

Time-Varying Association of Rheumatoid Arthritis Disease Activity to Subsequent Cardiovascular Risk

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Objective. It is unknown how the relationship between disease activity in rheumatoid arthritis (RA) and cardiovascular (CV) events may change over time. We examined the potentially time-varying association of RA disease activity to CV events.

Methods. We used the CorEvitas prevalent RA registry. The Clinical Disease Activity Index (CDAI) score category, averaged within each 6-month window since enrollment, was the exposure, and the outcome was major adverse CV events (MACEs). We used marginal structural models to estimate the hazard ratio (HR), comparing each CDAI score category with remission, allowing for differential association over time. We predicted MACE-free survival under several CDAI score scenarios.

Results. We found 44,816 eligible patients (77% female; mean age 58 years) with a crude event rate of 5.3/1000 person-years (median follow-up 3.4 years). The strongest association between higher CDAI score and MACEs was observed during the first 6 months of enrollment (HR for CDAI score low 2.29 [95% CI: 1.21–4.36], moderate 2.81 [95% CI: 1.46–5.43], and high 2.99 [95% CI: 1.48–6.02]). These estimates gradually diminished; by year 5, the HRs were 1.00 (95% CI: 0.49–2.05) for low, 1.18 (95% CI: 0.51–2.71) for moderate, and 1.04 (95% CI: 0.45–2.40) for high CDAI score. Predicted MACE-free survival suggested a potential decrease in MACEs with a hypothetical earlier transition to remission.

Conclusion. The association of higher disease activity with CV events may be stronger earlier in the disease course of RA. Interventional studies may be warranted to precisely determine the effect of disease activity suppression on CV events in RA.

INTRODUCTION

Rheumatoid arthritis (RA) has long been associated with increased risks of cardiovascular disease (CVD) (1,2). Studies have found that, compared with the general population, the

RA-associated increase in future CVD was similar to the increase due to type 2 diabetes (3,4). Increased cardiovascular (CV) morbidity and mortality is not fully explained by traditional CV risk factors among patients with RA (5–8). A previous study examined the influence of the Clinical Disease Activity Index

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The CorEvitas (formerly Corrona) dataset is based on a large US North American multicenter study adhering to a number of institutional review boards, with complex logistics. Patients did not provide consent to raw data sharing during the data collection for this purpose, and the CorEvitas data sharing policies do not permit raw data sharing for this purpose. An aggregated limited dataset from the current analyses is available to qualified investigators with an approved protocol. Data requests may be sent to CorEvitas, LLC, represented by Dr. Jeffrey D. Greenberg, MD, MPH, NYU School of Medicine, New York, NY, email jgreenberg@corevitas.com.

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SIGNIFICANCE & INNOVATIONS

- Rheumatoid arthritis (RA) disease activity is associated with future cardiovascular (CV) events. However, whether this association varies over time is unknown.
- We investigated the potential time-varying association of RA disease activity with CV events and found that the association may be greater earlier during the follow-up.
- Our findings may suggest that earlier control of disease activity might have a greater impact on long-term CV risk, warranting an interventional study.

(CDAI) score over time in the form of time-averaged CDAI score and found an association of increased CDAI score and CVD (9). Another study estimated that 10%-20% of CVD in patients with RA is attributable to RA disease activity, following only smoking and hypertension (8).

These epidemiological findings are consistent with the increased appreciation of the role that inflammation plays in the pathogenesis of atherosclerotic CVD in the general population (10,11). Among patients with RA, an ultrasound follow-up study of carotid intima-media thickness found that erythrocyte sedimentation rate (ESR), a component of the Disease Activity Score in 28 joints (DAS28), was associated with more rapid carotid intima-media thickening (12). Imaging studies found that RA was associated with increased fluorodeoxyglucose uptake on positron emission tomography/computed tomography (PET/CT), compared with stable patients with stable CVD (13) and osteoarthritis (14).

Previous studies, however, did not examine how the contribution of RA disease activity to CV risk may differ over time. If the detrimental association of RA disease activity and CV risk is greater during the earlier period of follow-up, there may be a rationale for further studies of early aggressive RA treatment to mitigate the increased CV morbidity burden of patients with RA. Anti-inflammatory medications initially developed in rheumatology recently started demonstrating CV benefits (eg, canakinumab (15) and colchicine (16,17)). Thus, we conducted a longitudinal cohort study using the CorEvitas RA Registry to estimate the potentially time-varying association of RA disease activity with CV events among routine care patients with RA.

