Future Economic Evaluations in Rheumatoid Arthritis

A case for considering comprehensive benefits and costs of interventions

Evo Anthony Alemao

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Future Economic Evaluations in Rheumatoid Arthritis

A case for considering comprehensive benefits and costs of interventions

Toekomstige economische evaluaties bij reumatoïde artritis

de noodzaak van een bredere set van baten en kosten van interventies

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Evo Anthony Alemao
Born in Mumbai, India

Erasmus University Rotterdam

Doctoral committee:

Doctoral dissertation supervisor:
Prof.dr. M.P.M.H. Rutten-van Mölken

Other members:
Prof. dr. J.L.Severens
Prof. dr. A.A. Boonen
Prof. dr. M.E. Weinblatt

Co-supervisor:
Dr. M.J.Al

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CHAPTER 1

General Introduction

1

RA A MULTIFACETED DISEASE THAT REQUIRES NOVEL CONSIDERATIONS FOR EVALUATING COST EFFECTIVENESS OF INTERVENTIONS

Evidence suggests that rheumatoid arthritis (RA) as a disease has been present since ancient times [1]. In more recent history, RA has been described by Sydenham, Fuller, Heberden and Beauvais using various terms such as rheumatic gout, chronic rheumatism, rheumalgia, scorbutic rheumatism, asthenic gout [2-5]. Beauvais is credited with describing the typical RA case with pathology suggesting this disease has a separate entity compared to gout [5]. Garrod named it RA in his treatise of 1859 and presented the differential diagnosis for the disease with illustrations [6].

Our understanding of RA and the immunologic mechanisms driving the disease has greatly increased over the years. RA is currently described as a chronic progressive inflammatory disease of the joint synovium, leading to progressive disability and loss of function. In addition to inflammation in the joints, RA is also associated with bone loss, erosions, and osteoporosis [7,8]. Apart from the effect in the joints, RA is often associated with extra-articular manifestations. These extra-articular manifestations affect various tissues and organ systems, such as the lungs and the cardio-vascular system, and are distinct from the common co-morbidities occurring in the same bodily compartments [9]. Given the debilitating impact of RA on the joints and other organ systems it is not surprising that RA ranks high on the global disability list [10].

Apart from the clinical burden that RA poses, there is a substantial economic burden associated with RA [11]. Numerous studies with varying methodology have reported the direct and indirect costs of RA and these have been summarized in recent publications [12,13]. Given the differences in methodologies, objectives, and countries, the cost-of-illness studies in RA report wide variation in average cost, particularly in regard to productivity losses. A 2008 publication reported total costs of RA from a societal perspective to be €45.3 billion in Europe and €41.6 billion in the United States (US). Indirect costs constituted 32%, while medical costs were 21% and drug costs were around 19%. In Sweden, the rheumatology quality register estimated the total direct costs of RA to be €524 million in 2009 [14]. The US Center for Disease Control (CDC) reported 9,100 hospitalizations with RA listed as the principal diagnosis with total hospital charges of $374 million (mean charge of $41,000 per person) [15]. Women and people 45 years and older accounted for the majority of these stays. Since RA affects patients during their most productive working years (average age of onset is 45 years), work productivity losses due to RA are generally high [16].

RA treatments include corticosteroids (CS), non-steroidal anti-inflammatory drugs (NSAIDs), and disease-modifying antirheumatic drugs (DMARDs). The term DMARD

is applied to medications that can alter the course of the disease and thus prevent joint erosion. Traditional or conventional (c)DMARDs include gold, sulfasalazine, azathioprine, cyclophosphamide, antimalarials and methotrexate. Biologic (b) DMARDs were introduced around 2000; these agents have greatly improved overall clinical outcomes, and health related quality of life (HRQOL) of patients. However, these therapies are expensive compared to the cDMARDs. With the introduction of the bDMARDs, the cost of managing RA patients has shifted from hospital settings to outpatient ambulatory setting [17,18]. This cost shift is viewed favorably by hospital payers and DRG committees. Recently, biosimilars have been approved by regulatory and payer authorities in the EU and have considerable lower cost. Introduction of biosimilars has the potential to reduce cost to the overall health system and significantly increase affordability of bDMARDs. In parallel, new therapies as well as combination therapies (of different bDMARDs or of bDMARDs in combination with synthetic (sc) DMARDs) targeting multiple immune pathways are being developed and entering the market. In this type of environment, tools that enable a broader and more precise estimation of cost and benefits will reduce the risk of inefficient resource allocation.

This thesis builds towards taking a more comprehensive approach in evaluating benefits and costs of future therapies in RA. It focuses on multiple aspects of the disease such as treatment target measures, the heterogeneous nature of RA in terms of baseline patient characteristics (through considerations of subgroups) and outcomes that are not joint-related. By focusing on these aspects of the disease, a case is built for the incorporation of appropriate treatment response, the need to identify subgroups of RA patients at risk of rapid progression of disease and consideration of outcomes that are not joint related in future economic evaluations. Deliberation of these aspects when performing economic evaluations of interventions in RA could facilitate stratification of cost-effectiveness analysis by subgroups and a more complete evaluation of benefits versus cost of interventions. This could pave the way for policies leading to personalized medicine in RA by incorporation of genetic, environmental and clinical/biochemical profiling into economic modeling. To support the more comprehensive evaluation approach, this thesis is divided into 4 parts:

Part I: Real world evidence on treatment targets and outcomes
Part II: Presence of multiple poor prognostic factors
Part III: Extra-articular manifestation of cardiovascular risk in RA
Part IV: Improvements of future cost effectives studies in RA

For each part, we briefly summarize the most important evidence and then explain what this thesis adds to the existing evidence.

1

PART I: REAL WORLD EVIDENCE ON TREATMENT TARGETS AND OUTCOMES

The consensus treatment guidelines by the EU League Against Rheumatism (EULAR 2016) focus on the joint-aspect of the disease and have advocated a treat to target approach [19]. The 2016 EULAR guidelines recommend two treatment targets: remission, especially in DMARD-naïve patients, and low disease activity, primarily in patients who failed previous therapies. Regarding remission, the EULAR and American College of Rheumatology (ACR) have agreed on Boolean* and index-based definitions, the latter based on the Simplified or Clinical Disease Activity Index** (SDAI, CDAI). Multiple studies have demonstrated that attaining a state of remission or low disease activity leads to better structural and functional outcomes than allowing residual disease activity. The hypothesis that an improved outcome can be achieved by employing a strategy of intensive outpatient management of patients with RA was tested in a single-blind randomized controlled trial involving 183 patients.[20] Intensive management was based on monthly review of disease activity using the Disease Activity Score (DAS), escalation of DMARD therapy in patients with persistent disease activity (DAS>2.4) according to a treatment protocol, liberal use of intramuscular triamcinolone in the first three months of a new DMARD being prescribed, and intra-articular injections of triamcinolone into swollen joints. Based on the findings the authors concluded that intensive outpatient management of RA substantially improves disease activity, radiographic disease progression, physical function, and HRQOL at no additional cost. Similarly, the efficacy and safety of adalimumab plus methotrexate (ADA+MTX) compared with methotrexate monotherapy in achieving stable low disease activity (LDA; DAS in 28 joints using C-reactive protein level (DAS28-CRP <3.2 at weeks 22 and 26) and clinical, radiographic and functional outcomes in methotrexate-naive patients with early active RA was studied in 1032 patients. In this trial patients were randomly assigned 1:1 to ADA+MTX or placebo plus methotrexate (PBO+MTX) for 26 weeks. Post-hoc analyses compared patients achieving stable remission using DAS28-CRP and 2010 ACR/EULAR criteria with those achieving LDA. Patients achieving ACR/EULAR remission, particularly in the PBO+MTX group, had some advantage in radiographic outcomes compared with patients who only achieved LDA. Similar findings were observed by other investigators [21]. However, the majority of this empirical evidence is based on randomized controlled trials [22-24]. Limited data is available on patients with established RA in routine clinical practice to support the benefits of achieving different definitions of target measures of disease activity in relation to functional status, HRQOL, and health care resource utilization.

In chapter 2 of the thesis, we utilized real life data from clinical practice to conduct an observational study to assess the potential clinical implications of achieving dif-

ferent disease states (remission, low, moderate and severe disease activity states), based on various measures of disease activity. This analysis tested the hypothesis that achieving target measures of disease activity would lead to improved outcomes in clinical practice in a longitudinal cohort of RA patients. Disease activity measures used in this analysis were those recommended by EULAR/ACR guidelines and included the DAS28-CRP <2.6, the SDAI ≤3.3, or the CDAI ≤2.8. Outcomes evaluated in this analysis included both clinical i.e. physical functioning (daily activities) according to the modified Health Assessment Questionnaire (mHAQ), HRQOL measured by EuroQol 5-domain (EQ-5D) measure and economic i.e. resource utilization indicators like hospitalizations and durable medical equipment (DME) use.

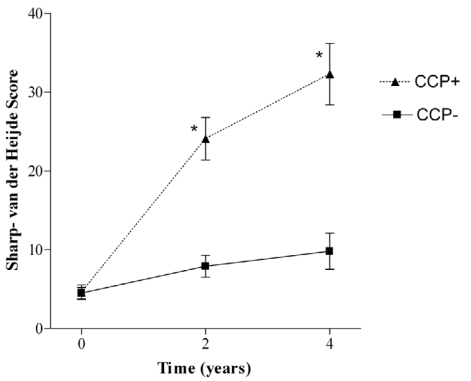
PART II: PRESENCE OF MULTIPLE POOR PROGNOSTIC FACTORS

Early in the disease course of RA, various factors associated with a poor prognosis of disease have been identified. These include certain genotypes, young age at disease onset, high disease activity based composite measures, high acute phase reactant levels (CRP), erythrocyte sedimentation rate (ESR), presence of rheumatoid factors (RF) and/or anti-citrullinated protein antibody (ACPA), especially at high levels, presence of early erosions and failure of two or more cDMARDs [24]. Contemporary RA management guidelines recommend more intensive treatment of patients with poor prognostic factors. The 2016 EULAR RA treatment guidelines recommend the addition of a bDMARD or a cDMARD when poor prognostic factors are present and treatment target is not achieved with the first CS strategy [16]. The EULAR Guideline Task Force desired to give stratification of RA patients based on prognostic factors more prominence and hence called this out as a separate recommendation.

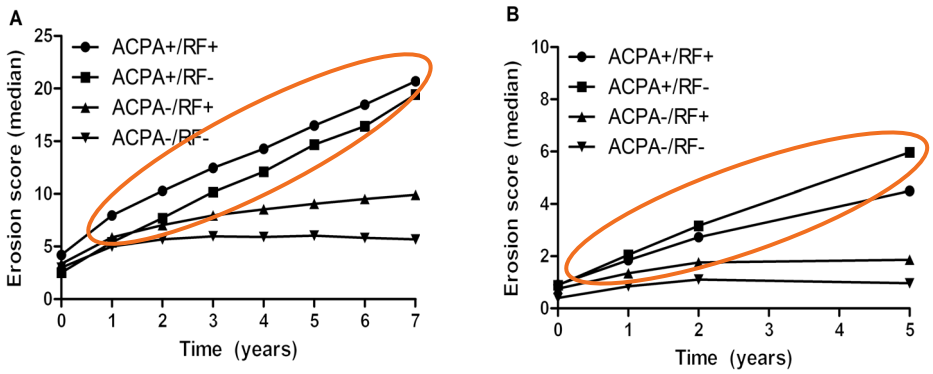
These prognostic factors are correlated and there is sufficient evidence in the literature indicating that ACPA positivity is associated with erosive disease as shown by panel A of figure 1, where the Sharp-Van der Heijde scores increase over time in ACPA positive patients. In addition to this there is also evidence that ACPA positivity is more strongly associated with erosion than RF positivity (panel B, figure 1) [25,26]. As per treatment guidelines, patients with multiple poor prognostic factors have a poor prognosis. The impact of the multiple prognostic factors on rapid radiographic progression has been evaluated in various risk prediction models and have been discussed in detail in a review manuscript, [27-32] Though these models provide estimates of the probability of having rapid radiologic progression at one year if one predictor or a combination of predictors are present, their validation with an external dataset has not been positive [33]. The prognostic factors for rapid radiographic progression in these models

1

Figure 1: Association of seropositivity with erosions in early RA patients*



Radiological destruction in patients with and without anti-cyclic-citrullinated peptide antibodies.Total Sharp–van der Heijde scores (mean ± standard error of the mean) at inclusion and at 2 and 4 years follow-up in rheumatoid arthritis patients with (CCP+) and without (CCP-) anti-cyclic-citrullinated peptide antibodies.



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include serum levels of RF (2 of the 4 models), ACPA (2 of the 4 models), CRP (all 4 models), baseline joint counts (2 of the 4 models) and baseline erosions (2 of the 4 models). All of these models use data from early RA patients either from RCTs or from RA registries. Thus, limited empirical data exists in established RA on the impact of combinations of prognostic factors on clinical and economic outcomes.

Part II of the thesis focuses on the impact of having multiple poor prognostic factors on clinical and economic outcomes in established RA.

The following research hypothesis were tested in the various studies conducted in this Part:

a) Established RA patients that are ACPA positive, have increased odds of erosive disease and greater bone loss [hand Digital X-Ray Bone Mineral Density (DXR–BMD)]), indicating prognostic factors are inter-related.
b) Reduction in ACPA titer is associated with reduction in disease activity and resource utilization.
c) The presence of multiple poor prognostic factors leads to poor clinical and economic outcomes in RA patients.
d) The presence of poor prognostic factors in RA patients leads to treatment acceleration in clinical practice setting.

Data from real world RA registries were used to address the above hypotheses. Recent studies have suggested that ACPA can stimulate bone loss by inducing the differentiation of precursors into bone-resorbing osteoclasts [33]. In patients who are positive for ACPA, structural bone damage can start even before the clinical onset of RA [34].

In chapter 3 we present results from the study evaluating the associations between presence of ACPA/RF seropositivity and the binary outcome variable of the presence or absence of joint erosions as well as the loss of bone mineral density on DXR. In chapter 4, we assess the association between the change in the level of auto-antibody i.e. ACPA on disease activity as well on resource utilization and work activity. In chapter 5, we evaluate the impact of having multiple poor prognostic factors of ACPA/RF seropositivity and erosions on outcomes. The outcomes evaluated in this analysis included remission and LDA based on the composite measures of disease activity [DAS28-CRP < 2.6 or SDAI ≤ 3.3], hospitalization, the use of durable medical equipment use (canes, wheelchairs, walkers etc.) and employment status (proportions employed, retired, disabled, and earning <$50,000 annually). In chapter 6, we evaluate the impact of having multiple poor prognostic factors on initiating treatment with bDMARDs as well as clinical and work productivity outcomes. Patients in this study were categorized at baseline based on number of prognostic factors present into 0-1, 2 and 3+ groups using the 2008 ACR treatment recommendations. As per the 2008 ACR criteria the following factors were considered as poor prognostic factors: functional limitation (based on mHAQ > 0.5), extra-articular disease (Sjögren's syndrome, RA lung disease and/or nodules), seropositivity (RF and/or ACPA), and erosions (as per radiograph at enrollment).

PART III: EXTRA-ARTICULAR MANIFESTATION OF CARDIOVASCULAR (CV) RISKS IN RA

RA is a systemic autoimmune disease associated with extra-articular RA manifestations. Extra-articular manifestations of RA effects various tissues. Extra-articular manifestation is associated with increased comorbidity and premature mortality [35]. Severe extra-articular manifestations are also associated with an increased risk of cardiovascular disease (CVD) in patients with RA [36]. The 2009 EULAR recommendations for CV risk management identified the following disease-specific criteria for higher CV risk in RA patients: disease duration of >10 years, RF or ACPA positivity and the presence of certain extra-articular manifestations.

CV events represent a significant and important outcome in RA patients. There is a general consensus that RA patients have a substantially increased risk of CVD versus the general population, leading to reduced life expectancy, diminished HRQOL, and increased health care costs [37]. Coronary artery and cerebrovascular atherosclerosis (CVA) are likely to occur in RA patients earlier than in general population [38]. Epidemiological studies have indicated the relative risk of acute myocardial infarction (AMI) in RA patients to be 1.5 to 2.0 and for stroke to be 1.4 – 2.7 fold higher [39,40]. Investigators have found that several treatment regimens for RA modify the traditional CV risk factors and CV morbidity/mortality. A positive association between AMI and CS use was reported in a study of patients in the National Data Bank for Rheumatic Diseases [41]. CS might increase CV risk by increasing the prevalence of hypertension, diabetes, and hyperlipidemia. Methotrexate, the most frequently used DMARD for the treatment of RA, has been associated with a lower risk of CV death, CV morbidity, AMI, and heart failure compared to other treatments [42, 43]. Recent meta-analysis reported that in cohort studies, anti-TNF therapy was associated with a reduced risk for all CV events, AMI and CVA but these findings are not consistent [44, 45]. The recent published phase III RCT with an anti-interleukin 1 beta compound demonstrated that reducing inflammation among men and women who have had a prior event can reduce the risk of another CV event happening in the future [46].

Chapters 7 to 9 focus on the CV manifestation in RA, primarily because CV events have substantial implications for costs, survival as well as quality of life. Since RA is associated with a 50 to 60% increase in risk of CV death, the aim of chapter 7 was to evaluate, whether the increased CV risk in RA patients can be explained by the lack of appropriate management of traditional CV risk factors (such as hypertension, smoking and cholesterol). We tested the hypothesis that traditional risk factors are managed poorly in RA patients compared to matched non-RA patients. We utilized

data from two large health systems i.e. the UK and the US (Southern California). In UK analysis, RA patients were matched 1:4 to non-RA patients based on their year of entry into the database, CV risk category based on National Cholesterol Education Program classification, treatment status at index date and a propensity score estimating the probability of having RA. In the US analysis, two RA cohorts were identified, the first was matched to the general population (general controls) in a ratio of 1:4. The second RA cohort was matched to individuals with a diagnosis of osteoarthritis in a ratio of 1:1 [47].

If CV events are to be incorporated in the economic evaluation of RA treatments, then it would be important to understand the predictors and risk modifiers of CV events and the impact of treatment on these predictors and risk modifiers. The 2009 EULAR recommendations for CVD risk management suggested a multiplication factor of 1.5 to the CVD risk calculated using traditional risk calculators such as the Framingham and SCORE algorithms [48, 49] However, these algorithms were not developed in RA-specific populations and recent attempts to develop RA-specific CV risk calculators have encountered mixed success [50, 51]. Thus, another aspect of CV manifestation of RA investigated in chapter 8 of this thesis was the performance of CV risk prediction algorithms in RA. We tested the hypothesis that markers of inflammation such as CRP improve the CV risk prediction in RA and thus could help explain some of the increased CV risk in RA patients. We conducted a retrospective analysis, using clinical practice data from the UK to test this hypothesis.

The final chapter in this Part focuses on the association between lowering low-density lipoproteins cholesterol (LDL-C) levels and CV outcomes among RA patients. Elevated cholesterol is a risk factor for increased CV events in the general population; however, a growing level of evidence suggests a complex relationship between lipid levels and CV risk in patients with RA [52]. There is considerable evidence that an atherogenic lipid profile may be detected in patients with early RA. For example, treatment-naïve active RA patients with disease duration of less than one year exhibited significantly higher total cholesterol (TC) and LDL-C with lower high-density lipoproteins (HDL-C) levels when compared to matched controls and the ratio of TC to HDL-C was less favorable in RA patients [53]. These findings are potentially due to the altered lipid metabolism from systemic inflammation, drug therapy, and several genetic factors in RA. The evidence regarding the benefits of lowering elevated LDL-C in patients with RA is not clear. The hydroxymethylglutaryl CoA reductase inhibitor (statin) therapy has been shown to be beneficial in primary and secondary prevention of CV diseases in the general population [54]. Although several post-hoc analysis suggest potential CV protective effects of statin therapy in RA, there has been no RCT evaluating this ques-

tions (a recent prospective RCT was terminated early owing to low CV event rates) [55]. Thus in chapter 9 we investigated whether a lower LDL-C in RA patients was associated with any reductions in CV events. We utilized data from a US managed care setting on RA subjects and age- and sex-matched controls who are prescribed statin therapy.

PART IV: IMPROVEMENT IN FUTURE COST EFFECTIVES ANALYSIS IN RA

Various types of economic models have been developed in RA with the primary objective to evaluate the cost and benefits of treatments in RA and estimate the cost-effectiveness of interventions including bDMARDs and cDMARDs. A comprehensive overview of these modeling approaches were published in 2014 [56, 57]. These economic models have used a number of different RA disease activity measures, including the EULAR, ACR criteria and various composite disease activity measures that were mentioned in Part I of this thesis, to determine the number of patients responding to and continuing treatment (i.e. treatment response). In general, these models convert the change in disease activity measure after treatment initiation into a change in HAQ score and focus on the progression of HAQ scores for the population over time. The HAQ scores are then generally mapped to the patient's HRQOL, mortality rates and resource use, using validated mapping algorithms [58]. Thus, models used in RA generally are able to simulate the experiences of RA patients by replicating the clinical reality of the disease using clinical efficacy data from trials to assess the initial response to a treatment and then using limited data from registries to model long-term disease progression.

In the first section (chapter 10) of this Part, we use an individual patient simulation model to simulate the impact of treatment in subgroups of RA patients with various titers of ACPA, a marker of poor prognosis as stated in Part II. In this analysis we evaluated the cost-effectiveness to two branded bDMARDs with different mechanism of actions. The model concept was similar to that of the 'Birmingham rheumatoid arthritis model' with certain elements incorporated from the 'The Sheffield rheumatoid arthritis health economic model' and was programmed in Microsoft Excel [59, 60]. The model tracked a large number of individual patients with different baseline characteristics (age, gender, and HAQ score) over a lifetime, with the follow-up time being divided into six-month cycles. The outcome of the analysis was quality adjusted life year (QALY) gained in RA patients stratified according to baseline ACPA levels.

The current modeling approach has advantages and has served to establish economic benefits of bDMARDs, in moderate to severe RA patients who inadequately respond to methotrexate. In our opinion previously, published models have potential room for improvement. The current modeling approaches in RA do not account for the fact that RA is a heterogeneous condition and has impact on extra-articular regions. In chapter 11, we propose a new conceptual model for evaluation of the cost-effectiveness of RA interventions. The conceptual framework was developed by following recommendations from the International Society of Pharmacoeconomics and Outcomes Research-Society of Medical Decision Making (ISPOR-SMDM) Modeling Good Research Practices Task Force-2. The process involved scoping the decision problem by a working group and drafting a preliminary cost-effectiveness model framework. An expert panel reviewed and provided input on the conceptual model. The revised conceptual framework incorporates the findings from Part I to Part III and proposes a more comprehensive approach in evaluating benefits and costs of future therapies in RA. The proposed conceptual framework concurs with some of the recommendations of the consensus recommendations from the 2015 'Consensus Working Party' [60]. However, there are some major differences between the Consensus Working Party's recommendations and the current proposed conceptual model. Overall, the proposed conceptual model reflects on six preselected areas and could serve as a foundation for developing future cost-effectiveness models for the 21th century drug treatment in moderate to severe RA patients.

1

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CHAPTER 2

Effects of Achieving Target Measures in Rheumatoid Arthritis on Functional Status, Quality of Life and Resource Utilization: Analysis of Clinical Practice Data

Evo Alemao[1]*, Seongjung Joo[2], Hugh Kawabata[2], Maiwenn J. Al[3], Paul D. Allison[4], Maureen P.M.H. Rutten-van Mölken[3], Michelle L. Frits[5], Christine K. Iannaccone[5], Nancy A. Shadick[5] and Michael E. Weinblatt[5]

[1]Bristol-Myers Squibb, Princeton, NJ, USA;
[2]Bristol-Myers Squibb, Hopewell, NJ, USA;
[3]Institute of Health Policy & Management (iBMG), Institute for Medical Technology Assessment (iMTA), Erasmus University, Rotterdam, The Netherlands;
[4]Department of Sociology, University of Pennsylvania, Philadelphia, USA;
[5]Department of Rheumatology, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA, USA.
* PhD student at Erasmus University Rotterdam, supervised by M.P.M.H.R.M. and M.J.A.

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ABSTRACT

Objective. To evaluate associations between achieving guideline-recommended targets of disease activity, defined by Disease Activity Score 28-C-reactive protein (DAS28-CRP) < 2.6, Simplified Disease Activity Index (SDAI) ≤ 3.3, or Clinical Disease Activity Index (CDAI) ≤ 2.8, and other health outcomes in a longitudinal, observational study. **Methods.** Other defined thresholds included low, moderate, or severe disease activity (LDA, MDA, SDA). To control for intraclass correlation and estimate effects of independent variables on outcomes of the Modified Health Assessment Questionnaire (MHAQ), EuroQol-5D (EQ-5D; a quality-of-life measure), hospitalization, and durable-medical-equipment (DME) use, we employed mixed models for continuous outcomes and generalized estimating equations for binary outcomes. **Results.** Among 1,297 subjects, achievement (vs. non-achievement) of recommended disease targets was associated with enhanced physical functioning and lower health resource utilization. After controlling for baseline covariates, achievement of disease targets (vs. LDA) was associated with significantly enhanced physical functioning based on SDAI ≤ 3.3 (ΔMHAQ = –0.047; $P = 0.0100$) and CDAI ≤ 2.8 (–0.073; $P = 0.0003$) but not DAS28-CRP < 2.6 (–0.022; $P = 0.1735$). Target attainment was associated with significantly improved EQ-5D (0.022–0.096; $P < 0.0030$ vs. LDA, MDA, or SDA). Patients achieving guideline-recommended disease targets were 36%–45% less likely to be hospitalized ($P < 0.0500$) and 23%–45% less likely to utilize DME ($P < 0.0100$). **Conclusion.** Attaining recommended target disease-activity measures was associated with enhanced physical functioning and HRQOL. Some health outcomes were similar in subjects attaining guideline targets versus LDA. Achieving LDA is a worthy clinical objective in some patients.

INTRODUCTION

Rheumatoid arthritis (RA) affects 0.5%–1.0% of adults in industrialized societies [1]. This chronic, systemic, inflammatory disorder causes erosive damage to articular cartilage and subchondral bone, with joint swelling, deformity, pain, stiffness, and fatigue. Many patients with RA experience diminished health-related quality of life (HRQOL) as well as increased disability and comorbidities. Because of related disability, reduced worker productivity, expensive biologic drug therapy, institutionalization, joint-replacement surgery, and increased use of durable medical equipment (DME), RA is a costly condition, accounting for annual health-care expenditures of approximately $128 billion in the United States [2-4].

Although there is no cure for RA, treatment with disease-modifying antirheumatic drugs (DMARDs) and biologic DMARDs (bio–DMARDs) has improved health outcomes for RA patients. Increasingly, treatments oriented toward prespecified disease targets are emerging as the prevailing RA management paradigm. This treat-to-target approach involves aiming for a prespecified target of disease activity, frequently monitoring disease levels, and titrating medication regimens to goals (where therapies are acceptably tolerated). Such strategies have proved to be more effective than routine care, with randomized controlled trials (RCTs) and other studies supporting their value in attenuating RA signs and symptoms, ameliorating functional status, and mitigating or halting radiographic progression [5-8].

The most desirable target measure of disease activity is remission, which signifies a condition of negligible or no inflammatory activity, total arrest of structural joint damage, and the optimum achievable reversal of disability [6, 8-11]. In previous consensus guidelines, remission was operationally defined as a Disease Activity Score 28-C-reactive protein (DAS28-CRP) < 2.6 [12]. However, some patients with DAS28-CRP < 2.6 experience residual disease activity, including inflammation, pain, and joint tenderness and swelling in ankle and foot joints [5, 13-18]. Although DAS28-CRP < 2.6 no longer constitutes remission, it remains a valid treatment target.

In more recent times, more stringent consensus definitions of remission have been developed that are both index based (Simplified Disease Activity Index [SDAI] score ≤ 3.3 [13, 19]) and Boolean based. The Boolean-based definition [13] requires a score of ≤1 on each of the following items: tender joint count 28 (TJC28), swollen joint count 28 (SJC28), CRP (in mg/dL), and patient global assessment (on a 0 to 10-cm visual analog scale [13, 19]).

Clinical studies have increasingly included different target measures of disease activity as primary efficacy endpoints [20-23]. Because such trials typically include "selected" patient populations with high adherence, severe RA activity, and short study durations, their findings may be less generalizable to clinical practice compared with data from observational studies [7, 24-29].

Limited empirical evidence is available concerning patients with established RA in routine clinical practice to support the benefits of achieving different definitions of target measures of disease activity in relation to functional status, HRQOL, and health-care resource utilization. To our knowledge, no observational study has assessed the potential clinical implications of achieving each of these different disease activity cut points across various efficacy and resource-use outcome measures.

To close this gap in knowledge, we sought to evaluate associations between achieving different definitions of target measures of disease activity and the following health outcomes in a longitudinal, observational study of a clinically representative RA patient cohort: 1) physical functioning (daily activities) according to the Modified Health Assessment Questionnaire (MHAQ), 2) HRQOL according to the EuroQol-5D (EQ-5D), and 3) health-care resource utilization according to hospitalizations and DME use.

PATIENTS AND METHODS

We utilized data from the Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study (BRASS; ClinicalTrials.gov Identifier NCT01793103), which was initiated in 2003–2004. Details concerning the study design have been reported elsewhere [30-32]. (For further details, see http://www.brassstudy.org.) The BRASS Registry is a single-center, prospective, observational, longitudinal cohort of >1,200 adults with established or recent-onset RA who are being followed by a hospital-based practice of 21 rheumatologist in Boston. Physicians assessed patient demographic and clinical characteristics, disease activity, and laboratory parameters at baseline and annually thereafter. Follow-up postal questionnaires to assess patient-reported outcomes were also mailed to patients every 6 months. In the BRASS Registry, disease activity was evaluated during each annual rheumatology visit. However, because visits seldom occurred exactly at 12 months, for this analysis windows of 6 months (± 3 months) around the 12-month physician visits were created to evaluate annual disease activity. In addition, windows of 3 months (± 1.5 months) were created around the 6-month patient survey. Thus, the follow-up time was divided into distinct intervals: time in-

terval 1 extended from 5 to 8 months (midpoint = 6 months); interval 2, from 9 to 15 months (midpoint = 12 months); interval 3, from 16 to 20 months (midpoint = 18 months); interval 4, from 21 to 27 months (midpoint = 24 months), and so on, extending up to 5 years.

Measures of disease activity assessed annually by physicians included the DAS28-CRP, SDAI, and Clinical Disease Activity Index (CDAI). Three different desired target measures of disease activity were considered in the current analysis: DAS28-CRP < 2.6, SDAI ≤ 3.3, and CDAI ≤ 2.8 [33-35]. These disease targets were categorized as having been met or not met: DAS28-CRP < 2.6 versus ≥ 2.6, SDAI ≤ 3.3 versus > 3.3, and CDAI ≤ 2.8 versus > 2.8.

In addition to categorizing and comparing disease activity in a binary manner, we also compared achievement of the target measures to attainment of multiple other cut points. Achievement of DAS28-CRP < 2.6 was compared to attainment of LDA (2.6 < DAS28-CRP ≤ 3.2), moderate disease activity (MDA; 3.2 < DAS28-CRP ≤ 5.1), or severe disease activity (SDA; DAS28-CRP > 5.1) [33, 35]. Similarly, achievement of SDAI ≤ 3.3 was compared to attainment of LDA (3.3 < SDAI ≤ 11.0), MDA (11.0 < SDAI ≤ 26), or SDA (SDAI > 26) [36, 37]. Finally, achievement of CDAI ≤ 2.8 was compared to attainment of LDA (2.8 < CDAI ≤ 10.0), MDA (10.0 < CDAI ≤ 22.0), or SDA (CDAI > 22.0) [34].

The patient-reported outcomes of physical functioning, as measured by the MHAQ, HRQOL as measured by the EQ-5D using US population-based preference weights, [36] and health-care resource utilization as measured by whether patients did (or did not) use DME or were (or were not) hospitalized, were captured during the 6-month postal survey. The patient-reported outcome measures incorporated within the BRASS case report forms were validated questionnaires that have been widely used in other RA registries as well as clinical trial settings [33-35, 37]. DME included walkers, wheelchairs, standers, and patient lifts.

Ethics

The BRASS Registry has been conducted in accordance with International Society for Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practices, applicable regulatory requirements, and ethical tenets originating in the Declaration of Helsinki. The study protocol and informed-consent document were reviewed and approved by the Brigham and Women's Hospital Institutional Review Board. All pa-

tients provided written informed consent before participating in the BRASS Registry. Anonymous (de-identified) patient data in the present study were compliant with the Health Insurance Portability and Accountability Act. Maintenance of patient confidentiality was assured by assigning each subject a randomized identification number upon enrollment in the BRASS Registry.

Statistical analyses

Baseline characteristics were expressed as means (SDs) and numbers (%). Univariate and multivariate analyses were conducted to evaluate associations between achievement of prespecified, guideline-recommended target measures of disease activity (independent variables of interest) and the outcome measures of MHAQ (continuous variable), EQ-5D (continuous variable), DME use (categorical variable), and all-cause hospitalization (categorical variable; dependent variables).

Univariate analyses involved comparisons of mean scores on the MHAQ and EQ-5D, in patients who either did or did not achieve the above definitions of targets for the DAS28-CRP, SDAI, and CDAI, using Student's t-test and analysis of variance (ANOVA) for comparing these measures in individuals attaining target, LDA, MDA, or SDA. Similarly, proportions of patients using DME or being hospitalized were compared, in patients who either did or did not achieve the above definitions of targets, using the Chi-square test and visual-inspection comparisons between individuals attaining guideline-recommended targets, LDA, MDA, or SDA.

To control for intraclass correlation of the panel data in BRASS, we used mixed models with Toeplitz covariance structure to estimate both the effects of the achievement of target measures or other levels of disease activity on the dependent variables—the primary outcome measure of physical functioning assessed by the MHAQ and the secondary outcome measure of HRQOL assessed by the EQ-5D. Generalized estimating equations (GEEs) with binomial distribution, and logit link function, were utilized for binary outcomes such as DME use and all-cause hospitalization. Baseline covariates included in these models were sociodemographic, laboratory measures, subjective (patient-reported), and physician-diagnosed comorbidities (Supplementary Appendix Table1). A purposeful selection method was used for identifying variables to be considered for the multivariate models; that is, we included in the multivariate model only variables that had some association with the outcome variable (i.e. had a P value of ≤ 0.10, which was the prespecified threshold). The selection of the final model was based on evaluation of overall model fit statistics and included an iterative

model selection (backward as well as stepwise) process and examination of variables that were associated with outcomes.

Analyses were conducted using SAS PROC MIXED and PROC GENMOD procedures (SAS Institute Inc., Cary, NC) for continuous and categorical outcome variables.

RESULTS

Baseline characteristics of the 1,297 included subjects (n =1,067 [82.3%] women) are summarized in Table 1. The mean (SD) age was 56.6 (14.1) years, and the mean (SD) symptom duration was 15.3 (13.0) years. Most (70.7%) patients were seropositive and/or had received DMARDs (86.7%) —with some patients receiving bio–DMARDs

Table 1. Baseline Characteristics

Characteristic	Mean (SD) No. (%)
Age, yr (n = 1297)	56.6 (14.1)
Symptom duration, yr (n =1286)	15.3 (13.0)
Body mass index, kg/m² (n =1227)	26.8 (5.7)
Diastolic blood pressure, mmHg (n =1157)	75.8 (10)
DAS28-CRP (n =1255)	3.8 (1.6)
Swollen joints, total (n =1295)	6.9 (7.2)
Painful joints, total (n =1295)	7.7 (7.9)
Total SP joints (n =1295)	14.7 (14.2)
Female gender (n =1297)	1,067 (82.3)
Anti–CCP positive (n =1117)	703 (62.9)
RF positive (n =1092)	693 (63.5)
Seropositive (n =1128)	797 (70.7)
MHAQ (n =1220)	0.43 (0.46)
RA disease target measures: (n =1297)	
DAS < 2.6	389 (30.0)
CDAI ≤ 2.8	134 (10.3)
SDAI ≤ 3.3	91 (7.0)
DMARD at baseline (n =1297)	1,124 (86.7)
Biologic DMARD at baseline (n =1297)	477 (36.8)

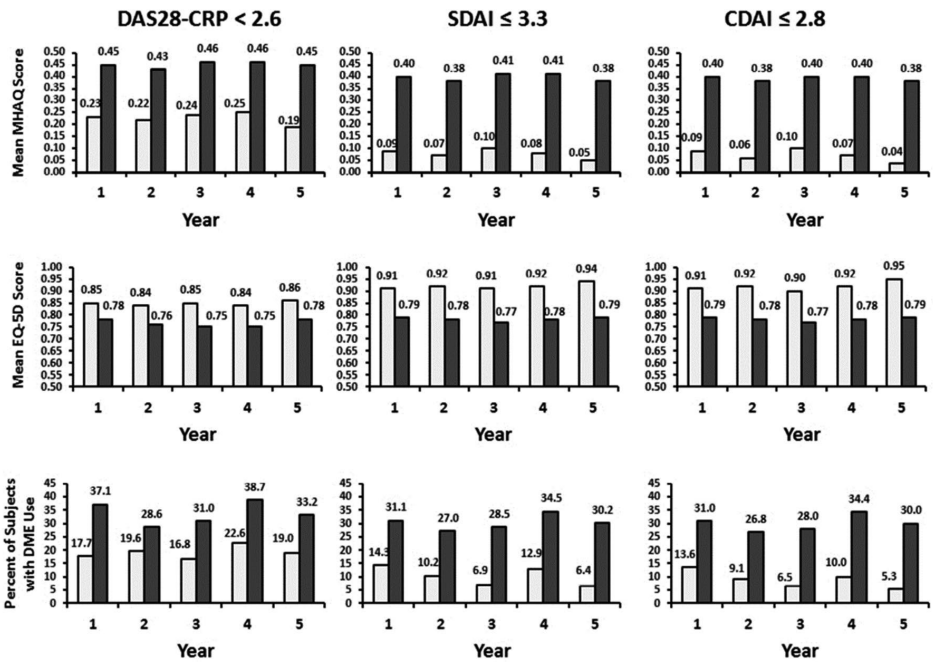
CCP, cyclic citrullinated protein; CDAI, Clinical Disease Activity Index;
CRP, C-reactive protein; DAS28-CRP, Disease Activity Score 28-C-reactive protein;
DMARD, disease-modifying antirheumatic drug; MHAQ, Modified Health Assessment Questionnaire; RADAI, Rheumatoid Arthritis Disease Activity Index; RF, rheumatoid factor; SDAI, Simplified Disease Activity Index; SP, swollen and painful.

(n = 477; 36.8% of entire population) — at baseline. In addition, some patients had DAS28-CRP < 2.6 (n = 389; 30.0%), SDAI ≤ 3.3 (n = 91; 7.0%), or CDAI ≤ 2.8 (n = 134; 10.3%) at baseline

Primary outcome measure: physical functioning (MHAQ)

Subjects who achieved target measures of disease activity (i.e. DAS28-CRP < 2.6, SDAI ≤ 3.3, CDAI ≤ 2.8) experienced improved physical functioning on the MHAQ compared to subjects who did not attain these target measures (Figure 1). In addition, BRASS registrants with incrementally worse disease activity levels (i.e. LDA, MDA, SDA) experienced decreased physical functioning on the MHAQ compared to patients attaining the foregoing target measures (Figure 2). After controlling for baseline covariates in the mixed models, we found that achievement of DAS28-CRP < 2.6 was associated with a mean reduction (improvement) of 0.0823 in MHAQ scores

Figure 1. Mean longitudinal Modified Health Assessment Questionnaire (MHAQ) disability scores, EQ-5D health-related quality of life scores, and durable-medical-equipment (DME) use among patients with DAS28-CRP < 2.6, SDAI ≤ 3.3, or CDAI ≤ 2.8 (light-gray bars) compared to those attaining higher (i.e. more severe) target measures of disease activity (dark-gray bars).

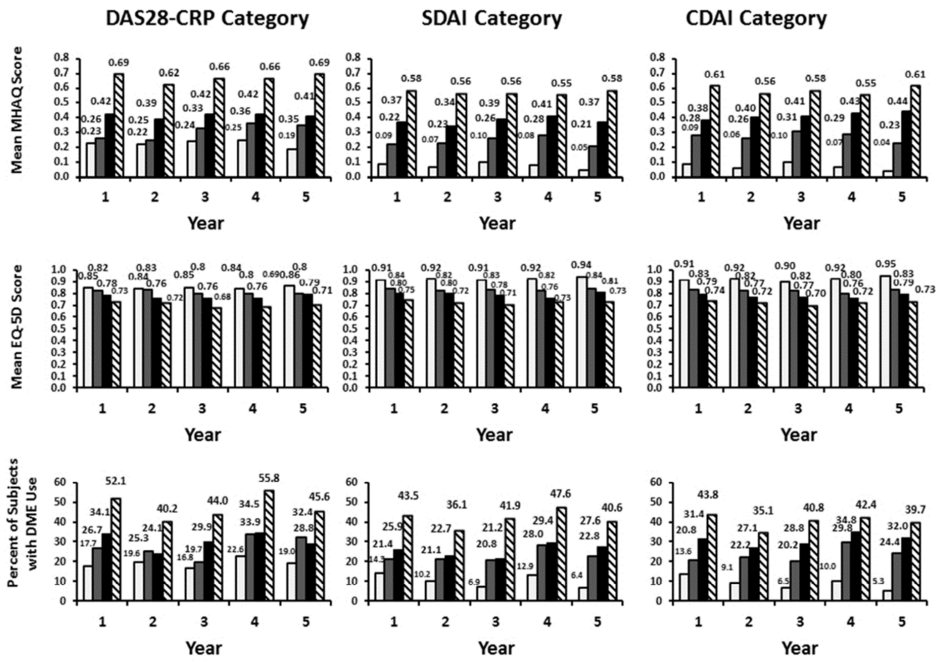


DAS28-CRP ≥2.6, SDAI > 3.3, and CDAI > 2.8. CDAI, Clinical Disease Activity Index; DAS28-CRP-28, Disease Activity Score-28-C-reactive protein; EQ-5D, EuroQol-5D; SDAI, Simplified Disease Activity Index

($P < 0.0001$) compared to not achieving DAS28-CRP < 2.6. Similarly, achieving (vs. not achieving) SDAI ≤ 3.3 or CDAI < 2.8 was associated with reductions in MHAQ of 0.0834 ($P < 0.0001$) and 0.1035 ($P < 0.0001$), respectively (Table 2).

Compared to individuals with LDA, subjects who achieved these target measures of disease activity had mean reductions (improvements) on MHAQ of 0.0221 ($P = 0.1735$), 0.0471 ($P = 0.0100$), and 0.0734 ($P = 0.0003$) based on DAS28-CRP, SDAI, and CDAI criteria, respectively. When compared to individuals with MDA, subjects achieving these same target measures of disease activity experienced mean reductions on MHAQ of 0.0875 ($P < 0.0001$), 0.0909 ($P < 0.0001$), and 0.1192 ($P < 0.0001$) based on DAS28-CRP, SDAI, and CDAI criteria, respectively. Similar findings on physical functioning were observed in BRASS registrants achieving the target measures of disease activity compared to SDA (Table 2): significant improvements in MHAQ across DAS28-CRP, SDAI, and CDAI categories ($P < 0.0001$ for each comparison).

Fig 2 Mean longitudinal Modified Health Assessment Questionnaire (MHAQ) disability scores, EQ-5D health-related quality of life scores, and durable-medical-equipment (DME) use among patients with DAS28-CRP < 2.6, SDAI ≤ 3.3, or CDAI ≤ 2.8 (light-gray bars) compared to low disease activity (LDA; dark-gray bars), moderate disease activity (MDA; solid-black bars), and severe disease activity (SDA; hatched bars).



CDAI, Clinical Disease Activity Index; DAS28-CRP, Disease Activity Score 28-C-reactive protein; SDAI, Simplified Disease Activity Index

Table 2. Improvements in Physical Functioning (MHAQ) and Quality of Life (EQ-5D) Based on Achieving Target Measures of Disease Activity by Different Definitions

	Mean difference in MHAQ based on:					
	DAS28- CRP categories	*P*	SDAI categories	*P*	CDAI categories	*P*
Achieving target (vs. not achieving)	–0.0823	<0.0001	–0.0834	<0.0001	–0.1035	<0.0001
Achieving target (vs. achieving LDA)	–0.0221	0.1735	–0.0471	0.0100	–0.0734	0.0003
Achieving target (vs. achieving MDA)	–0.0875	<0.0001	–0.0909	<0.0001	–0.1192	<0.0001
Achieving target (vs. achieving SDA)	–0.2040	<0.0001	–0.1476	<0.0001	–0.1611	<0.0001
	Mean difference in EQ-5D based on:					
	DAS28- CRP categories	*P*	SDAI categories	*P*	CDAI categories	*P*
Achieving target (vs. not achieving)	0.04780	<0.0001	0.06580	<0.0001	0.0735	<0.0001
Achieving target (vs. achieving LDA)	0.02247	0.0026	0.05180	<0.0001	0.06117	<0.0001
Attaining target (vs. achieving MDA)	0.05143	<0.0001	0.06656	<0.0001	0.08014	<0.0001
Attaining target (vs. achieving SDA)	0.08492	<0.0001	0.09145	<0.0001	0.09602	<0.0001

CDAI, Clinical Disease Activity Index; DAS28-CRP, Disease Activity Score 28-C-reactive protein; EQ-5D, Euro-Qol-5D;HAQ, Modified Health Assessment Questionnaire; SDAI, Simplified Disease Activity Index. Targets: DAS28-CRP < 2.6, SDAI ≤ 3.3 or CDAI ≤ 2.8. LDA, low disease activity: 2.6 < DAS28-CRP ≤ 3.2; 3.3 < SDAI ≤ 11.0; 2.8 < CDAI ≤ 10. MDA, moderate disease activity: 3.2 < DAS28-CRP ≤ 5.1; 11 < SDAI ≤ 26; 10 < CDAI ≤ 22. SDA, severe disease activity:DAS28-CRP > 5.1; SDAI > 26.0; CDAI >22.

Other covariates significantly associated with improved MHAQ scores across all three composite measures included prior treatment with methotrexate (MTX), lower baseline MHAQ score (i.e. less physical dysfunction at baseline), shorter RA duration, an absence of osteoporosis, and being a former (vs. current) smoker (Supplementary Appendix Table 2).

Secondary outcome measures: HRQOL (EQ-5D) and health-care resource use

Similar findings to MHAQ were evident concerning HRQOL on the EQ-5D and health-care resource use (DME and hospitalizations). Subjects who achieved guideline-recommended targets measures of disease activity experienced enhanced HRQOL and decreased resource use, compared to those who did not attain these targets, during each year of follow-up (Figure 1). (Numbers of patients who achieved [or did not achieve] targets at each time point are tabulated in Supplementary Appendix Table 3.)

Conversely, with each increasing (worsening) measure of disease activity (i.e. LDA, MDA, SDA), subjects experienced decreased HRQOL and increased resource use

compared to their counterparts who achieved the target measures (Figure 2). After controlling for baseline covariates in mixed models, we found that subjects who achieved (vs. did not achieve) the foregoing target measures of disease activity experienced significant improvements on the EQ-5D across all three composite indices: increases of 0.0478 to 0.0735 ($P < 0.0001$ for each; Table 2). Subjects who achieved the target measures of disease activity for DAS28-CRP, SDAI, and CDAI experienced significantly improved HRQOL compared to individuals with LDA, MDA, or SDA (each $P < 0.0030$).

Subjects who attained guideline-recommended target measures of disease activity also had significantly (or borderline-significantly) lower odds of DME use and hospitalization (Table 3). The probability of DME use in subjects who achieved (vs. did

Table 3. Improvements in Resource Utilization Based on Achieving Target Measures of Disease Activity by Different Definitions

	Odds Ratios for Durable Medical Equipment (DME) Use Based on:					
	DAS28- CRP categories	95% CI	SDAI categories	95% CI	CDAI categories	95% CI
Achieving target (vs. not achieving)	0.77	0.64–0.94	0.61	0.46–0.82	0.55	0.40–0.75
Achieving target (vs. achieving LDA)	0.79	0.60–1.00	0.64	0.46–0.88	0.61	0.43–0.86
Achieving target (vs. achieving MDA)	0.84	0.67–1.00	0.70	0.50–0.96	0.55	0.39–0.77
Achieving target (vs. achieving SDA)	0.60	0.45–0.80	0.51	0.37–0.70	0.45	0.32–0.63
	Odds Ratios for All-Cause Hospitalization Based on:					
	DAS28- CRP categories	95% CI	SDAI categories	95% CI	CDAI categories	95% CI
Achieving target (vs. not achieving)	0.64	0.51–0.80	0.61	0.46–0.82	0.55	0.40–0.75
Achieving target (vs. achieving LDA)	0.73	0.51–1.05	0.73	0.44–1.21	0.66	0.40–1.10
Achieving target (vs. achieving MDA)	0.72	0.54–0.95	0.55	0.33–0.91	0.55	0.33–0.92
Achieving target (vs. achieving SDA)	0.38	0.27–0.52	0.39	0.24–0.64	0.44	0.27–0.27

CDAI, Clinical Disease Activity Index; CI, confidence interval; DAS28-CRP, Disease Activity Score 28-C-eactive protein; LDA, low disease activity; MDA, moderate disease activity; SDA, severe disease activity; SDAI, Simplified Disease Activity Index. Targets: DAS28-CRP < 2.6, SDAI ≤ 3.3, or CDAI ≤ 2.8. LDA, low disease activity: 2.6 < DAS28-CRP ≤ 3.2; 3.3 < SDAI ≤ 11.0; 2.8 < CDAI ≤ 10. MDA, moderate disease activity: 3.2 < DAS28-CRP ≤ 5.1; 11 < SDAI ≤ 26; 10 < CDAI ≤ 22. SDA, severe disease activity: DAS28-CRP > 5.1; SDAI > 26.0; CDAI >22.

not achieve) the targets was reduced by approximately 23%–45% for: DAS28-CRP < 2.6 (odds ratio [OR] = 0.77; $P = 0.0086$), SDAI ≤ 3.3 (OR = 0.61; $P = 0.0011$), and CDAI ≤ 2.8 (OR = 0.55; $P = 0.0002$). Reductions in the odds of DME use were also observed when subjects achieving target measures were compared to those with LDA on the SDAI and CDAI: decreases of 36%–39%. Across all three-disease measures, subjects who achieved the desired targets had significantly reduced odds of DME use compared to individuals with SDA (reductions of 40%–55%; $P < 0.0090$ for each comparison; Table 3).

Findings on the odds of hospitalization were similar to the data on DME use (Table 3). The odds of hospitalization were significantly decreased, by approximately 36%–45%, among subjects who achieved (vs. did not achieve) the target measures of disease activity. Similar, significant reductions in the odds of hospitalization were also observed when comparing subjects who achieved the desired targets to their counterparts with MDA or SDA (but not LDA) across all measures. .

As with the MHAQ data, baseline covariates significantly associated with improved HRQOL on the EQ-5D included lower MHAQ scores (i.e. less physical dysfunction) and shorter RA duration across all three disease measures (Supplementary Appendix Table 4). A history of MTX therapy was also associated with a significant improvement in EQ-5D (+0.018; $P \leq 0.0021$) for DAS28-CRP < 2.6 but was not uniformly significantly associated with improvements in EQ-5D according to SDAI or CDAI disease targets ($P > 0.07$ for each).

DISCUSSION

This longitudinal observational cohort study demonstrated that achieving (vs. not achieving) guideline-recommended target measures of disease activity of DAS28-CRP < 2.6, SDAI ≤ 3.3, and/or CDAI ≤ 2.8 was associated with significant improvements in physical functioning, HRQOL, and health-care resource utilization. Our findings are consistent with consensus guidelines, which have been evolving toward a strategy of treating RA to targets. Recently, a EULAR panel stated that LDA "defined by composite measures is a good alternative goal for ... patients who cannot attain remission even today, especially those with long-standing disease who ... constitute the majority of patients in clinical care.[5]"

In this context, subjects who achieved the most desirable target of DAS28-CRP < 2.6 in our study did not differ significantly compared to those with LDA (2.6 ≤ DAS28-CRP

< 3.2) in terms of physical functioning as measured by the MHAQ. Attainment of DAS28-CRP <2.6, SDAI ≤ 3.3, or CDAI ≤ 2.8 did not result in significant reductions in hospitalization compared to achievement of LDA (although there were trends toward reduced odds of hospitalization in subjects achieving target measures across all three indices) but did differ in HRQOL and DME use (significant or borderline-significant differences between DAS28-CRP < 2.6, SDAI ≤ 3.3, or CDAI ≤ 2.8 vs. LDA, MDA, or SDA). Our findings thus suggest that differentiation on outcome measures for achieving target measures versus LDA is not uniform. We also observed that attainment of LDA (vs. MDA or SDA) was associated with favorable clinical and economic outcomes.

Most of the differences in outcomes observed between groups were both statistically significant and clinically relevant, in that they met minimum important differences (MIDs). Even though there is no consensus concerning the MID for MHAQ in clinical practice settings, a –0.09 change in the HAQ-DI has been associated with "somewhat improved" outcomes [38]. Assuming that a change of –0.09 is the MID for MHAQ, most of the comparisons in Table 2 either approach or are above this threshold, except for comparisons between achieving guideline-recommended disease targets and LDA, where only the CDAI–based comparisons approached this difference.

To our knowledge, no investigators have reported an MID for the EQ-5D in RA. However, work done in other disease states indicates that the MID is a change of 0.05–0.08 on the EQ-5D [39]. Based on an MID of 0.05, all comparisons in our analysis evaluating attainment of target versus LDA, MDA, and SDA (based on CDAI and SDAI) crossed the MID. On the other hand, consistent with the MHAQ – based analysis, DAS28-CRP – based comparisons crossed or approached the MID, with the exception of attaining target compared to LDA. Taken together, these findings support both the value of treating to targets and the assertion that LDA is a plausible alternative clinical objective for treat-to-target strategies when guideline recommended goals cannot be achieved in clinical practice.

In our study, previous treatment with MTX was associated with significantly enhanced physical functioning on the MHAQ, while duration of RA, baseline MHAQ, current (vs. former) smoking, and osteoporosis (vs. absence of osteoporosis) were associated with significantly worse physical functioning. These findings extend data from a Swedish case-control study, which determined that smoking was dose dependently associated with occurrence of anti-cyclic citrullinated peptide (anti–CCP) antibodies [40]. An interaction between human leukocyte antigen-D (HLA-DR) shared-epitope genes and smoking triggered immune responses only in patients positive for anti–

CCP. In this context, most (63%) of our patients were anti–CCP positive at baseline. Finally, a study of patients with LDA or MDA revealed a significant association between radiographic damage in RA and low femoral-neck bone mineral density [41].

All outcome measures did not perform consistently in discriminating dependent variables of physical functioning, HRQOL and health-care resource utilization across guideline-recommended target measures and levels of disease activity in our study. Previous reports indicated that data from all three indices are overall highly intercorrelated and show similarly high C-statistics (area under the curve values > 0.80) for receiver-operating-characteristic curves when using, as "gold standards," clinicians' decisions either to initiate DMARDs or to increase their dosages. The SDAI and CDAI include both patient and evaluator ratings of global disease activity, which are frequently discrepant [36]. Perhaps the inclusion of both perspectives on global disease activity in the SDAI and CDAI (but not DAS28-CRP) renders these indices more effective assessments of physical functioning on the MHAQ (vs. DAS28-CRP).

Data concerning improvements in patient-reported and resource-use outcomes based on achievement of specific levels of disease activity in patients with established or chronic RA are limited. Most studies were conducted in subjects with recent-onset RA [26-28, 42, 43]. Unlike many RCTs involving individuals with recent-onset RA, the BRASS Registry was an observational cohort study that included subjects with a mean age of 56.6 years and a mean RA duration of 15.3 years. At baseline, the mean DAS28-CRP was 3.8 (consistent with moderate RA), fewer than 11% of subjects were in CDAI or SDAI remission, approximately 87% received conventional DMARDs, and 37% received bio–DMARDs. Given these characteristics, we consider our findings to be generalizable to most established–RA populations typically encountered in clinical practices.

To our knowledge, this is the only study that formally evaluated associations between achievement of guideline-recommended targets and the likelihood of using durable equipment, such as canes, walkers, and wheelchairs. Utilization of DME was significantly (or borderline significantly) reduced in subjects with DAS28-CRP < 2.6, SDAI ≤ 3.3, or CDAI ≤ 2.8 (vs. LDA, MDA, or SDA on each of these measures). BRASS registrants who achieved (vs. did not achieve) guideline disease targets were at significantly (up to 45%) reduced odds of DME use and hospitalization. The magnitudes of these benefits were stronger with SDAI and CDAI compared to DAS28-CRP for DME use.

In a somewhat similar, but smaller (N = 356), study of patients with established RA, Radner and Austrian co-workers recently demonstrated significant benefits associated with achieving a guideline-recommended disease target (vs. LDA) in subjects with a baseline mean age of 59.9 years and a mean disease duration of 11.5 years [6]. This trial assessed changes in dependent variables, including physical functioning, HRQOL (by EQ-5D and 36-Item Short Form Health Survey [SF-36]), worker productivity, overall activity impairment, and health-care costs, as functions of the independent variable of achieving SDAI ≤ 3.3 (vs. LDA or moderate to severe disease activity [SDAI > 11]) but not the other disease targets evaluated in our study (i.e. DAS28-CRP, CDAI). Unlike our investigation, the study by Radner's group pooled data for patients with MDA and SDA because there were small numbers of patients with SDA. Patients achieving SDAI ≤ 3.3 in Radner's investigation had significantly better physical functioning, work productivity, and superior HRQOL compared to those achieving LDA. When explaining their findings, Radner's group suggested that the long RA duration may have resulted in an overall very disabled cohort. In this same European study, subjects with more severe levels of disease had higher total direct costs as well as costs for both sick leave and disability [6]. These findings were extended by the Dutch Rheumatoid Arthritis Monitoring (DREAM) study which demonstrated a larger gain in quality-adjusted life years with a treat-to-target (versus usual-care) clinical approach and an incremental cost-effectiveness ratio of €3,591 per subject in remission after 2 years with the treat-to-target strategy [7].

The observational nature of our study permitted enrollment of a large number of subjects who were followed over prolonged intervals (up to 5 years). In theory, our findings may have been influenced by selection bias, in that patients who responded to postal surveys and/or visited clinics to measure disease activity might have differed from non-respondents. DME use and hospitalization were self-reported, opening the possibility of recall bias or nonrandom missing values. Nonrandom patient attrition also could also have introduced biases. A previous study of the BRASS Registry identified disease duration, disease activity, and differences in drug therapy to be associated with attrition. However, during the years included in the current analysis, patient follow-up in the BRASS Registry was highly acceptable.[32] Of approximately 1,300 patients enrolled in the BRASS Registry, 83% had follow-up data at year 1, 78% at year 2, 73% at year 3, 77% at year 4, and 76% at year 5. Hence, we believe that the impact of patient attrition on the findings of our analysis was small.

Findings from observational studies are typically more generalizable to usual-care settings compared with RCTs. On the other hand, observational analyses are of an inherently associational nature and cannot conclusively assign causality or rule out

certain biases, even though we controlled for all relevant baseline covariates. Longitudinal studies such as ours are also potentially subject to limitations related to missing data. Outcome measures within a single individual over time are also intercorrelated. To handle these issues, mixed models such as those employed in our represent potentially advantageous approaches because all available data are included, irrespective of whether subjects had unequal numbers of observations or unequal time intervals between them.

Finally, we did not evaluate associations between achievement of different disease cut points and other patient-reported outcomes, such as pain, depression, anxiety, or fatigue, as well as objective measures such as radiographic progression.

