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# Cardiovascular disease in patients with rheumatoid arthritis

*Katherine P. Liao, MD, MPH**

*Division of Rheumatology, Immunology, and Allergy, Brigham and Women's Hospital, 75 Francis St, PBB-B3, Boston, MA 02115*

ABSTRACT

The risk of cardiovascular disease (CVD) in patients with rheumatoid arthritis (RA) is 1.5–2-fold higher than age- and sex-matched individuals from the general population. This excess risk is attributed to the systemic chronic inflammation which is a hallmark of RA. Challenges to optimizing CV risk management in RA include the need for improved methods to predict CV risk, and defining the target risk factor(s) to reduce CV risk. Lessons learned from RA studies can also inform CV risk prevention in the general population, where inflammation also has an important role in the pathogenesis of atherosclerosis.

**Key words:** Cardiovascular disease, Rheumatoid arthritis, Inflammation, Lipids, Lipoproteins.



J.S. is a 34-year-old woman who presented with "pain in the joints of her fingers, wrists, and knees. The first symptoms (included) pain, redness, swelling, and difficulty moving set in." This classic presentation of rheumatoid arthritis (RA) was written by Dr. Landre–Beauvais in 1800, where RA was identified for the first time as a distinct clinical entity [1]. The presentation of RA remains the same to this day. However, we now know that the inflammation of RA affects more than just the joints. Inflammation is considered the major contributor of the 1.5–2.0-fold excess CV risk in RA compared to the general population [2–5]. While overall the absolute rates of CVD are declining in the population, the relative risk of CVD in RA compared to the general population appears stable over the past 2 decades despite improvements in both RA and CVD management [3,6,7]. This review will survey a few of the challenges toward optimizing CV risk and the available evidence to address these issues.

## Calculating CV risk in RA

In the general population, CVD is a preventable condition, with established methods for screening, and interventions that can prevent or mitigate the risk of disease. While these strategies appear to be utilized in RA patients in a similar manner as the general population [8], RA patients continue to have excess CV risk. To improve CV outcomes in RA, more studies are needed to identify and target CV risk factors which may be specific to RA patients. The lessons learned from studying RA may inform CV prevention in the general population where inflammation also plays an important role in CV risk. As an example, the Cardiovascular Inflammation Reduction Trial (CIRT) study [9] is randomizing patients without inflammatory diseases at high risk for myocardial infarction (MI) to the first-line RA treatment, methotrexate (MTX), or a placebo. CIRT builds on studies in RA demonstrating that treatment with MTX, which reduces inflammation, also reduced CV risk in RA patients [10].

Dr. Liao is supported by the NIH (K08 AR060257 and R01 HL127118), and the Harold and Duval Bowen Fund.
The author has indicated that there is no conflict of interest.

* *Corresponding author*. Tel.: +1 617 732 5325; fax: +1 617 713 3030.
E-mail address: kliao@partners.org (K.P. Liao).

http://dx.doi.org/10.1016/j.tcm.2016.07.006
1050-1738/

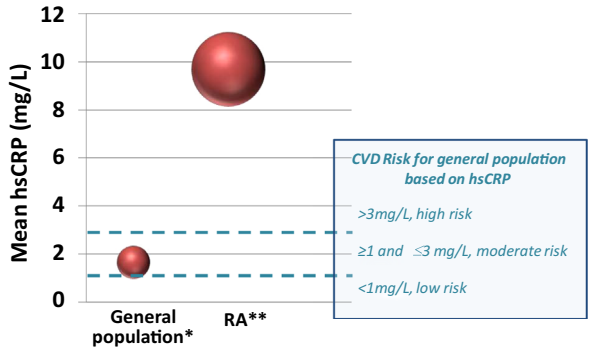


**Fig – The mean hsCRP from a general population cohort, hsCRP cut-off values for CV risk estimation in the general population, compared to the mean hsCRP from a typical RA cohort**. [*National Health and Nutrition Examination Survey (NHANES), **Brigham Rheumatoid Arthritis Sequential Study (BRASS).]**