PATIENTS AND METHODS

This study was carried out in accordance with the Declaration of Helsinki, and all patients in the registry were required to provide written informed consent and authorization prior to participating. All participating investigators were required to obtain full institutional review board (IRB) approval for conducting noninterventional research involving human subjects. Sponsor approval and continuing review was obtained through a central IRB (the New England

Independent Review Board, NEIRB No. 120160610). For academic investigative sites that did not receive a waiver to use the central IRB, full approval was obtained from the respective governing IRBs, and documentation was submitted to CorEvitas, LLC prior to initiating any study procedures. The current study was approved by Mass General Brigham IRB (P002533).

Patients. CorEvitas prevalent RA registry is a prospective, national observational cohort of patients with RA treated by rheumatologists in routine practice. Patients with RA are enrolled into the registry at a convenient time point during a routine clinical encounter. Data such as demographics, comorbidities, RA disease characteristics, disease activity, patient-reported outcomes, medications, and adverse events are gathered by both patients and their treating rheumatologist. The data collection is conducted at clinical visits at the baseline at the time of enrollment and every approximately 5-6 months thereafter. Currently, the registry includes longitudinal data on more than 56,000 patients contributed by more than 800 rheumatologists (18). For the current study, eligible patients had a diagnosis of RA (initially by the 1987 criteria (19); by the new criteria since 2010 (20); by clinical judgement since 2019), were aged 18 years or older, and had a baseline CDAI score measured between October 2001 and May 2019. The baseline visit at the registry enrollment with the CDAI score measurement was defined as the index date. All patients in the registry were required to provide written informed consent and authorization prior to participating. The study was approved by Mass General Brigham IRB (P002533). There was no patient or public involvement.

Outcome. The outcome of interest in the current study was the three-component major CV adverse events (MACEs) defined as nonfatal myocardial infarction, nonfatal stroke (both hemorrhagic and ischemic, but excludes transient ischemic attacks), and CV deaths as reported by treating rheumatologists. In a previous validation, 93% of such events were confirmed to be definite or probable MACEs by an adjudication committee of cardiology and neurology experts although medical records were obtainable for 35% of events (9). Patients were followed until MACE, death from other causes, or loss to follow-up.

Exposure. The exposure of interest in the current study was RA disease activity as measured by CDAI score at study visits (21). CDAI score is a sum of the 28-joint tender joint count, 28-joint swollen joint count, patient's global assessment (0-10), and physician's global assessment (0-10). For clinical interpretability and ease of statistical modeling, CDAI score was classified into the typically used four ordinal categories: remission (≤ 2.8), low disease activity (2.9-10.0), moderate disease activity (10.1-22.0), and high disease activity (22.1-76).

Covariates. Baseline and time-varying variables potentially associated with both the risk of MACE (outcome) and time-varying CDAI score (exposure) were accounted for as confounders. The baseline variables included age, gender, race, body mass index, smoking (never, former, or current), work status, duration of RA at enrollment, RA seropositivity (positivity of rheumatoid factor or anticitrullinated protein antibodies), comorbid conditions (hypertension, hyperlipidemia, diabetes, and CV disease), and relevant drug use (prednisone, nonsteroidal anti-inflammatory drugs, statin, and aspirin). The time-varying variables that we used in the longitudinal confounding adjustments were tumor necrosis factor inhibitors (TNFi), non-TNFi biologics (tocilizumab and abatacept), methotrexate, oral glucocorticoid, nonsteroidal anti-inflammatory drugs, statins, and aspirin. Rituximab and targeted synthetic antirheumatic drugs were not included in the analyses because of less frequent use.

Statistical methods

The baseline patient characteristics were summarized in means and standard deviations, medians and interquartile ranges, or proportions as appropriate. We employed the marginal structural model framework (22,23) to account for confounding of the relationship between CDAI score and MACEs by time-varying treatment through the following steps.

Data construction. To facilitate inverse probability weight (IPW) estimation and subsequent analyses, we constructed a fixed 6-month interval longitudinal dataset (to reflect the typical 5-6 months follow-up interval in the registry). Time-varying variables were summarized in each interval. When multiple visits were available within a 6-month interval, continuous CDAI score was averaged. For the time-varying drug use, use on any visits during the interval was deemed as use. Similarly, any MACE during the interval was considered as a presence of the outcome of interest during that interval. Missing variables were handled with multiple imputation with chained equations (24,25). Two-level multiple imputations were used for time-varying variables to use repeated measurements within individuals.