In conclusion, this longitudinal observational study of a typical RA cohort (BRASS Registry) demonstrated benefits of treat-to-target strategies, with clinical objectives of DAS28-CRP < 2.6, SDAI ≤ 3.3, and CDAI ≤ 2.8, in enhancing physical function and HRQOL, as well as reducing DME use and hospitalization. Evidence also supported the value of treat-to-target strategies with an objective of low (vs. moderate or severe) disease activity. Our finding are compatible with the use of guideline-recommended target measures of disease activity as treatment objectives in clinical practice as well as LDA in patients who cannot attain guideline-recommended targets. Additional studies are needed to evaluate associations between achievement of different target measures of disease activity and other patient-reported (e.g. pain, fatigue) and radiographic (e.g. Total Sharp Score) outcomes, as well as actual costs rather than the odds of DME use and hospitalization, in other typical clinical settings.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1. Baseline Covariates

Categories	Variables	Levels
Sociodemographic	Gender	Male, Female
	Marital status	Never married, Married, Separated, Divorced, Widowed/widower, Cohabitating
	Age	Measured in years
	Years of RA disease	Duration of RA from year of diagnosis
	Year of RA symptoms	Duration of RA symptoms from date of symptom reporting
	Education	Less than high school, High school, Some college, Graduated from junior college Undergraduate degree, Attended advanced-degree program, Completed advanced-degree program
	Body mass index, kg/m²	<18.5 (underweight), 18.5–24.9 (normal), 25.0–29.9 (overweight), 30.0–39.9 (moderately to severely obese), ≥40 (extremely obese)
	Race/ethnicity	Caucasian, African-American, Asian, Hispanic
	Smoking status	Never, former, current (number of years smoking for ever-smokers)
	Health insurance	Insured (yes/no [Y/N]); Private, Public
	Social support	Number of close family members, Number of close friends
	Diseases of family history	Alzheimer's (Y/N), Diabetes (Y/N), Cardiovascular disease (Y/N), Systemic lupus erythematosus (SLE; Y/N), Irritable-bowel disease (Y/N), Rheumatoid arthritis (Y/N)
Patient Reported Outcomes	Functional status	MHAQ, Activities of daily living, Duruoz's Hand Index, Sollerman Function Test
	Patient ratings of global disease activity	Measured using a visual analog scale (VAS)
	Patient ratings of pain	Measured using a VAS
	Patient-reported health-related quality of life (HRQOL)	Patient-reported HRQOL measured by the EuroQol (EQ-5D), 36-Item Short Form Health Survey (SF-36), and SF-12
	Sleep	Sleep measured using the Medical Outcomes Study Sleep Scale
	Fatigue	Measured using a VAS
	Mental health/cognitive measures	Patient Health Questionnaire (PHQ) Generalized Anxiety Disorder 7-Item (GAD-7 Scale)

Supplementary Table 1. (*continued*)

Categories	Variables	Levels
Clinical Measures	Lung function	Dyspnea ratings
	Biochemical indices/ inflammatory biomarkers	C-reactive protein (CRP), Erythrocyte sedimentation rate (ESR), Rheumatoid factor (RF)
	Vaccinations before onset of rheumatoid arthritis (RA)	Varicella, Hepatitis A, Hepatitis B, Pneumonia, Rubella, Tetanus, Influenza
	Dental evaluation	Gum disease (Y/N), Bone loss (Y/N), Periodontal treatment (Y/N)
	Physician-diagnosed comorbid conditions	Cardiovascular: Angina (Y/N), Myocardial infarction (Y/N)
		Neurologic: Dementia (Y/N), Demyelinating illness (Y/N), Psychiatric illness (Y/N)
		Pulmonary: Infectious pneumonitis (Y/N), Drug-induced pneumonitis (Y/N), Asthma (Y/N), Chronic obstructive pulmonary disease (Y/N)
		Renal: Nephrotic syndrome (Y/N), Elevated creatinine/renal insufficiency (Y/N)
		Musculoskeletal: Fibromyalgia (Y/N), SLE (Y/N), Degenerative joint disease (Y/N), Osteoporosis/bone fractures (Y/N)
		Endocrine: Grave's disease (Y/N), Hashimoto's thyroid (Y/N)
		Hematologic/oncologic: Lymphoma (Y/N), Other cancers (Y/N), Aplastic anemia (Y/N), Thrombocytopenia (Y/N)
		Gastrointestinal (GI): Peptic ulcer (Y/N), Viral hepatitis (Y/N), Drug-induced hepatitis (Y/N), Other liver disease (Y/N), Crohn's disease (Y/N), Ulcerative colitis (Y/N), Inflammatory bowel disease (Y/N), Pancreatitis (Y/N), GI perforations or obstructions (Y/N)
	Surgery-related variables	Total number of surgeries; types of surgery
Treatments	RA–specific therapies	Biologic disease-modifying antirheumatic drugs (bio-DMARDs; Y/N) Non–bio-DMARDs (Y/N), Methotrexate (Y/N)
	Concomitant medications	Pain treatments: Steroids (Y/N), Nonsteroidal anti-inflammatory drugs (NSAIDs; Y/N)

Supplementary Table 2. Associations Between Different Baseline/Patient Factors and Changes in Physical Functioning (MHAQ)*

	Attainment of different target measures of disease activity (Target Definitions:)					
	DAS28-CRP < 2.6		SDAI ≤ 3.3		CDAI ≤ 2.8	
Variable	MHAQ estimate	*P*	MHAQ estimate	*P*	MHAQ estimate	*P*
Female gender	0.021	0.3805	0.014	0.5348	0.013	0.5909
RA duration	0.004	<0.0001	0.005	<0.0001	0.005	<0.0001
Baseline MHAQ	0.547	<0.0001	0.563	<0.0001	0.563	<0.0001
Current smoker (vs. former)	0.087	0.0140	0.084	0.0136	0.089	0.0096
Never (vs. former) smoker	–0.014	0.4685	–0.008	0.6698	–0.011	0.5653
Physician diagnosis of osteoporosis	0.068	0.0280	0.066	0.0232	0.066	0.0237
Baseline MTX (vs. no MTX)	–0.032	0.0239	–0.034	0.0109	–0.033	0.0161

*Data are per 1-unit increases in variables within regression equations, after controlling for baseline covariates. CDAI, Clinical Disease Activity Index; DAS28-CRP, Disease Activity Score 28-C-reactive protein; MHAQ, Modified Health Assessment Questionnaire; MTX, methotrexate; RA, rheumatoid arthritis; SDAI, Simplified Disease Activity Index.

Supplementary Table 3. Numbers of Patients With Rheumatoid Arthritis (RA) Who Were (or Were Not) at Targets at Each Time Point (Supplement to Figure 1)

DAS28-CRP					
RA status	Year 1	Year 2	Year 3	Year 4	Year 5
At Target	311	255	185	221	205
Not at Target	480	402	310	256	277
SDAI					
RA status	Year 1	Year 2	Year 3	Year 4	Year 5
At Target	98	98	58	70	63
Not at Target	729	616	477	461	440
CDAI					
RA status	Year 1	Year 2	Year 3	Year 4	Year 5
At Target	88	88	46	60	57
Not at Target	739	626	489	471	446

CDAI, Clinical Disease Activity Index; CRP, C-reactive protein;
DAS28-CRP, Disease Activity Score 28-CRP; SDAI, Simplified Disease Activity Index.

Supplementary Table 4. Associations Between Different Baseline/Patient Factors and Changes in Health-Related Quality of Life (EQ-5D)*

	Target measures of disease activity:					
	DAS28-CRP < 2.6		SDAI ≤ 3.3		CDAI ≤ 2.8	
Variable	EQ-5D Estimate	*P*	EQ-5D Estimate	*P*	EQ-5D Estimate	*P*
Female gender	–0.004	0.6503	–0.015	0.2034	–0.013	0.2724
RA duration	–0.001	0.0473	–0.001	<0.0001	–0.001	0.0002
Baseline MHAQ	–0.137	<0.0001	–0.153	<0.0001	–0.150	<0.0001
Baseline MTX (vs. no MTX)	0.018	0.0021	0.012	0.0855	0.012	0.0740

*Data are per 1-unit increases in variables within regression equations, after controlling for baseline covariates. CDAI, Clinical Disease Activity Index; DAS28-CRP, Disease Activity Score 28-C-reactive protein; EQ-5D, EuroQol-5D; MHAQ, Modified Health Assessment Questionnaire; MTX, methotrexate; RA, rheumatoid arthritis; SDAI, Simplified Disease Activity Index.

CHAPTER 3

Association of Low Bone Mineral Density with Anti-Citrullinated Protein Antibody Positivity and Disease Activity in Established Rheumatoid Arthritis: Findings from a US Observational Cohort

Harris A. Ahmad[1], Evo Alemao[1]*, Zhenchao Guo[2], Christine K. Iannaccone[2], Michelle L. Frits[2], Michael Weinblatt[2] and Nancy A. Shadick[2]

[1]Bristol-Myers Squibb, 3401 Princeton Pike, Lawrenceville, New Jersey, USA;
[2]Bristol-Myers Squibb, Wallingford, Connecticut, USA;
[3]Department of Rheumatology, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA, USA.
* PhD student at Erasmus University Rotterdam, supervised by M.P.M.H.R.M. and M.J.A.

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ABSTRACT

Introduction: To assess the relationship between low bone mineral density (BMD), anticyclic citrullinated peptide-2 (anti-CCP2) antibodies, and disease activity in patients with established rheumatoid arthritis (RA). **Methods:** Patients enrolled in a single-center, observational cohort registry of patients with RA. Eligible patients had known BMD, as measured by digital X-ray radiogrammetry (DXR–BMD), and anti-CCP2 antibody measurements at the same time point or within 6 months. Anti-CCP2–immunoglobulin (Ig)G positive (+) patients (≥ 20 U/mL) were distributed into three equal groups (Gp1–3), representing increasing anti-CCP2 antibody concentrations. Associations between BMD and anti-CCP2 antibody status and titer were explored in multivariate regression analyses controlling for covariates (including age, duration of RA, use of steroids, use of osteoporosis medication). Association between disease activity (DAS28 [CRP]<2.6) and bone loss was also explored. **Results:** A total of 149 patients (all women) were included (47 anti-CCP2 antibody negative [-], 102 anti-CCP2+ [34\titer group]). Mean disease duration was greater in the three anti-CCP2+ groups vs. the anti-CCP2- group. DXR BMD was lower in the anti-CCP2+ vs. the anti-CCP2- groups (Gp1–3 vs. anti-CCP2-: $P < 0.0001$ for left and right hands). DXR–BMD decreased with increasing anti-CCP2 titer ($P < 0.001$ for left and right hands). Patients with low DXR–BMD were less likely to have a DAS28 (CRP) < 2.6 ($P = 0.0181$). **Conclusion:** Among patients with established RA, data suggest that anti-CCP2+ patients, particularly those with high anti-CCP2 antibody titers, have lower hand BMD, and patients with lower hand BMD are less likely to have low disease activity.

INTRODUCTION

Rheumatoid arthritis (RA) is associated with bone loss, erosions, and osteoporosis [1–3]. Several studies suggest that both erosive RA and osteoporosis share a common cellular pathway, which involves inflammatory activation of osteoclasts and decreased osteoblast activation [4, 5]. Low bone mineral density (BMD) in patients with RA increases the risk of fractures and overall mortality, especially in postmenopausal women [6–8]. Hand BMD loss, as measured by digital X-ray radiogrammetry (DXR)—a sensitive quantitative method for detecting early bone loss by measuring the cortical bone of metacarpal diaphysis—is an independent predictor of radiographic joint damage progression, including erosions [9–11].

A comparison of DXR and dual-energy X-ray bsorptiometry (DXA) revealed that DXR appears to be more sensitive than DXA in detecting early bone loss in patients with RA [9]. Several studies have demonstrated a treatment effect of conventional and biologic diseasemodifying antirheumatic drugs (bDMARDs) on BMD loss using DXR [4, 12–17]; however, data are limited on identifying factors that are associated with BMD loss. Given the correlation of DXR–BMD with increased fracture risk and mortality [7, 8], it would be beneficial to identify a reliable prognostic factor that is associated with hand BMD loss and treatment outcomes in patients with RA. The identification of such prognostic factors could assist rheumatologists in identifying patients at risk of radiographic progression and inform treatment decisions, with the aim of preventing bone erosion.

Anti-citrullinated protein antibody (ACPA) positivity is associated with poor prognosis in RA, and testing for ACPA has become standard practice in the diagnosis of RA [18, 19]. Recent studies have suggested that ACPA can stimulate bone loss by inducing the differentiation of precursors into bone-resorbing osteoclasts [20, 21]. In patients who are positive for anticyclic citrullinated peptide-2 (anti-CCP2, a surrogate of ACPA) antibodies, structural bone damage can start before the clinical onset of RA [22]. Elevated anti-CCP2 antibody levels have been found to be independent predictors of localized hand DXR–BMD loss in patients with early RA [23]. Furthermore, analysis of data from the Pavia Early Arthritis Clinic, a singlecenter cohort of patients, showed that anti-CCP2 antibodies and rheumatoid factor were associated with systemic bone loss in patients with early, untreated RA [24]. However, the relationship between hand BMD loss and anti-CCP2 antibodies in patients with established RA is unclear. Data from a recent single-center population study using DXA–BMD showed a negative, titer-dependent effect of ACPA on systemic bone mass at femoral sites in patients with established RA [5]. This analysis was performed to assess the association between hand DXR–BMD

and anti-CCP2 antibody status, DXR–BMD and anti-CCP2 titer, as well as DXR–BMD and RA disease activity among patients with established RA.

METHODS

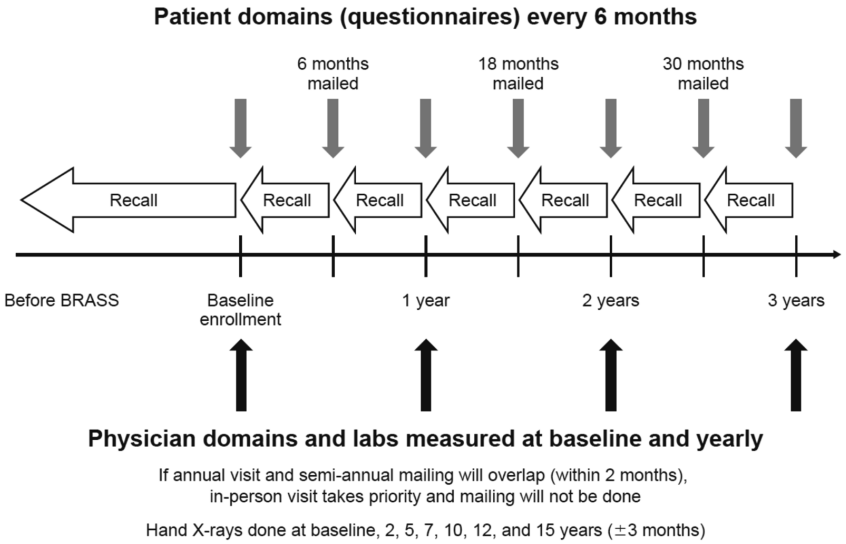
Study Population

The Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study (BRASS; ClinicalTrials.gov identifier NCT01793103) registry was initiated in 2003. Details regarding the design of the registry have been reported previously [25–27]. BRASS is a single-center, prospective, observational, longitudinal cohort of more than 1400 adults with established or recent-onset RA who are being followed in a hospital-based practice of 21 rheumatologists in Boston, Massachusetts. The BRASS Registry has been conducted in accordance with International Society for Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practices, applicable regulatory requirements, and ethical tenets originating in the Declaration of Helsinki. The study protocol and informed consent document were reviewed and approved by the Brigham and Women's Hospital Institutional Review Board (approval number 2002P001763). All patients provided written informed consent before participating in the BRASS Registry. The present study population represents a subset of the BRASS cohort, and eligible patients had DXR–BMD and anti-CCP2 antibody measurements at the same time point or within 6 months.

Measures and Data Collection

Patient demographic data and clinical characteristics, disease activity, and laboratory parameters were assessed at baseline and annually thereafter. Digitized hand radiographs were collected at baseline and at 2, 5, 7, 10, and 12 years and will be collected to at least 15 years (Fig. 1). Hand BMD was measured at the metacarpal bones of the second, third, and fourth digits using DXR–BMD (DXR-online, Sectra Imtec AB, Linkoping, Sweden) as described previously [28]. Anti-CCP2 antibody level was measured using a validated ELISA (Inova Diagnostics, San Diego, California, USA until its discontinuation in 2011; thereafter Euro-Diagnostica [distributed by IBL-America, Minneapolis, Minnesota, USA]). Patient-reported outcomes were assessed with a follow-up questionnaire every 6 months (Fig. 1)

Fig. 1 BRASS* study design.



* *BRASS* Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study

Study Outcomes

Patient demographic data and clinical characteristics were reported by anti-CCP2 antibody status (anti-CCP2 positive [+] and anti-CCP2 negative [-]), and anti-CCP2 antibody titer group (Group [Gp] 1–3). Anti-CCP2 antibody status was defined either as anti-CCP2+ (≥ 20 U/mL) or anti-CCP2- (< 20 U/mL). Anti-CCP2+ patients were divided equally into three subgroups based on the tertiles of anti-CCP2 antibody titers as Gp1, 20–96.6 U/mL; Gp2, 96.7–309.6 U/mL, and Gp3, 309.7–580 U/mL. Mean DXR–BMD was reported by anti-CCP2 antibody status and titer groups. The association between Disease Activity Score in 28 joints (DAS28) (C-reactive protein [CRP]) <2.6 and bone loss was analyzed in patients with DXR–BMD <0.5 g/cm2 (left or right hand) vs. ≥ 0.5 g/cm2 (both hands).

Statistical Analysis

A cross-sectional analysis was performed on available data for DXR–BMD and anti-CCP2 antibody level measured within 6 months of the DXR–BMD measurement. For descriptive statistics, Wilcoxon rank-sum test (or Kruskal–Wallis test) was used for continuous variables and Pearson's Chi-square test for categorical variables. Associa-

tions between DXR–BMD (left, right, and combined [average of left and right hands]) and anti-CCP2 antibody status and titer (Gp1–3) were explored in multivariate analyses using linear regression controlling for covariates of age, duration of RA, body mass index (BMI), DAS28 (CRP), smoking status, use of steroids, bDMARDs, and osteoporosis medication. With DXR–BMD as the dependent variable, we explored anti-CCP2 antibody level as a continuous variable (linear trend) in relation to DXR–BMD, and explored anti-CCP2 antibody status as a categorical variable and included different anti-CCP2 antibody groups as reference groups. Associations between DXR–BMD and DAS28 (CRP) < 2.6 in patients with DXR–BMD ≥ 0.5 and < 0.5 g/cm2 were explored using a logistic model controlling for covariates of age, duration of RA, BMI, smoking status, use of steroids, bDMARDs, and osteoporosis medication.

RESULTS

Patient Disposition and Patient Characteristics by Anti-CCP2 Antibody Status and Titer Group

A total of 149 patients (all postmenopausal women) had an anti-CCP2 antibody measurement within 6 months of a DXR–BMD measurement: 47 (31.5%) were anti-CCP2-; 102 (68.5%) were anti-CCP2+. Sample sizes for the left and right hands were similar. Of the 102 patients with anti-CCP2+ status, 34 were included in each titer group (Gp1, Gp2, and Gp3). Patient characteristics by anti-CCP2 antibody status and titer group are shown in Table 1. Age, BMI, DAS28 (CRP), smoking status, use of steroids, bDMARDs, and osteoporosis medication did not differ significantly by anti-CCP2 antibody status (±) or between groups (Table 1). Mean duration of RA was different between the groups ($P < 0.05$); a longer duration of RA was also reported in anti-CCP2+ Patients vs. anti-CCP2- patients (Table 1; $P < 0.05$). However, there was no clear pattern of disease duration between anti-CCP2 titer groups.

DXR–BMD by Anti-CCP2 Antibody Titer Group

In the univariate analysis, DXR–BMD was lower in the anti-CCP2 group vs. the anti-CCP2- titer groups (Gp1–3 vs. anti-CCP2-: $P<0.0001$ for left and right hands). DXR–BMD decreased with increasing anti-CCP2 antibody titer for the left hand (mean [SD]; anti-CCP2- group, 0.56 [0.08]; Gp1, 0.51 [0.09]; Gp2, 0.51 [0.08]; Gp3, 0.48 [0.1]), and right hand (0.58 [0.08]; 0.52 [0.09]; 0.52 [0.08]; 0.49 [0.1], respectively) (Fig. 2).

Table 1. Patient characteristics by anti-CCP2 antibody status and titer group

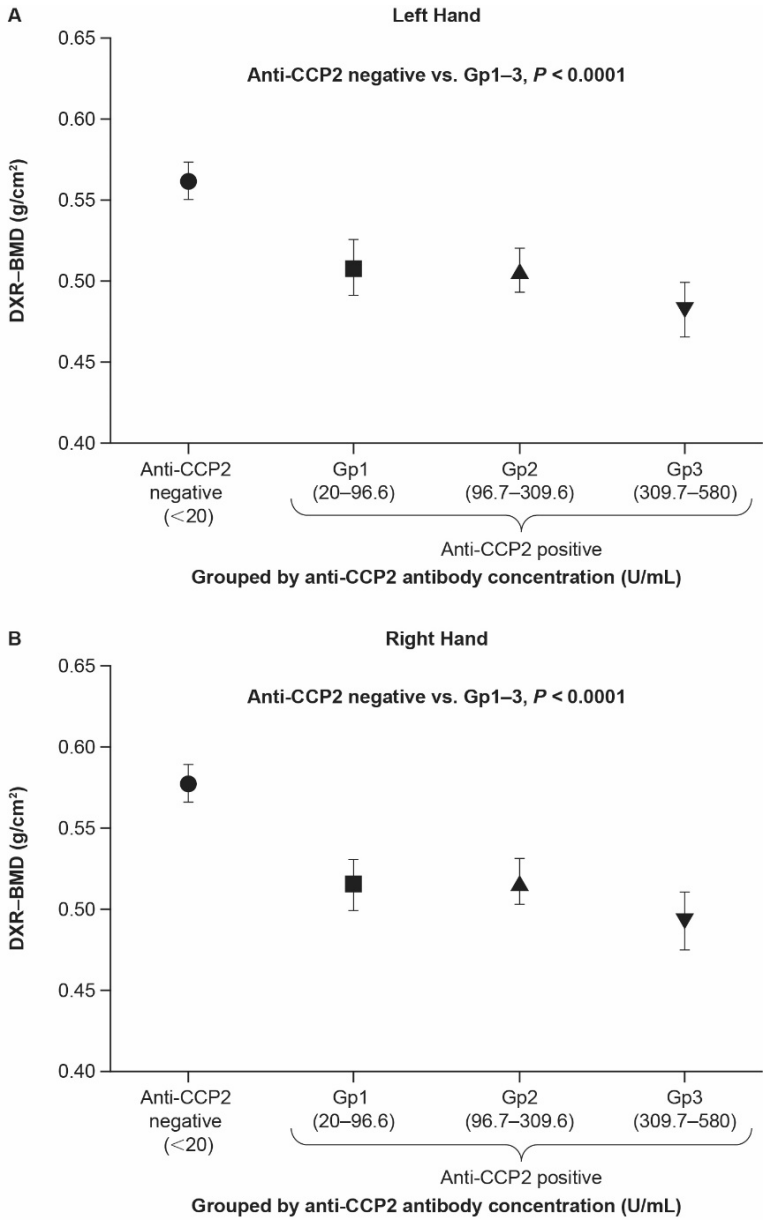
	Anti-CCP2– *n* = 47	Anti-CCP2+ *n* = 102	Anti-CCP2+ Gp1 *n* = 34	Anti-CCP2+ Gp2 *n* = 34	Anti-CCP2+, Gp3 *n* = 34	Overall population *N* = 149
Anti-CCP2 antibody range, U/mL	3.0–15.4	20.0–580	20.0–96.6	96.7–309.6	309.7–580	3–580
Anti-CCP2 antibody level, U/mL, mean (SD)	5.1 (2.9)**	226.4 (157.0)**	55.2 (21.4)**	208.1 (61.4)**	415.7 (61.2)**	156.6 (165.7)
Age, years, mean (SD)	60.3 (8.4)	61.9 (9.6)	60.4 (9.0)	62.0 (9.5)	63.4 (10.3)	61.4 (9.3)
RA duration, years, mean (SD)	12.2 (12.0)*	16.7 (10.8)*	18.0 (11.3)*	15.1 (8.7)*	17.0 (12.1)*	15.3 (11.3)
BMI, kg/m², mean (SD)	27.3 (5.8)	26.9 (5.9)	26.0 (4.8)	25.6 (4.9)	29.2 (7.1)	27.0 (5.9)
DAS28 (CRP), mean (SD)	3.5 (1.4)	4.0 (1.5)	3.9 (1.5)	4.0 (1.6)	4.1 (1.5)	3.8 (1.5)
Steroid use, n (%)						
Never	10 (21.3)	18 (17.6)	6 (17.6)	6 (17.6)	6 (17.6)	28 (18.8)
1–6 months	12 (25.5)	29 (28.4)	8 (23.5)	13 (38.2)	8 (23.5)	41 (27.5)
>6 months	25 (53.2)	55 (53.9)	20 (58.8)	15 (44.1)	20 (58.8)	80 (53.7)
Ever/current smoker, n (%)	23 (48.9)	55 (53.9)	16 (47.1)	19 (55.9)	20 (58.8)	78 (52.3)
Biologic DMARD, n (%)	20 (42.6)	51 (50.0)	17 (50.0)	19 (55.9)	15 (44.1)	71 (47.7)
Osteoporosis medication, n (%)	6 (12.8)	15 (14.7)	6 (17.6)	7 (20.6)	2 (5.9)	21 (14.1)

*$P < 0.05$; **$P < 0.001$ comparing anti-CCP2– versus anti-CCP2+ or between the three anti-CCP2+ groups. Anti-CCP2 antibody status was defined as either anti-CCP2+ (≥20 U/mL) or anti-CCP2– (<20 U/mL)
Anti-CCP2 anti-cyclic citrullinated peptide-2 antibody, *anti-CCP2–* anti-CCP2 antibody negative, *anti-CCP2+* anti-CCP2 antibody positive, *BMI* body mass index, *CRP* C-reactive protein, *DAS28* Disease Activity Score in 28 joints, *DMARD* disease-modifying antirheumatic drug, *Gp* group, *RA* rheumatoid arthritis

Associations Between DXR–BMD and Anti-CCP2 Antibody Status: Multivariate Analysis

When anti-CCP2 antibody level was used as a continuous variable, combined hand DXR–BMD was negatively associated with anti-CCP2. For every 10-unit increase in anti-CCP2 antibody level, DXR–BMD decreased by 0.0014 units ($P < 0.001$; see Supplementary Table 1). The overall model fit based on adjusted R^2 for the total hand DXR–BMD model was 0.406. When anti-CCP2 antibody status was used as a categorical variable, combined hand DXR–BMD was associated with anti-CCP2+ Gp1–3 vs.

Fig. 2 Association between DXR–BMD and anti-CCP2 antibody status and titer in **A** left hand and **B** right hand.



Number of patients in each titer group: anti-CCP2–, *n* = 47; Gp1, *n* = 34; GP2, *n* = 34; Gp3, *n* = 34. Timeframe between DXR–BMD and anti-CCP2 measurements (months [SD]) were 0.6 (1.4) for anti-CCP2–, 1.8 (2.3) for Gp1, 1.1 (1.8) for GP2, and 1.0 (1.7) for Gp3 ($P > 0.05$ for comparison between the anti-CCP2+ groups and the anti-CCP2– group)

Anti-CCP2 anti-cyclic citrullinated peptide-2 antibodies, *anti-CCP2–* anti-CCP2 antibody negative, *anti-CCP2+* anti-CCP2 antibody positive, *DXR–BMD* digital X-ray radiogrammetry–bone mineral density, *Gp* group

anti-CCP2- ($P < 0.001$; Table 2). Combined hand DXR–BMD was negatively associated with each individual anti-CCP2 antibody titer group (Gp1, Gp2, or Gp3) vs. anti-CCP2- ($P < 0.05$). Adjusted R^2 for the total hand DXR–BMD model was 0.426. This negative association between DXR–BMD and each individual anti-CCP2 antibody titer group vs. anti-CCP2- remained significant in the multivariate analysis (Table 2).

Results for individual hands were similar to those for the combined analysis (Table 2 and Supplementary Table 1). When anti-CCP2 antibody level was used as a continuous variable, for every 10-unit increase in anti-CCP2, DXR–BMD for the left or right hand decreased by 0.0014 units ($P < 0.001$; see Supplementary Table 1). Similarly, when anti-CCP2 antibody status was used as a categorical variable, left or right hand DXR–BMD was associated with anti-CCP2+ Gp1–Gp3 vs. anti-CCP2- ($P < 0.001$; Table 2). DXR–BMD was negatively associated with age, duration of RA, and use of osteoporosis medication. In the model with anti-CCP2 antibody status as a categorical variable, steroid use >6 months was also a significant factor for DXR–BMD (left or average; Table 2).

Table 2. Exploration of anti-CCP2 antibody status and titer as a categorical variable in relation to DXR–BMD

Variable	Left-hand DXR–BMD			Right-hand DXR–BMD			Average of left and right hands		
	Coefficient	*P* value	Adjusted *P* value[c]	Coefficient	*P* value	Adjusted *P* value[c]	Coefficient	*P* value	Adjusted *P* value[c]
Anti-CCP2– (vs. anti-CCP2+ Gp1–3)[a]	0.0523	< 0.001	0.0007	0.0586	< 0.001	0.0001	0.0568	< 0.001	0.0001
Anti-CCP2+ Gp1 (vs. anti-CCP2–)[a]	–0.0475	0.007	0.029	–0.0555	0.002	0.0089	–0.0542	0.002	0.0097
Anti-CCP2+ Gp2 (vs. anti-CCP2–)[a]	–0.0394	0.020	0.0608	–0.0477	0.006	0.0183	–0.0464	0.005	0.0166
Anti-CCP2+ Gp3 (vs. anti-CCP2–)[a]	–0.0683	< 0.001	0.0005	–0.0715	< 0.001	0.0003	–0.0686	< 0.001	0.0002
Anti-CCP2+ Gp1 (vs. Gp3)[a]	0.0208	0.268	0.268	0.0161	0.395	0.395	0.0144	0.442	0.442
Anti-CCP2+ Gp2 (vs. Gp3)[a]	0.0289	0.113	0.226	0.0238	0.201	0.395	0.0221	0.215	0.43
Anti-CCP2+ Gp3 (vs. anti-CCP2–, Gp1, and Gp2)[a]	–0.0442	0.004	0.0188	–0.0433	0.006	0.0183	–0.0422	0.006	0.0166
Age, years	–0.0037	< 0.001	–	–0.0036	< 0.001	–	–0.0036	< 0.001	–
RA duration, years	–0.0013	0.030	–	–0.0013	0.026	–	–0.001	0.081	–
BMI, kg/m²	0.0018	0.112	–	0.0021	0.063	–	0.0016	0.148	–

Table 2. (*continued*)

Variable	Left-hand DXR–BMD			Right-hand DXR–BMD			Average of left and right hands		
	Coefficient	*P* value	Adjusted *P* value[c]	Coefficient	*P* value	Adjusted *P* value[c]	Coefficient	*P* value	Adjusted *P* value[c]
DAS28 (CRP)	–0.0023	0.603	–	–0.0014	0.760	–	–0.0015	0.736	–
Steroid use 1–6 months (vs. never)	–0.0248	0.174	–	–0.0014	0.940	–	–0.0076	0.664	–
Steroid use >6 months (vs. never)	–0.0358	0.040	–	–0.0324	0.061	–	–0.0346	0.038	–
Smoker (ever/current vs. never)	–0.0059	0.637	–	–0.0125	0.324	–	–0.0103	0.400	–
Biologic DMARD (yes vs. no)	–0.013	0.332	–	0.0118	0.378	–	0.0042	0.746	–
Osteoporosis medication (yes vs. no)	–0.0481	0.008	–	–0.0477	0.009	–	–0.0469	0.008	–
R^2, adjusted[b]	0.399	–	–	0.421	–	–	0.426	–	–

[a]Four separate models with different reference groups or comparisons as specified in the table for each of the three outcomes. [b]The model included all covariates in the table (age, duration of RA, BMI, smoking status, use of steroids, bDMARDs, and osteoporosis medication) and three dummy variables for the three anti-CCP2+ groups (vs anti-CCP2–). [c]*P* values were adjusted for multiple comparison based on Hochberg's method that controls the familywise error rate under independence[29]

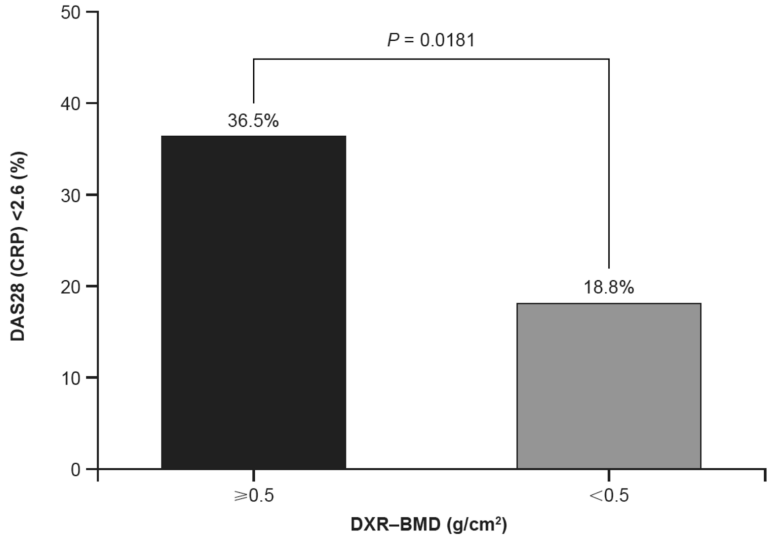
Anti-CCP2 antibody status was defined as either anti-CCP2+ (≥20 U/mL) or anti-CCP2– (<20 U/mL). Anti-CCP2+ titer groups were defined as Gp1, 20.0–96.6 U/mL; Gp2, 96.7–309.6 U/mL; or Gp3, 309.7–580 U/mL

Anti-CCP2 anti-cyclic citrullinated peptide-2 antibody, *anti-CCP2–* anti-CCP antibody negative, *anti-CCP2+* anti-CCP2 antibody positive, *BMI* body mass index, *BMD* bone mineral density, *CRP* C-reactive protein, *DAS28* Disease Activity Score in 28 joints, *DMARD* disease-modifying antirheumatic drug, *DXR* digital X-ray radiogrammetry, *Gp* group, *RA* rheumatoid arthritis

Association Between Disease Activity and Bone Loss

Evaluation of the association between DXR–BMD and disease activity indicates that patients with low DXR–BMD were less likely to have a DAS28 (CRP) < 2.6 (DXR–BMD ≥ 0.5, 36.5% vs. DXR–BMD < 0.5, 18.8%; P = 0.0181) (Fig. 3). After controlling for confounding factors, the odds of having a DAS28 (CRP) < 2.6 were significantly lower for patients with DXR–BMD<0.5 (n = 64) vs. ≥ 0.5 (n = 85; odds ratio 0.355 [95% CI 0.126–0.998]; P = 0.0496).

Fig. 3 Association between DXR–BMD and DAS28 (CRP) <2.6.



CRP C-reactive protein, *DAS28* Disease Activity in 28 joints, *DXR–BMD* digital X-ray radiogrammetry–bone mineral density

DISCUSSION

Our results show that, among patients with long-standing RA, hand DXR–BMD is negatively associated with the presence of anti-CCP2 antibodies. Patients with anti-CCP2+ status, particularly those with high anti-CCP2 antibody titers, had lower hand BMD; therefore, as anti-CCP2 antibody titers increased, hand BMD decreased. This is consistent with previous studies in patients with early RA, demonstrating a correlation between elevated anti-CCP2 antibody baseline levels and DXR–BMD loss [23, 24].

In the present analysis, patients with low DXR–BMD were less likely to have low disease activity. Similar observations have also been reported in patients with early RA [30], suggesting an association between disease activity and bone loss. Hand BMD loss has also been shown to indicate an increased risk of erosive disease [10, 11, 31, 32]. Data from an observational study demonstrated that BMD loss at 6 months was associated with higher erosion scores, and a higher proportion of patients with BMD loss at 6 months had at least one erosion and a higher risk of erosion progression at 12 months [31]. Furthermore, although there is evidence that hand joint damage in RA is related to use and hand dominance [33], our data show that bone loss occurs in both hands, which is consistent with RA being defined as a symmetrical disease. Such

patients with low hand BMD may be at an increased risk of vertebral and non-vertebral fractures [6, 7].

Pro-inflammatory cytokines are generally the key drivers of articular and extra-articular bone damage [34–36]. However, recent evidence has shown that RA-associated autoantibodies, such as ACPA, can directly induce bone loss by stimulating osteoclast differentiation [20, 21]. In vivo, human ACPA causes bone loss in immune-deficient mice [20]. ACPA has been shown to be associated with bone loss as demonstrated through DXR–BMD in this study as well as DXA–BMD in a separate study [24]. Patients with ACPA develop cortical thinning, leading to a decrease in bone mass and increasing the risk of bone erosions [3, 22]. Given the evidence suggesting that ACPA is a key driver of bone loss [23, 24], treatment options for RA that reduce ACPA titers and induce seroconversion may be effective in lowering the risk of bone loss. This should be explored in future clinical trials.

The strength of this analysis is that these data are from an observational cohort of patients with RA, including clinical measures such as serological status and DXR–BMD. Limitations of this analysis include those inherent in observational cross-sectional studies, including the absence of a comparator (e.g., DXR–BMD in healthy, postmenopausal women) and hand radiographs and ACPA testing may not have been done on the same day. Even though our statistical models controlled for several covariates and observed significant relationships between DXR–BMD and ACPA or disease activity, this does not imply causation or rule out certain biases without further controlled analyses. Confounding by unmeasured variables should also be considered when evaluating these results. The selection of < 0.5 as compared with ≥ 0.5 g/cm2 in relation to DAS28 (CRP) < 2.6 should also be considered as a potential limitation. However, the cutoff was selected in reference to the DXR–BMD median of Gp3 and needs further validation in future studies. In addition, antibodies to individual citrullinated proteins (e.g. fibrin, filaggrin, vimentin) or other serological markers (e.g., rheumatoid factor) were not evaluated. The patient population primarily reflects postmenopausal women; therefore, future studies should be conducted in pre- and postmenopausal women as these results may have implications for osteoporosis prevention.

CONCLUSIONS

Our results show that, in routine clinical practice, anti-CCP2 antibody positivity in patients with established RA is associated with lower hand BMD, and patients with hand bone loss were less likely to have low disease activity. This suggests that DXR–BMD

and anti-CCP2 antibody status could help identify patients at risk for joint progression and fracture; however, a direct causal relationship cannot necessarily be implied from this cross-sectional analysis. Disease-modifying treatment for RA that not only targets inflammation but improves cortical bone density should be considered in order to achieve better prevention of bone erosions in patients with RA.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1 Exploration of anti-CCP2 as a continuous variable (linear trend) in relation to DXR–BMD

	Left-hand DXR–BMD		Right-hand DXR–BMD		Average of left and right hands	
Variable	**Coefficient**	***P* value**	**Coefficient**	***P* value**	**Coefficient**	***P* value**
Anti-CCP2 per 10-unit increase	–0.0014	< 0.001	–0.0014	< 0.001	–0.0014	< 0.001
Age, years	–0.0036	< 0.001	–0.0035	< 0.001	–0.0035	< 0.001
RA duration, years	–0.0015	0.010	–0.0016	0.008	–0.0012	0.034
BMI, kg/m2	0.0019	0.089	0.0023	0.043	0.0018	0.100
DAS28 (CRP)	–0.0036	0.415	–0.0027	0.545	–0.0025	0.570
Steroid use 1–6 months (vs. never)	–0.022	0.231	0.0004	0.984	–0.0055	0.757
Steroid use >6 months (vs. never)	–0.0335	0.055	–0.0297	0.090	–0.0311	0.065
Smoker (ever/current vs. never)	–0.0085	0.497	–0.0149	0.247	–0.0133	0.283
Biologic DMARD (yes vs. no)	–0.0128	0.339	0.0105	0.436	0.0042	0.750
Osteoporosis medication (yes vs. no)	–0.0481	0.008	–0.0493	0.008	–0.499	0.005
R2, adjusted	0.388		0.399		0.406	

Anti-CCP2 anti-cyclic citrullinated peptide-2, *BMI* body mass index, *CRP* C-reactive protein, *DAS28* Disease Activity Score in 28 joints, *DMARD* disease-modifying antirheumatic drug, *DXR–BMD* digital X-ray radiogrammetry–bone mineral density, *RA* rheumatoid arthritis

CHAPTER 4

Association of Changes in Anti-Citrullinated Protein Antibody Levels with Resource Use and Disease Activity Measures in a US Observational Cohort

Evo Alemao[1]*, Zhenchao Guo[2], Christine K. Iannaccone[3], Michelle L. Frits[3], Michael E. Weinblatt[3] and Nancy A. Shadick[3]

[1]Bristol-Myers Squibb, 3401 Princeton Pike, Lawrenceville, New Jersey, USA;
[2]Bristol-Myers Squibb, Wallingford, Connecticut, USA;
[3]Department of Rheumatology, Brigham and Women's Hospital, 75 Francis Street, Boston, Massachusetts 02115, USA.
* PhD student at Erasmus University Rotterdam

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ABSTRACT

Here, we evaluate associations between changes in anti-citrullinated protein antibody (ACPA) levels and outcomes, including durable medical equipment (DME) use, hospitalizations, and disease activity, in patients with established rheumatoid arthritis. Patients from the Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study who had ACPA measurements at baseline and month 12 were included. Changes in ACPA levels from baseline to month 12 were categorized as decrease (>10%), no change (–10% to +10%), or increase (> +10%). DME use and hospitalizations were assessed twice-yearly using patient questionnaires; disease activity was assessed annually. Binary multivariate logistic regression was used to analyze the relationship between changes in ACPA levels and DME use and hospitalizations; linear regression was used to assess the relationship with disease activity. Of 840 patients included in the analysis, 291 (34.6%), 266 (31.7%), and 283 (33.7%) had a decrease, no change, or increase in ACPA levels, respectively. Decrease in ACPA levels was associated with reduction in DME use (adjusted odds ratio [aOR]: 0.64; 95% confidence interval [CI]: 0.44–0.93; $P = 0.019$) and hospitalizations (aOR: 0.62; 95% CI: 0.41–0.95; $P = 0.029$) versus no change or increase. Adjusted mean changes in disease activity score in 28 joints (C-reactive protein), total and swollen joint counts, and pain scores were significantly greater in patients with decreased ACPA levels versus those with no change or increase ($P < 0.05$). Among patients with established rheumatoid arthritis, reductions in ACPA levels of >10% were associated with reductions in DME use, hospitalizations, and disease activity.

INTRODUCTION

Anti-citrullinated protein antibodies (ACPAs) are sensitive and highly specific biomarkers for the diagnosis of rheumatoid arthritis (RA) that are present years before the onset of clinical RA [1, 2]. ACPA assessment has become standard practice in the diagnosis of RA, partly due to superior assay specificity and similar sensitivity as detection techniques for rheumatoid factor (RF) [3]. ACPA positivity has been associated with more severe, erosive disease than is seen in ACPA-negative patients [4, 5]. A high ACPA concentration, beyond ACPA positivity, is indicative of more rapid radiographic progression, worse disease severity, and greater bone loss in RA patients [4, 6].

ACPA levels fluctuate over time, with an increase observed prior to the onset of clinical symptoms [7], and patients are known to seroconvert or enter immunologic remission following treatment [8]. However, the impact of these changes has been little studied. There is limited information on changes in ACPA levels in clinical practice settings, and whether an association exists between changes in ACPA levels and measures of resource use or disease activity. The objective of this analysis was to evaluate the association between changes in ACPA levels and resource use (including durable medical equipment [DME] use and hospitalizations), and disease activity in patients with established RA.

MATERIALS AND METHODS

Study design

Details regarding the design of the Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study (BRASS) registry have been reported previously [9-11]. Briefly, the BRASS registry is a single-center, prospective, observational, longitudinal cohort of >1300 adults with established or recent-onset RA who are being followed up by a hospital-based practice of 21 rheumatologists in Boston, Massachusetts, USA. Patient demographics and clinical characteristics, disease activity, and laboratory parameters were assessed at baseline and annually thereafter. Patients followed the treatment plan provided by their rheumatologist when they enrolled in the study and throughout follow-up. Patients were eligible for the current analysis if they had documented ACPA values at baseline and the month 12 follow-up visit.

This study was performed in accordance with the Declaration of Helsinki and was approved by the Partners Institutional Review Board at Brigham and Women's Hospital. All patients gave signed informed consent.

Measures and data collection

ACPA levels were measured using a validated enzyme-linked immunosorbent assay (Inova Diagnostics, San Diego, California, USA, until discontinuation in 2011; after Euro-Diagnostica, distributed by IBL-America, Minneapolis, Minnesota, USA). RF was measured by an immunoturbidimetric method using a Cobas Integra 700 Analyser (Roche Diagnostics, Indianapolis, Indiana, USA). ACPA and RF seropositivity were defined as ≥20 and >15 U/mL, respectively. Total swollen and tender joint counts (SJC/TJC), Disease Activity Score in 28 joints, C-reactive protein (DAS28 [CRP]), and clinical disease activity index (CDAI) and simplified disease activity index (SDAI) scores were assessed by investigators at each annual visit. Pain and active arthritis on the day of assessment were assessed by the patient using a scale from 0 to 10, with 0 indicating not active/no pain and 10 indicating extremely active/extreme pain. Follow-up postal questionnaires were completed by patients biannualy to determine work productivity, use of DME (including canes, stands, walkers, wheelchairs, and commodes), hospitalizations, other resource use, and clinical and societal variables.

Study outcomes

The main independent variable of interest was the change in ACPA levels from baseline to month 12 (categorized as decrease [>10%], no change [–10% to +10%], or increase [> +10%]). The dependent variables evaluated included the proportion of patients using DME or being hospitalized during the 12-month follow-up, and the mean change from baseline to month 12 in disease activity (DAS28 [CRP], SDAI, CDAI, SJC/TJC) and pain.

Statistical analysis

Descriptive statistics are used to describe baseline characteristics. Baseline characteristics were compared using the Chi-square test for categorical variables and the Wilcoxon sum rank test for continuous variables. A P value of <0.05 (two-sided) was considered statistically significant. Multivariate logistic regression analyses were used to determine the relationship between change in ACPA levels and binary outcome variables (i.e., DME use and hospitalizations), and linear regression analyses were used to investigate the relationship between change in ACPA levels and disease activity measures, controlling for baseline covariates (age, sex, race, body mass index [BMI], RA duration, number of comorbidities, and previous biologic disease-modifying

antirheumatic drug [DMARD] treatment; baseline disease activity was also a covariate for the logistic regression analysis). All odds ratios (OR) and mean changes from baseline were adjusted for baseline covariates. All statistical analyses were performed using SAS® version 9.4 (SAS institute Inc., Cary, NC, USA).

RESULTS

Baseline patient characteristics by change in ACPA levels

A total of 840/1350 (62%) patients in the BRASS registry had baseline and month 12 ACPA values, and were included in the analysis (Table 1). Overall, 291 (34.6%), 266 (31.7%), and 283 (33.7%) patients in the current study had a decrease, no change, or increase in ACPA levels, respectively. The mean (standard deviation) change in ACPA levels was –35.4 (19.3), –0.5 (4.9), and 196.8 (1368.8) U/mL for the patients with a decrease, no change and increase in ACPA levels, respectively ($P < 0.001$). At baseline, there was no significant difference in mean age, sex, BMI, duration of RA, number of comorbidities, prior use of biologic DMARDs, or disease activity scores among the change in ACPA level groups. The proportion of patients who were ACPA positive at baseline was, however, significantly different across the three ACPA groups (decrease, 69.4%; no change, 62.8%; increase, 59.4%; $P = 0.039$).

Table 1. Baseline patient characteristics by change in ACPA levels

Characteristic	Change in ACPA level			*P* value[a]	Total included (*n* = 840)	Total BRASS cohort[b] (*n* = 1350)	*P* value[c]
	Decrease (< –10%) (*n* = 291)	No change (–10% to +10%) (*n* = 266)	Increase (> +10%) (*n* = 283)				
Age, years Mean (SD)	56.6 (13.1)	57.4 (13.1)	55.8 (14.3)	0.452	56.6 (13.5)	56.5 (14.1)	0.898
Sex, *n* (%) Female Male	240 (82.5) 51 (17.5)	217 (81.6) 49 (18.4)	239 (84.5) 44 (15.5)	0.656	696 (82.9) 144 (17.1)	1112 (82.4) 238 (17.6)	0.547
Race, *n* (%) White Other	272 (93.5) 17 (5.8)	245 (92.1) 20 (7.5)	261 (92.2) 20 (7.1)	0.719	778 (92.6) 57 (6.8)	1238 (91.7) 102 (7.6)	0.163
BMI, kg/m² *n* Mean (SD)	278 26.9 (5.3)	256 26.8 (5.7)	273 26.3 (5.2)	0.411	807 26.7 (5.4)	1275 26.8 (5.7)	0.710
Duration of RA, years Mean (SD)	12.9 (12.1)	14.1 (11.7)	13.3 (12.4)	0.257	13.4 (12.1)	12.9 (12.0)[d]	0.009

Table 1. (*continued*)

Characteristic	Change in ACPA level			*P* value[a]	Total included (*n* = 840)	Total BRASS cohort[b] (*n* = 1350)	*P* value[c]
	Decrease (< −10%) (*n* = 291)	No change (−10% to +10%) (*n* = 266)	Increase (> +10%) (*n* = 283)				
No. comorbidities				0.595			0.999
Mean (SD)	1.9 (1.5)	1.9 (1.4)	1.9 (1.4)		1.9 (1.4)	1.9 (1.5)	
Biologic DMARD, *n* (%)				0.383			0.794
Yes	139 (47.8)	118 (44.4)	119 (42.0)		376 (44.8)	608 (45.0)	
No	152 (52.2)	148 (55.6)	164 (58.0)		464 (55.2)	742 (55.0)	
DAS28 (CRP)				0.193			<0.001
Mean (SD)	3.9 (1.6)	4.0 (1.5)	3.8 (1.6)		3.9 (1.6)	3.7 (1.6)[e]	
SDAI				0.316			<0.001
n	273	245	260		778	1187	
Mean (SD)	23.7 (18.2)	23.7 (16.4)	22.1 (17.5)		23.2 (17.4)	22.0 (17.3)	
CDAI				0.347			<0.001
n	273	245	260		778	1205	
Mean (SD)	22.8 (17.5)	22.8 (16.1)	21.1 (16.5)		22.2 (16.7)	21.1 (16.7)	
SJC/TJC				0.305			<0.001
Mean (SD)	15.8 (14.8)	16.0 (13.6)	14.5 (13.7)		15.4 (14.1)	14.3 (14.1)[d]	
Active arthritis, 0–10 scale				0.517			0.843
n	279	247	260		786	1219	
Mean (SD)	3.7 (2.8)	3.5 (2.8)	3.4 (2.7)		3.5 (2.8)	3.6 (2.8)	
Pain, 0–10 scale				0.476			0.725
n	279	248	260		787	1220	
Mean (SD)	3.5 (2.7)	3.3 (2.7)	3.2 (2.7)		3.3 (2.7)	3.3 (2.8)	

ACPA anti-citrullinated protein antibody, *BRASS* Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study, *SD* standard deviation, *BMI* body mass index, *RA* rheumatoid arthritis, *DMARD* disease-modifying antirheumatic drug, *DAS28* disease activity score in 28 joints, *CRP* C-reactive protein, *SDAI* simplified disease activity index, *CDAI* clinical disease activity index, *SJC/TJC* swollen and tender joint count

[a]Including patients who did not have ACPA measurement at baseline and month 12

[b]Overall difference between the three ACPA groups

[c]Included vs not included

[d]n = 1349

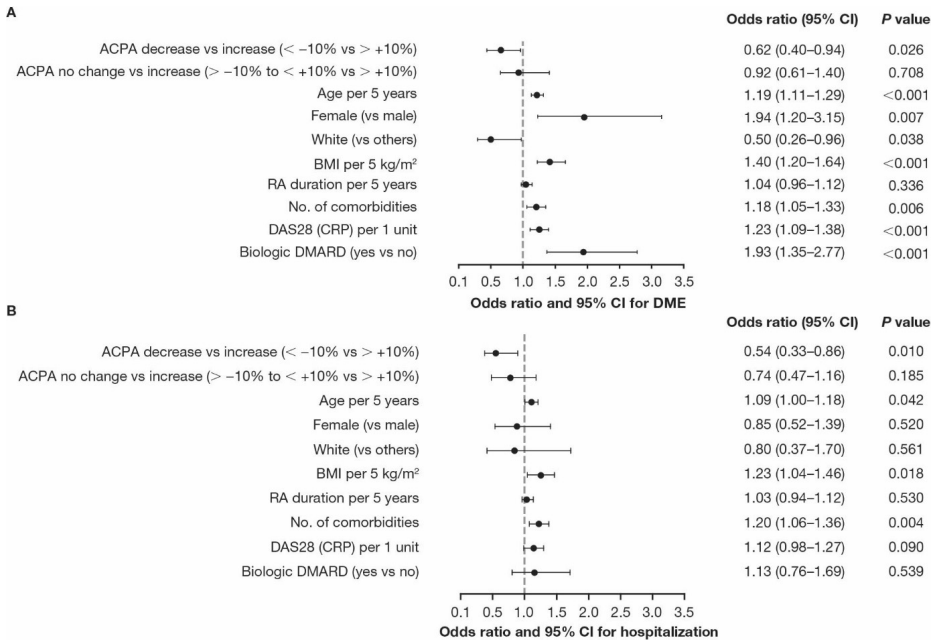
[e]n = 1328

Those patients excluded (*n* = 510) from the full BRASS cohort (*n* = 1350) for this analysis had a shorter mean duration of RA (11.9 years) than those patients included (13.4 years; *P* = 0.009). In addition, the baseline mean DAS28 (CRP) score of the excluded patients was significantly lower (3.5) than that of the patients included in this study (3.9; *P* < 0.001).

Association between resource use and change in ACPA levels

During the 12-month follow-up, DME use was 23.4%, 30.1%, and 28.6%, and the hospitalization rate was 13.4%, 16.5%, and 20.1% in patients with a decrease, no change, or increase in ACPA levels, respectively. Multivariate analysis demonstrated that a decrease in ACPA levels was associated with a reduction in DME use (adjusted OR [aOR]: 0.62; 95% confidence interval [CI] 0.40–0.94; $P = 0.026$) and hospitalizations (aOR: 0.54; 95% CI: 0.33–0.86; $P = 0.010$) compared with an increase in ACPA levels (Fig. 1); there was no significant difference in DME use (aOR: 0.92; 95% CI 0.61–1.40; $P = 0.708$) or hospitalizations (aOR: 0.74; 95% CI 0.47–1.16; $P = 0.185$) between no change and an increase in ACPA levels (Fig. 1). After controlling for baseline covariates, the aORs associated with a decrease versus no change or an increase in ACPA levels were 0.64 (95% CI: 0.44–0.93; $P = 0.019$) for DME use and 0.62 (95% CI: 0.41–0.95; $P = 0.029$) for hospitalizations. Further controlling for ACPA positivity at baseline, the aORs associated with a decrease versus no change or an increase in ACPA levels were 0.66 (95% CI 0.45, 0.96; $P = 0.028$) for DME use and 0.63 (95% CI

Figure 1: Odds ratios for (A) DME use and (B) hospitalization by ACPA change from baseline to 12 months and by baseline characteristics



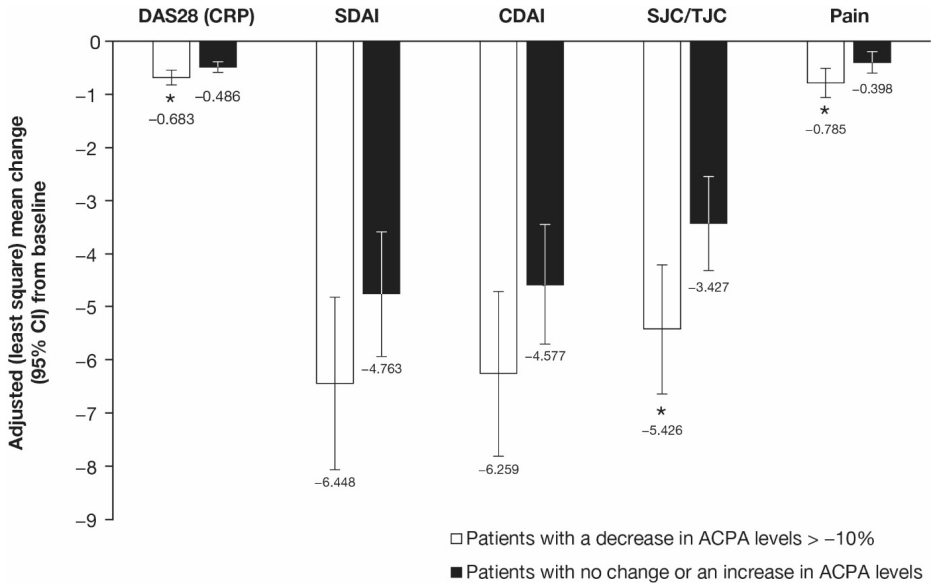
ACPA anti-citrullinated protein antibodies, *CI* confidence interval, *BMI* body mass index, *RA* rheumatoid arthritis, *DAS28* disease activity score in 28 joints, *CRP* C-reactive protein, *DMARD* disease-modifying antirheumatic drug, *DME* durable medical equipment

0.41, 0.96; $P = 0.032$) for hospitalizations. Changes in RF levels were associated with DME use (aOR: 0.62; 95% CI: 0.39–0.99; $P = 0.044$) but not with hospitalizations (aOR: 0.79; 95% CI: 0.47–1.34; $P = 0.383$).

Association between disease activity and change in ACPA levels

The r^2 values for DAS28 (CRP), CDAI, SJC/TJC, SDAI, and pain were 0.27, 0.31, 0.30, 0.32, and 0.34, respectively, indicating a good fit for the multivariate regression models. The adjusted mean changes from baseline in DAS28 (CRP), SJC/TJC, and pain in patients with a decrease in ACPA levels (> 10%) were significantly greater than in those patients with an increase (> +10%) or no change in ACPA ($P < 0.05$; Fig. 2). A similar trend was observed for SDAI and CDAI, where there were greater adjusted mean changes from baseline to month 12 in patients with a decrease in ACPA levels compared with those with an increase or no change in ACPA (SDAI: –6.448 versus –4.763, $P = 0.099$; CDAI: –6.259 versus –4.577, $P = 0.087$; Fig. 2). Multivariate analysis

Figure 2: Adjusted mean (95% CI) change from baseline in disease activity and pain (visual analog scale, 0–100 mm) in patients with a decrease versus no change or an increase in ACPA levels



DAS28 disease activity score in 28 joints, *CRP* C-reactive protein, *SDAI* simplified disease activity index, *CDAI* clinical disease activity index, *SJC/TJC* swollen and tender joint count, *CI* confidence interval, *ACPA* anti-citrullinated protein antibody

*$P < 0.05$, indicates difference between patients with a decrease in ACPA levels versus no change or an increase in ACPA

also showed that changes in DAS28 (CRP), SDAI, CDAI, SJC/TJC, and pain scores were all significantly associated with their respective baseline score (all $P < 0.001$), RA duration (all $P < 0.001$ except for pain, $P = 0.042$) and prior use of biologic DMARDs (all $P < 0.05$). None of the disease activity outcomes was significantly associated with age or race; SDAI was significantly associated with comorbidities ($P = 0.032$), SJC/TJC with sex ($P = 0.035$), and pain with BMI ($P < 0.001$).

DISCUSSION

This study demonstrates that among patients with established RA, decreases in ACPA levels were associated with reductions in DME use, hospitalizations, and disease activity (assessed using a range of standard composite measures).

In current clinical practice, ACPA levels are measured only as part of the diagnostic work-up for RA and there is limited information on changes in ACPA over time. However, data from clinical trials show that RA therapies such as abatacept and rituximab can decrease the levels of anti-cyclic citrullinated peptide in patients with RA [8, 12]. In addition, abatacept and adalimumab have demonstrated superior efficacy in patients with RA who are seropositive for anti-cyclic citrullinated peptide compared with those who are seronegative [13] and, in a prospective analysis of a phase III trial evaluating therapy reduction in patients with RA in ongoing remission, relapse following treatment reduction or withdrawal was associated with ACPA positivity [14]. Hence, the measurement of ACPA levels throughout disease progression could potentially be used to determine how a patient will respond to a particular treatment, thus helping physicians make more informed treatment decisions. However, the implications of changes in ACPA levels within clinical practice have not been previously studied. The present study is the first to highlight the association between outcomes and changes in ACPA levels.

The 2016 update to the European League Against Rheumatism (EULAR) guidelines recommends the addition of a biologic DMARD or JAK inhibitor for patients with an inadequate response to methotrexate and who have poor prognostic factors (i.e., RF/ACPA positivity [particularly those with high levels], high disease activity, early joint damage, or failure of at least two conventional synthetic DMARDs) [15], demonstrating the increasing importance of ACPA in treatment decision-making. However, there is currently no guidance on which biologic DMARD should be given to patients with poor prognostic factors, including ACPA. Further investigations are necessary to better understand the changes in ACPA levels during RA progression and treatment.

The current data are from an observational cohort of patients with RA; such studies allow large numbers of patients to be observed over longer durations of time compared with randomized controlled trials. In addition, data collected from observational studies are more reflective of real-world clinical practice than those derived from clinical trials. A further strength of this study is that it was conducted at a single site, which limits methodologic heterogeneity compared with multicenter studies, avoiding potential differences in study procedures and personnel training.

