

Editorial

# Defeating the Hydra of Excess Cardiovascular Disease Risk in Rheumatoid Arthritis — How Close Are We to Completing the Task?



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For his Second Labor, Heracles was tasked with slaying the Hydra, a serpentine monster from ancient Greek mythology who possessed many heads. When Heracles attempted to decapitate the monster, two new heads grew in place of each severed head, an expression of hopelessness of such struggle for anyone but the hero. The invulnerability of the Hydra was because of its one immortal head. Once the immortal head was cut off, the monster was defeated, and Heracles' second task was completed.

Much like slaying the monstrous Hydra, conquering the disproportionately increased risk of nearly all forms of fatal and nonfatal cardiovascular disease (CVD) in patients with rheumatoid arthritis (RA) compared to the general population has been an unsolved lingering problem, long awaiting the arrival of its hero. Fueled by systemic autoimmune inflammation, this 1.5- to 2-fold excess CVD risk has been invulnerable to traditional CVD management strategies. Growing attention to tight control of RA disease activity and widespread use of conventional synthetic disease-modifying antirheumatic drugs (csDMARD) and biologic DMARD (bDMARD) have dramatically changed the landscape of RA outcomes in the new millennium, providing hopes for defeating the increased CVD risk.

A metaanalysis of observational studies highlighted the potential for up to 30% CVD risk reduction in RA with the use of methotrexate (MTX) and tumor necrosis factor- $\alpha$  inhibitors (TNFi)<sup>1</sup>. A large retrospective study from Sweden demonstrated even greater benefits, including the reduction of CVD risk in RA patients who responded to TNFi to that of the general popula-

tion level<sup>2</sup>. Remission of RA disease activity, especially if achieved early in the disease course, has been associated with reduction of the CVD risk to a level comparable to the general population level<sup>3,4</sup>, identifying systemic inflammation as the “immortal head” of the excess CVD risk in RA, and reiterating the importance of early and effective control of RA disease activity. Research on comparative effectiveness of various antirheumatic treatments and combinations on clinically relevant (“hard”) CVD outcomes in real-world population is gaining momentum.

In this issue of *The Journal*, Ozen, *et al*<sup>5</sup> examine comparative effects of TNFi, non-TNFi biologics, and tofacitinib versus csDMARD on rates of nonfatal and fatal CVD events in adult patients with RA (n = 18,754) participating in FORWARD, the National Databank for Rheumatic Diseases longitudinal prospective observational study, between 1998 and 2017. The authors can be complimented on the rigorous methodological approach aimed at minimizing bias and confounding inherent to observational studies. They carefully address the possibility of overlap or carryover effect from the previous treatments by allowing a 3-month risk window for exposure lag following discontinuation of the previous medications, adjustment for the number of prior csDMARD and bDMARD, and use of mutually exclusive medication categories with time-varying exposure variables. Although not employing propensity scoring, given the multiple potential confounders, the authors used a comprehensive list of adjusters, including sociodemographic factors, traditional CVD risk factors and comorbidities, use of medications influencing CVD risk, RA disease characteristics, prior antirheumatic medication use, prednisone exposure, and calendar year. The study features several important findings.

### *Reduction in risk of CVD events with TNFi use*

Ozen, *et al*<sup>5</sup> report an 18% reduction in risk of composite CVD events [i.e., myocardial infarction (MI), stroke, hospitalized heart failure (HF), death from CVD] with TNFi use versus any csDMARD. When patients with prior CVD were excluded,

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the association remained statistically significant, with 17% risk reduction in incident CVD with TNFi use versus csDMARD.

These findings extend the existing knowledge of the role of TNFi in primary and secondary CVD prevention in RA<sup>6</sup>. Significant CVD risk reduction was observed for the individual CVD events (i.e., MI, stroke, CVD-related death) with no increase in risk of hospitalized HF with TNFi use. When the csDMARD comparator group was prespecified to include MTX, TNFi use was associated with reduced risk of MI, while association with other individual outcomes or composite CVD outcome did not reach statistical significance. In this context, there are 2 questions to ask: To what extent may bDMARD, including TNFi as the most widely used bDMARD, be superior to MTX for CVD risk reduction, and what are the underlying mechanisms of this additional CVD benefit?

CVD benefits of TNFi use on surrogate and “hard” CVD outcomes in RA are becoming increasingly established and presumed to be largely due to effective control of systemic inflammation as observed in TNFi responders, current but not prior TNFi users, and those with prolonged TNFi use<sup>2,7,8,9,10</sup>. The extent of TNFi-specific effects on CVD health beyond inflammation control is an area of active research. Studies of surrogate CVD outcomes show plaque stabilization, reduction in aortic stiffness, and improvement of endothelial function in TNFi users with RA, irrespective of RA disease activity<sup>8,11,12</sup>. Whether these improvements in surrogate CVD markers translate into improved long-term CVD outcomes that may account for superior CVD benefits in TNFi users, and whether this is a class effect, requires further study. Recent preliminary data from the Norwegian DMARD (NOR-DMARD) registry using data from 3251 patients with RA show higher risk estimates for a composite CVD outcome in RA remission on csDMARD (HR 0.75) compared to patients on various bDMARD (HR 0.3)<sup>13</sup>. While the difference did not reach statistical significance, these findings substantiate the rationale for further studies evaluating effects of different modes of inflammation control on CVD risk in RA.

