated with a higher left ventricular mass compared with lower ACPA levels, suggesting that seroreactivity towards citrullinated proteins may result in myocardial remodeling and ultimately impaired myocardial function in RA [49].

Additional autoantibodies, such as anti-malondialdehyde-acetaldehyde adducts (MAA) and antibodies against carbamylated proteins (anti-CarP) have been identified in the sera of RA patients, and potential associations with CVD have also been described [50–54]. Carbamylation is another form of post-translational modification leading to homocitrullination. In a study evaluating subclinical atherosclerosis by brachial artery flow mediated dilation (FMD) and cIMT, anti-CarP antibodies were associated with FMD ($r = 1.6$,

$p = 0.05$) and cIMT ($r = 1.1$, $p = 0.03$), respectively [54]. Similarly, MAA, a molecular complex resulting from oxidative degradation of lipids that function as a potent cytokine, has been described in atheromas of patients with advanced atherosclerosis in whom increased serum levels of anti-MAA antibodies have also been observed [50].

T Cell Subsets

The basic pathophysiology underlying RA is thought to be driven by the presence of the “shared epitope,” a five-amino-acid sequence motif located on the DR chain encoded by several *HLA-DRB1* alleles, which leads to activation and clonal expansion of specific CD4 T cell populations differing from those seen in matched healthy controls [55, 56]. Evaluation of peripheral blood mononuclear cells (PBMC) by flow cytometry in 108 RA patients revealed marked clonal expansion of CD4 + CD28[−] (CD28^{null}) T cells compared with that of 53 controls [57]. In these RA patients, loss of CD28, a co-stimulatory molecule required for normal T cell activation, correlated with a preponderance for extra-articular manifestations including vasculitis, lung disease, and CAD [57]. Though potentially confounded by failure to control for conventional atherosclerotic risk factors, Gerli et al. [58] proposed a link between CD28^{null} T cells and accelerated atherosclerosis, reporting that 20 RA patients with the highest percentage of CD28^{null} T cells ($\geq 15\%$), had higher cIMT and lower flow-mediated vasodilation compared with those with lower percentages of CD28^{null} T cells. Liuzzo et al. [59] additionally showed that clonally expanded CD28^{null} T cells were present in unstable atherosclerotic plaques and absent in stable plaques in a patient who had suffered a fatal myocardial infarction, suggesting that loss of CD28 promotes differentiation of these T cells into an effector memory phenotype with autoreactive potential. Gene profiling of CD28^{null} cells obtained from 24 otherwise-healthy patients with unstable angina supports the pathogenicity of these clones, revealing upregulation of perforin and killer cell immunoglobulin-like receptors in this T cell

subset, with potential direct cytotoxic effects on endothelial cells leading to plaque rupture and thrombosis [60, 61].

Additional PBMC subpopulations have also been implicated in the development of sub-clinical atherosclerosis [29]. In a cross-sectional study of 72 RA patients who underwent CAC assessment by cardiac CT, higher circulating CD28-CD57 + CD56 + effector memory CD4 T cells and CD14^{high}CD16 + intermediate monocyte subsets were seen in the RA patients with CAC deposition compared with those without CAC, independent of traditional CVD risk factors. In sum, these findings suggest that progressive expansion of specific PBMC subsets is an intrinsic process in the pathogenesis of RA and not only do they serve as markers for the presence of CAC but also may directly or indirectly promote atherosclerosis [29].

IMPACT OF RA THERAPIES ON CVD-RELATED EVENTS

Current EULAR guidelines encourage rheumatologists to assess and coordinate CVD risk management in RA patients [9]. Yet, despite the increasing knowledge of the high CV risk in RA, the optimal means of minimizing it remain unclear due to scarceness of comparative studies and limited understanding of the precise physiologic effects of these drugs on CV risk. With aims to address this gap in knowledge, The Treatments Against RA and Effect on FDG PET-CT (TARGET trial, NCT02374021) is an ongoing clinical trial that directly evaluates the degree to which reductions in inflammation and disease activity with different therapeutic agents reduce CV risk in RA [62]. Based on data suggesting a close relationship between lower disease activity and reduced CV risk, current EULAR guidelines recommend aggressive control of RA disease activity in order to mitigate both joint damage and CV risk with effective DMARD use [9, 23]. Current guidelines prioritize disease control over the particular choice of therapy. While data remain limited, available data suggest a differential impact of nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, non-biologic DMARDs, biologics, and small-

Table 1 Select studies that illustrate the relationship between particular therapeutic agents and CV risk in RA

