

UNMET NEEDS IN EARLY RHEUMATOID ARTHRITIS

LESSONS FROM THE
CARERA STUDY



Sofía Pazmiño Lucio

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“Out of doom and misery, the most beautiful song may rise”

De mensen hebben hun gebreken. A. Van Duinkerken, 1958.

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Sofía Pazmiño Lucio



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Abbreviations

ACPA	Anti-Citrullinated Cyclic Peptide/Protein Antibodies
ACR	American College of Rheumatology
AEs	Adverse events
ANOVA	Analysis of Variance
AUC	Area Under the Curve
BeSt	Behandel Strategieën in reumatoïde artritis
BL	Baseline
BMI	Body Mass Index
CAPHRI	Care and Public Health Research Institute
CareRA	Care in Early Rheumatoid Arthritis
CF	Clinical Factor
CI	Confidence Interval
COBRA Avant-Garde	Methotrexate with leflunomide
COBRA Classic	Methotrexate with sulfasalazine
COBRA Slim	Methotrexate with step-down prednisone 30mg scheme
COBRA	Combinatietherapie Bij Reumatoïde Artritis
CRP	C-Reactive Protein
csDMARDs	Conventional Synthetic Disease Modifying Antirheumatic drugs
DAS28CRP	28-joint Disease Activity Score calculated using C- Reactive Protein
DC	Daily Chronically
DMARD	Disease-Modifying Anti-Rheumatic Drugs
eCRF	Electronic Case Record Form
EFA-HD	Exploratory Factor Analysis for Hierarchical Data
EFAs	Exploratory Factor Analyses
EQ-5D	Euro Quality of Life-5 Dimension
ESR	Erythrocyte Sedimentation Rate
EULAR	The European League Against Rheumatism
GC	Glucocorticoid
GDP	Gross Domestic Product per Capita
GH	Global Health
GP	General Practitioner
HAQ	Health Assessment Questionnaire
HRQoL	Health Related Quality of Life
ICER	Incremental Cost Effectiveness Ratio
iNMB	Incremental Net Monetary Benefit
IQR	Interquartile Range
ITT	Intention to Treat
IWT	Agency for Innovation by Science and Technology
LDA	Low Disease Activity
LEF	Leflunomide
LF	Laboratory Factor
MSK	Musculoskeletal
MTX	Methotrexate
PaGH	Patient Global Assessment

PhD	Philosophies Doctor
PhGH	Physician Global Assessment
PRF	Patient Report Factor
PRO	Patient-Reported Outcome
QALYs	Quality Adjusted Life Years
QoL	Quality of Life
R	The R project for Statistical Computing
RA	Rheumatoid Arthritis
RCT	Randomized Controlled Trial
RF	Rheumatoid Factor
RIZIV	National Institute of Health and Disability Insurance
SAS	Statistical Analysis Software
SD	Standard Deviation
SDAI	Simplified Disease Activity Index
SE	Standard Error
SJC	Swollen Joint Count
SPSS	Statistical Package for the Social Sciences
T ₂ T	Treating to a Target
TJC	Tender Joint Count
TNF	Tumor Necrosis Factor
TNFi	Tumor Necrosis Factor Inhibitor
TSU	Tight-Step-Up, Methotexate weekly, no oral GC allowed
TTCUA	Time to initiation of chronic use of analgesics
VAS	Visual Analogue Scale
WTP	Willingness to Pay

Chapter 1.

General introduction

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is one of the most prevalent (0.5-1%) chronic inflammatory joint diseases.¹ This autoimmune condition is characterized by pain and stiffness of joints, mostly hands and feet. On top of that, RA can lead to extra-articular manifestations such as fatigue, vasculitis, pericarditis, pleuritis or nodules.¹ RA is a medication controllable but until now incurable disease. Hence, patients diagnosed with RA will most likely have to take medication for the rest of their life. Insufficiently controlled RA can result in joint damage, physical disability and increased mortality. All of this causes considerable burden on activities of daily life, work productivity and overall emotional well-being. These impairments are associated with socio-economic burden for patients, their environment and society.²

1.1 A Disease as Old as Time

Like in many other diseases, both environmental and genetic factors contribute to development of RA. The history of RA is disputed, with some arguing that it is a disease of modern times -quite likely precipitated by environmental toxins such as cigarette smoke- and others claim that it has existed since older times.³

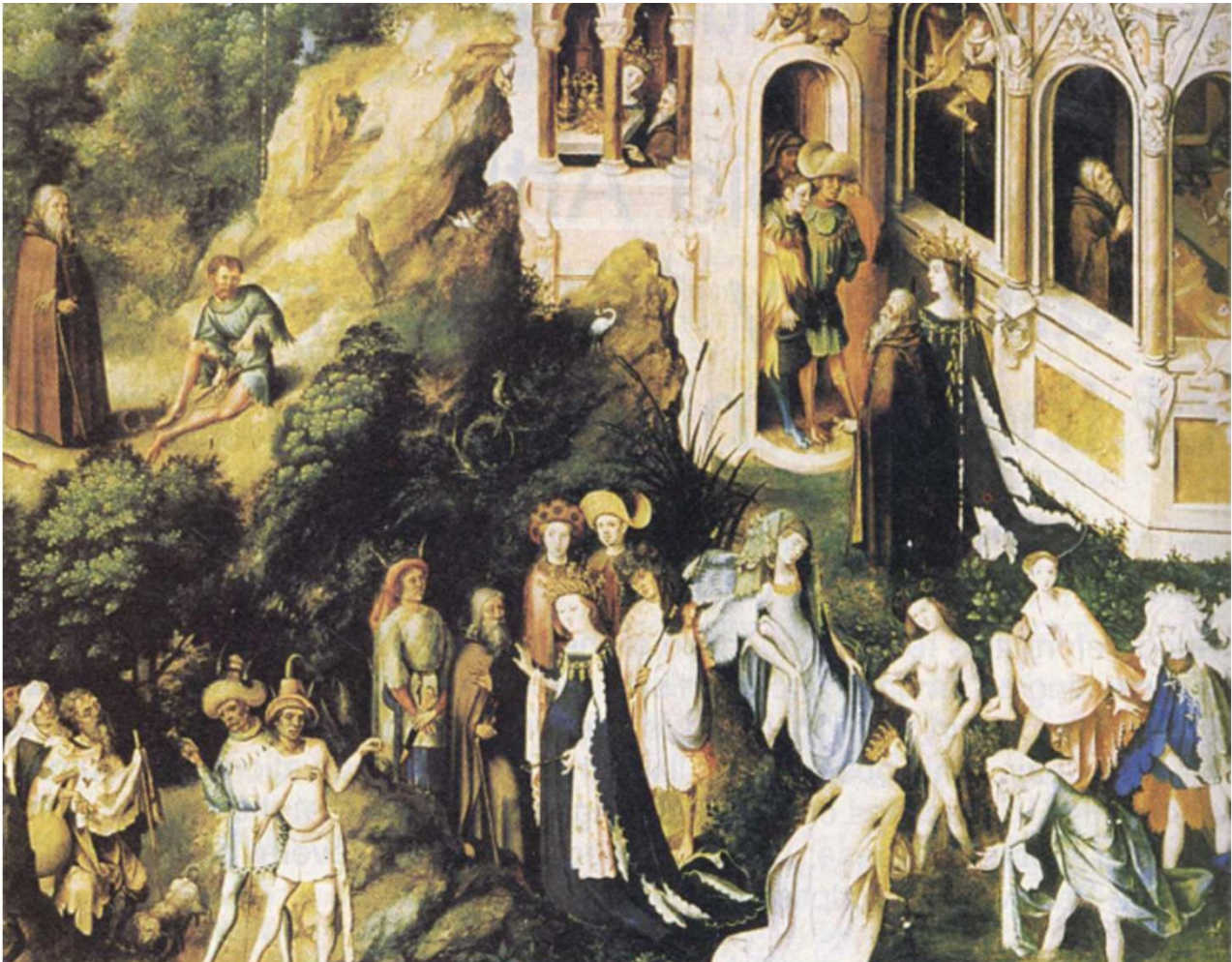
Historically, since Hippocrates, the various types of arthritis had been presumed to be gout in one form or another.⁴ In 400BC, Hippocrates, the Greek philosopher, is thought to have been referencing RA in one of his writings as well as the Greek physician Arateus, Cesar's physician Scribonius, the Byzantine physician Soranus and other ancient physicians.⁵ However, earlier descriptions have been found. The Ebers Papyrus –a medical text from ancient Egypt dating to 1500 BC- describes what is probably RA and mummy examinations have also pointed to this.³ The first medically accepted description of RA dates back to the 1800s with Landré-Beauvais' dissertation and the term “rheumatoid arthritis” was introduced in the 1890 by the English physician Alfred Garrod.^{3,6}

Artistically, paintings from the Middle Ages, suggest that RA is not a modern disease.⁷ Hand deformities resembling those pathognomonic to RA have been depicted in a painting by an anonymous artist of the Flemish-Dutch School, mid-15th to early 16th century.⁷ The beggar in the depiction of “The temptation of St Anthony” (16th Century anonymous

Flemish painter) shows a deformed hand with slight ulnar deviation, finger contractures and wrist luxation.(Figure 1-1)⁵ The painting of the “Three Graces “of Peter Paul Ruben’s seems to depict an RA pattern of damage in the left-most figure’s hand. (Figure 1-2)

Moreover, famous artists like Pierre-Auguste Renoir, one of the great French impressionist painters, suffered from severe rheumatoid arthritis.⁸

Figure 1-1: Anonymous Flemish painter. “The temptation of St Anthony” 16th Century by, El Escorial, Spain and zoomed in the beggar's hand



<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3119866/>

Figure 1-2: Paul Rubens. "The Three Graces", Oil in Canvas, 221cm x 181cm. Museo Nacional del Prado and zoomed in the left-most figure's hand



<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC319866/>

Figure 1-3: Jacob Jordaens. "The Family of the Artist". Oil on canvas, 1810 x 1870 mm (71 1/4 x 73 5/8"). Museo Nacional del Prado, Madrid. The picture shows the painter himself with his wife Catharina van Noort, his eldest daughter Elizabeth and a maid (zoomed maid's hand)



<https://www.museodelprado.es/en/the-collection/art-work/the-painters-family/oiee4803-c9cf-45a2-810c-6cac7f63d31f>

1.2 The window of opportunity in RA

Over the past decades, new insights in diagnosis, assessment and treatment have made disease control possible for the large majority of patients with RA. Evidence suggests that maximal success in controlling disease activity and radiographic progression depends largely on early, intensive and to-target medical therapy.⁹ The rationale for earlier treatment initiation is to modulate biologic processes while they are still “reversible”.¹⁰ This stage has been referred to as the therapeutic window of opportunity.¹¹ Nevertheless, how early is early? And how accurately can we identify/diagnose early?

The crucial goal is to detect symptoms suggestive of RA as early as possible and to delay and prevent the progression of undifferentiated arthritis or very early RA. (Figure 1-4) Some groups even attempt to identify and preventively treat patients at risk of developing RA at the preclinical stage.¹² In most patients, the pathogenesis of RA begins years before the clinical disease becomes evident. The terms used to describe the different stages before the development of RA are broad.¹³ In the “Susceptibility to RA”, the genetic and environmental risk factors have to be considered. Several risk factors are known to be involved in the pathophysiology of RA. There is a strong genetic component, including a long-established association with the human leukocyte antigen (HLA)–DRB1 locus leading to increased susceptibility for the disease.¹⁴ Women are twofold to threefold more likely to develop RA and environmental risk factors such as smoking, dust inhalation, diet, obesity, infections and microbiota have been found to be contributors.^{1,14}

The progression to disease involves initiation and propagation of autoimmunity against modified self-proteins, the “preclinical RA” stage.¹ RA is defined as a systemic autoimmune disease. This dysregulation of the adaptive immune response includes several mediators and cellular components. Adaptive immune cells, T and B lymphocytes might contribute to the pathogenesis of RA at different levels.¹⁴ Environmental stressor, such as smoking will trigger post-translational modifications -citrullination- at mucosal sites. The presence of circulating anti-citrullinated peptide antibody (ACPA), other antibodies, such as rheumatoid factor (RF) and circulating pro-inflammatory cytokines and chemokines can be detected up to 10 years before clinical disease onset.¹ The modified proteins can trigger an immune response and autoantibody formation.

There is continuous research looking into predictive and therapeutic approaches in patients with symptoms before they fulfil the classification criteria for RA.¹⁵⁻¹⁸ There is no single RA diagnostic test, so a combination of clinical features and laboratory test are used. The 1987 American College of Rheumatology (ACR) classification criteria (Criteria for the classification of rheumatoid arthritis Table 1-1) had been previously used to define RA.¹⁹ However, since these criteria were developed in a population with long-term RA, it had poor sensitivity and low specificity for early RA.²⁰ Later on, a collaboration between European League Against Rheumatism (EULAR) and ACR to define RA at early stages led to the new 2010 classification criteria (Table 1-1).²¹ These criteria have allowed for a common understanding and nomenclature for the phases in the patient's journey.¹³

Table 1-1: Criteria for the classification of rheumatoid arthritis

1987 ACR classification criteria	2010 EULAR/ACR classification criteria	
Criteria	Criteria	Score
Present for at least 6 weeks	A. Joint involvement	
1. Morning stiffness (lasts at least 1 hour)	1 large joint	0
2. Arthritis of 3 or more joint areas	2-10 large joints	1
3. Arthritis of hand joints (at least 1 area swollen)	1-3 small joints (with/out involvements of large joints)	2
4. Symmetric arthritis	4-10 small joints (with/out involvements of large joints)	3
	>10 joints (at least one small joint)	5
Duration not part of the criteria	B. Serology (at least one is needed for classification)	
5. Rheumatoid nodules	Negative RF and negative ACPA	0
6. Serum rheumatoid factor	Low positive RF or low positive ACPA	2
7. Radiographic changes	High positive RF or high positive ACPA	3
	C. Acute phase reactants	
	Normal CRP and normal ESR	0
	Abnormal CRP or abnormal ESR	1
	D. Duration of symptoms	
	< 6 weeks	0
	≥ 6 weeks	1
Satisfy at least 4 of the 7 criteria	A score ≥6/10 is needed for classification	

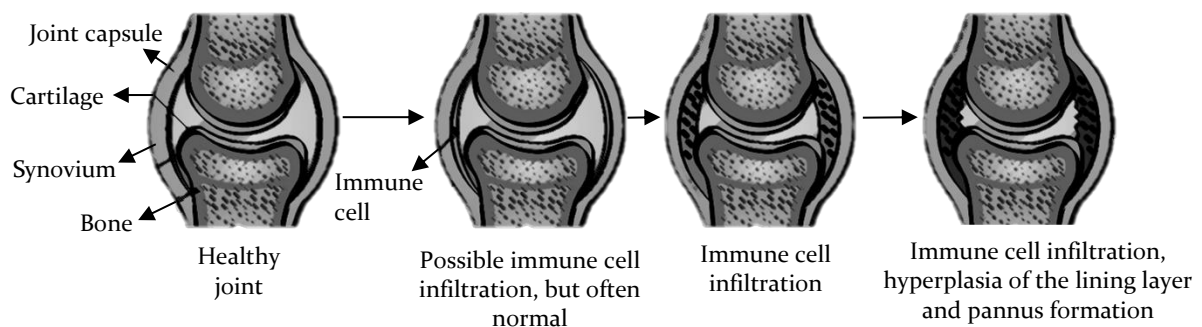
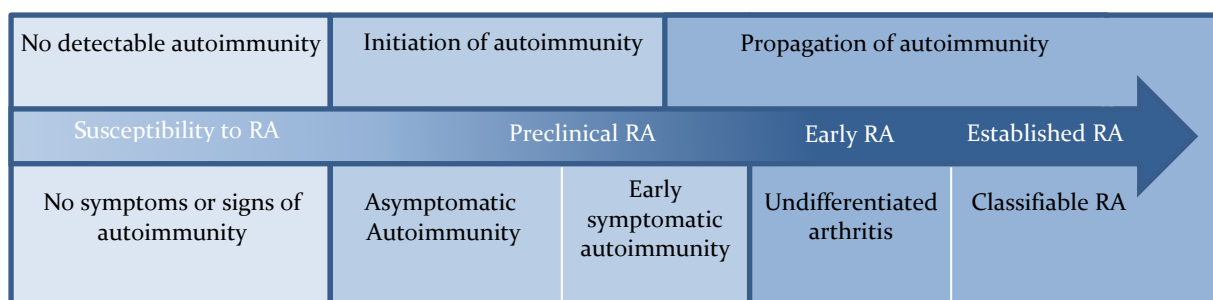
RF= rheumatoid factor, ACPA= anti-citrullinated peptide antibody,

CRP= C-reactive protein, ESR= erythrocyte sedimentation rate

High positive RF or ACPA is > 3 times the upper limit of normal (ULN)

Both in early and established RA joint swelling results predominantly from synovial inflammation consequent to immune activation and based on mononuclear cell infiltration, dominated by CD4+, T cells and macrophages, and stromal cell activation.^{1,22} The synovium has two main roles in homeostasis: producing lubricants that enable the cartilage surfaces to operate in a low-friction environment and providing nutrients to cartilage. Damage to cartilage and bone due to synovial invasion into adjacent articular structures is a cardinal sign of RA. The invasive and destructive front of synovial tissue attached to the articular surface is known as pannus. The mechanism for the damage is quite likely heterogeneous with several mechanisms of action.¹ Moreover, RA is a systemic disease and a variety of immunological events will also occur outside the joint at mucosal surfaces and primary lymphoid tissues.¹