IPW estimation. We modeled CDAI score with the 4-level ordinal categories (remission, low, moderate, or high) and ordinal logistic regression models. The exposure denominator model included both the baseline and time-varying covariates, whereas the exposure numerator model included the baseline covariates. The IPW was the cumulative product of the interval-specific predicted probability of the CDAI score category from the numerator model divided by the predicted probability from the denominator model. The censoring IPW was similarly calculated except that we used binary logistic regression models for censoring probabilities. The final weights were truncated at 5 and 95 percentiles to reduce outliers. The weighted IPW dataset conceptually attempts to "randomize" the CDAI score and censoring during each interval

by dissociating it from measured time-varying covariates (RA and CV medications) (26).

Outcome analyses. The outcome analysis relating the time-varying CDAI score and the subsequent MACE was conducted using the IPW dataset. The outcome models included the baseline covariates and the time-varying CDAI score exposure, but the time-varying covariates were not included as these were accounted for by IPW. We used pooled logistic regression models, which more readily accommodate time-varying IPW, to approximate Cox regression models (27). The approximation is reasonable in our case because of the generally rare nature of MACEs in a 6-month period (28). The time-varying baseline hazard was modeled as a quadratic trend over time. We estimated the potential influence of each non-remission CDAI score level (high, moderate, or low) at each interval compared with the reference level of remission. We initially conducted exploratory analysis allowing for most flexible but imprecise estimates to time-varying association (ie, interval-specific estimates by categorical time \times CDAI score category interaction terms). After observing an approximately linear trend, we constrained the model with continuous time \times CDAI score interaction terms. To avoid overextrapolation, we truncated our analysis at 5 years (10 intervals) from index date, at which the cohort size decreased below 40% of the baseline.

Predicted MACE-free survival curves. We then used the estimates at each interval to construct predicted MACE-free survival under different CDAI score trajectories given an otherwise average baseline covariate pattern. We used the estimates from the IPW outcome analyses to calculate the interval-specific MACE-free survival during each 6-month interval. We then cumulatively multiplied these interval-specific MACE-free survivals to predict MACE-free survival over the 5-year study period. We made predictions for having always high, moderate, low, or remission CDAI score over the 5-year follow-up. Furthermore, we made predictions for a transition from sustained high, moderate, or low CDAI score to sustained remission at a different time point.

Additional analyses. To examine alternative explanations for the lessened association over time between CDAI score and MACEs, we also described the average CDAI score composition over time and patient composition by follow-up duration as well as patient composition by follow-up duration.

RESULTS

We identified 44,816 eligible patients with RA for our analysis (Table 1). Briefly, the average age was 58 years and 77% were female. The average RA duration was 8.7 years (median 5 years); 74% were autoantibody seropositive. The baseline mean CDAI score was 14, which is in the moderate range (10.1-22.0). Major comorbidities included hypertension (32%), hyperlipidemia

Table 1. Baseline characteristics of the study cohort

Variable	Summary statistics
N	44,816
Age, y, mean (SD)	58.4 (13.4)
Gender (female %)	76.7
White (%)	83
Disease duration, y, mean (SD)	8.7 (9.7)
Disease duration, y, median (range)	5.0 (0-75)
Baseline CDAI score, mean (SD)	13.9 (12.9)
Modified HAQ, mean (SD)	0.38 (0.46)
Seropositivity (%)	74.2
Insurance (%)	
Private	73.5
Medicare	19.2
Medicaid	2.9
Medicare & Medicaid	2.6
None	1.8
Education (%)	
College and above	56.0
High school	39.5
Primary	3.8
Do not remember	0.8
Smoking (%)	
Current	14.5
Former	28.0
Never	57.5
Work (%)	
Full time	37.7
Part time	9.0
At home	10.6
Disabled	12.2
Retired	29.7
Comorbidities (%)	
Hypertension	32.2
Diabetes mellitus	8.9
Hyperlipidemia	18.8
Cardiovascular disease	4.7
Family history of myocardial infarction	
Brothers	5.5
Sisters	1.8
Father	16.0
Mother	7.4
Medications (%)	
Methotrexate	62.8
TNFi	34.1
Non-TNFi biologics	6.1
NSAIDs	41.3
Prednisolone	29.5
Aspirin	18.1
Statins	20.0

Abbreviations: CDAI, Clinical Disease Activity Index; HAQ, Health Assessment Questionnaire; NSAID, nonsteroidal anti-inflammatory drug; TNFi, tumor necrosis factor inhibitor.

Note: Variables with >5% missingness were seropositivity (43%), insurance (11%), hyperlipidemia (49%), and family history of myocardial infarction (brothers/sisters 81%; father/mother 49%).