Medication	Studies	N	Study type	Summary of results
Nonbiologic DMARDs (HCQ, SSZ, MTX)	Widdifield et al. [70]	23,994	Prospective cohort	20% reduction in CV events (stroke, MI, or congestive heart failure) in the setting of recent continuous MTX, either in combination or as monotherapy
TNF inhibitors	Ljung et al. [76]	6864	Prospective cohort	47 ACS events occurred in 1 year. A 50% lower ACS risk was seen in TNF responders compared with non-responders
Abatacept (vs. TNF inhibitors)	Jin et al. [77]	13,036	Retrospective cohort	Abatacept was associated with an approximately 20% greater reduction in CV risk compared with TNF inhibitors
Tocilizumab (vs. TNF inhibitor)	Giles et al. [84]	3080	RCT	No significant difference in the risk of MACE between treatment groups
Sarilumab	Fleischmann et al. [81]	3358	Pooled cohort	Exposure-adjusted incidence of MACE with sarilumab combination and monotherapy was no greater than that seen in the general RA population
Anakinra	Ikonomidis et al. [82]	23	RCT	Improved vascular and left ventricular function in RA patients treated with anakinra, particularly those with prior documented CAD
Rituximab	Van Vollenhoven et al. [83]	2578	Pooled cohort	Similar rates of MI (0.41 per 100 person-years) in RA patients treat with rituximab compared to those treated with methotrexate and placebo
JAK inhibitors	Taylor et al. [90]	3492	Prospective cohort	No association between baricitinib treatment and the incidence of MACE, arterial thrombotic events, or congestive heart failure

DMARD disease-modifying antirheumatic drug, *HCQ* hydroxychloroquine, *SSz* sulfasalazine, *MTX* methotrexate, *CV* cardiovascular disease, *MI* myocardial infarction, *TNF* tumor necrosis factor, *ACS* acute coronary syndrome, *RCT* randomized controlled trial, *MACE* major adverse cardiac event, *CAD* coronary artery disease, *JAK* Janus kinase

molecule-based therapy, on CV risk [63–67] (Table 1). Larger studies with longer observation periods are required.

NSAIDs and Glucocorticoids

Glucocorticoids and non-steroidal anti-inflammatory drugs (NSAIDs) are frequently utilized for pain control during episodes of acute flares. Despite the beneficial anti-inflammatory effects, the myriad of potential side effects due to these two medication classes are well known to providers. The precise CV risk imparted by NSAIDs and glucocorticoids, however, is a more

nuanced question. In a prospective cohort study by Rincon et al. [68], 779 patients RA patients with a total of 7203 person years, exposure to glucocorticoids was found to be associated with a dose-dependent increase in death from all causes with a HR of 1.07 per mg of prednisone per day (95% CI 1.05–1.08). Of the 237 patients who died during follow-up, 120 deaths were due to CV causes, yielding a CV mortality rate of 1.8 (95% CI 1.5–2.1). In a systemic review and meta-analysis by Roubille et al. [69] including 28 studies specifically in patients with RA, corticosteroids were found to increase the risk of all CV events (RR 1.47, 95% CI 1.34–1.60;

$p < 0.001$). Similarly, NSAIDs increased the risk of all CV events (RR 1.47; 95% CI 1.01–1.38, $p = 0.04$), though this effect size may be over-estimated due to inclusion of studies specifically pertaining to rofecoxib, which is now removed from the market due to increased risk of CV events [69].

Non-Biologic DMARDs

Conventional DMARDs, such as methotrexate (MTX), sulfasalazine (SSz), and hydroxychloroquine (HCQ) have been shown to improve CV risk [70]. In a Canadian population-based inception cohort including 23,994 RA patients diagnosed after age 75, Widdifield et al. [70] observed an approximately 20% reduction in CV events (stroke, MI, or congestive heart failure) in the setting of recent continuous MTX, either in combination or as monotherapy (hazard ratio (HR) 0.79 for continuous use vs. no use in past 12 months, 95% CI 0.70–0.88; $p < 0.0001$). Similarly, a large meta-analysis of ten smaller RA cohort studies illustrated an approximately 21% decrease in CVD-related events, including MI, stroke, and death, in the setting of MTX therapy [71]. While a precise mechanism for this effect is unclear, the beneficial effects of MTX and other conventional DMARDs are likely driven by the amelioration of chronic inflammation. Triple therapy with MTX, SSz, and HCQ has also been associated with a decrease in CV risk, by decreasing inflammation and improving lipid profiles [70, 72]. Furthermore, in the Treatment of Early Aggressive Rheumatoid Arthritis (TEAR) trial, increases in HDL, decreases in LDL, and an improved ratio of total cholesterol to HDL were noted in those receiving triple therapy compared with patients receiving MTX monotherapy or MTX in combination with etanercept [72].