This observational study reports the analysis of cross-sectional data, which is associated with a number of limitations including the lack of a comparator. The associations between ACPA levels and DME use and hospitalizations were expressed as categorical (rather than continuous) variables, and therefore may not indicate the full extent of any correlation. In addition, confounding by unmeasured variables should also be considered when evaluating these results. Other limitations of this study include the self-reporting of DME use and hospitalizations, which introduces the possibility of recall bias, and the lack of adjustment for specific biologic treatments, preventing explorations of treatment effect.

The results of the current study show that reductions in ACPA levels are associated with increased clinical benefit and decreased healthcare resource utilization in a real-world setting. Similar associations were seen between RF levels and DME use but not hospitalizations. These results could help inform physicians regarding treatment decisions, specifically when selecting treatments for patients with higher ACPA levels. Further research is necessary to evaluate the significance of these findings.

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CHAPTER 5

Association of Anti-Cyclic Citrullinated Protein Antibodies, Erosions, and Rheumatoid Factor with Disease Activity and Work Productivity: A Patient Registry Study

Evo Alemao[1]*, Zhenchao Guo[2], Christine K. Iannaccone[3], Michelle A. Frits[3], Nancy A. Shadick[3] and Michael E. Weinblatt[3]

[1]Bristol-Myers Squibb, Princeton, New Jersey, USA;
[2]Bristol-Myers Squibb, Wallingford, Connecticut, USA;
[3]Department of Rheumatology, Brigham and Women's Hospital, and Harvard Medical School, Boston, Massachusetts, USA.
* PhD student at Erasmus University Rotterdam

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ABSTRACT

Objectives: To evaluate associations between the presence of anti-cyclic citrullinated protein antibodies (anti-CCP) and rheumatoid factor (RF) and other outcomes, including joint erosions and both clinical and economic endpoints, in patients with rheumatoid arthritis (RA). **Methods:** Data from the Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study (BRASS), a prospective registry of adult RA patients with established or recent-onset RA, were analyzed. Logistic regression models were constructed to test associations between anti-CCP/RF seropositivity and erosive disease and the presence of anti-CCP/RF seropositivity plus erosive disease and (1) RA severity; (2) hospitalizations; (3) durable medical equipment (DME) use; and (4) worker productivity (e.g., employment status). Covariates in these models included patient age, gender, race, body mass index (BMI), number of comorbidities, and treatment. **Results:** Among 1309 registrants, those who were positive (vs. negative) for anti-CCP were 2.72 times more likely to have erosions (OR = 2.72; 95% CI: 1.77–4.18; $P < 0.001$). Individuals positive (vs. negative) for RF were 36% more likely to have erosions (95% CI: 0.88–2.08; $P = 0.162$). Patients with anti-CCP seropositivity and erosions were significantly more likely to: (1) have higher disease activity as measured by the Disease Activity Score in 28 joints C-reactive protein (DAS28-CRP ≥ 2.6); (2) be hospitalized; (3) use DME; and (4) be unemployed, disabled, or long-term disabled. **Conclusions:** For the first time in a "real-world" setting including patients with both recent-onset and chronic RA, this study demonstrated that the combination of anti-CCP seropositivity and erosions were significantly associated with more adverse clinical and health-economic consequences, including a lower probability of low disease activity and higher health resource utilization, despite use of biologic disease-modifying antirheumatic drugs by many patients. This dual presentation may signal a need for more intensive therapies, even when observed in patients with chronic, as well as recent-onset, RA.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic progressive condition that affects approximately 0.5–1.0% of western industrialized societies, including approximately 1.5 million US residents [1]. This immune-mediated inflammatory disease has a variable natural history and prognosis; some patients (or sub-populations) experience an overall more aggressive disease trajectory with different patterns of articular and extra-articular damage, more rapid radiographic progression, and a poorer prognosis (including worse treatment responses) compared to others [2–6].

In patients with early RA, various factors have been associated with a poor prognosis, including certain genotypes and young age at disease onset. Contemporary RA management guidelines recommend more intensive treatment of patients with poor prognostic factors [7, 8]; clinical practice guidelines from the American College of Rheumatology (ACR) have placed less emphasis [and the European League Against Rheumatism (EULAR) more emphasis] on the clinical role of prognostic factors. Biologic disease-modifying antirheumatic drugs (bio-DMARDs), with or without methotrexate (MTX) or other conventional DMARDs, are recommended for patients with high disease activity and poor prognostic factors. These factors include early-onset damage to joints and autoantibodies to cyclic citrullinated protein [anti-cyclic citrullinated protein antibodies (anti-CCP; and other citrullinated proteins] and rheumatoid factor (RF), which are believed to play a role in disease pathogenesis [7, 9–11]. In fact, some of these prognostic factors are interrelated. For example, anti-CCP production is associated with more erosive disease, rapid radiographic progression, and/or extra-articular manifestations; whereas elevated acute-phase reactants are often associated with higher disease activity [12–19].

Data concerning the impact of combinations of prognostic factors (anti-CCP, RF, and joint erosions) on other health outcomes are limited. The objective of the current study was twofold: to evaluate the association between (1) anti-CCP/RF seropositivity and joint erosions and between (2) the impact of these prognostic factors when present together on disease activity, resource use, and work productivity.

PATIENTS AND METHODS

Study design and setting

We utilized data from the Brigham and Women's Hospital (BWH) Rheumatoid Arthritis Sequential Study (BRASS). This prospective registry commenced in March 2003 (http://www. brassstudy.org) [20–22].

Study participants

The BRASS Registry is a single-center, prospective, observational, longitudinal cohort of 41,300 adults with established or recent-onset RA who are being followed by a hospital-based practice of 21 rheumatologists at BWH in Boston. To be eligible for inclusion in the registry, patients had to have a confirmed diagnosis of RA by an independent rheumatologist. BRASS registrants included in the current analysis had available baseline data for pivotal variables, including anti-CCP and RF.

The BRASS Registry has been conducted in accordance with International Society for Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practices, applicable regulatory requirements, and ethical tenets originating in the Declaration of Helsinki. The study protocol and informed consent document were reviewed and approved by the BWH Institutional Review Board.

In accordance with local regulations, participants in the BRASS Registry provided written informed consent before enrolling into the study and having any study assessment or procedure. Investigators ensured that patients were clearly and fully informed about the purposes of the study, potential risks, and the subject's rights and responsibilities when participating in this study.

De-identified patient data in the present study were compliant with the Health Insurance Portability and Accountability Act. Maintenance of patient confidentiality was assured by assigning each subject a randomized identification number upon enrollment in the BRASS Registry, and limiting access to these numbers.

In terms of patient follow-up, physicians evaluated patient demographic and clinical characteristics, disease activity, and laboratory parameters at baseline and annually thereafter. Total swollen and painful joint counts (TJC) were measured by the investigator at each annual visit. Anti-CCP levels at baseline and annual follow-up visits

over time (1–5 years) were measured using validated enzyme-linked immunosorbent assays [ELISAs; from Inova Diagnostics (San Diego, CA) and Euro-Diagnostica (IBL—American, Minneapolis, MN)] [23].

Certain outcomes, such as disease activity measures, were assessed at 12-month intervals, during annual rheumatologist visits. Follow-up postal questionnaires to assess patient-reported outcomes and other clinical and societal variables were mailed to patients. These outcomes included worker productivity, hospitalization, and use of durable medical equipment (DME), which included stands, walkers, and wheelchairs.

Variables

Consistent with the study's objectives, we evaluated associations between (1) seropositivity (anti-CCP$^+$/RF$^+$) and joint erosions at baseline. Seropositivity for anti-CCP was defined as a minimum value of 20 U/mL and seropositivity for RF as a value greater than 15 U/mL. Also assessed were associations between seropositivity (± erosions) and (1) a Disease Activity Score in 28 joints C-reactive protein (DAS28-CRP) o 2.6 or a Simplified Disease Activity Index (SDAI) score of ≤3.3 (associated with remission); (2) health care resource utilization in terms of whether patients were hospitalized or used DME, and (3) worker productivity in terms of numbers of days lost as well as the number (%) of BRASS registrants who were employed, retired, short-term disabled, long-term disabled, or had an annual family income of $50,000. Hospitalization and DME use represent direct costs of RA, whereas days of work lost and proportions of patients employed, retired, disabled, and/or earning low incomes are considered indirect costs.

Statistical analysis

Descriptive statistics included the Wilcoxon rank sum test for continuous variables and Pearson χ^2 for categorical variables. Logistic regression models were constructed to test associations between anti-CCP/RF seropositivity and the binary outcome variable of the presence or absence of joint erosions. Models also tested associations between the presence of these prognostic factors and the categorical variables of: (1) having DAS28-CRP < 2.6 or SDAI ≤ 3.3 (SDAI remission), (2) hospitalization (yes or no), (3) DME use (yes or no), and (4) employment status (proportions employed, retired, disabled and earning oF $50,000 annually). For associations between anti-CCP/RF seropositivity and/or joint erosions and the likelihood of having a DAS28-CRP

score < 2.6 or SDAI ≤ 3.3 (SDAI remission), forest plots based on logistic regression models were constructed showing odds ratios (OR) and 95% confidence intervals (CIs). Covariates in these models included patient age, gender, race, body mass index (BMI), number of comorbidities, and treatment. An *a priori* two-sided $\alpha = 0.05$ was specified for statistical significance. Analyses were conducted using SAS PROC GLM and PROC LOGISTIC procedures (SAS Institute Inc., Cary, NC) for continuous and categorical outcome variables.

RESULTS

Descriptive data

A total of 1309 patients were included. Table 1 summarizes characteristics of RA patients included in the analysis according to baseline anti-CCP, RF, and erosion status. Patients who were positive (vs. negative) for anti-CCP, RF, and erosions at baseline tended to have a significantly:

- Longer history of RA (15.0 vs. 9.6 years for anti-CCP; 14.8 vs. 10.1 years for RF; and 17.2 vs. 7.3 years for erosions; each $P < 0.001$ for pairwise comparisons),
- Greater number of comorbidities (2.1 vs. 1.7 for anti-CCP and RF; and 2.2 vs. 1.6 for erosions; each $P < 0.001$ for pairwise comparisons); and
- Higher mean CRP levels (10.1 vs. 7.6 mg/L for anti-CCP; 10.3 vs. 7.9 mg/L for RF; and 11.6 vs. 5.6 mg/L for erosions; each $P < 0.001$).

Compared to all other BRASS study participant, patients who were anti-CCP positive with joint erosions were significantly older [mean (SD) age = 59.0 (12.9) vs. 54.8 (14.5) years; $P < 0.001$]; had higher RA activity as measured using the DAS28-CRP [mean (SD) = 4.3 (1.6) vs. 3.4 (1.5); $P < 0.001$], Clinical Disease Activity Index [CDAI; mean (SD) = 26.9 (17.7) vs. 17.3 (15.0); $P < 0.001$], and SDAI [mean (SD) = 28.0 (18.4) vs. 18.1 (15.5); $P < 0.001$]; and were significantly more likely to be using bio-DMARDs (59.6% vs. 38.2%; $P < 0.001$). The remaining BRASS population included patients who were seropositive only, patients with only joint erosions, and those who were seronegative and did not have joint erosions (Table 2).

Outcome data

In general, we observed consistently significant associations between anti-CCP and clinical disease activity and erosions, whether RF was or was not included in models

Table 1. Patient characteristics according to anti-cyclic citrullinated protein antibodies (anti-CCP), rheumatoid factor (RF), and erosions

Characteristic	Anti-CCP$^+$	Anti-CCP$^-$	Total	RF$^+$	RF$^-$	Total	Erosion$^+$	Erosion$^-$	Total
Total N	803	506	1,309	798	488	1,286	692	434	1,126
Anti-CCP, mean (SD) U/mL	205.0 (149.6)	6.5 (4.3)	128.3[a] (151.9)	186.8 (155.4)	32.5 (75.1)	127.8[a] (150.6)	154.5 (153.6)	87.8 (145.3)	128.6[a] (153.9)
Age, mean (SD) yr	57.2 (13.8)	55.5 (14.4)	56.5 (14.1)	57.1 (13.8)	55.7 (14.5)	56.6 (14.1)	58.9 (12.9)	52.2 (14.5)	56.3[a] (13.9)
Female	663 (82.6%)	411 (81.2%)	1074 (82.0%)	667 (83.6%)	389 (79.7%)	1056 (82.1%)	580 (83.8%)	360 (82.9%)	940 (83.5%)
White	726 (90.4%)	473 (93.5%)	1,199 (91.6%)	723 (91.4%)	454 (93.6%)	1,177 (92.2%)	634 (91.6%)	398 (91.7%)	1032 (91.7%)
BMI, mean (SD) kg/m^2	26.8 (5.8)	26.9 (5.4)	26.9 (5.7)	26.8 (5.7)	27.0 (5.5)	26.8 (5.6)	26.5 (5.5)	27.3 (6.0)	26.8 (5.7)
Duration of RA yr, mean (SD)	15.0 (12.2)	9.6 (11.0)	12.9[a] (12.0)	14.8 (12.2)	10.1 (11.5)	13.0[a] (12.1)	17.2 (12.6)	7.3 (8.6)	13.4[a] (12.2)
Comorbidities, mean (SD)	2.1 (1.7)	1.7 (1.2)	1.9[a] (1.5)	2.1 (1.7)	1.7 (1.2)	1.9[a] (1.5)	2.2 (1.7)	1.6 (1.1)	1.9 [a] (1.6)
RF, mean (SD) IU/mL	190.3 (365.0)	27.6 (84.4)	127.7[a] (301.6)	202.0 (363.1)	8.6 (2.8)	128.6[a] (301.0)	166.7 (359.9)	64.6 (168.5)	127.4[a] (305.0)
CRP, mean (SD), mg/L	10.1 (21.6)	7.6 (17.9)	9.1[a] (20.3)	10.3 (22.0)	7.9 (18.4)	9.4[a] (20.7)	11.6 (25.4)	5.6 (10.0)	9.2 [a] (21.1)
MHAQ, mean (SD)	0.4 (0.5)	0.4 (0.4)	0.4 (0.5)	0.4 (0.5)	0.4 (0.4)	0.4 (0.5)	0.5 (0.5)	0.3 (0.4)	0.4[a] (0.5)

[a] $P < 0.001$ for pairwise comparisons between anti-CCP$^+$ and anti-CCP$^-$, RF$^+$, and RF$^-$, and erosion$^+$, and erosion$^-$. CRP, C-reactive protein; MHAQ, Modified Health Assessment Questionnaire.

Table 2. BRASS registrant characteristics according to baseline status of anti-cyclic citrullinated protein antibodies (anti-CCP) and erosions, on univariate analyses

Characteristic	Anti-CCP$^+$ / Erosion$^+$ (N=498)	All other RA patients (N=727)	*P*
Mean (SD) age, yr	59.0 (12.9)	54.8 (14.5)	<0.001
No. (%) female	420 (84.3)	593 (81.6)	0.208
Mean (SD) BMI, kg/m^2	26.7 (5.7)	27.0 (5.7)	0.345
No. (%) receiving bio–DMARDs	297 (59.6)	278 (38.2)	<0.001
Mean (SD) DAS28–CRP	4.3 (1.6)	3.4 (1.5)	<0.001
Mean (SD) CDAI	26.9 (17.7)	17.3 (15.0)	<0.001
Mean (SD), SDAI	28.0 (18.4)	18.1 (15.5)	<0.001
Mean (SD) TJC	19.2 (15.3)	11.1 (12.3)	<0.001

Anti-CCP, anti-cyclic citrullinated protein antibody; bio-DMARD, biologic disease-modifying antirheumatic drug; BMI, body mass index; CDAI, Clinical Disease Activity Index; DAS28-CRP, Disease Activity Score in 28 joints C-reactive protein; MHAQ, Modified Health Assessment Questionnaire; SDAI, Simplified Disease Activity Index; TJC, total swollen and painful joint count.

(Appendices Table A1 through A9). In a logistic model that included RF and anti-CCP (Table A9), BRASS registrants who were positive (vs. negative) for anti-CCP were nearly 3 times more likely to have erosions (OR = 2.72; 95% CI: 1.77–4.18; $P < 0.001$). Individuals positive (vs. negative) for RF were 36% more likely to have erosions (95% CI: 0.88–2.08; $P = 0.162$).

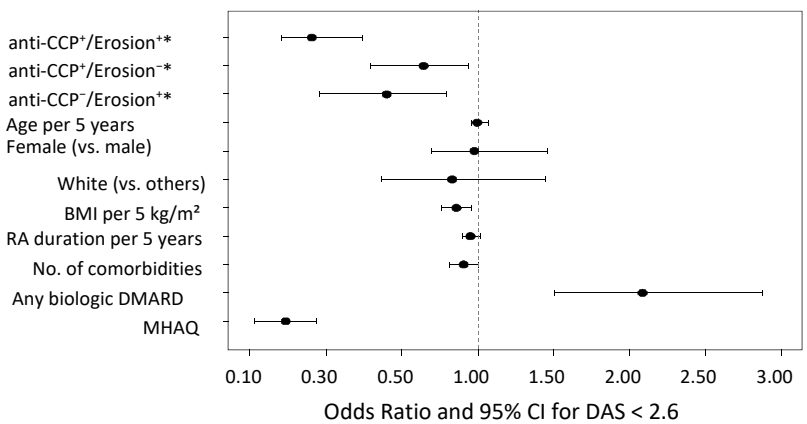
In the logistic model that included both RF and anti-CCP, patients positive for anti-CCP were 39% less likely (OR = 0.61; 95% CI: 0.41–0.90; $P = 0.012$) to have DAS28-CRP < 2.6 than their anti-CCP- counterparts, whereas RF+ (vs. RF-) patients were 2% less likely (OR = 0.98; 95% CI: 0.66–1.44; $P = 0.899$; Table A7). With respect to the SDAI, anti-CCP+ (vs. anti-CCP-) registrants were significantly less likely to have SDAI ≤ 3.3, whereas RF+ (vs. RF-) individuals were not (Appendix Table A8).

Among those with both anti-CCP and RF data ($N = 1274$), 53.9% were anti-CCP+/RF+, 7.6% were anti-CCP+/RF-, 7.8% were anti- CCP-/RF+ and 30.6% were anti-CCP-/RF-. The adjusted ORs for anti-CCP+/RF+, anti-CCP+/RF- and anti-CCP-/RF+ compared to anti-CCP-/RF- were 0.59 (95% CI: 0.42–0.83), 0.67 (0.38–1.19), 1.07 (0.63–1.82) for DAS28-CRP < 2.6, and 0.53 (0.32–0.87), 0.28 (0.10–0.75) and 1.23 (0.59–2.57) for SDAI ≤ 3.3, respectively.

Associations of baseline anti-CCP and erosion status with disease activity

We evaluated the effect of having the prognostic factors in combination (i.e., both anti-CCP positivity and joint erosions) compared to having these individually (i.e., anti-CCP positivity only or joint erosions only). From this comparison, we observed that patients with multiple prognostic factors had an even lower odds of experiencing DAS28-CRP < 2.6, even after treatment with standard-of-care bio-DMARDs (Fig. 1A). As compared to those without anti-CCP and without erosions (anti-CCP-/Erosion-), the OR for DAS28-CRP < 2.6 was 0.25 (95% CI: 0.16–0.38; $P < 0.001$) for those with both anti-CCP+ and erosions (anti-CCP+/Erosion+), 0.61 (95% CI: 0.41–0.92; $P = 0.018$) for those with anti-CCP+ only (anti-CCP+/Erosion-), and 0.45 (95% CI: 0.27–0.75; $P = 0.002$) for those with erosions only (anti-CCP-/Erosion+). Patients who were *both* anti-CCP+/Erosion+ (not just anti-CCP+ *or* Erosion+) were also significantly less likely to experience low disease activity according to the SDAI (Fig. 1B). As compared to those without anti-CCP and without erosions (anti-CCP-/Erosion-), the OR for SDAI ≤ 3.3 was 0.19 (95% CI: 0.10–0.37; $P < 0.001$) for those with both anti-CCP and erosions (or anti-CCP+ /Erosion+), 0.62 (95% CI: 0.33 –1.14; $P = 0.122$) for those with anti-CCP only (anti-CCP+/ Erosion-) and 0.49 (95% CI: 0.24–1.02; $P = 0.057$) for those with erosions only (anti-CCP-/Erosion+).

Figure 1. Anti-CCP$^+$/erosion$^+$ patients have high disease activity even after treated with standard-of-care biological disease-modifying antirheumatic drugs.



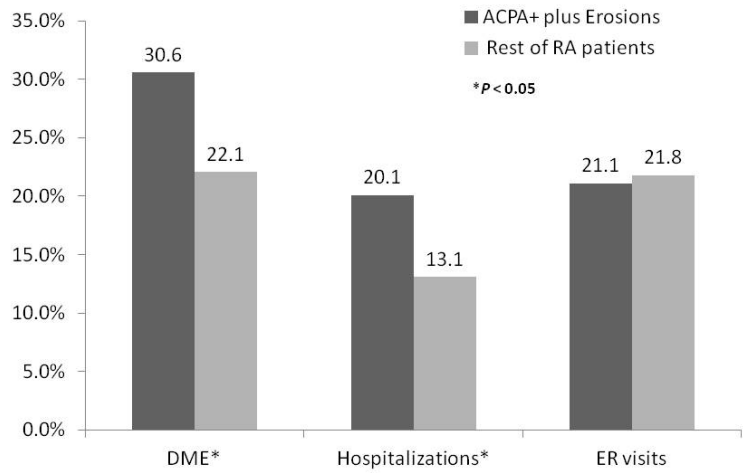
Forest plots of odds ratios [ORs; with 95% confidence intervals (CIs)] for multivariate analyses of BRASS registrants who were positive for anti-cyclic citrullinated protein antibodies (anti-CCP) and erosions at baseline compared to their counterparts without these baseline features. anti-CCP$^+$ and erosion$^+$ registrants were significantly less likely to have a Disease Activity Score in 28 joints C-reactive protein (DAS28-CRP) < 2.6 (*upper panel*) and Simple Disease Activity Index (SDAI) ≤ 3.3 (SDAI remission; *lower panel*). *Compared to the referent of anti-CCP$^-$/Erosions$^-$.

As compared to those with RF-/Erosion-, the OR for DAS28-CRP < 2.6 was 0.28 (95% CI: 0.18–0.44; $P < 0.001$) for those with RF+/ Erosion+, 0.72 (95% CI: 0.48–1.08; $P = 0.113$) for those with RF+ / Erosion- and 0.42 (95% CI: 0.25–0.71; $P = 0.001$) for those with RF-/Erosion+. The corresponding OR for SDAI ≤ 3.3 was 0.30 (95% CI: 0.15–0.59; $P < 0.001$) for those with RF+/Erosion+, 0.63 (95% CI: 0.36–1.10; $P = 0.105$) for those with RF+ /Erosion- and 0.35 (95% CI: 0.16–0.75; $P = 0.007$) for those with RF-/Erosion+.

Associations of baseline anti-CCP and erosion status with direct and indirect resource use

RA patients who were anti-CCP positive and had erosive disease at baseline had significantly higher frequencies of hospitalization and DME use (Fig. 2) compared to the rest of the BRASS cohort.

Figure 2. Health-care resource utilization among BRASS registrants who were positive for anti-cyclic citrullinated protein antibodies (anti-CCP) and erosions at baseline compared to their counterparts without these baseline features.



DISCUSSION

This was the first study to evaluate the clinical, direct medical resource use, and indirect costs of RA in patients with poor prognostic factors (seropositivity/erosions) in a longitudinal study of a large, real-world population of patients with established

RA. Clinically, seropositive patients with joint erosions were significantly less likely (than their counterparts without these prognostic factors) to have DAS28-CRP < 2.6 or SDAI ≤ 3.3. With regard to direct health care costs, the likelihoods of hospitalization and DME use were significantly higher in patients with adverse prognostic factors. With respect to indirect health care costs, greater proportions of patients without the adverse prognostic factors were employed and lower proportions were on short-term and long-term disabilities and in the lower income bracket.

These findings are unprecedented in demonstrating that a combination of anti-CCP seropositivity and erosions at baseline augurs a more adverse disease trajectory and may signal more marked needs for health-care resources even in patients who do not necessarily have recent-onset or early disease that falls within the long-established "clinical window." A potential clinical implication of our results is that a combination of adverse prognostic risk factors may warrant more intensive therapy involving combinations of treatment modalities, including MTX, potentially high-dose-tapering corticosteroids, and DMARDs.

Potentially validating the premise that anti-CCP+ patients derive special benefit from more intensive therapy were findings reported by the randomized controlled CARDERA (Combination Anti-Rheumatic Drugs in Early RA) trial investigators. In a prospective, factorial-designed trial of 467 early-RA patients, antiCCP+ patients who received the most intensive, triple DMARD therapy, including MTX and prednisolone, experienced the smallest increases (i.e., least severe erosions) in mean Larsen scores over 2 years: 3.66 (95% CI: 2.27–5.05) compared to 9.58 (95% CI: 6.76–12.39) for MTX alone [23]. Regardless of treatment intensity, anti-CCP+ patients experienced modest radiologic progression in the CARDERA trial.

Also in the CARDERA trial, only anti-CCP+ patients had significant improvements in DAS-28 at 6 months when treated with binary or ternary regimens including prednisolone [23]. In fact, the CARDERA study found that MTX monotherapy actually resulted in *worsening* of radiologic damage in anti-CCP+ patients. In fact, only RA patients with elevations in this biomarker significantly benefited from triple therapy, and the investigators reported improved health status and decreased disease activity only in anti-CCP+ patients receiving high-dose corticosteroids [23]. The CARDERA study data in turn extended conclusions of the Induction Therapy with Methotrexate and Prednisone in Rheumatoid or Very Early Arthritic Disease (IMPROVED; http://www.isrctn.com/ISRCTN11916566) and *Behandel Strategieën* (BeST) studies. The IMPROVED trial demonstrated that reductions in disease activity were more marked, and the likelihood of disease remission significantly greater, in anti-CCP$^+$ (vs. anti-CCP$^-$) patients with RA

or undifferentiated inflammatory arthritis who received high-dose corticosteroids [24]. The BeST trial found that the likelihood of radiologic progression was increased nearly 13-fold [odds ratio (OR) = 12.6; 95% CI: 3.0–51.9] in patients receiving monotherapy but much less so in those receiving both DMARDS and corticosteroids (OR =1.7; 95% CI: 0.5–5.4) [25,26]. Unlike our trial, however, neither of these studies—or any others to our knowledge—have established significant associations between a combination of anti-CCP seropositivity and the presence of erosions at baseline and both a reduced likelihood of low disease activity and an increase in health resource utilization (including hospital admissions) among real-world patients with heterogeneous RA histories.

Elevations in the anti-CCP biomarker may even inform treatment decisions related to selecting bio-DMARDs. Studies have suggested that anti-CCP+ patients experience superior treatment outcomes in response to T-cell inhibition with abatacept or B-cell inhibition with rituximab, whereas anti-CCP- patients may experience improved outcomes in response to tumor necrosis factor-α (TNF-α) inhibitors [27–30].

Paralleling our findings, a study of 276 adults with RA also found that combinations of risk factors presaged less favorable outcomes [31]. Significantly more marked decrements in functional status and more severe disease were observed in patients who were seropositive for both anti-CCP and RF. Although these patients received more intensive therapy with MTX and combination DMARDs, a smaller proportion of them experienced disease remission at 1 year compared to those who were anti-CCP-/RF- (12% vs. 18%). Proportions of patients with hand erosions were 77% in the anti-CCP+/RF+ group, 73% in the anti-CCP-/RF+ group, 83% in the anti-CCP+/RF- group but only 32% in the anti-CCP-/RF- group ($P < 0.001$ for trend) [31].

In general, prognostic factors are important because they assist in categorizing potential outcomes and stratifying treatment of patients, which in turn enables better clinical management by providing appropriate resources for patients who need them most or who are more likely to benefit. Much research has been devoted to understanding poor prognostic factors in an early-RA setting, with the motivation that early control of systemic rheumatoid inflammation can delay or even prevent irreversible clinical complications of bone and joint damage. However, there is limited information on the importance of prognostic factors in established RA and more importantly, there is no study that evaluated the impact of combined prognostic factors on disease activity. Established RA is not a homogeneous disease, given that our registry study showed that, even among established-RA patients, adverse prognostic factors have important ramifications. The findings also point to a major potentially unmet treatment need in RA. Although seropositive patients with erosive joints were significantly more likely

(vs. the rest of the cohort) to be taking standard-of-care bio-DMARDs [e.g., TNF-α inhibitors], they were still significantly less likely to have DAS28-CRP < 2.6 compared to their counterparts without these adverse prognostic factors.

The published RA literature refers to serologic, genetic, clinical, radiologic, and immunologic prognostic factors. Our analysis focused on immunologic, serologic, and radiologic factors and evaluated associations between the combination of these factors and clinical outcomes. Overall, our findings are in line with those in the recent RA literature [32–36]. Echoing our results, a systematic review by Jilani and Mackworth-Young determined that anti-CCP positivity was a strong predictor of erosive disease, and anti-CCP+ patients were 4 times more likely to have erosive disease compared to anti-CCP- patients. In addition to anti-CCP, baseline erosions conferred additive prognostic information over that of elevated anti-CCP alone in predicting joint erosions [34]. Previous investigators in the BRASS Registry reported that the presence of the HLA-DRB1 shared epitope was associated with a nearly 2-fold increased risk of anti-CCP (OR = 1.8; 95% CI: 1.24–2.66) and was also significantly related to an erosive phenotype. However, the latter association was abrogated after conditioning the results on anti-CCP levels. Taken together, these findings pointed toward a "causal pathway" for anti-CCP in predicting erosions [34,37].

Also compatible with our findings were results from a study revealing that anti-CCP had a higher predictive value for erosions than RF, as well as CRP and ESR [38]. In our study, decreases (vs. increases) in anti-CCP, but not RF, over time were associated with significantly lower odds of both hospitalization and DME use. There is some controversy concerning the relative clinical or prognostic value of anti-CCP and RF. Several studies have challenged the predictive value of RF, whereas the presence of anti-CCP autoantibodies has been associated nearly uniformly with erosive RA and, according to certain investigators, "have established themselves as the single most reliable prognostic factor in clinical practice" [39]. On the other hand, a recent study by Aletaha's group reported that RF^+ patients had the most active RA, irrespective of anti-CCP levels [40]. However, this analysis was based on clinical trial data with a complex analysis involving propensity scores to match patients based on anti-CCP and RF while controlling for anti-CCP levels, age, and duration of disease. A major limitation is that this analysis excluded approximately 64% of the patients; of those included, 82% were both anti-CCP and RF positive.

Our data suggest that anti-CCP seropositivity, either alone or in combination with other prognostic factors, most likely drove the observed findings on disease activity. Although we found that double seropositivity (anti-CCP^+/RF^+) compared to double

sero-negativity (anti-CCP-/RF-) was associated with the lowest odds of attaining RA remission, the inconsistent results regarding RF+ in relation to SDAI when considering anti-CCP in the analysis may be due to insufficient sample size and/or to the fact that SDAI may be a more stringent measure of disease activity and remission compared to DAS (especially DAS < 2.6 for remission, in which there may be residual disease). Published findings suggest that anti-CCP and RF seropositivity are related: patients who are anti-CCP seropositive are more likely to be RF seropositive as well [41], making it further difficult to parse out the biologic effect of anti-CCP+ and RF+.

Taken together with published data, our findings suggest that it is important to assess prognostic factors in patients with RA (even in more established, rather than only in early disease). Evaluating patients for anti-CCP seropositivity and joint erosions may assist in targeting therapy to minimize clinical, health-economic, and socioeconomic consequences of RA. Recent evidence suggests that treatment outcomes may vary depending on the presence of these prognostic factors [29].

The prospective, longitudinal, observational nature of the BRASS Registry is central to both its strengths and limitations. Such studies enable large cohorts of patients to be observed over longer durations as compared with randomized controlled trials (RCTs). To date, published data on the effects of bio-DMARDs on anti-CCP derive largely from RCTs, especially in early-RA cohorts [42–44]. Whereas RCTs are typically conducted in highly selected patient populations, including individuals with minimal comorbidities and high treatment adherence, observational studies such as the BRASS Registry may be more generalizable to naturalistic care settings involving more heterogeneous patient populations with established RA. Observational studies are also more likely to include dynamic treatment strategies compared to the more rigid, protocol-based treatment strategies of RCTs.

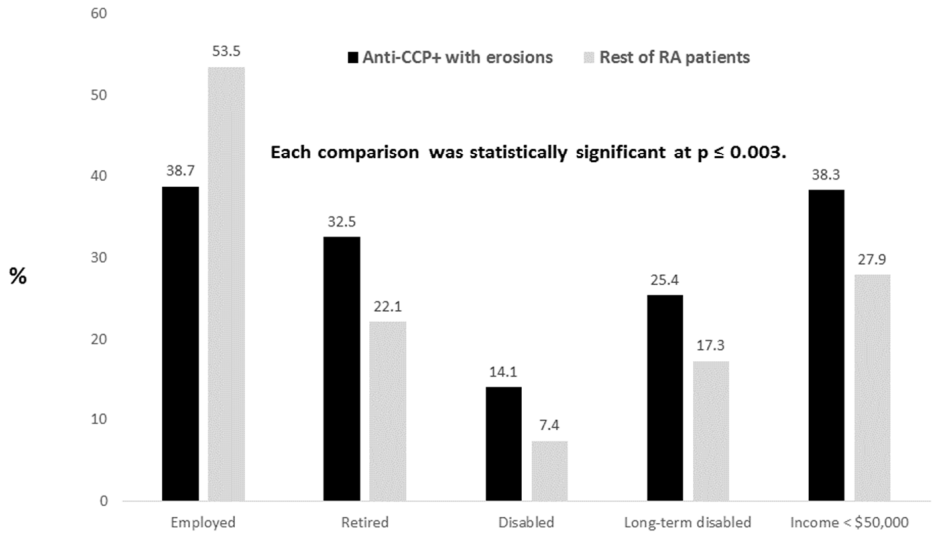
The BRASS Registry treatment center also has a high (80–90%) patient retention rate, supporting the stability of longitudinal data (i.e., minimizing patient attrition effects) and the reliability of temporal trends. Finally, the study was conducted at a single site (BWH), limiting methodological heterogeneity compared to a multicenter study with potential differences in study procedures and personnel training.

However, observational analyses are of an inherently associational nature and cannot conclusively assign causality or rule out certain biases, even though our statistical models controlled for many relevant baseline covariates. Confounding by unmeasured variables (e.g., treatment adherence and socioeconomic status) also cannot be excluded. Our study documented associations between anti-CCP seropositivity

and baseline erosions and both hospitalization and DME use expressed as categorical (binary), rather than continuous, variables. DME use and hospitalization were self-reported, opening the possibility of recall bias. Given the observational, largely descriptive and associational nature of our work, which did not test specific hypotheses, we did not seek to rigorously determine patient sample size. No attempt was undertaken to limit biases using propensity score matching, nonrandom missing data using mixed models, or intracorrelated patient data over time using generalized estimating equations or generalized linear models.

Unlike certain other investigators, we did not evaluate antibodies to individual citrullinated proteins (e.g., fibrin, filaggrin, and vimentin) or other potentially suitable serological markers, such as cartilage oligometric matrix protein (CIOMP) and matrix metal-loproteinase [13,45]. Evaluating associations between anti-CCP and extra-articular manifestations and other RA signs (e.g., nodules) and symptoms also exceeded the purview of our study [46]. Other, potential statistical limitations include the fact that our analysis did not control for multiple comparisons or intracorrelation of each registrant's data over time, and that numbers of study participants with available anti-CCP data at later years were relatively small. Finally, given the advanced, tertiary-care setting of the BRASS Registry, socioeconomic status (including household income), resources to afford care, and health literacy may skew the data toward more (rather than less) favorable outcomes compared to other patient populations. It is possible that a family (household) income of less than $50,000/year is not the most sensitive and specific index or marker of disability and may indicate an inability to find employment rather than an inability to work. It is not entirely clear if personal, rather than family or household; income might represent a more appropriate metric. On the other hand, we find it reassuring that significant differences in employment, retirement, and disability (and long-term-disability) status and anti-CCP/ erosion positivity were in the same overall direction as a family income of less than $50,000: 38.7% of BRASS registrants with anti-CCP/erosion positivity were employed ($P < 0.05$ vs. 53.5% for the rest of the RA subjects), 32.5% were retired ($P < 0.05$ vs. 22.1%), and 14.1% were disabled ($P < 0.05$ vs. 7.4%; Fig. 3).

Figure 3. Worker productivity among BRASS registrants who were positive for anti-cyclic citrullinated protein antibodies (anti-CCP) and erosions compared to their counterparts without these baseline features.



CONCLUSIONS

In this prospective observational study of a diverse patient population (i.e., adults with both established and early RA), baseline anti-CCP levels (especially when combined with baseline erosions) were associated with threefold adverse outcomes: clinical, health-economic, and socioeconomic. Clinically, higher anti-CCP levels were associated with greater disease activity and lower odds of having DAS28-CRP o 2.6, even after therapy with standard-of-care bio-DMARDs (e.g., TNF-α inhibitors). The unique value of this study was in identifying that patients with a combination of both anti-CCP seropositivity and erosions experienced significantly more adverse clinical (e.g., likelihood of low disease activity), health-economic (e.g., hospitalization and durable-medical-equipment use) and socioeconomic (i.e., reduced worker productivity) outcomes in a naturalistic, longitudinal setting that is likely highly generalizable to ambulatory-care practices. Further research is needed to determine the actual cost consequences of these findings, from the perspectives of different stakeholders (e.g., patients, providers, payers, and society). These findings point to a potentially unmet treatment need and the importance of assessing prognostic factors, even in patients who have had RA for several years.

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APPENDICES: ASSOCIATIONS INVOLVING POTENTIAL PROGNOSTIC FACTORS IN DIFFERENT LOGISTIC REGRESSION ANALYSES

Table A1. Odds Ratios for DAS28-CRP < 2.6 - anti-CCP with Covariates

Variables	Odds Ratio	95% CI	*P*
Anti-CCP$^+$ (vs. Anti-CCP$^-$)	0.61	0.45–0.83	0.001
Age per 5-yr increase	0.98	0.93–1.04	0.577
Female (vs. male)	0.99	0.68–1.45	0.977
White (vs. other races)	0.78	0.44–1.38	0.392
BMI per 5-kg/m^2 increase	0.83	0.72–0.95	0.008
RA duration per 5-yr increase	0.90	0.84–0.97	0.005
No. of comorbidities	0.87	0.77–0.99	0.040
Any bio–DMARD (vs. no bio–DMARD)	1.90	1.41–2.57	<0.001
MHAQ	0.16	0.10-0.25	<0.001

Anti-CCP, anti-cyclic citrullinated protein antibodies; BMI, body mass index; DAS28-CRP, Disease Activity Score in 28 joints C-reactive protein; DMARD, disease-modifying antirheumatic drug; MHAQ, Modified Health Assessment Questionnaire; RA, rheumatoid arthritis.

Table A2. Odds Ratios for SDAI≤3.3 - anti-CCP with Covariates

Variables	Odds Ratio	95% CI	*P*
Anti-CCP$^+$ (vs. Anti-CCP$^-$)	0.46	0.30–0.73	<0.001
Age per 5-yr increase	1.01	0.93–1.10	0.779
Female (vs. male)	0.98	0.56–1.72	0.949
White (vs. others)	0.57	0.23–1.39	0.218
BMI per 5-kg/m^2 increase	0.70	0.55–0.90	0.005
RA duration per 5-yr increase	0.78	0.69–0.89	<0.001
No. of comorbidities	0.73	0.56–0.96	0.022
Any bio–DMARD (vs. no bio–DMARD)	2.15	1.37–3.37	<0.001
MHAQ	0.00	0.00-0.02	<0.001

Anti-CCP, anti-cyclic citrullinated protein antibodies; BMI, body mass index; DMARD, disease-modifying anti-rheumatic drug; MHAQ, Modified Health Assessment Questionnaire; RA, rheumatoid arthritis; SDAI, Simple Disease Activity Index.

Table A3. Odds Ratios for Erosions - anti-CCP with Covariates

Variables	Odds Ratio	95% CI	*P*
Anti-CCP$^+$ (vs. Anti-CCP$^-$)	3.29	2.38–4.55	<0.001
Age per 5-yr increase	1.15	1.08–1.22	<0.001
Female (vs. male)	0.92	0.60–1.41	0.692
White (vs. others)	0.98	0.54–1.76	0.942
BMI per 5-kg/m^2 increase	0.82	0.71–0.94	0.006
RA duration per 5-yr increase	1.43	1.31–1.56	<0.001
No. of comorbidities	1.06	0.92–1.22	0.437
Any bio–DMARD (vs. no bio–DMARD)	2.14	1.54–2.99	<0.001
MHAQ	1.64	1.12-2.41	0.011

Anti-CCP, anti-cyclic citrullinated protein antibodies; BMI, body mass index; RA, rheumatoid arthritis; MHAQ, Modified Health Assessment Questionnaire; RA, rheumatoid arthritis.

Table A4. Odds Ratios for DAS28-CRP < 2.6 - RF with Covariates

Variables	Odds Ratio	95% CI	*P*
RF$^+$ (vs. RF$^-$)	0.72	0.53–0.96	0.027
Age per 5-yr increase	0.99	0.93–1.04	0.641
Female (vs. male)	1.04	0.72–1.52	0.820
White (vs. others)	0.86	0.48–1.53	0.599
BMI per 5-kg/m^2 increase	0.83	0.72–0.95	0.009
RA duration per 5-yr increase	0.90	0.83–0.96	0.003
No. of comorbidities	0.85	0.74–0.97	0.015
Any bio–DMARD (vs. no bio–DMARD)	1.88	1.40–2.54	<0.001
MHAQ	0.17	0.11–0.27	<0.001

Anti-CCP, anti-cyclic citrullinated protein antibodies; BMI, body mass index; DAS28-CRP, Disease Activity in 28 joints C-reactive protein; MHAQ, Modified Health Assessment Questionnaire; RA, rheumatoid arthritis; RF, rheumatoid factor.

Table A5. Odds Ratios for SDAI ≤3.3 - RF with Covariates

Variables	Odds Ratio	95% CI	*P*
RF^+ (vs. RF^-)	0.78	0.50–1.21	0.270
Age per 5-yr increase	1.01	0.93–1.09	0.878
Female (vs. male)	0.99	0.57–1.74	0.986
White (vs. others)	0.64	0.26–1.58	0.338
BMI per 5-kg/m² increase	0.70	0.55–0.90	0.004
RA duration per 5-yr increase	0.76	0.66–0.87	<0.001
No. of comorbidities	0.66	0.49–0.89	0.006
Any bio–DMARD (vs. no bio–DMARD)	1.88	1.20–2.92	0.006
MHAQ	0.01	0.00–0.02	<0.001

Covariates include age, BMI, and RA duration per 5 yr. BMI, body mass index; RA, rheumatoid arthritis; RF, rheumatoid factor; MHAQ, Modified Health Assessment Questionnaire; RA, rheumatoid arthritis; RF, rheumatoid factor; SDAI, Simple Disease Activity Index.

Table A6. Odds Ratios for Erosions - RF with Covariates

Variables	Odds Ratio	95% CI	*P*
RF^+ (vs. RF^-)	2.55	1.85–3.51	<0.001
Age per 5-yr increase	1.14	1.07–1.22	<0.001
Female (vs. male)	0.86	0.57–1.32	0.496
White (vs. others)	0.87	0.48–1.56	0.632
BMI per 5-kg/m² increase	0.80	0.69–0.92	0.002
RA duration per 5-yr increase	1.43	1.31–1.57	<0.001
No. of comorbidities	1.08	0.94–1.25	0.281
Any bio–DMARD (vs. no bio–DMARD)	2.23	1.61–3.10	<0.001
MHAQ	1.51	1.04-2.20	0.031

BMI, body mass index; DMARD, disease-modifying antirheumatic drugs; MHAQ, Modified Health Assessment Questionnaire; RA, rheumatoid arthritis; RF, rheumatoid factor.

Table A7. Odds Ratios for DAS28-CRP < 2.6 - anti-CCP and RF with Covariates

Variables	Odds Ratio	95% CI	*P*
RF^+ (vs. RF^-)	0.98	0.66–1.44	0.899
Anti-CCP^+ (vs. Anti-CCP^-)	0.61	0.41–0.90	0.012
Age per 5-yr increase	0.98	0.93–1.04	0.568
Female (vs. male)	0.99	0.68–1.45	0.972
White (vs. others)	0.78	0.44–1.40	0.408
BMI per 5-kg/m^2 increase	0.84	0.72–0.96	0.013
RA duration per 5-yr increase	0.90	0.84–0.97	0.007
No. of comorbidities	0.86	0.75–0.98	0.023
Any bio–DMARD (vs. no bio–DMARD)	1.96	1.44–2.66	<0.001
MHAQ	0.17	0.11-0.26	<.001

Covariates include age, BMI, and RA duration per 5 years. Anti-CCP, anti-cyclic citrullinated protein antibodies; BMI, body mass index; DAS28-CRP, Disease Activity in 28 joints C-reactive protein; MHAQ, Modified Health Assessment Questionnaire; RA, rheumatoid arthritis; RF, rheumatoid factor.

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Table A8. Odds Ratios for SDAI ≤3.3 - anti-CCP and RF with Covariates

Variables	Odds Ratio	95% CI	*P*
RF^+ (vs. RF^-)	1.45	0.82–2.56	0.205
Anti-CCP^+ (vs. Anti-CCP^-)	0.37	0.21–0.66	<0.001
Age per 5-yr increase	1.01	0.93–1.10	0.814
Female (vs. male)	0.94	0.53–1.66	0.836
White (vs. others)	0.53	0.22–1.32	0.175
BMI per 5-kg/m^2 increase	0.71	0.56–0.92	0.009
RA duration per 5-yr increase	0.78	0.68–0.89	<0.001
No. of comorbidities	0.65	0.48–0.88	0.006
Any bio–DMARD (vs. no bio–DMARD)	2.20	1.39–3.49	<0.001
MHAQ	0.01	0.00–0.02	<0.001

Anti-CCP, anti-cyclic citrullinated protein antibodies; BMI, body mass index; DMARD, disease-modifying anti-rheumatic drug; MHAQ, Modified Health Assessment Questionnaire; RA, rheumatoid arthritis; RF, rheumatoid factor; SDAI, Simple Disease Activity Index.

Table A9. Odds Ratios for Erosions - anti-CCP and RF with Covariates

Variables	Odds Ratio	95% CI	*P*
RF^+ (vs. RF^-)	1.36	0.88–2.08	0.162
Anti-CCP^+ (vs. Anti-CCP^-)	2.72	1.77–4.18	<0.001
Age per 5-yr increase	1.15	1.08–1.23	<0.001
Female (vs. male)	0.92	0.59–1.42	0.696
White (vs. others)	0.97	0.53–1.75	0.908
BMI per 5-kg/m^2 increase	0.80	0.69–0.92	0.002
RA duration per 5-yr increase	1.42	1.30–1.55	<0.001
No. of comorbidities	1.07	0.93–1.24	0.341
Any bio–DMARD (vs. no bio–DMARD)	2.14	1.53–2.99	<0.001
MHAQ	1.61	1.10–2.37	0.015

Anti-CCP, anti-cyclic citrullinated protein antibodies; BMI, body mass index; DMARD, disease-modifying antirheumatic drug; MHAQ, Modified Health Assessment Questionnaire; RA, rheumatoid arthritis; RF, rheumatoid factor; SDAI, Simple Disease Activity Index.

Table A10. Summary of Tables A1–A9 for anti-CCP and RF: Odds Ratios for DAS28-CRP < 2.6, SDAI ≤ 3.3, and Erosions

	Anti-CCP^+ vs. Anti-CCP^-	RF^+ vs. RF^-
	Separate models for Anti-CCP and RF	
DAS28-CRP < 2.6✲	0.61 (0.45–0.83)	0.72 (0.53–0.96)
SDAI ≤ 3.3✲	0.46 (0.30–0.73)	0.78 (0.50–1.21)
Erosion	3.29 (2.38–4.55)	2.55 (1.85–3.51)
	Anti-CCP and RF in one model	
DAS28-CRP < 2.6	0.61 (0.41–0.90)	0.98 (0.66–1.44)
SDAI ≤ 3.3	0.37 (0.21–0.66)	1.45 (0.82–2.56)
Erosion	2.72 (1.77–4.18)	1.36 (0.88–2.08)

DAS28-CRP, Disease Activity Score in 28 joints C-reactive protein; SDAI, Simple Disease Activity Index.

CHAPTER 6

Does Presence of Poor Prognostic Factors in Rheumatoid Arthritis Impact Treatment Choices and Outcomes? Analysis of a US Rheumatoid Arthritis Registry

Evo Alemao[1]*, Heather J. Litman[2], Sean E. Connolly[1], Sheila Kelly[1], Winnie Hua[2], Lisa Rosenblatt[1], Sabrina Rebello[2], Joel M. Kremer[2,3] and Leslie R. Harrold[2,4]

[1]Bristol-Myers Squibb, Princeton, New Jersey, USA;
[2]Corrona, LLC, Southborough, Massachusetts, USA;
[3]Albany Medical College and The Center for Rheumatology, Albany, New York, USA;
[4]University of Massachusetts Medical School, Worcester, Massachusetts, USA.
* PhD student at Erasmus University Rotterdam

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ABSTRACT

Objectives. To characterize patients with rheumatoid arthritis (RA) by number of poor prognostic factors (PPFs: functional limitation, extra-articular disease, seropositivity, erosions) and evaluate treatment acceleration, clinical outcomes, and work status over 12 months by number of PPFs. **Methods.** Using the Corrona RA registry (01/2005–12/2015), biologic-naive patients with diagnosed RA having 12-month (± 3 months) follow-up were identified and categorized by PPFs (0–1, 2, ≥3). Changes in medication, Clinical Disease Activity Index (CDAI), and work status (baseline–12 months) were evaluated using linear and logistic regression models. **Results.** 3458 patients met the selection criteria; 1489 (43.1%), 1214 (35.1%), and 755 (21.8%) had 0–1, 2, or ≥3 PPFs, respectively. At baseline, patients with ≥3 PPFs were older, and had longer RA duration and higher CDAI versus those with 0–1 PPFs. In 0–1, 2, and ≥3 PPF groups, respectively, 20.9%, 23.2%, and 26.5% of patients received ≥1 biologic ($p = 0.011$). Biologic/targeted synthetic disease-modifying anti-rheumatic drug (tsDMARD) use was similar in patients with/without PPFs ($p = 0.57$). After adjusting for baseline CDAI, mean (standard error) change in CDAI was –4.95 (0.24), –4.53 (0.27), and –2.52 (0.34) for 0–1, 2, and ≥3 PPF groups, respectively. More patients were working at baseline but not at 12-month follow-up in 2 (13.9%) and ≥3 (12.5%) versus 0–1 (7.3%) PPF group. **Conclusions.** Despite high disease activity and worse clinical outcomes, number of PPFs did not significantly predict biologic/tsDMARD use. This may warrant reconsideration of the importance of PPFs in treat-to-target approaches.

INTRODUCTION

The rate of disease progression in patients with rheumatoid arthritis (RA) is dependent on several factors and varies between patients [1.2].Factors associated with a poor prognosis in patients with RA, which predict a more rapid and aggressive disease course, include, but are not limited to, functional limitation (evaluated by the Health Assessment Questionnaire [HAQ] - Disability Index or similar validated tools), extra-articular disease (Sjögren's syndrome, RA lung disease, and/or nodules), seropositivity (rheumatoid factor or anti-cyclic citrullinated peptide antibodies), or the presence of radiographic bone erosions [3].

The presence of multiple poor prognostic factors in patients with recent-onset RA has been associated with increased risk of disease progression in both clinical trials and observational studies [4,5]. The European League Against Rheumatism guidelines (2010 and 2013) recommend more aggressive management for patients with RA who have poor prognostic factors [2.6]. This was also true for the American College of Rheumatology (ACR) 2008 guidelines and the 2012 update, in which management was determined by disease duration, disease activity, current medication regimen, and presence of poor prognostic factors [3,7]. However, current (2015) ACR guidelines [1] focus on patient disease activity and a treat-to-target method for all patients regardless of prognosis.

Limited real-world data, based on studies with small patient numbers, exist on the impact of poor prognostic factors on treatment decisions and outcomes in patients with newly diagnosed RA [8,9]. Furthermore, to our knowledge there are no studies evaluating the proportion of patients with poor prognostic factors in patients with longer-standing RA.

This analysis had 2 objectives: to characterize a cohort of patients with RA in a typical practice setting based on the number of poor prognostic factors (defined by the presence of functional limitation, extra-articular disease, seropositivity, and erosive changes) and to evaluate treatment acceleration, clinical outcomes, and work status by number of poor prognostic factors over 12 months in this cohort.

MATERIALS AND METHODS

Patient population

The Corrona RA registry is an ongoing, independent, prospective, national, observational cohort. Patients are recruited from 169 private and academic practice sites across 40 states in the US, with 656 participating rheumatologists. As of June 30, 2016, the Corrona database included information on approximately 43,009 patients with RA. Data on 326,613 patient visits and approximately 145,527 patient-years of followup observation time have been collected. The average length of patient followup is 4.13 years (median 3.33 years).

The registry was set up in accordance with the Declaration of Helsinki. All participating investigators were required to obtain full board approval for conducting non-interventional research involving human subjects with a limited dataset. Sponsor approval and continuing review was obtained through a central Institutional Review Board (IRB; New England Independent Review Board, NEIRB No. 120160610). For academic investigative sites that did not receive a waiver to use the central IRB, full board approval was obtained from the respective governing IRBs and documentation of approval was submitted to Corrona, LLC prior to initiating any study procedures. All registry patients were required to provide written informed consent and authorization prior to participating.

Study population

This analysis included patients diagnosed with RA (excluding early undifferentiated arthritis) by their rheumatologist who were 18 years of age or older, and naive to therapy with biologics and/or targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs; tofacitinib was the only approved tsDMARD at the time of this analysis) at the time of enrollment in the Corrona RA registry between January 1, 2005 and December 1, 2015. Eligible patients had a follow-up visit at 12 months (± 3 months) and Clinical Disease Activity Index (CDAI) measured at baseline (i.e., enrollment) and at the 12-month follow-up. Work status was also assessed at both baseline and the 12-month follow-up. The index date was the date of enrollment.

Measures and data collection

Patients were characterized at baseline in terms of RA prognosis based on the 2008 ACR treatment recommendations [7], including functional limitation (based on modified HAQ disability index > 0.5) [10,11], extra-articular disease (Sjögren's syndrome, RA lung disease, and/or nodules), seropositivity (rheumatoid factor and/or anti-cyclic citrullinated peptide antibodies), and erosions (as per radiograph at enrollment). If patients met none of the 4 criteria, they would be classified as having 0 poor prognostic factors; similarly, if they had met 1, 2, 3, or 4 criteria they would be classified as having 1, 2, 3, or 4 poor prognostic factors. Due to sample size limitations, patients were then categorized into groups having 0–1, 2, or ≥3 poor prognostic factors; each of the 4 categories contributed 1 point. Patients with missing information for any factor were excluded from the analysis.

Study outcomes

Baseline characteristics were evaluated and stratified by poor prognostic factors. To ensure an adequate sample size for statistical analysis, treatment changes over a duration of 12 months (± 3 months) were investigated. The primary outcome was the process measure of initiating a biologic or tsDMARD by poor prognostic factor group, as well as the process measure of any treatment acceleration (addition of, or switching to, a conventional synthetic [cs]DMARD, and/or initiation of a different biologic or tsDMARD) of medication used at enrollment. Use of biologic/tsDMARD treatment was assessed from baseline to the 12-month follow-up visit (± 3 months). Specifically, patients were grouped into "no biologic use" or "use of 1 or more biologic" over the 12-month period (0 or ≥1 categories). Secondary outcomes included change in disease activity at 12 months, assessed by the change from baseline in CDAI in all patients, and achievement of low disease activity (LDA)/remission (CDAI ≤ 10) in patients with moderate or high disease activity at baseline. Other secondary outcomes included a dichotomous variable for work status, constructed with "yes" defined as paid full-time or part-time working, and "no" including those patients who were not working or who worked at home or were students, disabled, or retired. Changes in work status from baseline to the 12-month follow-up were evaluated.

Statistical analysis

Baseline differences between poor prognostic factor groups in treatment acceleration, disease activity, and work status were evaluated via chi-square tests for categorical variables and Wilcoxon rank sum tests for continuous variables due to the skewed nature of the data. Logistic regression models (unadjusted and adjusted for age, sex, duration of RA, and baseline CDAI) evaluated the association of poor prognostic factors with receipt of biologics/tsDMARDs as well as any treatment acceleration. Linear regression models (unadjusted and adjusted for baseline CDAI) evaluated the impact of poor prognostic factors on change in CDAI. Logistic regression models (unadjusted and adjusted for baseline CDAI) evaluated the impact of poor prognostic factor category on LDA/remission in patients with moderate or high disease activity at baseline.

The relationship between poor prognostic factor groups and work status was investigated at baseline and the 12-month followup using chi-square tests. A frequency-matching approach (coarsened exact matching) was used to match patients across poor prognostic factor categories according to age group (18–44, 45–54, 55–64, 65–74, ≥75 years), as the relationship between poor prognostic factor category and work status could be driven by age difference (retirees are generally older). The sample size for each age category was the size of the smallest poor prognostic factor category. To assess whether the relationship between work status at baseline and follow-up differed according to number of poor prognostic factors, the Cochran–Mantel–Haenszel test was performed for all patients.

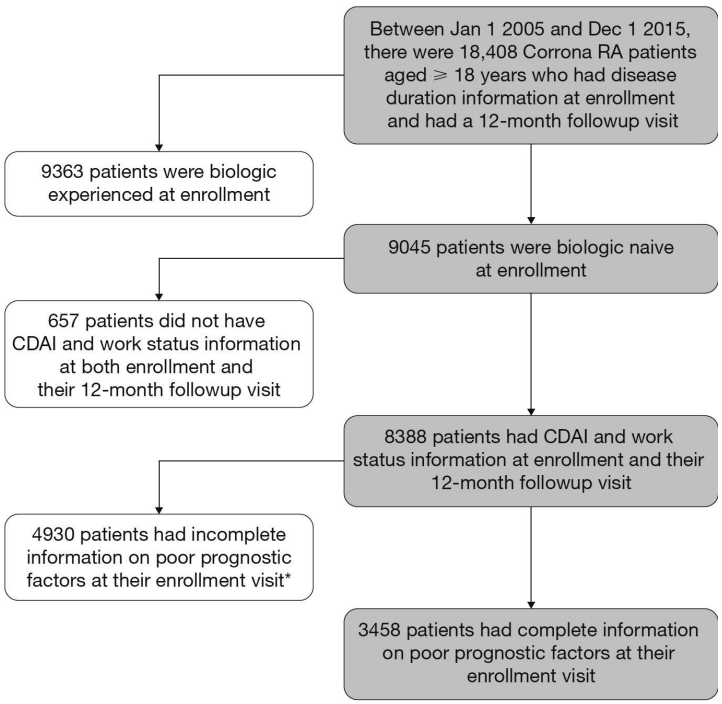
RESULTS

Patient disposition and baseline characteristics

Of the 18,408 patients aged 18 years or older who were enrolled in the Corrona RA registry from January 1, 2005 through December 1, 2015 and had disease duration information at enrollment and a 12-month follow-up visit, 3458 met the selection criteria (Figure 1). Of these, 1489 (43.1%), 1214 (35.1%), and 755 (21.8%) were categorized into prognosis groups of 0–1, 2, or ≥3 poor prognostic factors, respectively.

Baseline demographic data and clinical characteristics indicated that patients with a greater number of poor prognostic factors were older, had a longer duration of RA, and had higher CDAI compared with those with fewer poor prognostic factors

Figure 1. Criteria for study inclusion.



Of note, 4930 patients had incomplete information on poor prognostic factors (PPF) at enrollment. Of these, 3588 patients had no seropositive status information and 1342 patients had incomplete other poor prognostic factors at enrollment. Among the 1342 patients with incomplete PPFs, the majority (1315 of the 1342 patients) had erosive disease information missing, 22 were missing functional limitation and 5 were missing functional limitation and erosive disease. CDAI: Clinical Disease Activity Index; RA: rheumatoid arthritis.

(Table 1). Of note, an additional 4930 patients had incomplete information on poor prognostic factors at enrollment (3588 patients had no seropositive status information and 1342 patients had incomplete other poor prognostic factors at enrollment). These 4930 patients were demographically similar to the group of 3458 patients with poor prognostic factors; 74% of the 3458 with poor prognostic factors were female compared with 75% of those without prognostic information. Mean age (standard deviation [SD]; 59.0 [13.2] versus 60.1 [13.5] years) and baseline disease activity as measured by the CDAI (9.0 [16.9] versus 8.6 [14.8]) were also similar between these two groups. Median (interquartile range) disease duration was slightly shorter in the group with poor prognostic factors: 2 (7) versus 3 (9) years.

Table 1. Baseline demographic data and clinical characteristics.