(19%), diabetes (8.9%), and CVD (4.7%). The breakdown of patient characteristics by the baseline CDAI score categories is presented in Supplementary Table 1.

Follow-up information and crude description of outcomes. The median follow-up duration after baseline was 3.4 years, with a maximum of 19.3 years prior to 5-year

truncation. The mean (median) follow-up visit interval was approximately 200 days (180 days) throughout the follow-up. The crude event count of MACEs was 1103 events over a total of 207,544 person-years among the 44,816 patients (incident rate 5.31 events/1000 person-years). To ensure enough observations under the follow-up to allow for flexible modeling, we focused on the first 5 years of follow-up, at which point about 38% of the cohort was still undergoing follow-up. We retained 707 MACEs (Supplementary Table 2), of which CV death slightly increased over time in proportion.

Main results from marginal structural models. We initially allowed a different association during each 6-month interval during the 5-year follow-up for maximum flexibility. The estimates were unstable but showed an approximately linear trend over time (Supplementary Figure 1). We then fit a linear trend model, which allowed for a smooth trend in the association of each CDAI score level during the follow-up (Figure 1; Supplementary Figure 2). The results suggested that having a high, moderate, and low CDAI score compared with remission was associated with an increase in the risk of MACE earlier during follow-up, and the estimated hazard ratio (HR) diminished during follow-up. However, the continuous time \times CDAI score category product terms were not statistically significant. The HR estimates during the first 6-month interval were HR 2.99 (95% CI: 1.48-6.02) for high CDAI score, HR 2.81 (95% CI: 1.46-5.43) for moderate CDAI score, and HR 2.29 (95% CI: 1.21-4.36) for low CDAI score (see Supplementary Table 3, row Year 0.5). Over time, high, moderate, and low CDAI score categories had more similar associated HRs (see Figure 1). At 5 years, the estimates were HR 1.04 (95% CI: 0.45-2.40) for high CDAI score, HR 1.18 (95% CI: 0.51-2.71) for moderate CDAI score, and HR 1.00 (95% CI: 0.49-2.05) for low CDAI score (see Supplementary Table 3, row Year 5.0). To mitigate the issue with the prevalent (vs. inception) nature of the CorEvitas cohort, we conducted a sensitivity analysis limiting the study sample to patients who had a disease duration of 5 years or less (approximately 50% of the cohort). In this subset, the continuous time \times CDAI score category product terms reached statistical significance (Supplementary Table 4).

Predicted MACE-free survival curves under hypothetical scenarios. We then used the time-varying approximate HR estimates in the final model for outcome prediction for hypothetical scenarios. Figure 2 shows the MACE-free survival predictions under the hypothetical constant CDAI score scenarios (eg, always remain in high, moderate, low, or remission CDAI score) for otherwise average individuals (Supplementary Figure 3 for the corresponding risk plot). The predicted MACE-free survival curves under the always-high and always-moderate scenarios were similar, followed by the always-low scenario. The predicted MACE-free survival curve under the always-remission scenario was more clearly separate. We then simulated transition to