Biologic DMARDs

TNF inhibitors have a positive impact on surrogate markers of cardiovascular disease, including improvement in cIMT, FMD, and reduction in circulating levels of CRP and IL-6

[73, 74]. A systematic review by Barnabe et al. [75] including 16 observational RA cohort studies showed that anti-TNF therapy was associated with a reduced risk for all CV events (pooled adjusted RR 0.46; 95% CI 0.28–0.77), MI (pooled adjusted RR 0.81; 95% CI 0.68–0.96), and cerebrovascular accidents (pooled adjusted RR 0.69; 95% CI 0.53–0.89). More recently, this association was similarly investigated by Ljung et al. [76] in a large prospective cohort study that included 6864 RA patients initiating TNF inhibitors. With 47 acute coronary syndrome (ACS) events in the group, a 50% lower ACS risk was seen in responders (defined as a significant decrease in disease activity score [DAS] or DAS28 of ≥ 1.2 , or low disease activity score: DAS ≤ 2.4 or DAS28 ≤ 3.2) compared with non-responders. Although the relatively small number of events during the 1-year study period is a limiting factor, those with a moderate response (defined as a significant change in DAS with moderate/high DAS > 3.7 or DAS28 > 5.1 or patients with a change ≤ 1.2 and > 0.6 with low/moderate disease activity), had equal risk to non-responders, implying that optimal disease control is needed to have an effect on CV events. Yet, larger studies with a longer observation period are required to adequately evaluate this clinical question.

The effects of non-TNF biologics on CVD risk, such as abatacept (a fusion protein consisting of the extracellular domain of human CTLA-4 and a modified Fc portion of human IgG1), tocilizumab and sarilumab (humanized anti-IL6 receptor monoclonal antibodies), anakinra (a recombinant IL-1 agent), and rituximab (an anti-CD20 monoclonal antibody), have also been explored, though data remains limited for most of these drugs. The cardiovascular benefits of abatacept were evaluated in comparison with TNF inhibitors in 6102 matched pairs of abatacept and TNF initiators from Medicare, as well as 6934 matched pairs from MarketScan [77]. Among these patients, 35% and 14% of the Medicare and MarketScan subjects, respectively, had baseline CVD. After accounting for this baseline risk, abatacept was associated with an approximately 20% greater reduction in CV risk compared with TNF inhibitors. In regards to

tocilizumab, despite initial concerns for worsened CV outcomes due to increases in total cholesterol levels, long-term follow-up studies show that rates of stroke and MI after tocilizumab treatment (mean duration of 2.4 years) are comparable to that of RA patients on MTX alone or in conjunction with placebo [78, 79]. The MEASURE study by McInnes et al. [80] showed that a possible explanation for this paradox was tocilizumab's ability to alter HDL particles towards an anti-inflammatory composition (decreased serum amyloid A, phospholipase A2, lipoprotein A, fibrinogen, and D-dimer) that may ameliorate associated CV risk. Comparatively, limited data are available on the association between sarilumab and CV risk. Though a recent study by Fleischmann et al. [81] showed that exposure-adjusted incidences of major adverse cardiac events with sarilumab combination (0.5 per 100 patient-years) and monotherapy (0.2 per 100 patient-years) were no greater than that seen in the general RA population (1.4 per 100 patient-years without exposure to DMARDs, 1.1 with exposure to DMARDs, and 1.2 overall). In addition, a small, double-blind, crossover, placebo-controlled study showed improved vascular and left ventricular function in RA patients treated with anakinra, particularly those with prior documented CAD [82]. Finally, a study assessing the long-term safety of rituximab in 2578 RA patients showed similar rates of MI (0.41 per 100 person-years) to those seen in RA patients treat with methotrexate and placebo [83]. Interestingly, in the general non-RA population, the results of the CANTOS study suggest that targeting the IL-1 pathway with canakinumab 150 mg every 3 months led to a significantly lower rate of MI compared to placebo, independent decreases in lipid levels (HR 0.85, 95% CI 0.74–0.98; $p = 0.021$) [84].

The comparative effect of different classes of biologic DMARDs has not been optimally studied by direct head-to-head assessment, yet there are data to suggest a differential impact of specific therapies on CV risk. In a retrospective review of 47,193 Medicare RA patients without CAD at the time of initiation of a biologic therapy, the incidence of acute MI was significantly elevated among anti-TNF initiators