	0–1 Poor Prognostic Factors (n = 1489)	2 Poor Prognostic Factors (n = 1214)	≥3 Poor Prognostic Factors (n = 755)	p
Demographic data				
Age, yrs, median (IQR)	58 (19)	60 (18)	63 (18)	< 0.001
Sex, female, n (%)	1070 (71.9)	887 (73.1)	600 (79.5)	< 0.001
Race, white, n (%)	1290 (86.8)*	1008 (83.3)†	608 (80.6)‡	0.001
Work status, n (%)				< 0.001
Full-time	706 (47.4)	501 (41.3)	225 (29.8)	
Part-time	126 (8.5)	87 (7.2)	54 (7.2)	
Other				
Working at home	145 (9.7)	117 (9.6)	82 (10.9)	
Student	16 (1.1)	7 (0.6)	1 (0.1)	
Disabled	51 (3.4)	96 (7.9)	111 (14.7)	
Retired	445 (29.9)	406 (33.4)	282 (37.4)	
Medical comorbidities and lifestyle				
Smoking status, n (%)				< 0.001
Never	867 (58.6)§	652 (54.0)‖	377 (50.0)‡	
Former	421 (28.4)§	360 (29.8)‖	230 (30.5)‡	
Current	192 (13.0)§	196 (16.2)‖	147 (19.5)‡	
History of CV disease, n (%)	69 (4.6)	65 (5.4)	61 (8.1)	0.003
History of cancer (excluding NMSC), n (%)	109 (7.3)	108 (8.9)	84 (11.1)	0.010
History of serious infections¶¶), n (%)	44 (3.8%)¶	46 (5.2%)**	26 (5.2%)††	0.21
Poor prognostic factors, n (%)				
Functional limitation	56 (3.8)	331 (27.3)	434 (57.5)	< 0.001
Extra-articular disease	109 (7.3)	570 (47.0)	655 (86.8)	< 0.001
Seropositivity	1003 (67.4)	1108 (91.3)	736 (97.5)	< 0.001
Erosions	63 (4.2)	419 (34.5)	554 (73.4)	< 0.001
Duration of RA, yrs, median (IQR)	1 (4)	2 (7)	4 (11)	< 0.001
RA medications, n (%)				
Current MTX use	1059 (71.1)	916 (75.5)	583 (77.2)	0.003
Current prednisone use	392 (26.3)	359 (29.6)	240 (31.8)	0.018
Prior number of csDMARDs				0.001
0	1263 (84.8)	1027 (84.6)	595 (78.8)	
1	180 (12.1)	156 (12.9)	122 (16.2)	
≥2	46 (3.1)	31 (2.6)	38 (5.0)	

Table 1. (*continued*)

	0–1 Poor Prognostic Factors (n = 1489)	2 Poor Prognostic Factors (n = 1214)	≥3 Poor Prognostic Factors (n = 755)	p
RA disease activity, median (IQR)				
mHAQ	0 (0.25)	0.14 (0.63)	0.63 (0.88)	< 0.001
CDAI	7 (13.0)	9.6 (17.5)	14 (20.5)	< 0.001
Patient pain (0–100)	20 (35)‡‡	26 (43)§§	40 (55)‖‖	< 0.001

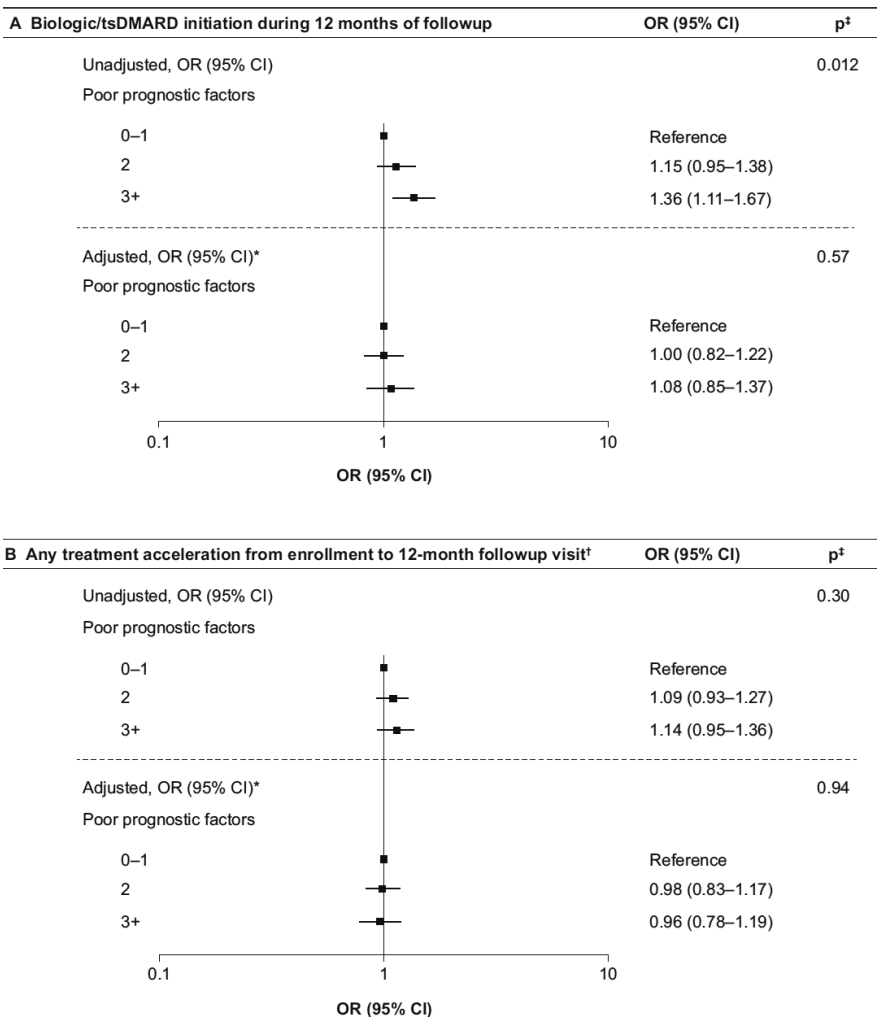
Chi-square tests for categorical variables and Wilcoxon rank sum tests for continuous variables were performed; p values were based on omnibus tests of any difference among the 3 groups. * n = 1486; † n = 1210; ‡ n = 754; § n = 1480; ‖ n = 1208; ¶ n = 1159; ** n = 877; †† n = 502; ‡‡ n = 1484; §§ n = 1209; ‖‖ n = 750. ¶¶ Data on the history of serious infections were limited (collected only from June 2008). CDAI: Clinical Disease Activity Index; csDMARD: conventional synthetic disease-modifying antirheumatic drug; CV: cardiovascular; IQR: interquartile range; mHAQ: modified Health Assessment Questionnaire; MTX: methotrexate; NMSC: nonmelanoma skin cancer; RA: rheumatoid arthritis.

Change in treatment acceleration from baseline to 12-month follow-up by number of poor prognostic factors

The proportion of patients with biologic treatment during the 12-month follow=up period was lowest in the group with 0–1 poor prognostic factors and highest in the group with 3+ poor prognostic factors. In the 0–1, 2, and ≥3 poor prognostic factor groups, respectively, 20.9%, 23.2%, and 26.5% of patients received 1 or more biologic (p = 0.011). In the 0–1, 2, and ≥3 poor prognostic factor groups, respectively, 38.5%, 40.6%, and 41.7% of patients initiated treatment with any DMARD (p = 0.30).

Adjusted analyses controlling for age, sex, duration of RA, and CDAI showed that there was no statistically significant relationship between poor prognostic factor category and the ability to predict biologic/tsDMARD use at the 12-month follow-up (≥3 poor prognostic factors vs 0–1 poor prognostic factors: odds ratio [OR] 1.08; 95% confidence interval [CI] 0.85–1.37; p = 0.57; Figure 2A). The proportion of patients with any treatment acceleration from baseline to the 12-month follow-up was similar between poor prognostic factor groups, with no significant relationship between poor prognostic factor category and treatment acceleration in both unadjusted and adjusted models (Figure 2B).

Figure 2. Logistic regression analysis of (A) biologic/tsDMARD initiation during the 12-month followup according to poor prognostic factor category and (B) any treatment acceleration from baseline to 12-month followup according to poor prognostic factor category (0–1, n = 1489; 2, n = 1214; ≥3, n = 755).

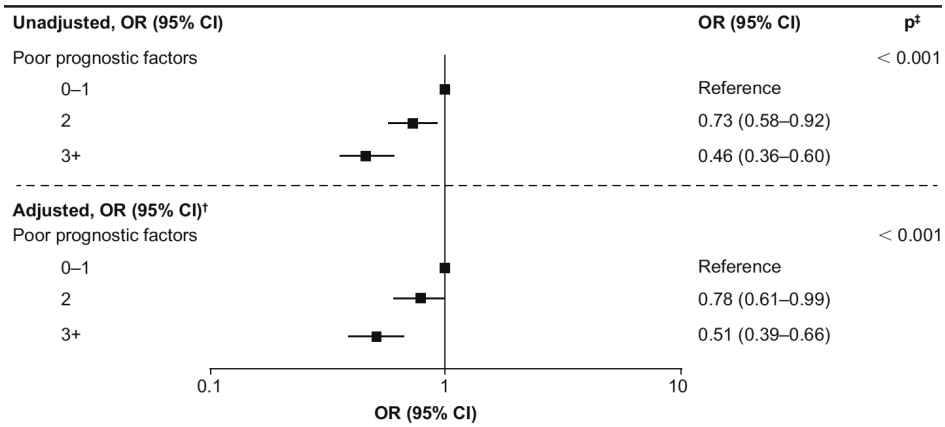


*p value was calculated based on an overall likelihood ratio test of the impact of poor prognosis on biologic use by 12-month followup. †Adjusted for age, sex, duration of RA, and CDAI. ‡Addition of, or switching to, a conventional synthetic DMARD, and/or initiation of a biologic or tsDMARD . CDAI: Clinical Disease Activity Index; CI: confidence interval; OR: odds ratio; RA: rheumatoid arthritis; tsDMARD: targeted synthetic disease-modifying antirheumatic drug.

Change in disease activity from baseline to 12-month follow-up by number of poor prognostic factors

After adjusting for CDAI at baseline, the mean (standard error) change in CDAI from

Figure 3. Logistic regression analysis of achievement of LDA/remission during the 12-month followup by number of poor prognostic factors.*



* Among patients who had moderate and/or severe disease activity at baseline (0–1 poor prognostic factors, n = 547; 2 poor prognostic factors, n = 594; ≥3 poor prognostic factors, n = 470). † p value was calculated based on an overall likelihood ratio test of the impact of poor prognosis on achievement of LDA/remission during the 12-month followup. ‡Adjusted for CDAI at baseline. CDAI: clinical disease activity index; CI: confidence interval; LDA: low disease activity; OR: odds ratio.

baseline to the 12-month follow-up was –4.95 (0.24), –4.53 (0.27), and –2.52 (0.34) for the 0–1, 2, and ≥3 poor prognostic factor groups, respectively ($p < 0.001$). Patients with moderate and/or severe disease activity at baseline (n = 1611) with ≥3 poor prognostic factors were approximately half as likely to reach LDA/remission at the 12-month follow-up as patients with 0–1 poor prognostic factors (OR 0.46; 95% CI 0.36–0.60; $p < 0.001$; Figure 3). After adjusting for CDAI at baseline, results remained similar (OR 0.51; 95% CI 0.39–0.66; $p < 0.001$) as the LDA/remission assessment included only patients with moderate and/or severe disease activity.

Change in work status from baseline to 12-month follow-up by number of poor prognostic factors

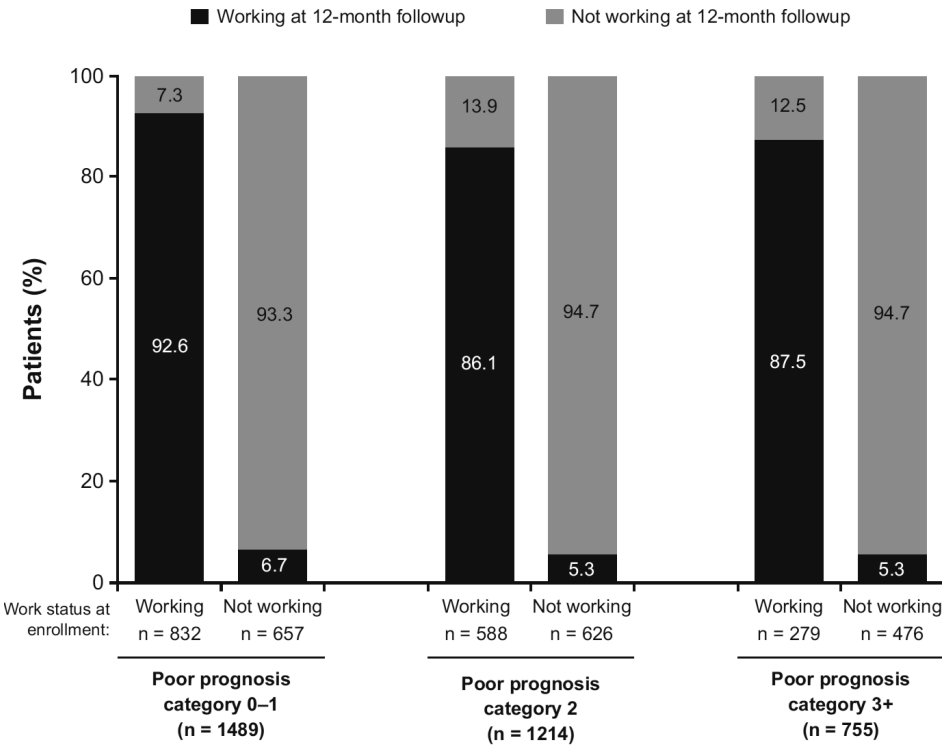
At baseline, 46.6%, 43.7%, and 37.0% of patients with 0–1, 2, and ≥3 poor prognostic factors, respectively, reported working full- or part-time. At the 12-month follow-up, these figures were 44.8%, 40.8%, and 35.6%, respectively. After adjusting for age at baseline, a lower proportion of patients in the worst prognosis category were working full- or part-time compared with those in the best prognosis category ($p < 0.001$ at baseline and $p = 0.001$ at follow-up; Table 2).

Table 2. Work status (full-time/part-time versus all other categories) at baseline and 12-month follow-up by poor prognosis category after adjusting for age.

	Poor Prognostic Factors (N = 2265)			
	0–1 n = 755	2 n = 755	≥3 n = 755	p*
Work status at baseline				
Full-time/part-time, n (%)	352 (46.6)	330 (43.7)	279 (37.0)	< 0.001
All others, n (%)†	403 (53.4)	425 (56.3)	476 (63.0)	
Work status at 12-month followup				
Full-time/part-time, n (%)	338 (44.8)	308 (40.8)	269 (35.6)	0.001
All others, n (%)†	417 (55.2)	447 (59.2)	486 (64.4)	

* p value was calculated based on chi-square tests of the relationship between work status and poor prognosis category. † All others include those reporting working at home and those who were reported as students, disabled, or retired.

Figure 4. Work status (full-time/part-time versus all other categories) at baseline and 12-month followup by poor prognosis category (N = 3458).



The proportion of patients whose work status changed over time (baseline to 12-month follow-up) differed according to the number of poor prognostic factors (Cochran–Mantel–Haenszel test; $p < 0.001$). The proportion of patients working both at baseline and at the 12-month follow-up visit was highest (92.6%) in those with 0–1 poor prognostic factors compared with the 2 and ≥3 groups (86.1% and 87.5%, respectively; Figure 4). In the less favorable poor prognostic factor groups (2 and ≥3), higher proportions of patients were working at baseline but not at the 12-month follow-up (13.9% and 12.5%) compared with those in the best prognosis group (7.3%; Figure 4).

DISCUSSION

In this population of adult patients with RA, who were biologic- and tsDMARD-naive at enrollment into the Corrona registry, the number of poor prognostic factors did not influence treatment decisions. However, a greater number of poor prognostic factors was associated with worse clinical outcomes, as well as ability to work, at 12 months. In adjusted analyses, the changes in both CDAI and LDA/remission from baseline to the 12-month follow-up were significantly lower in patients with a greater number of poor prognostic factors compared with those with 0–1 poor prognostic factors. In addition, the proportion of patients with RA in full- or part-time employment was directly associated with the number of poor prognostic factors.

This was the largest real-world study to date to evaluate poor prognostic factors in patients with RA. These results highlight the burden of poor prognostic factors in patients with RA and the importance of evaluating these factors even in an established disease, which is common practice in other therapeutic areas such as cardiovascular disease. Our results suggest that, despite the worse outcomes in patients with a greater number of poor prognostic factors, the presence of these factors did not significantly predict treatment accelerations in terms of the initiation of biologics or the addition/switching of therapies.

While the underlying mechanisms that result in patients with poor prognostic factors having worse clinical outcomes are unknown, they warrant further investigation. In the meantime, providers may wish to reconsider how they approach treatment decisions for patients with poor prognostic factors (e.g., it may be appropriate to follow these patients more closely than patients without poor prognostic factors). Current treatment guidelines recommend treating patients to achieve a specific target, such as remission or LD [1,2,6], and, consistent with this treat-to-target approach, physicians should routinely assess disease activity and adjust therapy until the specific target is

achieved. As our results indicate, attainment of LDA was inversely associated with the number of prognostic factors. It may be beneficial to consider the use of prognostic factors to guide treatment decisions. Furthermore, providers should engage patients in conversations about poor prognostic factors and how they may wish to tailor their RA care based on this information.

A strength of this study is that Corrona is the largest national US registry in RA that contains both patient- and provider-reported measures and represents a typical practice setting in the US. This was a real-world cohort of patients with varying durations of RA; hence, findings are more generalizable compared with controlled studies. However, given the observational nature of the design, there may be unmeasured confounding. In addition, operationalization of some of the outcome variables, such as work status, might underestimate the full productivity of patients with RA, as this study focused on full- or part-time paid work only and classified patients working at home and students as "not working". Corrona is a US registry, and it is possible that the results may differ in other countries [12]. Additionally, this study focused on only a subset of poor prognostic factors, since this is not a widely accepted consensus definition [13]. Significant differences were observed among patients based on number of poor prognostic factors with respect to several parameters, including age, sex, race, work status, smoking status, disease duration, prior number of csDMARDs, and disease activity, which deserve further study. Furthermore, the study included only patients with a follow-up visit at 12 months, and additional analyses will be required to understand the impact of poor prognostic factors on long-term treatment outcomes. Finally, this study excluded 4930 patients due to a lack of documented data related to poor prognostic factors; however, these patients were similar to the population with poor prognostic factors included in the analyses with respect to sex, age, median disease duration, and mean baseline disease activity.

In conclusion, adjusted analyses showed that a greater number of poor prognostic factors was not associated with a greater likelihood of biologic/tsDMARD initiation or any treatment acceleration (biologic, tsDMARD, or csDMARD). These findings suggest that the presence of poor prognostic factors does not notably influence clinicians' treatment decisions. This strategy warrants reconsideration as patients with a greater number of poor prognostic factors had worse outcomes (including reduction in CDAI and achievement of LDA/remission) and were less likely to be in full-/part-time work compared with those with fewer poor prognostic factors in adjusted analyses. As the definition of a treat-to-target approach in RA evolves, providers may wish to consider incorporating the number of poor prognostic factors into their conversations with patients regarding their treatment plan.

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CHAPTER 7

Cardiovascular Risk Factor Management in Patients with Rheumatoid Arthritis compared to Matched Non-Rheumatoid Arthritis Patients

Evo Alemao[1]*, Helene Cawston[2], Francois Bourhis[2], Maiwenn Al[3], Maureen P.M.H. Rutten-van Mölken[3], Katherine P. Liao[4] and Daniel H. Solomon[4]

[1]Worldwide Health Economics and Outcomes Research, Bristol-Myers Squibb, Princeton, NJ, USA;
[2]Real World Strategy & Analytics, MAPI, Nanterre, France;
[3]Institute of Medical Technology Assessment, Erasmus University Rotterdam, Rotterdam, The Netherlands;
[4]Institute of Health Policy and Management, Erasmus University Rotterdam, Rotterdam, The Netherlands;
[5]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, USA.
* PhD student at Erasmus University Rotterdam, supervised by M.P.M.H.R.M. and M.J.A.

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ABSTRACT

Objective. RA is associated with a 50-60% increase in risk of cardiovascular (CV) death. This study aimed to compare management of CV risk factors in RA and matched non-RA patients. **Methods.** A retrospective cohort study was conducted using UK clinical practice data. Patients presenting with an incident RA diagnosis were matched 1:4 to non-RA patients based on a propensity score for RA, entry year, CV risk category and treatment received at index date (date of RA diagnosis). Patients tested and treated for CV risk factors as well as those attaining CV risk factor management goals were evaluated in both groups. **Results.** Between 1987 and 2010, 24,859 RA patients were identified and matched to 87,304 non-RA patients. At index date, groups had similar baseline characteristics. Annual blood pressure, lipids and diabetes-related testing were similar in both groups, although CRP and ESR were higher in RA patients at diagnosis and decreased over time. RA patients prescribed antihypertensives increased from 38.2% at diagnosis to 45.7% at 5 years, from 14.0 to 20.6% for lipid-lowering treatments and from 5.1 to 6.4% for antidiabetics. Similar treatment percentages were observed in non-RA patients, although slightly lower for antihypertensives. Modest (2%) but significantly lower attainment of lipid and diabetes goals at 1 year was observed in RA patients. **Conclusion.** There were no differences between groups in the frequency of testing and treatment of CV risk factors. Higher CV risk in RA patients seems unlikely to be driven by differences in traditional CV risk factor management.

INTRODUCTION

RA is associated with increased morbidity and mortality. Meta-analyses of published literature have shown that RA is associated with a 50-60% increase in risk of CV death *vs* the general population [1-3]. Despite improvements in RA therapies, it appears that the mortality gap between RA patients and the general population persists, and may even be increasing [2]. Cardiovascular (CV) complications are the primary cause for this increase in mortality and also contribute to increased risk for CV events in RA patients compared with the non-RA population [4, 5].

The pathogenic mechanisms underlying increased CV risk in RA have yet to be elucidated. There is emerging evidence to suggest that traditional CV risk factors do not fully account for the increased likelihood of CV complications in RA, and the immune dysregulation, chronic high-grade inflammation and metabolic disturbances found in RA, along with RA disease activity and treatments such as corticosteroids, contribute to CV risk in RA patients [6-9]. Investigators have found that several treatment regimens for RA reduce the risk of CV events [10]. Long-term use of DMARDs may modify atherosclerosis via beneficial effects on endothelial function as well as inflammatory markers [11]. With regard to biologic DMARDs (bio-DMARDs), a meta-analysis reported that therapy with TNF-a inhibitors was associated with a reduced risk of all CV events, myocardial infarction and stroke in cohort studies [12]. A meta-analysis of randomized controlled trials also produced a point estimate indicating a lower risk of CV events with TNF-a inhibitor therapies, but this was not statistically significant [13].

Although the literature on CV risk in RA patients is extensive, there are a few limitations. The current literature does not fully address how the traditional CV risk factors of hypertension, lipids, weight and haemoglobin A1c (HbA1c) are managed in RA patients in comparison to the general population. Thus, the literature fails to inform whether the increased risk of CV events observed in RA patients could partly be due to worse CV risk management. Some studies indicate a lack of screening for CV risk factors by the rheumatologist (*vs* primary care providers) in RA patients and relatively low statin use among RA patients [14, 15]. However, these studies did not have a comparator non-RA group.

Although traditional CV risk factors may not fully explain the excess CV risk in RA patients, it is important to understand how these are managed in RA patients, especially with the introduction of agents such as Janus kinase inhibitors and anti-IL6 in the management of RA. These newer therapies are associated with changes in lipid levels, including increases in both low-density lipoprotein (LDL) and high-density lipoprotein

(HDL) [16]. The objective of this analysis was to describe the management of traditional CV risk factors, such as lipids, blood pressure and HbA1c, in RA patients in clinical practice settings and compare this management with that of matched non-RA patients.

METHODS

Study population and design

This was a retrospective cohort analysis based on the UK clinical practice database from 1987 to 2011. The database was obtained from the Clinical Practice Research Datalink (CPRD), which contains information on resources managed by general practitioners. It is one of the largest computerized databases of anonymized longitudinal medical records from primary care. The current CPRD data set includes information on around 5 million currently active patients of research standard quality from about 590 primary care practices in the UK, representing "'8% of the UK population. The CPRD population is representative of the general UK population. Selected laboratory data are available for a subset of patients. These mainly concern CV and diabetes-related laboratory data. The CPRD has been granted multiple research ethics committee approval (05/MRE04/87) to undertake purely observational studies, with external data linkages including Hospital Episode Statistics (HES) and Office for National Statistics (ONS) mortality data. The work of CPRD is also covered by National Information Governance Board (NIGB)-Ethics and Confidentiality Committee (ECC) approval ECC 5-05 (a) 2012. This study was approved by the Independent Scientific Advisory Committee for Medicines and Healthcare products Regulatory (MHRA) database research (ISAC) under protocol number 12_079Ra.

The study population included all adult patients (age ≥18 years) recorded in the CPRD database with records of sufficient quality, identified through the acceptable patient flag. The RA population was defined as all patients presenting at least one RA read code after 1 January 1988 (index code), with no RA or juvenile RA codes before the index code. The read codes for RA were those that were included in group 1 or 2 of Thomas *et al.* [17], and the list of codes was also validated by clinical experts. The index date was defined as the date of the first RA-related clinical or referral record, that is, index code. Patients were required to have at least 12 months of follow-up before the index date.

In the CPRD database, medical diagnoses and events were identified through read codes, and medcodes were used for treatments. Lists of codes were constructed to

define covariates and CV risk factors, based upon most recent values within 2 years preceding the index date. In order to create the code list for each condition, published lists of codes were used and supplemented by additional searches of the medical and product browsers. The list was then screened by an analyst in order to exclude all non-relevant codes and then a second screening was conducted by a person with medical qualification with expertise in read codes. Laboratory values were identified and calculated at the index date for baseline and updated for each subsequent year after the index date considering the most recent value, within 2 years of the date of interest. The CV risk as defined by the National Cholesterol Education Program (NCEP, 2002) is composed of four categories of low, medium, high and secondary prevention, by summing the following risk factors: dyslipidaemia (LDL ≥4 mmol/l or HDL ≤1 mmol/l), hypertension (>140/90 mmHg), age (>45 years for males and >55 years for females) and current smoker [18]. If patients had none of the risk factors they were considered low risk, one risk factor was medium risk and more than one risk factor was high risk. Patients with diabetes, heart disease, a history of a CV event or a history of a CV procedure were considered the target group for secondary prevention.

Matched non-RA cohort

RA patients were matched 1:4 to non-RA patients based on their year of entry in the CPRD database, CV risk category (NCEP classification), treatment status at index date and a propensity score estimating the probability of having RA [18]. The propensity score probability was based on a logistic regression model that included gender, smoking, obesity, Charlson Co-morbidity Index and family history of RA as covariates. Each RA patient was categorized into low, medium or high CV risk at the index date. CV risk categories and treatment status for CV risk were calculated for all non-RA patients every 6 months. Non-RA patients were selected as potential matches based on the CV risk category and treatment status of the closest cut-off to the case's index date. Potential matches were also required to have entered the CPRD database during the same year as the case and to have an activity in the database within 2 months of the case's index date. Based on the pool of potential matches, each RA patient was matched to a non-RA patient using the nearest neighbour match method of its RA risk score, and consequently removed from the pool of potential non-RA matches. This matching based on a risk score was performed in order to select patients with similar characteristics with the exception of RA diagnosis, thereby reducing bias due to confounding variables. An index date was assigned to the non-RA patient based on the closest observation date to the RA patient's index date, and the match was confirmed based on the recalculated non-RA patient's CV risk category at the assigned index

date. The process was repeated to match a maximum of four controls to each case. Standardized differences were used to compare the measured baseline characteristics between the RA and the non-RA populations. A standardized difference of <0.1 will be considered indicative of good balance [17].

Outcomes

Management of traditional CV risk factors was evaluated in terms of the percentage of patients evaluated for CV risk factors, the percentage of patients receiving treatment with lipid-lowering therapies, antihypertensive therapies and antidiabetic therapies at index and up to 5 years after the index date. In addition, we evaluated the percentage of patients attaining blood pressure, lipids and HbA1c goals annually up to 5 years post index date. The goals were based on UK clinical guidelines; for blood pressure the goal was <140/90 mmHg, for dyslipidaemia the goal was either an LDL cholesterol of <2 mmol/l or total cholesterol of <4 mmol/l, and for diabetes the goal was HbA1c <7.5%.

Statistical analyses

Baseline characteristics between RA and matched non-RA patients were compared using standard statistical tests and standardized differences. Statistical analysis involved comparing between RA and matched non-RA patients the percentage of patients evaluated for CV risk factors, treated for CV risk factors and attaining CV risk factor management goals at baseline and at 5 years post baseline. Evaluation of CV risks was based on comparing the mean number of CV risk factor lab values (such as HDL-C, LDL-C, Total Cholesterol, Triglyceride, Diastolic BP, Systolic BP, CRP, ESR, HbA1c, Fast Glucose) during each year between the RA cohort and the matched non-RA cohort. The proportion of patients attaining blood pressure, lipid and HbA1c goals at yearly intervals up to 5 years was compared between RA and matched non-RA patients using χ^2 statistics. The analysis of attainment of goals for blood pressure, lipids and HbA1c was based on a last observation carried forward approach. No additional adjustments besides imputation for missing values on laboratory tests using last observation carried forward were made because the matching was successful. The analysis was carried out using the statistical software SAS 9.2. Graphs were plotted using Excel 2007. An α level of 0.05 was used for determination of statistical significance.

RESULTS

Between 1987 and 2010, there were 24,859 patients with RA who were identified in the CPRD data set with a mean (S.D.) follow-up of 5.8 (4.4) years, representing 144,342 patient-years. Each RA patient was matched to four non-RA patients (n = 87,304) with a mean (S.D.) follow-up of 5.7 (4.4) years. At the time of RA diagnosis, the mean (S.D.) age for the RA cohort was 60.0 (15.1) years, and 69.2% were females. In terms of CV risk stratification, 20% of RA patients were categorized as secondary prevention; 30% of the primary prevention patients were high risk, 31% were medium risk and 19% low risk. The RA and non-RA patients received similar baseline therapies to treat hypertension, diabetes or dyslipidaemia (41.8 *vs* 40.7%). Overall, the RA and the non-RA cohort were well matched on the baseline age and baseline CV risks. Despite statistically significant differences, the effect size is very marginal as confirmed by standardized differences close to 0. The incremental difference in Charlson Co-morbidity Index

Table 1. Baseline Characteristics summary

Characteristics	RA patients (N=24,859)	Non-RA patients (N=87,304)	p-value	d
Number of patient-years, sum	144,342	494,938		
Follow-up (years), mean (SD)	5.8 (4.4)	5.7 (4.4)	<.0001	0.023
Age[a] (years), mean (SD)	60.0 (15.1)	60.2 (15.9)	0.071	-0.013
Charlson comorbidity index[a], mean (SD)	1.4 (0.9)	0.3 (0.9)	<.0001	1.222
Females, n (%)	17,202 (69.2)	57,939 (66.4)	<.0001	0.060
Obesity[b], n (%)	2,880 (11.6)	9,530 (10.9)	0.003	0.022
Current smoker[b], n (%)	6,977 (28.1)	24,122 (27.6)	0.175	0.011
Hypertension[c], n (%)	9,798 (39.4)	33,382 (38.2)	0.001	0.025
Dyslipidemia[c], n (%)	6,761 (27.2)	24,202 (27.7)	0.103	-0.011
Diabetes[c], n (%)	1,742 (7.0)	7,012 (8.0)	<.0001	-0.038
Treatment status, n (%)	10,393 (41.8)	35,530 (40.7)	0.027	0.022
Cardiovascular risk category (NCEP algorithm)			<.0001	0.000
Low	4,788 (19.3)	18,169 (20.8)		
Medium	7,683 (30.9)	24,650 (28.2)		
High	7,461 (30.0)	25,322 (29.0)		
Secondary prevention	4,927 (19.8)	19,163 (21.9)		

d: standardized difference; NCEP: National Cholesterol Education Program; SD: standard deviation

Notes:

[a]Age and Charlson comorbidity index evaluated at time of index date;

[b]Obesity, current smoker: based on read codes of the 2 years preceding index date;

[c]Hypertension, dyslipidemia and diabetes based on diagnoses read codes, prescriptions and tests of the 2 years preceding index date

Table 2. Summary of Laboratory Tests Over Time Since Index Date, in RA and Non-RA Patients

Blood test	At index date		1 year after index		3 years after index		5 years after index	
	n (%)	mean (SD)	n (%)	mean (SD)	n (%)	mean (SD)	n (%)	mean (SD)
RA patients (N=24,859)								
HDL-C, mmoL/L	5,709 (23.0%)	1.4 (0.5)	5,378 (21.6%)	1.4 (0.5)	4,474 (18.0%)	1.5 (0.5)	3,688 (14.8%)	1.5 (0.5)
LDL-C, mmoL/L	4,621 (18.6%)	3.0 (1.0)	4,386 (17.6%)	3.0 (1.0)	3,597 (14.5%)	3.0 (1.0)	3,030 (12.2%)	2.9 (1.0)
Total cholesterol, mmoL/L	8,018 (32.3%)	5.2 (1.2)	7,485 (30.1%)	5.2 (1.2)	6,025 (24.2%)	5.1 (1.1)	4,815 (19.4%)	5.1 (1.1)
Triglyceride level, mmoL/L	5,847 (23.5%)	1.6 (1.0)	5,458 (22.0%)	1.6 (1.0)	4,437 (17.8%)	1.6 (1.0)	3,661 (14.7%)	1.6 (0.9)
Diastolic BP, mmHg	17,779 (71.5%)	79.0 (10.1)	16,021 (64.4%)	79.0 (10.0)	12,173 (49.0%)	79.0 (10.0)	9,157 (36.8%)	78.5 (10.0)
Systolic BP, mmHg	17,779 (71.5%)	136.2 (19.2)	16,021 (64.4%)	136.5 (18.9)	12,173 (49.0%)	136.5 (18.9)	9,157 (36.8%)	136.3 (18.1)
CRP, mg/L	8,434 (33.9%)	24.6 (34.9)	8,607 (34.6%)	18.8 (29.8)	4,967 (20%)	18.8 (29.8)	3,647 (14.7%)	14.8 (25.9)
ESR, mm/hr	11,694 (47.0%)	31.9 (26.0)	11,440 (46.0%)	27.0 (23.5)	6,912 (27.8%)	27.0 (23.5)	5,165 (20.8%)	23.9 (20.9)
HbA1c, %	1,448 (5.8%)	7.1 (1.5)	1,475 (5.9%)	6.9 (1.5)	1,222 (4.9%)	6.9 (1.5)	1,009 (4.1%)	7.0 (1.6)
FG, mmol/L	1,645 (6.6%)	5.5 (1.5)	1,515 (6.1%)	5.5 (1.7)	1,215 (4.9%)	5.5 (1.7)	1,029 (4.1%)	5.4 (1.4)

between RA and non-RA patients (1.1) can be explained by the Charlson Co-morbidity Index calculation itself, because RA activity is counted as a co-morbidity (Table 1).

The reporting of laboratory tests was similar in both groups overall, although CRP and ESR were reported more often in RA *vs* non-RA patients (33.9 *vs* 5.8% and 47.0 *vs* 12.2%, respectively, at index date). Overall, mean blood pressure, lipid and diabetes-related laboratory test results were stable and similar in the RA and non-RA cohorts over time since diagnosis, although CRP and ESR were higher in RA patients at diagnosis, decreasing over time [average (S.D.) from 24.6 mg/l (34.9) at index date to 14.8 mg/l (25.9) at 5 years for CRP, and from 31.9 mm/h (26.0) to 23.9 mm/h (20.9) for ESR; Table 2].

The percentage of RA patients who were prescribed treatments for hypertension, lipid-lowering therapies and diabetes at RA diagnosis was 38.2, 14.0 and 5.1%, respectively, and these values were comparable to those in the non-RA cohort (37.4, 14.8 and

Table 2. (*continued*)

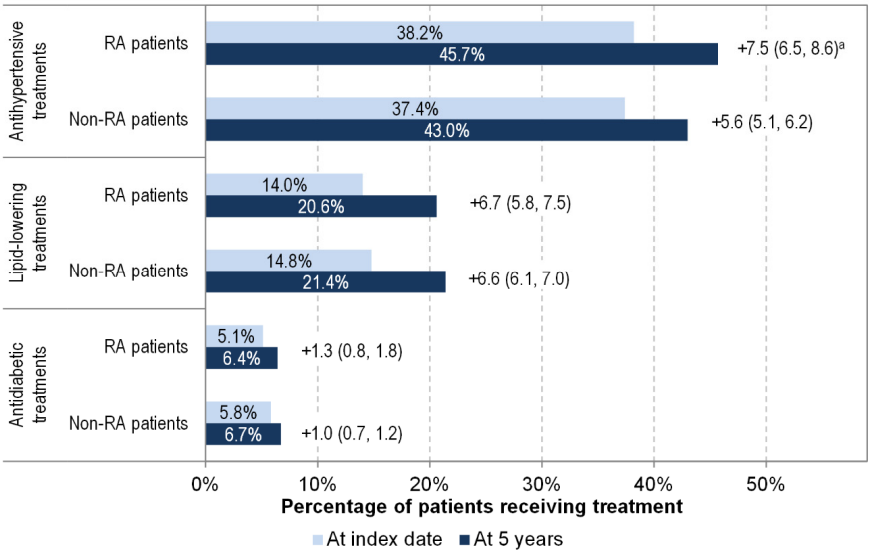
Blood test	At index date		1 year after index		3 years after index		5 years after index	
	n (%)	mean (SD)	n (%)	mean (SD)	n (%)	mean (SD)	n (%)	mean (SD)
Non-RA patients (N=87,304)								
HDL-C, mmoL/L	19,754 (22.6%)	1.4 (0.5)	18,791 (21.5%)	1.4 (0.5)	16,092 (18.4%)	1.5 (0.5)	13,113 (15.0%)	1.5 (0.5)
LDL-C, mmoL/L	16,340 (18.7%)	3.0 (1.0)	15,558 (17.8%)	3.0 (1.0)	13,282 (15.2%)	2.9 (1.1)	10,953 (12.5%)	2.9 (1.0)
Total cholesterol, mmoL/L	27,177 (31.1%)	5.2 (1.2)	25,524 (29.2%)	5.2 (1.2)	21,041 (24.1%)	5.1 (1.2)	16,786 (19.2%)	5.1 (1.2)
Triglyceride level, mmoL/L	20,462 (23.4%)	1.6 (1.0)	19,361 (22.2%)	1.6 (1.0)	16,251 (18.6%)	1.6 (0.9)	13,123 (15%)	1.6 (0.9)
Diastolic BP, mmHg	60,889 (69.7%)	79.3 (10.7)	54,339 (62.2%)	78.9 (10.1)	40,515 (46.4%)	78.9 (10.1)	30,049 (34.4%)	78.5 (9.7)
Systolic BP, mmHg	60,889 (69.7%)	136.4 (19.6)	54,339 (62.2%)	136.4 (58.9)	40,515 (46.4%)	136.4 (58.9)	30,049 (34.4%)	136.4 (17.7)
CRP, mg/L	5,095 (5.8%)	10.6 (24.6)	4,915 (5.6%)	10.8 (25.7)	4,229 (4.8%)	10.8 (25.7)	3,482 (4%)	10.7 (25.9)
ESR, mm/hr	10,630 (12.2%)	17.2 (19.1)	9,986 (11.4%)	16.8 (17.2)	7,876 (9.0%)	16.8 (17.2)	6,382 (7.3%)	17.2 (17.0)
HbA1c, %	5,365 (6.1%)	7.2 (1.5)	5,116 (5.9%)	7.2 (1.6)	4,264 (4.9%)	7.2 (1.5)	3,479 (4.0%)	7.1 (1.5)
FG, mmol/L	5,730 (6.6%)	5.7 (1.8)	5,529 (6.3%)	5.7 (1.7)	4,751 (5.4%)	5.7 (1.6)	3,967 (4.5%)	5.6 (1.6)

BP: blood pressure; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; FG: fast blood glucose; HbA1c: hemoglobin A1c; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; SD: standard deviation

5.8%). When comparing these treatment percentages between baseline and 5 years, there was a general trend towards an increased proportion of patients being managed for CV risk factors in RA and non-RA patients at 5 years (Fig. 1). The trend was slightly higher in RA patients (+7.5%, 95% CI 6.5, 8.6) than in non-RA patients (+5.6%, 95% CI 5.1, 6.2) for antihypertensive use. There was no difference in the proportion of RA patients treated for CV risk factors compared with matched non-RA patients treated for CV risk factors over the 5 year analysis based on the comparison of CIs (Fig. 1).

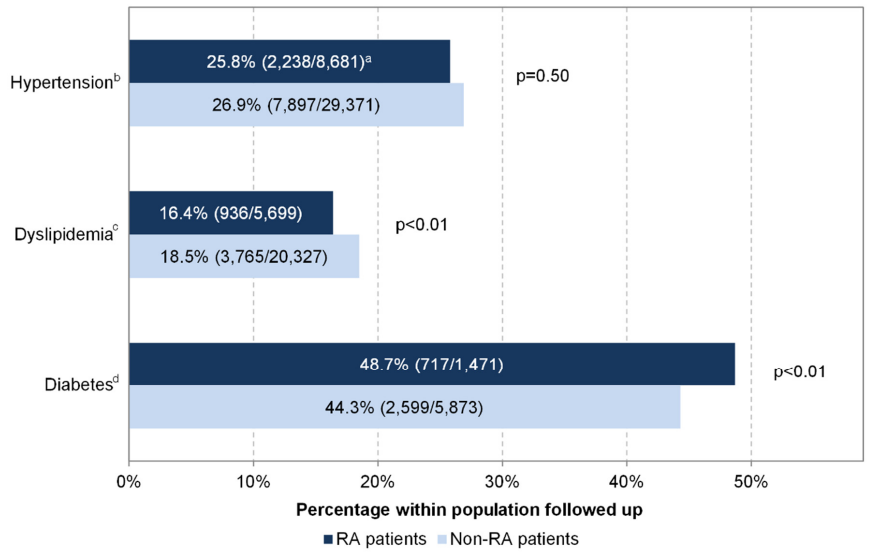
Within patients with the same risk factors at the index date, there was no difference between RA and non-RA patients reaching goals for hypertension at 1 year (Fig. 2; $P = 0.50$) although small but significant differences were found for dyslipidaemia and diabetes (16.4 *vs* 18.5%, $P < 0.01$ for lipid goals in RA and non-RA patients, respectively, and 48.7 *vs* 44.3%, $P < 0.01$ for HbA1c goals).

Figure 1. Summary of treatments prescribed at Index date



Notes:
All data are percentages
[a]Change in percentage of patients receiving treatment (95% confidence interval)

Figure 2. Summary of patients reaching blood pressure, lipids and A1c goals at 1 year post index date



Notes:
[a]Percentage (Number of patients reaching target level/number of patients followed up)
[b]Hypertension target levels: blood pressure <140/90 mm/Hg;
[c]Dyslipidemia target levels: low-density lipoprotein cholesterol < 2 mmol/L or total cholesterol < 4 mmol/L;
[d]Diabetes target levels: hemoglobin A1c <7.5%

DISCUSSION

This study is the first to describe the management of CV risk factors of RA patients in a UK clinical practice setting and compare it with matched non-RA patients. Given that the risk of a CV event is dependent on multiple factors, its management is dictated by the evaluation of these risk factors and the determination of overall CV risk. Thus, it is important to control for the baseline CV risk when evaluating the management of CV risk factors. To our knowledge, this is the only study to have matched RA patients to non-RA patients on baseline CV risks when evaluating the management of CV risks factors in RA patients. Given the large number of patients included in the study and the average follow-up of >5 years, we believe that the study population and its management of CV risk factors is representative of general RA patients seen in a clinical practice setting.

No meaningful differences were found between RA and non-RA patients in terms of the frequency of CV risk factor evaluation and treatments at baseline. However, there were more patients managed for hypertension in the RA-cohort *vs* the non-RA cohort at 5 years, and there was a modest difference of 2% fewer patients in the RA cohort reaching lipid goals. The evidence for hypertension being more prevalent in RA patients is mixed, because reports are contradictory and dependent on the definition of hypertension used in the analysis [19]. However, results from a recent study indicate a significantly increased prevalence of hypertension in RA patients *vs* controls and would support our findings [20]. Our study also found that RA patients experienced a modest absolute 2% lower achievement in lipid goals. Studies of lipid levels in RA are inconclusive and seem to be influenced by the duration of RA and treatment for RA. Studies conducted prior to RA diagnosis seem to indicate that RA patients have low HDL *vs* matched controls [21]. However, other studies have shown that RA patients have lower LDL and total cholesterol levels and, in spite of these lower levels, there is a paradoxical increase in CV risk [22, 23]. Our study was not designed to compare the lipid levels between RA and non-RA patients. Given that we matched patients on baseline CV risk factors, we could not observe a difference in baseline lipid levels in our cohort. However, in spite of the similarity in testing and treatment for lipid lowering between RA and non-RA patients, we found that attainment of lipid goals was modestly lower in RA patients. Further studies would need to be conducted to confirm our observation and its relevance. Studying the patterns of lipid management in RA patients is important because new therapies introduced to manage RA have been associated with increasing lipid levels [17].

Some of our findings are contrary to those reported in the literature on management of CV risk factors in RA patients. A recent study concluded that RA patients were less

likely to be diagnosed with hypertension than patients without RA [24]. Another study found that one-third of eligible patients lacked appropriate lipid testing despite the presence of traditional CV risk factors [25], whereas others concluded that the health-care quality in RA appears to be suboptimal for co-morbid disease [26]. We postulate that the difference between our findings and those from other studies can be explained partly by the difference in methodology and the settings of the studies. Firstly, as stated previously, we controlled for baseline CV risk in our study via matching, which was not done in the other studies. Secondly, our study was conducted in the general practice setting *vs* rheumatologist setting, because there is evidence to support that rheumatologists identify and manage CV risk factors significantly less frequently in RA patients when compared with primary care providers [26]. Thirdly, it is the only study based on data from the UK, whereas the other studies were based on US data.

Our general finding that there is no substantial difference in the evaluation, treatment and attainment of CV risk factor goals indicates that the higher incidence of CV events among RA patients observed in our data (CV event incidence rate in our data set of 4.29, 95% CI 4.15, 4.44 in RA patients *vs* 3.11, 95% CI 3.04, 3.17 in non-RA patients per 100 patient-years; 8.97% of RA patients and 6.97% of non-RA primary prevention patients had a CV event over a 5 year follow-up) may not be driven by poor management of traditional CV risk factors alone. This finding indirectly supports the literature indicating that there might be other factors contributing to increased CV events in RA patients. Although traditional risk factors are known to play an important role in the general population, their relative contributions to CV risk in RA is less clear [19]. Moreover, there is evidence that the increased CV risk in RA patients might not be explained by traditional risk factors alone [27]. The mechanisms underlying increased CV events in RA have yet to be elucidated fully. However, there is emerging evidence to suggest that the immune dysregulation, chronic high-grade inflammation and metabolic disturbances found in RA patients could contribute to the increased CV events in RA patients [6-9]. The increase in CV risk in RA patients is acknowledge by the consensus guidelines for the management of RA, which recommend the evaluation for CV risk at baseline using a traditional CV risk algorithm, such as Framingham Heart Study-based algorithm or the MONIC Study-based SCORE algorithm. The Dutch guidelines recommend the application of CV risk management (CVRM) in RA patients, because RA is considered as an independent risk factor for CV disease. A recent study showed that CVRM guidelines performed poorly in RA patients, with an overall increase in 10 year CV risk despite implementation of CVRM [28]. Given that these algorithms were not developed in the RA-specific population, and to account for the increased CV risk in RA patients *vs* the general population, the EULAR guidelines recommend that the risk calculated, using these algorithms, should be multiplied by a factor of 1.5.

There were several limitations to our analysis. Our study was retrospective, implying the potential presence of some sources of bias due to confounding factors. However, this was partly accounted for by propensity score matching of patients on both their RA and CV risk profiles. Only data from a general practice setting were available, and no data from rheumatologists were available. This could impact the identification of RA patients into our study, which is based on read codes in groups 1 and 2 of *Thomas et al.* [17]. This list of codes did not include seronegative for RF RA codes and had a high sensitivity (93%) but a relative low specificity (49%); thus, there could be some false positives in our case cohort [15]. In addition, the present analysis used the NCEP guidelines, which were cited by the British Society of Cardiology and in effect during the time when these patients were managed for their CV risk, that is, before 2011. The NCEP guidelines were used to categorize the RA into different CV risk categories, which were later used to match patients. The results could be different if the new ACC/AHA guidelines were used to match patients. However, as the new guidelines were not in place when these patients were evaluated and managed for CV risk, it would not be appropriate to use the new guidelines in this analysis. There were also a large number of missing values for laboratory test data. The method of last observation carried forward was used to handle missing data after the index date. Other imputation methods were also investigated, such as the simple mean imputation approach, producing similar results. Finally, only prescription data were available, which are known to differ from dispensed or taken medications.

Despite limitations, the study was based on data with both a large sample size and a good follow-up period. The results are generalizable to the UK population and are representative of its clinical practice, because the study was based on the CPRD general practice database, which covers a large proportion of the UK population.

CONCLUSION

There were no differences observed between RA and non-RA patients in terms of CV risk management and testing, although RA patients had experienced a modest 2% lower achievement of lipid goals, which may not be clinically meaningful. Based on this analysis, it seems that the higher CV risk in patients with RA is unlikely to be driven by differences in traditional CV risk factor management alone. A focus should be placed on CV risk stratification of RA patients and studies to determine how best to tailor management of CV risk to the different risk groups.

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CHAPTER 8

Comparison of Cardiovascular Risk Algorithms in Patients with *vs* without Rheumatoid Arthritis and the Role of C-Reactive Protein in Predicting Cardiovascular Outcomes in Rheumatoid Arthritis

Evo Alemao[1]*, Hélène Cawston[2], François Bourhis[2], Maiwenn Al[3], Maureen Rutten-van Molken[4], Katherine P. Liao[5] and Daniel H. Solomon[5]

[1]Worldwide Health Economics and Outcomes Research, Bristol-Myers Squibb, Princeton, NJ, USA;
[2]Real World Strategy & Analytics, MAPI, Nanterre, France;
[3]Institute of Medical Technology Assessment, Erasmus University Rotterdam, Rotterdam, The Netherlands;
[4]Institute of Health Policy and Management, Erasmus University Rotterdam, Rotterdam, The Netherlands;
[5]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, USA.
* PhD student at Erasmus University Rotterdam, supervised by M.P.M.H.R.M. and M.J.A.

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ABSTRACT

Objectives. The aims were to compare the performance of cardiovascular risk calculators, Framingham Risk Score (FRS) and QRISK2, in RA and matched non-RA patients and to evaluate whether their performance could be enhanced by the addition of CRP. **Methods.** We conducted a retrospective analysis, using a clinical practice data set linked to Hospital Episode Statistics (HES) data from the UK. Patients presenting with at least one RA diagnosis code and no prior cardiovascular events were matched to non-RA patients using disease risk scores. The overall performance of the FRS and QRISK2 was compared between cohorts, and assessed with and without CRP in the RA cohort using C-Index, Akaike Information Criterion (AIC) and the net reclassification index (NRI). **Results.** Four thousand seven hundred and eighty RA patients met the inclusion criteria and were followed for a mean of 3.8 years. The C-Index for the FRS in the non-RA and RA cohort was 0.783 and 0.754 ($P < 0.001$) and that of the QRISK2 was 0.770 and 0.744 ($P < 0.001$), respectively. Log[CRP] was positively associated with cardiovascular events, but improvements in the FRS and QRISK2 C-Indices as a result of inclusion of CRP were small, from 0.764 to 0.767 ($P = 0.026$) for FRS and from 0.764 to 0.765 ($P = 0.250$) for QRISK2. The NRI was 3.2% (95% CI: -2.8, 5.7%) for FRS and -2.0% (95% CI: -5.8, 4.5%) for QRISK2. **Conclusion.** The C-Index for the FRS and QRISK2 was significantly better in the non-RA compared with RA patients. The addition of CRP in both equations was not associated with a significant improvement in reclassification based on NRI.

INTRODUCTION

Patients with RA compared with the general population have an increased risk of mortality [1-3]. There is evidence to suggest that this mortality gap is increasing, although recent studies indicate a decreasing trend in cardiovascular (CV) fatality in RA patients [2, 4]. The main cause of increased mortality in RA patients is CV-related events [5, 6]. Several epidemiological studies have shown that the relative risk of acute myocardial infarction in RA patients ranges from 1.5 to 2.0, and for stroke it is 1.4 to 2.7 fold higher [7-10].

The pathophysiological mechanism underlying the increased CV risk in RA patients is not fully understood. RA patients have chronic high-grade inflammation, which is an important contributor towards the development of premature atherosclerosis and CV events [11, 12]. It is unclear whether the markers of inflammation, such as CRP and ESR, and other markers, such as RF and RA disease activity, are more strongly associated with CV events in RA and thus could weaken the association of the traditional CV risk factors to CV events. In addition, there is evidence to suggest that traditional CV risk factors and markers of RA severity both contribute to predicting CV events in RA patients [2, 13, 14].

One consensus recommendation for the management of RA recommends the evaluation for CV risk at baseline using traditional CV risk algorithms, such as Framingham Risk Scores (FRS), which is based on the Framingham Heart Study, or the SCORE algorithm, which is based on the WHO MONICA Study [15]. Given that these algorithms were not developed in the RA-specific population, the recommendation suggest adjusting the risk to account for the increased CV risk in RA patients [15]. Recent studies reporting RA-specific CV risk calculators have had mixed success in developing an improved CV risk calculator in RA patients [14, 16].

The primary objective of this analysis was to evaluate and compare the performances of CV risk algorithms in RA *vs* matched non-RA patients. The secondary objective was to evaluate the association of CRP with CV events in RA patients and explore whether the performance of the CV risk algorithms could be enhanced by the addition of CRP, as was the case in the Reynolds Risk Score [17].

METHODS

Study design and database

This was a retrospective cohort analysis, based on electronic medical records from the Clinical Practice Research Datalink (CPRD). The CPRD is jointly funded by the National Health Service (NHS), National Institute for Health Research and the Medicines and Healthcare products Regulatory Agency. It currently comprises ~5 million active patients with long-term follow-up information. To obtain a complete picture of CV events, the CPRD data were linked to the Health Episode Statistics (HES) data from April 1997 onwards, which contain details of all admissions and outpatient appointments in NHS hospitals.

Study population

The study included all adult RA patients (age ≥18 years) with records of sufficient quality, identified through the acceptable patient flag. The RA population was defined as all patients presenting at least one RA diagnosis read code after 01/01/1988 (index code), with no RA or juvenile RA codes before the index code. Read codes are standard medical diagnosis codes used in the UK general practice system. The index date was defined as the date of first RA-related clinical or referral record. Patients were required to have at least 12 months of data reported before the index date.

RA patients were matched 1:4 to non-RA patients based on their year of entry into the CPRD database using a disease risk score for RA, CV risk category (National Cholesterol Education Program classification) and CV treatment status. The disease risk score was based on a logistic regression model evaluating the probability of having RA and included gender, smoking, obesity, psoriasis, Charlson Co-Morbidity Index and family history of RA as covariates [18]. RA patients were categorized into CV risk categories of low, medium or high at index date based on the number of risk factors, explained further in the next subsection, on exposure and outcomes definitions. CV risk categorization and treatment status of CV risk for all non-RA patients were calculated for each 6-month window. Non-RA patients were selected as potential matches within each CV risk category and treatment status that was closest to the case's index date. Potential matches were also required to have entered the CPRD database during the same year as the case and to have at least one health-care encounter within 2 months of the case's index date. From the pool of potential matches, each RA patient was matched to a non-RA patient, with replacement based on the disease risk score

and using the nearest neighbour match method [18]. An index date was assigned to the non-RA patient based on the closest observation date to the RA patient's index date, and the match was confirmed based on the recalculated non-RA patient's CV risk category at the assigned index date. The process was repeated to match a maximum of four controls to each case. Standardized differences were used to compare the measured baseline characteristics between the RA and the non-RA populations. A standardized difference of <0.1 was considered indicative of a good balance [19].

The CPRD has been granted Multiple Research Ethics Committee approval (05/MRE04/87) to undertake purely observational studies, with external data linkages including HES and Office of National Statistics mortality data. The work of CPRD is also covered by National Information Governance Board - Ethics and Confidentiality Committee approval ECC 5-05 (a) 2012. This study was approved by the Independent Scientific Advisory Committee for Medicines and Healthcare products Regulatory Agency database research under protocol no. 12_079Ra.

Exposure and outcomes definitions

Medical diagnoses and events were identified through read codes, whereas medical product codes were used for treatments. Lists of codes were constructed to define baseline covariates, CV risks and CV events. In order to create the code list for each condition, published lists of codes were used and supplemented by additional searches of the medical and product browser. Group 1 or 2 read codes were used for RA diagnosis as defined in a previous published study using CPRD data [20]. The compiled list was then screened by an analyst in order to exclude all non-relevant codes, and a second screening was then conducted by a clinician. For the HES analysis, ICD 10 codes were used to record medical diagnoses and events. Based on the Framingham Heart Study definition, the CV event list was a composite of myocardial infarction, stroke, heart failure, aortic aneurysm, transient ischemic attack, unstable angina or intermittent claudication. The QRISK2 definition of CV events included myocardial infarction, coronary heart disease (CHD), stroke and transient ischemic attack [21]. Laboratory values were identified and calculated at index date, considering the most recent value within 2 years of the date of interest. CRP values were also obtained from the laboratory tests data. The presence of hypertension at the index date was based on a record of a diagnosis of hypertension via read code or a diastolic blood pressure of >90 mmHg or systolic blood pressure of >140 mmHg or both within the 2 years prior to the index date. Dyslipidaemia at the index date was based on a diagnosis or treatment for dyslipidaemia or high-density lipoprotein cholesterol <1.03 mmol/l

or low-density lipoprotein cholesterol >4.14 mmol/l or total cholesterol (TC) >5.17 mmol/l or triglyceride >2.26 mmol/l. Atrial fibrillation, family history of CHD and renal disease were evaluated at the index date based on a record of corresponding diagnosis codes within 2 years of the index date. Obesity was identified by a record of a read code or a BMI >30 kg/m² occurring within 2 years of the index date. The covariates for the QRISK2 model were age, sex, smoking status (yes/ no), treated hypertension (yes/no, hypertension with prescribed treatment), obesity (yes/no, instead of BMI), diabetes (yes/no), atrial fibrillation (yes/no), family history of CHD (yes/no), RA (yes/no) and renal disease (yes/no). RA was not included as covariate because of complete separation of populations in the RA and non-RA populations, respectively. In addition, the Townsend deprivation score and ethnicity were not included in the analysis because of their unavailability in our data set.

Treatment status was defined as a bivariate variable for patients who received therapy to treat diabetes, hypertension or dyslipidaemia within 2 years of the index date. The CV risk categories, used for the matching only, were based on National Cholesterol Education Program definitions and were composed of the four categories of low, medium, high and very high risk by summing the following risk factors: dyslipidaemia (low-density lipoprotein cholesterol ≥ 4.14 mmol/l or high-density lipoprotein cholesterol ≤ 1.03 mmol/l), hypertension, age (>45 years for males and >55 years for females) and current smoker [22]. If patients had none of the risk factors they were considered low risk, one risk factor was medium risk and more than one risk factor was high risk. Patients with diabetes, heart disease, a history of cardiovascular event or procedure were considered in the very high-risk class.

Statistical analysis

Descriptive statistics were used to summarize the demographic characteristics of the RA and non-RA cohorts. The differences in CV risk factors in the two cohorts were tested using χ^2 tests. The associations between CRP, lipids and CV events were evaluated by plotting Kaplan-Meier survival curves (time to CV event) by baseline CRP tertiles and TC categories based on UK treatment guidelines (low: <5.172 mmol/l; medium: 5.172-6.180 mmol/l; high: ≥6.180 mmol/l [22]) and using log rank tests. Negative binomial models were used to evaluate the risk of CV events (based on the FRS definition) by CRP and TC categories.