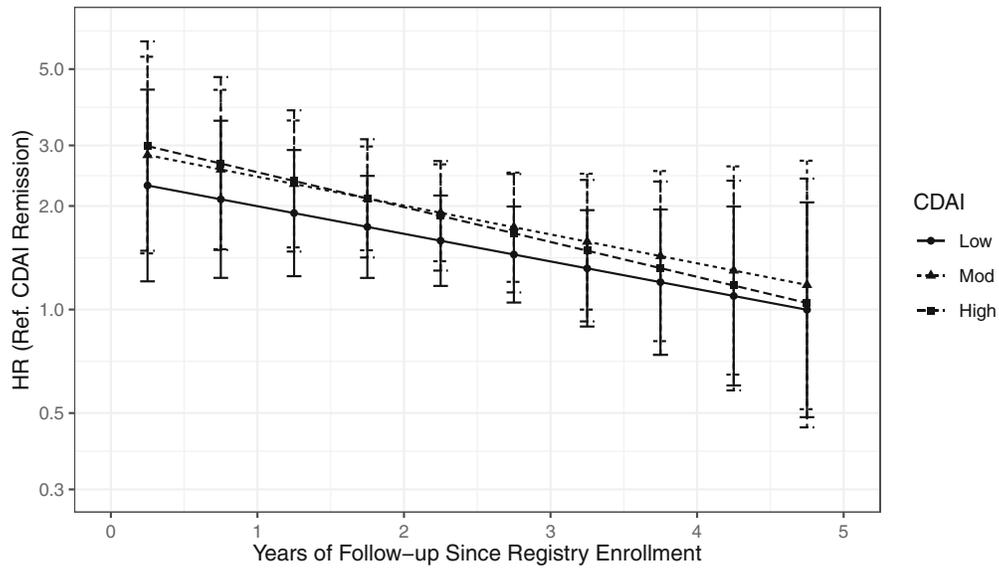


Figure 1. Time-varying hazard ratio estimates for MACEs associated with each CDAI score level compared with remission for each 6-month interval. See Supplementary Figure 2 for a non-superimposed version. The Y axis is on the log HR scale with the ticks at representative HR values. CDAI, Clinical Disease Activity Index for rheumatoid arthritis; HR, hazard ratio; MACE, major cardiovascular event.

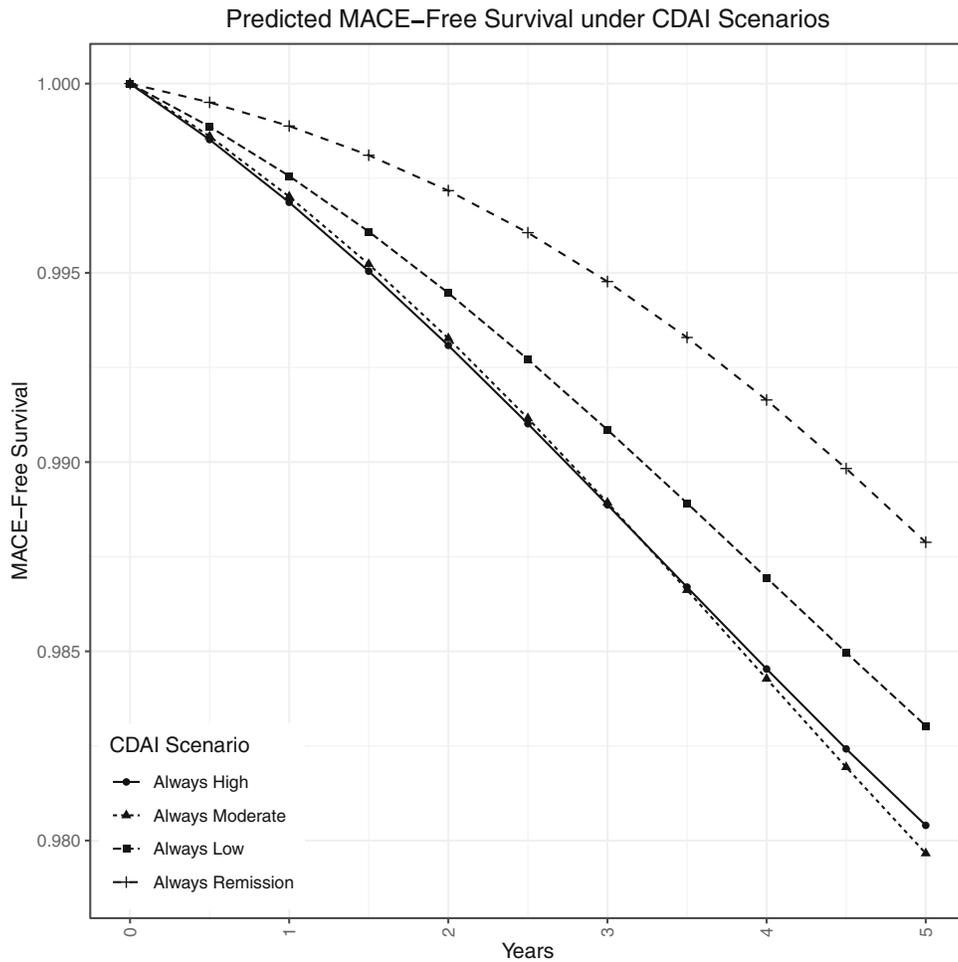


Figure 2. Predicted MACE-free survival under hypothetical sustained CDAI score levels based on time-varying hazard ratio estimates from the final model (estimates in Figure 1). CDAI, Clinical Disease Activity Index for rheumatoid arthritis; MACE, major adverse cardiovascular event.