(adjusted HR 1.3; 95% CI 1.0–1.6) compared with those initiated on abatacept [64]. Interestingly, tocilizumab initiators had a reduced risk of the composite outcome (acute MI and/or need for coronary revascularization) compared with those initiated on abatacept (adjusted HR 0.64, 95% CI 0.41–0.99) [64]. Furthermore, a recent head-to-head randomized controlled trial (RCT), ENTRACTE, comparing the cardiovascular safety of tocilizumab and etanercept in 3080 RA patients followed for a mean duration of 4.9 years showed no significant difference in the risk of major adverse CV events between treatment groups (HR 1.05, 95% CI 0.77–1.43) [84]. To reconcile these findings, Singh et al. [66] performed a systematic review and meta-analysis of 14 cohort studies evaluating the risk of CV events in RA patients treated with conventional DMARDs, TNF inhibitors, or non-TNF biologics. Upon review, they noted tocilizumab to be associated with a lower risk of major adverse cardiac events (MACE) compared with TNF inhibitors; with no difference in such risk seen when comparing tocilizumab with abatacept. While adjustment for RA disease activity, baseline CV risk factors, and methodological differences between studies were accounted for, a key weakness was that with the exception of ENTRACTE, the analyzed studies were observational and not RCTs [66].

Kinase Inhibitors

Data remain relatively scant regarding the effects of newer agents such as the small molecule inhibitors of Janus kinase (JAK), tofacitinib and baricitinib, on CV risk. A 10–20% increase in total and LDL cholesterol levels, similar to that seen with tocilizumab therapy, has been noted in the tofacitinib RCTs, raising concerns about worsened CV outcomes [85, 86]. Evaluation of the effects of 24 weeks of tofacitinib treatment showed that increases in HDL cholesterol levels and decreases in the total cholesterol to HDL cholesterol ratio were associated with a diminished risk for future MACE, whereas increases in total cholesterol and LDL cholesterol levels lacked this protective effect [87, 88]. The occurrence of venous thromboembolisms with JAK

inhibition, however, has further accentuated initial concerns, and a formal comparison of the effects of tofacitinib on the risk of major adverse cardiac events is being investigated in a phase IIIb/IV prospective comparative study versus TNF inhibitors (NCT02092467) [88, 89]. In addition, recent data from a pooled cohort of 3492 RA patients with over 7860 patient-years of exposure to baricitinib showed no association between baricitinib treatment and the incidence of MACE (incidence rates (IR) per 100 patient-years, placebo vs. 4 mg baricitinib = 0.5 vs. 0.8), arterial thrombotic events (0.5 vs. 0.5), or congestive heart failure (4.3 vs. 2.4). In regards to deep vein thrombosis (DVT) or pulmonary embolism (PE) risk, six events occurred in patients treated with 4 mg baricitinib, with no cases seen in the placebo group; though all six cases were in patients who had pre-existing risk factors for venous thromboembolism. In an extended 2 mg vs. 4 mg baricitinib analysis, IRs of DVT/PE were comparable between the doses (IR per 100 patient-years in the 2 mg vs. 4 mg baricitinib doses = 0.5 vs. 0.6) [90].

Ultimately, given the myriad of therapeutic options and a movement towards precision medicine, it is becoming increasingly important for rheumatologists to incorporate these data in the context of an individual patient's unique traditional CV risk factors and intrinsic RA features to generate treatment plans that optimally mitigate not only the articular manifestations of RA but also the excessive cardiovascular events and overall mortality. Clinical trials and prospective studies comparing the relative impact of different DMARDs on CVD risk in RA are currently ongoing, and will further shed light on the optimal DMARD choice in specific subsets of RA patients using a precision medicine approach.

CONCLUSIONS

RA patients have an increased risk of CV-related morbidity and mortality. Both traditional CV risk factors and RA-specific features contribute to the excess CV death. Hence, traditional CV risk assessing tools used in the general population largely underperform in RA. RA is an

independent risk factor for CVD and close association with disease activity has been shown in multiple studies. Pro-inflammatory molecules such as ESR and CRP, cytokines such as TNF and IL-6, autoantibodies, and circulating T cell subsets, are thought to drive this association through the promotion of atherosclerotic plaque formation and cardiac remodeling. Current EULAR guidelines highlight the role of the rheumatologist in the assessment and coordination of CVD risk management in patients with RA, and emphasize an aggressive treat-to-target approach with aims to diminish the systemic effects of chronic inflammation. While guidelines currently prioritize attaining disease control over the precise class of medication choice, there appears to be a differential impact on CVD risk amongst DMARD classes, yet further research into the relative effects of specific treatments on CVD risk in RA is required. In an era of increasing therapeutic options and precision medicine, it is becoming imperative for rheumatologists to consider a patient's unique subset of traditional CV risk factors, intrinsic RA features, and prior medical history to guide treatment choices that best mitigate the risk of CVD and mortality in patients with RA.

ACKNOWLEDGEMENTS

Funding. No funding or sponsorship was received for the publication of this article.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosures. Daniel DeMizio and Laura Geraldino-Pardilla have nothing to disclose.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human

participants or animals performed by any of the authors.

Data Availability. This manuscript has no associated data.

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