The 10-year FRS and QRISK2 are Cox proportional hazard models, which include the traditional CV risk factors. They were compared for discriminatory ability and model

fit in the RA and non-RA cohorts. The proportional hazard assumption was evaluated for each covariate in univariate models by testing the interaction between the covariate and time in its logarithm transformation: $H(_t) = H_0(t)exp(\beta_k x_k + \gamma_k x_k * log(t))$. If the γ_k estimate was significantly different from 0 ($P < 0.05$) then the covariate x_k was considered to violate the proportional hazard assumption. Model discriminatory properties were evaluated using the area under the receiver operating characteristic curve measured by Harrell's C-Index, and the model fit was evaluated using the Akaike Information Criterion (AIC). The 95% CIs for the C-Index and the difference in the C-Index were calculated using 1000 bootstrap samples. Harrell's C-Index is a measure that assesses the ability of a model to distinguish subjects who will develop events from those who will not and can be interpreted as the conditional probability that, for any pair of event and non-event patients, the predicted risk of an event is higher for the patient with an event [23]. The net reclassification index (NRI) was used to evaluate the reclassification ability of the addition of the logarithm of CRP concentration (log[CRP]) to the base FRS and QRISK2 prediction model. The NRI is a measure of the added predicted value of a new marker (CRP). In the context of survival data, it is calculated using a prospective approach, summarizing the upward and downward reclassifications, in terms of predicted risk categories, of the original model compared with the new model with the added covariate [24]. In the RA cohort, the base FRS and QRISK2 models were extended to include the baseline log[CRP] in addition to the traditional CV predictors. The C-Index and AIC were used to evaluate the performance of the FRS with and without CRP in RA patients.

RESULTS

From 1997 to 2010, 12,747 primary prevention RA and 44,452 non-RA patients met the inclusion criteria. On average (S.D.) at baseline, RA patients were 58.5 (14.8) years old, with a follow-up of 6.0 (4.5) years (76,003 patient-years) and had CRP of 23.5 (33.5) mg/l. Females represented 71% of the population; 38% were hypertensive and 24% dyslipidaemic (Table 1). The median reported time between CRP record and the index date was 49 days (interquartile range: 14-137). Non-RA patients had similar characteristics at baseline, with the exception of mean CRP and ESR values, which were 2.5 and 1.8 times lower, respectively. The incidence of CV events based on FRS definition of CV events was 4.29/100 patient-years (95% CI: 4.15, 4.44) in RA patients and 3.11/ 100 patient-years (95% CI: 3.04, 3.17) in non-RA patients. Using the QRISK2 CV definition, the incidence of CV events was 1.78/100 patient-years (95% CI: 1.69, 1.88) in RA patients and 1.38/100 patient-years (95% CI: 1.33, 1.42) in non-RA patients. Within the RA and non-RA cohorts, based on a Kaplan-Meier analysis,

Table 1. Baseline Characteristics of RA and non-RA primary prevention patients

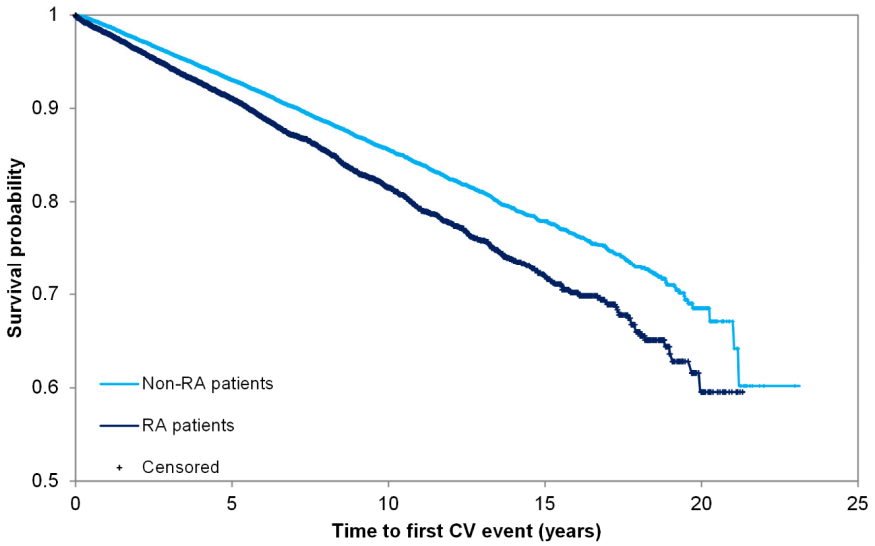
	RA Patients		Non-RA Patients	
Characteristics	**N**	**Mean (SD) or n (%)**	**N**	**Mean (SD) or n (%)**
Number of patient-years (years), Sum	12,747	76,003	44,452	260,206
Years of follow-up (years)	12,747	6.0 (4.5)	44,452	5.9 (4.5)
Age at index date (years)	12,747	58.5 (14.8)	44,452	58.3 (15.4)
Charlson Comorbidity Index	12,747	1.3 (0.9)	44,452	0.3 (0.8)
Total Cholesterol (mmol/L)	3,874	5.3 (1.2)	12,801	5.4 (1.2)
HDL Cholesterol (mmol/L)	2,774	1.4 (0.4)	9,459	1.4 (0.5)
Diastolic blood pressure (mm of Hg)	9,042	79.5 (9.9)	30,300	79.8 (11.1)
Systolic blood pressure (mm of Hg)	9,042	136 (19.1)	30,300	136 (19.4)
C-reactive protein (mg/L)	4,780	23.4 (33.5)	2,816	9.9 (24)
Erythrocyte sedimentation rate (mm/hr)	6,377	30.9 (24.7)	5,477	16 (16)
HbA1c (%)	681	7.1 (1.6)	2,554	7.2 (1.6)
Females	12,747	9046 (71)	44,452	30422 (68.4)
Obesity	12,747	1423 (11.2)	44,452	4761 (10.7)
Dyslipidemia	12,747	3094 (24.3)	44,452	10883 (24.5)
Diabetes	12,747	780 (6.1)	44,452	3114 (7.0)
Hypertension	12,747	4870 (38.2)	44,452	16198 (36.4)
Current smoker	12,747	3551 (27.9)	44,452	12322 (27.7)
Atrial fibrillation	12,747	127 (1.0)	44,452	343 (0.8)
Family history of CHD	12,747	372 (2.9)	44,452	1,396 (3.1)
Renal disease	12,747	152 (1.2)	44,452	530 (1.2)
CV risk category*	12,747		44,452	
Low risk		2721 (21.3)		10283 (23.1)
Medium risk		4342 (34.1)		14073 (31.7)
High risk		4410 (34.6)		15093 (34.0)
Very high risk		1274 (10.0)		5003 (11.3)

[a]National Cholesterol Education Program definition. CHD: coronary heart disease; CV: cardiovascular; HbA_{1c}: glycosylated haemoglobin; HDL: high-density lipoprotein.

the probability of a CV event at 5 years was 8.97 and 6.97%, respectively (log-rank $P < 0.001$; Fig. 1).

CRP and TC were categorized into three levels (low, medium and high). The threshold values for CRP levels (corresponding to tertiles) were CRP ≤6, 6 < CRP ≤20 and CRP >20 mg/l, and the values for TC were based on treatment guidelines defined in the statistical analysis subsection of the Methods. Based on the Kaplan-Meier analysis, probabilities of a CV event at 5 years based on FRS definition in patients with low,

Figure 1. Time to CV event (FRS CV definition) in RA and non-RA patients



medium and high CRP levels were 6.57, 7.20 and 12.20%, respectively (log-rank P < 0.001; Fig. 2). The respective probabilities by TC levels were 9.97, 9.62 and 12.68% (log-rank P = 0.366; Fig. 2). Within each TC category, the risk of a CV event increased with the CRP level (P = 0.011; Fig. 3).

The analysis of univariate models indicated no significant interaction between time in its logarithmic transformation and the covariates of the FRS and QRISK2 Cox models, so the proportional hazard assumption was deemed acceptable. The multivariate Cox analyses with the FRS and QRISK2 risk factors showed that all the traditional CV risk factors were significantly associated with CV events except for dyslipidaemia, in both the RA and the non-RA cohorts for the FRS based model. For the QRISK2-based analysis, in addition to dyslipidaemia, obesity, atrial fibrillation and renal disease were not significant in RA (Table 2). Based on the hazard ratios (HRs), all risk factors had a similar magnitude of effect in the RA *vs* non-RA cohort. The C-Index for the FRS in the non-RA *vs* RA cohort was 0.783 and 0.754 (P < 0.001) and that of the QRISK2 was 0.744 and 0.770 (P < 0.001), respectively (Table 2). The observed and predicted event rates at 3 years were plotted for both RA and non-RA patients based on the predictions from both the FRS and QRISK2 models. Overall, similar patterns were observed between FRS and QRISK2 in RA and non-RA cohorts (plots as supplementary material).

Table 2. FRS and QRISK2 model results for any cardiovascular event in RA and non-RA Patients

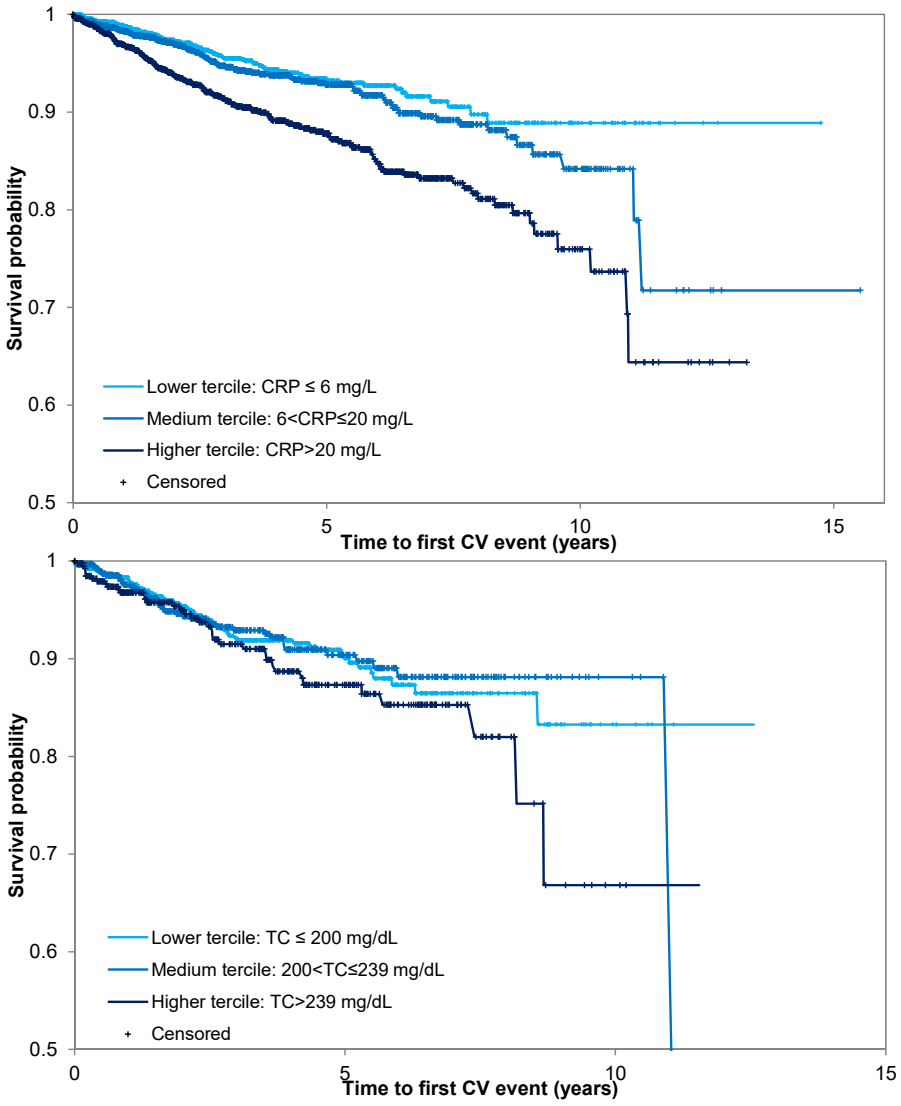
Covariates	FRS Model				QRISK2			
	RA patients (N=12,747)		Non-RA patients (N=44,452)		RA patients (N=12,747)		Non-RA patients (N=44,452)	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.07 (1.07, 1.08)	<.001	1.08 (1.07, 1.08)	<.001	1.06 (1.06, 1.07)	<.001	1.07 (1.07, 1.08)	<.001
Gender (Ref=Male)	0.67 (0.60, 0.75)	<.001	0.63 (0.59, 0.68)	<.001	0.71 (0.62, 0.82)	<.001	0.65 (0.6, 0.71)	<.001
Hypertension (Ref=No)	1.10 (0.98, 1.23)	0.093	1.05 (0.97, 1.13)	0.204	1.15 (0.99, 1.34)	0.061	1.14 (1.03, 1.26)	0.012
Treatment for hypertension (Ref=No)	1.44 (1.28, 1.62)	<.001	1.56 (1.45, 1.69)	<.001	1.48 (1.27, 1.73)	<.001	1.33 (1.2, 1.47)	<.001
Current smoker (Ref=No)	1.25 (1.09, 1.42)	0.001	1.20 (1.10, 1.30)	<.001	1.19 (0.99, 1.42)	0.059	1.09 (0.97, 1.21)	0.135
Diabetes (Ref=No)	1.66 (1.38, 2.00)	<.001	1.59 (1.43, 1.76)	<.001	1.53 (1.20, 1.96)	<.001	1.43 (1.24, 1.64)	<.001
Dyslipidaemia (Ref=No)	0.93 (0.81, 1.07)	0.302	1.01 (0.93, 1.10)	0.746	1.02 (0.85, 1.22)	0.841	1.03 (0.92, 1.14)	0.633
Obesity (Ref=No)					0.95 (0.75, 1.21)	0.693	1.05 (0.91, 1.21)	0.542
Atrial fibrillation (Ref=No)					0.88 (0.53, 1.48)	0.636	1.48 (1.11, 1.97)	0.008
Family history of CHD (Ref=No)					0.50 (0.25, 1.00)	0.049	1.13 (0.84, 1.53)	0.406
Renal disease (Ref=No)					0.96 (0.45, 2.03)	0.911	1.14 (0.79, 1.66)	0.491
C-Index (95%CI)	0.754 (0.733, 0.775)		0.783 (0.770, 0.795)		0.744 (0.714, 0.774)		0.770 (0.753, 0.788)	
ΔC-Index (95% CI)	+0.029 (0.012; 0.042), p<.001				+0.026 (0.008, 0.043), p<.001			

CI: confidence interval; HR: hazard ratio; RA: rheumatoid arthritis; Ref: reference category

Note: Analysis performed on all primary prevention RA and non-RA patients.

Confidence intervals of the difference in C-index were computed based on the percentiles obtained after using bootstrap sampling on 200 simulations

Figure 2. Time to CV event (FRS CV definition) by baseline TC and CRP levels in RA patients



The addition of log[CRP] was positively associated with CV events in the RA cohort for the FRS model (HR = 1.12; 95% CI: 1.03, 1.23) but not in the QRISK2 model (HR = 1.03; 95% CI: 0.91, 1.16; Table 3). The model discriminations due to the addition of log[CRP] were improved by very small amounts, with C-Index increments between the two models of 0.003 (P = 0.026) for the FRS model and 0.0005 (P = 0.250) for the QRISK2 (Table 3). Likewise, very small AIC differences were observed in the models with and without log[CRP] (4881 *vs* 4877 in the FRS and 2741 *vs* 2743 for QRISK2).

Table 3. FRS and QRISK2 model results for any cardiovascular events, in RA patients, with and without CRP

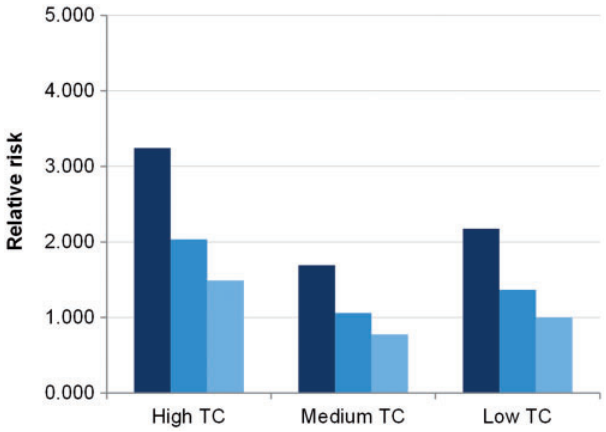
	FRS Model				QRISK2			
	Without CRP		With CRP		Without CRP		With CRP	
Covariates	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.08 (1.06, 1.09)	<.001	1.07 (1.06, 1.08)	<.001	1.07 (1.05, 1.08)	<.0001	1.07 (1.05, 1.08)	<.0001
Gender (Ref=Male)	0.68 (0.54, 0.84)	<.001	0.70 (0.56, 0.88)	0.002	0.73 (0.54, 0.99)	0.042	0.74 (0.54, 1.00)	0.049
Hypertension (Ref=No)	0.94 (0.74, 1.19)	0.594	0.93 (0.73, 1.17)	0.532	0.98 (0.71, 1.35)	0.897	0.98 (0.71, 1.34)	0.884
Treatment for hypertension (Ref=No)	1.60 (1.25, 2.05)	<.001	1.59 (1.24, 2.03)	<.001	1.83 (1.31, 2.55)	0.000	1.82 (1.30, 2.55)	0.000
Current smoker (Ref=No)	1.58 (1.26, 1.98)	<.001	1.58 (1.26, 1.98)	<.001	1.58 (1.16, 2.14)	0.004	1.58 (1.16, 2.14)	0.004
Diabetes (Ref=No)	1.61 (1.16, 2.25)	0.005	1.60 (1.15, 2.22)	0.006	1.65 (1.05, 2.6)	0.031	1.65 (1.05, 2.6)	0.031
Dyslipidaemia (Ref=No)	0.83 (0.64, 1.06)	0.138	0.85 (0.66, 1.10)	0.217	0.8 (0.57, 1.13)	0.203	0.81 (0.57, 1.14)	0.221
Obesity (Ref=No)					0.75 (0.46, 1.24)	0.268	0.75 (0.46, 1.24)	0.264
Atrial fibrillation (Ref=No)					0.55 (0.14, 2.24)	0.403	0.56 (0.14, 2.26)	0.412
Family history of CHD (Ref=No)					0.53 (0.17, 1.67)	0.280	0.53 (0.17, 1.68)	0.282
Renal disease (Ref=No)					0.39 (0.10, 1.59)	0.190	0.39 (0.10, 1.60)	0.191
Log (CRP)			1.12 (1.03, 1.23)	0.012			1.03 (0.91, 1.16)	0.626
AIC	4881.1		4876.7		2740.8		2742.6	
C-Index (95%CI)	0.764 (0.720, 0.809)		0.767 (0.723, 0.812)		0.764 (0.699, 0.829)		0.765 (0.700, 0.830)	
ΔC-Index (95% CI)	+0.003 (0.00017, 0.00827), p=0.026				+ 0.0005 (-0.00087, 0.00561), p=0.250			
Net Reclassification Index (NRI)	3.2% (95%CI: -2.8%; 5.7%)				-2.0% (95%CI: -5.8%; 4.5%)			

CRP: C-reactive protein; CI: confidence interval; HR: hazard ratio; RA: rheumatoid arthritis; Ref: reference category

Note: Analysis on primary prevention RA patients with available value of CRP at baseline (N=4,780).

Confidence intervals of the difference in C-index and NRI were computed based on the percentiles obtained after using bootstrap sampling on 1000 simulations

Figure 3. Relative Risk of CV event (FRS definition) by TC and CRP categories in RA patients



CRP: C-reactive protein; CV: cardiovascular; TC: total cholesterol

The overall re-classification as a result of the addition of CRP was characterized by a non-significant NRI of 3.2% (95% CI: -2.8, 5.7%) in the FRS model and a negative improvement of -2.0% (95% CI: -5.8, 4.5%) in the QRISK2 model (Table 3).

DISCUSSION

Our study investigated the performance of the FRS and QRISK2 equations in RA and matched non-RA patients and assessed the additional value of including CRP, assessed at the index date, to the FRS and QRISK2 risk algorithm. This is the first UK study to compare the FRS and QRISK2 risk algorithm in RA and non-RA patients matched on the baseline CV risk factors.

Several studies have confirmed the higher CV risks in RA patients [7-10]. The CV incidence rates in the RA cohort observed in our analysis are comparable to a recent publication from the UK using The Health Improvement Network data set, a clinical practice data set similar to CPRD [25]. However, the observed event rates appear relatively high compared with other observational studies from The Netherlands and Sweden, highlighting difference in CV event rates in RA populations across countries [4].

There is evidence that the increased CV risk in RA patients might not be explained by traditional risk factors alone [26]. In addition, traditional risk calculators, such as FRS, underestimate the CV risk among RA patients, especially with high CV risk [27]. RA

patients have chronic high-grade inflammation, but the only CV risk calculator that includes markers of inflammation is the Reynolds Risk Score, which was also developed in the general population [28]. Thus, the Reynolds Risk Score would be likely to underestimate the CV risk in RA patients [29, 30]. The QRISK2 score incorporates RA but it is not specific and there is evidence that it overestimates CV risk [31, 32].We evaluated the performance of FRS and QRISK2 in RA patients and matched non-RA patients and tested whether the addition of CRP would improve the performance of these calculators in the RA cohort.

We used the FRS risk algorithm, because EULAR guidelines in RA recommends using FRS for CV risk stratification of RA patients and it is also referenced in the UK clinical guidelines by the Joint British Recommendations on the Prevention of CHD [27, 33]. The QRISK2 has been recommended for CV risk estimation by the National Institute of Health and Care Excellence in the UK.

To compare the algorithms in the two cohorts, we controlled for traditional CV risk factors by matching RA to non-RA patients based on their CV risk profile. Overall, we found that the algorithms had a good discrimination in RA patients, although the C-Index was lower compared with the CV risk-matched non-RA cohort. Similar to our findings, other studies reported that the FRS algorithm underestimates the CV risk in established and early RA patients, especially in patients with high baseline deciles of predicted risks, but ours is the first study having a comparator group matched for baseline CV risks [29, 32].

Further examination of the Cox model indicated that almost all the traditional risk factors in FRS had a similar magnitude of effect in the RA and non-RA cohorts except smoking, hypertension and diabetes, whose HRs were ~5% higher in the RA compared with the non-RA cohort. There is evidence to suggest that RA patients have a different CV risk factor profile compared with non-RA patients because they are more likely to be obese and more likely to be smokers and hypertensive [34]. There is emerging evidence to suggest that the immune dysregulation, chronic high-grade inflammation and metabolic disturbances found in RA patients could contribute to the increased CV events [26, 35-37]. We observed baseline CRP, but not TC, to be associated with a higher CV event risk in RA. This observation was found to hold even after controlling for all the traditional risk factors. We further evaluated the association between TC, CRP and CV events in RA patients and noticed that within each category of TC (low, medium and high), an increase in CRP levels increased CV events. Thus, we hypothesize that CRP could have a risk-modifying effect in RA patients. However, the inclusion of CRP as a risk factor in the FRS and QRISK2 did not improve the

reclassification of CV risks; in fact, it worsened the reclassification in QRISK2. Thus, CRP itself might not explain the overall increased CV events observed in RA patients.

These findings are consistent with those observed in two other analyses using a similar methodology and based on electronic medical record databases from the USA [38, 39]. Given the findings of our analysis, we think that studies focusing on developing and validating RA-specific risk CV algorithms are most appropriate [14, 32]. Some studies have reported success in developing and validating such algorithms; therefore, future research should focus on further testing of these RA-specific CV algorithms [14].

There were several limitations to our analysis. First, this was a retrospective analysis, implying some sources of bias attributable to confounding factors. However, this was partly accounted for by matching patients based on disease risk score for RA and CV risk profiles. The identification of RA patients was based on RA diagnosis records in groups 1 and 2 of Thomas *et al.* [20], and seronegative RF read codes were not included. However, the list of codes is associated with a sensitivity of 93% and a specificity of 49% and thus there could be some false-positive patients in our case cohort. As the findings from our study are similar to those of two other studies using similar methodology and based on US electronic medical records, we anticipate that false positives have minimal impact on the overall conclusion [38, 39]. In the non-RA cohort, neither lipids nor hypertension was predictive of future CVD events. This could be explained by the fact that the patient data for this analysis were from a general practice database and thus the patients were managed for their CV risk factors. Treatment for hypertension is on the causal pathway of risk factors for CVD and, in fact, we noticed that treatment for hypertension was a predictor. In our data set, there were a number of missing laboratory values for non-traditional CV risk factors and so categorical yes/no variables were used instead in both the FRS and QRISK2 models. For example, dyslipidaemia was based on a combination of laboratory value thresholds, treatment and diagnosis codes. However, as this would impact the two cohorts equally, we do not think this would affect the overall findings of our analysis. In addition, we were not able to include some of the QRISK2 covariates, such as ethnicity or the Townsend deprivation score, because of their unavailability. The imputation of missing values for CRP and continuous laboratory values in general could have been undertaken. For CRP, a variety of imputation approaches could have been used. Although this would have enabled us to retain the full sample size, imputation can introduce bias. For instance, the missing information might not be random; that is, CRP might be tested only when general practitioners suspect a high value. This means that the missing CRP values might be lower than the recorded ones. Given that data on UK postal codes was not available via CPRD, we used the approach as stated by

the developers of QRISK2 [40]. As the average follow-up time was 6.0 and 3.8 years in the overall RA cohort and RA patients with CRP measures, respectively, we estimated 5- and 3-year CV risks in this analysis. Although we do agree that this apparent inconsistency could introduce confusion, the aim of the present paper was to estimate the incremental improvement in prediction with the addition of inflammatory measures and not the 10-year estimated risk of CVD. Furthermore, focusing on patients with CRP data available in the second analysis may have resulted in a selection bias. Our analysis of the non-traditional risk factor was limited to CRP because other factors, such as RA disease activity, were not available for analysis. Another limitation was the 49-day delay between the reported CRP value and the index date.

Despite limitations, the study was based on data with both a large sample size and a good follow-up period. Thus, the results are generalizable to the UK population and are representative of its clinical practice.

CONCLUSION

The FRS and QRISK2 have a good discrimination in the RA population, but it was significantly lower than the general population. Even though CRP is associated with an increased risk of CV events, the inclusion of CRP in the FRS equation and the QRISK2 model did not result in an improvement in reclassification of CV risk.

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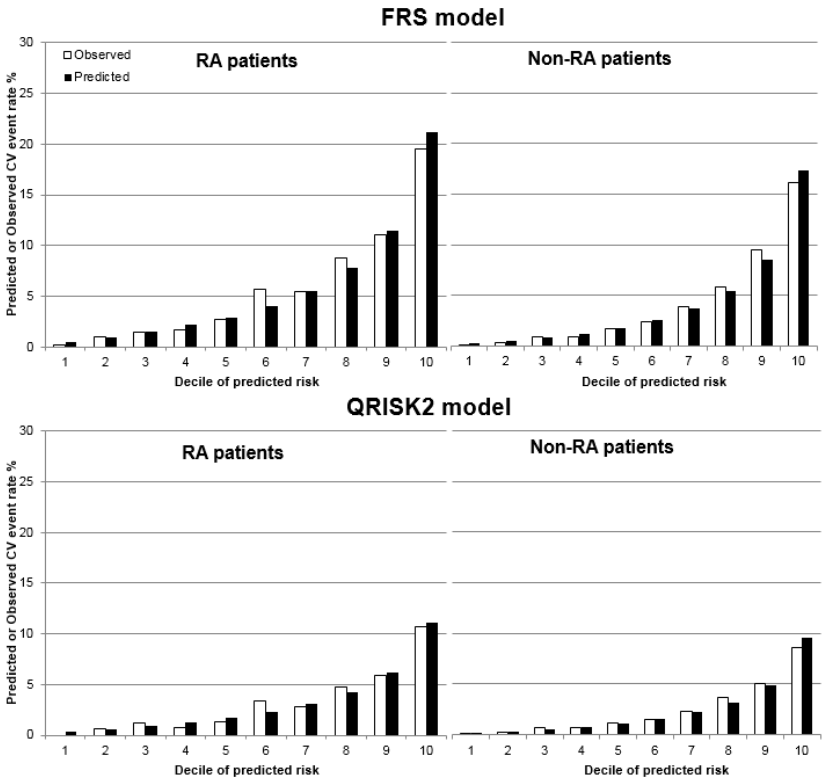
CHAPTER 8 SUPPLEMENT MATERIAL

Supplementary Figure S1. Observed vs. predicted 3-year cardiovascular risk in RA and non-RA patients



Supplementary table S1: Relative Risk of cardiovascular event (FRS definition) by TC and CRP categories in RA patients

		TC		
		Low TC	**Medium TC**	**High TC**
CRP	**Low**	1.000	0.776	1.489
		(N=345)	(N=234)	(N=163)
	Medium	1.366	1.060	2.034
		(N=321)	(N=217)	(N=132)
	High	2.177	1.690	3.243
		(N=367)	(N=197)	(N=103)

P-values: TC (p=0.096); CRP (p=0.011). TC: total cholesterol.

CHAPTER 9

Cardiovascular Outcomes Associated with Lowering Low-density Lipoprotein Cholesterol in Rheumatoid Arthritis and Matched Nonrheumatoid Arthritis

JaeJin An[1], Evo Alemao[2]*, Kristi Reynolds[3], Hugh Kawabata[2], Daniel H. Solomon[4], Katherine P. Liao[4], Fang Niu[5] and Craig Cheetham[3]

[1]Department of Pharmacy Practice and Administration, Western University of Health Sciences, Pomona, California;
[2]Bristol-Myers Squibb, Princeton, New Jersey;
[3]Research and Evaluation, Kaiser Permanente Southern California, Pasadena, California;
[4]Division of Rheumatology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts;
[5]Drug Information Services, Kaiser Permanente Southern California, Downey, California.
* PhD student at Erasmus University Rotterdam, supervised by M.P.M.H.R.M. and M.J.A.

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ABSTRACT

Objective. To examine the associations between lowering low-density lipoprotein cholesterol (LDL-C) and cardiovascular (CV) outcomes among patients with rheumatoid arthritis (RA) and patients without it. **Methods.** Adult patients with RA and 2 age- and sex-matched control cohorts [RA plus general controls (RA/GN), RA plus osteoarthritis (OA) controls (RA/OA)] were identified between January 1, 2007, and December 31, 2011. Patients with a diagnosis of hyperlipidemia who initiated statin therapy without prior CV events were included. Multivariable Cox proportional hazard analyses were used. **Results.** The study identified 1522 patients with RA with 6511 general controls (RA/GN cohort); and 1746 patients with RA with 2554 OA controls (RA/OA cohort). During followup, mean (SD) LDL-C (mg/dl) was 96.8 (32.7) for RA, 100.1 (35.1) for general controls, and 99.1 (34.3) for OA. The relationship between lowering LDL-C and CV outcomes was similar for both RA and non-RA controls (p for interaction = 0.852 in RA/GN cohort, and p = 0.610 in RA/OA cohort). After adjusting for baseline CV risk factors, lowering LDL-C was associated with a 29%-50% lower risk of CV events (HR [95% CI] = 0.71 [0.57-0.89] in RA/GN, 0.50 [0.43-0.58] in RA/OA). Subgroup analyses showed that lowering LDL-C was associated with a similar degree of reduction of CV events in RA and non-RA controls (HR of 0.67-0.68 for RA, 0.72 for general controls, 0.76 for OA controls). **Conclusion.** Lowering LDL-C levels was associated with reduced CV events. The relationship between lowering LDL-C and CV outcomes in RA was similar to the relationship found in matched general and OA controls.

INTRODUCTION

Cardiovascular (CV) disease is a common comorbidity for patients with rheumatoid arthritis (RA). It is estimated that patients with RA have a 50% increased risk of CV events or early mortality relative to the general population [1,2]. A high systemic inflammatory burden [3] as well as traditional risk factors such as hypertension (HTN), diabetes, and smoking appear to be key contributors to the increased CV events in RA [4]. High cholesterol is an important factor for the increased risk of CV events for the general population; however, growing evidence suggests a complex relationship between lipid levels and CV risk in patients with RA [5,6,7]. Epidemiological studies reported lower lipid levels in patients with RA compared to the general population [6,8], but at the same time, patients with RA had higher rates of myocardial infarction (MI) and ischemic stroke [6]. These findings are potentially due to the altered lipid metabolism from systemic inflammation, drug therapy, and several genetic factors in RA [9].

Because of this complex relationship between lipid levels and CV diseases in RA, there is a lack of clinical guidelines to identify patients at high risk for CV disease and to manage these groups. The European League Against Rheumatism [10] currently recommends an annual CV risk assessment, treatment, and management according to guidelines that apply to the general population [11]. The hydroxymethylglutaryl CoA reductase inhibitor (statin) therapy has been shown to be beneficial in primary and secondary prevention of CV diseases in the general population [12,13]. However, evidence regarding the benefits of lowering elevated low-density lipoprotein cholesterol (LDL-C) in patients with RA is not clear. Although several studies suggest potential CV protective effects of statin therapy in RA, the results are from posthoc analyses [14,15], and a recent prospective randomized controlled trial was terminated early owing to low CV event rates [16]. Specifically, differences in CV disease associated with lowering lipid levels between patients with RA and without need to be further investigated.

Given these uncertainties, the purpose of our study was to evaluate the association between lowering LDL-C levels and CV outcomes among RA subjects and age- and sex-matched controls who are prescribed statin therapy in a US managed care setting. Understanding differences in benefits of lowering LDL-C levels for patients with RA will be helpful to better manage these patients.

MATERIALS AND METHODS

Data source

A retrospective cohort study of patients enrolled in Kaiser Permanente Southern California (KPSC) was conducted using information from the KPSC electronic medical records (EMR) and administrative databases between January 1, 2006, and December 31, 2011. KPSC is a nonprofit, integrated health insurance provider with a current membership of over 4 million in Southern California. KPSC also provides comprehensive medical services through its own facilities, which include hospitals, out-patient sites, and a centralized laboratory. All aspects of care and interaction with the healthcare delivery system are included.

Study cohort

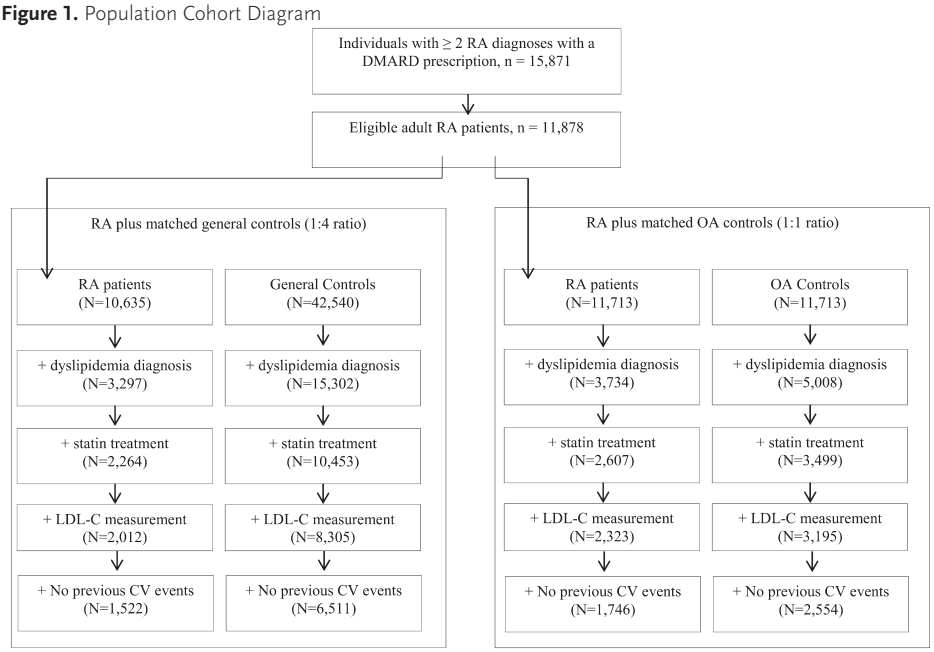
Adult patients aged ≥ 18 years were required to have 2 or more diagnoses of RA [International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code, 714.xx] from January 1, 2007, to December 31, 2011 (identification period), to be eligible for the RA cohort. Patients were also required to have at least 1 prescription for a disease-modifying antirheumatic drug (DMARD) within 12 months (before or after) the RA diagnosis [17]. The first RA diagnosis date or DMARD prescription date was defined as an index date. Continuous membership with drug benefit for 12 months prior to the index date (baseline period) was required to be included in the RA cohort.

Two RA cohorts were identified. The first was matched to the general KPSC population (general controls) in a ratio of 4:1. The second RA cohort was matched to individuals with a diagnosis of osteoarthritis (OA; ICD-9-CM of 715.xx; OA controls) in a ratio of 1:1. OA is a chronic condition that brings patients into regular contact with the healthcare system similar to RA. Matching of both RA cohorts to general and OA controls was based on sex and birth year (within a window of ± 2 yrs). Matched controls were required to have at least 1 outpatient or inpatient encounter so that an index date could be assigned during the matching process. They could not have an RA diagnosis or be receiving any DMARD therapy during the study period. Matched controls were also required to have continuous KPSC membership plus drug benefit for 12 months prior to the index date as well as continuous membership plus drug benefits until the matched reference individual completed the qualification criteria. Unmatched patients with RA were dropped from the RA cohort (n = 1243 for RA matched to general controls; n = 165 for RA matched to OA controls).

Patients with a hyperlipidemia diagnosis (ICD-9-CM of 272.0, 272.1, 272.2, 272.4, 272.5, 272.8, or 272.9) and ≥ 1 statin prescription (Generic Product Identifier Class Codes of 3940, 3999) in the baseline period were included in the study. We excluded patients with a history of CV disease [MI, old MI, revascularization process, angina, stroke, transient ischemic attack (TIA), intermittent claudication, heart failure, abdominal aortic aneurysm, acute carotid procedures] during the baseline period because the focus of our study was a primary prevention population. Patients without an LDL-C laboratory result during the follow-up period were excluded from the analyses. Patients were followed from their index date until the first CV outcome, end of enrollment in the health plan, death from other causes, or the end of the study (December 31, 2011), whichever occurred first.

Through the matching procedure, we were successful in matching 10,635 patients with RA to 42,540 general controls (1:4 match) and 11,713 patients with RA to 11,713 OA controls (1:1 match). After restricting the population to those with a hyperlipidemia diagnosis plus ≥ 1 statin prescription during the baseline period, no previous CV events and ≥ 1 LDL-C measurements during the follow-up period, our sample was reduced to 1522 patients with RA matched with 6511 general controls, and 1746 patients with RA matched with 2554 OA controls (Figure 1). Median follow-up periods for the final study

Figure 1. Population Cohort Diagram



Abbreviations: RA = Rheumatoid Arthritis; DMARD = Disease Modifying Anti-Rheumatic Drug; LDL-C = Low-density Lipoprotein Cholesterol; CV = Cardiovascular

samples were 3.1 years for RA plus general controls and 4.0 years for RA plus OA controls. The study protocol was approved by the KPSC Institutional Review Board (#6331).

Lowering LDL-C levels

LDL-C during follow-up was categorized as whether the LDL-C was lowered to the recommended levels by the National Cholesterol Education Program Expert Panel — Adult Treatment Panel III guidelines [18]. Though this guideline was updated in 2013 [19], it was the standard of care during the time period for our study. The LDL-C recommended levels were < 100 mg/dl (2.6 mmol/l) for individuals at high risk, < 130 mg/dl (3.4 mmol/l) for those with moderate CV risk, and < 160 mg/dl (4.1 mmol/l) for those in the lowest CV risk category. The risk category was assigned to each individual based on coronary heart disease (CHD) status or a 10-year risk for CHD using baseline information [18]. Multiple LDL-C measurements during the follow-up period were observed and the analyses were conducted using the closest LDL-C value to the CV event or end of follow-up.

Other variables

Baseline patient characteristics including demographics (age, race/ethnicity, sex), body mass index, smoking status, comorbidities (Charlson comorbidity index, HTN and anti-HTN medication use, and diabetes) and baseline CV risk were obtained from the EMR. Among these variables, age, sex, HTN, anti-HTN medication use, smoking status, and diabetes were used as covariates to investigate the relationship between LDL-C and CV events, consistent with Framingham risk prediction[20].

Study outcomes

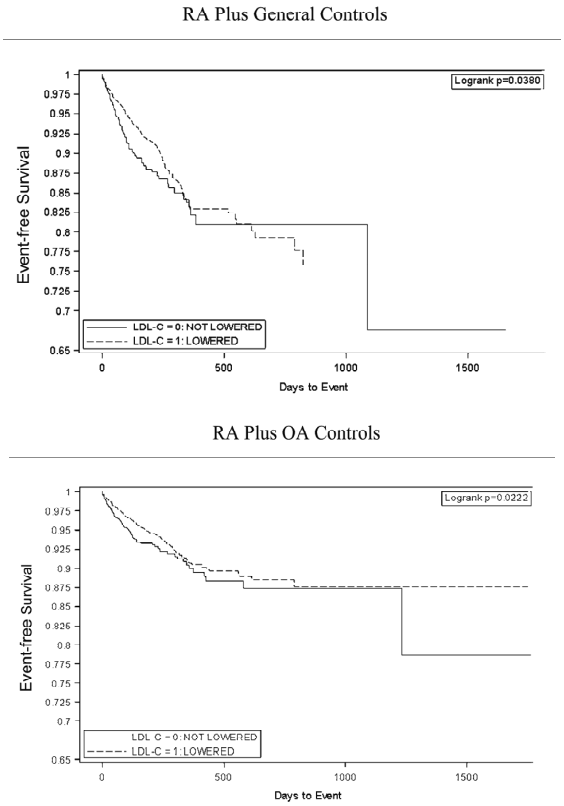
The study outcomes of interest included MI, angina, stroke, TIA, intermittent claudication, heart failure, or death from CV disease [20]. Primary hospital discharge records were used to define MI, angina, and stroke. The ICD-9-CM codes for each outcome are listed in Appendix 1. Outpatient and/or emergency department visit records were further used to define TIA, intermittent claudication, and heart failure. Any death occurring within 1 month after a defined CV event was classified as death from CV disease. Death was identified from health plan databases, Social Security Administration vital status files, and California state death files.

Statistical analyses

Baseline demographic information was summarized using descriptive statistics. Comparisons between RA and matched controls were conducted using t tests or Wilcoxon-Mann-Whitney tests for continuous variables, and chi-square tests for categorical variables. To investigate the association between LDL-C and CV outcomes, univariable and multivariable Cox proportional hazard analyses were conducted. HR and 95% CI were reported. Interaction terms between having RA and LDL-C levels were investigated to examine the differences in LDL-C and CV outcomes across RA and matched controls. Subgroup analyses were conducted for RA and non-RA controls separately.

Kaplan-Meier survival curves with log-rank tests were used to demonstrate the event-free survival over time for the group that lowered LDL-C to the recommended levels compared with the group that did not (Figure 2). Sensitivity analyses were conducted

Figure 2. Kaplan-Meier survival curves show the event-free survival over time for the group that lowered LDL-C to the recommended levels compared with the group that did not.



RA: rheumatoid arthritis; LDL-C: low-density lipoprotein cholesterol; OA: osteoarthritis.

using different LDL-C results (average LDL-C during followup, median LDL-C during followup) or different followup periods (starting to followup from the last LDL-C). Statistical analysis was performed with SAS version 9.2 (SAS Institute Inc.).

RESULTS

The baseline demographic information for the 2 cohorts is presented in Table 1. Overall, traditional CV risk factors were higher in patients with RA compared with general and OA controls. In the RA cohort matched to general controls, 74.2% had HTN, 40.9% had diabetes, 33.9% were obese, and 10.4% were smokers. These were all higher than the proportions found in the matched controls. Similarly, higher proportions of CV risk factors were found in RA cohort matched to OA controls except for obesity, which was higher in OA controls. Patients with RA had higher CV risk at baseline compared to general controls (high risk: 41.3% vs 38.1%) and compared to OA controls (high risk: 40.3% vs 36.2%).

Identified statin therapy included atorvastatin 10-80 mg, simvastatin 5-80 mg, fluvastatin 20-80 mg, lovastatin 10-40 mg, rosuvastatin 5-40 mg, and pravastatin 10-80 mg. Lower baseline lipid levels were observed in RA cohorts compared to general [mean LDL-C for RA vs general controls: 104.6 vs 109.6 in mg/dl; 2.70 vs 2.83 in mmol/l] and OA controls [mean LDL-C for RA vs OA controls: 104.5 vs 109.8 in mg/dl; 2.70 vs 2.84 in mmol/l]. The same trend was observed for total cholesterol and triglyceride levels. High-density lipoprotein cholesterol (HDL-C) levels did not differ between the RA and the control groups.

During follow-up, mean LDL-C levels were 96.8 mg/dl (2.50 mmol/l) for RA group matched to general controls, 100.1 mg/dl (2.59 mmol/l) for general controls, 96.5 mg/dl (2.50 mmol/l) for RA group matched to OA controls, and mg/dl (2.56 mmol/l) for OA controls. The proportion of patients who lowered LDL-C to the recommended levels was 78.7% for both RA and general controls, and 80.0% for OA controls.

The association between lowering LDL-C levels and CV outcomes is shown in Table 2. After adjusting for other risk factors (RA status, age, sex, HTN, anti-HTN medication use, smoking status, and diabetes), a reduction of LDL-C was associated with a 29% lower risk of CV events in patients with RA plus general control cohort (HR 0.71, 95% CI 0.57–0.89) and a 50% lower risk of CV events in RA patients plus OA control cohort (0.50, 0.43–0.58). Having an RA disease was associated with a 76% increased risk of CV events after controlling for other risk factors including LDL-C status. These factors

Table 1. Baseline Characteristics

Cohort	RA vs. General Controls					RA vs. OA Controls				
Variables	**RA Population (N=1,522)**		**General Controls (N=6,511)**		**p-value**	**RA Population (N=1,746)**		**OA Controls (N=2,554)**		**p-value**
Mean (SD) Age	63.0	(10.4)	63.6	(10.1)	0.0403	63.8	(10.3)	63.4	(10.9)	0.2371
Age Category										
<50	137	(9.0%)	533	(8.2%)	0.1839	139	(8.0%)	264	(10.3%)	0.043
50-59	442	(29.0%)	1,774	(27.2%)		470	(26.9%)	671	(26.3%)	
60-69	529	(34.8%)	2,278	(35.0%)		618	(35.4%)	845	(33.1%)	
≥70	414	(27.2%)	1,926	(29.6%)		519	(29.7%)	774	(30.3%)	
Race/Ethnicity					<.0001					0.0008
White	721	(47.4%)	3,283	(50.4%)		833	(47.7%)	1,339	(52.4%)	
Hispanic	448	(29.4%)	1,642	(25.2%)		505	(28.9%)	624	(24.4%)	
Black/African American	198	(13.0%)	752	(11.5%)		233	(13.3%)	365	(14.3%)	
Asian/Pacific Islander	135	(8.9%)	792	(12.2%)		152	(8.7%)	210	(8.2%)	
Other/Unknown	20	(1.3%)	42	(0.6%)		23	(1.3%)	16	(0.6%)	
Female	1,105	(72.6%)	4,632	(71.1%)	0.2562	1,305	(74.7%)	1,954	(76.5%)	0.1845
Number of Charlson Comorbidity Index Excluding Rheumatic or Cardiovascular Diseases										
0	936	(61.5%)	4,206	(64.6%)	0.0158	1,070	(61.3%)	1,625	(63.6%)	0.0651
1	494	(32.5%)	1,872	(28.8%)		563	(32.2%)	742	(29.1%)	
2 or more	92	(6.0%)	433	(6.7%)		113	(6.5%)	187	(7.3%)	
Smoking Status										
Smoker	159	(10.4%)	569	(8.7%)	0.0036	171	(9.8%)	207	(8.1%)	0.1404
Non smoker	1,230	(80.8%)	5,210	(80.0%)		1,430	(81.9%)	2,120	(83.0%)	
Unknown	133	(8.7%)	732	(11.2%)		145	(8.3%)	227	(8.9%)	

Table 1. (*continued*)

Cohort	RA vs. General Controls					RA vs. OA Controls				
Variables	**RA Population (N=1,522)**		**General Controls (N=6,511)**		**p-value**	**RA Population (N=1,746)**		**OA Controls (N=2,554)**		**p-value**
Body Mass Index (BMI) Category										
Obese (BMI ≥30)	516	(33.9%)	1,950	(29.9%)	0.0742	557	(31.9%)	998	(39.1%)	<.0001
Overweight (BMI 25-29.9)	359	(23.6%)	1,612	(24.8%)		404	(23.1%)	555	(21.7%)	
Normal (BMI <25)	229	(15.0%)	904	(13.9%)		260	(14.9%)	276	(10.8%)	
Unknown	418	(27.5%)	2,045	(31.4%)		525	(30.1%)	725	(28.4%)	
Baseline Cardiovascular Risk Stratification										
Low	114	(7.5%)	650	(10.0%)	0.0033	126	(7.2%)	232	(9.1%)	0.007
Medium	780	(51.2%)	3,382	(51.9%)		916	(52.5%)	1,397	(54.7%)	
High	628	(41.3%)	2,479	(38.1%)		704	(40.3%)	925	(36.2%)	
Diabetes	622	(40.9%)	2,440	(37.5%)	0.0142	695	(39.8%)	912	(35.7%)	0.0064
10 year risk >20%	16	(1.1%)	62	(1.0%)	0.7229	20	(1.1%)	21	(0.8%)	0.2841
Hypertension	1,130	(74.2%)	4,079	(62.6%)	<.0001	1,316	(75.4%)	1,737	(68.0%)	<.0001
Hypertension Diagnosis	1,152	(75.7%)	4,945	(75.9%)	0.0005	1,343	(76.9%)	2,045	(80.1%)	0.013
Anti-hypertensive Medication Use (Overall)	1,203	(79.0%)	5,102	(78.4%)	<.0001	1,400	(80.2%)	2,063	(80.8%)	0.6302
Lipid Panel, Mean (SD)	1,447		6,090			1,659		2,400		
Baseline low density lipoprotein cholesterol	104.6	(34.4)	109.6	(37.6)	<.0001	104.5	(34.0)	109.8	(35.3)	<.0001
Baseline high density lipoprotein cholesterol	51.0	(14.0)	50.8	(13.5)	0.6903	51.6	(14.2)	51.4	(13.3)	0.5969
Baseline triglycerides	150.6	(81.2)	158.8	(90.4)	0.002	150.2	(80.5)	156.9	(82.0)	0.0113
Baseline total cholesterol	185.1	(41.2)	191.8	(44.5)	<.0001	185.6	(40.8)	192.0	(42.0)	<.0001

[†]Diagnosis = Medication use only for patients with diagnosed with the condition

Abbreviations: RA= Rheumatoid Arthritis; OA = Osteoarthritis

Table 2. Association between Lowering Low-density Lipoprotein Cholesterol up to Clinically Recommended Levels and Cardiovascular Outcomes for Each Cohort

RA vs. General controls, N = 8,033		
Independent Variable	**HR (95% CI)**	**p-value**
RA (vs. controls)	1.76 (1.43, 2.17)	<.0001
Lowered LDL-C (vs. not lowered)	0.71 (0.57, 0.89)	0.003
Age	1.07 (1.06, 1.08)	<.0001
Male Gender (vs. Female)	1.34 (1.10, 1.64)	0.004
Hypertension (Yes vs. No)	1.41 (1.03, 1.64)	0.031
Antihypertensive Medications (Yes vs. No)	1.45 (0.96, 2.20)	0.078
Smoker (vs. Non-smoker)	1.53 (1.10, 2.13)	0.011
Unknown Smoking Status (vs. Non-smoker)	1.21 (0.88, 1.68)	0.248
Diabetes (Yes vs. No)	1.56 (1.28, 1.90)	<.0001
Interaction term of RA X lowered LDL-C	-	0.852
RA vs. OA controls, N = 4,300		
Independent Variable	**HR (95% CI)**	**p-value**
RA (vs. controls)	1.13 (0.92, 1.40)	0.245
Lowered LDL-C (vs. not lowered)	0.50 (0.43, 0.58)	<.0001
Age	1.06 (1.05, 1.07)	<.0001
Male Gender (vs. Female)	1.30 (1.04, 1.64)	0.024
Hypertension (Yes vs. No)	1.32 (0.93, 1.88)	0.125
Antihypertensive Medications (Yes vs. No)	1.58 (1.00, 2.48)	0.049
Smoker (vs. Non-smoker)	1.61 (1.12, 2.32)	0.011
Unknown Smoking Status (vs. Non-smoker)	0.92 (0.61, 1.40)	0.698
Diabetes (Yes vs. No)	1.32 (1.07, 1.64)	0.011
Interaction term of RA X lowered LDL-C	-	0.610

Abbreviations: RA= Rheumatoid Arthritis; OA = Osteoarthritis; LDL-C= Low-density Lipoprotein Cholesterol

were also associated with an increased risk of CV events: older age, male sex, having HTN or anti-HTN medication use, smoking, and having diabetes. The overall model showed that there were no differences in relationships between lowering LDL-C and CV outcomes among RA and general or OA controls [p for interaction term (RA × LDL-C levels) was 0.852 for RA vs general controls, and 0.610 for RA vs OA controls; Table 2].

Although there were no significant differences in the relationship between lowering LDL-C and CV outcomes, we conducted *a priori* subgroup analyses to further show that the LDL-C effects on CV outcomes are in the same direction for RA and non-RA controls. Univariable and multivariable regression analyses for the RA and matched controls were conducted separately (Table 3). After adjusting for other risk factors

Table 3. Association between Lowering Low-density Lipoprotein Cholesterol to Clinically Recommended Levels and Cardiovascular Outcomes for Each Subgroup

Cohort	RA vs. General Controls		RA vs. OA Controls	
	RA patients N=1,522		RA patients N=1,746	
RA patients	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Lowered LDL-C (vs. not lowered)*	0.72 (0.49, 1.07)	0.104	0.70 (0.49, 1.00)	0.053
Lowered LDL-C (vs. not lowered)§	0.68 (0.46, 1.02)	0.060	0.67 (0.46, 0.96)	0.028
	General controls N=6,511		OA controls N=2,554	
Non-RA patients	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Lowered LDL-C (vs. not lowered)*	0.83 (0.63, 1.09)	0.179	0.93 (0.65, 1.31)	0.659
Lowered LDL-C (vs. not lowered)§	0.72 (0.55, 0.95)	0.021	0.76 (0.53, 1.07)	0.118

* Results from univariable analyses

§ Results from multivariable analyses adjusting for age, sex, hypertension, antihypertensive medication use, smoking, diabetes

Abbreviations: RA= Rheumatoid Arthritis; OA = Osteoarthritis; LDL-C = Low-density Lipoprotein Cholesterol

(age, sex, HTN, anti-HTN medication use, smoking status, and diabetes), lowering LDL-C levels was associated with a similar degree in reduction of CV events in patients with RA identified from both cohorts (HR 0.68, 95% CI 0.46–1.02 for matched RA to general controls and HR 0.67, 95% CI 0.46–0.96 for matched RA to OA controls). A decrease in LDL-C was also associated with a reduction in CV events in general controls (HR 0.72, 95% CI 0.55–0.95), and similar HR results were found in OA controls (HR 0.76, 95% CI 0.53–1.07). Sensitivity analyses showed that the results were consistent, applying average or median LDL-C values to define LDL-C status instead of the closest value to the end of followup.

DISCUSSION

We investigated the effect of lowering LDL-C in patients with RA compared with age- and sex-matched general and OA controls. Among patients with a diagnosis of hyperlipidemia and taking statins, we found that a decrease in LDL-C to the clinically recommended levels based on baseline CV risk was associated with 29% and 50% reduced CV events in RA plus matched general controls, and in RA plus matched OA controls, respectively. Interaction terms consistently showed that the effect of lowering LDL-C levels on CV outcomes was similar for both RA and matched general as well as matched OA controls. These findings are meaningful due to the complex relationship between lipid profiles and CV events for patients with RA. Myasoedova,

et al [5] reported increased CV risk with low and high levels of total cholesterol and LDL-C. This nonlinear relationship was also observed in independent RA cohorts by Zhang, et al [21] and Liao, et al [22].

Our results of reduced CV effects associated with lowering LDL-C confirm previous findings. A recent prospective statin-placebo controlled clinical trial in patients with RA found that treatment with atorvastatin 40 mg daily resulted in a 34% risk reduction for major CV events compared to placebo, although these findings are not statistically significant because of early termination of the trial[16]. Posthoc analyses from 2 large clinical trials also reported that patients with inflammatory joint disease (IJD) including RA and non-IJD patients had comparable lipid reduction and protection against CV events both regarding intensive and conventional lipid lowering with statins [14.15].

It is important to note that our inclusion criteria allowed patients with hyperlipidemia who initiated statin therapy. From previous studies investigating LDL-C and CV outcomes in RA, only 17%–30% among patients with RA received a statin [5, 21]. Other interventional studies compared statin users and placebo [14,15,16]. Our study design requiring only statin initiators was intended to avoid treatment selection bias; patients who initiated statin therapy may be different from patients who did not. Also, additional antiinflammatory properties of statin may further bias the results [23, 24] . Thus, our study shows the benefits of lowering LDL-C levels in hyperlipidemia patients who initiated statin treatment.

Similar reductions in CV outcomes were found in subgroup analyses. The HR ranged from 0.67 to 0.76 in 4 different subgroups. Although 2 of the HR (1 in RA subgroup, 1 in matched OA controls) are not statistically significant, this should be interpreted with caution [25, 26, 27]. False-negatives and false-positives due to small sample sizes may lead to these findings [25].

Our RA study population is currently taking DMARD therapy, with 11% taking biologic DMARD. About 30% of patients with RA were positive either for rheumatoid factor (RF) or anticitrullinated protein antibodies (ACPA). Also, 50% of patients with RA were considered positive for either C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) even if a large proportion of data was missing (45% missing for either RF or ACPA, and 24% missing for either CRP or ESR). It may be important to note the treatment and inflammatory status in this study population because these could influence the study results. Studies showed that inflammatory status may change lipid levels; lower levels of total cholesterol, HDL-C, and LDL-C were found among RA patients with active inflammation [8, 28].

Consistent with previous findings, patients with RA in this study reported lower levels of LDL-C and total cholesterol compared to lipid levels in matched general or OA controls at baseline. During the followup, the mean LDL-C levels were further decreased, and patients with RA still had lower lipid levels compared to matched controls. However, the proportion of patients who lowered their LDL-C to recommended levels was the same in RA and general controls, and the benefits of lowering LDL-C levels were also similar.

Our analyses further verified that having RA itself increased CV risk by 76% even after adjusting for traditional risk factors such as age, sex, smoking, HTN, and diabetes. These findings are consistent with previous findings, which suggest about a 50% higher risk of CV events and mortality among patients with RA relative to the general population [1,2]. High inflammation may explain these findings [29, 30, 31, 32]; currently emerging studies on this matter may determine the reasons for the additional CV risk for patients with RA.

Our study has several potential limitations. First, this observational study design limits the causal inferences that can be made between the LDL-C levels and CV outcomes. Patients with lower LDL-C levels may have healthier lifestyles or may adhere to other CV prevention measures compared to patients with higher LDL-C levels. These factors are usually unmeasured and may result in biased effect estimates. Therefore, we should emphasize that this study investigated an "association" between LDL-C and CV outcomes rather than a "causal relationship" between the two. This study was not designed to address the CV benefits of a specific LDL-C treatment target. Instead, we emphasize that the relationship between lowering LDL-C levels and CV outcomes was not different between patients with RA and non-RA controls. Moreover, this study was not able to disentangle the benefits of lowering LDL-C and statin adherence. Our findings might be better explained by the benefits from higher adherence to statin therapy rather than lowering LDL-C.

Another limitation is that our study population is solely from 1 healthcare system and thus our results may not be generalizable to other settings. However, the relationship between LDL-C and CV outcomes should be similar in other populations, and the KPSC population has been shown to be generalizable to that of Southern California [33]. Moreover, we assumed that patients continue their statin therapy during the followup. Also, we considered that 1-time LDL-C measurement during the followup represents the LDL-C status for the entire followup period. This may not be plausible; statin medication adherence and/or LDL-C levels may change over time and this may affect the CV outcomes. However, results were consistent from sensitivity analyses

using different LDL-C values (average or median LDL-C instead of closest LDL-C to the end of followup) or a different followup period (start to followup from the last LDL-C to the end of followup). We were unable to evaluate inflammatory factors in this study investigating CV outcomes because about 50% of the data on those factors were missing. Also, our study focused only on patients already taking statin therapy with a hyperlipidemia diagnosis. There may be higher-risk patients who did not initiate statin therapy or who were not diagnosed with hyperlipidemia and who were not included in our study. However, we believed that investigating LDL-C status and comparing outcomes among the treated hyperlipidemia patients may be reasonable because the population is homogeneous.

Despite these limitations, our study has a number of strengths. This study investigated the association between lowering LDL-C and CV outcomes in a relatively large patient cohort having RA. Also, we were able to create age- and sex-matched non-RA and OA controls based on an ethnically diverse population so that we could examine the LDL-C and CV outcome across a diverse cohort. An additional strength is the relatively rich and high-quality clinical data. Most of the statin users (89% for patients with RA and 79% for non-RA controls) had at least 1 followup LDL-C value so that we could minimize missing data.