#### *CVD benefits of non-TNFi use*

As one of the main findings, Ozen, *et al*<sup>5</sup> report a 50% risk reduction in CVD events (primarily MI) with abatacept (ABA), a selective inhibitor of T cell co-stimulation, as compared to csDMARD. A subgroup analysis that excluded patients with prior TNFi use revealed a similar degree of CVD risk reduction of ~50% with ABA versus csDMARD, although the strength of association was attenuated. Similar to TNFi use, this CVD risk reduction with ABA was primarily in comparison to non-MTX csDMARD and became borderline significant when the reference group was set to include MTX (rather than any csDMARD).

While the role of ABA in CVD is less studied as compared to TNFi, the findings of Ozen, *et al*<sup>5</sup> concur with the growing body of research suggesting clinical CVD benefits of ABA as a first-line and second-line non-TNFi biologic<sup>14,15,16</sup>. Individual observational studies suggest superior CVD benefits of ABA as compared to TNFi in subgroups of patients with RA who

have high CVD risk. Indeed, decrease in risk of CVD outcomes (primarily MI) with ABA was somewhat more prominent than with TNFi use in large US-based cohorts of patients with RA of advanced age, or who have preexisting CVD and diabetes mellitus<sup>14,15,17</sup>. However, a recent metaanalysis of large cohort studies showed no difference in risk of major adverse cardiac events between ABA and TNFi in patients with RA overall, without examination of CVD risk subgroups<sup>18</sup>. Similarly, Ozen, *et al*<sup>5</sup> found no additional CVD benefit of ABA compared to TNFi use in RA. Randomized controlled studies (RCT) addressing CVD safety of ABA in patients with RA overall and across different baseline CVD risk phenotypes would be helpful in informing treatment decisions about the use of ABA in RA.

The study by Ozen, *et al*<sup>5</sup> did not detect any statistically significant associations with regard to CVD risk for other non-TNFi biologics and tofacitinib compared to csDMARD, although event numbers were small. Previous observational studies and clinical trial data suggest a good potential for interleukin 6 inhibitors in management of CVD risk, particularly MI risk, in RA and acceptable comparative CVD safety of tocilizumab versus TNFi<sup>18,19</sup>. Janus kinase (JAK) inhibitors demonstrate higher proportion of patient responders according to the American College of Rheumatology 20/50/70 response rates than other targeted therapies used in RA, suggesting that more patients with RA may be benefiting from JAK inhibitor use from a standpoint of inflammation control. However, information on comparative CVD safety of these compounds is scarce<sup>18</sup>, and there is a possibility of increased risk of venous thromboembolism with JAK inhibitors<sup>20</sup>. More studies with guards against selection bias and confounding are needed to evaluate effect of JAK inhibitors on CVD risk.

#### *Role of glucocorticoid use in combination with DMARD on CVD outcomes*

Adverse CVD effects of systemic glucocorticoid (GC) use are well established<sup>10,21</sup>. Ozen, *et al*<sup>5</sup> used a weighted cumulative exposure (WCE) model that considered the effects of dosage, duration, and timing of GC use on the risk of CVD in RA. Augmenting the existing evidence of dose- and duration-dependent increased risk of CVD events with GC use, this study found that GC exposure as WCE of prednisone was associated with increased CVD risk in RA (HR 1.15, 95% CI 1.11–1.19). Importantly, concomitant use of GC with DMARD in this study abated the protective effect of TNFi, ABA, and MTX. While confounding by indication is a possibility (i.e., patients with more severe RA and inherent adverse CVD risk profile may be more likely to use GC), their adverse cardiometabolic effects are well known and may play a role in outweighing the CVD benefits of csDMARD and bDMARD use. This reinforces the recommendations for minimal possible GC exposure as one of the overarching principles of CVD management in patients with RA<sup>22</sup>.

As the evidence on association between the use of antirheumatic medications and CVD outcomes in patients with RA is mounting, it is important to understand the implications of these findings in the context of existing literature on trends in CVD in RA. Has there been a change in epidemiology of CVD

in RA in recent decades? What is the effect on the population of csDMARD and targeted therapies on CVD morbidity and mortality in RA?

Following decades of persistent excess in risk of CVD in RA, recent population-based studies from several developed countries show a closing of the CVD mortality gap and diminishing gap in excess incidence of CVD in RA versus the general population<sup>23,24</sup>. While causation cannot be established from the observational studies, these improvements in CVD outcomes in RA come in parallel with widespread use and early initiation of MTX, growing use of targeted therapies, and declining disease activity of RA at baseline and up to 10 years of follow-up<sup>25</sup>. These trends in CVD incidence and mortality were observed primarily in high-income countries and are unlikely to be universal, but they highlight a potential for significant improvements in CVD outcomes in the setting of improved control of RA disease activity with csDMARD and bDMARD. Prospective studies, ideally RCT, are needed to define the most effective approaches for primary and secondary CVD prevention in RA.

In summary, heroic efforts of the rheumatology community have led to increasing recognition of early initiation of DMARD, acceptance of a “treat-to-target” (i.e., treat-to-remission) approach, and discovery of an expanding range of targeted therapies as means of improving outcomes of RA disease overall, with growing potential for improved CVD outcomes in RA. Successfully combating systemic inflammation as the Hydra’s immortal head makes decreasing CVD risk in RA an achievable goal in patients with access to effective antirheumatic treatments.

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