Figure 1-4: Pathogenic evolution of RA (Smolen J. et al, 2018)¹



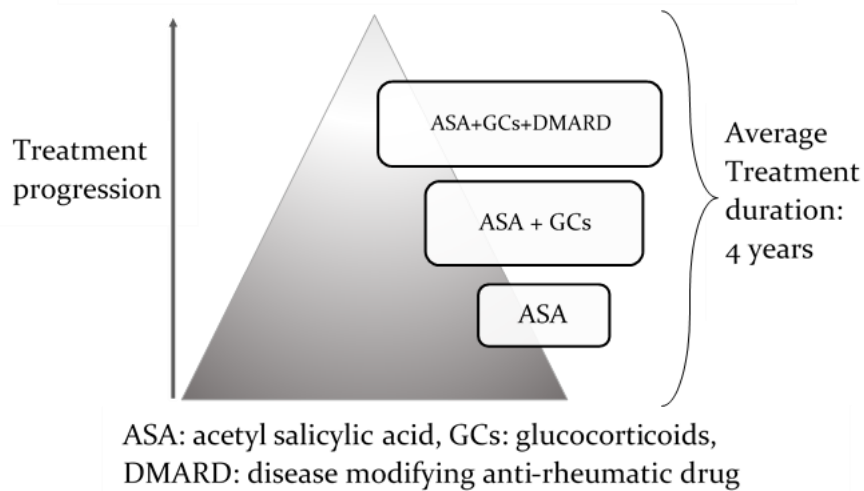
As previously mentioned, the first weeks/months after the onset of symptoms represent an important therapeutic window. Starting disease-modifying anti-rheumatic drug (DMARD) treatment during this window of opportunity may have a much greater effect than at a later stage.²³ The change in strategy to start a DMARD as soon as possible after diagnosis, with a goal of treating to remission or at least low disease activity (LDA),⁹ has led to dramatic

improvements in outcomes for RA.¹ The American College of Rheumatology (ACR) currently defines RA to be “early” if the disease duration is less than 6 months, and this is the window in which treatment should be initiated.²⁴ However, currently, early is considered to be 3 months. EULAR guidelines recommend that a first improvement after treatment initiation should be expected by month 3, and if target of remission or low disease activity has not been reached by month 6, treatment should be adjusted.⁹ Early treatment of RA has been shown to prevent irreversible structural damage, chronic functional impairment, increase chances of achieving long term remission, and has even been associated with favourable patient reported health and illness perceptions.^{25,26} Moreover, studies have shown that patients who do not respond significantly to treatment within 3 months have a low chance of reaching remission by 6 months.^{27,28} This is of special importance since a study in Belgium demonstrated that only one out of five early RA patients was initiated treatment within 3 months of symptom onset, being the patient-related delay the most common reason.²⁹

The treatment of RA, being a painful disease, was initially based on pain relief. The first pain medications introduced were acetylsalicylic acid in 1897 and phenylbutazone in the 1940s.³⁰ Other non-steroidal anti-inflammatory drugs (NSAIDs) were later on incorporated. Glucocorticoids (GCs) were discovered in 1948 by Philip Hench and introduced for RA treatment as prednisone in 1955. One of the first DMARDs, gold, was introduced in 1929 followed by hydroxychloroquine (HCQ) in the 1950s. Treatment of RA, even in patients with a very active and destructive disease course, followed a “wait and see” approach with the treatment pyramid starting always with acetylsalicylic acid while reserving GCs and DMARDs for the most severe patients. (Figure 1-5)

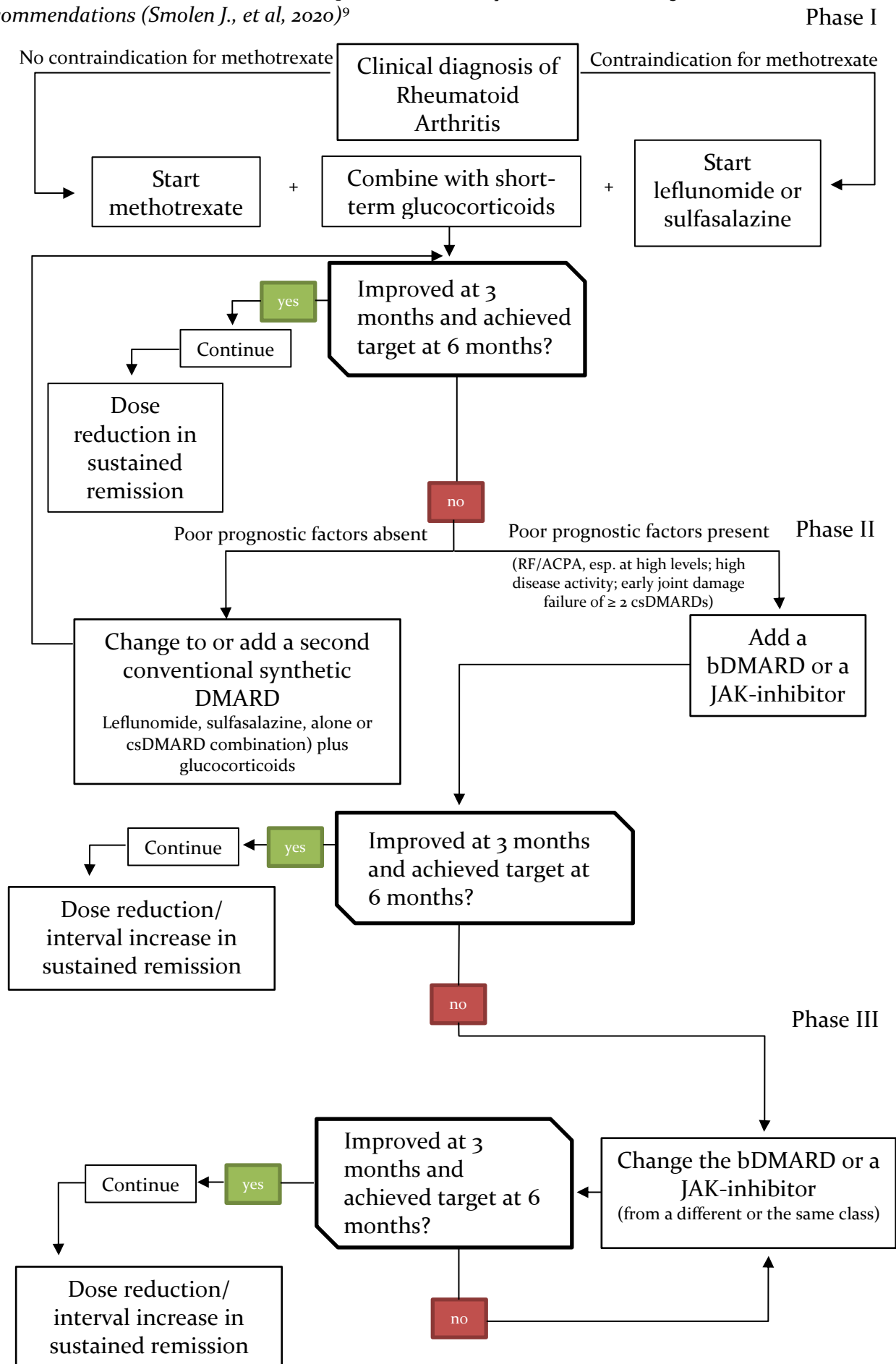
Figure 1-5: Treatment scheme in patients with RA applied until about the 1990's

Original RA treatment pyramid: 1950's – 1990's



This traditional treatment approach, as illustrated by the pyramid in Figure 1-5, did not suppress inflammation to a sufficient extent as to prevent joint damage.³¹ Despite the introduction of the DMARDs methotrexate (MTX), sulfasalazine (SSZ) and leflunomide (LEF), rheumatologists learned how to use the immunosuppressant MTX optimally in an appropriate dose in the nineties. In the late 1990s, the COBRA trial was the first to try out a step-down scheme. The investigators compared the combination of sulfasalazine (2 g/day), methotrexate (7.5 mg/week), and prednisolone (initially 60 mg/day, tapered in 6 weekly steps to 7.5 mg/day) with sulfasalazine alone.³² Tight control of disease activity (TICORA trial) was then proven to improve disease activity, radiographic disease progression, physical function, and quality of life at no additional cost.³³ The BeSt trial, demonstrated initial combination with either prednisone or infliximab resulted in earlier functional improvement and less radiographic damage after 1 year than sequential monotherapy or step-up combination therapy.³⁴ The state-of-the-art treatment of RA has become dramatically different. The current treatment paradigm is early, intensive and to a target of remission or at least low disease activity and maintained for the longest time period possible.⁹ MTX has now become the anchor drug for managing RA.^{1,9} The new strategies that were explored in the COBRA, TICORA and BeSt trial, resulted in a paradigm shift leading to beneficial outcomes for patients, effectively converting a disabling disease into a controllable one with improved quality of life.

Figure 1-6: Current treatment scheme in patients with early RA: EULAR management recommendations (Smolen J., et al, 2020)⁹



The care and management of patients with RA is complex and requires a pharmacological as well as a non-pharmacological multidisciplinary approach. The EULAR recommendations comprehensively summarize the basic principles for the pharmacological management of early and established RA (Figure 1-6).⁹

1.3 Care in early RA (CareRA)

This PhD research project is based on data from the Care in early RA (EudraCT number: 2008-007225-39) study. CareRA is a 2-year randomized controlled (RCT), multicentre, pragmatic, investigator-initiated trial. This RCT was conducted in a setting close to daily clinical practice, in 13 Flemish Rheumatology centres and without excessive inclusion and exclusion criteria, making the population representative.

In total, 400 DMARD naïve patients with recently diagnosed RA (<1 year) were assessed for eligibility between January 2009 and May 2013 and 379 were included in the trial.³⁵ Patients were stratified into a high- or low-risk group based on classical poor prognostic factors and randomized into four different treatment strategies (Figure 1-7).

High-risk patients (75% of the population) were randomized to one of the following treatment schemes:

- COBRA Classic (n=98): 15 mg MTX weekly, 2g sulfasalazine (SSZ) daily and a weekly step-down scheme of oral prednisone starting at 60mg QD and tapering to a maintenance dose of 7.5 mg, with further tapering from week 28, before completely stopping at week 34.
- COBRA Slim (n=98): 15 mg MTX weekly and a weekly step-down scheme of oral prednisone starting at 30mg QD and tapering to a maintenance dose of 5 mg, with further tapering from week 28, before completely stopping at week 34.
- COBRA Avant Garde (n=93): 15 mg MTX weekly, 10 mg leflunomide (LEF) daily and a weekly step-down scheme of oral prednisone starting at 30mg QD and tapering to a maintenance dose of 5 mg, with further tapering from week 28, before completely stopping at week 34.

Low-risk patients (25% of the population) were randomized to either:

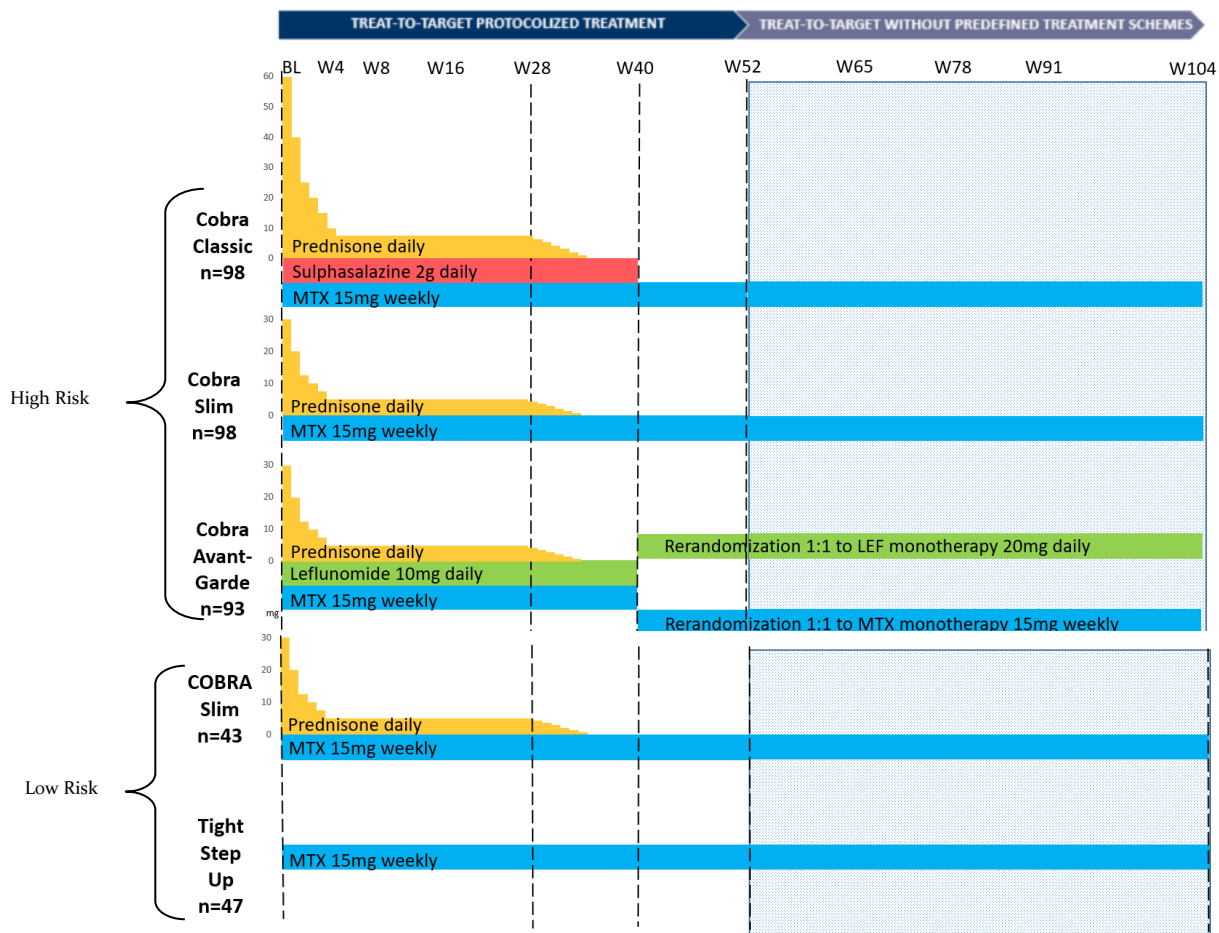
- Tight-Step-Up -TSU- (n=47): 15 mg MTX weekly, no oral glucocorticoids allowed
- COBRA Slim (n=43)

All patients were treated-to-target. The first year of the trial had pre-specified (per protocol) treatment adaptations when low disease activity was not reached ($\text{DAS28CRP} \leq 3.2$) Further treatment adaptations could include bDMARD initiation according to the Belgian reimbursement rules (Figure 1-8).

Patients were assessed at screening, baseline and then followed-up as part of daily clinical practice at week 4, 8, 16, 28, 40, 52, 65, 78, 91 and 104 (See Figure 1-7). An optional visit, when treatment adjustment was required, could also be performed. An electronic case report form (eCRF) was filled out on every visit and was routinely monitored. Clinical parameters such as ACR core measures³⁶ were collected at every visit.

Performed adaptations during CareRA have already been published and can be found in Table 1-2.³⁵ Overall, around 70% of the patients achieved a status of good disease control after 2 years ($\text{DAS28CRP} < 2.6$) with a treat-to-target approach.³⁵

Figure 1-7: CareRA treatment schemes



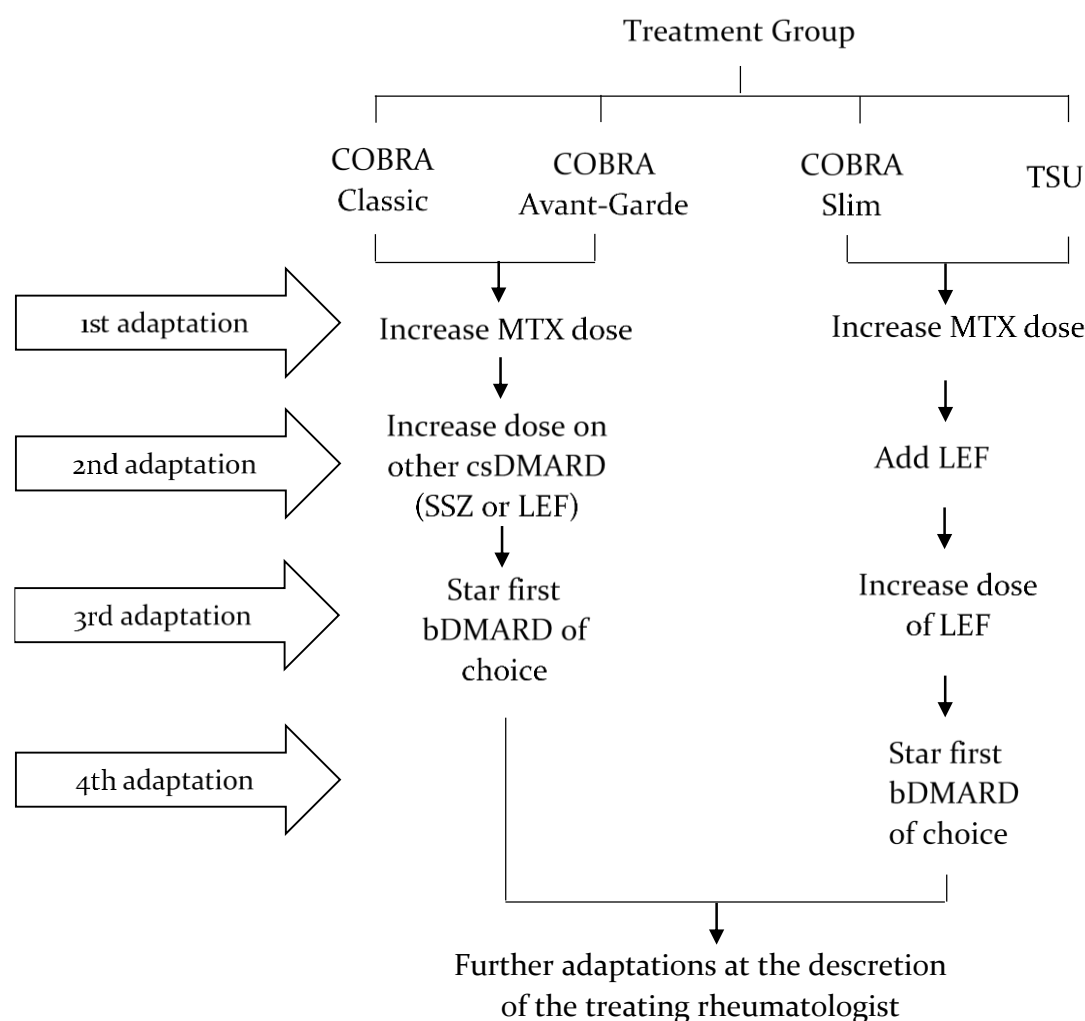
BL: baseline, W: week, Prednisone is an oral glucocorticoid, MTX: methotrexate (cs DMARD), Leflunomide and Sulfasalazine: are both csDMARDs, mg: milligrams

Table 1-2: Number of patients with adaptations in DMARD treatment during the 2-year trial (Stouten V., et al, 2019)³⁵

	COBRA Classic n=98 n (%)	COBRA Slim (high-risk) n=98 n (%)	COBRA Avant- Garde n=93 n (%)	COBRA- Slim (low-risk) n=43 n (%)	TSU n=47 n (%)
DMARD treatment adaptations	33 (34)	38 (39)	29 (31)	13 (30)	20 (43)
1 DMARD adaptation	24 (24)	29 (30)	24 (26)	6 (14)	14 (30)
2 DMARD adaptations	9 (9)	9 (9)	5 (5)	7 (16)	6 (13)
Type of DMARD adaptations					
Starting additional csDMARD	10 (10)	31 (32)	12 (13)	11 (26)	17 (36)
Continuing combi csDMARDs	8 (8)	0 (0)	6 (6)	0 (0)	0 (0)
Switching csDMARD	6 (6)	5 (5)	1 (1)	1 (2)	3 (6)
Starting bDMARD	18 (18)	11 (11)	15 (16)	8 (19)	6 (13)
during first year	10	2	7	4	4
during second year	8	9	8	4	2

Data are presented as absolute numbers (percentages); csDMARD = conventional synthetic disease-modifying antirheumatic drug; bDMARD = biological disease-modifying antirheumatic drug.