Our study showed that lowering LDL-C levels to clinically recommended levels based on baseline CV risk was associated with a decreased CV risk. The relationship between LDL-C and CV outcomes in RA was similar to the relationship found in matched general and OA controls. These findings are consistent with a previous study showing the similar relationship in LDL-C and CV outcomes in RA and non-RA subjects [22], and support CV protective effects of lowering LDL-C with statins in RA suggested by interventional studies [14, 15, 16]. Even though specific LDL-C treatment targets are no longer recommended, our study supports the benefits of lowering LDL-C for patients using statin therapy, for both RA and non-RA controls. Future prospective studies to address this matter will be essential to better understand the benefits of lowering LDL-C in patients with RA. Further, our study showed that patients with RA still had a 76% higher risk of CV even after controlling for LDL-C status. Future studies should address excessive CV risk management strategies in addition to LDL-C in RA.

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CHAPTER 9: SUPPLEMENTARY MATERIAL

APPENDIX 1. Definition of cardiovascular outcomes.

Outcome	Definition
CV death	Fatal CV events defined as death occurring within 1 month after CV events
Myocardial infarction	Primary hospital discharge record with ICD-9-CM of 410.x0, 410.x1
Angina	Primary hospital discharge record with ICD-9-CM of 411.x
Stroke	Primary hospital discharge record with ICD-9-CM of 430.x, 431.x, 433.x, 434.x, 436.x
TIA	Hospital or emergency visit with ICD-9-CM of 435.x
Intermittent claudication	Any encounter with ICD-9-CM of 440.21, 443.9
Heart failure	Primary hospital discharge record of 428.x, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, and 404.93, OR ≥ 3 ambulatory, nonemergency department visits coded for heart failure, with at least 1 of the visits being with a cardiologist

CV: cardiovascular; ICD-9-CM: International Classification of Disease, Ninth Revision, Clinical Modification; TIA: transient ischemic attack.

CHAPTER 10

Cost-Effectiveness Analysis of Abatacept Compared with Adalimumab on Background Methotrexate in Biologic-Naive Adult Patients with Rheumatoid Arthritis and Poor Prognosis

Evo Alemao[1]*, Sukhvinder Johal[2], Maiwenn J. Al[3] and Maureen Rutten-van Mölken[4]

[1]Bristol-Myers Squibb (BMS), USA;
[2]PAREXEL International, London, UK;
[3]Institute for Health Policy and Law, Erasmus University, Rotterdam, The Netherlands;
[4]Institute for Medical Technology Assessment, Erasmus University, Rotterdam, The Netherlands.
*PhD student at Erasmus University Rotterdam, supervised by M.P.M.H.R.M. and M.J.A.

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ABSTRACT

Objectives: To assess cost-effectiveness of abatacept versus adalimumab, each administered with methotrexate, in treating patients with rheumatoid arthritis (RA) stratified according to baseline anticitrullinated protein antibody (ACPA) levels (marker of poor prognosis in RA). **Methods:** A payer-perspective cost-effectiveness model simulated disease progression in patients with RA who had previously failed conventional disease-modifying anti-rheumatic drugs and were starting biologic therapy. Patients commenced treatment with abatacept or adalimumab plus methotrexate and were evaluated after 6 months. Therapy continuation was based on the European League Against Rheumatism treatment response; disease progression was based on the Health Assessment Questionnaire Disability Index score. These score changes were used to estimate health state utilities and direct medical costs. Quality-adjusted life-years (QALYs) and incremental cost per QALY gained were calculated by baseline ACPA groups (Q1, 28–234 AU/ml; Q2, 235–609 AU/ml; Q3, 613–1045 AU/ml; and Q4,1060–4894 AU/ml). Scenario analysis and one-way and probabilistic sensitivity analyses were used to evaluate robustness of model assumptions. **Results:** Abatacept resulted in QALY gain versus adalimumab in ACPA Q1, Q3, and Q4; between-treatment difference (difference: Q1, -0.115 Q2, -0.009 Q3, 0.045; and Q4, 0.279). Total lifetime discounted cost was higher for abatacept versus adalimumab in most quartiles (Q2, £77,612 vs. £77,546; Q3, £74,441 vs. £73,263; and Q4, £78,428 vs. £76,696) because of longer time on treatment. Incremental cost per QALY for abatacept (vs. adalimumab) was the lowest in the high ACPA titer group (Q4, £6,200/QALY), followed by the next lowest titer group (Q3, £26,272/QALY). **Conclusions:** Abatacept is a cost-effective alternative to adalimumab in patients with RA with high ACPA levels.

INTRODUCTION

Rheumatoid arthritis (RA) imposes substantial economic burden on patients, their carers, and the health care system. In 2009, the economic burden of RA was estimated to be up to £4.75 billion per year in the United Kingdom [1], with other sources estimating the overall cost to the UK economy of productivity losses at almost £8 billion per year [2]. About 30% of patients give up work within 1 year of diagnosis, whereas 60% do so within 6 years [2]. RA is characterized by progressive disability, systemic complications, and early mortality [3]. Autoantibody production, including rheumatoid factor (RF) and anticitrullinated protein antibody (ACPA), is believed to play a role in RA disease pathogenesis, and both RF and ACPA assays may be used to detect RA [4]. Although the sensitivities of ACPA and RF appear to be similar, ACPA has demonstrated a higher specificity than RF in detecting early RA [4], resulting in the incorporation of ACPA testing into RA diagnostic criteria in 2010 [5].

In ACPA-positive patients, ACPA is associated with the human leukocyte antigen - antigen D related, which is associated with severe RA through the involvement of $CD4^+$ T cells [3,6]. Thus, patients with RA who are ACPA-positive have a less favorable prognosis and develop a more aggressive disease than those who are ACPA-negative [7,8], suggesting that this distinction may be of clinical value [3]. ACPA is relatively stable over time for an individual patient [9] and, as a biomarker, has been shown to improve the identification of those at risk of developing clinical RA [10,11]. In addition, it appears that ACPA positivity may be important in assessing the mortality risk in patients presenting with early RA [12].

Although clinical practice data demonstrate that presence of ACPA is people with RA is a strong predictor of structural damage (joint erosions) and radiographic progression, its predictive value for treatment outcomes is not well understood [4,13]. Recent studies have shown that outcomes of biologic treatment can vary by ACPA status, and certain biologic disease-modifying antirheumatic drugs (DMARDs) such as abatacept (Orencia®, Bristol-Myers Squibb, New York, NY, USA) have demonstrated a better clinical response in ACPA-positive patients compared with ACPA-negative patients [14].

In the phase IIIB, multinational, prospective, randomized Abatacept versus adaliMumab comParison in bioLogic naivE (AMPLE) study of subjects with RA with background methotrexate (MTX), abatacept was compared directly with adalimumab (Humira®, AbbVie Inc, North Chicago, IL, USA) in biologic-naive patients with analysis by baseline ACPA levels, each treatment was more effective in ACPA-positive patients than in

ACPA-negative patients observed for patients who received abatacept compared with those who received adalimumab in the highest ACPA quartiles with regard to the Disease Activity Score 28 (DAS28) and the Health Assessment Questionnaire Disability Index (HAQ-DI) score [17]. Notably, the mean improvements in DAS28 and HAQ-DI scores with abatacept were significantly greater for the highest ACPA concentration quartile than for the lower three quartiles combined, whereas for adalimumab the improvements were similar for patients with higher ACPA titers may be driven in part by modulator of T-cell activation [6]. Abatacept is thought to block CD28 costimulatory signals required for T-cell activation, thereby limiting the activation of T cells [19].

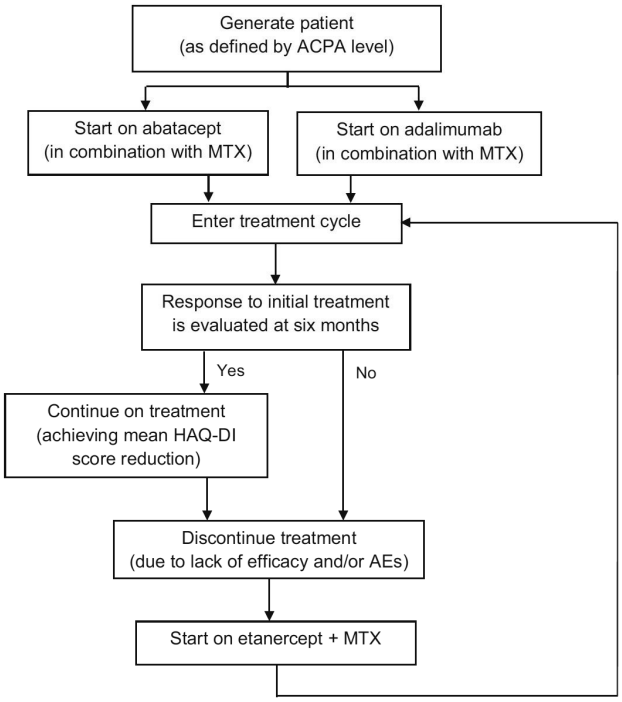
Given the observed clinical benefits of abatacept in ACPA-positive patients, the objective of this analysis was to assess the benefits and costs of abatacept compared with those of adalimumab, each administered with MTX, in treating patients with RA who had inadequate response to MTX and stratified by their baseline ACPA levels. The choice of adalimumab as a comparator was driven by data availability, and the AMPLE study was the only published study to provide a direct comparison with another agent and presented data by patient ACPA level. Anti–tumor necrosis factors (TNFs), and in particular adalimumab, are currently the standard of care in patients who fail MTX; thus, the choice of the comparator is appropriate from a payer perspective. Given the mechanism of action of the anti-TNFs, one could assume that the results of this analysis could be similar to non-adalimumab anti-TNFs.

METHODS

Overall Model Structure

A cost-effectiveness simulation model was developed on the basis of an individual patient simulation (IPS) approach. The model concept is similar to that of the "Birmingham rheumatoid arthritis model" [20] with certain elements incorporated from the "Sheffield rheumatoid arthritis health economic model" [21], and it was programmed in Microsoft Excel. The model (Fig. 1) adopted a payer perspective and tracked a large number of individual patients with different baseline characteristics (age, sex, and HAQ-DI score) over a lifetime, with the follow-up time being divided into 6-month cycles. Model simulation began after a patient had failed conventional DMARDs and was eligible for a biologic DMARD and assumed that each patient received a given treatment until switching to an alternative treatment. All eligible patients were prescribed a biologic DMARD in the model. Patients were generated by sampling from baseline distributions of sex, age, and HAQ-DI score on the basis

Fig. 1 – Overview of the patient-level simulation model



ACPA, anti-citrullinated protein antibodies; HAQ, Health Assessment Questionnaire; MTX, methotrexate

of the AMPLE study population. Each generated patient commenced treatment with either abatacept or adalimumab in combination with MTX and was evaluated on that treatment after a fixed time period (i.e., 6 months), after which the patient either remained on treatment, if the therapy was effective and there were no adverse effects, or switched to another biologic DMARD, that is, anti-TNF drug etanercept. Patients failing on etanercept were switched to palliative care.

Treatment responses for adalimumab and abatacept were based on the European League Against Rheumatism (EULAR) criteria at 6 months as measured in the AMPLE study. The EULAR response criteria classify patients as good responders, moderate responders, or nonresponders, on the basis of the DAS28-C- reactive protein (CRP) value at baseline and the change in DAS28-CRP from baseline to 6 months, using the method of Fransen and van Riel [22]. Patients who achieved EULAR good or moderate response were retained on therapy. Apart from lack of response, switching could also be due to a patient experiencing adverse effects. For patients who continued on therapy, the length of time on each treatment was estimated from data presented in a health technology assessment of RA treatments [23]. Similar to current modeling

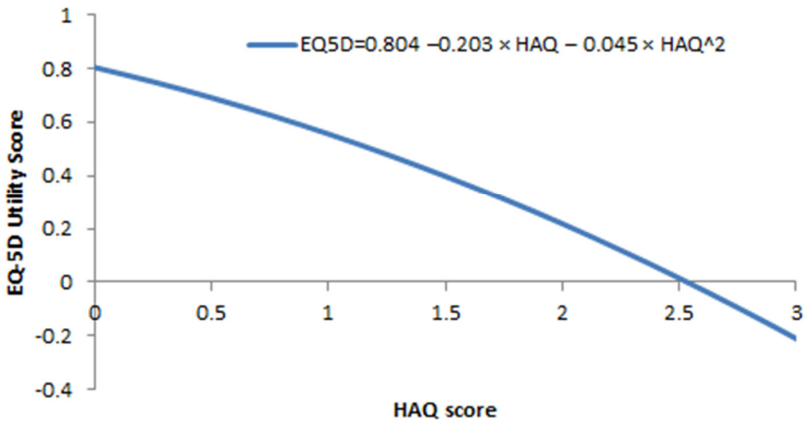
approaches in RA, we do not discriminate between primary treatment failure and secondary treatment. The first treatment switch was treated as a single event, that is, a composite of lack of efficacy and/or adverse events [24].

Change in the HAQ-DI score (a measure of physical functioning) over a lifetime was used to simulate disease progression for each patient (including mortality). The HAQ-DI score ranged from 0 (best) to 3 (worst) in multiples of 0.125 [25]. If a patient responded to therapy, then the therapy was assigned with an initial drop in the HAQ-DI score (i.e., improvement). This HAQ-DI score change was subtracted from the baseline HAQ-DI score to simulate the impact of treatment on disease progression. Any improvement in the HAQ-DI score was lost on quitting the treatment over the 6-month cycle. At the point of treatment failure, the patient experienced a further increase in the HAQ-DI score (rebound effect) before commencing the next predefined treatment within the sequence, at which point the process started again. The baseline HAQ-DI score and the treatment-specific HAQ-DI score change were derived from the AMPLE study. The HAQ-DI score change was used to estimate health state utility (quality of life) and direct medical costs (disease-related hospitalization and joint replacement costs); change in the HAQ-DI score was therefore the prime driver of both benefits and costs in the model. It was assumed that a patient's HAQ-DI score remained constant over time while receiving treatment with biologic DMARDs, which was tested in a sensitivity analysis. Patients experienced disease progression after their initial response to therapy if they discontinued biologic DMARD and moved to palliative care, in which case the HAQ-DI score increased at the rate of 0.06/y [23]. HAQ-DI progression was separated into initial response (i.e., the first 6 months) and subsequent response on the basis of treatment and long-term disease progression.

Death was able to occur at any time within the model (at 6-month intervals) and was RA- and HAQ-DI–dependent. The probability of mortality was a function of age, sex, and having RA, using age and sex-specific mortality rates for the general population and estimates of increased mortality risk by the HAQ-DI score. Mortality rates were related to the HAQ-DI score over a given period [26]. A relative risk of 1.33 per unit HAQ-DI was applied to the general population mortality probabilities [26].

Quality-adjusted life-years (QALYs) were calculated on the basis of the National Institute for Health and Care Excellence (NICE) reference case [27]. An inverse relationship between the HAQ-DI score (disease progression) and quality of life was applied using the EuroQol five-dimensional questionnaire (EQ-5D) utility score based on UK tariffs [23]. The regression equation used in the model to link the HAQ-DI score to EQ-5D scores was a quadratic equation, of the form EQ-5D utility = $0.804 - 0.203 \times$ HAQ-DI $- 0.045$

Fig.2 – Correlation of HAQ score to EQ-5D utility (EQ-5D = 0.804 –0.203 × HAQ – 0.045 × HAQ^2) [23]



× HAQ-DI^2 (see Fig. 2) [23]. This equation estimates utilities less than 0 for the highest values of the HAQ-DI score. Other linear mapping equations were tested in a sensitivity analysis. We chose the nonlinear mapping algorithm for the base case because it provided a better overall model fit compared with a linear regression model. It was assumed that events (transitions) occurred about halfway through a cycle and hence a half-cycle correction was applied by taking the average of the HAQ-DI score at the beginning and the end of a cycle. Parameter uncertainty from the mapping algorithm regression equations was taken into account in the probabilistic sensitivity analysis (PSA).

MODEL INPUTS

Patient Baseline Characteristics

The initial run of the model simulated 15,000 patients with baseline characteristics taken from the AMPLE study [15,16]. Of the 646 patients randomized and treated in the AMPLE study, 86.2% (274 of 318) of the abatacept-treated patients and 82% (269 of 328) of the adalimumab-treated patients completed the study. The overall AMPLE study population is described elsewhere [15,16]. Patients had baseline ACPA levels in the range of 28 to 4894 AU/ml. In line with the AMPLE study [15,16], patients were divided into four ACPA groups based on quartiles: Q1 (28–234 AU/ml), Q2 (235–609 AU/ml), Q3 (613–1045 AU/ml), and Q4 (1060–4894 AU/ml). The use of ACPA level quartiles rather than ACPA level as a continuous measure enabled the analysis of subgroups on the basis of ACPA level while overcoming the limitation of skewed patient distribution across the ACPA level range. The baseline patient characteristics of

patients in the AMPLE study according to baseline ACPA groups are presented in Table 1. The model was run for each ACPA group separately, with efficacy data (Tables 2 and 3) for the individual quartile groups being derived from the AMPLE study in each case.

Table 1 – Key baseline characteristics of patients modelled in the economic model.

	Quartile by ACPA (anti-CCP2 concentration, AU/mL)							
	Q1: 28–234		Q2: 235–609		Q3: 613–1045		Q4: 1060–4894	
Character-istic	ABA (n=42)	ADA (n=55)	ABA (n=51)	ADA (n=46)	ABA (n=46)	ADA (n=51)	ABA (n=46)	ADA (n=51)
Age, years	52.0 (24.0, 80.0)	58.0 (21.0, 83.0)	50.0 (22.0, 70.0)	50.0 (19.0, 78.0)	52.0 (21.0, 78.0)	49.0 (22.0, 73.0)	47.5 (25.0, 73.0)	52.0 (26.0, 78.0)
Female, %	84.8	85.2	88.1	83.6	80.4	87.0	82.6	80.4
HAQ	1.3 (0.0, 2.9)	1.4 (0.0, 2.6)	1.4 (0.0, 2.5)	1.3 (0.0, 2.5)	1.7 (0.0, 2.8)	1.6 (0.0, 2.9)	1.4 (0.0, 2.8)	1.6 (0.0, 3.0)
CRP (mg/dL)	0.8 (0.1, 8.4)	0.6 (0.0, 4.8)	0.9 (0.0, 9.4)	1.3 (0.1, 5.8)	0.9 (0.1, 11.3)	1.0 (0.0, 9.0)	0.9 (0.0, 13.9)	0.7 (0.0, 11.8)
DAS28	5.0 (3.1, 7.6)	5.5 (3.1, 7.3)	5.6 (3.5, 7.6)	6.0 (2.8, 7.4)	5.5 (2.8, 8.1)	5.7 (3.7, 7.9)	6.0 (2.7, 7.8)	5.3 (1.7, 7.8)

ABA, abatacept; ACPA, anti-citrullinated protein antibodies; ADA, adalimumab; CCP2, cyclic citrullinated peptide-2; CRP, C-reactive protein; DAS28, Disease Activity Score 28; HAQ, Health Assessment Questionnaire–Disability Index score; Q, quartile.
Data are expressed as median (min, max), unless otherwise stated.

Table 2 – EULAR response probabilities at six months.

Treatment	EULAR response at six months (% probability)							
	Q1		Q2		Q3		Q4	
	Good	Moderate	Good	Moderate	Good	Moderate	Good	Moderate
ABT + MTX	55.00	22.50	47.92	39.58	40.00	46.67	62.22	33.33
ADA + MTX	56.00	34.00	52.27	36.36	51.02	30.61	52.08	35.42
ENT + MTX	49.67	31.74	46.36	33.95	45.25	28.58	46.19	33.06

ABT, abatacept; ADA, adalimumab; ENT, etanercept; EULAR, European League Against Rheumatism; MTX, methotrexate; Q, quartile.

Table 3 – Estimated mean HAQ change from baseline for each therapy by quartile

	HAQ change from baseline (SE) at six months			
	Q1	Q2	Q3	Q4
ABT + MTX	–0.58 (0.09)	–0.62 (0.08)	–0.67 (0.09)	–0.95 (0.09)
ADA +MTX	–0.64 (0.08)	–0.59 (0.09)	–0.63 (0.09)	–0.75 (0.09)
ENT + MTX	–0.59	–0.54	–0.58	–0.69

Source: [15]
ABT, abatacept; ADA, adalimumab; ENT, etanercept; HAQ, Health Assessment Questionnaire–Disability Index score; MTX, methotrexate; Q, quartile; SE, standard error

Disease Progression and Treatment Sequence

Clinical inputs applied to determine treatment switching and simulate disease progression comprised EULAR responses for abatacept and adalimumab at 6 months, on the basis of the AMPLE study. Patients in the AMPLE study were categorized by the type of response they achieved at 6 months. No data were available for etanercept by quartile; its EULAR response by quartile was derived by estimating the relative rate of response between each quartile and the overall population for adalimumab in the AMPLE arm and applying these relative rates to the EULAR response rate for etanercept in an overall population obtained from a previous mixed treatment comparison [28] (Table 2). Patients who did not achieve a good or moderate EULAR response 6 months after switching to etanercept were switched to palliative care for the remaining duration of the time horizon.

Treatment Duration

Patients who attained a good or moderate response continued on therapy, with the length of treatment based on a time on treatment survival curve derived from the British Society for Rheumatology Biologics Registry data using a Weibull model [23]. Following the approach used previously, the time on treatment was sampled from this distribution [23]. A curve was generated for each treatment and a random sample estimate was drawn from this distribution to determine a time on each treatment for each simulated patient (mean 4.06 years for abatacept plus MTX and for adalimumab plus MTX) [23]. In the base case, mean time on treatment was assumed to be the same for abatacept and adalimumab in patients with an initial moderate or good response. In a sensitivity analysis, the mean time on treatment was allowed to differ between abatacept and adalimumab. A lifetime time horizon was applied in the base case, aligning with NICE guidance [27]. Further time horizons were analyzed in sensitivity analyses. Age-specific yearly mortality probabilities were sourced for the UK population and converted to 6-monthly rates by applying the methodology of Briggs et al. [29].

Treatment Costs and Outcomes

Costs comprised drug costs and monitoring costs and were calculated in 2015 pound sterling. The model included an annual drug cost for each treatment, including any initial loading cost reflecting higher dosage and additional monitoring early

Table 4 – Drug treatment costs, treatment monitoring costs, and acquisition costs.

Treatment	Drug cost (steady state annual cost) (£)	
ABT	9244	
ADA	9156	
ETN	9295	
MTX	31.20	
	Monitoring cost (in first 6 months only) (£)	**Monitoring cost (subsequent 6-month cycles) (£)**
ABT + MTX	904.53	164.88
ADA + MTX	904.53	164.88
ETN + MTX	904.53	164.88

ABT, abatacept; ADA, adalimumab; ETN, etanercept; MTX, methotrexate.

in treatment. Drug costs were applied within the model on the basis of the recommended dosage over each of the model's 6-month cycles. Drug cost data inputs for the United Kingdom and annual administration and drug monitoring costs are presented in Table 4. Unit costs for adalimumab and etanercept were drawn from the British National Formulary [30]. Given that a patient access scheme for abatacept is in place in the United Kingdom, the cost of abatacept was estimated to be the average cost of a number of biologic DMARDs approved in the United Kingdom (£9244), to fairly reflect actual treatment costs for abatacept in the country. Additional sensitivity analyses were conducted on the abatacept cost using average cost across five major markets as well as using the British National Formulary list price. To reflect clinical practice, no additional loading dose cost was assumed in the first year; this assumption was also tested in a sensitivity analysis. Monitoring resource use and costs (biochemical profile, chest x-ray, full blood cell count, and erythrocyte sedimentation rate) for MTX were calculated to be £137.13 for the first 6 months and £59.63 after 6 months. It was assumed that monitoring for biologic therapies was included within the monitoring for MTX or administration costs. Cossts for hospitalization and joint replacement were assumed to increase as the HAQ-DI score increased and were derived from a previous study [28] and inflated to 2015 costs using the National Health Service pay and prices index [31]. The values assumed in the base case are presented in Table 5.

The cost of ACPA testing was not included in the model because it is routinely conducted in clinical practice [32] and EULAR guidelines [33] recommend testing for seropositivity irrespective of the treatment selected. In addition, the exclusion of ACPA testing cost is not expected to change the study findings because, if included, it would have incurred the same cost for both treatment arms. Outcomes included discounted

Table 5 – Annual cost of hospitalization by HAQ score.

HAQ score range	Annual cost (£)
0 < 0.5	173.69
0.5 < 1.0	106.39
1 < 1.5	378.36
1.5 < 2.0	543.33
2.0 < 2.5	1,293.02
2.5 < 3.0	2,788.83

HAQ, Health Assessment Questionnaire–Disability Index score.

disaggregated costs, QALY, and incremental cost per QALY gained (incremental cost-effectiveness ratio [ICER]) as well as undiscounted life-years. Costs and outcomes were discounted at 3.5% annually, as specified for NICE reference case [27]

Sensitivity and Scenario Analyses

Outcomes included discounted disaggregated costs, QALY, and incremental cost per QALY gained (incremental cost-effectiveness ratio [ICER]) as well as undiscounted life-years. Costs and outcomes were discounted at 3.5% annually, as specified for NICE reference case [27] Outcomes included discounted disaggregated costs, QALY, and incremental cost per QALY gained (incremental cost-effectiveness ratio [ICER]) as well as undiscounted life-years. Costs and outcomes were discounted at 3.5% annually, as specified for NICE reference case [27] Univariate sensitivity analysis was used to determine the key drivers in the model; these were then applied to ACPA Q4, because this had shown the lowest ICER for abatacept versus adalimumab. Each variable was varied individually to assess the proportional effect on model results. The variables investigated were abatacept drug cost, abatacept EULAR response rate (good), initial 6-month HAQ-DI score change, and annual HAQ-DI score change while on long-term treatment. Additional scenario analyses were conducted on the basis of different time horizons, the incorporation of an additional (first year) loading dose cost for abatacept, the application of alternative utility mapping equations, and the incorporation of a longer term of treatment (6.17 years) for abatacept.

A PSA was performed for ACPA Q4 for 1000 sets of 1000 patients to assess the impact of parameter uncertainty around major model inputs. Key model parameters were sampled from parametric distributions to generate 1000 estimates of the costs and effects in each arm. EULAR response rates followed beta distributions, nondrug costs, and HAQ-DI score changes; parameters of the utility equation followed normal distri-

Table 6 – Parameters considered in PSA (applied to quartile 4).

Parameter	Distribution	Mean	Standard error
ABT and ADA EULAR response rates	Beta	*See Table 2*	*Assumed 10% of mean*
Utility mapping algorithm parameters			
a	Normal	0.804	0.05
b1	Normal	0.203	0.08
b2	Normal	0.045	0.03
Mortality per unit HAQ	Lognormal	1.33	0.13
ABT and ADA HAQ reductions	Normal	*See Table 3*	*See Table 3*
Annual cost of hospitalization by HAQ score	Gamma	*See Table 5*	*Assumed 10% of mean*

ABT, abatacept; ADA, adalimumab; HAQ: Health Assessment Questionnaire–Disability Index score; QALY: quality-adjusted life year.

butions; mortality relative risk followed a lognormal distribution; and hospitalization costs followed gamma distributions (Table 6)

RESULTS

Primary Economic Analyses

The primary analysis considered the cost-effectiveness of abatacept plus MTX as a first-line treatment after conventional DMARD failure compared with a base-case strategy of adalimumab plus MTX as a first-line treatment in ACPA-positive patients with varying ACPA concentration levels. For patients with poor prognosis (Q3 and Q4), the analysis resulted in increased costs for abatacept but additional benefits (QALYs).

The costs incurred by abatacept treatment compared with adalimumab treatment for patients categorized by ACPA groups are presented in Table 7. With the exception of Q1, treatment with abatacept resulted in higher treatment costs, because of the higher response rates for abatacept and hence higher proportion of patients on long-term therapy, but generally lower hospitalization costs because of various factors, including greater HAQ-DI score reductions after initiating therapy, and delayed disease progression. Treatment and administration/monitoring costs were broadly equivalent for patients who received abatacept and adalimumab across all quartiles. The QALYs gained with abatacept versus adalimumab tended to increase with increase in ACPA titer groups, ranging from -0.115 QALYs for Q1 to 0.279 QALYs for Q4 (Table 8). The

Table 7 – Lifetime per-patient costs of treatment with abatacept vs. adalimumab for patients categorized by ACPA quartile.

	Treatment cost (£)		Administration and monitoring costs (£)		Hospitalisation costs (£)		Total lifetime cost (£)	
	ABT	ADA	ABT	ADA	ABT	ADA	ABT	ADA
Q1	50,188	47,680	9,519	9,488	16,511	16,189	73,710	75,825
Q2	49,212	49,172	9,452	9,451	18,949	18,923	77,612	77,546
Q3	47,314	45,976	9,178	9,211	17,949	18,076	74,441	73,263
Q4	50,685	48,491	8,939	8,971	18,803	19,234	78,428	76,696

ABT, abatacept; ACPA, anti-citrullinated protein antibodies; ADA, adalimumab.

Table 8 – Cost-effectiveness of abatacept vs. adalimumab for patients categorized by ACPA quartile.

	Difference[a] in total cost (£)	Life years (undiscounted)			QALYs			ICER (£/QALY)
		ABT	ADA	Difference[a]	ABT	ADA	Difference[a]	
Q1	-2115	28.12	28.14	-0.02	5.546	5.661	-0.115	18397[b]
Q2	66	28.32	28.32	-0.01	4.700	4.709	-0.009	Dominated
Q3	1178	26.62	26.61	0.00	4.697	4.652	0.045	26272
Q4	1732	25.92	25.84	0.08	4.343	4.064	0.279	6200

ABT, abatacept; ACPA, anti-citrullinated protein antibodies; ADA, adalimumab; ICER, incremental cost effectiveness ratio; Q, quartile; QALY, quality-adjusted life year.

[a]Difference refers to abatacept – adalimumab.

[b]Lower costs and lower benefits.

difference between treatments in life-years gained was small and tended to increase with ACPA titer groups.

In terms of cost-effectiveness for Q3 and Q4, the ICER for abatacept (vs. adalimumab) reduced as the baseline ACPA level increased with an ICER of £26,272/QALY in Q3 to £6,200/QALY in Q4 (Table 8). In the first ACPA group (Q1), abatacept had a lower QALY gain and a lower cost, resulting in an ICER of £18,397/QALY in the southwest quadrant. In the southwest quadrant, the incremental cost reduction should be much larger to accept an intervention with lower benefits; thus, to be considered cost-effective, the ratios should be higher. In the second ACPA group (Q2), abatacept was dominated because it cost slightly more than adalimumab (+£66) and resulted in a slight decrease in QALYs (-0.009).

Sensitivity Analyses

The consequences of modifying model parameters applied in the sensitivity and scenario analysis for Q4 are presented in Table 9, which presents the range of the

Table 9 – Sensitivity analysis of the effect of alternative assumptions (applied to quartile 4).

Analyses	Base case	Sensitivity analysis	Cost per QALY (£)
Base-case			6,200
Time horizon	40 years	10 years	5954
		5 years	5046
ABT HAQ reduction	-0.950	-1.14 (+20%)	4365
		-0.76 (-20%)	21,456
ADA HAQ reduction	-0.750	-0.9 (+20%)	9337
		-0.6 (-20%)	4253
ABT Response rate (Good)	62.22%	49.78% (-20%)	Dominant
ABT annual cost	£9,275	£15,756 (Full UK list price)	81,345
		£12,257	39,775
ABT loading dose cost included in first year (£907.20)	£0	£907.20	8770
ABT time on treatment = 6.17 years	4.06	6.17	12,539
Utility equation	$0.804 - 0.203 \times HAQ - 0.045 \times HAQ^2$	EQ-5D = $0.89 - (0.28 \times HAQ)$	6447
		EQ-5D = $0.76 - (0.28 \times HAQ)$	6299

ABT, abatacept; ADA, adalimumab; HAQ: Health Assessment Questionnaire–Disability Index score; QALY, quality-adjusted life year.

ICER between the different assumptions tested in the analysis. For time horizon, the ICER ranged from £5046/QALY for 5 years to £5954/QALY for 10 years. Changes in the HAQ-DI score reduction on abatacept treatment had the highest impact on the ICER result; even with a 20% decrease in the HAQ-DI score reduction on abatacept, the abatacept treatment strategy remained cost-effective at £21,159 per QALY, which was less than the accepted National Health Service threshold for the cost-effectiveness of new therapies [34]. Incorporating the loading dose cost for the first year of abatacept treatment and extending the abatacept time on treatment to 6.17 years to reflect a more severe population [23] increased the ICER but the abatacept treatment strategy remained cost-effective.

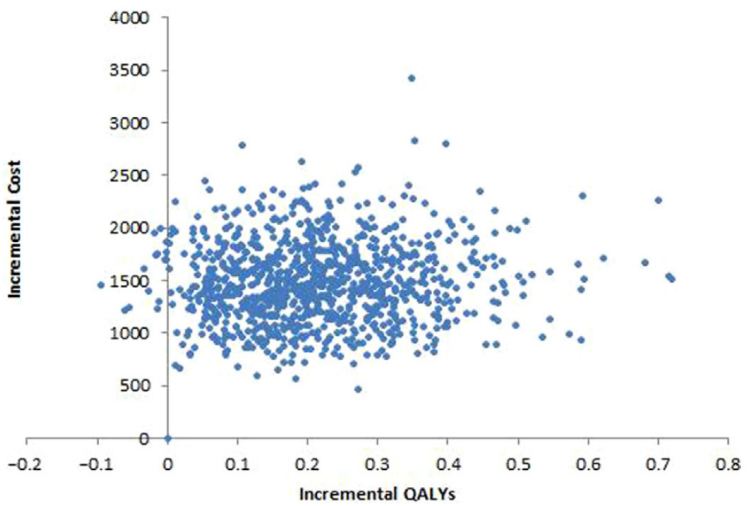
The model was stable when different HAQ-DI score to utility mapping algorithms were applied, in terms of the ICER. Nevertheless, using the HAQ-DI score utility algorithm, which estimated all utilities greater than 0 (0.89 – [0.28 x HAQ-DI]), had a major impact on total QALYs calculated compared with the base case (6.298 vs. 4.343 for abatacept and 6.057 vs. 4.064 for adalimumab), although the incremental difference

between abatacept and adalimumab was similar when using the different algorithms (0.241 vs. 0.279, respectively). The analysis indicated that the cost-effectiveness results remained robust in the face of plausible variations of the main assumptions used in the model.

Probabilistic Sensitivity Analysis

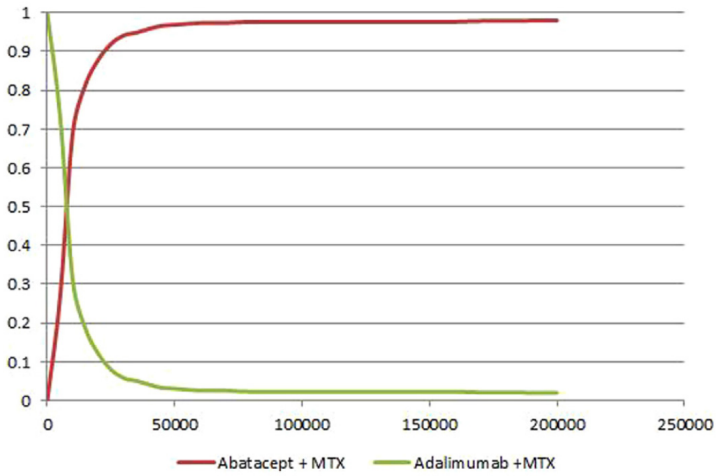
In the PSA of abatacept versus adalimumab for Q4 patients, 98.5% of all 1000 simulation results fell in the northeast quadrant of the cost-effectiveness plane, indicating that the abatacept strategy was more effective but also more costly in all simulated runs for the model (Fig. 3). On the basis of the PSA, the probability of each treatment strategy being cost-effective at different decision-making thresholds (i.e., willingness to pay per QALY gained) is presented in Fig. 4. There was a 94.2% likelihood that the abatacept strategy was cost-effective at a willingness-to-pay threshold of £30,000 per QALY gained.

Fig. 3 – Cost-effectiveness plot of probabilistic sensitivity analysis results (abatacept vs. adalimumab).



QALY: quality-adjusted life year.

Fig. 4 – Cost-effectiveness acceptability curve (abatacept vs. adalimumab).



MTX: methotrexate.

DISCUSSION

This is the first published economic evaluation to estimate the cost-effectiveness of RA treatments stratified by subgroups of patients with RA on the basis of prognostic factor defined by baseline ACPA levels. This model projected abatacept to be a cost-effective alternative to adalimumab in Q3 and Q4 of ACPA-positive patients with RA, showing trends toward increasing incremental total cost and QALY gain with abatacept versus adalimumab with increasing ACPA level. The ICER for abatacept compared with that for adalimumab was the lowest for patients with the poorest prognosis (ACPA Q4 ICER = £6200/QALY). An intervention with an ICER lower than £20,000/ QALY to £30,000/ QALY gained is generally considered to be cost-effective in the UK health care setting [34]. In the group with the lowest ACPA level, the ICERs were in the southwest quadrant, that is, lower cost and lower QALY gains, and therefore the ICERs should be interpreted with caution.

Previous studies have identified serum parameters such as RF and ACPA to be associated with destructive RA [35–38]. Although the predictive value of RF for joint erosion is mixed, the data on ACPA are more uniform, with several studies linking ACPA to erosive disease, comprising structural damage (joint erosions) and radiographic progression [4,7,8,13]. A systematic review by Jilani and Mackworth-Young [13] concluded the presence of ACPA to be a strong predictor of erosive disease. Because established

RA is a heterogeneous disease, some patients experience aggressive disease in spite of treatment. These patients also have higher use of direct medical resource as well as overall and RA-specific costs [39–41]. Thus, targeting these patients with biologic DMARDs is important.

Reliable markers of prognoses of aggressive RA, such as ACPA, can provide at baseline the rationale for aggressive therapy in patients with a substantial risk of developing destructive disease. In addition to evaluating the clinical benefit of aggressive treatments in patients at risk, one would need to consider the cost-effectiveness of pursuing such a policy. Our analysis was geared toward evaluating the appropriate cost-effective alternative biologic DMARD intervention in managing patients with poor prognosis and thus at risk of disease progression. Similar to our findings, another analysis has also shown biologic DMARDs to be cost-effective in patients at risk of rapid disease progression [42]. Our analysis, however, takes this work a step further by specifying the prognostic factors and comparing one biologic DMARD with another, demonstrating that abatacept provided a cost-effective alternative to adalimumab in patients with poor prognosis who had an inadequate response to MTX.

The AMPLE study was chosen as a source of model inputs by way of it being the only head-to-head, randomized, controlled study between two biologics that incorporates radiographic progression end points, provides data on erosions and joint space narrowing in patients with RA, and includes data presented by patient ACPA level [15,16]. The demographic and clinical characteristics of the patients at AMPLE study baseline were balanced across the treatment groups and were considered to be typical for RA studies (the mean age of the patients was 51 years and the mean DAS28-CRP score was 5.5 ± 1.1 in both groups, with equal proportions of patients with moderate and high disease activity in each group [15]). Abatacept and adalimumab provided similarly effective treatment outcomes in patients with RA [15,16]. As in the AMPLE study, the model compared abatacept with adalimumab; the lack of ACPA quartile data for other treatments currently prohibits running such comparisons for other treatment combinations. Apart from the AMPLE study, data based on real-world RA registries have demonstrated an association between higher ACPA concentrations and improved abatacept efficacy and retention [14,42–45]. Therefore, we believe that the AMPLE study provided the model with reliable comparative efficacy data for a population representative of the general RA population and for two agents where patient ACPA level could be expected to influence outcomes and costs.

A key strength of this model is the application of the approach considered by evidence review groups responsible for assessing the cost-effectiveness of RA treatments in the

United Kingdom [1,23]. Decision making on the use of treatments for RA in the United Kingdom is based on IPS models, such as the Birmingham rheumatoid arthritis model [20] and the Sheffield rheumatoid arthritis health economic model [21]. As with other IPS models, this cost-effective analysis enabled patient progression while on a certain treatment if a specific disease level was met, allowed treatment sequences to be evaluated rather than single therapy, and incorporated the uncertain duration of treatment effect on each patient [21].

As with any economic evaluation study, it is important to acknowledge the limitations of the analysis and to reflect on the assumptions and data upon which the conclusions have been drawn.

In terms of the patient population characteristics taken from the AMPLE study, although the study population was reasonably large (646 participants), the number of patients in each trial arm by ACPA quartile was relatively small (42–55 participants), which may reduce confidence in the effectiveness estimates by ACPA quartile that were used as inputs.

The present analysis explored the relationship between ACPA level and ICER using ACPA level quartiles and did not attempt to identify any ACPA threshold corresponding to a single ICER value or model outcomes according to ACPA levels of clinical significance. As such, the association is deserving of further study. Such an analysis might require an alternative outcome, such as response rate. Thresholds at which the best response rate occurs could then be investigated using, for example, a receiver-operating characteristic curve to determine the best combination of sensitivity and specificity. This is not possible using the model in its current form because the model uses response rate as an input parameter rather than as an outcome. A future economic analysis might also consider the cost-effectiveness of a treatment algorithm incorporating screening for ACPA level and subsequent treatment of a pre-determined patient subset versus no screening and the treatment of all patients. The present study evaluated the impact of prognostic factor such as ACPA levels on cost-effectiveness and not the impact of a screening strategy.

In addition, the base case assumed that HAQ-DI score progression while on biologic therapy was 0. This assumption is used in most cost-effectiveness models and the literature is mixed because some analyses show that patients with RA treated with a TNF inhibitor have continued disease activity [23]. For patients on palliative care, a constant annual rate of HAQ-DI score progression was assumed. A recent NICE appraisal (Technology Appraisal 375 [28]) has suggested a nonlinear HAQ-DI score

progression model, derived from an early RA data registry, for patients on conventional DMARDs and palliative care is a more appropriate reflection of a chronic disease, and that the choice of model to inform HAQ-DI score progression had an impact on ICERs. It is not clear how the use of a cubic representation of HAQ-DI score progression would affect the results of the current model, but it is expected that because the treatment strategy after failure of first-line treatment is the same for both treatment arms, the incremental results would not change greatly.

The utility measures of the EQ-5D were based on a mapping of the HAQ-DI score to utility described by Malottki et al. [23] and used in multiple cost-effectiveness models. Such mapping studies usually overestimate the utilities of bad health states and underestimate the utilities of good health states. It has been suggested that a substantially better estimate of utility is obtained by the inclusion of pain alongside the HAQ-DI than via the HAQ-DI alone [28]. The application of different utility mapping algorithms in this study was investigated in sensitivity analyses and had little impact on the incremental results, but the use of a mapping algorithm incorporating pain as well as the HAQ-DI score should be investigated in future work.

Finally, because of availability of data, the model evaluated abatacept against one anti-TNF agent only (adalimumab) and incorporated clinical data for these two agents only from the observational trial. The model also did not assess the introduction of a second conventional. DMARD after MTX failure because the model and the AMPLE trial were reflecting treatment guidelines for the patients with poor prognosis. The limited use of comparators in this study creates an opportunity for further research to assess the cost-effectiveness of abatacept versus other conventional and biologic treatment options.

For the next treatment in the sequence (etanercept), it was assumed that the relative difference in EULAR response probabilities observed for adalimumab between the AMPLE study and a recent previous mixed treatment comparison [28] would be similar for etanercept. It is, however, unlikely that this would have favored either abatacept or adalimumab, because patients in each treatment arm moved on to etanercept after failure on the first line of therapy. We tested the impact of these assumptions on the findings via various sensitivity and scenario analyses. Overall, we found that the results were robust in the face of changes in input parameters, yet the opportunity remains to evaluate abatacept against other agents and to increase the clinical data inputs contributing to the robustness of the model.

CONCLUSIONS

Abatacept provided a cost-effective alternative to adalimumab in ACPA-positive patients with RA with an inadequate response to MTX. For ACPA-positive patients with higher ACPA levels (Q4 and Q3), higher EULAR response rates for abatacept patients compared with adalimumab patients resulted in higher proportions of patients on long-term therapy resulting in increased treatment costs, but these were partially offset by a greater reduction in disability (HAQ-DI) and lower hospitalization costs. The increased cost per QALY gained for abatacept was lower in those patients with higher ACPA levels. This economic evaluation, therefore, suggests that the use of abatacept in patients with RA with poor prognosis should be seen as a cost-effective approach to the management of RA in the United Kingdom, with clear advantages seen in health-related quality of life.

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CHAPTER 11

Conceptual Model for the Health Technology Assessment of Current and Novel Interventions in Rheumatoid Arthritis

Evo Alemao[1]*, Maiwenn J. Al[2], Annelies A Boonen[3], Matthew D Stevenson[4], Suzanne Verstappen[5], Kaleb Michaud[6], Michael E. Weinblatt[7] and Maureen P.M.H. Rutten-van Mölken[2,8]

[1]Bristol-Myers Squibb (BMS), USA;
[2]Erasmus School of Health Policy and Management (ESHPM,), Erasmus University Rotterdam, the Netherlands;
[3]Maastricht University Medical Centre, the Netherlands;
[4] School of Health and Related Research, University of Sheffield, Sheffield, UK;
[5]Arthritis Research UK Centre for Epidemiology, Centre for Musculoskeletal Research, Division of Musculoskeletal and Dermatological Sciences, School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK; NIHR Manchester Biomedical Research Centre, Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, UK;
[6]University of Nebraska, US;
[7]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard University, US;
[8]Institute for Medical Technology Assessment (iMTA), Erasmus University Rotterdam, the Netherlands.
*PhD student at Erasmus University Rotterdam, supervised by M.P.M.H.R.M. and M.A.

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ABSTRACT

Objective: To evaluate current approaches to economic modeling in rheumatoid arthritis (RA) and propose a new conceptual model for evaluation of the cost-effectiveness of RA interventions. **Methods:** We followed recommendations from the International Society of Pharmacoeconomics and Outcomes Research-Society of Medical Decision Making (ISPOR-SMDM) Modeling Good Research Practices Task Force-2. The process involved scoping the decision problem by a working group and drafting a preliminary cost-effectiveness model framework. A systematic literature review (SLR) of existing decision-analytic models was performed and analysis of an RA registry was conducted to inform the structure of the draft conceptual model. Finally, an expert panel was convened to seek input on the draft conceptual model. **Results:** The proposed conceptual model consists of three separate modules: 1) patient characteristic module, 2) treatment module, and 3) outcome module. Consistent with the scope, the conceptual model proposed six changes to current economic models in RA. These changes proposed are to: 1) use composite measures of disease activity to evaluate treatment response as well as disease progression (at least two measures should be considered, one as the base case and one as a sensitivity analysis); 2) conduct utility mapping based on disease activity measures; 3) incorporate subgroups based on guideline-recommended prognostic factors; 4) integrate realistic treatment patterns based on clinical practice/registry datasets; 5) assimilate outcomes that are not joint related (extra-articular outcomes); and 6) assess mortality based on disease activity. **Conclusions:** We proposed a conceptual model that incorporates the current understanding of both clinical and real-world evidence in RA, as well as of existing modeling assumptions. The proposed model framework was reviewed with experts and could serve as a foundation for developing future cost-effectiveness models in RA.

INTRODUCTION

Rheumatoid arthritis (RA) is a progressive disease characterized by inflammation of synovial tissue with symmetric involvement of peripheral joints of the hand, feet, and wrists[1-2]. The prevalence of RA ranges from 0.4% to 1.3% [3]. RA not only contributes to reduced survival, health related quality of life (HRQOL), activities of daily living and work productivity, but is also associated with higher health resource utilization and costs [4-7]. Most RA-related direct costs are associated with biologic disease modifying anti-rheumatic drugs (bDMARDs), which have improved outcomes in RA patients [8-10]. Since the introduction of these agents, our knowledge of RA as a disease has greatly increased and new therapies as well as combination therapies (of different bDMARDs or of bDMARDs in combination with synthetic (sc)DMARDs) targeting multiple immune pathways are being developed [11,12]. Accompanying development of novel interventions is the introduction of bioequivalents or biosimilars of existing bDMARDs. In an environment featuring multiple therapeutic options to manage RA patients, and in the face of constrained health resources, cost-effectiveness models in drug treatment that enable more precise estimations of cost and benefits could reduce the risk of inefficient resource allocation.

The framework for cost-effectiveness models for treatments in RA has evolved since first published in early 2000s, with the introduction of bDMARDs [13,14]. The current modeling approach has served to establish economic benefits of bDMARDs in most countries, in moderate to severe RA patients with inadequately respond to methotrexate [15,16]. In our opinion previously, published models have potential room for improvement in six areas. First, current models base treatment response on composite measures of disease activity such as European League Against Rheumatism (EULAR) response [17], American College of Rheumatology (ACR) response [18], and Disease Activity Scores in 28 joints C-reactive protein (DAS28-CRP)[19]. These disease activity measures are not aligned to guideline-recommended target measures of remission and hence cannot evaluate the cost-effectiveness of policies designed to implement treatment guideline-based targets [20,21]. In addition, these measures are biased (favorably) to certain therapeutic interventions, as discussed further in results section under new conceptual model.

Second, disease progression in these models is based on physical functioning measured by the Health Assessment Questionnaire (HAQ) [22]. More rapid decline in HAQ on treatment has been observed in patients with RA of recent onset, compared to those with established RA [23]. Hence change in HAQ is greater in patients with

early (versus established) RA, potentially underestimating treatment benefits in patients with established RA, as HAQ might have a ceiling effect.

Third, contemporary models derive utility scores from the HAQ, based on mapping algorithms. Nonlinear models are now recommended, and overall mapping of HAQ to European Quality of life 5 dimension (EQ-5D) [24] has been improved by including disease activity and pain in these models [25,26]. However, no study (to our knowledge) has evaluated the impact of other dimensions of RA or of different composite measures on utility scores.

Fourth, certain baseline characteristics, such as age, gender, and HAQ score, are accounted for in current models. However, most of these models do not report incremental cost-effectiveness ratios (ICERs) according to important subgroups. Recent studies have evaluated ICER within a limited number of RA subgroups [27,28].

Fifth, current modeling approaches focus on joint-related outcomes in RA, largely at the expense of extra-articular manifestations. Extra-articular manifestations occur in 18% to 41% of patients with RA [29-32]. A growing body of evidence—mainly derived from observational databases and registries—suggests that specific RA therapies, including methotrexate and bDMARDs, may reduce the risk of extra-articular cardiovascular disease [CVD] manifestations with RA [33,34].

Sixth and finally, long-term treatment discontinuation in current models is based on real-world registry data, and these models allow for patients to cycle through tumor necrosis factor (TNF-α) inhibitor via limited sequential use of bDMARDs [26,35]. However, these same models do not allow for data in which health providers escalate doses or re-initiate bDMARDs once treatment has been discontinued. These factors may result in underestimating both increasing therapeutic benefits and costs. Although contemporary RA therapy is moving toward lowering the dose of the bDMARDs in patients once they have attained a predefined target disease activity state, such dose de-escalation is not incorporated in previously reported models [36-39].

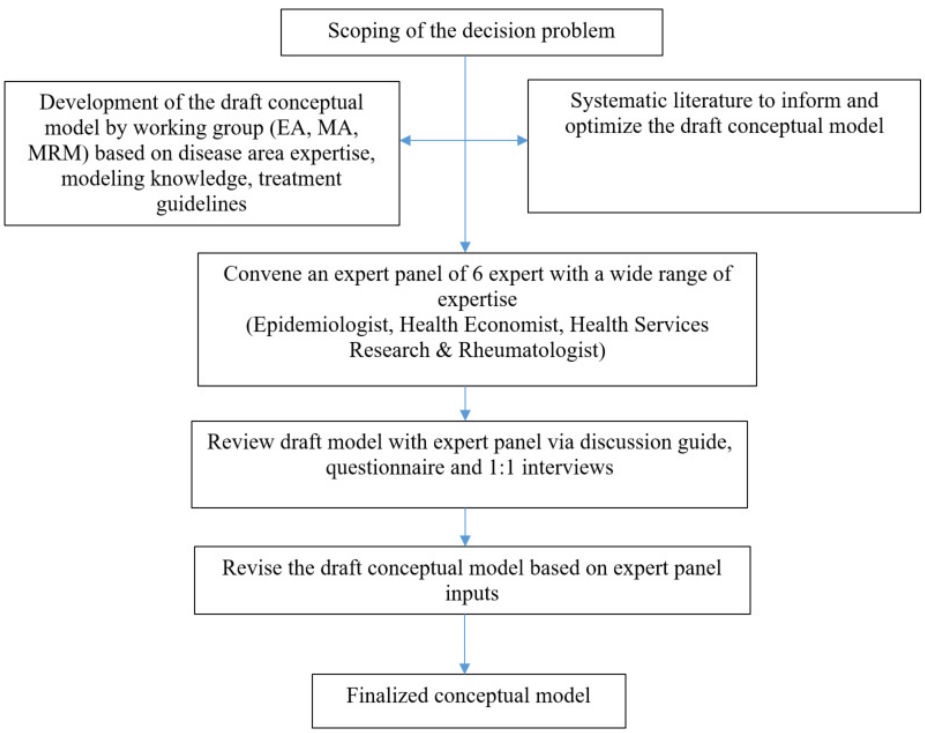
Taken together, these factors point to unmet needs related to pharmacoeconomic modeling in RA. Consideration of these aspects in future economic modeling of RA treatments could enable evaluation of costs and benefits of therapies in manner that reflects prevailing clinical realities with the aim of producing more accurate cost-effectiveness estimates. The objective of this analysis was to review current economic models in RA and propose a revised conceptual model framework.

METHODS

In developing the conceptual model, the recommendations outlined by the International Society of Pharamacoeconomic and Outcomes Research-Society of Medical Decision Making (ISPOR-SMDM) Modeling Good Research Practices Task Force-2 were followed [40]. As depicted in Figure 1, the process involved scoping out the decision problem by a working group and drafting a preliminary cost effectiveness model framework. A systematic literature review (SLR) of existing decision-analytic models was performed and analysis of a RA registry was conducted to inform the structure of the draft conceptual model. Finally, an expert panel was convened to seek input on the draft conceptual model.

Scoping: The knowledge gaps in current models as explained in the introduction were elucidated in a three-member (EA, MA, MR) working group. The working group focused on various aspects of the model, such as 1) measures to access treatment responses/ treatment targets, 2) measure to assess RA disease progression, 3) utility mapping, 4) RA subgroups, 5) treatment patterns (e.g. dose escalation, dose de-escalation) 6)

Figure 1: Schematic overview of the development process of the conceptual model



extra-articular outcomes, and mortality. Based on these aspects the working group put together a list of revisions of existing models (S1 Appendix) and drafted a conceptual model (S2 Appendix). The draft conceptual model was based on the working group analyses of a RA registry to explore treatment targets and extra-articular manifestation of RA, and RA subgroups, which have been published elsewhere [41-44]. In addition, the working group relied on literature and knowledge of clinical guidelines to inform model development.

SLR: A review of existing decision-analytic models on the cost-effectiveness of RA therapies published in English since 2006 was conducted as part of the scoping process. The search strategy is depicted in S3 Appendix. Primary searches were conducted in Medline, EMBASE, and EconLit simultaneously using Ovid® based on the search strategy outlined. In addition to the SLR, recent publication on methodologies of economic modeling in RA was also reviewed [45]. To supplement the database search, a manual search of previous health technology assessment (HTA) reports was conducted on the UK National Institute for Health and Clinical Excellence website (https://www.nice.org.uk/guidance/ta375/history [last accessed Nov 2017]). The primary objective of the SLR was to identify published economic evaluations of bDMARDs for RA to evaluate model structure, short-term treatment targets/responses, RA disease progression (long-term response when treatment is initially successful), utility mapping, patient subgroups (with characteristics that could be treatment effect modifiers), treatment aspects (e.g. switching, does escalation, dose-escalation), time horizon, and mortality associated with RA.

Analysis to Inform Conceptual Model: To inform disease progression and utility mapping in the conceptual model, the WG conducted a retrospective analysis of a RA registry. A longitudinal sequential registry of primarily established RA patients was used for this analysis in which disease activity was measured annually during rheumatology visits using multiple composite functional measures [46]. These included the DAS28-CRP, Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI) [47]. The generic HRQOL index EQ-5D was evaluated every 6 months via both mailed questionnaires and in-person interview (during annual visit). The progression of RA using various composite measures as well as changes in these disease activity over time was evaluated using general linear models. Mapping algorithms based on DAS28-CRP, SDAI, and CDAI were compared to the physical functioning (HAQ)-based mapping algorithm. Fixed-effects models were used to estimate the best predictors of EQ-5D, because within-patient variability over time is more important than between patient variability in economic models [48].

Expert Panel: An expert panel comprising two rheumatologist (AB, MW), one health economist (MS), and two epidemiologists/health services researchers (KM, SV) was convened to provide input to the conceptual model. The draft conceptual model was presented to each expert in a multistep approach. In the first step, a member of the working group (EA) shared the discussion guide developed by the working group with the expert panel members. The discussion guide contained an overview and limitations of current modeling approaches in RA as well as the proposed conceptual model structure. It also included a brief questionnaire that focused on the proposed modifications to the cost-effectiveness model. In the second step, opinions from all experts of the panel were gathered via individual interviews. The third step involved updating the draft conceptual model and collating all responses to questions and comments. The revised document was shared with all experts for additional inputs. Additional updates were then incorporated, and the conceptual model was sent back to the panel for a final opportunity to provide suggestions.

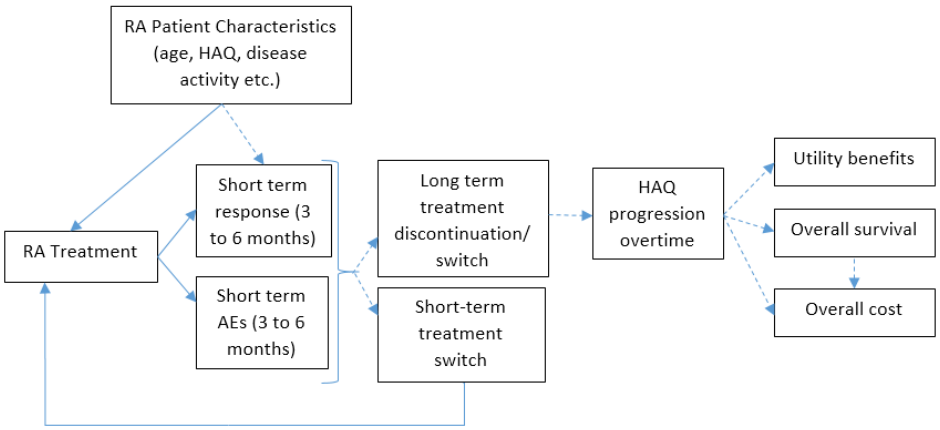
RESULTS

Scoping: The decision problem that the conceptual model would address was defined as identifying cost-effective drug interventions for moderate-to-severe RA that result in the most health benefits for the overall RA population as well as for specific subgroups (such as those with poor prognostic factors). This includes current and novel interventions that are being developed and may be introduced in clinical practice in the future as monotherapy or combination therapies.

SLR: A total of 32 economic evaluation studies were identified by the initial SLR, 5 of which were review articles. The remaining 27 manuscripts evaluated are summarized in S3 Appendix Table 3 [27,34,49-73]. The primary model structures were cohort based or individual patient simulations, which included discrete event simulations and individual patient Markov models. More recent published models tended to be primarily individual patient simulations.