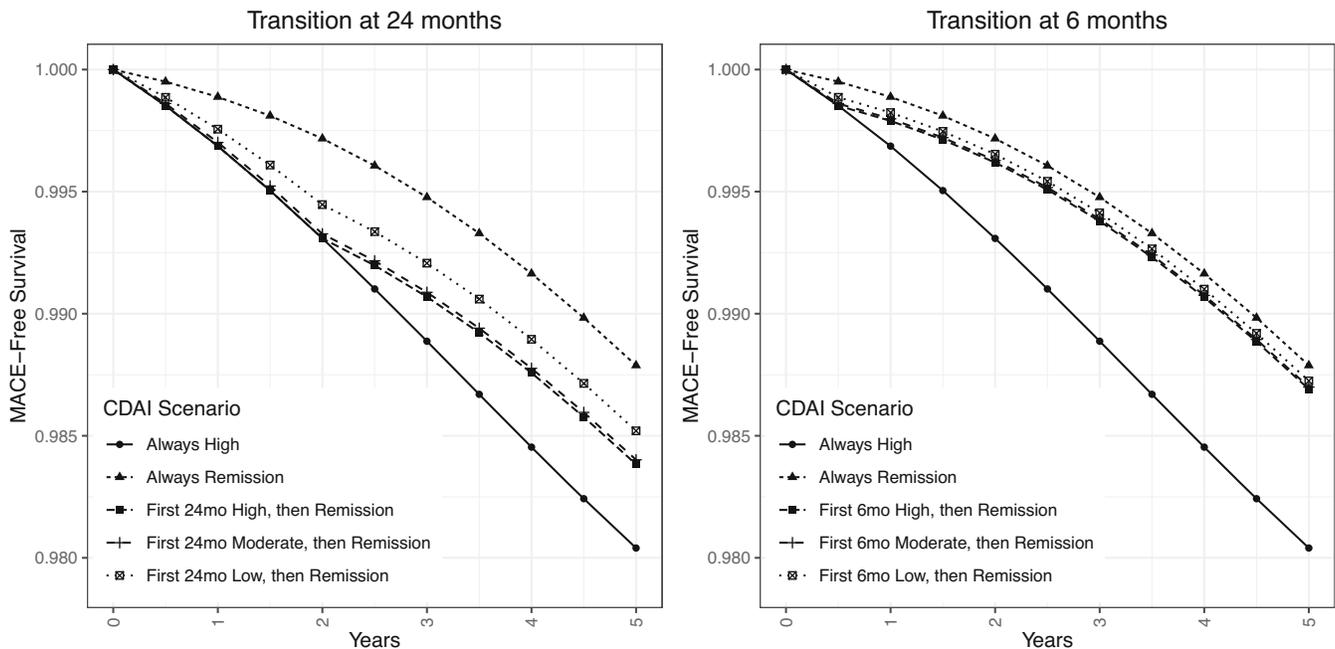


Figure 3. Predicted MACE-free survival under hypothetical transition to sustained remission at 24 months and 6 months in comparison to hypothetical scenarios of having always-remission-level CDAI score (top curve: best-case scenario) and having always high CDAI score (bottom curve: worst-case scenario). A hypothetical transition to sustained remission at 24 months (left panel; middle three curves) was predicted to carry less dramatic CV benefit compared with transition to sustained remission at 6 months (right panel; middle three curves), which gave predicted MACE-free survival curves fairly close to the hypothetical scenario of having always-remission-level CDAI score (top curve: best-case scenario). CDAI, Clinical Disease Activity Index for rheumatoid arthritis; CV, cardiovascular; MACE, major adverse cardiovascular event.

sustained remission from higher CDAI score at different time points. Figure 3 shows transition at 24 months (2 years) and 6 months to sustained remission in comparison with the always-high CDAI score (worst-case scenario; solid line at the bottom) and always-remission scenarios (best-case scenario; broken line at the top). The predicted MACE-free survival curves for prevalent RA cases who started with high, moderate, or low CDAI score were very similar to the best-case always-remission scenario with an early transition to sustained remission at 6 months during the follow-up (Figure 3 right panel). However, with a late transition to sustained remission at 24 months during the follow-up, the predicted MACE-free survival curves for prevalent RA cases who started with high, moderate, or low CDAI score fell quite separated from the best-case always-remission scenario (Figure 3 left panel). A full range of predictions for different transition times to remission are shown in Supplementary Figures 4-12. A corresponding prediction for a hypothetical transition to low disease activity at 6 months indicated somewhat improved predicted MACE-free survival (Supplementary Figure 13), approximately corresponding to a hypothetical transition to remission at 30 months in terms of the predicted MACE-free survival at 5 years.