Figure 1-8: Algorithm of pre-specified treatment adaptations in CareRA



1.4 The price tag of RA

RA, as other chronic diseases, represents a clinical and economic burden for healthcare systems.³⁷ This burden involves both direct medical and non-medical costs, as well as indirect costs (productivity loss, premature mortality, and burden for caregivers).³⁷ With an ever growing pharmaceutical industry, medical devices, test and imaging procedures, economic analysis has become more relevant. Especially because, resources are scarce and needs are unlimited which means that there is always a choice to be made. Of course, benefits for patients must be maximized but without expending all of society's resources. In healthcare, we need a fair strategy to make trade-offs between needs, benefits and resources.

RA causes high individual, medical, and societal costs; especially when new and ambitious treatment goals add to the expenses.³⁸ Direct medical costs come from healthcare related expenses. From these expenses, medication cost are nowadays the major contributor, especially when targeted synthetic (ts-) or biological (b-) DMARDs have been initiated. Cost-effectiveness analyses have stated that bDMARD therapy should be started only after failure to less-costly alternatives such as conventional synthetic (cs-) DMARDs and GCs.^{38,39} The treating rheumatologist needs to carefully consider all these aspects when initiating a new treatment.⁴⁰

The total societal cost for rheumatic disorders based on data from 2010 in the Netherlands, was estimated at €4.7 million a year, which was €2655 per person with a rheumatic disorder.⁴¹ In 2006, it was estimated that about €45.3 billion are spent annually (direct costs + indirect costs + informal care) in Europe for patients with RA, and the per-patient annual cost is estimated around €13,500.⁴² If we differentiate between early and established RA the costs differ. In Belgium, the annual health care costs per patient with RA in the year 2000 were reported to be €3055 for early in contrast to € 9946 for established.⁴³ Indirect costs represent a considerable proportion of total costs, with work disability being the main cost component.⁴⁴ Work disability relates not only to costs to society but also to patient's self-sufficiency due to loss of income⁴⁵ leading to a potential impoverishing effect of RA, further contributing to intergenerational socio-economic vulnerability when a parent is affected by RA and loses his/her job.⁴⁶

The Global Burden of Disease Study found that musculoskeletal disorders contribute extensively to the worldwide disease burden and health expenditure in many countries.^{47,48} Each country has a different culture⁴⁹ and health care system, which means that resource utilisation and costs will differ not only in terms of health care utilisation but also in terms of sick leave and work disability.⁵⁰ Moreover, access to and use of health-care services have been recognised as independent determinants of health, especially in patients with chronic conditions.⁴⁵ These health inequalities and even inequities -as differences can be considered unfair- are present both within and between countries.⁴⁵ Hence, it is complicated to compare costs between countries and even more between continents.

From a health economical point of view, it is important to investigate to what extent different initial treatment choices and consecutive treatment steps within a treat- to- target strategy lead to differences in longer-term costs. Therefore, in this PhD research a full economic evaluation of the 2-year open-label investigator-initiated pragmatic superiority CareRA trial comparing different intensive treatments to study the cost per quality-adjusted life years (QALYs) was performed.

1.5 Seronegative RA, the sometimes-underestimated stepsister

It is now current practice that as soon as the diagnosis of RA is made, a DMARD is started with short-term GC.⁹ The therapy started should be intensive enough to control inflammation and hence it is prescribed aiming to reach a target of sustained remission or at least low disease activity as an end goal.⁹ However, the target or level of disease activity used for steering treatment adaptations might differ. Moreover, some rheumatologists might still be reluctant to initiate early intensive treatment strategies to patients perceived as having a benign prognosis such as those rheumatoid factor and anticitrullinated peptide antibody negative.

In line with the above thinking and remaining questions, the CareRA trial encompasses the early and intensive approach of effective treatments with broadening the knowledge on the patient's perspective by collecting different proxies for pain, fatigue, quality of life and coping among others. Moreover, while still stratifying patients based on poor prognostics

factors, an intensive treatment that would normally be reserved for the high-risk group was given to the low-risk group. Analyses after 1 and 2 years of treatment showed that MTX, a csDMARD with a moderate step-down GC scheme (COBRA Slim) had a good risk/benefit profile with comparable effectiveness to other intensive initial schemes and to traditional step-up for all patients irrespective of prognostic factors.^{35,51} Hence, European guidelines now recommend as first treatment strategy for all RA patients MTX with a short-term GC course that should be tapered as quickly as possible. Not all patients with early RA will respond favourably to this initial treatment scheme and some will need adaptations that can be for instance increasing the dose, switching or adding medications.⁵² These recommended adaptations depend on the presence or absence of poor prognostic factors. In patients with poor prognostic factors such as serological positivity for RF or ACPA antibodies, highly active disease or early radiographic damage (erosions), a bDMARD or more recently also a targeted synthetic (ts-) DMARD should be added. In the absence of these factors, other csDMARD should be considered.⁵² Commonly used DMARDs and their classification can be found in Table 1-3.⁹ The influence of serological markers of poor prognosis (RF/ACPA autoantibodies) on the clinical course and treatment choice is still controversial.⁵³ The population without these markers accounts for approximately one in three to four RA patients. Most analyses on this small population in trials are secondary and therefore, little has been defined about this subgroup. The response of seronegative patients to early intensive therapies has not been comprehensively studied. Consequently, we compared the disease course of seronegative and seropositive patients with early RA, especially the response on intensive treatment, as part of this thesis.

Table 1-3: Disease modifying anti-rheumatic drugs classification

Disease modifying anti-rheumatic drug (DMARD) nomenclature		
Synthetic DMARDS	Conventional synthetic (cs-)	Eg, methotrexate, leflunomide, sulfasalazine, hydroxychloroquine
	Targeted synthetic (ts-)	Eg, baricitinib, tofacitinib, upadacitinib
Biological DMARDS	Biological originator	TNFi: adalimumab, certolizumab, etanercept, golimumab, infliximab; IL-6Ri: sarilumab, tocilizumab; Costimulation-i: abatacept; anti-B cell (CD20): rituximab
	Biosimilar	currently for: adalimumab, etanercept, infliximab, rituximab

IL- 6Ri, interleukin 6 receptor inhibitor; TNFi, tumour necrosis factor inhibitor

1.6 How to measure the unobservable

The primary clinical manifestation of RA is inflammation of the peripheral joints resulting in swelling, stiffness and pain. However, a wider range of symptoms can be present, including functional impairment and constitutional manifestations such as fatigue as well as a global health impact.⁵⁴ This symptom heterogeneity may hinder easy diagnosis but also the evaluation of changes in disease status, which may complicate the management of RA patients (beyond modulating disease activity). In RA, unlike other diseases such as hypertension or diabetes, the severity or level of disease activity cannot be evaluated by a single clinical or laboratory measurement. Hence, reliable instruments for clinical assessment have been developed that can be used for research and clinical practice.^{55,56}

RA disease activity is evaluated by multiple clinical and laboratory measurements. When evaluating patients, the swollen (SJC) and tender (TJC) joint count obtained by physical examination, with acute phase reactants (C-reactive protein -CRP- or erythrocyte sedimentation rate -ESR-) measured in blood, patient (PaGH) and physician's (PhGH) global health assessment on a visual analogue scale (VAS) are brought together for creating a composite index. Several composite indices like the disease activity score in 28 joints with C-reactive protein (DAS28CRP), the simplified disease activity index (SDAI) or the clinical disease activity index (CDAI) exist. These indices translate the severity of disease activity into a numerical value allowing to have cut-offs for determining active (high and moderate activity) or inactive (remission or LDA) disease status. These scores allow frequent tight monitoring of the patient's disease status and facilitate target steered DMARD medication adaptations when the predefined target is not reached. It is paramount to understand what is being measured by each single component of a composite score, especially if this is driving the physician's decision making. Hence, in this PhD an in-depth view of all the components of the disease measurement tools will be further studied.

1.7 Painful RA

The current treatment goal for RA is remission -according to a composite score- or at least low disease activity.¹ While this is the clinical emphasis, patient's priorities might not necessarily align. Some well-treated patients with RA continue to experience moderate pain, despite early and ongoing DMARD treatment resulting in perfect disease control or

remission in view of the treating physician.² Hence, remaining pain of non-inflammatory origin seems to exist that might require a different approach. Moreover, pain has been indicated as the patient's highest priority for improvement alongside fatigue and regaining functionality.^{57,58} Pain is a multidimensional problem that should ideally be explained and treated using a combination of biological, psychological, and social approaches.⁵⁹ However, because pain is a private, internal experience; self-reporting has remained the gold standard for its measurement.⁶⁰ Pain management with analgesics has been historically part of RA therapy. However, little has been explored on the role of analgesics in the context of current early, intensive and to-target treatment. Pain management is of great importance for patients and physicians alike and we aim to explore the use of analgesics in patients with early RA treated intensively and to target.

1.8 Overall objective and research questions

Even with considerable progress in diagnosis and treatment for RA, there are still **unmet needs**.

The purpose of this PhD research is to tackle some of those remaining **unmet needs** in an era of adequate RA treatment from a societal and patient-centred perspective. I will be taking into account a few indicators of this unmet need including: 1) the risk of an excessively growing price tag for successful treatment of RA, i.e. which strategy has the most favourable balance between costs and health benefits (economic evaluation), 2) the uncertainty about the required treatment intensity for patients with RA without serological markers of poor prognosis, 3) the ambiguity of measurement instruments used to steer therapy, and 4) the challenge of remaining pain despite well-controlled disease activity.

The working hypothesis, based on the first published CareRA outcomes is that COBRA Slim, the combination of MTX and a moderate dose GC bridging scheme, is a good starting strategy for patients with early RA irrespective of prognostic markers in a treat-to-target setting.^{35, 51} However, a more tailored approach might be necessary for patients not responding to the proposed initial “one size fits all” strategy in order to provide them a long-term effectiveness in disease control and quality of life while also being applicable and economically sustainable for every patient in daily clinical practice.

The following research questions (RQ) will be addressed to study the **unmet needs in patients with early RA**:

- ➔ RQ1: How **cost-effective** is the COBRA Slim strategy for patients with early RA, compared to other intensive combination strategies, after a 2-year follow-up?
 - CHAPTER 2: The price tag of RA: how we piggybacked CareRA
- ➔ RQ2: Do patients with early RA who do not have serological markers of poor prognosis (**seronegative RA**) require an equally intensive treatment strategy as patients with seropositive RA and do they differ in their **response**?
 - CHAPTER 3: Seronegative RA, the sometimes-underestimated stepsister
- ➔ RQ3: How do the **components of composite scores** used for evaluating disease activity in RA fluctuate over time, and do they reflect different types of disease burden?
 - CHAPTER 4: How to measure the unobservable
- ➔ RQ4: Is the chronic consumption of analgesics a reflection of **remaining pain** in an early RA population treated with intensive treat-to-target strategies?
 - CHAPTER 5: Painful RA

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Chapter 2.

The price tag of RA: how we piggybacked CareRA

Two-year cost-effectiveness of different COBRA-like intensive remission induction schemes in early rheumatoid arthritis: a piggyback study on the pragmatic randomized controlled CareRA trial*

2.1 ABSTRACT

Objectives: To evaluate the cost-effectiveness of treat-to-target strategies among recently diagnosed patients with rheumatoid arthritis (RA) using methotrexate (MTX) and a step-down glucocorticoid (GC) scheme (COBRA Slim) compared with 1) this combination with either sulphasalazine (COBRA Classic) or leflunomide (COBRA Avant-Garde) in high-risk patients and 2) MTX without GCs (Tight-step-Up, TSU) in low-risk patients.

Methods: The incremental cost-utility was calculated from a healthcare perspective in the intention-to-treat population (n=379) of the 2-year open-label pragmatic randomized controlled care in early RA trial. Healthcare costs were collected prospectively through electronic trial records. Quality-adjusted life years (QALYs) were estimated using mapping algorithms for EuroQol-5 dimension. Multiple imputation was used to handle missing data and bootstrapping to calculate CIs.

Robustness was tested with biological disease-modifying antirheumatic drugs at biosimilar prices.

Results: In the high-risk group, Classic ($\Delta k€1.464$, 95% CI -0.198 to 3.127) and Avant-Garde ($\Delta k€0.636$, 95% CI -0.987 to 2.258) were more expensive compared with Slim and QALYs were slightly worse for Classic ($\Delta -0.002$, 95% CI -0.086 to 0.082) and Avant-Garde ($\Delta -0.009$, 95% CI -0.102 to 0.084). This resulted in the domination of Classic and Avant-Garde by Slim. In the low-risk group, Slim was cheaper ($\Delta k€-0.617$, 95% CI -2.799 to 1.566) and QALYs were higher ($\Delta 0.141$, 95% CI 0.008 to 0.274) compared with TSU, indicating Slim dominated. Results were robust against the price of biosimilar.

Conclusions: The combination of MTX with a GC bridging scheme is less expensive with comparable health utility than more intensive step-down combination strategies or a conventional step-up approach 2 years after initial treatment.

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KEY MESSAGES

What is already known about this subject?

- While treat-to-target strategies are cost-effective in rheumatoid arthritis (RA), initial biological disease-modifying antirheumatic drug (bDMARD) therapy is not cost-effective and conventional synthetic DMARDs (csDMARDs) are to be preferred over bDMARDs or targeted synthetic DMARDs as first-line treatment.

What does this study add?

- In patients with classical factors of poor prognosis, csDMARD combination therapy with step-down glucocorticoids (GCs) was not cost-effective compared with methotrexate (MTX) monotherapy also with step-down GCs within a remission induction strategy.
- For patients without classical factors of poor prognosis, MTX plus a short-term course of GCs was clearly more cost-effective than the traditional MTX only.

How might this impact on clinical practice or future developments?

- Initiating a step-down GC bridging combined with MTX in newly diagnosed patients with RA could be key to delay or even avoid use of second line expensive medication such as bDMARDs in both high-risk and low-risk patients.

2.2 INTRODUCTION

Insufficient control of disease activity in rheumatoid arthritis (RA) can lead to persistent pain, joint destruction, functional impairment and thus reduced health-related quality of life (QoL). Evidence suggests that controlling disease activity depends on early, intensive and to-target medical therapy.¹ Therapy with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) should be started as soon as possible after diagnosis, preferably methotrexate (MTX) and a short course of glucocorticoids (GCs).² The ideal dosing scheme and the value of classical risk factors as therapeutic prognostics (theragnostic) are still a matter of debate. Over the years, several trials have demonstrated increased efficacy of initial csDMARD combinations over monotherapy, but evidence remains scarce for the superiority of combining csDMARDs within strategies including a step-down-bridge GC scheme. It has not been elucidated whether effectiveness of such strategies differs depending on prognostic risk profile.³⁻⁵ Care in early RA (CareRA), a randomized treat-to-target strategy trial showed no superiority combinations of csDMARDs and bridging GCs (COBRA Classic or COBRA Avant-Garde) over MTX-only with a moderate-dose step-down GC bridging scheme (COBRA Slim), but COBRA Slim had a more favourable safety profile.⁶⁻⁸ In addition, COBRA Slim showed a better initial response and overall disease control than the traditional Tight-Step-Up (TSU) approach, starting MTX without oral GCs, in so-called low-risk patients.⁹

From a health economical point of view, it is important to investigate to what extent different initial treatment choices and consecutive treatment steps within a treat-to-target strategy lead to differences in longer-term costs. Therefore, we conducted a full economic evaluation of the CareRA trial to study the cost per quality-adjusted life years (QALYs).

2.3 PATIENTS AND METHODS

Using the 2-years data from the open label CareRA pragmatic treat-to-target randomized controlled trial (RCT) (EudraCT- number: 2008-007225-39), the incremental cost-utility and incremental net monetary benefit (iNMB) from a payer's perspective were estimated. In the high-risk group, both COBRA Classic and COBRA Avant-Garde were compared with COBRA Slim. In the low-risk group, COBRA Slim was compared with TSU.

CareRA clinical trial

In total, 400 DMARD naïve patients with recently diagnosed RA (≤ 1 year) were assessed for eligibility between January 2009 and May 2013 and 379 were included.

Patients were stratified into a high-risk or low-risk group based on an algorithm with prognostic factors ^{7,8} (erosions, rheumatoid factor (RF) or anticitrullinated cyclic peptide (ACPA)) positivity and baseline Disease Activity Score in 28 joints with C-reactive protein (DAS28CRP) > 3.2) and randomized into four different treat-to target schemes.

High-risk patients were randomized to one of the following initial treatment schemes:

- COBRA Classic: 15 mg MTX weekly, 2 g sulfasalazine daily and a weekly step-down scheme of oral prednisone starting at 60 mg daily and tapering through 40-25-20-15-10-mg daily to a maintenance dose of 7.5 mg, with further tapering from week 28, before completely stopping at week 34.
- COBRA Avant-Garde: 15 mg MTX weekly, 10 mg leflunomide (LEF) daily and a weekly step-down scheme of oral prednisone starting at 30 mg daily and tapering through 20-12.5-10-7.5 mg daily to a maintenance dose of 5 mg, with further tapering from week 28, before completely stopping at week 34.
- COBRA Slim: 15 mg MTX weekly and a weekly step-down scheme of oral prednisone starting at 30 mg daily and tapering through 20-12.5-10-7.5 mg daily to a maintenance dose of 5 mg, with further tapering from week 28, before completely stopping at week 34.