The assumed relationship between different model variables is summarized in the influence diagram represented in Figure 2. Each solid arrow represents a direct effect of one variable on the other, while the dashed lines represent the mathematically derived structural relationships. In general, these models evaluate short-term (3 to 6 months) treatment effects based on clinical trial efficacy. Based on the short-term efficacy and probability of adverse events (AEs), a decision rule was included in the model for a patient to continue treatment or not. If treatment is continued, then

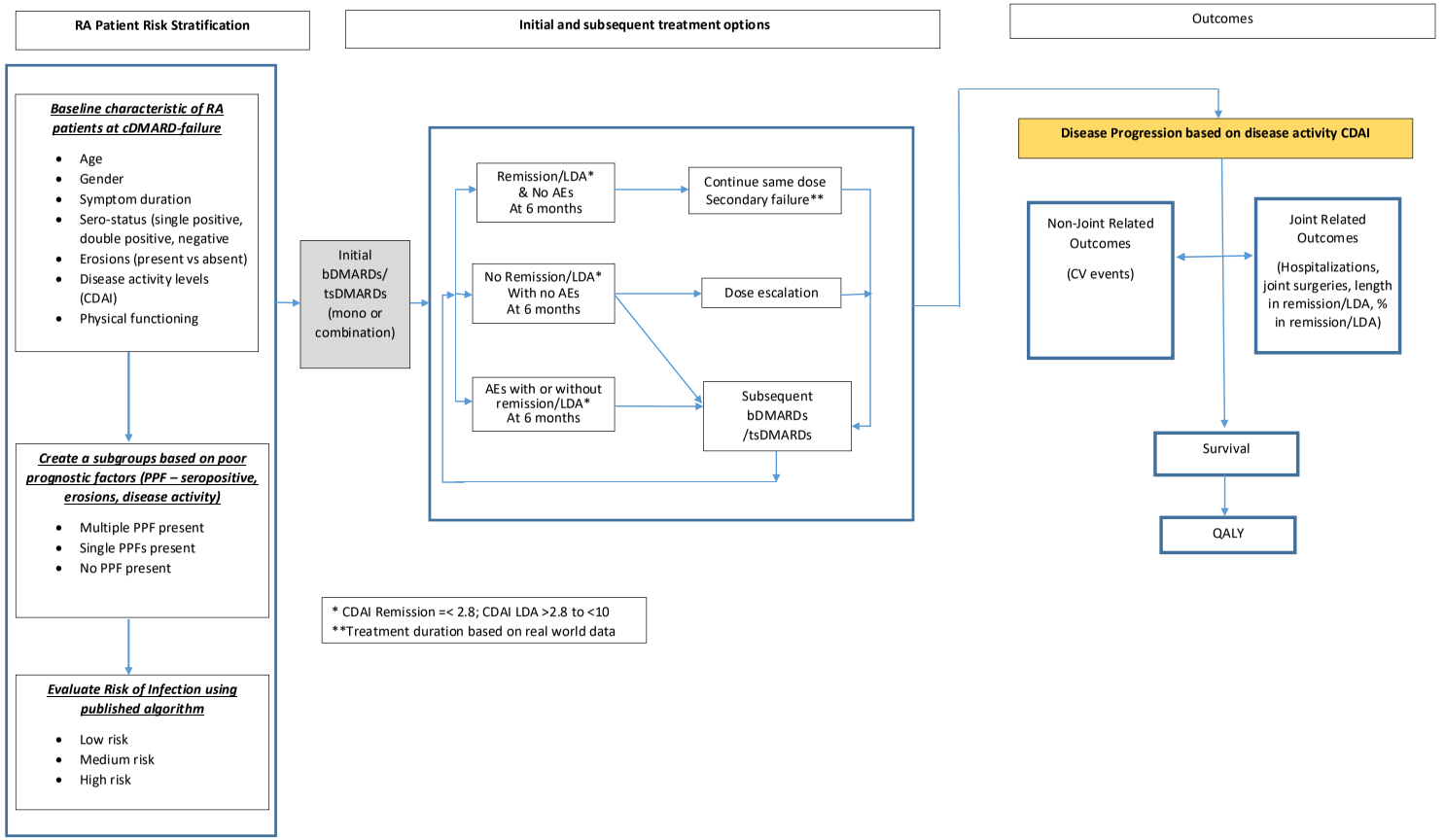
Figure 2: RA Economic Model Influence Diagram for Structural Relationship



disease progression is estimated based on HAQ change over time. In recent models HAQ change over time is based on mixture models, while earlier models used linear progression (0 per annum for bDMARDs and 0.03 to 0.045 per annum for cDMARDs) [27, 60]. HAQ scores are then mapped to HRQOL, mortality rates and resource use, using mapping algorithms. The long-term treatment duration in the majority of the simulation models is based on real-world registry data, extrapolated using survival models with time to treatment discontinuation as outcomes. The endpoint driving cost-effectiveness models in RA is primarily physical functioning, whereas other endpoints such as radiographic progression are rarely used [72].

New Conceptual Model: The conceptual model drafted by the working group is represented in Figure 3. The proposed conceptual model is an individual patient simulation model with a lifetime horizon proposed to capture short-term and long-term benefits and cost of interventions. Outcomes are defined as quality-adjusted life years (QALYs) and life-years gained (LYG). This model is intended for HTA and is based on the payer's perspective and has three distinct modules: 1) *patient characteristic module*, 2) *treatment module* and 3) *outcome module*. This framework enables addressing issues of treatment responses, RA subgroups, real world treatment patterns and extra-articular manifestation of RA mentioned in the introduction. This proposed conceptual model should be seen as "aspirational" because not all data elements required to populate the model are not available (at the time of writing) but are likely to become available in the future. The ISPOR-SMDM Modeling Good Research Practices Task Force-2 stresses that conceptual models should not be driven solely by the presence or absence of clinical data [40].

Figure 3: Proposed Conceptual Model to Evaluate Cost Effectiveness in RA



To improve the clinical relevance of the economic models in RA, it is important to align treatment responses to guideline-recommended targets [20,21]. The working group proposed the expert panel to consider CDAI as a measure of treatment response in the conceptual model (change 1a). This was primarily based on observed associations between treatment targets and outcomes of physical functioning (HAQ), HRQOL (i.e. EQ-5D), and health resource use. A greater improvement was observed in these outcomes among patients attaining (vs. not attaining) a CDAI based target, compared to SDAI and DAS28-CRP based targets [43]. In addition, CDAI has acceptable psychometric properties, including validity and sensitivity to change [74-77]. CDAI remission does not include levels of CRP or erythrocyte sedimentation rate (ESR) which are primarily impacted by therapies such as interleukin-6 and janus kinase inhibitors. Thus, the new conceptual model includes a CDAI score of <2.8 (remission) or ≤10 (LDA) as a definition for responder for treatment continuation. In terms of disease progression, the working group proposed CDAI change over time (change 1b). This was based on analysis of changes in CDAI, SDAI and DAS28-CRP in a cohort of patients with mostly established RA [46]. Results of these analyses indicate that CDAI is most responsive to change over time (S4 Appendix).

Finally, the mapping exercise of disease activity measures and physical functioning to EQ-5D indicates that mapping models predicated on CDAI and Routine Assessment of Patient Index Data-3 (RAPID-3) measures have the best fit according to r^2 and root mean square error values (Table 1). Based on these findings, the working group proposed to the expert panel that the conceptual framework should include utilities based on disease activity measure (CDAI) and patient reported outcomes of physical function such as RAPID-3 (change 2).

Based on current evidence, the conceptual model accommodates subgroups with a high risk of disease progression such as those with multiple prognostic factors (change 3). Additional subgroups that the working group considered important for inclusion were patients with susceptible to infections. The *patient characteristic module* accounts for patient characteristics when entering the model and at subsequent time points. This module enables risk stratification of RA patients based on prognostic factors. Some commonly reported prognostic factors for a more rapid and aggressive disease are double seropositivity for anti-cyclic citrullinated peptide antibody (ACPA) and rheumatoid factor (RF), as well as erosions, disease activity and measures of inflammation (CRP/ESR) [78-82]. There is evidence that certain prognostic factors can be considered as treatment effect modifiers [83-85]. Subgroups based on patients' risks of infections were considered as there is evidence that corticosteroids and certain

Table 1: Fixed Effects Regression Models for EQ5D

Models	R-Square	Root MSE	F- value
Patient global, Patient pain scale RADAI Joint Score	0.702795	0.093454	14.20
RAPID3, RADAI Joint Score	0.717904	0.091493	14.33
RAPID3	0.708717	0.092986	13.76
RAPID3, CDAI	**0.750240**	**0.091260**	**7.35**
mHAQ	0.677473	0.095895	15.36
mHAQ, RADAI Joint Score	0.696132	0.093075	16.68
mHAQ, CDAI	0.713277	0.094982	7.80
mHAQ, mHAQ square	0.677589	0.095883	15.35
mHAQ, pain	0.705025	0.092921	14.38
mdHAQ, RADAI Joint Score	0.699629	0.092616	17.00
mdHAQ	0.682759	0.095187	15.77
Models with baseline co-variates of age, duration, CRP and serostatus			
Patient global, Patient pain scale RADAI Joint Score	0.742697	0.091409	7.49
RAPID3, RADAI Joint Score	0.725320	0.090025	15.11
RAPID3	0.708010	0.092828	13.96
RAPID3, CDAI	**0.748709**	**0.090882**	**7.41**
mHAQ	0.675191	0.095998	15.38
mHAQ, RADAI Joint Score	0.694265	0.093129	16.71
mHAQ, CDAI	0.710554	0.094827	7.78
mHAQ, mHAQ square	0.675278	0.095990	15.37
mHAQ, pain	0.703512	0.092886	14.49
mdHAQ, RADAI Joint Score	0.704798	0.092786	14.61
mdHAQ	0.680225	0.095338	15.7

DMARDs increase the risk of infection in RA patients [86,87] and because prevalent RA patients tend to be elderly and thus at increased risk for infections.

The treatment module accommodates all treatment changes (change 4), including; patients who do not attain remission or low disease activity (LDA) or patients who experience AEs within 6 months (or secondary failure) after treatment initiation. In addition, the proposed conceptual model allows for flexibility in dose escalation. Data from observational studies have shown that some patients require upward dose adjustments, reduced dose interval for bDMARDS, or addition of corticosteroids and/or nonsteroidal anti-inflammatory drugs (CS/NSAIDs) to some bDMARDs in order to achieve or maintain a clinical response [88,89]. Upward dose adjustments are associated with increased medication costs and potentially adverse reactions.

The outcome module incorporates disease progression and its impact on both joint and extra-articular outcomes. The conceptual model accommodates extra-articular disease outcomes, principally CVD events (change 5). These events were considered by the working group primarily based on available epidemiologic data, as well as on the treatment effects and the cost implications of these outcomes. The working group proposed incorporation of RA-specific mortality risk based on disease activity in the economic model once more data become available (change 6).

Expert Panel: Members of the expert panel debated the draft model structure, challenging the level of evidence to support several proposed changes. Nevertheless, a majority of the panel agreed that the model should enable subgroup analysis by prognostic factors, and also investigate the need to accommodate increased risk of infection (change 3). The experts agreed on QALYs should be the main outcomes of, mortality based on RA disease activity (change 6), and should explore the impact of including extra-articular manifestations on cost effectiveness ratios (change 5).

The expert panel also acknowledged the advantage of having a disease activity measure for both treatment response and disease progression (change 1). Questions were raised on CDAI data availability from historic phase 3 programs and concerns were mentioned about the subjective elements of CDAI, such as estimation of tender joint counts, patient and physician global health, which are unweighted and can make the measure less reliable. At the same time, the members of the expert panel acknowledged that this perceived limitation might also apply to other currently available composite measures. The least agreement among experts was on the proposed mapping of only disease activity (change 2) to HRQOL utilities (i.e. EQ-5D). Recommendation was to explore the use of mixed logit models, based on disease activity and HAQ with other dimensions of RA such as pain, fatigue. Strengths and limitations of the recommended changes, along with expert inputs and level of agreement among experts concerning the proposed changes, are summarized in Table 2.

After expert panel inputs had been incorporated, the draft conceptual model was further modified and these further changes are reflected in the updated conceptual model (Figure 4). Because there is no clinical criterion or reference standard disease activity measure, the conceptual framework was revised to incorporate at least two disease activity measures: one as a "base case" and the other for sensitivity analyses concerning treatment effect as well as disease progression (change 1). For example CDAI could be used as the base case and DAS28-CRP for a sensitivity analysis. The updated conceptual model also includes, in the same framework, patients who have not been exposed to csDMARDs or who have not responded adequately to them.

Table 2: Summary of pros and cons of proposed changes, expert input and agreement

Changes proposed	Pros and Cons	Expert Inputs	Expert Agreement*
Model Structure	Pros: aligned with clinical practice and guidelines; allows to captures patient subgroups, treatment heterogeneity, non-joint outcomes; Cons: increase in complexity; data availability	1. This is ideal, however the data may not be available to populate. 2. Include cDMARD-naïve and cDMARD inadequate responders 3. Changes may not materially impact ICER. The time involved in incorporating the changes might not be worth the extra accuracy	3 of 5
1) Use of (at least two) disease activity measures for treatment response and disease progression	Pros: Aligns to treatment guidelines; less biased estimates (vs. single measure) Con: Data availability;	1. Data might not be available to populate the model	4 of 5
2) Disease activity based mapping of utilities	Pros: Overcomes the limitation of HAQ changes, which is dependent on disease duration and severity; Allows the model to be based entirely on disease activity; could lead to further improvements in mapping of utility Cons: Data availability	1. HAQ would still be an unbiased estimator of disease progression 2. Reasons for the RA models to be based on HAQ was its association to cost in RA. 3. Would not recommend RAPID3 by itself as it based entirely on patient report. Good to see that we are combining disease activity and RAPID3	3 of 5
3) Incorporation of subgroups	Pros: Allows for more specific and targeted HTA evaluations; Cons: No general agreement that the prognostic factors are well established in RA; data availability	1. Double sero-positives are at a higher risk of progressing vs. single positive patients. Also, the double positive represents a significant population of RA patients. 2. Patients who have erosive disease at baseline are high risk of progression. 3. Additional subgroups could include elderly (age >65 yrs) as these are increased risk of infections, CV and other RA related extra-articular manifestations. 4. These are not just baseline factors.	5 of 5
4) Real world treatment patterns:	Pros: Allows for realistic estimates of cost and clinical benefits of standard of care; Cons: data availability;	1. Generalizability of real world data to those in the trials where efficacy was gained 2. No controlled studies that have examined switching therapy in patients who are well controlled on their existing therapy 3. GPs behavior cannot be clearly defined and consistent when it comes to dose reduction	4 of 5

Table 2 (*continued*)

Changes proposed	Pros and Cons	Expert Inputs	Expert Agreement*
5) Incorporating extra-articular manifestations of RA:	Pros: Allows for improved estimation of benefit and cost of interventions; Cons: data availability;	1. CV and lung disease should considered in the economic evaluations. 2. These would be important if treatment would differentially impact extra-articular manifestations 3. The strength of this evidence, particularly with respect to changes in markers and changes in hard outcomes is limited	5 of 5
6) Mortality Associated with RA	Pros: allows for disease activity be the driver of benefits Cons: potential for overestimation of survival; data availability	No comments	5 of 5

*Agreement in principal that these need to be evaluated in future economic models

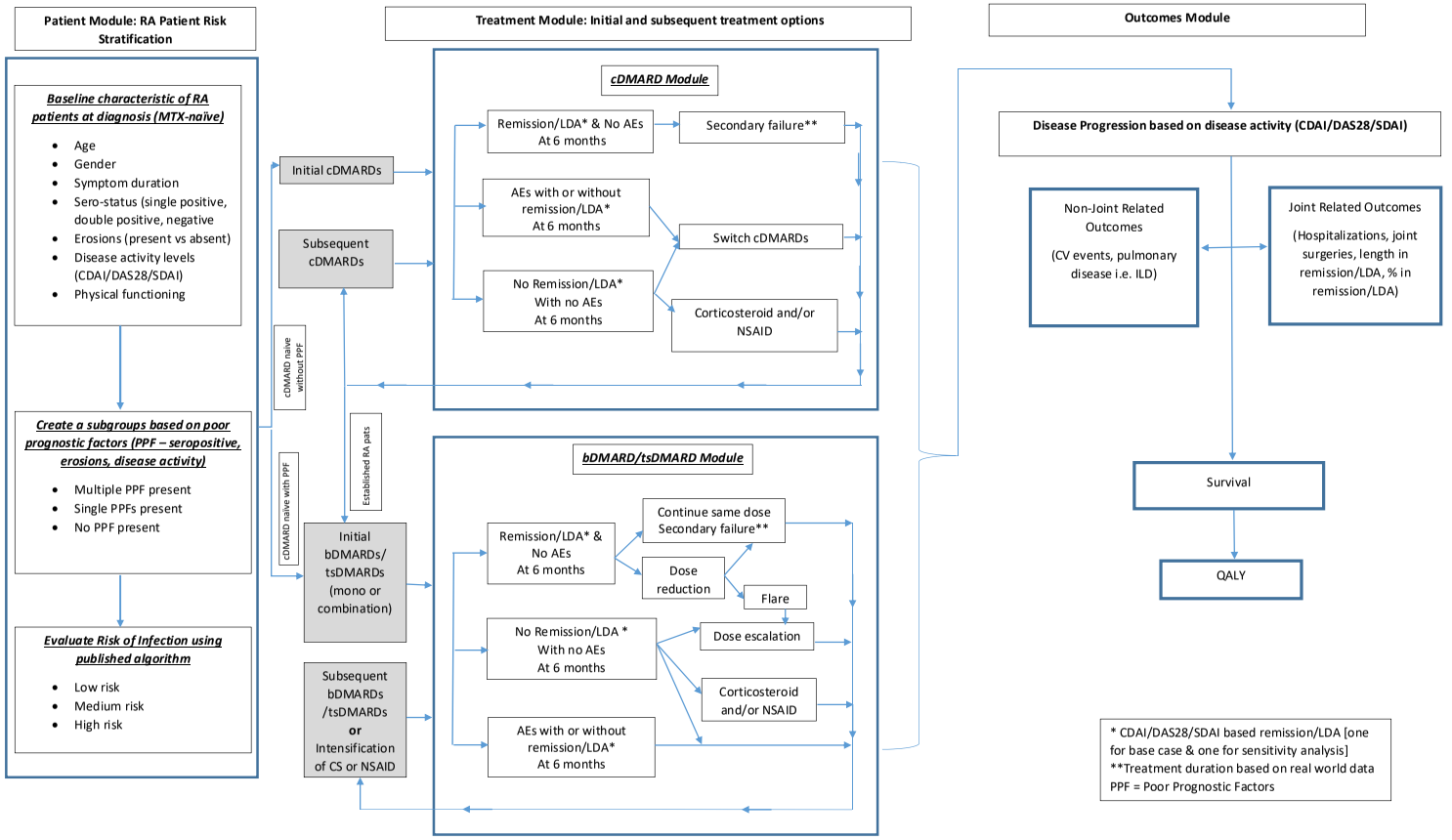
According to input from the expert panel, the conceptual model included treatment intensification (corticosteroids and/or NSAIDs) before the patient received bDMARD switch and also de-escalation of bDMARD dose in patients attaining remission (change 4). The final update based on expert input was the inclusion of pulmonary extra-articular manifestation in addition to CV extra-articular effects of RA (change 5).

DISCUSSION

This study used a well-established methodology to propose a conceptual framework for developing future models in RA to evaluate the cost effectiveness of therapies [40]. The current cost effectiveness modeling framework in RA was introduced with the advent of anti-TNFs. Since then our knowledge of RA disease mechanism, impact on joints as well as on other organ systems has greatly increased. In addition, maturation of existing electronic medical records, claims datasets and registries enable us to better understand RA treatment patterns. Thus, the proposal of an updated conceptual model that incorporates these understandings may be timely. In proposing the conceptual model we leveraged the earlier modeling approaches as certain aspects are well established.

Overall, the proposed conceptual model reflects on 6 preselected areas of modelling cost-effectiveness of drug treatment in moderate to severe RA in the 21th century. The major changes that this conceptual model proposes are 1) use of at least two

Figure 4: Revised Conceptual Model to Evaluate Cost Effectiveness in RA*



* difference between figure 3 & figure 4 include definition of primary failure: inclusion in treatment module a) cDMARD submodule b) primary and secondary failure c) inclusion of CS as treatment escalation; inclusion in outcome module pulmonary disease

composite measures of disease activity, with one used in sensitivity analyses, to evaluate both treatment response as well as disease progression; 2) utility mapping based on disease activity 3) the consideration of subgroups based on prognostic factors and potential treatment effect modifiers 4) the incorporation of realistic treatment patterns based on clinical practice/registry datasets 5) incorporation of non-joint related (extra-articular) outcomes and 6) mortality based on disease activity.

Implementation of these structural changes could be prioritized based on the expected impact on model estimates and on availability of data to populate the model. Incorporation of subgroups based on prognostic factors ranked high on the prioritization order as this is relatively straightforward. In addition, recent cost effectiveness analyses have demonstrated the importance of incorporation of subgroups as these patients may have characteristics which are potentially effect modifiers [27,28]. However, these analyses are still limited and further work needs to be done to understand and define RA subgroups with combinations of prognostic factors. Stratification of cost-effectiveness analysis by subgroups could have implication for targeting specific therapies or combination of therapies to certain subgroups improving the overall clinical outcomes and cost. This could pave the way for policies leading to personalized medicine in RA.

The second priority is deemed to be the use of a disease activity measure, to model treatment response/stopping, disease progression, mapping of utility and mortality. The conceptual model allows for at least two disease activity measures one as base case and one as sensitivity analysis. Until an objective measure of disease activity is established in RA and used in routine clinical practice, impact of treatment on multiple disease activity measures will have to be evaluated in the same model/analysis. Based on the available evidence the working group considered CDAI appropriate for the base case model and DAS28 for sensitivity analysis. Though current mapping algorithms for utility use mixed models based on HAQ, pain and disease activity. We believe further research is required comparing mapping algorithms using different disease activity measures. In addition, future research should also evaluate the benefits of having direct measure of utility from RA clinical trials vs. mapping EQ5D.

Next on the priority list is the incorporation of more realistic treatment algorithms into the cost effectiveness model. Components of this proposed change such as CS and NSAID intensification, treatment discontinuation, dose escalation can be informed by current RA registries, administrative claims and EMR database analysis. However, bDMARD dose de-escalation is a new development based on a recent de-escalation trial design [33-36]. Current evidence on real world dose de-escalation will be limited

and hence the model will have to be informed by clinical trial data at present. The last prioritized item is the incorporation of extra-articular manifestation since more research is needed to develop RA-specific risk models for both CV and pulmonary disease however, in the interim, treatment-specific risk reduction of CV could be incorporated in sensitivity analysis.

The conceptual model presented in this manuscript concurs with some of the recommendations of the consensus recommendations from the 2015 'Consensus Working Party' such as incorporation of AE based discontinuation, mapping of utility to disease activity [90]. However, there are also some major differences between the Consensus Working Party's recommendation and the current proposed conceptual model. The reliance by the Consensus Working Party on DAS28 for treatment response could lead to biased estimates for therapies such as anti-IL6 that have a disproportionate impact on acute phase reactants in DAS28. Additional differences include incorporation of detailed treatment patterns versus only treatment discontinuation, specification of prognostic factors and incorporation of extra-articular manifestations.

This analysis represent the first step in a model building exercise, the appropriate next step would be to build a model prototype and evaluate the feasibility of operationalizing the proposed changes. Limitations of the current analysis is that it was beyond scope to empirically evaluate the impact of the different proposed changes in reducing the current uncertainty in economic models. Secondly, we did not evaluate the association between CDAI reduction and resource use/cost. However, there is evidence that attainment of CDAI remission and LDA is associated with lower resource utilization, higher quality of life and improved physical functioning [41].

Though we developed this conceptual model to meet payer/HTA needs, the focus has been on payers using cost per QALY or cost per life year gained as a metric for decision-making. Thus, our proposed model might not be applicable to address certain payer needs. For example US payers are interested in shorter time horizon with outcomes such as remission. In addition, treatment modules will have to be adapted to each country based on clinical practice data. Due to our focus on HTA bodies that consider only direct cost in economic evaluations, our model does not accommodate the indirect cost of RA into the analysis. Further work is required to specifically address modeling of cost effectiveness from the societal perspective. Finally, it was beyond the scope of this analysis to evaluate the impact of the availability of robust, comparative, head-to-head clinical trials in reducing the short-term efficacy uncertainties in economic evaluations of RA products.

Despite these limitation the conceptual model presented in this manuscript is based on a comprehensive approach that aims to incorporate both clinical and real-world evidence in the economic evaluation of RA interventions. We believe that the proposed model framework can potentially serve as a foundation for developing future cost effectiveness models in RA.

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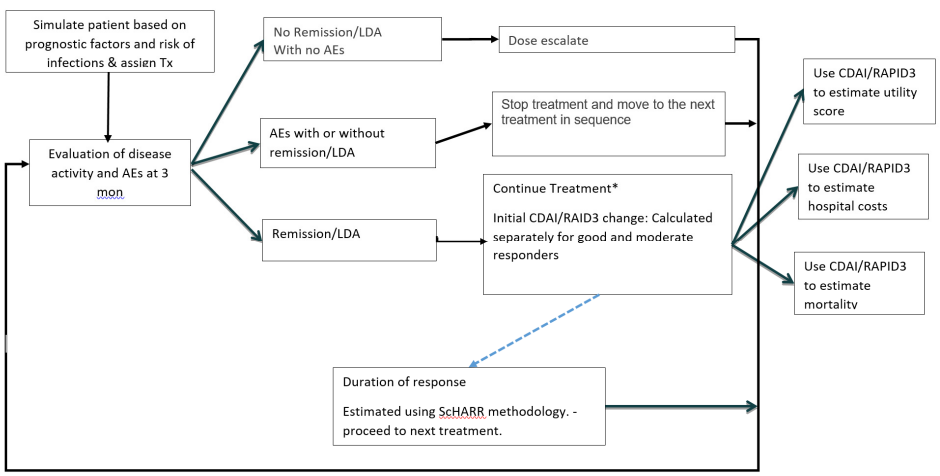
SUPPLEMENTARY MATERIAL

Appendix S1: Working Groups RA CEA Model Framework "Wish List"

Model Parameters	Common to most current modeling approaches	Proposed Model
Technique	Discrete event simulation, Individual patient simulation, Markov cohort	TBD*
Baseline Patient Characteristics	Age, gender, HAQ & weight	Demographic: age, gender, duration of disease, weight Prognostic factors: Sero positivity (RF and/or ACPA), auto immune co-morbidities Risk of infections: age, diabetes, BMI, corticosteroid use
Extra-articular manifestation	None	CVD: CV related risk factors
Treatment effect	ACR20, DAS28, EULAR (DAS28 baseline & change from baseline)	TBD*
Disease progression	HAQ	TBD*
Utility	through HAQ	TBD*
Treatment patterns	Sequential switching	Real world based Dose escalation
Treatment adverse effects	Same across all treatments	Treatment class specific
	Same across all patients	Subgroups of patients at high risk for AEs and infections

* To be determined based on literature and database analysis

Appendix S2: RA Draft Cost Effectiveness Model Concept

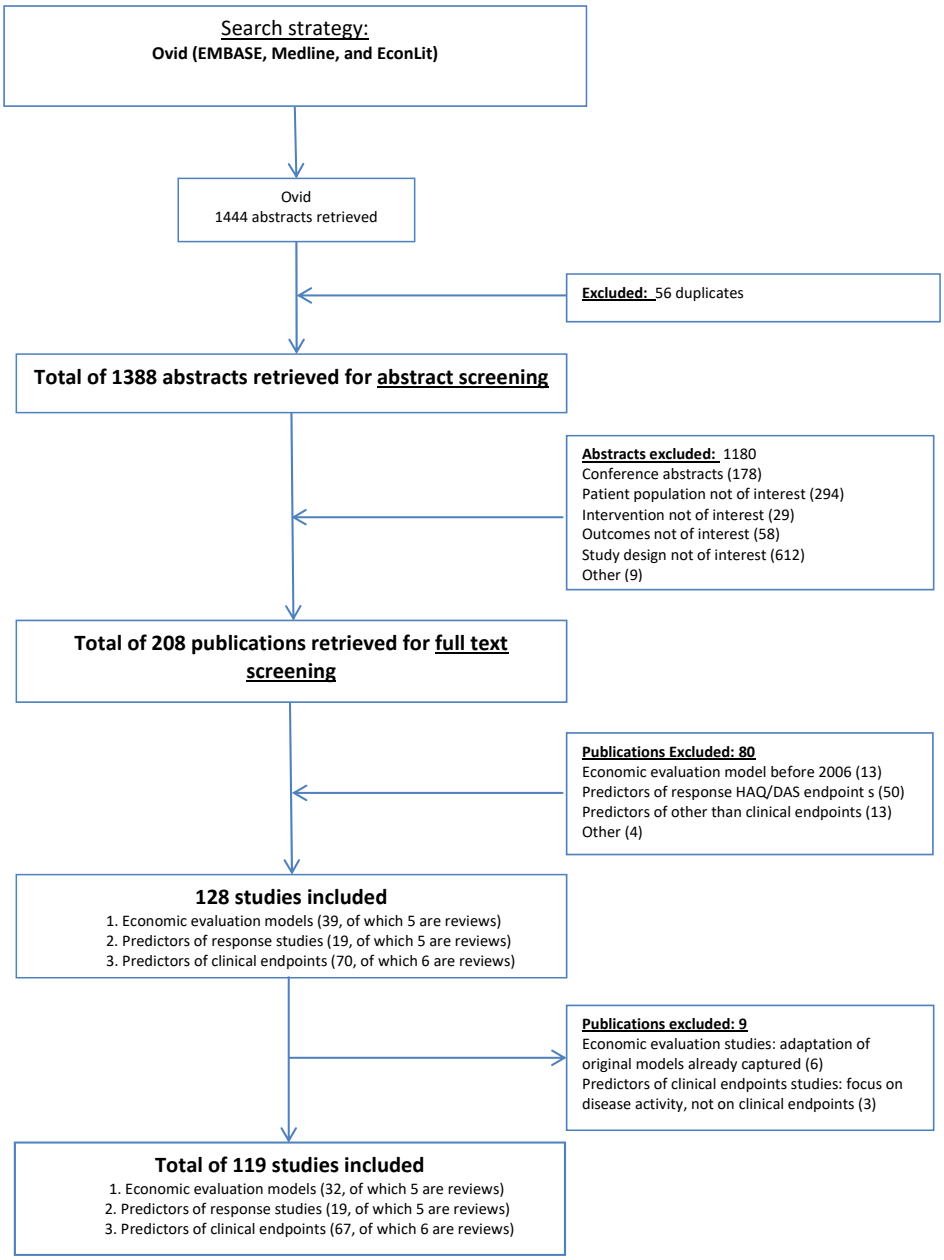


Appendix S3: Systematic Literature Review Results

S3 Table 1: Literature Search Strategy

#	Search Strategy
1	rheumatoid arthritis.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui, ct]
2	arthritis, rheumatoid/ or rheumatoid arthritis/
3	(tocilizumab or Actemra or RoActemra or golimumab or simponi or adalimumab or humira or etanercept or enbrel or rituximab or mabthera or abatacept or orencia or infliximab or remicade or certolizumab pegol or cimzia).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui, ct]
4	(Anakinra or Rituxan or Methotrexate or Rhemumatrex or Trexall or Sulfasalazine or Azulfidine or Salazopyrin or Hydroxychloroquine or Plaquenil).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui, ct]
5	(1 or 2) and (3 or 4)
6	limit 5 to english language
7	limit 6 to human
8	limit 7 to yr="2001 -Current"
9	(economic evaluation or economic model or cost effectiveness or cost benefit or cost utility).ti,ab.
10	"cost benefit analysis"/
11	(9 or 10) and 8
12	(Predict$ and (Outcome$ or Risk$ or Model$)).mp.
13	(Prognostic and (History or Variable$ or Criteria or Scor$ or Characteristic$ or Finding$ or Factor$ or Model$)).mp.
14	predict*.ti.
15	(13 or 12 or 14) and 8
16	11 or 15
17	remove duplicates from 16
18	limit 17 to (editorial or letter or note or autobiography or bibliography or biography or case reports or clinical conference or clinical trial, phase i or clinical trial, phase ii or comment or in vitro or interactive tutorial or interview or lectures or legal cases or legislation or news or newspaper article or periodical index or portraits) [Limit not valid in Embase,Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process,Econlit; records were retained]
19	17 not 18

S3 Figure 1. Flowchart of study identification and selection



S3 Table 2: Summary of the Systematic Literature Review

Reference	Study Population	Comparators* & perspective	Modelling Approach	Initial treatment response (3 to 6 month)	Long-term (life time) disease progression and Outcome Modelled	Mortality	QALY
Kievit W et al 2016[23]	patients with RA using adalimumab or etanercept and enrolled in the DRESS study	• a standardized tight control treatment protocol vs. dose optimisation group, patients received identical care as the control group, with the addition of a dose reduction advice	1000 bootstraps of 18 months mean QALY and cost outcome from DRESS trial	DAS28-CRP	none	none	Direct from EQ5D data captured in DRESS trial
Vermeer M et al 2014[24]	early RA patients in real-life daily clinical practice	• T2T strategy aiming at remission compared to usual care for	No model; CE based on a , 3 yr data from 2 early RA registries	DAS28	None	None	EuroQol-5D (EQ-5D) values[18] were estimated from the Health Assessment Questionnaire (HAQ) scores
Eriksson JK et al 2015[25]	early RA patients with insufficient response to MTX	• adding infliximab or sulfasalazine and hydroxychloroquine to methotrexate in	No model; CE based on a , 21 month data from SWEFOT study	EULAR	None (21 month ICER based on trial results)	none	Direct EQ-5D from the SWEFOT trial

Reference	Study Population	Comparators* & perspective	Modelling Approach	Initial treatment response (3 to 6 month)	Long-term (life time) disease progression and Outcome Modelled	Mortality	QALY
Manders SH et al 2015[26]	139 patients that failed previous TNFi treatment	• abatacept, rituximab or a different TNFi	No model; CE based on a pragmatic, 1-year randomized trial	DAS28	None (1 year ICER based on trial results)	none	Direct EQ-5D from the pragmatic trial
de Jong PH et al 2016[27]	Patients with a high probability (>70%) according to their likelihood of progressing to persistent arthritis in Rotterdam Early Arthritis Cohort	• A) initial triple DMARD therapy (iTDT) with glucocorticoids (GCs) intramuscular vs. B) iTDT with an oral GC tapering vs C) initial MTX monotherapy with GCs similar to B • societal perspective	No model; based on registry data	DAS remission	EQ5D at 1 yr	None	Directly from EQ5D
Davies et al. 2009[28]	Patients with early RA in the US.	• TNFα inhibitors (infliximab, etanercept and adalimumab) + MTX as a group • Payer	• IPS model • life time horizon	ACR categorized in 4 intervals (ACR0–20, ACR20–50, ACR50–70, and ACR70–100).	• H HAQ • Cost/ QALY	Mortality (age specific all-cause mortality was adjusted using HAQ).	Function of HAQ.
Finckh et al. 2009[29]	Adult very early RA (symptom duration 3 months).	• cDMARD with MTX vs bDMARDs + MTX • Healthcare provider & societal	• Individual sampling model • lifetime horizon	HAQ categorized as excellent, moderate/ good response: induced remission using a threshold of DAS28 less than <2.6.	• HAQ • Cost/ QALY	Radiographic joint damage Mortality (adjusted by HAQ, gender, and age).	Function of HAQ.

Reference	Study Population	Comparators* & perspective	Modelling Approach	Initial treatment response (3 to 6 month)	Long-term (life time) disease progression and Outcome Modelled	Mortality	QALY
Kobelt et al. 2009[30]	Patients with RA treated with bDMARD	• Etanercept, infliximab, adalimumab • Societal	DES model 5- and a 10-year time horizon.	HAQ and DAS	• HAQ & DAS • Cost/ QALY	Mortality (assumed to be independent of treatment lines)	Utilities were directly available in the SSATG Register dataset.
Schipper et al. 2011[31]	Patients with early RA in the Netherlands.	• Three outcome-directed strategies were compared: MTX, LEF, MTX + anti-TNF vs. MTX+LEF combination, MTX+anti-TNF vs. MTX + anti-TNF • Healthcare payer and societal perspective	A Markov model with a cycle length of three months and a time horizon of 5 years.	DAS28 .	• DAS • Cost/ QALY	Not reported.	Estimated as a function of DAS28.
Spalding & Hay. 2006[32]	Hypothetical cohort of women 55-60 years of age and diagnosed with RA in the US	• TNFα inhibitors (both as monotherapy and in combination with methotrexate) • Payer	• Markov model • cycle length of 1 year • lifetime time-horizon	• HAQ	• HAQ • Cost/QALY	Mortality (individualised for each of the states based on age, HAQ and gender).	Function of HAQ.

Reference	Study Population	Comparators* & perspective	Modelling Approach	Initial treatment response (3 to 6 month)	Long-term (life time) disease progression and Outcome Modelled	Mortality	QALY
Tanno et al. 2006[33]	Patients with chronic RA based on phase III clinical trial of etanercept.	• Etanercept + methotrexate (MTX) vs MTX • Societal	• Markov model • 6-month cycles • lifetime time horizon	• ACR20.	• HAQ • Cost/QALY	Mortality (individualised for each of the time cycles based on age, HAQ and gender).	Function of HAQ.
Brennan et al. 2007[34]	UK NHS patients in th British Society for Rheumatology Biologics Registry with RA who have failed at least two traditional DMRDs	• TNFα inhibitors (infliximab, etanercept and adalimumab) + MTX as a group • UK NHS	• IPS model • lifetime time horizon	EULAR response criteria	• HAQ • Cost/QALY	Mortality (assumed to be equivalent in the two arms of the model).	
Kielhorn et al. 2008[35]	RA patients with inadequately to a bDMARD (patient demographics match those of patients in the pivotal rituximab trial – REFLEX).	• Rituximab + MTX vs Standard practice (leflunomide) • UK NHS and PS in England and Wales	• Micro simulation Markov model • 6-month cycles • lifetime time horizon.	ACR20, ACR50, ACR70	• HAQ • Cost/QALY	Mortality (individualized by HAQ score).	Function of HAQ.
Vera-Llonch et al. 2008[36]	Moderate to severe RA patients with inadequate response to MTX in the US.	• Abatacept + MTX vs. MTX • Third-payer	• Simulation model • time frame of both 10 years and lifetime.	*HAQ-DI improvements of 0.50 or greater at 6 months*	• HAQ • Cost/-QALY	Mortality (individualized by age, HAQ and gender).	Function of HAQ.

Reference	Study Population	Comparators* & perspective	Modelling Approach	Initial treatment response (3 to 6 month)	Long-term (life time) disease progression and Outcome Modelled	Mortality	QALY
Wailoo et al. 2008[37]	US Medicare patients with a diagnosis of RA treated with each of the 4 bDMARDs (adalimumab, anakinra, etanercept, infliximab)	• Adalimumab, Anakinra, Etanercept, Infliximab • Medicare	• Simulation model • lifetime horizon	ACR20 and ACR50	• HAQ • Cost/QALY	Mortality (US life tables were adjusted by standardized mortality rates for RA).	Estimated as a function of HAQ.
Russell et al. 2009[38]	moderate to severe RA with an inadequate response to one or more DMARDs and/ or anti-TNF agents in Canada.	3 treatment sequences: • Etanercept, infliximab, adalimumab, DMARDs vs. • Abatacept, etanercept, infliximab, DMARDs vs. • Etanercept, abatacept, infliximab, DMARDs • Payer	• Simulation model • Two-year time horizon.	DAS28	• DAS • cost / additional LDAS gained.	Not relevant	Not relevant
Hallinen et al. 2010[39]	Patients with severe RA after TNF-inhibitor failure in Finland.	• adalimumab vs. abatacept vs. etanercept vs. infliximab vs. • payer	• Micro-simulation Markov model • life-time horizon.	ACR (20/50/70)	• HAQ • Cost/ QALY	Mortality (adjusted by HAQ score)	function of HAQ.
Lekander et al. 2010[40]	Patients with RA in Swedish clinical practice	• Infliximab vs. • natural progression (i.e., no biologic treatment) • Societal	Markov cohort model with one-yearly cycles and a 20-year time-horizon.	HAQ and DAS28	• HAQ • Cost/ QALY	Mortality (adjusted by functional status [HAQ] and disease activity [DAS]).	Estimated as a function of HAQ.

Reference	Study Population	Comparators* & perspective	Modelling Approach	Initial treatment response (3 to 6 month)	Long-term (life time) disease progression and Outcome Modelled	Mortality	QALY
Merkesdal et al. 2010[41]	Patients with active RA who failed at least one prior DMARD therapy in Germany.	• adalimumab + MTX followed by infliximab + MTX, followed by gold, followed by cyclosporine A, and finally supportive therapy (MTX) vs. rituximab + MTX, followed by adalimumab + MTX, followed by infliximab + MTX, followed by gold, followed by cyslosporine A, and finally supportive therapy (MTX). • payer	A micro simulation Markov model with 6-month cycles and a lifetime time horizon.	ACR (20/50/70)	• HAQ • Cost/ QALY	Mortality (individualized by employing mortality tables of the German population that were adjusted according to the patient's stage of RA).	Estimated as a function of HAQ.
Saraux et al. 2010[42]	moderate to severe active RA patients and an insufficient response to at least one anti-TNF agent in France.	• 4 treatment sequences were compared: abatacept, adalimumab vs. rituximab, adalimumab vs. adalimumab, abatacept vs. adalimumab, infliximab. • payer	Simulation-decision analytical model with a two year time-horizon	DAS28	Not relevant	LDAS (DAS28≤3.2) Remission (DAS28<2.6)	Estimated as a function of HAQ.

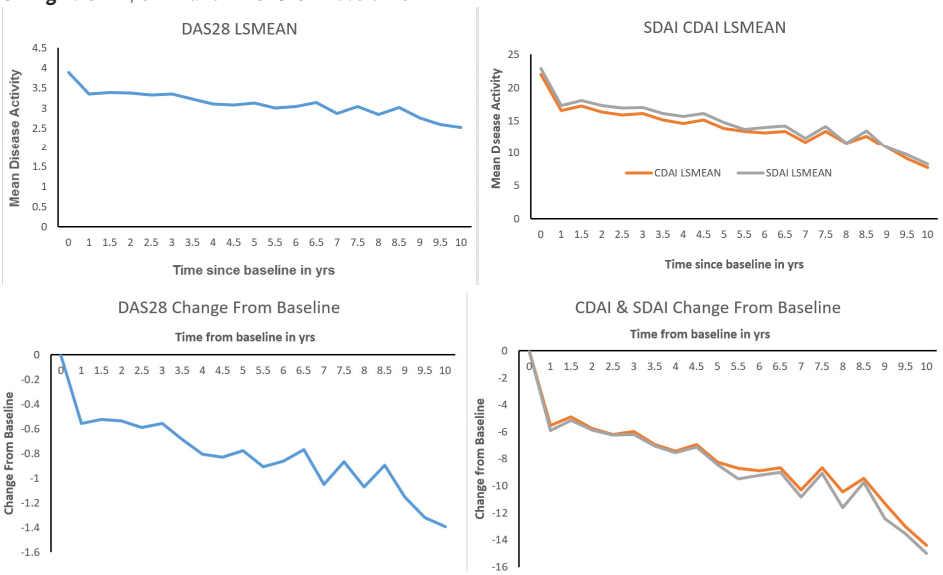
Reference	Study Population	Comparators* & perspective	Modelling Approach	Initial treatment response (3 to 6 month)	Long-term (life time) disease progression and Outcome Modelled	Mortality	QALY
Yuan et al. 2010[43]	Patients with active RA and who have had an inadequate response to anti-TNFα therapy in the US.	• Abatacept + MTX vs. Rituximab + MTX vs.MTX alone • US third-party payer	patient-level simulation model with 3-month cycles and a life time horizon.	HAQ-DI	• HAQ • Cost/ QALY	Mortality (was individualized by gender, age and HAQ).	Estimated as a function of HAQ.
Kobelt et al. 2011[44]	Patients with early active RA in Sweden.	• etanercept, followed by dose-reduction in the case of remission vs.standard treatment with MTX. • Societal	Markov model with 6 monthly cycles and a 10-year time horizon.	HAQ and DAS	• HAQ & DAS • Cost/ QALY	Mortality (adjusted by HAQ and DAS28)	Estimated as a function of HAQ and DAS28.
Valle-Mercado C 2013 et al[45]	150 patients in different disease stages at the Hospital Militar, one of the largest university hospitals in Colombia	• BDMARDs vs. MTX	Markov model	HAQ	HAQ	standardized mortality ratio	As a function of HAQ
Tanaka E et al 2015[46]	RA patients failing cDMARDs enrolled in the IORRA registry	• bDMARD therapy with tociluzimab vs. without	state-transition model				

Reference	Study Population	Comparators* & perspective	Modelling Approach	Initial treatment response (3 to 6 month)	Long-term (life time) disease progression and Outcome Modelled	Mortality	QALY
Stephens S et al 2015[47]	1000 early RA patients based on PREMIER study	• Adalimumab + MTX versus MTX	microsimulation	ACR based on DAS28	Disease activity and mTSS were linked to an individual's HAQ	Not stated	derived from the HUI3, were estimated based on data from PREMIE
Gissel C et al 2016[48]	10,000 hypothetical RA patients based characteristics from RABBIT registry	• Adalimumab + MTX vs, MTX	individual patient sampling	ACR response	HAQ	German life tables based on age and gender	Estimated as a function of HAQ.
Stevenson MD et al 2017[49]	Patients with moderate to severe RA and with severe RA with prior experience of MTX. patient characteristics from the BSRBR for those receiving their first bDMARD,	• adalimumab. etanercept. infliximab (IFX), certolizumab pegol (CTZ), golimumab (GOL), tocilizumab (TCZ), and abatacept (ABA) vs. MTX • (RTX) + MTX, then TCZ + MTX (if TCZ + MTX was not used first-line), followed by a range of nonbiologic therapies	individual patient time-to-event simulation	EULAR response	HAQ	mortality conditional on HAQ score	mixture model proposed based on HAQ & pain

*Includes both individual treatment comparisons as well as comparison of interventions for treat to target approach

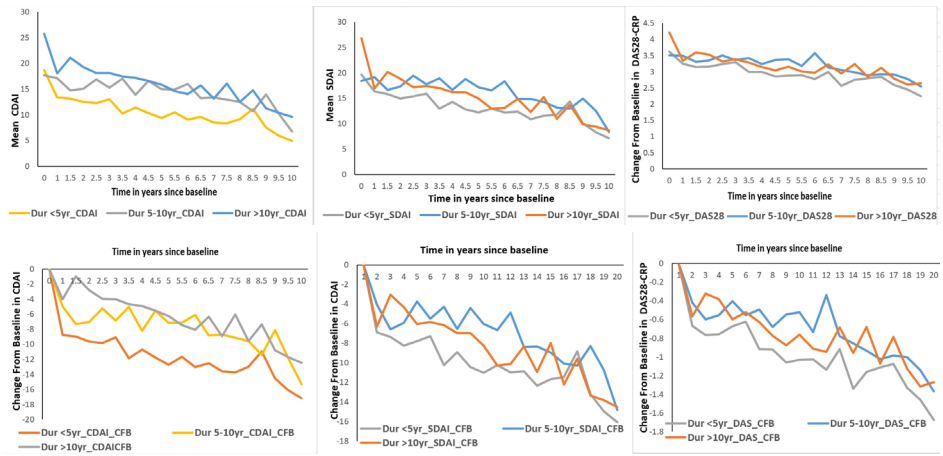
Appendix S4: Disease activity (change) overtime and association of HAQ change by baseline DAS categories

S4 Fig 1: CDAI, SDAI and DAS28-CRP overtime



Means are based on generalized linear models adjusted for baseline age, disease activity, gender, disease duration, serostatus, CRP, time since baseline

S4 Fig 2: CDAI, SDAI and DAS28-CRP overtime by disease duration and change overtime

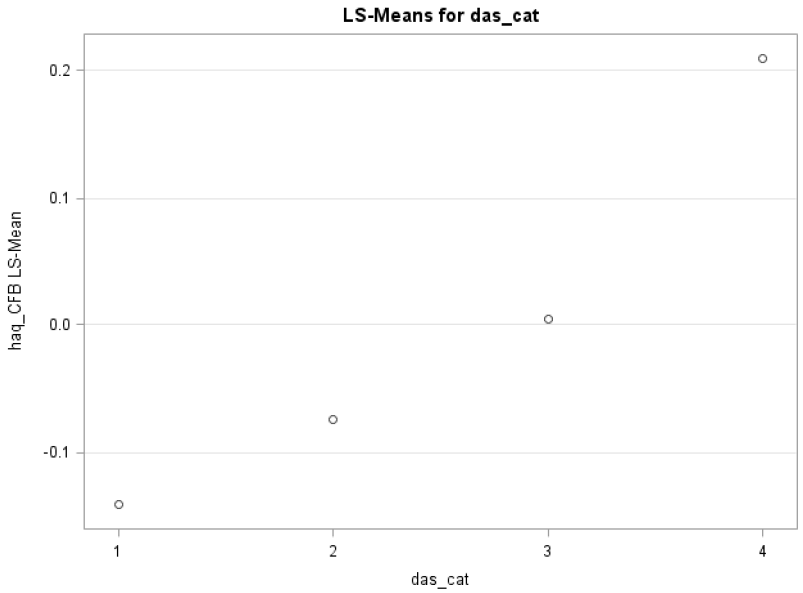


Means are based on generalized linear models adjusted for baseline age, disease activity, gender, disease duration, serostatus, CRP, time since baseline

S4 Table 1: HAQ change by DAS28 categories

	DAS28 ≤ 2.6 (remission) N = 1820	< 2.6 DAS28 ≤ 3.2 (LDA) N = 608	< 3.2 DAS28 ≤ 5.1 (MDA) N = 1350	> 5.1 DAS28 ≤ 5.2 (SDA) N = 516
	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)
mHAQ	0.254 (0.008)	0.320 (0.013)	0.399 (0.009)	0.603(0.015)
mHAQ change from baseline*	0.140 (0.008)	-0.073 (0.013)	0.004 (0.009)	0.209 (0.015)

* negative change is worsening of HAQ; means based on general linear model adjusted for baseline co-variates



Das_cat : 1= DAS28 ≤ 2.6 ; 2 ≤ 2.6 DAS28 ≤ 3.2 ; 3 ≤ 3.2 DAS28 ≤ 5.1 ;4 ≥ 5.1 DAS28 ≤ 5.2

CHAPTER 12

Discussion

A CASE FOR A COMPREHENSIVE APPROACH TO EVALUATING COST AND BENEFITS IN RA

Recent years have seen a tremendous progress in our understanding of the autoimmune mechanism underlying RA leading to rapid development of innovative disease modifying anti-rheumatic Drugs (DMARDs) for RA patients [1,2]. Various combination therapies of different biologic (b)DMARDs or of bDMARDs in combination with synthetic (sc)DMARD blocking multiple immune pathways are being explored for development [3]. Complemented by 'Big Data', these innovations in drug development can enable interventions to be targeted to specific RA patients and/or patient populations with the highest unmet needs [4]. At the same time various currently available biologic therapies will have biosimilars, potentially expanding the pool of RA patients managed with bDMARDs by lowering the price of bDMARD treatment. To accurately capture the benefits and costs of therapies in RA and enable stratified medicine for specific subgroups, it will be important to take a comprehensive approach when modeling disease progression and cost drivers for RA patients in future cost effectiveness evaluations. In this thesis, the first three Parts focused on exploring multiple aspects of RA that could inform a framework for evaluating the potential value of future therapies in RA. Primarily, we focused on defining the appropriate disease target measures and the impact of the various definitions on resource use and health related quality of life (HRQOL), the heterogeneous nature of RA both in terms of baseline characteristics of RA patients (through considerations of subgroups) and outcomes that are non-joint related. The first chapter in the final Part, focused on the conventional cost effectiveness modeling approach to evaluate the cost effectiveness of bDMARD stratified by baseline level of anti-citrullinated protein antibody (ACPA) levels (marker of poor prognosis in RA). While, the final chapter was devoted to incorporating the learnings from previous chapters into a new conceptual model that potentially improves the evaluation of the cost effectiveness of future therapies in RA.

The following list of hypotheses was addressed in the different Parts of this thesis:

Part I: Real world evidence on treatment targets and outcomes
Hypothesis tested: Achieving guideline recommended disease target measures in established RA patients is associated with higher health related quality of life (HRQOL), lower hospitalization and durable medical equipment use
Part II: Presence of multiple poor prognostic factors
Hypothesis tested 1: Established RA patients that are seropositive, have higher odds of erosive disease and greater bone loss [hand Digital X-Ray Bone Mineral Density (DXR–BMD)]

Hypothesis tested 2: Changes in anti-citrullinated protein antibody (ACPA) levels are directly associated to outcomes such as durable medical equipment use, hospitalizations, and disease activity, in patients with established RA.
Hypothesis tested 3: RA patients with multiple prognostic factors compared to those without multiple prognostic factors have worse clinical and economic outcomes.
Hypothesis tested 4: The presence of poor prognostic factors in RA patients leads to treatment acceleration in clinical practice setting.

Part III: Extra-articular manifestation of cardiovascular (CV) risk in RA

Hypothesis tested 1: Traditional CV risk factors are managed poorly in RA patients compared to matched non-RA patients
Hypothesis tested 2: Markers of inflammation such as C-reactive protein (CRP) improve the CV risk prediction in RA
Hypothesis tested 3: Higher low-density lipoprotein cholesterol (LDL-C) in RA patients is associated with increase in CV events.

Part IV: Improvements of future cost effectives studies in RA

Hypothesis tested: The cost-effectiveness of disease modifying anti-rheumatic drugs in RA is higher (lower ICER) with increasing levels of anti-citrullinated protein antibody titers

In this chapter, the clinical and policy implications of the findings are discussed, as well as some methodological considerations. The chapter is concluded with recommendations about some main areas for future research.

CLINICAL IMPLICATIONS OF THE FINDINGS

Summary of findings and clinical implications of "Real World Evidence of Treatment Targets and Outcomes"

The major findings in Part I were based on a longitudinal observational study and demonstrated that achieving (versus not achieving) guideline-recommended target measures of disease activity of Disease Activity Score-28 joints C-reactive protein (DAS28-CRP < 2.6), Standardized Disease Activity Index (SDAI ≤ 3.3), and/or Clinical Disease Activity Index (CDAI ≤2.8) was associated with significant improvements in physical functioning as measured by modified Health Assessment Questionnaire (mHAQ), HRQOL (measured by EQ-5D), and health care resource utilization. More importantly, this analysis found that subjects who achieved the most desirable target of DAS28-CRP < 2.6 did not differ significantly compared to those with low disease activity (LDA; 2.6 ≤ DAS28-CRP < 3.2) in terms of physical functioning as measured

by the mHAQ. Attainment of DAS28-CRP < 2.6, SDAI ≤ 3.3, or CDAI ≤ 2.8 did not result in significant reductions in hospitalization compared to achievement of LDA (although there were trends toward reduced odds of hospitalization in subjects achieving target measures across all 3 indices) but did differ in HRQOL (patients attaining remission vs. LDA had improved HRQOL) and similar results were observed with durable medical equipment use except for DAS28-CRP (which was borderline significant). These findings therefore suggest that differentiation on outcome measures for achieving target remission versus LDA is not uniform. Clear benefits were observed with HRQOL and durable medical equipment use across all composite measures. However, the evidence for lower mHAQ and reduced hospitalizations with remission depended on the composite measure being used. DAS28-CRP remission vs. LDA did not differentiate on mHAQ or hospitalization, whereas SDAI and CDAI differentiated on mHAQ but not hospitalizations. We also observed that attainment of LDA [versus moderate disease activity (MDA) or severe disease activity (SDA)] was associated with favorable clinical and economic outcomes.

Taken together, these findings support both the value of treating to target and the assertion that LDA is a plausible alternative clinical objective for treat to target strategies when guideline-recommended goals of remission cannot be achieved in clinical practice. This is an important finding from a clinical as well as health policy perspective, specifically for patients with longstanding disease since guideline targets might not be a viable option for all patients. In addition, we also noticed that not all disease measures performed consistently in discriminating physical functioning, HRQOL, and health care resource utilization across guideline-recommended target measures. Compared to DAS28-CRP, measures of SDAI and CDAI were more consistent in their differentiations on outcomes evaluated. There is evidence to suggest that DAS28-CRP < 2.6 might not be an appropriate measure of remission as there might still be some underlying disease present [5]. The SDAI and CDAI include both patient and evaluator ratings of global disease activity, which are frequently discrepant. Perhaps the inclusion of both perspectives on global disease activity in the SDAI and CDAI (but not DAS28-CRP) renders these indices more effective assessments of physical functioning on the mHAQ (versus DAS28-CRP). Thus, evaluation of benefits in health economic evaluations should consider multiple composite endpoints.

Summary of findings and clinical implication of "Presence of Multiple Poor Prognostic Factors":

The key findings in Part II were the association between single and multiple prognostic factors and clinical and economic outcomes. The first major finding in this section demonstrates that, among patients with long-standing RA, hand DXR–BMD is negatively associated with the presence of ACPA. Patients with ACPA+ status, particularly those with high ACPA titers, had lower hand BMD. In addition, we observed that patients with low DXR–BMD were less likely to have high disease activity and low likelihood of attaining remission. Hand BMD loss has also been shown to indicate an increased risk of erosive disease. Data from an observational study demonstrated that BMD loss at 6 months was associated with higher erosion scores, and a higher proportion of patients with BMD loss at 6 months had ≥1 erosion and a higher risk of erosion progression at 12 months. In a separate analysis, a decrease in ACPA levels (compared to no change or increase in ACPA levels) was associated with a reduction in durable medical equipment use and hospitalizations. Adjusted mean changes in DAS28-CRP, total and swollen joint counts and pain scores were significantly greater in patients with decreased ACPA levels versus those with no change or increase. Other studies supported the finding that patients with seropositivity and joint erosions were significantly less likely (than their counterparts without these prognostic factors together) to have DAS28-CRP < 2.6 or SDAI ≤ 3.3. With regard to direct health-care costs, the likelihoods of hospitalization and durable medical equipment use were significantly higher in patients with adverse prognostic factors. With respect to indirect health-care costs, greater proportions of patients without the adverse prognostic factors were employed, lower proportions were on short-term and long-term disabilities and in the lower income bracket. The final study in this Part of the thesis, again focused on RA patients with multiple prognostic factors and observed that the changes in both CDAI and LDA/remission from baseline (enrollment) to 12-month follow-up were significantly lower in patients with a greater number of poor prognostic factors. In addition, the worst prognostic factor category i.e. those with 3+ prognostic factors had the lowest proportion of patients working full or part-time at both baseline and after the 12-month follow-up, whereas those with 0–1 prognostic factors had the highest proportion of patients working at baseline and still working at follow-up. However, in this analysis it was observed that despite high disease activity and worst clinical outcomes, the number of poor prognostic factors was not a significant predictor of biologic/targeted synthetic DMARD use.

Taken together, the findings of this section warrant consideration of the importance of poor prognostic factors in treat-to-target strategies. Given that patients with a greater

number of poor prognostic factors have the worse clinical and social outcomes, it would be beneficial to consider use of prognostic factors to guide decisions on the treatment for RA. Recent EULAR treatment guidelines have highlighted the importance of stratification of RA patients by prognostic factors by prominently calling it out as a separate recommendation i.e. recommendation #8. However, findings from studies in this thesis indicate that prognostic factors are not associated with treatment accelerations in RA patients. This could be partly driven by a lack of understanding on the Part of clinicians and payers on the unmet need associated with patients having multiple prognostic factors. Current economic analysis and payer policies do not distinguish patients based on poor prognostic factors and physicians do not systematically document all prognostic factors in clinical practice. Thus, it could be beneficial for patients, physicians and payers if health care providers engage patients in conversations about poor prognostic factors and how they may wish to tailor their RA care, based on a treat-to-target approach.

Summary of findings and clinical implication of "Extra-articular Manifestation of Cardiovascular Risk in RA"

The major findings of Part III suggest that the traditional CV risk factors are equally important in RA patients as in the general non-RA population. Additionally, findings in this Part indicate that the increased CV risks experienced by RA patients cannot be fully explained by the traditional risk factors. Analysis based on data from two different health care systems, one from the UK and one from the US, indicate that there were no differences between RA and matched non-RA patients in the frequency of testing and treatment of traditional CV risk factors. Thus, it is unlikely that the higher CV risk in RA patients is driven by differences in the management of traditional CV risk factor by rheumatologists. More importantly, when the associations between higher LDL-C and CV outcomes among patients with RA and patients without RA was examined, we observed that higher LDL-C levels were associated with increased CV events. The relationship between LDL-C and CV outcomes in RA was similar to the relationship found in matched general and OA controls. Hence, lowering LDL-C levels in RA patients would provide similar benefits in RA patients as in non-RA patients leading to the conclusion that LDL-C levels is not anticipated to explain the increased CV risk observed in RA patients. The final study in this Part of the thesis evaluated if other markers of inflammation such as CRP could explain some of the increased CV risk observed in RA patients. The study aimed to compare the performance of CV risk calculators, Framingham Risk Score (FRS) and QRISK2, in RA and matched non-RA patients and to evaluate whether their performance could be enhanced by the addition

of CRP. Findings from this study indicate that the C-Index for the FRS and QRISK2 was significantly better in the non-RA compared with RA patients. The addition of CRP in both equations was not associated with a significant improvement in reclassification based on net reclassification index (NRI).

Based on this body of research, it should be concluded that it is important to manage the traditional CV risk factors in RA patients and ensure that RA patients meet the guideline recommend targets of hypertension, lipids, A1C, weight, smoking etc. In addition, these findings demonstrate that RA patients are being managed similarly to non-RA patients with similar CV risks for their traditional CV risk factors. Hence, the increase in CV events in RA patients could be due to factors other than the traditional CV risk factors or a combination of traditional CV risk factors and non-traditional CV risk factors in RA patients. In terms of the management of traditional risk factors our findings indicate that rheumatologist are managing RA patients in accordance with the current guidelines that state when treating RA patients, health care providers and policy makers should consider the impact of RA therapies on traditional CV risk factors and CV events. In the Netherlands, the Dutch guidelines recommend the application of CV risk management (CVRM) in RA patients, because RA is considered as an independent risk factor for CV disease.[6] However, a recent study showed that CVRM guidelines performed poorly in RA patients, with an overall increase in 10 year CV risk despite implementation of CVRM [7].