Additional analyses. The average composition of CDAI score (Supplementary Table 5) indicated a slight change over

time. At the baseline, 28% of CDAI score was because of swollen joint count, whereas 23% was due to patient global. During the last interval (4.5-5.0 years), 25% of CDAI score was due to swollen joint count, whereas 32% was due to patient global. The baseline patient characteristics were relatively similar regardless of the follow-up time (Supplementary Table 6). However, several baseline variables, such as current smoking, hypertension, and diabetes, show slightly more favorable profiles among those with longer follow-up.

DISCUSSION

We found that the detrimental CV association of higher CDAI score levels compared with CDAI score remission may be more pronounced earlier in the 5-year study period among prevalent patients with RA (median RA duration 5 years) in the CorEvitas registry. The trend was significant among patients within the first 5 years of their RA onset at registry enrollment although our data did not allow an inception cohort analysis. In our predicted CV event-free survival curves, the predicted CV benefit was most pronounced for hypothetical early CDAI score remission induction and maintenance after registry enrollment. In this scenario, patients avoided that period with the largest estimated association of higher RA disease activity on the CV event rate. The finding may provide a rationale for examining earlier anti-inflammatory

treatment for residual inflammatory risk of CV disease in patients with RA, although the prevalent RA nature of our study cohort limits our conclusion.

Whether the elevated CV risk among patients with RA is due to conventional risk factors or RA specific in nature (ie, disease activity related) has been actively investigated (29). Traditional CV risk scores, such as the Framingham (30) and Reynolds (31) scores, have been demonstrated to underperform in patients with RA identified in a population-based cohort (7). A previous CorEvitas study (6) showed the improvement of CV risk prediction performance by adding markers of RA severity, such as disease duration, modified Health Assessment Questionnaire, and high CDAI score, to traditional CV risk factors. As the study focused on CV risk prediction at baseline, the specific contribution of CDAI score over time was not examined. A more recent CorEvitas study (9) found that time-averaged CDAI score adjusting for baseline conventional CV risk factors and medication use was associated with CV outcomes.

The current study can be distinguished from prior literature in that we accounted for post-baseline covariates (ie, RA and CV medications) through the marginal structural model framework (22) and examined the time-varying nature of the association of CDAI score over time and predicted event-free survival. We found that the detrimental association of CDAI score, which had been pointed out previously, may itself be time varying with the strength of association diminishing over time during the follow-up. Although the prevalent cohort nature of the CorEvitas registry limits our inference, this may suggest that high levels of CDAI score experienced earlier in the disease course of RA might have a stronger association with CVD than experiencing the same level of elevated CDAI score later. Such a time trend was statistically significant in a subset of our cohort within 5 years of RA diagnosis. Accordingly, our predicted CV event-free survival analyses indicated that, for individuals with a high CDAI score, earlier transition to sustained remission might be more beneficial than a later transition both because of the greater reduction from avoiding the early stronger association of high CDAI score to CVD as well as because of accumulation of potential negative impact over time.

Our finding may have implications for the large set of literature related to the "therapeutic window of opportunity" in RA (32). That is, treating RA aggressively during early years (eg, 2 years) after diagnosis can help avoid the severe articular consequences of structural damage and disability (32,33). Whether this notion of a therapeutic window of opportunity might apply to extra-articular consequences of RA is less known (34), although the observation of the relatively early increase in CVD among patients with RA is compatible (35). Our study could not directly address this earliest period of RA disease activity because the MACE count was limited among those who were within the first 2 years of RA onset in our prevalent RA cohort. Our finding on the association of RA disease activity with CVD may be

compatible with the "sensitive period model" (36), in which earlier exposure is potentially more important but the detrimental association is not exclusive to this period.

The underlying mechanism for such a time-varying CV association to CDAI score is of interest. Although constructed from clinical variables only, CDAI score is considered a reasonable representation of the inflammatory disease activity of RA (37,38). In the general CV literature, the roles that inflammation plays in the pathogenesis of atherosclerotic CVD has long been discussed (39,40). Cholesterol crystals in vascular walls can serve as an endogenous danger signal activating inflammasome (11). Such vascular wall inflammation and inflammatory cells are thought to play fundamental roles in atherogenesis and subsequent vascular events (41). This inflammatory hypothesis of atherosclerosis is attracting more interest in recent years with the success of anti-inflammatory medications (15–17) in the general high-risk patients with CV. In patients with RA, such vascular inflammation may be present related to RA disease activity. In a cross-sectional study among 91 patients with RA (mean RA duration 7.6 years), aortic inflammation as measured by 18F-fluorodeoxyglucose-PET/CT was associated with RA disease activity measured in DAS28-C-reactive protein (CRP) adjusting for traditional CV risk factors (42). Furthermore, ESR predicts more rapid carotid intima-media thickening (12). Given the cumulative nature of atherosclerosis (43), an additional detrimental impact of inflammation may be bounded by the atherosclerotic vascular damage already incurred in the earlier inflammatory processes.