Low-risk patients were randomized to either:

- COBRA Slim.
- TSU: 15 mg MTX weekly, no oral GCs allowed.

In all treatment arms, low disease activity (DAS28CRP ≤ 3.2) was used for steering treatment adaptations. The first trial year had prespecified (per-protocol) treatment adaptations. During the second year, adaptations were left at the discretion of the treating rheumatologist. An increase in the weekly MTX dose to 20 mg was the first adjustment in all treatment schemes. Next, the dose of the other csDMARD was increased in the combination arms (COBRA Classic and COBRA Avant-Garde) or 10 mg. LEF was added in the non-combination arms (COBRA Slim and TSU). Further treatment changes could include bDMARD initiation according to Belgian reimbursement rules.¹⁰ Details on patient

eligibility criteria, randomization process, study design and treatment intensifications have been published.⁶⁻⁹ Patients were assessed at screening, baseline and then followed up at week 4, 8, 16, 28, 40, 52, 65, 78, 91 and 104. Optional visits, if clinically required, could be performed. Physicians filled out at every patient visit the electronic case record form (eCRF), comprising American College of Rheumatology core measures,¹¹ medications and adverse events (AEs).

Outcomes

Health utility and QALYs

A health utility represents the preference of value attributed to a health state. It is expressed on a continuous scale from zero (equalling death) to one (full health). Scores can also be below zero (states worse than death). By multiplying the utility value with years of survival, QALYs are calculated. For this study, QALYs were determined as the time-weighted average of reconstructed EuroQoL-5 Dimension (EQ-5D) values for each visit in the total follow-up (area under the curve). EQ-5D health utilities were reconstructed based on Health Assessment Questionnaire (HAQ), age, pain on a Visual Analogue Scale and gender, using the validated UK algorithm of Hernández Alava et al.¹²⁻¹⁴ For patients experiencing AEs that were either severe or lasted for more than 3 months, the QALY was adjusted by a disutility, accounting for the duration of the AE. Based on an extensive literature search, disutilities per AE were constructed Supplemental Table 2-2¹⁵⁻²⁴ If no specific disutility was found, a general moderate-intensity treatment associated disutility (0.002) was applied.²⁵

Resource utilization and direct healthcare costs

Healthcare costs in the economic analysis were rheumatology visits, RA-related medication (cs- and bDMARDs, GCs and all recorded analgesics including paracetamol, non-steroidal, tramadol and opioids), hospital admissions, laboratory and radiographs occurring during the 2-year trial.

Costs for rheumatology visits included scheduled and additional visits. Cost per visit was retrieved from the National Institute of Health and Disability Insurance (RIZIV) tariffs.²⁶ RA-related medication costs were calculated from the eCRF reported medication name, dose, intake duration and frequency, then valued according to the Belgian Centre for Pharmacotherapeutic Information.²⁷ Hospitalization costs were calculated from AEs requiring hospitalization and were price-weighted depending on coded diagnosis

(International Classification of Diseases, Ninth Revision, Clinical Modification), physician registered severity (mild, moderate, severe) and number of inpatient days with INAMI-RIZIV tariffs (tct.fgov.be).²⁸ Supplemental costs for laboratory and radiographs were also incorporated.²⁹ All prices were converted to 2018 euros using the general Belgian health index rate (statbel.fgov.be). Total costs per resource were calculated by multiplying the number of resources by the cost unit price extracted from Belgian national websites.^{26–29} Total costs per patient were obtained by summing costs of all resources. No discounting was considered due to the study's short follow-up period (2 years).³⁰

Cost-effectiveness analyses

This piggyback study, an economic evaluation alongside a clinical trial, follows the superiority design of CareRA and was performed on the intention-to-treat (ITT) population. Differences in costs and QALYs between COBRA Classic and COBRA Avant-Garde compared with COBRA Slim for the high-risk group and between COBRA Slim and TSU for the low-risk group were analysed over 2 years. An incremental cost-effectiveness ratio (ICER) was calculated by dividing the cost difference by the QALY difference per pair of treatment schemes. The uncertainty analysis in the estimation of the ICER was plotted on cost-effectiveness planes (via non-parametric bootstrapping with 25 000 iterations of random sampling with replacement). Cost differences were depicted on the y-axis and QALY differences on the x-axis.

The incremental net monetary benefit (iNMB) of each comparison was calculated as

$$\text{iNMB} = [\text{incremental benefit} * \text{willingness to pay (WTP)}] - \text{incremental cost}.$$

The impact on the iNMB for varying thresholds of WTP (€0–€150 000) for one QALY gain was calculated. This reflects absolute economic gain (positive) or loss (negative), given how much society is willing to pay per QALY gained (λ). The World Health Organization proposes that it is reasonable to pay for an intervention that provides one additional year of healthy life per capita.³¹ An intervention is considered cost-effective when the cost for one QALY gained falls below three times the gross domestic product per capita (GDP) and highly cost-effective when below the GDP.³² In Belgium, no prespecified WTP exists, but the 2018 GDP was k€40.320.³³ For this study, we used a WTP threshold (λ) of k€40 per QALY gained.

Considering the increased use of biosimilar, the base case analysis was repeated pricing bDMARDs at the lowest price of a biosimilar (Benepali) in Belgium (€153.15 for 50 mg weekly as of December 2018).

Sustained remission was used as an alternative health outcome to calculate the ICER. Sustained remission was defined as DAS28CRP <2.6 from week 16 to 104 at every visit.

Statistical analyses

Missing data were assumed to be missing at random and were imputed with multiple imputation (classification and regression trees) by chained equations.³⁴ Missingness in clinical variables used to estimate utility, disease activity per time point, and total costs were imputed. Besides the incomplete variables, treatment strategy, centre of recruitment, age, gender, presence of comorbidities, AEs, RF, ACPA, erosions at baseline and trial completion were included as predictors in the matrix. Fifteen imputed datasets were created and analysed separately. Results of the 15 analyses were pooled using Rubin's rules.^{35, 36}

For comparisons in complete cases, non-parametric Mann-Whitney U or Kruskal-Wallis and X² bootstrapped-corrected were used when appropriate.

All analyses were performed with R V.3.6.1.

2.4 RESULTS

Patients

Of the 379 patients included in the CareRA trial, 289 patients were stratified to the high-risk (COBRA Classic n=98, COBRA Avant-Garde n=93, COBRA Slim n=98) and 90 to the low-risk group (COBRA Slim n=43, TSU n=47). Patient characteristics in each treatment arm are presented in Table 2-1. Good retention rates of up to 89% were observed (Supplemental Figure 2-1). Missingness in the clinical variables over 2 years ranged from 12% to 39% per different time point and was 15% for total costs (n=328 for total cost).

Health outcomes

QALYs over 2 years were comparable in the high-risk group (1.551, 1.544, and 1.553) between COBRA Classic, COBRA Avant-Garde and COBRA Slim, respectively (table 2-2). In the low-

risk group, 2-year-QALYs were higher in COBRA Slim (1.629) compared with TSU (1.488), resulting in an incremental gain of 0.141.

Sustained remission rates (Table 2-2) were also comparable in the high-risk group, whereas in the low-risk group COBRA Slim (42%) had better sustained remission rates than TSU (26%).

Table 2-1 Demographic and clinical characteristics at baseline per treatment scheme

	High-risk			Low-risk	
	COBRA Classic n=98	COBRA Avant-Garde n=93	COBRA Slim n=98	COBRA Slim n=43	TSU n=47
Demographic variables					
Age, years	53 (12)	51 (13)	52 (13)	51 (14)	51 (14)
Women, n (%)	64 (65)	64 (69)	63 (64)	33 (77)	38 (81)
Smokers, n smoked ever (%)	56 (57)	56 (60)	58 (59)	21 (49)	18 (38)
Current work n (%)	44 (45)	48 (52)	52 (53)	22 (51)	27 (57)
Clinical variables					
Body mass index, kg/m ²	26 (4)	27 (4)	27 (4)	25 (4)	27 (4)
Symptom duration, weeks; median (IQR)	22 (14-44)	25 (15-51)	24 (15-39)	21 (14-35)	19 (13-33)
RF positive, n (%)	78 (80)	70 (75)	82 (84)	11 (26)	11 (23)
ACPA positive, n (%)	76 (78)	72 (77)	78 (80)	12 (28)	11 (23)
Erosive disease, n (%)	32 (33)	32 (34)	32 (33)	1 (2)	0 (0)
DAS28-CRP	4.67 (1.13)	4.45 (1.20)	4.55 (1.12)	4.28 (1.61)	4.30 (1.63)
Pain, mm (0-100)	59 (24)	57 (24)	57 (22)	48 (31)	52 (23)
Fatigue, mm (0-100)	51 (26)	49 (24)	49 (21)	39 (28)	46 (22)
HAQ score (0-3)	1.10 (0.77)	0.93 (0.78)	0.92 (0.78)	0.81 (0.85)	0.85 (0.72)
Health utility (-0.59 to 1)	0.47 (0.27)	0.51 (0.27)	0.53 (0.26)	0.59 (0.32)	0.55 (0.25)

Data are presented as mean and SD unless otherwise specified. Symptom duration=number of weeks between onset of symptoms and start of treatment. Health utility was derived using an EQ-5D mapping algorithm. ACPA, anti-citrullinated cyclic peptide; CRP, C-reactive protein; DAS28, Disease Activity Score in 28 joints; EQ-5D, EuroQoL-5 Dimension; HAQ, Health Assessment Questionnaire; RF, rheumatoid factor; TSU, Tight-Step-Up.

Table 2-2 Results of base-case and additional cost-effectiveness analyses comparing COBRA Classic and COBRA Avant-Garde to COBRA Slim in high-risk patients and COBRA Slim to TSU on low-risk patients (the last strategy being the comparator/reference scheme in every case)

	High-risk				Low-risk	
	COBRA Classic n=98	COBRA Avant-Garde n=93	COBRA Slim n=98		COBRA Slim n=43	TSU n=47
Base case: QALY as outcome	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Base case: QALY as outcome	Mean (95% CI)	Mean (95% CI)
Total costs, k€	6.086 (4.710 to 7.462)	5.257 (3.909 to 6.605)	4.622 (3.649 to 5.594)	Total costs, k€	4.007 (2.631 to 5.383)	4.624 (2.685 to 6.562)
QALYs	1.551 (1.491 to 1.611)	1.544 (1.473 to 1.615)	1.553 (1.494 to 1.612)	QALYs	1.629 (1.569 to 1.688)	1.488 (1.394 to 1.581)
Δ Costs vs Slim, k€	1.464 (−0.198 to 3.127)	0.636 (−0.987 to 2.258)	Reference	Δ Costs vs TSU, k€	−0.617 (−2.799 to 1.566)	Reference
Δ QALYs vs Slim ICER (k€ per QALY)	−0.002 (−0.086 to 0.082)	−0.009 (−0.102 to 0.084)		Δ QALYs vs TSU ICER (k€ per QALY)	0.141 (0.008 to 0.274)	
	Dominated	Dominated			Dominant	
Sustained remission as outcome				Sustained remission as outcome		
SR (w16-104), %	29 (20 to 38)	32 (22 to 42)	30 (21 to 39)	SR (w16-104), %	42 (33 to 52)	26 (13 to 38)
Δ SR vs Slim, %	−1 (−14 to 12)	2 (−12 to 16)	Reference	Δ SR vs TSU, %	17 (−3 to 37)	Reference
ICER (k€ per %SR)	Dominated	36.191		ICER (k€ per %SR)	Dominant	
bDMARDs priced to biosimilar				bDMARDs priced to biosimilar		
Total costs, k€	5.510 (4.347 to 6.673)	4.851 (3.734 to 5.968)	4.340 (3.421 to 5.258)	Total costs, k€	3.851 (2.688 to 5.014)	3.856 (2.479 to 5.232)
Δ Costs vs Slim, k€	1.170 (−0.285 to 2.625)	0.511 (−0.904 to 1.926)	Reference	Δ Costs vs TSU, k€	−0.004 (−1.718 to 1.709)	Reference
ICER (k€ per QALY)	Dominated	Dominated		ICER (k€ per QALY)	Dominant	
ICER (k€ per %SR)	Dominated	29.113		ICER (k€ per %SR)	Dominant	

Data are expressed as bootstrapped mean and 95% CIs of costs and benefits from all 25 000 replications from each of the 15 multiply imputed datasets. bDMARDs, biological disease-modifying antirheumatic drugs; ICER, incremental cost-effectiveness ratio, either for cost per QALY or cost per percent sustained remission; k€, thousand euros; QALY, quality-adjusted life years, time-weighted as area under the curve for the 2-year trial; SR, sustained remission measured with Disease Activity Score in 28 joints with C reactive protein <2.6 from week 16 onwards until week 104 and at every time point in between; TSU, Tight-Step-Up.

Healthcare use and costs

Healthcare costs in complete cases, including costs of medication, were presented in Figure 2-1: Costs across treatment schemes: mean € per patient and percentage (%) of the total cost in complete cost cases (n=328). The healthcare cost of rheumatology consultations and use of laboratory and X-rays was comparable across all schemes. In both high-risk and low-risk groups, differences in average cost per patient between treatment strategies could be attributed mainly to bDMARDs use and hospitalizations (Supplemental Table 2-1).

Combination arms (COBRA Classic and COBRA Avant- Garde) had a higher number of patients that were started on bDMARDs in the entire 2 years (Supplemental Table 2-1), although not significant in all comparisons.

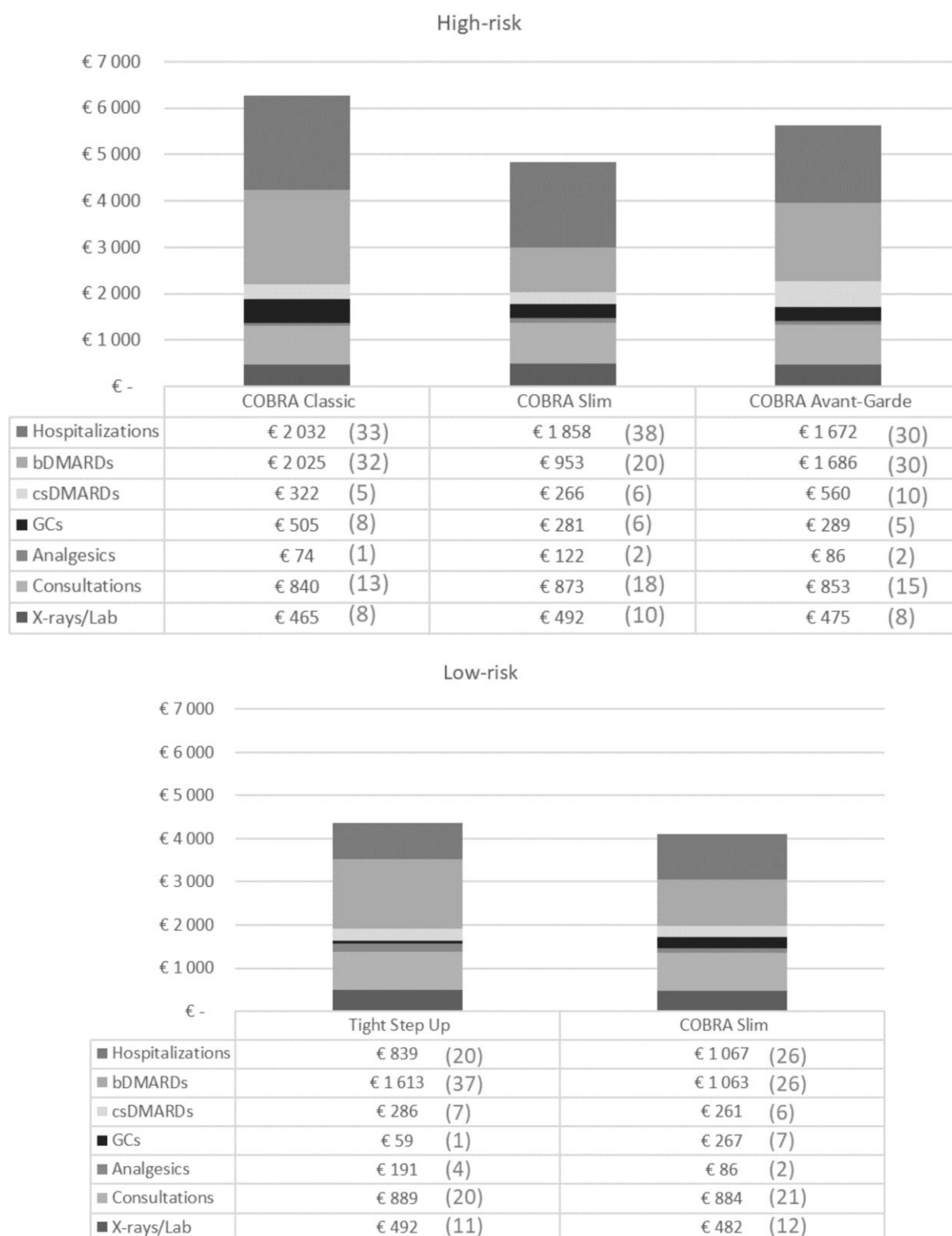
Total healthcare costs in the ITT population were for COBRA Classic (k€6.086), COBRA Avant-Garde (k€5.257) and COBRA Slim (k€4.622) in the high-risk group. In the low-risk group, costs were for COBRA Slim (k€4.007) and TSU (k€4.624).

Incremental cost per QALY

Given the higher costs and lower QALYs gained, COBRA Classic and COBRA Avant-Garde were dominated by COBRA Slim in the base-case analysis of the high-risk group (Table 2-2). In the low-risk group, COBRA Slim also dominated TSU in view of the lower costs and higher number of QALYs gained (Table 2-2). The sensitivity analyses considering biosimilar-prices for all bDMARDs yielded similar results (Table 2-2)

Results from the 25 000 bootstrapped replications of the incremental cost–utility ratios for each comparison are presented in Figure 2-2. In the high-risk group, COBRA Classic was more costly than COBRA Slim in 96% of the bootstrapped replications and was dominated by Slim in 68% of these replications (Figure 2-2a). The bootstrapped uncertainty of COBRA Avant-Garde indicated this strategy to be more costly in 78% of replications compared with COBRA Slim (Figure 2-2b) and in 56% of replications, this strategy was dominated. In the low-risk group, COBRA Slim dominated TSU (Figure 2-2c) in 71% of the bootstrapped replications.