One of the major challenges to understanding CV risk in RA is accurately defining the at-risk population. The excess CV risk in RA is attributed to inflammation; however, current methods to assess CV risk cannot account for long-term exposure to inflammation. The Framingham Risk Score (FRS) [11] and SCORE [12] underestimate CV risk in RA by as much as 2-fold [13]. Similar findings were observed when the 2013 ACC/AHA CV risk assessment guidelines [14] were applied to an RA population [15]. The Reynolds Risk Score (RRS), which includes an inflammatory marker, high-sensitivity C-reactive protein (hsCRP), also underestimated CV risk in RA similar to FRS [13]. The most likely reason for this was because RRS was developed and validated in populations where the median hsCRP was 2.0 mg/L (IQR: 0.8–4.3 mg/L). In a typical RA cohort, the mean hsCRP was 9.7 mg/L (SD = 0.66) [16], well above the hsCRP of 1.66 mg/L (SD = 0.08) observed in the general population [17] (Fig.). The QRISK2, the CV risk calculator used in the United Kingdom (UK), includes RA as a risk factor, but was found to overestimate CV risk in one study [18]. The European League Against Rheumatism (EULAR) published recommendations for use of a 1.5 multiplier on FRS or SCORE for RA patients who have specific risk factors, such as positive rheumatoid factor (RF) or disease duration >10 years [19]. This strategy was based on expert opinion and has not undergone external validation.

Additionally, the use of carotid intima media thickness (cIMT) as a potential tool to better identify RA patients at high CV risk has been studied. A meta-analysis demonstrated increased cIMT in RA compared to controls [20], suggesting higher atherosclerotic burden. Higher levels of inflammation are also associated with increased cIMT [21]. However, only one study of 47 RA patients has been published demonstrating an association between cIMT and future CV events in RA [22]. Larger prospective studies are needed to examine the utility of cIMT integrated with clinical factors to assess CV risk. Presently, there are no widely accepted approaches for CV risk stratification for RA. Approaches that rely on traditional risk factors to estimate CV risk have led to misclassification largely toward underestimating risk. Thus, an important next step is to develop and validate a CV risk score tailored for RA patients by incorporating either more clinical factors or additional biomarkers.

In the general population, the adoption of FRS into the clinic was estimated to have cut CV deaths by 50% [23]. The FRS was effective not only because it identified patients at elevated risk, but because it also identified risk factors that could be modified, for example, cholesterol, to reduce this risk. Work is underway to develop a similar tool for RA, which builds upon risk factors in FRS [24]. To date, there is one published study of a CV risk score developed in an RA population [25]. While this RA CV risk score still requires external validation, it provides a potential starting point for a clinical CV risk prediction tool. In this study, a baseline model was created using risk factors from the FRS including age, gender, diagnoses of diabetes, hyperlipidemia, hypertension, and current tobacco use. RA clinical factors were then tested for their value in improving the accuracy of predicting a CV event. The final published model includes traditional risk factors plus the following RA clinical factors: RA clinical disease activity index (CDAI), functional status, corticosteroid use, and RA disease duration. Of the RA-specific factors, the CDAI, functional status, and corticosteroid use were modifiable risk factors. The fact that CDAI was predictive for future CV risk raises an important question about the target for RA treatment—whether reducing CDAI would reduce CV risk. In the 2012 American College of Rheumatology (ACR) and the 2013 EULAR treatment guidelines for RA, the target for therapy is low disease activity (LDA) or remission. This target was selected based on studies demonstrating that LDA or remission can slow or halt the progression of joint damage [26]. Based on data that there is a linear relationship between lower disease activity and reduced CV risk, a more stringent target of remission for RA patients may not only mitigate joint damage, but also reduce CV risk [27,28]. The Treatments Against RA and Effect on FDG PET-CT (The TARGET Trial), a randomized controlled multi-center study, is now enrolling to directly test the hypothesis that reducing inflammation reduces CV risk in RA [29]. A study demonstrating CV benefit in RA patients with tighter control of disease activity may lead to changes in the current approach to RA treatment toward tighter control of inflammation.

## Links between inflammation and increased CV risk

Inflammation may modify traditional risk factors such as routine lipids, rendering them as suboptimal measures of future CV risk in RA. In a cross-sectional study, RA patients have a lower TC and LDL-C when compared to age- and sex-matched individuals from the general population [30]. These data appear contrary to the known excess CV risk observed among RA patients. Furthermore, data from RA treatment studies have found that potent disease modifying anti-rheumatic drugs (DMARDs), specifically the biologic DMARDs, are linked to changes in routine lipids. Routine lipids measurements performed from samples collected before and after tumor necrosis factor inhibitor (TNFi) from randomized controlled trials showed that TC and LDL-C levels increased by as much as 30% after TNFi use [31]. Observational and retrospective