The major strength of CorEvitas is that it is a large observational longitudinal registry of patients with RA. One important limitation is that the average disease duration of RA was 8.8 years in our study at enrollment although half of the patients were in their first 5 years of onset. This is due to a trade-off that the CorEvitas registry made to ensure the representative, real-world nature of its routine practice data, in which existing (prevalent) patients with RA were allowed to enter the registry whenever the treating rheumatologist felt it appropriate. In our sensitivity analysis within the patients with RA with 5 years or less since onset, a clearer sign of decreasing HR trend was seen. Our analyses were restricted to the 5-year follow-up time horizon because the cohort shrunk substantially beyond this point (to <40% of the initial size), and time-varying estimates of CDAI score associations were less reliable. Thus, we also limited our prediction to the 5-year time horizon, and later changes in the time-varying association (eg, recurrent increase in the time-varying association because of aging and inflammation) cannot be ruled out. Also, our predictions were generated under idealized sustained remission. In clinical practice, disease flare is common (44) although earlier disease may be more amenable to sustained remission (45). The generalizability may be somewhat limited by the relatively young age and high proportion of college graduates. This may be a reason for the relatively small absolute magnitude of predicted impact seen in our prediction curves, which was based on the average CV risk

profile in the cohort. The same relative impact of CDAI score could translate to a greater absolute predicted impact in a higher-risk RA population.

We chose CDAI score rather than the Simple Disease Activity Index (SDAI) score because of the inconsistent availability of CRP in the registry. However, CDAI score is considered a pragmatic alternative to SDAI score (38). Our study specifically examined the association of RA disease activity with CVD and how it might differ over time. However, RA disease activity should not be the sole focus, and careful assessment and addressing of conventional CV risk factors should remain in place (46). Although we focused on 6-month average RA disease activity, flares may carry additional importance (47). Our outcome definition likely had a high positive predictive value, but there may have been underreporting if the treating rheumatologists did not receive MACE information. Furthermore, we cannot ignore the fact that different classes of treatments for RA may have different CV effects. For example, methotrexate did not decrease CV risk among patients without RA with elevated CV risk (48), whereas IL-1 β inhibition (canakinumab (15), colchicine (16,17)) showed more promise. However, among patients with RA, both conventional and biologic antirheumatic drugs have demonstrated their ability to reduce arterial wall inflammation (49). Additionally, we note that our study is restricted to patients with RA, who historically had a twofold increase in CV risk compared with the general population (3) although the increased risk may be improving in recent years (50). We also acknowledge that our study cannot inform the best timing of antirheumatic drug initiation (most of our cohort were already on treatment) that confers CV benefits although the study may provide a rationale for earlier treatment intensification to reduce RA disease activity. As an observational study, residual confounding from factors such as venous thromboembolism and cancer cannot be ruled out. Potential alternative explanations of the time-varying CDAI-MACE associations need to be acknowledged. CDAI score is a composite score. The proportion of CDAI score due to the swollen joint count slightly decreased during the 5-year follow-up, which might have influenced the reducing association of higher CDAI score and MACEs. Although patient composition change was minor, we observed slightly more favorable CV risk profiles of patients with RA remaining under follow-up, which could have partly explained the weakened association between CDAI score and MACEs.

To summarize, we examined the time-varying association of CDAI score to subsequent CVD. We found that having a higher CDAI level earlier during the follow-up may be more strongly associated with CVD than having the same CDAI level later during the follow-up among patients who were within 5 years of onset at the time of registry enrollment. Our finding may provide an additional rationale for conducting a clinical trial on aggressive therapy to achieve early and sustained remission in the search for the "CV window of opportunity."

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Yoshida had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Yoshida, Harrold, Stryker, Karis, Solomon.

Acquisition of data. Yoshida, Harrold, Middaugh, Guan, Solomon.

Analysis and interpretation of data. Yoshida, Harrold, Middaugh, Guan, Stryker, Karis, Solomon.

ROLE OF THE STUDY SPONSOR

The data collection was conducted by CorEvitax. The study design, data analysis, interpretation of data, and the writing of the manuscript were led by the authors (some of whom are employees of CorEvitax and Amgen, Inc). Publication of the manuscript was not contingent upon approval by Amgen or CorEvitax.

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