Figure 2-1: Costs across treatment schemes: mean € per patient and percentage (%) of the total cost in complete cost cases (n=328).



Data are presented as mean and proportion of total scheme cost (%)

DMARDs= disease modifying anti-rheumatic drugs, cs- = conventional synthetic, b- = biological

GCs= glucocorticoids, Analgesics= include paracetamol, non-steroidals, tramadol and opioids,

X-rays/Lab= radiographs of hand and feet + laboratory assessment of safety, rheumatoid factor and anti-citrullinated peptide antibody.

Incremental net monetary benefit per QALY

Figure 2-3 represents the iNMB per comparison of schemes at different thresholds for WTP from €0 to k€150 per QALY. In the high-risk group, when comparing COBRA Classic and COBRA Avant-Garde versus COBRA Slim, the iNMB estimate (black full line) was negative and remained below zero on the y-axis (Figure 2-3a,b) regardless of the WTP. In other words, there was no economic benefit of choosing COBRA Classic or COBRA Avant-Garde over COBRA Slim. In the low-risk group, COBRA Slim versus TSU had a positive iNMB. COBRA Slim's estimate never crossed the zero, indicating COBRA Slim was cost-effective even at a very low WTP range (Figure 2-3c).

Incremental net monetary benefit per sustained remission

Figure 2-4 represents the iNMB per comparison of schemes at different thresholds for WTP from €0 to k€150 per sustained remission (DAS28CRP <2.6 from week 16 to 104). The iNMB approach represents the monetary benefit (in €) for each extra percentage (%) of patients that reached sustained remission at different WTP values. In the high-risk group, when comparing COBRA Classic versus COBRA Slim, the iNMB estimate (black full line) was negative and remained below zero on the y-axis (Figure 2-4a). Regardless of the WTP, there was no economic benefit. When comparing COBRA Avant-Garde versus COBRA Slim, there was an added economic benefit from k€20 onwards. However, the lower CI remained negative at any WTP range (figure 2-4b). In the low-risk group, COBRA Slim was dominant to TSU with higher proportions of sustained remission at a lower cost, making it consistently beneficial across the WTP range (figure 2-4c).

Figure 2-2: Cost-effectiveness planes of the base-case analysis (€/QALY). ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; TSU, Tight-Step-Up; WTP, willingness to pay.

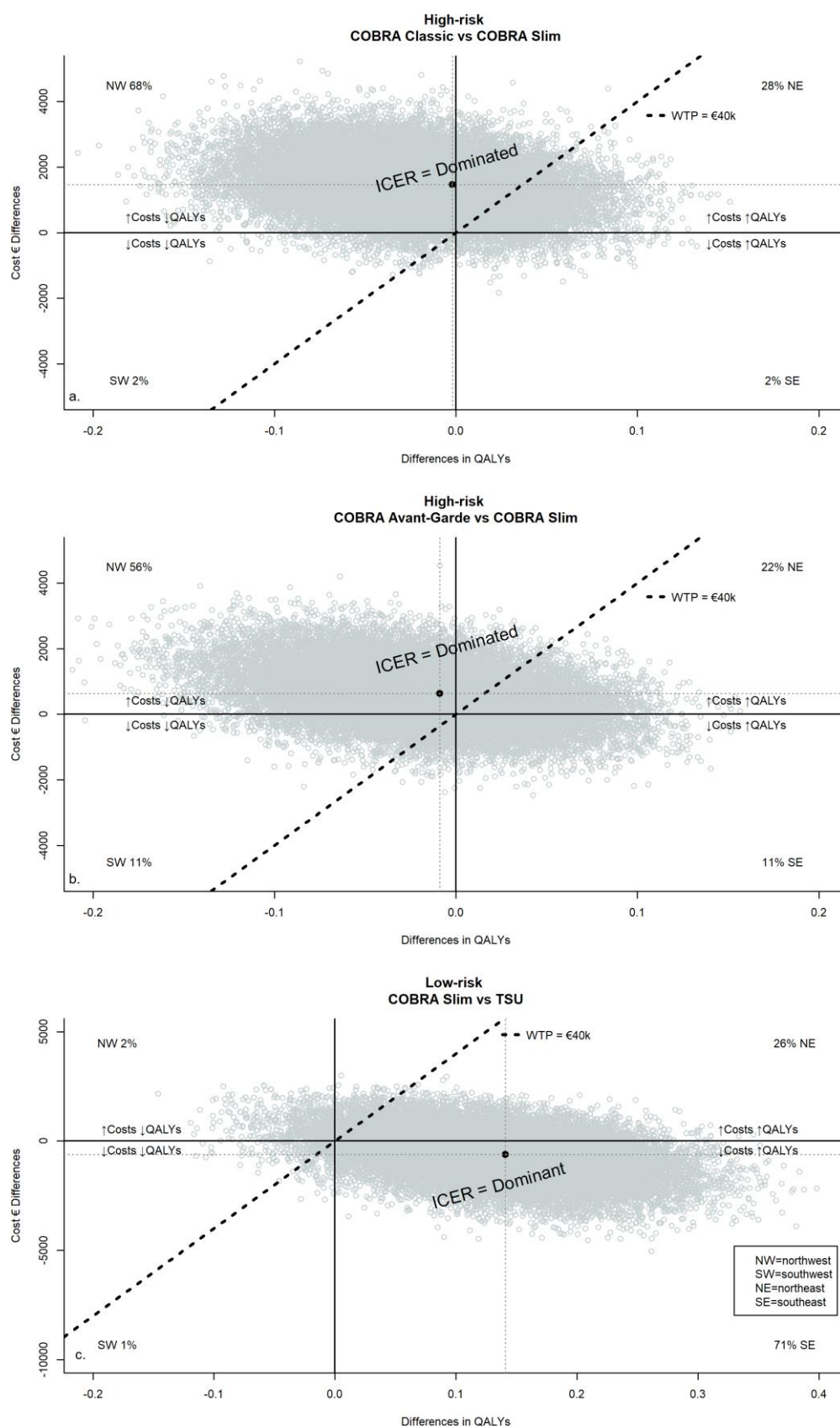


Figure 2-3: Mean incremental net monetary benefit (iNMB) with 95% CIs across different thresholds of willingness to pay (WTP) of the base- case cost-utility analyses with quality-adjusted life-years (QALYs) as health outcome. The black line is the estimate and the dotted lines its 95% CIs.

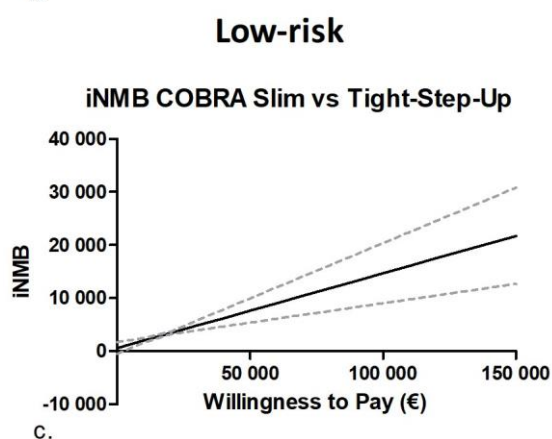
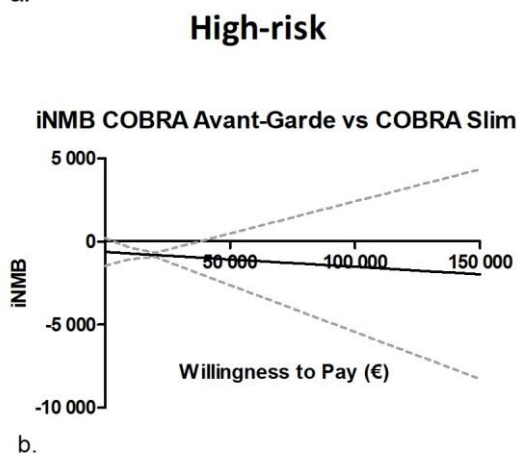
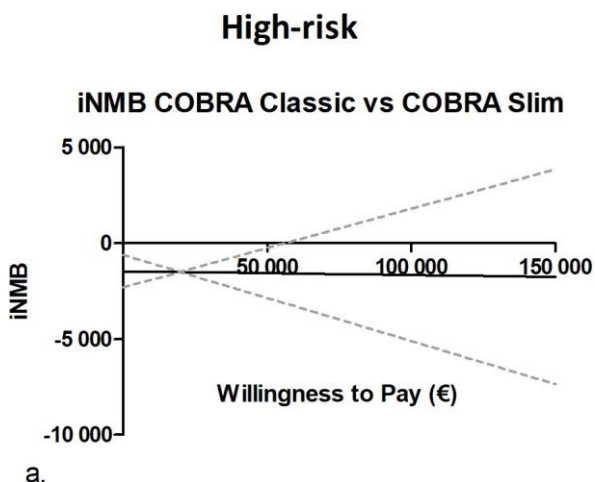
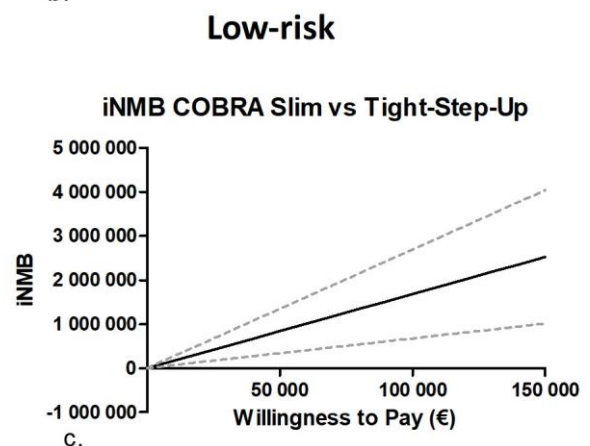
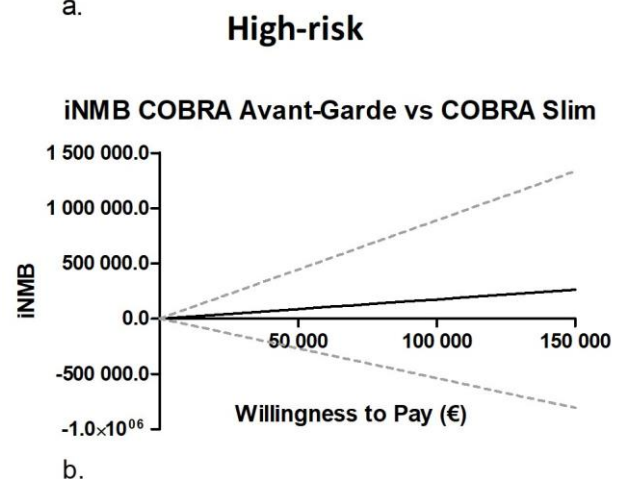
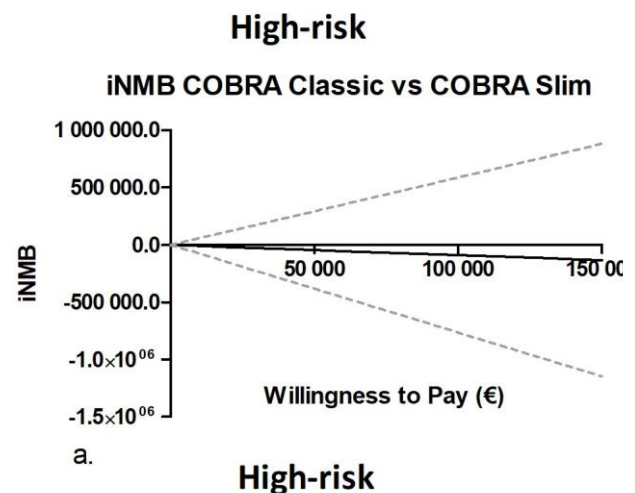


Figure 2-4: Mean incremental net monetary benefit (iNMB) with 95% CIs across different thresholds of willingness to pay (WTP) of the secondary analyses with sustained remission ($\text{DAS28CRP} < 2.6$ from week 16 to 104) as health outcome. The black line is the estimate and the dotted lines its 95% CIs.



2.1 DISCUSSION

This study showed that for high-risk early RA patients, csDMARD combination schemes with GCs (COBRA Classic and COBRA Avant-Garde) were not cost-effective or even dominated in the first 2 years when compared with COBRA Slim, MTX monotherapy together with a moderate-dose step-down GC bridging scheme, for initial remission induction within a treat-to-target strategy. In the low-risk group, COBRA Slim dominated the traditional MTX monotherapy without GC in patients with early RA treated-to-target. However, selecting the most appropriate first-line DMARD regimen remains a complex clinical decision.¹

We published previously that COBRA Slim treatment resulted in similar remission rates but less therapy-related AEs compared with COBRA Classic or COBRA Avant-Garde.⁸ Such adverse drug events have been associated with higher costs of illness³⁷ and also reduced patient's QoL. This piggyback, trial-based economic evaluation, provides evidence that MTX with step-down GCs is an effective initial treatment choice for all patients with RA by balancing the necessary treatment intensity to control the disease with a favourable safety profile, resulting in an adequate QoL. This strategy could moreover minimize chances of an interruption or modification of the treatment scheme leading to more frequent discomfort and higher costs.

This study's results were comparable to other cost-effectiveness analyses of early RA strategy trials. In the BeSt trial, the COBRA Classic-like strategy had a total cost of €9.2 of which €5.0 were direct medical costs (calculated from US dollars; exchange rate of 1:0.90),³⁸ comparable to our cost of €6.086 in COBRA Classic. In the COBRA-light trial, using strategies comparable to COBRA Classic and Slim, the total costs were €9.7 and €5.6, respectively, and differences in QALYs comparable to CareRA.³⁹ The robust comparability with previous trials reinforces our message that COBRA Slim seems a cost-saving strategy.

In patients perceived as high-risk, the main driver for the lower cost of COBRA Slim was the lower number of bDMARDs initiated in the 2 years of the CareRA trial (Supplemental Table 2-1). Because COBRA Classic and COBRA Avant-Garde combined two csDMARDs,

patients insufficiently responding to these schemes were, after failing to dose escalation of both csDMARDs, eligible for bDMARDs according to Belgian reimbursement criteria.⁴⁰ In contrast, patients on COBRA Slim therapy had to first initiate and fail a second csDMARD before being eligible for bDMARDs. In line with good clinical practice, this approach, including if necessary different adaptation steps depending on the initial treatment effect, delays the need for initiating bDMARDs, resulting in cost benefits but also potentially patient benefits, in terms of risk: benefit ratio.⁴⁰ The long-term CareRA outcomes from the observational follow-up (3 years) will provide additional insights into cost-effectiveness and further bDMARD use.

Despite the fact that several trials and meta-analyses have demonstrated that efficacy outcomes improve when using tumour necrosis factor inhibitor (TNFi) bDMARDs as first-line treatment^{41, 42} they have poor cost-effectiveness profiles.^{43, 44} One of the challenges with these earlier analyses is that prices from before the approval of biosimilar TNFis were used for cost-effectiveness calculations. To estimate the hypothetical impact of using biosimilar in CareRA, an uncertainty analysis was performed changing every bDMARD to the lowest priced biosimilar in Belgium at the time of this study. This analysis demonstrated robustness of the initial results. To further explore the use of earlier bDMARD use, we initiated the CareRA 2020 trial (EudraCT # 2017-004054-41) examining the cost-effectiveness of accelerated but temporary bDMARD access after failing to MTX monotherapy with a GC bridging scheme.

Since pragmatic effectiveness trials seem best for economic studies, the use of data from the pragmatic CareRA study is a major strength for this economic analysis.⁴⁵ As CareRA is a pragmatic, treat-to-target, multicentre investigator-initiated RCT with less stringent inclusion and exclusion criteria, the study population may represent a typical day-to-day healthcare population with no artificially enhanced compliance, using strategies already in place in clinical practice.⁴⁶⁻⁴⁸ The protocol-driven treatment adaptations were limited to two logical escalations of csDMARDs, meaning that when a bDMARD was needed, it was left at the discretion of the treating rheumatologist, just as in daily practice. However, this post hoc study of an RCT, provided no data on indirect costs nor direct non-medical costs. There might also be direct medical costs missing when it comes to general practitioner appointments and use of paramedical or alternative therapies. Intangible costs are

complicated to account for, yet our study provides a glimpse into them by recreating the EQ-5D values considering pain and physical function among others. Moreover, the estimation of health utility was corrected for disutility produced by AEs.

2.2 CONCLUSION

Based on this economic analysis, compared with more intensive step-down combination strategies or to a conventional step-up approach, COBRA Slim, the combination of MTX and a moderate-dose GC bridging scheme, was less expensive and lead to comparable or better gain in QALYs. Therefore, we consider COBRA Slim a good starting strategy for all patients with early RA, irrespective of prognostic markers, in a treat-to-target setting.