Though our findings indicate the importance of traditional risk factors in RA they did not explain the increased CV risk observed in RA patients. Our attempts to improve the traditional CV risk calculators (algorithms) by including measures of inflammation was not successful. Others have attempted in recent years to develop such algorithm but with mixed success [8.9]. Given that the traditional CV risk algorithms were not developed in the RA-specific population, and to account for the increased CV risk in RA patients vs the general population, the EULAR guidelines recommend that the risk calculated, using these algorithms, should be multiplied by a factor of 1.5. Further development and testing of RA specific CV algorithm is warranted.

Summary of findings and clinical implication of "Improvements of Future Cost Effectiveness Studies in RA":

Part IV of the thesis evaluated the impact of incorporation of subgroups, primarily based on poor prognostic factors of ACPA levels and proposed the development of a revised conceptual model for evaluating the cost effectiveness of future therapies in RA.

As mentioned above, in Part II, patients having multiple poor prognostic factor tended to have worst clinical and economic outcomes, highlighting that the cost effectiveness ratios might not be uniform across all RA patients. We evaluated this hypothesis by conducting a cost effectiveness analysis by worsening prognostic factors (based on ACPA titers) and were able to show that the ICERs of intervention reduced when prognosis worsened. In addition there is now evidence that certain mechanism of actions might perform differently in patients with certain prognostic factors. [10, 11].

Based on the findings from Parts I to III of this thesis as well as our understanding of the current modeling approaches in RA we propose a revised conceptual framework that will potentially improve the modeling of cost and benefits of future innovative technologies in RA. The proposed conceptual model consists of three separate modules: 1) patient characteristic module, 2) treatment module, and 3) outcome module. Consistent with the scope, the conceptual model proposed six changes to current economic models in RA. These changes proposed are to: 1) use composite measures of disease activity to evaluate treatment response as well as disease progression (at least two measures should be considered, one as the base case and one as a sensitivity analysis); 2) conduct utility mapping based on disease activity measures; 3) incorporate subgroups based on guideline-recommended prognostic factors; 4) integrate realistic treatment patterns based on clinical practice/registry datasets; 5) assimilate outcomes that are not joint related (extra-articular outcomes); and 6) assess mortality based on disease activity.

METHODOLOGICAL CONSIDERATIONS

One of the main limitation of the body of work presented in this thesis is that it very much focused on established RA patients. In recent years tremendous strides have been made in the understanding of the disease in early phases and how the disease progresses from arthralgia to undifferentiated RA to fully established disease. Experts believe that early treatment interventions might be clinically as well as economically beneficial as it could cure the disease in some patients. However, the evidence is still debatable and evolving. Cost effectiveness analysis for bDMARD based on early RA studies have not shown these therapies to be cost effective. However, it could be different in subgroups of early RA patients who are at risk of rapid progression of disease and could benefit from early bDMARD use, especially at the prices of the biosimilar.

Another limitation of the body of work in Parts II and III is that it only focused on certain prognostic factors (i.e. erosive disease and seropositivity) and certain extra-articular

manifestation of RA (CV events). In recent years, seropositivity, particularly ACPA has gained importance both for its diagnosis as well as for its prognostic abilities. Historically, the worst outcomes were associated with the presence of erosive disease, which was in turn associated with the presence of seropositivity. However, the simultaneous presence of multiple prognostic factors had not been evaluated prior to this body of work. Other prognostic factors that were not considered in our work include functional disability, imaging markers, and novel multi-biomarkers. The reason to focus on these particular prognostic factors is because they are correlated and there is evidence that these could be treatment modifiers.

It is increasingly understood that RA is a systemic disease and thus affects multiple organ system; this thesis focused on the CV aspect of RA. Other extra-articular conditions like lung abnormalities in RA are gaining attention because of evidence that certain RA treatments such as methotrexate, leflunomide and anti-TNFs are associated with ***new onset*** and acceleration of existing interstitial lung disease (ILD).[13] The reasons to focus on CV aspects of RA in this thesis were multiple and included overall impact on disease burden, cost and ability of treatment to impact outcomes as well as the availability of data in clinical practice settings.

In the final, 'Improvement of Future Cost Effectiveness Studies in RA' Part, the ISPOR-SMDM Modeling Good Research Practice Task Force-2 recommended method was used to arrive at the conceptual frame. However, no model prototype was built and thus the importance of the different variables in reducing the current uncertainty in economic models was not evaluated. Additionally, though the model concept was developed to meet payer/HTA needs, the focus has been on payers using cost per QALY or cost per life year gained as a metric for decision-making. Thus, the proposed conceptual model might not be applicable to certain payer needs, for example, US payers are interested in time horizons of 1 to 5 years and outcomes of remission to calculate the cost per remission. Finally, the treatment module will have to be adapted to each country based on clinical practice data. Another aspect that was not included in the conceptual model, due to its focus on the payer perspective, was the costs of production loss, the costs of informal care and the costs borne by the patients themselves.

Given the overall objective of the thesis and nature of the research hypothesis tested, we considered that the most relevant data source to inform this thesis was real world clinical practice data. Unlike randomized clinical trials, real world registry data are less prescriptive in their inclusion/exclusion criteria as well as the treatments and hence provide an appropriate data source for evaluating the benefits of various RA disease health states (remission, LDA, MDA, SDA) on outcomes. In addition, a real world data

source is the only economically viable option when the research hypothesis requires a longitudinal follow-up of large numbers of patients as is in the case of evaluating the impact of RA on CV risk/events. Finally, since results of cost effectiveness analysis are used to implement health policy decisions basing these analyses on real world data that represent the entire target population is preferable. However, the hypothesis tested in the cost effectiveness of interventions by ACPA titers in chapter 10 is based on data from just one randomized clinical trial data and would benefit from additional data from real world setting. Besides the advantages of using real world data to address research questions in health services research, there are also some limitations of this type of research. Firstly, given the nature of the data and confounders, conclusions drawn from this type of work are associational at best.

Secondly, these datasets seldom have complete information and can either suffer from missing information and/or censored information. We tried to control for selection biases and confounders by using statistical methods and procedures such as propensity score matching and by using appropriate mixed effects models to control for missing information. In spite of these measures caution should be exercised in implying causality and further research is needed to support these findings. Despite these limitations, the studies presented in this thesis highlight the importance of considering the following aspects in future cost effectiveness models – 1) use composite measures of disease activity to evaluate treatment response as well as disease progression (at least two measures should be considered, one as the base case and one as a sensitivity analysis); 2) conduct utility mapping based on disease activity measures; 3) incorporate subgroups based on guideline-recommended prognostic factors; 4) integrate realistic treatment patterns based on clinical practice/registry datasets; 5) assimilate outcomes that are not joint related (extra-articular outcomes); and 6) assess mortality based on disease activity

POLICY CONSIDERATIONS:

As biosimilar therapies get wider acceptance from rheumatologist and with health care policy makers, it is possible that more RA patients would be treated with bDMARDs. This could even open up the possibility of treating early RA patients (6 months from diagnosis) with clinically efficacious and cost effective interventions. Thus, biosimilars can improve the overall clinical and societal benefits by making bDMARDs affordable to a wider patient population. This is likely to increases the total number of RA patients being treated with bDMARDs. This phenomenon of expansion of the treated patient pool has been observed in other therapeutic areas that experienced

entry of generics. However, current bDMARD therapies do have limitations in terms of adverse effects as well as efficacy (remission rates are still in the range of 10% to 30% depending on measures used) and there will continue to be groups of patients with high unmet need in RA with even lower remission rates. Patients failing on biosimilars will require branded bDMARDs or newer targeted synthetic DMARDs and hence the cost savings/reductions anticipated by healthcare systems might be challenging. However, incorporating our knowledge on the nature of RA being a heterogeneous and systemic disease, availability of newer interventions with multiple mechanism of actions, complemented with availability of large data, policies could be implemented that are more targeted rather than one size fits all i.e. implementing a personalized medicine approach in managing RA patients.

The research in this thesis has highlighted that treatment and reimbursement policies in RA should consider treatment targets that are better associated to multiple outcomes such as physical functioning, quality of life and resource use. This is especially true in RA, since the primary outcomes of ACR and DAS28-CRP measured in clinical trials are not generally measured in clinical practice settings and might only be informative from a drug efficacy point of view for regulatory drug approval requirements. However, these measures are less sensitive to other outcomes relevant for payer needs compared to CDAI/SDAI.

In addition, future policy in RA should consider exploring the management of RA based on subgroups of high unmet need, as has been done in multiple other therapeutic areas such as cardiovascular, diabetes, hepatitis etc. Finally, future health policies in RA should take a more holistic approach for managing RA, since there is increasing evidence of the systemic inflammatory nature of the disease. Thus, focusing on only the joint aspects of the condition in cost effectiveness evaluations does not provide the estimate of the true cost and benefit of interventions and incorporation of the non-joint aspect of the condition will be important. Though our work did not focus on the patient reported outcomes measures (PROMS) or patient reported experience measures (PREMS), incorporation of these measures in future policy considerations for RA will be important. The current measures of treatment responses (ACR, DAS28-CRP, SDAI and CDAI), though informative from an efficacy perspective and including certain PRO components such as patient global assessment measure, are not very meaningful to patients. Patients are more concerned and familiar with their daily symptoms of RA such as morning stiffness, fatigue, joint pains etc. (vs. a state of DAS28-CRP < 2.6).

IMPLICATIONS FOR FUTURE RESEARCH

The first Part of the thesis evaluated the impact of attaining remission, LDA, MDA, SDA through various disease activity measures on outcomes such as physical functioning, HRQOL, hospitalizations and durable medical equipment use. Other important endpoints such as PROMS and radiographic progression were not considered. Future studies should evaluate the benefit of remission on these outcomes. Part II, highlighted that not all RA patients are alike in terms of their disease profile and that patients with certain prognostic factors have worse clinical and economic outcomes. In addition, there is evidence that some of the prognostic factors are treatment effect modifiers [10, 11]. Future research should be devoted to the understanding the impact of treatments by prognostic factors and the inclusion of multiple prognostic factors into economic evaluations. In Part III, the extra-articular CV effects of RA were studied. However, in treating RA patients the focus is primarily on the joints and the impact of current treatment on extra-articular manifestation is ignored. There is now evidence that anti-inflammatory therapy can reduce the risk of CV events [14]. Also, there is evidence that certain RA therapy might contribute to worsening of RA lung conditions.[13] Future research should consider the non-joint impact of RA treatment and the inclusion of these aspect into the economic modeling.

In addition to the above, future economic models should devote more effort to understanding how the composite measures of disease change over time and the impact of measures such as CDAI on EQ-5D. In addition, the treatment patterns considered in these models should be real world based and include aspects of drug holiday, de-escalation and dose escalation. Evidence generated through these research topics will inform the future economic models in terms of treatment responses, subgroups and clinical benefits. This will enable to more accurately characterize the treatment benefits and cost of intervention and implement policies that are more targeted paving the way for personalized medicine in RA.

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Summary / Samenvatting

PhD. Portfolio

Acknowledgements

Curriculum vitae

SUMMARY

Background

Rheumatoid Arthritis (RA) is described as a chronic progressive inflammatory disease of the joint synovium, leading to progressive disability and loss of function. RA through its articular as well as extra-articular impact contributes not only to reduced survival, health related quality of life (HRQOL), activities of daily living and work productivity, but is also associated with higher health resource utilization and costs. The prevalence of RA ranges from 0.4% to 1.3%.

RA treatments include corticosteroids (CS), non-steroidal anti-inflammatory drugs (NSAIDs), and disease-modifying antirheumatic drugs (DMARDs). Traditional or conventional (c)DMARDs include gold, sulfasalazine, azathioprine, cyclophosphamide, antimalarials and methotrexate. Biologic (b)DMARDs were introduced around 2000 and more recently targeted synthetic (ts)DMARDs; these agents have greatly improved overall clinical outcomes, and HRQOL of patients. However, these therapies are expensive compared to the cDMARDs. Recently, biosimilars have been approved by regulatory and payer authorities in the EU and these agents have considerable lower cost. In parallel, new therapies as well as combination therapies (of different bDMARDs or of bDMARDs in combination with tsDMARDs) targeting multiple immune pathways are being developed. In this type of environment, tools that enable a broader and more precise estimation of cost and benefits will reduce the risk of inefficient resource allocation.

This thesis builds towards taking a comprehensive approach in evaluating benefits and costs of future therapies in RA. It focuses on the heterogeneous nature of RA, both in terms of baseline characteristics of RA patients through considerations of subgroups as well as outcomes that are not joint related. It is important to consider these aspect of the disease as future economic analysis will need to take these into account to further differentiate vs. standard of care.

The thesis is divided into 4 parts:
Part I: Real world evidence on treatment targets and outcomes
Part II: Presence of multiple poor prognostic factors
Part III: Extra-articular manifestation of cardiovascular risk in RA
Part IV: Improvements of future cost effectives studies in RA

Part I: Real world evidence on treatment targets and outcomes

Consensus treatment guidelines by EU League Against Rheumatism (EULAR 2016) focus on the joint aspect of the disease and have advocated a treat to target approach. In *Chapter 2* of the thesis, data from clinical practice was utilized to conduct an observational study to test the hypothesis that achieving target measures of disease activity would lead to improved outcomes in clinical practice in a longitudinal follow-up of RA patient cohort. Outcomes evaluated in this analysis included both clinical i.e. physical functioning (daily activities) according to the modified Health Assessment Questionnaire (M-HAQ), quality of life measured by EuroQol 5-domain (EQ-5D) measure and economic i.e. resource utilization according to hospitalizations and durable medical equipment (DME) use. Disease activity measures used in this analysis were those recommended by guidelines and included the Disease Activity Score in 28 joints using C-reactive protein level (DAS28-CRP) <2.6, the Simplified Disease Activity Index (SDAI) ≤3.3, or the Clinical Disease Activity Index (CDAI) ≤2.8.

Data from the Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study (BRASS; Clinical- Trials.gov identifier NCT01793103) was utilized to address research objectives. BRASS was initiated in 2003–2004. The BRASS Registry is a single-center, prospective, observational longitudinal cohort of 1,200 adults with established or recent-onset RA. Physicians assessed patient demographic and clinical characteristics, disease activity, and laboratory parameters at baseline and annually thereafter. To control for intraclass correlation of the panel data, mixed models with Toeplitz covariance structure were utilized to estimate both the effects of the achievement of target measures or other levels of disease activity on the dependent variables, i.e., the primary outcome measure of physical functioning assessed by the M-HAQ and the secondary outcome measure of HRQOL assessed by the EQ-5D. Generalized estimating equations with binomial distribution and logit link function were utilized for binary outcomes such as DME use and all-cause hospitalization. Baseline covariates included in these models were sociodemographic, laboratory measures, subjective (patient-reported), and physician-diagnosed comorbidities.

The findings of the analysis suggest that attaining recommended target disease-activity measures was associated with enhanced physical functioning and health-related quality of life. Some health outcomes were similar in subjects attaining guideline targets versus LDA. Achieving LDA is a worthy clinical objective in some patients.

Part II: Presence of multiple poor prognostic factors

Contemporary RA management guidelines recommend more intensive treatment of patients with poor prognostic factors. The new 2016 EULAR RA treatment guidelines give stratification of RA patients by prognostic factors more prominence and call it out as a separate recommendation i.e. recommendation #8. The guidelines do mention that the combination of these factors as having poor prognosis. However, there is no empirical data in established RA on the impact of multiple prognostic factors on clinical and economic outcomes. Part II of the thesis focuses on the presence of multiple poor prognostic factors on clinical and economic outcomes in established RA.

The following research hypothesis were tested in the various studies conducted in this part of the thesis:

a) Established RA patients that are anti-cyclic citrullinated peptide antibody (ACPA) positive, have increased odds of erosive disease and greater bone loss [hand Digital X-Ray Bone Mineral Density (DXR–BMD)], indicating prognostic factors are inter-related.
b) Reduction in ACPA titers is associated with reduction in disease activity and resource utilization.
c) The presence of multiple poor prognostic factors leads to poor clinical and economic outcomes in RA patients.
d) The presence of poor prognostic factors in RA patients leads to treatment acceleration in clinical practice setting.

Data from the BRASS registry and CORRONA RA registry were used to address hypothesis in this section. In *Chapter 3*, the BRASS database, was used to evaluate the associations between ACPA positivity and the binary outcome variable of the presence or absence of joint erosions as well as the loss of DXR-BMD. In this analysis we used logistic regression models controlling for baseline covariates. Models also tested associations between the presence of multiple prognostic factors and the categorical variables of: 1) having DAS28-CRP < 2.6 or SDAI ≤ 3.3 (SDAI remission), 2) hospitalization (yes or no), 3) DME use (yes or no), and 4) employment status (proportions employed, retired, disabled, and earning <$70,000 annually). For associations between seropositivity and/or joint erosions and the likelihood of having a DAS28-CRP score < 2.6 or SDAI ≤ 3.3 (SDAI remission), Forest plots based on logistic regression models were constructed showing odds ratios (OR) and 95% confidence intervals (CIs). Covariates in these models included patient age, gender, race, body mass index (BMI), number of comorbidities, corticosteroid use and DMARDs. The findings demonstrated that that ACPA seropositive patients, particularly those with

high ACPA titres, have lower hand BMD, and patients with lower hand BMD are less likely to achieve DAS28 (CRP) <2.6.

In *Chapter 4* the associations between changes in ACPA levels and outcomes, including DME use, hospitalizations, and disease activity, in patients with established RA was evaluated using BRASS registry data. Findings from this analysis highlight that decrease in ACPA levels was associated with reduction in DME use (adjusted odds ratio [aOR]: 0.64; 95% confidence interval [CI]: 0.44–0.93; $P = 0.019$) and hospitalizations (aOR: 0.62; 95% CI: 0.41–0.95; $P = 0.029$) versus no change or increase. Adjusted mean changes in disease activity score in 28 joints (C-reactive protein), total and swollen joint counts, and pain scores were significantly greater in patients with decreased ACPA levels versus those with no change or increase ($P < 0.05$). Thus, among patients with established RA, reductions in ACPA levels of >10% were associated with reductions in DME use, hospitalizations, and disease activity.

Chapters 5-6 focused on the presence of multiple prognostic factors in RA patients. In *Chapter 5* logistic regression models were used to test associations between ACPA/rheumatoid factor (RF) seropositivity and erosive disease and the presence of ACPA/RF seropositivity plus erosive disease and (1) RA severity; (2) hospitalizations; (3) durable medical equipment (DME) use; and (4) worker productivity (e.g., employment status). Covariates in these models included patient age, gender, race, body mass index (BMI), number of comorbidities, and treatment. The findings indicated that ACPA positive (vs. negative) RA patients were 2.72 times more likely to have erosions (OR = 2.72; 95% CI: 1.77–4.18; P < 0.001). Patients with ACPA seropositivity and erosions were significantly more likely to: (1) have higher disease activity as measured by the DAS28-CRP ≥ 2.6; (2) be hospitalized; (3) use DME; and (4) be unemployed, disabled, or long-term disabled. This analysis was the first "real-world" study in patients with both recent-onset and chronic RA, that demonstrated the combination of ACPA seropositivity and erosions were significantly associated with adverse clinical and health-economic outcomes, including a lower probability of low disease activity and higher health resource utilization, despite use of bDMARDs by many patients. Thus highlighting that the presence of multiple prognostic factors may signal a need for more intensive therapies, even when observed in patients with chronic, as well as recent-onset, RA.

Chapter 6 is based on data from the CORRONA RA registry. The objective of this analysis was to characterize patients with RA by number of poor prognostic factors (such as functional limitation, extra-articular disease, seropositivity, erosions) and evaluate treatment acceleration, clinical outcomes, and work status over 12 months

by number of poor prognostic factors. Changes in medication, CDAI, and work status (baseline–12 months) were evaluated using linear and logistic regression models. The relationship between poor prognostic factor groups and work status was investigated at baseline and 12-month follow-up using chi-squared tests. A frequency-matching approach (coarsened exact matching) was used to match patients across poor prognostic factor categories according to age group (18–44, 45–54, 55–64, 65–74, 75+ years) as the relationship between poor prognostic factor category and work status could be driven by age difference (retirees are generally older). At baseline, patients with greater number of poor prognostic factors (vs. those with fewer prognostic factors) were older, and had longer RA duration and higher CDAI ($p = 0.011$). B/tsDMARD use was similar in patients with/without prognostic factors. After adjusting for baseline CDAI, mean (standard error) change in CDAI was –4.95 (0.24), –4.53 (0.27), and –2.52 (0.34) for no-prognostic factor group, 1, 2, and ≥3 prognostic factor groups, respectively. More patients were working at baseline but not at 12-month follow-up in 2 (13.9%) and ≥3 (12.5%) versus 0–1 (7.3%) prognostic factor groups. This analysis again highlights that patients with multiple prognostic factors had suboptimal clinical and work status outcomes. More importantly, the findings indicate that despite high disease activity and worse clinical outcomes, prognostic factors did not significantly predict b/tsDMARD use. This may warrant reconsideration of the importance of poor prognostic factors in treat-to-target approaches.

Part III: Extra-articular manifestation of cardiovascular risk in RA

Treatment guidelines in RA have focused on the joint aspect of the disease however; extra articular manifestation of RA represents the significant and important outcome. The thesis focuses on the cardiovascular (CV) manifestation of RA, primarily because CV events impact overall patients survival, HRQOL and have substantial cost implications. Since RA is associated with a 50 to 60% increase in risk of CV death, *Chapter 7* assessed the management of traditional CV risk factors in RA patients so as to evaluate if the increased CV risk could be explained by poor management by traditional CV risk factors in RA. Data were utilized from the UK Clinical Practice Research Datalink (CPRD) for the analysis. RA patients were matched 1:4 to non-RA patients based on their year of entry in the CPRD database, CV risk category (NCEP classification), treatment status at index date and a propensity score estimating the probability of having RA. 24,859 RA patients were identified and matched to 87,304 non-RA patients. Annual blood pressure, lipids and diabetes-related testing were similar in both groups, although CRP and ESR were higher in RA patients at diagnosis and decreased over time. RA patients prescribed antihypertensives increased from 38.2% at diagnosis

to 45.7% at 5 years, from 14.0 to 20.6% for lipid-lowering treatments and from 5.1 to 6.4% for antidiabetics. Similar treatment percentages were observed in non-RA patients, although slightly lower for antihypertensives. Modest (2%) but significantly lower attainment of lipid and diabetes goals at 1 year was observed in RA patients. This analysis indicated that there were no differences between groups in the frequency of testing and treatment of CV risk factors. Higher CV events in RA patients seems unlikely to be driven by differences in traditional CV risk factor management.

Another aspect of CV manifestation of RA investigated in *Chapter 8* was the performance of CV risk prediction algorithms in RA. The aim was to compare the performance of cardiovascular risk calculators, Framingham Risk Score (FRS) and QRISK2, in RA and matched non-RA patients and to evaluate whether their performance could be enhanced by the addition of CRP. Retrospective analysis using CPRD linked to Hospital Episode Statistics (HES) data was performed. RA patients with no prior CV were matched to non-RA patients using disease risk scores. The overall performance of the FRS and QRISK2 was compared between cohorts, and assessed with and without CRP in the RA cohort using C-Index, Akaike Information Criterion (AIC) and the net reclassification index (NRI). The C-Index for the FRS in the non-RA and RA cohort was 0.783 and 0.754 ($P < 0.001$) and that of the QRISK2 was 0.770 and 0.744 ($P < 0.001$), respectively. Log[CRP] was positively associated with cardiovascular events, but improvements in the FRS and QRISK2 C-Indices as a result of inclusion of CRP were small, from 0.764 to 0.767 ($P = 0.026$) for FRS and from 0.764 to 0.765 ($P = 0.250$) for QRISK2. The NRI was 3.2% (95% CI: -2.8, 5.7%) for FRS and -2.0% (95% CI: -5.8, 4.5%) for QRISK2. The C-Index for the FRS and QRISK2 was significantly better in the non-RA compared with RA patients. The addition of CRP in both equations was not associated with a significant improvement in reclassification based on NRI.

The final *Chapter 9* of the section focused on the association between lowering low-density lipoproteins cholesterol (LDL-C) levels and CV outcomes among RA patients. Adult patients with RA and 2 age- and sex-matched control cohorts [RA plus general controls (RA/GN), RA plus osteoarthritis (OA) controls (RA/OA)] were analyzed. Multivariable Cox proportional hazard analyses were used. During study follow-up, mean (SD) LDL-C (mg/dl) was 96.8 (32.7) for RA, 100.1 (35.1) for general controls, and 99.1 (34.3) for OA. The relationship between lowering LDL-C and CV outcomes was similar for both RA and non-RA controls (p for interaction = 0.852 in RA/GN cohort, and p = 0.610 in RA/OA cohort). After adjusting for baseline CV risk factors, lowering LDL-C was associated with a 29%-50% lower risk of CV events (HR [95% CI] = 0.71 [0.57-0.89] in RA/GN, 0.50 [0.43-0.58] in RA/OA). Subgroup analyses showed that lowering LDL-C was associated with a similar degree of reduction of CV events in RA

and non-RA controls (HR of 0.67-0.68 for RA, 0.72 for general controls, 0.76 for OA controls). Lowering LDL-C levels was associated with reduced CV events. The relationship between lowering LDL-C and CV outcomes in RA was similar to the relationship found in matched general and OA controls.

Part IV: Improvements of future cost effectives studies in RA

The final Part of the thesis is based on evaluating the cost effectiveness of interventions in RA, primarily focusing on the application of existing model in certain subgroups of RA patients to evaluate the cost-effectiveness to two branded bDMARDs. The final chapter builds on the learning from the earlier Parts of the thesis namely, treatment targets (Part I), subsgroups based on prognostic factors (Part II) and extra-articular manifestations (Part III) to propose a new conceptual framework for evaluating future innovative technologies in RA.

In *Chapter 10*, an individual patient simulation model is used to simulate the impact of treatment in subgroups of RA patients with various titers of ACPA, a marker of poor prognosis in RA as demonstrated in Part II. The model simulated disease progression in patients with RA who had previously failed cDMARDs and were starting bDMARD therapy. Patients commenced treatment with abatacept or adalimumab plus methotrexate and were evaluated after 6 months. Therapy continuation was based on the EULAR treatment response; disease progression was based on the HAQ-DI score. Quality adjusted life years (QALYs) and incremental cost per QALY gained were calculated by baseline ACPA quartile groups (Q1, 28–234 AU/ml; Q2, 235–609 AU/ml; Q3, 613–1045 AU/ml; and Q4,1060–4894 AU/ml). Scenario analysis and one-way and probabilistic sensitivity analyses were used to evaluate robustness of model assumptions. Results indicated that abatacept resulted in QALY gain versus adalimumab in ACPA Q1, Q3, and Q4; between-treatment difference (difference: Q1, -0.115 Q2, -0.009 Q3, 0.045; and Q4, 0.279). Total lifetime discounted cost was higher for abatacept versus adalimumab in most quartiles (Q2, £77,612 vs. £77,546; Q3, £74,441 vs. £73,263; and Q4, £78,428 vs. £76,696) because of longer time on treatment. Incremental cost per QALY for abatacept (vs. adalimumab) was the lowest in the high ACPA titer group (Q4, £6,200/QALY), followed by the next lowest titer group (Q3, £26,272/QALY).

The current modeling approach has advantages and has served to establish economic benefits of bDMARDs, in moderate to severe RA patients who inadequately respond to methotrexate. In our opinion previously, published models have potential room

for improvement. In *Chapter 11* a new conceptual model for evaluation of the cost-effectiveness of RA interventions is proposed. Recommendations from the International Society of Pharmacoeconomics and Outcomes Research-Society of Medical Decision Making (ISPOR-SMDM) Modeling Good Research Practices Task Force-2 were followed in developing the conceptual model. The process involved scoping the decision problem by a working group and drafting a preliminary cost-effectiveness model framework. A systematic literature review (SLR) of existing decision-analytic models was performed and analysis of an RA registry was conducted to inform the structure of the draft conceptual model. Finally, an expert panel was convened to seek input on the draft conceptual model. The proposed conceptual model consists of three separate modules: 1) patient characteristic module, 2) treatment module, and 3) outcome module. Consistent with the scope, the conceptual model proposed six changes to current economic models in RA. These changes proposed are to: 1) use composite measures of disease activity to evaluate treatment response as well as disease progression (at least two measures should be considered, one as the base case and one as a sensitivity analysis); 2) conduct utility mapping based on disease activity measures; 3) incorporate subgroups based on guideline-recommended prognostic factors; 4) integrate realistic treatment patterns based on clinical practice/registry datasets; 5) assimilate outcomes that are not joint related (extra-articular outcomes); and 6) assess mortality based on disease activity. The conceptual model incorporates the current understanding of both clinical and real-world evidence in RA, as well as of existing modeling assumptions. The proposed model framework was reviewed with experts and could serve as a foundation for developing future cost-effectiveness models in RA.

Discussion

Given the overall objective of the thesis and nature of the research hypothesis tested, we considered that the most relevant data source to inform this thesis was real world clinical practice data. Unlike randomized clinical trials, real world registry data are less prescriptive in their inclusion/exclusion criteria as well as the treatments and hence provide an appropriate data source for evaluating the benefits of various RA disease health states (remission, LDA, MDA, SDA) on outcomes. One of the main limitation of the body of work presented in this thesis is that it very much focused on established RA patients. Another limitation of the body of work in Parts II and III is that it only focused on certain prognostic factors (i.e. erosive disease and seropositivity) and certain extra-articular manifestation of RA (CV events).

The research in this thesis has highlighted that treatment and reimbursement policies in RA should consider treatment targets that are better associated to multiple outcomes such as physical functioning, HRQOL and resource use. This is especially true in RA, since the primary outcomes of ACR and DAS28-CRP measured in clinical trials are not generally measured in clinical practice settings and might only be informative from a drug efficacy point of view for regulatory drug approval requirements. However, these measures are less sensitive to other outcomes relevant for payer needs compared to CDAI/SDAI. In addition, future policy in RA should consider exploring the management of RA based on subgroups of high unmet need, as has been done in multiple other therapeutic areas such as cardiovascular, diabetes, hepatitis etc. Finally, future health policies in RA should take a more holistic approach for managing RA, since there is increasing evidence of the systemic inflammatory nature of the disease. Thus, focusing on only the joint aspects of the condition in cost effectiveness evaluations does not provide the estimate of the true cost and benefit of interventions and incorporation of the non-joint aspect of the condition will be important. Though our work did not focus on the patient reported outcomes measures (PROMS) or patient reported experience measures (PREMS), incorporation of these measures in future policy considerations for RA will be important.

SAMENVATTING

Achtergrond

Reumatoïde Artritis (RA) wordt beschreven als een chronische progressieve ontstekingsziekte van het synovium (slijmvlies) in gewrichten, wat in toenemende mate leidt tot beperkingen en verlies van functie. Via haar articulaire evenals extra-articulaire effecten draagt RA niet alleen bij tot een vermindering van de overleving, de gezondheid gerelateerde kwaliteit van leven (HRQOL), activiteiten in het dagelijks leven en de arbeidsproductiviteit, maar is tevens verbonden aan hogere zorgvoorzieningen en kosten. De prevalentie van RA varieert van 0,4% tot 1,3%.

RA therapien omvatten corticosteroïden (CS), niet-steroïdale anti-inflammatoire geneesmiddelen (NSAIDs), en ziekteremmende antireumatische geneesmiddelen (DMARDs). Onder de traditionele of conventionele (c)DMARDs vallen goud, sulfasalazine, azathioprine, cyclophosphamide, anti-malaria middelen en methotrexaat. Biologisch (b)DMARDs werden geintroduceerd rond 2000 en meer recent werden de gerichte synthetisch (ts)DMARDs geintroduceerd; deze middelen hebben de algemene klinische resultaten en HRQOL van patiënten aanzienlijk verbeterd. Deze behandelingen zijn echter duur in vergelijking met de cDMARDs. Onlangs zijn biosimilars goedgekeurd door regelgevende en payer instanties in de EU en deze middelen hebben aanzienlijk lagere kosten. Tegelijkertijd worden nieuwe therapieën en combinatie therapieën (van verschillende bDMARDs of bDMARDs in combinatie met tsDMARDs) die zich op meerdere immuun trajecten richten ontwikkeld. In dit soort omgeving zullen hulpmiddelen waarmee een bredere en meer precieze schatting van de kosten en baten gemaakt kan worden het risico van een inefficiënte toewijzing van middelen beperken.

Deze scriptie werkt toe naar het nemen van een alomvattende benadering van de evaluatie van de kosten en baten van toekomstige behandelingen in RA. De focus is op de heterogene aard van RA, zowel in de baseline karakteristieken van RA patiënten door het overwegen van subgroepen alswel in het overwegen van uitkomsten die niet gewrichts gerelateerd zijn. Het is belangrijk om deze aspecten van de ziekte in overweging te nemen omdat toekomstige economische analyses deze in acht zullen moeten nemen om verdere differentiatie versus standaardzorg mogelijk te maken.

De scriptie is onderverdeeld in 4 delen:
Deel I: Real world evidence over behandel doelen en resultaten
Deel II: Aanwezigheid van meerdere factoren voor een slechte prognose

Deel III: Extra-articulaire manifestatie van cardiovasculair risico in RA
Deel IV: verbetering van toekomstige kosten effectiviteits studies in RA

Deel I: Real world evidence over behandel doelen en resultaten

Consensus richtlijnen voor de behandeling van EU-Liga tegen reuma (EULAR 2016) focussen op de gewrichts aspecten van de ziekte en hebben gepleit voor een 'treat to target' benadering. In *hoofdstuk 2* van het proefschrift zijn gegevens uit de klinische praktijk gebruikt voor een observationele studie die de hypothese testte dat het bereiken van streef maatregelen voor ziekte-activiteit zou leiden tot betere resultaten in de klinische praktijk in een longitudinale follow-up van een RA patienten cohort. Uitkomstmaten die in deze analyse geevalueerd werden omvatte zowel klinische, d.w.z. fysiek functioneren (dagelijkse activiteiten) volgens de modified Health Assessment Questionnaire (M-HAQ), kwaliteit van leven gemeten door de EuroQol 5-domain (EQ-5D) en economisch d.w.z. hulpbronnen gebruik gemeten door middel van ziekenhuisopnamen en duurzame medische apparatuur (DME). De ziekteactiviteits maten die gebruikt zijn in deze analyse zijn deze die werden aanbevolen door de richtlijnen en omvatte de Disease Activity Score in 28 joints using C-reactive protein (DAS28-CRP) <2.6, de Simplified Disease Activity Index (SDAI) =<3.3, en de Clinical Disease Activity Index (CDAI) =<2.8.

Gegevens van de Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study (BRASS; Clinical-Trials.gov identifier NCT01793103) werden gebruikt voor het addresseren van de onderzoekdoelstellingen. BRASS werd geinitieerd in 2003-2004. De BRASS registry is een single-centrum, prospectief, observerend longitudinaal cohort van 1.200 volwassenen met gevestigde of recent gediagnosticeerde RA. Artsen beoordeelden patiëntgegevens en klinische kenmerken, ziekteactiviteit en laboratorium parameters op baseline en daarna jaarlijks. Om te controleren voor de intraclass correlatie van de panel data, werden mixed models met Toeplitz covariance structuur gebruikt voor het schatten van de effecten van het bereiken van streef maatregelen of andere niveaus van ziekte-activiteit op de afhankelijke variabelen, namelijk de primaire uitkomstmaten van fysiek functioneren beoordeeld volgens de M-HAQ en de secundaire uitkomstmaten van HRQOL volgens de EQ-5D. Generalized estimating equations met binomiale verdeling en logit link-functie werden gebruikt voor de binaire uitkomsten zoals DME gebruik en all-cause hospitalisatie. Baseline covariates geincludeerd in deze modellen waren sociaal-demografische gegevens, laboratorium gegevens, subjectieve (patiënt-gerapporteerde) gegevens en arts-gediagnosticeerde comorbidities.

De bevindingen van de studie suggereren dat het bereiken van de aanbevolen streefmaatregelen in ziekteactiviteit werd geassocieerd met verbeteringen in fysiek functioneren en gezondheidsgerelateerde levenskwaliteit. Sommige gezondheidsresultaten waren vergelijkbaar in patienten die de streefmaatregelen bereikten versus LDA (lage ziekte activiteit). Het bereiken van LDA is een waardige klinische doelstelling voor sommige patiënten.

Deel II: Aanwezigheid van meerdere factoren voor een slechte prognose

Hedendaagse RA richtlijnen bevelen een meer intensieve behandeling van patiënten met slechte prognostische factoren aan. De nieuwe 2016 EULAR RA behandelrichtlijnen geven stratificatie van RA patiënten door prognostische factoren meer prominentie en vermelden het als een afzonderlijke aanbeveling namelijk aanbeveling #8. De richtlijnen vermelden uitdrukkelijk dat de combinatie van deze factoren duidt op een slechte prognose. Er zijn echter geen empirische gegevens in RA over het effect van meerdere prognostische factoren op klinische en economische resultaten. Deel II van het proefschrift richt zich op de aanwezigheid van meerdere slechte prognostische factoren op klinische en economische resultaten in gevestigd RA.

De volgende hypotheses werden getest in de verschillende studies in dit deel van het proefschrift:

a) Patienten met gevestigd RA die anti-cyclic citrullinated peptide antistoffen (ACPA) positief zijn, hebben een grotere kans op erosieve ziekte en groter botverlies [hand Digital X-Ray Bone Mineral Density (DXR-BMD)], wat aan duidt dat prognostische factoren onderling verbonden zijn.
b) Vermindering van de ACPA titers wordt geassocieerd met vermindering van ziekte activiteit en gebruik van resources.
c) De aanwezigheid van meerdere slechte prognostische factoren leidt tot slechte klinische en economische uitkomsten in RA patiënten.
d) De aanwezigheid van slechte prognostische factoren bij RA patiënten leidt tot acceleratie van de behandeling in de klinische praktijk.

Gegevens van de BRASS registry en de CORRONA RA registry werden gebruikt om de hypothese in dit hoofdstuk the onderzoeken. In *hoofdstuk 3* wordt de BRASS database, gebruikt voor het evalueren van de associaties tussen ACPA positiviteit en de binaire uitkomst variabele van de aanwezigheid of afwezigheid van erosies in de gewrichten en ook het verlies van DXR-BMD. In deze analyse gebruikten we logistische regressie modellen gecorrigeerd voor baseline covariates. Modellen testten de associaties tus-

sen de aanwezigheid van meerdere prognostische factoren en de categoriale variabelen: 1) DAS28-CRP < 2,6 of SDAI ≤ 3,3 (SDAI remissie), 2) hospitalisatie (ja of nee), 3) DME (ja of nee), en 4) arbeidsstatus (aandeel werkend, gepensioneerd, gehandicapt, en inkomen <$70.000 per jaar). Voor de associaties tussen seropositiviteit en/of gewrichts erosies en de waarschijnlijkheid van een DAS28-CRP score < 2,6 of SDAI ≤ 3,3 (SDAI remissie), werden Forest plots ontwikkeld op basis van logistische regressie modellen met odds ratio's (OR) en 95% betrouwbaarheidsintervallen (CI). De covariates die in deze modellen zijn opgenomen omvatten de patient's leeftijd, geslacht, ras, body mass index (BMI), aantal comorbiditeiten, gebruik van corticosteroiden en DMARDs. De resultaten tonen aan dat ACPA seropositieve patiënten, met name die met hoge ACPA titers, een lagere hand BMD hebben en patiënten met lagere hand BMD hebben kleinere kans op het bereiken van een DAS28 (CRP) <2.6.

In *hoofdstuk 4* werden de associaties tussen veranderingen in ACPA levels en uitkomsten, inclusief DME, ziekenhuisopnamen en ziekte activiteit, onderzocht in patiënten met gevestigd RA met behulp van data in de BRASS registry. Uit bevindingen van deze analyis blijkt dat daling van ACPA levels werd geassocieerd met een vermindering in gebruik van DME (aangepast odds ratio [aOR]: 0,64; 95% betrouwbaarheidsinterval [CI]: 0,44-0,93; $P = 0,019$) en het aantal ziekenhuisopnames (aOR: 0.62; 95% CI: 0,41-0,95; $P = 0,029$) versus geen verandering of toename. De gecorrigeerde gemiddelde verandering in de ziekte activiteit's score in 28 gewrichten (C-reactive protein), totaal en gezwollen gewrichten nummers, en pijn scores waren aanzienlijk groter bij patiënten met een vermindering in de ACPA levels versus degenen zonder veranderingen of verhoging ($p < 0,05$). In patiënten met gevestigd RA werden verlaging van ACPA levels van >10% geassocieerd met een vermindering van DME gebruik, ziekenhuisopnamen en ziekte-activiteit.

De hoofdstukken 5-6 richten zich op de aanwezigheid van meerdere prognostische factoren in RA patiënten. In *hoofdstuk 5* werden logistische regressie modellen gebruikt voor het testen van associaties tussen ACPA/ reumatoïde factor (RF) seropositiviteit en erosieve ziekte en de aanwezigheid van ACPA/RF seropositiviteit plus erosieve ziekte en (1) ernst van RA; (2) ziekenhuis opnames; (3) duurzaam medische apparatuur (DME) gebruik; en (4) werk productiviteit (bijv. arbeidsstatus). De covariates gebruikt in deze modellen includeren de patiënt's leeftijd, geslacht, ras, body mass index (BMI), aantal comorbiditeiten, en behandeling. De bevindingen geven aan dat ACPA positieve (vs. negatieve) RA patiënten een 2,72 maal hogere kans hebben op erosies (OR = 2,72; 95% CI: 1,77-4,18; P < 0,001). Patiënten met ACPA seropositiviteit en erosies hadden een aanzienlijk grotere kans op: (1) een hogere ziekte-activiteit, gemeten door DAS28-CRP ≥ 2,6; (2) ziekenhuis opname; (3) gebruik van DME; en

om (4) werkeloos, gehandicapt of langdurig uitgeschakeld te zijn. Deze analyse was de eerste "real-world"-studie bij patiënten met zowel recent gediagnosticeerde als chronische RA, waaruit bleek dat de combinatie van ACPA seropositiviteit en erosies significant geassocieerd zijn met negatieve klinische en economische resultaten, waaronder een geringere kans op een lage ziekte-activiteit en hoger zorg gebruik, ondanks het gebruik van bDMARDs door veel patiënten. Daarmee werd duidelijk dat de aanwezigheid van verschillende prognostische factoren mogelijk een signaal is voor een behoefte aan meer intensieve behandeling, zelfs wanneer waargenomen in patiënten met chronische RA, evenals recente gediagnosticeerde RA.

Hoofdstuk 6 is gebaseerd op gegevens van de CORRONA RA-registry. Het doel van deze analyse was om patiënten met RA te typeren door het aantal slechte prognostische factoren (zoals functionele beperking, extra-articulaire aandoeningen, seropositiviteit, erosies) en om versnelling van de behandeling, klinische uitkomsten en status van het werk over een periode van 12 maanden, te evalueren op basis van het aantal slechte prognostische factoren. Veranderingen in medicatie, CDAI en werkstatus (baseline-12 maanden) werden geëvalueerd aan de hand van lineaire en logistische regressie modellen. De relatie tussen slechte prognostische factor groepen en werkstatus werd onderzocht op baseline en 12 maanden follow-up met behulp van de chi-squared test. Een frequency-matching approach (coarsenend exact matching) werd gebruikt om patiënten the matchen over de slechte prognostische factor categorieën volgens leeftijdsgroep (18-44, 45-54, 55-64, 65-74, 75+ jaar) omdat de relatie tussen slechte prognostische factor categorie en werkstatus kan worden veroorzaakt door het leeftijdsverschil (gepensioneerden zijn over het algemeen ouder). Op baseline waren patiënten met een groter aantal slechte prognostische factoren (vs. die met minder prognostische factoren) ouder en hadden RA voor een langere duur en hadden een hogere CDAI ($p = 0{,}011$). B/tsDMARD gebruik was vergelijkbaar bij patiënten met/zonder prognostische factoren. De gemiddelde (standard error) verandering in CDAI was, na corrigeren voor baseline CDAI, -4.95 (0.24), -4.53 (0.27) en -2,52 (0,34) voor de geen-prognostische factor groep, 1, 2 en ≥3 prognostische factor groepen, respectivelijk. Meer patiënten werkten op baseline maar niet na 12 maanden follow-up in 2 (13,9%) en ≥3 (12,5%) versus 0-1 (7.3%) prognostische factoren groepen. Deze analyse benadrukt opnieuw dat patiënten met meerdere prognostische factoren suboptimale klinische en werkstatus uitkomsten hebben. Daarnaast gaven de bevindingen aan dat ondanks de hoge ziekte activiteit en slechtere klinische resultaten, de prognostische factoren niet significant het gebruik van b/tsDMARD voorspellen. Dit kan een heroverweging van het belang van slechte prognostische factoren in de treat-to-target aanpak rechtvaardigen.

Deel III: Extra-articulaire manifestatie van cardiovasculair risico in RA

Behandelrichtlijnen in RA hebben aandacht besteed aan het gewrichts aspect van de ziekte, echter de extra-articulaire manifestatie van RA vertegenwoordigt een significante en belangrijke uitkomst. Het proefschrift richt zich op de cardiovasculaire (CV) manifestatie van RA, vooral omdate CV incidenten een impact hebben op de overleving van de patient, HRQOL en aanzienlijke kosten hebben. Aangezien RA is gekoppeld aan een toename van 50 tot 60% in het risico op een cv sterfgeval, evalueert *hoofdstuk 7* de behandeling van de traditionele CV-risicofactoren in RA patiënten zodat vast gesteld kan worden of het toegenomen CV risico kan worden verklaard door slecht management van traditionele CV-risicofactoren in RA. Voor deze analyse werden de gegevens uit de UK Clinical Practice Research Datalink (CPRD) gebruikt. RA patiënten werden 1:4 gematched aan niet-RA-patiënten op basis van hun entry in de CPRD database, CV risicocategorie (NCEP classificatie), behandeling's status op de index datum en een propensity-score die het risico van het hebben van RA inschatte. 24,859 RA patiënten werden geïdentificeerd en gematched met 87,304 niet-RA-patiënten. De jaarlijkse bloeddruk, lipiden en diabetes-gerelateerde tests waren vergelijkbaar in beide groepen, hoewel CRP en ESR hoger waren in RA patiënten ten tijde van de diagnose en daalden in de loop van de tijd. Het voorschrijven van antihypertensiva in RA patiënten steeg van 38,2% bij de diagnose tot 45,7% na 5 jaar, lipideverlagende behandelingen steeg van 14,0 tot 20,6% en antidiabetica stegen van 5,1 tot 6,4%. Soortgelijke percentages in geneesmiddel gebruik werden waargenomen bij niet-RA-patiënten, hoewel iets minder voor antihypertensiva. Een bescheiden (2%) maar beduidend lagere verwezenlijking van de lipiden en diabetes doelen na 1 jaar werd waargenomen bij RA patiënten. Deze analyse toont aan dat er geen verschillen zijn tussen de groepen in de frequentie van de testen en de behandeling van CV-risicofactoren. Het lijkt onwaarschijnlijk dat de hogere CV incidenten in RA patiënten worden veroorzaakt door verschillen in de traditionele behandeling van de CV risico factoren.

Een ander aspect van CV manifestatie in RA dat wordt onderzocht in *hoofdstuk 8* was de prestatie van CV predictie algoritmen in RA. Het doel was om de prestatie van CV risico calculators, de Framingham risicoscore (FRS) en QRISK2, te vergelijken in RA en matched niet-RA-patiënten, en te beoordelen of hun prestaties kunnen worden verbeterd door de toevoeging van CRP. Een retrospective analyse is uitgevoerd met de gegevens van CPRD gekoppeld aan Hospital Episode Statistics (HES). RA patiënten zonder voorafgaande cardiovasculaire gebeurtenissen werden gematched met niet-RA patiënten met ziekte risicoscores. De algehele prestatie van de FRS en QRISK2 werd vergeleken tussen de cohorten en beoordeeld met en zonder CRP in het RA cohort met

de C-index, Akaike Information criterion (AIC) en de net reclassification index (NRI). De C-index voor de FRS in de niet-RA en RA cohorten was 0.783 en 0.754 (P < 0,001) en dat van de QRISK2 was 0.770 en 0.744 (P < 0,001) respectivelijk. Log[CRP] werd positief geassocieerd met cardiovasculaire gebeurtenissen, maar verbeteringen in de FRS en QRISK2 C-indexcijfers ten gevolge van de inclusie van CRP waren klein, van 0.764 naar 0.767 (P = 0,026) bij FRS en van 0.764 naar 0.765 (P = 0.250) voor QRISK2. De NRI was 3,2% (95% CI: -2,8, 5,7%) voor FRS en -2,0% (95% CI: -5,8, 4,5%) voor QRISK2. De C-index voor de FRS en QRISK2 was significant beter in de niet-RA in vergelijking met de RA patiënten. De toevoeging van CRP in beide algorithmes was niet geassocieerd met een significante verbetering van de herclassificatie op basis van NRI.

Het laatste *hoofdstuk 9* van de deze sectie richt zich op de associatie tussen het verlagen van low-density lipoproteïn cholesterol (LDL-C) levels en CV-uitkomsten in RA patiënten. Volwassen patiënten met RA en 2 leeftijd- en geslacht gematchte controle cohorten [RA plus algemene controles (RA/GN), RA plus osteoartritis (OA) controls (RA/OA)] werden geanalyseerd. Hiervoor zijn multivariable Cox proportionele hazard analyses gebruikt. Tijdens de studie follow-up was de gemiddelde (SD) LDL-C (mg/dl) 96,8 (32,7) voor RA, 100,1 (35,1) voor general controls en 99.1 (34.3) voor OA controls. De relatie tussen het verlagen van LDL-C en CV uitkomsten was vergelijkbaar voor beide RA en niet-RA controls (p voor interactie = 0,852 in RA/GN cohort, en p = 0,610 in RA/OA cohort). Na corrigeren voor baseline CV risicofactoren werd verlaging van LDL-C geassocieerd met een 29%-50% lager risico op cv events (HR [95% CI] = 0.71 [0.57-0.89] RA/GN, 0.50 [0.43-0.58] RA/OA). Een subgroep analyse toonde aan dat het verlagen van LDL-C was geassocieerd met een vergelijkbare mate van vermindering van CV events in RA en niet-RA controls (HR van 0.67-0.68 voor RA, 0,72 voor general controls, 0,76 voor OA controls). Het verlagen van LDL-C levels was geassocieerd met een vermindering in CV events. De relatie tussen het verlagen van LDL-C en CV uitkomsten in RA was vergelijkbaar met de relatie die werd gevonden in de matched general controls en de OA controls.

Deel IV: verbetering van toekomstige kosten effectiviteit studies in RA

Het laatste deel van het proefschrift is gebaseerd op de beoordeling van de kosteneffectiviteit van interventies in RA; met een focus op de toepassing van een bestaand model in bepaalde subgroepen van RA patiënten om de kosteneffectiviteit van twee niet-generieke bDMARDs te beoordelen. Het laatste hoofdstuk is gebaseerd op inzichten uit de eerdere delen van het proefschrift namelijk behandelingsdoelstellingen

(deel I), subgroepen gebaseerd op prognostische factoren (deel II) en extra-articulaire manifestaties (deel III) om een nieuw conceptueel kader voor de beoordeling van toekomstige innovatieve technologieën in RA voor te stellen.

In *hoofdstuk 10* wordt een individueel patiënt simulatie-model gebruikt voor het simuleren van het effect van behandeling in subgroepen van RA patiënten met verschillende ACPA titers, een teken van een slechte prognose in RA zoals aangetoond in deel II. Het model simuleerd ziekte progressie in patiënten met RA waarbij eerdere behandeling met cDMARDs is gefaald en die beginnen aan bDMARD therapie. Patiënten begonnen behandeling met abatacept of adalimumab plus methotrexaat en werden geëvalueerd na 6 maanden. De voortzetting van de middelen was gebaseerd op de EULAR treatment response criteria; ziekteprogressie was gebaseerd op de HAQ-DI-score. Kwaliteit gecorrigeerde levens jaren (QALYs) en incrementele kosten per gewonnen QALY werden berekend per baseline ACPA kwartiel groep (Q1, 28-234 AU/ml; Q2, 235-609 AU/ml; Q3, 613-1045 AU/ml; Q4,1060-4894 AU/ml). Scenario-analyses en one-way en probabilistische sensitiviteitsanalyses werden gebruikt voor het evalueren van de robuustheid van de aannames gebruikt in het model. Uit de resultaten bleek dat abatacept resulteerde in QALY winst versus adalimumab in ACPA Q1, Q3 en Q4; tussen-behandeling verschil (verschil: Q1 -0.115 Q2 -0.009 Q3, 0.045; en Q4, 0.279). De totale gedisconteerde lifetime kosten waren hoger voor abatacept versus adalimumab in de meeste kwartielen (Q2, £77,612 vs. £77,546; Q3, £74,441 vs. £73,263; Q4, £78,428 vs. £76,696) vanwege de langere behandel duur met abatacept. De incrementele kosten per QALY voor abatacept (vs. adalimumab) was het laagste in de hoogste ACPA titer groep (Q4, £6.200/QALY), gevolgd door de een na hoogste titer groep (Q3, £26,272/QALY).

De huidige aanpak van modellen heeft voordelen en heeft bijgedragen tot de totstandkoming van de economische voordelen van bDMARDs in patienten met matige tot ernstige RA die onvoldoende reageren op methotrexaat. Naar onze mening hebben eerder verschenen modellen potentiële ruimte voor verbetering. In *hoofdstuk 11* wordt een nieuw conceptueel model voor de evaluatie van de kosteneffectiviteit van RA interventies voorgesteld. Aanbevelingen van de International Society of Pharmacoeconomics and Outcomes Research-Society of Medical Decision Making (ISPOR-SMDM) Modeling Good Research Practices Task Force-2 werden gevolgd bij de ontwikkeling van het conceptuele model. Het volledige proces betrok het vaststellen van het beslissings probleem door een werkgroep en het opstellen van een voorafgaand kosten-effectiviteits model kader. Een systematische literatuur review (SLR) van bestaande analytische modellen werd uitgevoerd en analyse van een RA-registry werd gedaan om de structuur van het voorgestelde conceptmodel te informeren. Tenslotte werd

een panel van deskundigen bijeengeroepen om input op het draft conceptmodel te krijgen. Het voorgestelde conceptuele model bestaat uit drie afzonderlijke modules: 1) patiënt karakteristieken module, 2) behandelings module en 3) uitkomsten module. In overeenstemming met de scope stelt het conceptmodel zes wijzigingen op de huidige economische modellen in RA voor. Deze voorgestelde wijzigingen zijn: 1) het gebruik van een samengestelde parameter van de ziekte-activiteit om de respons op de behandeling te evalueren en ook de ziekteprogressie (ten minste twee maatregelen moeten worden overwogen, een in de base case en een in de gevoeligheidsanalyse); 2) utility mapping gebaseerd op ziekteactiviteit maten; 3) integreren van subgroepen gebaseerd op de door de richtlijn aanbevolen prognostische factoren; 4) integreren van realistische behandel patronen die gebaseerd zijn op de klinische praktijk/registry datasets; 5) verwerken van niet gewrichts-gerelateerde uitkomsten (extra-articulaire uitkomsten); en 6) vaststellen van sterfte op basis van ziekteactiviteit. Het conceptuele model integreert het huidige denkbeeld van zowel klinische als real-world gegevens in RA, als ook bestaande modeleer aannames. Het voorgestelde model kader is besproken met deskundigen en zou kunnen dienen als basis voor de ontwikkeling van toekomstig kosteneffectiviteits modellen in RA.

Discussie

Gezien de algemene doelstelling van het proefschrift en de aard van de geteste onderzoeks hypothese, waren we van mening dat de meest relevante bron voor dit proefschrift real world clinical practice data was. In tegenstelling tot gerandomiseerde klinische trials, zijn real world registries minder normatief in hun opneming/uitsluitingscriteria en de behandelingen en dus een gegevensbron voor de evaluatie van de baten van de verschillende RA ziekte gezondheidstoestanden (remissie, LDA, MDA, SDA) op de uitkomstmaten. Een van de belangrijkse beperkingen van het werk gepresenteerd in dit proefschrift is dat het met name gericht is op gevestigd RA patiënten. Een andere beperking van het werk in de delen II en III is dat het zich alleen concentreerd op bepaalde prognostische factoren (d.w.z. erosieve ziekte en seropositiviteit) en bepaalde extra-articulaire manifestatie van RA (CV events).

Het onderzoek beschreven in dit proefschrift geeft aan dat het beleid voor de behandeling en vergoeding van RA, behandelingsdoelstellingen die beter gekoppeld zijn aan meerdere uitkomstmaten, zoals fysiek functioneren, HRQOL en het hulpbronnen gebruik, zou moeten overwegen. Dit is vooral het geval bij RA, aangezien de primaire uitkomstmaten in klinische studies, ACR en DAS28-CRP, in het algemeen niet gemeten worden in de klinische praktijk en mogelijk alleen informatief zijn voor de werkzaam-

heid van het geneesmiddel voor goedkeuringseisen van regelgevende instanties. Deze uitkomstmaten zijn echter minder gevoelig voor andere uitkomsten relevant voor de behoeften van de payer ten opzichte van CDAI/SDAI. Daarnaast zou het toekomstige beleid in RA moeten overwegen de behandeling van RA gebaseerd op subgroepen met een hoge onvervulde behoefte te onderzoeken, zoals is gedaan in meerdere andere therapeutische gebieden zoals hart- en vaatziekten, suikerziekte, hepatitis enz. Tenslotte zou toekomstig gezondheidsbeleid in RA een meer holistische benadering moeten nemen voor de behandeling van RA omdat er steeds meer bewijs is voor de systemische inflammatoire aard van de ziekte. Zodoende zullen kosteneffecitviteits evaluaties die alleen focussen op de gewrichts aspecten van de aandoening geen schatting van de werkelijke kosten en baten van interventies leveren, en het integreren van de niet-gewrichts gerelateerde aspecten van de ziekte zal dan ook van belang zijn. Hoewel onze werkzaamheden niet zijn gericht op patiënt gerapporteerde uitkomst maten (patient reported outcomes measures (PROMS)) of patiënt gerapporteerde ervarings maten (patient reported experience measures (PREMS)) zal integratie van deze uitkomstmaten in toekomstige beleidsoverwegingen voor RA belangrijk zijn.

PHD. PORTFOLIO

Courses:

- SAS programming I: Essentials (SAS institute)
- SAS programming II: Manipulating data with the DATA step (SAS institute)
- SQL programming with SAS (SAS institute)
- Survival analysis using Cox Proportional Hazard Model (SAS institute)
- Modeling techniques for categorical response data. (SAS institute)
- DATA Pro advanced training for Health Care (TreeAge Software Inc.)
- Life time data analysis (Survival analysis) (School of Public Health, University of Medicine and Dentistry of New Jersey)
- Non-parametric analysis (Dept of Statistics, Rutgers University)
- Principal component analysis (Dept of Statistics, Rutgers University)

Other Publications:

1) Gossec L, Ahdjoudj S, **Alemao E**, Strand V. Improvements in Fatigue in 1536 Patients with Rheumatoid Arthritis and Correlation with Other Treatment Outcomes: A Post Hoc Analysis of Three Randomized Controlled Trials of Abatacept. Rheumatol Ther. 2017 Jun;4(1):99-109
2) Harrold LR, Litman HJ, Connolly SE, Kelly S, Hua W, **Alemao E**, Rosenblatt L, Rebello S, Kremer JM. A window of opportunity for abatacept in RA: is disease duration an independent predictor of low disease activity/remission in clinical practice? Clin Rheumatol. 2017 Jun;36(6):1215-1220
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CURRICULUM VITAE

Evo Alemao was born in Mumbai, India where he did his early schooling at Victoria High School, St. Andrew's College and St. Xavier's College. He completed his pharmacy training at Karnatak Lingayat Education (KLE) College of Pharmacy and graduated First Class with a Bachelor of Pharmacy from Karnataka University Dharwad in 1993. He moved to the US in 1996 to continue graduate studies in Pharmacy Practice and Administration at Idaho State University (ISU) with emphasis on Outcomes Research and Pharmaceutical Care. He earned his Master of Science degree in Pharmacy Administration from ISU in 1999 and completed a Fellowship in Pharmacoeconomics from Rutgers University in 2001. On completion of the Fellowship, he joined the pharmaceutical industry at Merck & Co., in their Global Outcomes Research Group. At Merck, he performed various roles of increasing responsibilities within therapeutic areas of cardiovascular disease and diabetes. In 2008 he joined Wyeth/Pfizer as the Global Outcomes Assessment Lead for inline products in oncology and anti-infectives and later as the Market Access Lead for the psoriasis portfolio. He joined his current organization, Bristol Myers Squib, in 2010 and is a Group Director in the Worldwide Health Economics and Outcomes Research. He is a registered pharmacist in the state of Idaho and worked in retail pharmacy for Rite-Aid. He is married to Loretta and they have three kids Keanan (13 yrs), Gwen (9 yrs) and Peanut (10 month Beagle).