2.3 REFERENCES

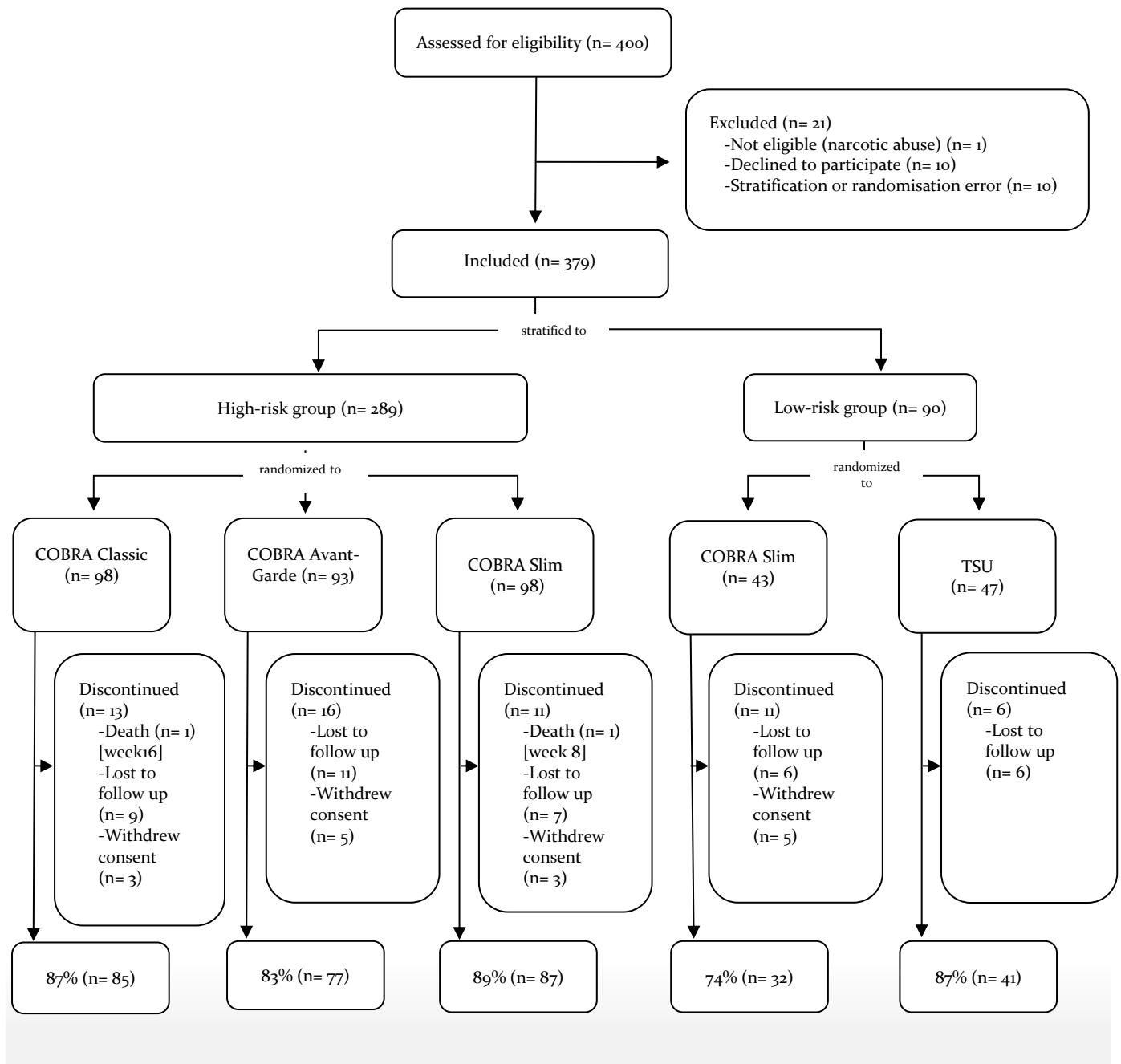
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SUPPLEMENTAL MATERIAL

Supplemental Figure 2-1: Flow chart of participants during the 2-year trial. All randomized patients.



Supplemental Table 2-1: Average costs per patient (incurring in the resource) for the different categories of health care utilisation over the 2 years follow-up of complete cost cases (n=328) per treatment scheme.

	High-risk		
	COBRA Classic n=88	COBRA Avant-Garde n=77	COBRA Slim n=88
Health care	Mean costs € (SD)	Mean costs € (SD)	Mean costs € (SD)
Rheumatologist consultations	839.63 (82.3)	853.26 (55.5) *	872.75 (90.4)
Hospitalizations†	6 386.85 (6 575.1) [n=28]	6 131.87 (5 150.7) [n=21] **	6 813.47 (6 461.5) [n=24]
Laboratory (safety blood sample)	201.05 (30.9)	208.05 (25.8) *	216.8 (22.4)
RF	8.68 (1.7)	8.70 (1.6) *	9.11 (1.0)
ACPA	42.63 (8.8)	43.24 (8.0) *	45.47 (5.6)
X-rays hands and feet	213.10 (35.1)	215.42 (28.7)	220.23 (26.2)
Medication			
csDMARDs	321.73 (144.4)*	559.82 (184.1) **	265.68 (163.0)
MTX	164.41 (76.9)	139.11 (59.9) **	184.81 (87.2)
SSZ†	125.44 (69.8) **	-	82.53 (25.4) [n=3]
LEF†	241.25 (174.4) [n=13]	422.93 (207.3) **	281.07 (144.3) [n=27]
HCQ†	-	-	43.03 (48.9) [n=2]
GCs	504.51 (320.8) **	293.88 (143.7)	292.78 (178.9)
bDMARDs†	10 482.98 (6 677.1) [n=17]**	9 988.42 (5691.8) [n=13]	7 623.04 (2 671.3) [n=11]
Analgesics†	89.72 (109.9) [n=73]	97.02 (140.8) [n=68]	141.69 (247.0) [n=76]

	Low-risk	
	COBRA Slim n=34	Tight-Step-Up n=41
Health care	Mean costs € (SD)	Mean costs € (SD)
Rheumatologist consultations	884.05 (62.7)	889.33 (84.1) *
Hospitalizations†	3 627.28 (2 778.4) [n=10]	4 302.19 (3 210.4) [n=8] **
Laboratory (safety blood sample)	214.17 (22.7)	217.95 (27.6) *
RF	8.84 (1.6)	9.01 (1.0) *
ACPA	44.13 (7.2)	44.98 (5.2) *
X-rays hands and feet	214.59 (28.3)	219.66 (24.1) *
Medication		
csDMARDs	260.67 (178.5)	285.99 (196.9)
MTX	191.96 (97.8)	181.69 (98.2)
SSZ†	-	24.89 (0.7) [n=2] **
LEF†	313.22 (143.5) [n=9]	307.99 (191.5) [n=15] **
GCs†	266.88 (107.2)	104.01 (197.8) [n=23] **
bDMARDs†	5 162.0 (3393.1) [n=7]	13 224.45 (9 861.5) [n=5] **
Analgesics†	104.60 (243.5) [n=28]	205.67 (243.5) [n=38] *

Data are expressed as mean and standard deviation unless otherwise specified. *p<0.05 **p<0.001 in mean cost difference with Kruskal-Wallis or Mann-Whitney U, taking COBRA Slim as reference. RF= rheumatoid factor, ACPA= anti-citrullinated peptide antibody, csDMARDs= conventional synthetic disease modifying anti-rheumatic drugs, MTX= methotrexate, SSZ= sulfasalazine, LEF= leflunomide, HCQ= hydroxychloroquine, GCs=glucocorticoids, bDMARDs= biological disease modifying anti-rheumatic drug, Analgesics= including paracetamol, non-steroidals, tramadol and opioids

†Not everyone incurred in these resources and therefore the n is different.

Supplemental Table 2-2: Disutilities (EQ-5D) per adverse event with their reference cohort which was used for discounting. Lowest literature available disutility was assumed.

Adverse event	Disutility	Source of disutility/assumption
Allergy	0.02	Olesen 2016
Allergic rhinitis	0.03	Al-Digheari 2018
Alopecia	0.031	Hagiwara 2018
Anemia	0.01	Park 2015
Angina	0.04	Sullivan 2006
Anxiety disorders	0.04	Sullivan 2005
Aphthosis	0.14	Lloyd 2006-assumed same stomatitis
Arrhythmia	0.02	ICER 2017
Arthralgia	0.041	Hagiwara 2018
Arthritis	0.04	George 2014
Arthrosis	0.04	Arrospide 2019
Asthma	0.11	Hernandez 2018
Back pain (chronic)	0.09	Tsiplova 2016
Blindness/low vision	0.05	Sullivan 2006
Bone marrow suppression	0.218	Nafees 2008 assumed same as thrombocytopenia
Breast cancer	0.12	Wood 2017
Cataract	0.02	Sullivan 2005 and 2006
Cervicalgia	0.041	Hagiwara 2018 assumed same as arthralgia
Cholelithiasis	0.03	Sullivan 2006
COPD	0.02	Hong 2015
COPD minor exacerbation	0.108	Einarson 2015
COPD major exacerbation	0.287	Einarson 2015
Cough	0.05	Doyle 2008
Chronic bronchitis	0.04	Sullivan 2011
Cystitis	0.218	Stein 2017 assumed same as UTI
Depression	0.03	Park 2019
Diabetes	0.06	Nafees 2008 assumed as hyperglycaemia
Diarrhea	0.176	Stein 2017
Dyspepsia	0.10	Mahadeva 2010
Dyspnea	0.219	Lachaine 2015a
Ear infection	0.218	Stein 2017 assumed same as infection
Edema	0.085	Hagiwara 2018
Eczema	0.06	Moberg 2009
Fatigue	0.115	Lloyd 2006
Fever	0.15	Lloyd 2006
Fibromyalgia (very mild)	0.1	Luo 2011
Fractures of wrist or hip	0.04	Hagino 2009
Fractures (all others)	0.07	Matza 2014 assumed as surgery for stabilization of bone
Foot deformity (acquired)	0.02	Sullivan 2005
Gastric ulcer	0.11	Groeneveld 2001
Gastritis	0.01	Sullivan 2005
Gastroenteritis	0.04	Sullivan 2006

Adverse event	Disutility	Source of disutility/assumption
Hip/knee pain	0.17	Kontodimopoulos 200
Hyperglycemia	0.06	Nafees 2008
Hypertension	0.02	ICER 2017
Hypotension	0.02	ICER 2017
Infection	0.218	Stein 2017
Interstitial lung disease	0.218	Stein 2017 assumed same as pneumonitis or pulmonary infiltrates
Irritable bowel syndrome	0.13	Akehurst 2002
Insomnia	0.28	Wu 2014
Knee replacement surgery	0.1	Φystein 2013
Leukocytosis	0.09	Hagiwara 2018
Leukopenia	0.09	Nafees 2008
Liver disturbances	0.16	Arrospide 2019
Lower respiratory tract infection	0.218	Stein 2017 assumed same as pneumonia
Migraine	0.03	Sullivan 2005, 2006 and 2011
Myalgia	0.123	Hagiwara 2018
Mycosis	0.218	Stein 2017 same as fungal infection
Nausea	0.051	Nafees 2008
Neck/shoulder pain	0.08	Burstrom 2001
Neutropenia	0.09	Nafees 2008
Oesophagitis	0.01	Areia 20014
Oral mucositis	0.087	Hagiwara 2018
Osteoporosis	0.03	Guillemin 2013
Pain	0.29	Wu 2014
Pericarditis/pleuritis	0.218	Stein 2017 assumed same as infection
Prolonged ileus/ bowel obstruction	0.11	Worbes-Cerezo 2019
Prostatic disorder	0.02	Sullivan 2006
Pruritus	0.03	Sullivan 2011
Psoriasis	0.02	Sullivan 2011
Pulmonary embolism	0.02	Tavoly 2016
Renal cell carcinoma	0.09	de Groot 2018
Renal insufficiency	0.15	Park 2016
Renal/ureteral calculus	0.02	Sullivan 2011
Septic bursitis	0.218	Stein 2017 assumed as sepsis
Stomatitis	0.14	Tabberer 2006
Thrombocytopenia	0.09	Nafees 2008
Upper respiratory tract infection	0.218	Stein 2017 assumed same as infection
Urinary tract infection	0.218	Stein 2017
Urticaria	0.03	Sullivan 2011 assumed same as pruritus

COPD=chronic obstructive pulmonary disease

UTI=urinary tract infection

ICER=The Institute of Clinical and Economic Review

Chapter 3.

Seronegative RA, the sometimes- underestimated stepsister

Impact of being seronegative for rheumatoid factor and anti-citrullinated cyclic peptide on the response to early intensive rheumatoid arthritis treatment: data from the CareRA trial*

3.1 ABSTRACT

Background: Rheumatoid factor and anti-citrullinated cyclic peptide negative Rheumatoid Arthritis (RA), has historically been considered a milder subtype. We aimed to explore disease outcomes in patients with seronegative RA treated with methotrexate and prednisone bridging (COBRA-Slim) in the Care in early RA (CareRA) trial.

Methods: Patients with early RA (≤ 1 year), naïve to disease modifying anti-rheumatic drugs, included in the CareRA trial and randomized to COBRA Slim ($n=141$), were selected for this post-hoc study. Clinical and radiological outcomes over 2 years were compared between seronegative and seropositive patients.

Kaplan Meier and Cox regression survival analysis compared (a) time to first remission ($\text{DAS28CRP} < 2.6$), (b) time to first loss of disease-control ($\text{DAS28CRP} > 3.2$) in those reaching remission, and all subsequent losses of disease-control as recurrent events.

Results: Seronegative patients starting COBRA Slim ($n=38$), had a similar age, BMI, symptom duration, presence of erosions and gender distribution, compared to seropositive patients ($n=103$). DAS28CRP was higher in seronegative patients at screening (5.1 vs 4.5 , $p=0.01$) and remained higher at week 8 (2.9 ± 1.2 vs 2.4 ± 2 – $p=0.006$) but became comparable by year 1. Time to first remission was significantly shorter for seropositive versus

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seronegative patients. Time to first loss of disease-control was not different and when considering all subsequent losses of disease-control, the only significant covariate was DAS28CRP at week 16.

Conclusions: CareRA patients with seronegative RA had a higher initial disease activity and longer time to first remission but ultimately achieved comparable remission rates as seropositive patients with COBRA Slim. Apparently seronegative RA requires an equally intensive initial therapy.

KEY MESSAGES

What is already known about this subject?

- Patients with seronegative rheumatoid arthritis (RA) have been considered to have a milder disease course than seropositive RA patients. Considering seropositive patients to have more radiographic progression.

What does this study add?

- Treatment response for achieving a first remission was slower in patients with seronegative compared to seropositive RA, although they had the same intensive treatment.
- Disease activity and radiographic progression was comparable after 2 year of follow-up.

How might this impact on clinical practice or future developments?

- These results would indicate that patients with seronegative RA are likely to have a more severe initial disease than what was historically considered.

3.2 INTRODUCTION

The main clinical manifestation of early Rheumatoid Arthritis (RA) is inflammation of the peripheral joints resulting in swelling, stiffness and pain.¹ However, a wider range of symptoms can be present including functional impairment and constitutional manifestations such as fatigue as well as global health impact.² European guidelines now recommend as first treatment strategy a disease modifying anti-rheumatic drug (DMARD) such as methotrexate (MTX) with a short-term glucocorticoid (GC) course that should be tapered as quickly as possible.³ However, in absence of serological markers of poor prognosis many physicians currently will not apply early intensive treatments as a first strategy. Moreover, not all patients with early RA will respond favourably to this initial treatment scheme and some will need adaptations that can be for instance increasing the dose, switching or adding medications.³ For such second-line treatment adaptations, current recommendations make a distinction between patients with or without poor prognostic factors. In patients with poor prognostic factors such as serological positivity for rheumatoid factor (RF) or anticitrullinated peptide antibodies (ACPA), highly active disease or early radiographic damage (erosions), a biological (b-) DMARD or targeted synthetic (ts-) DMARD should be added. In the absence of these factors, other conventional synthetic (cs-) DMARD should be considered.³ The influence of serological markers of poor prognosis (RF/ACPA autoantibodies) on the clinical disease course and treatment choice is still controversial.⁴ The population without these markers, accounts for approximately one in four RA patients. Most analyses on this subpopulation in trials are secondary, dealing mostly with X-ray progression as outcome, and therefore many aspects still need further study in this subgroup. The response of seronegative patients to early intensive therapies has also not been comprehensively studied. We aim to compare the

disease course as time to first remission and probability of relapse after initial remission in seronegative and seropositive patients in an explorative post-hoc analysis of the Care in early RA (CareRA) trial.⁵⁻⁷

3.3 PATIENTS AND METHODS

Study population

CareRA was a 2-year open-label investigator-initiated pragmatic superiority trial (EudraCT number: 2008-007225-39) conducted in 13 Flemish rheumatology centres (2 academic centres, 7 general hospitals and 4 private practices) in Belgium.

Patients with recently diagnosed RA (≤ 1 year) were included and stratified into a high- or low-risk group based on classical factors of poor prognosis (erosions, RF/ACPA positivity and baseline disease activity measured in 28 joints with C-reactive protein - DAS28CRP > 3.2). Patients were randomized to different intensive treatment regimens depending on their risk profile: one of three step-down-bridge treatment regimens (COBRA-Classic, COBRA-Avant-Garde and COBRA-Slim) for high-risk patients and either a Tight-Step-Up or a step-down-bridge treatment scheme for low-risk patients. Both high- and low-risk patients were eligible to be randomized to methotrexate (MTX) 15mg weekly with a step-down glucocorticoid (GC) scheme (COBRA-Slim). We chose this CareRA subpopulation treated with COBRA Slim for the primary analysis in the current study. Seronegative patients were defined as negative to both RF and ACPA for this post-hoc study.

For patients who did not respond sufficiently to the initial medication scheme, the protocol specified two subsequent treatment adaptation steps and afterwards treatment was left at the discretion of the treating rheumatologist. Details on patient eligibility criteria,

randomisation process, study design and treatment intensifications have been previously published.⁷

Clinical outcomes

Patients were assessed at screening, baseline and then followed-up at week 4, 8, 16, 28, 40, 52, 65, 78, 91 and 104. Optional visits, if clinically required, could be performed. An electronic trial record (eCRF) was filled out and routinely monitored. Clinical, patient and laboratory parameters were collected at every visit: tender (TJC28) and swollen (SJC28) joint count in 28 joints, patient's (PaGH) and physician's (PhGH) global health assessment, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). X-rays of hands and feet were obtained at baseline, week 28, year 1 and year 2. Radiographic evolution was assessed by the Sharp van der Heijde (SvdH) score.

Statistical analyses

All randomized patients having taken at least one study-medication dose were considered for analysis. Missing data were assumed to be missing at random and were imputed with multiple imputation (classification and regression trees) by chained equations.⁸ Missingness in clinical variables used to estimate disease activity per time point were imputed. Besides the incomplete variables, treatment strategy, centre of recruitment, age, gender, presence of comorbidities, RF, ACPA, erosions at baseline and trial completion were included as predictors in the matrix. Based on Bodner (2008), the number of imputed sets was set to 10, equal to the missing data percentage.⁹ Results of the 10 analyses were pooled using Rubin's rules.¹⁰

Survival analyses

For the primary analysis we concentrated exclusively on the CareRA subpopulation randomized to COBRA Slim. We considered by means of survival analyses the event of achieving a first remission ($\text{DAS28CRP} < 2.6$) after diagnosis, the event of losing disease control ($\text{DAS28CRP} > 3.2$) again, after having achieved remission and all the subsequent times of loss of disease control as recurrent events. For this analysis, the outcome of time to event considered imputed values only for patients who had a visit with at least one the DAS28CRP component measured, censored time was not imputed. Kaplan Meier and Cox regressions stratified for risk group were used for survival analysis of (a) time to first remission ($\text{DAS28CRP} < 2.6$), (b) time to first loss of disease control ($\text{DAS28CRP} > 3.2$) in those reaching remission, and all the subsequent times of loss of disease control as recurrent events, comparing seronegative and seropositive patients. Survival curves were compared using the Gehan-Breslow-Wilcoxon method which gives more weight to events at early time points and using the log-rank test which gives equal weight to all time points. To model recurrent events, an extended Cox model with random effect, a frailty model was used.¹¹⁻¹³ We chose clinically relevant predictors of clinical response¹⁴ to fit the model: serological status, early clinical response conceptualised by inclusion of DAS28CRP at baseline, week 4, 8 and 16, and week at which the first remission was attained, presence of erosions at baseline, disease duration, gender, and current smoking.

Sensitivity analyses

Apart from the primary analysis exclusively on the CareRA subpopulation treated with COBRA Slim ($n = 141$) which was also fitted without outliers, we also performed a survival analysis with Kaplan Meier and Cox regression on the low-risk subpopulation of CareRA ($n = 90$) and on the entire CareRA population ($n = 379$), stratified by treatment group. As in

the primary analysis the outcomes of interest were (a) time to first remission (DAS28CRP<2.6), (b) time to first loss of disease control (DAS28CRP>3.2) in those reaching remission, making a distinction between seronegative and seropositive patients.

To account for DAS28CRP improvement and not only remission, we performed a Kaplan Meier on time to first treatment response, being either clinically relevant DAS28CRP improvement ($\Delta > 1.2$) or reaching remission (DAS28CRP<2.6) in the “as observed” population.

All analyses were performed with R V.4.0.0.

3.4 RESULTS

Patients

Seronegative patients starting COBRA Slim (n=38), had a similar age (53 vs 51 years, p=0.52), BMI (25.5 vs 26.7, p=0.08), symptom duration (7.9 vs 7.2 months, p=0.23), presence of erosions (24% vs 23%, p=0.99) and gender distribution (82% vs 63% females, p=0.06), compared to seropositive patients (n=103).

Disease evolution

Disease activity was higher in seronegative patients at screening: DAS28CRP (5.1 vs 4.5, p=0.01), SJC28 (8.2 vs 5.7, p=0.02) and TJC28 (10.3 vs 6.9, p=0.006). DAS28CRP remained significantly higher at week 8 (2.9 ± 1.2 vs 2.4 ± 2 , p=0.006) but became comparable by year 1 (2.4 ± 1.0 for both seronegative and seropositive, p=0.929). A graphical representation of the evolution of DAS28CRP with its components and radiographic progression can be found in Figure 3-1. A difference was seen at early stages in DAS28CRP, SJC28 and TJC28, which is no longer present afterwards. Radiographic progression was similar between groups (Figure 3-1f).

Treatment response

Time to first remission is illustrated in Figure 3-2a. Both the Gehan-Breslow-Wilcoxon ($p=0.04$) and Log-rank test ($p=0.04$) indicated that seronegative patients achieved remission significantly later than seropositive patients with Kaplan Meier (Figure 3-2a). The last time point at which seronegative patients achieved remission was week 78 compared to week 40 in seropositive patients. The sensitivity analysis performed with Kaplan Meier on time to first treatment response being either clinically relevant DAS28CRP improvement ($\Delta > 1.2$) or reaching remission ($\text{DAS28CRP} < 2.6$) in the “as observed” population confirmed the delay in response for the seronegative compared to the seropositive (Supplemental Figure 3-1). A similar course was observed in the sensitivity analysis focusing on the low-risk population (Supplemental Figure 3-2) and on the entire CareRA population (Supplemental Figure 3-3).

Positivity to RF or ACPA was associated with a shorter time to first remission in the analysis of only COBRA Slim patients (HR 1.85, 95%CI 1.03-3.34, $p=0.04$), the low-risk population (HR 3.51, 95%CI 2.11-5.85, $p<0.001$), and the entire CareRA cohort (HR 1.63, 95%CI 1.09-2.45, $p=0.02$). When including DAS28CRP at baseline to each model, seropositivity was no longer significantly associated to time to first remission. Of the 141 patients, 129 reached remission ($\text{DAS28CRP} < 2.6$). The time to first loss of response ($\text{DAS28CRP} > 3.2$) after having reached remission is illustrated in Figure 3-2b. Both the Gehan-Breslow-Wilcoxon ($p=0.07$) and Log-rank test ($p=0.07$) indicated that there was no difference between seronegative and seropositive patients in time to first loss of disease control.

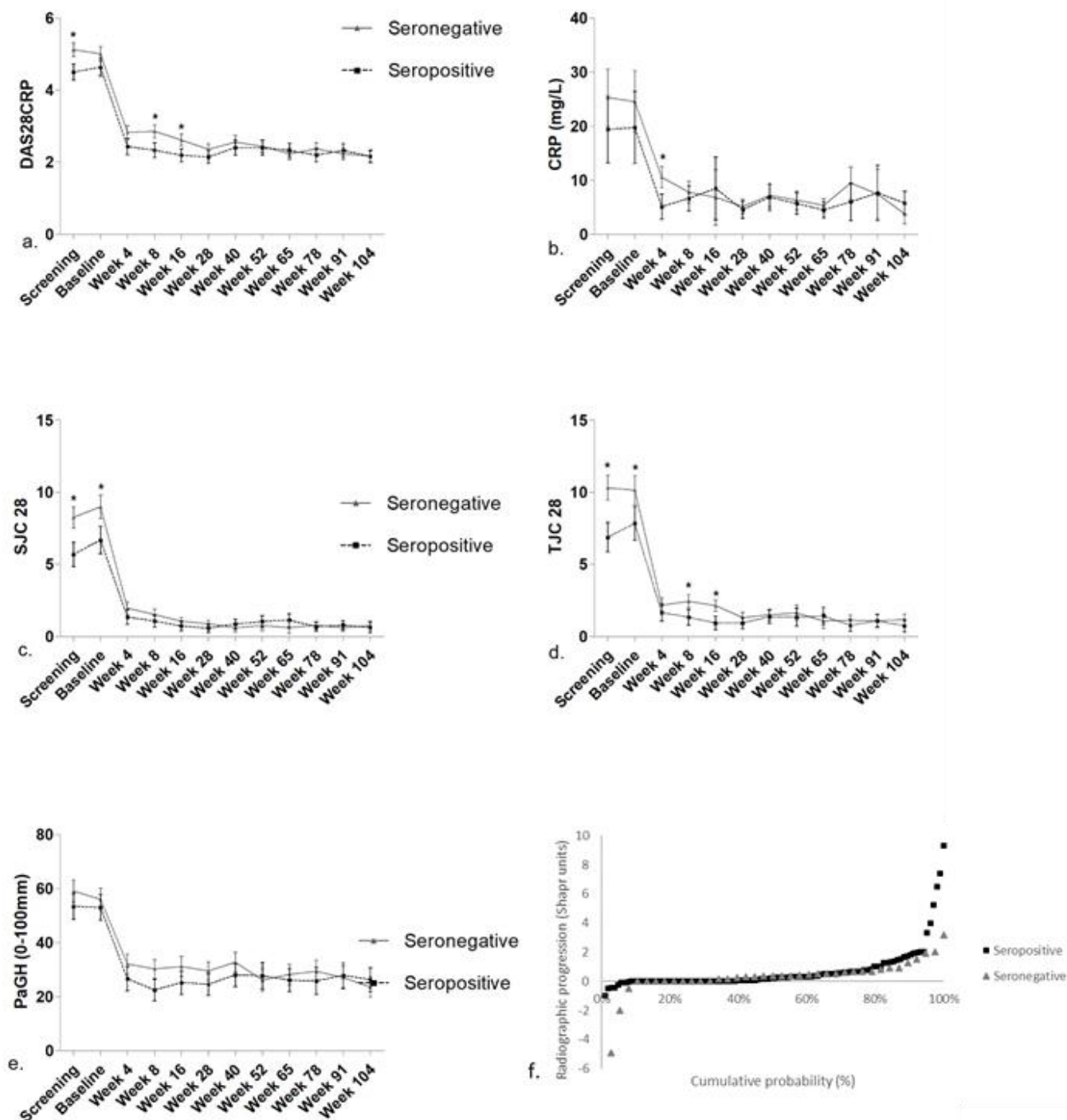
The maximum number of events of loss of disease control per patient was ten, which could be considered an outlier (Figure 3-3b). Without the outlier, the maximum number was 5. Of the 129 patients having reached remission, 57% had no loss of disease control afterwards, and 36% had a maximum of 3 events. For both seronegative and seropositive patients the

median (IQR) number of recurrent events was 0 (1) for seronegative and 0 (2) for seropositive RA, with no significant difference in number of events (Mann-Whitney U test $p=0.82$) (Figure 3-3b). Considering all recurrent events, a prediction model for loss of disease control was built with clinically relevant predictors of clinical response, amongst which the serologic status. Each of these predictors was tested in univariate models. Even though only DAS28CRP at baseline, week 8 and 16 were significant in the univariate models (Supplemental Table 3-1), we kept these variables due to historical clinical relevance. The frailty model had a good fit (Likelihood ratio test=45.98, 11 degrees of freedom, $p=0.000003$). In Table 3-1, all hazard ratios (HR) and p-values are presented. The HR for DAS28CRP at week 16 was significant, providing 91% increased risk of recurrent losses of disease control for every point increase and this independently of within-patient differences. Hence, the serology does not seem to be an independent predictor of loss of response, while the degree of disease control at week 16 would be a solid predictor of the long-term success of intensive early RA treatment. Figure 3-2b is a graphical representation of each patients' trajectory after reaching remission, until lost to follow-up or termination of the study. Highlighted in red are the recurrent events of losing disease control during the 2-year trial. As a sensitivity analysis, the model was also fitted without including the outlier. The models were comparable. (Supplemental Table 3-2)

Treatment adaptations

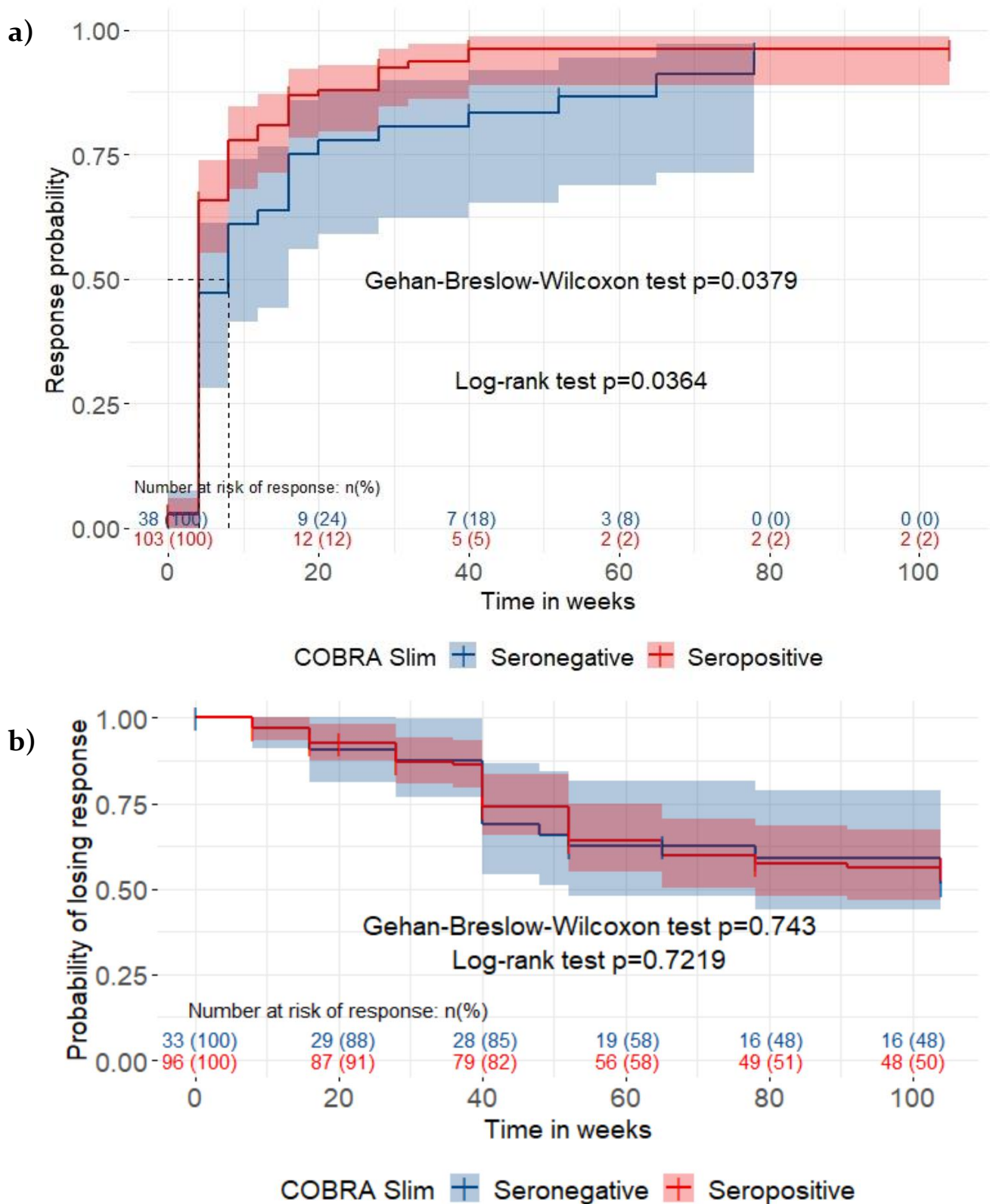
Treatment adaptations were comparable ($p=0.87$) across groups during the study. In seronegative patients, 24/38 (63%) remained with the original treatment scheme, 8/38 (21%) had a csDMARD adaptation and 6/38(16%) were initiated a bDMARD. For the seropositive patients the rates were as follows: 66/103 (64%), 24/103 (23%) and 13/103(13%) respectively.

Figure 3-1: Evolution of disease outcomes over the 2-year CareRA trial in seronegative (n=38) versus seropositive (n=103) early RA patients receiving COBRA Slim treatment: a) DAS28CRP, b) CRP, c) swollen (SJC28) and d) tender (TJC28) joint count in 28 joints, e) patient global health assessment (PaGH) and f) radiographic progression.



*confidence intervals (CI) do not overlap, quite likely a significant difference, p-value not calculated to avoid multiplicity

Figure 3-2: Kaplan Meier survival curve for a) time of first remission ($DAS28CRP < 2.6$) in patients receiving COBRA Slim treatment in CareRA ($n=141$) and b) time of first loss of disease control ($DAS28CRP > 3.2$) after having reached the first remission in the same population ($n=129$).



a)

Patients total (n=129)

Seronegative n=33

Seropositive n=96

Week

Status

- 1st Remission
- >LDA
- Lost to follow-up



Table 3-1: Model of recurrent loss of disease control (DAS28CRP>3.2) in patients having reached remission, with clinically relevant predictors of clinical response.

Predictors	Hazard Ratio	Lower 95%CI	Upper 95% CI	p-value
Seropositive	1.4625	0.8978	2.3823	0.13
DAS28CPR at baseline	1.0414	0.8900	1.2185	0.61
DAS28CPR at week 4	1.1698	0.9189	1.4892	0.20
DAS28CPR at week 8	1.2353	0.9601	1.5893	0.10
DAS28CPR at week 16	1.9086	1.4757	2.4685	0.00000084
Presence of erosions at baseline	1.1265	0.7198	1.7632	0.60
Disease duration (weeks)	1.002	0.996	1.007	0.55
Female	0.9261	0.6366	1.3474	0.69
Current smoking	1.1455	0.7689	1.7065	0.50
Week of first remission	0.9646	0.9415	0.9883	0.0037
Frailty				0.92

Seropositive: patient with RA that is positive to rheumatoid factor or anti-citrullinated peptide antibodies, DAS28CRP: disease activity score in 28 joints, remission: DAS28CRP<2.6 Likelihood ratio test=45.98, 11 degrees of freedom, p=0.000003

3.5 DISCUSSION

In this post-hoc study of patients with early RA treated rapidly, intensively and to target, disease activity and radiographic progression was similar between seronegative and seropositive patients after two years, despite more inflammatory activity during the first 16 weeks in the seronegative. Treatment response (time to achieving first remission) was slower in seronegative patients, both when considering DAS28CRP clinical improvement of >1.2 or remission as treatment response.

These findings suggest seronegative RA is not a mild or easy to control form of RA, and requires at least as intensive initial treatment as seropositive RA. In our study, a delay in response to first remission was shown in the seronegative patients, which could result in less favourable long-term outcomes. However, when considering the loss of disease control after remission either as a first event (Kaplan-Meier) or all subsequent events (frailty

model), RF or ACPA positivity seemed not to be the marker of poor prognosis that we have come to expect. Furthermore, when considering clinically relevant predictors of disease response¹⁴ alongside the heterogeneity of every patient (frailty model) in terms of frequency and timing of losing disease control again after having reached remission, the only significant covariate was DAS28CRP at week 16, emphasizing even more the importance of early response.

Clearly, early response is of paramount importance in early RA. Some studies have shown that patients who do not respond significantly to treatment within 3 months, have a lower chance of reaching remission by 6 months.¹⁵⁻¹⁷ Furthermore, rapid and persistent disease control and not treatment type has been found to be associated with favourable patient reported health outcomes and illness perceptions.¹⁸

The CareRA study already showed benefit of COBRA Slim (MTX + GC bridging) compared to MTX step-up therapy in patients without poor prognostic factors.^{5,7} Because patients both with and without poor prognostic factors were treated with COBRA Slim, the CareRA data are suitable to compare treatment outcomes in the two risk groups on the same early intensive treatment. Despite the fact that our post-hoc analysis, as well as many other studies in this RA population, suffers from low sample size, our results suggest that seronegative RA cannot be considered a less severe disease and should also be treated early, intensively and to target. Our results are in line with the ones from the ARCTIC trial showing more initial inflammation in seronegative patients¹⁹ and delayed treatment response.²⁰ It should be noted that the importance given to autoantibodies as diagnostic and prognostic factors historically may have influenced doctors in daily clinical practice to undertreat this subgroup.²¹ Current EULAR recommendations focus on treating all patients early, intensively and to a target of sustained remission or at least low disease activity. They also expand the concept of poor prognosis to include more than just seropositivity for RF

and/or ACPA. According to current standards of care, treatment decisions should be based on disease activity, safety issues and other patient factors, such as comorbidities and progression of structural damage.³

3.6 CONCLUSION

CareRA participants with seronegative RA had initially a higher disease activity and longer time to first treatment response but achieved comparable remission status as seropositive patients with COBRA Slim. Early response (week 16) and not serological status, is the most important predictor for losing disease control, even after having achieved a first remission. It seems that seronegative RA requires at least an equally intensive initial treat-to-target therapy as seropositive RA.

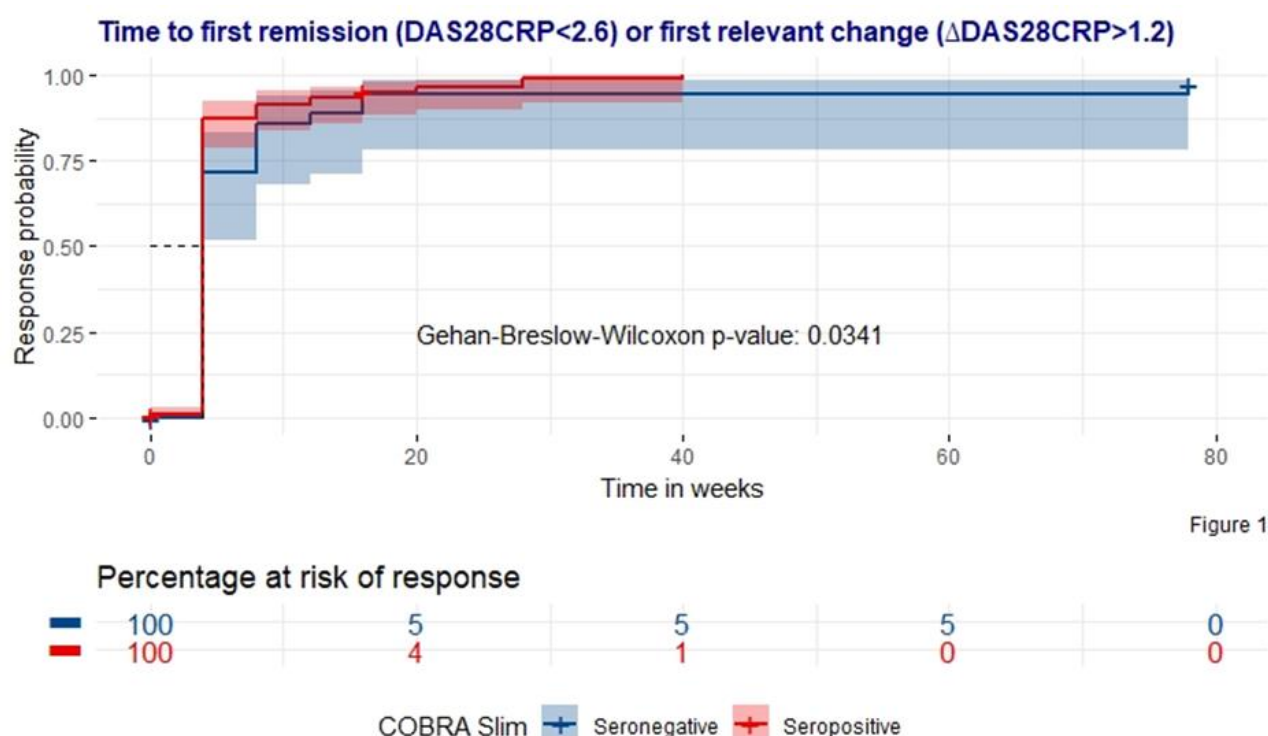
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SUPPLEMENTAL MATERIAL

Supplemental Figure 3-1: Kaplan Meier on time to first treatment response being either clinically relevant DAS28CRP improvement ($\Delta > 1.2$) or reaching remission ($\text{DAS28CRP} < 2.6$) in the “as observed” population of patients being treated with COBRA-Slim ($n=141$) in the CareRA trial.



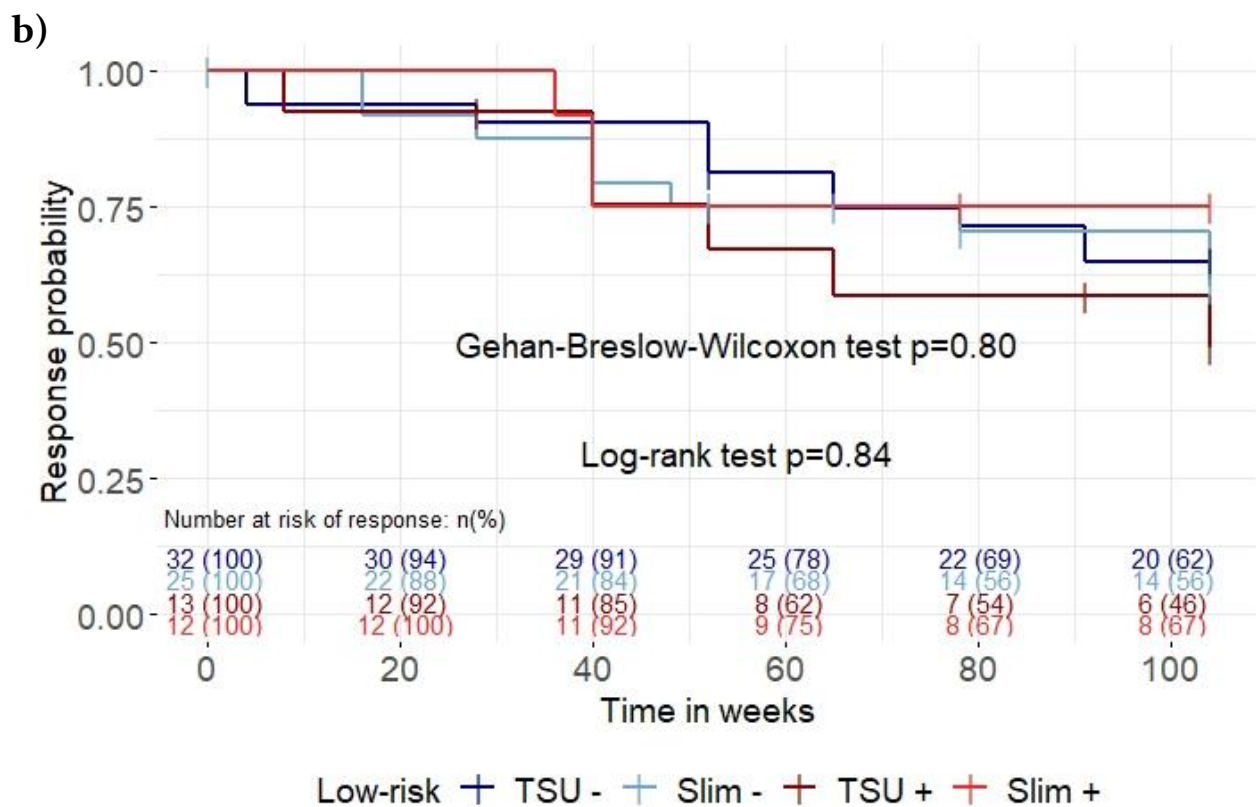
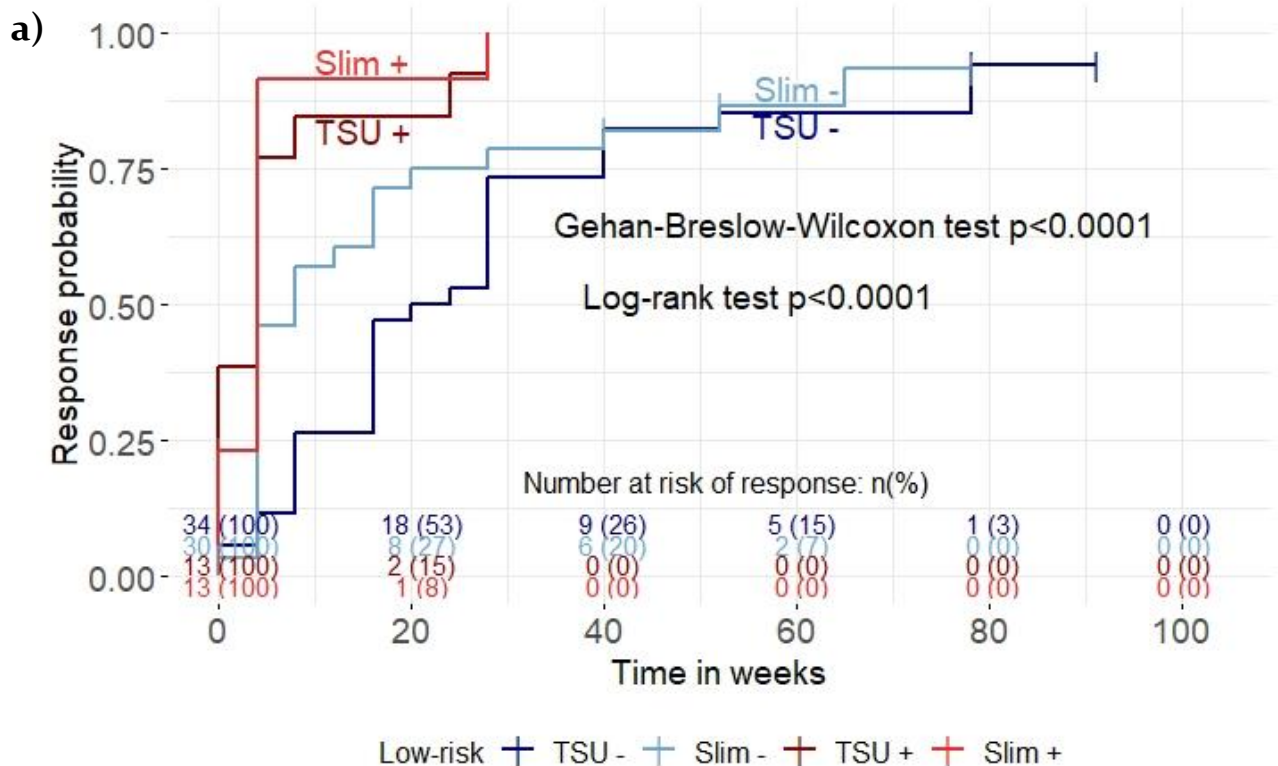
Supplemental Table 3-1: Univariate model estimates with each of the predicting covariates.

Predictors	Hazard Ratio	Lower 95%CI	Upper 95% CI	p-value	Likelihood ratio test	Model p-value
Seropositive	1.085	0.6629	1.776	0.750	54.26	0.001
DAS28CPR at baseline	1.197	1.023	1.400	0.025	50.31	0.0005
DAS28CPR at week 4	1.167	0.969	1.405	0.100	56.34	0.0005
DAS28CPR at week 8	1.329	1.083	1.630	<0.001	53.08	0.0002
DAS28CPR at week 16	1.763	1.422	2.185	<0.0001	45.58	0.0000009
Presence of erosions at baseline	0.9838	0.6092	1.589	0.950	54.95	0.001
Disease duration (weeks)	1.002	0.9964	1.008	0.45	26.71	0.0009
Female	0.7453	0.4949	1.122	0.16	51.81	0.0009
Current smoking	1.258	0.8234	1.922	0.290	52.58	0.001

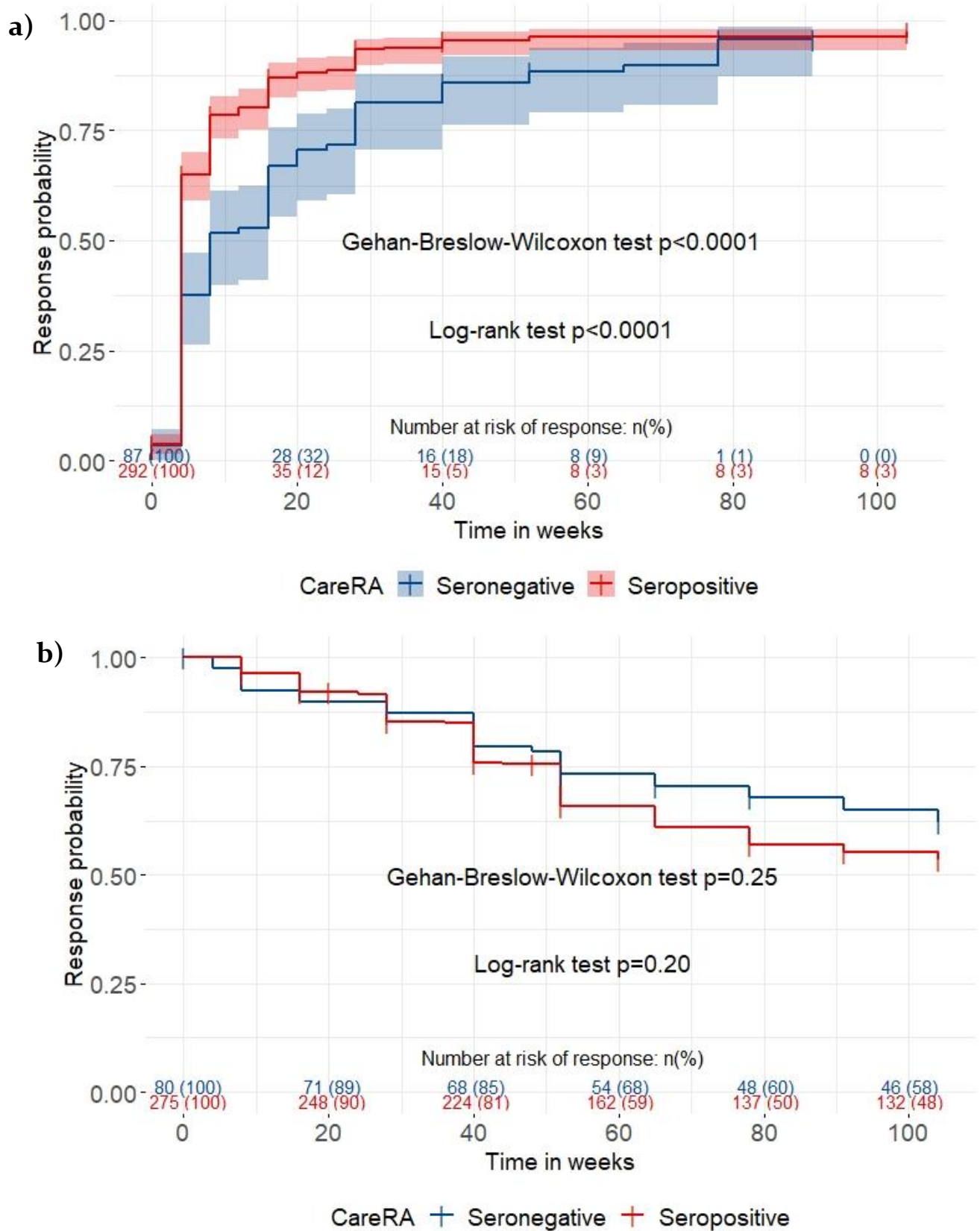
Supplemental Table 3-2: Frailty model estimates without outlier (Likelihood ratio test=25.79, 9 degrees of freedom, p=0.002)

Predictors	Hazard Ratio	Lower 95%CI	Upper 95%CI	p-value
Seropositive	1.523	0.923	2.513	0.10
DAS28CPR at baseline	1.058	0.897	1.248	0.50
DAS28CPR at week 4	1.001	0.796	1.260	0.99
DAS28CPR at week 8	1.073	0.824	1.398	0.60
DAS28CPR at week 16	1.678	0.299	2.169	0.00075
Presence of erosions at baseline	1.120	0.716	1.753	0.62
Disease duration (weeks)	1.001	0.996	1.006	0.74
Female	0.9979	0.672	1.483	0.99
Current smoking	1.029	0.680	1.559	0.89
Frailty (ID)				0.92

Supplemental Figure 3-2: Kaplan Meier survival curve for a) time of first remission ($DAS28CRP < 2.6$) in low-risk patients from the CareRA trial ($n=90$) and b) time of first loss of disease control ($DAS28CRP > 3.2$) after having reached the first remission in the same population ($n=82$).



Supplemental Figure 3-3: Kaplan Meier survival curve for a) time of first remission ($DAS_{28}CRP < 2.6$) in the entire CareRA study population ($n=379$) and b) time of first loss of disease control ($DAS_{28}CRP > 3.2$) after having reached the first remission in the same population ($n=355$).



Chapter 4.

How to measure the unobservable

A. Including pain, fatigue and physical function when assessing patients with early rheumatoid arthritis provides a comprehensive picture of disease burden*

4.1 ABSTRACT

Objective: To explore the possibility of integrating patient-important outcomes like pain, fatigue and physical function into the evaluation of disease status in early rheumatoid arthritis (ERA), without compromising correct disease activity measurement.

Methods: Patients from the 2-year Care in early Rheumatoid Arthritis (CareRA) trial were included. Pain and fatigue (visual analogue scales), Health Assessment Questionnaire (HAQ), standard components of disease activity (swollen/tender joint counts (SJC/TJC), C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR), Physician (Ph) and Patient's (Pa) global health (GH)) were recorded at every visit (n=10). Pearson correlation and exploratory factor analyses (EFAs), using multiple imputation (15 times) and outputation (1000 times), were performed per time point and overall, on standard components of disease activity scores with and without pain, fatigue and HAQ. Each of the 15 000 datasets was analysed with principal component extraction and oblimin rotation to determine which variables belong together.

Results: We included 379 patients. EFAs on standard composite score components extracted 2 factors with no substantial cross-loadings. Still, pain (0.83), fatigue (0.65) and HAQ (0.59) were strongly correlated with PaGH. When rerunning the EFAs with the inclusion of pain, fatigue and HAQ, the 2-factor model had substantial cross-loadings between factors. However, a 3-factor model was optimal, with Factor 1: Patient's

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assessment, Factor 2: Clinical assessment (PhGH, SJC and TJC), and Factor 3: Laboratory (ESR/CRP).

Conclusions: PaGH, pain, fatigue, and physical function represent a separate aspect of the disease burden of ERA patients that could be further explored as a target for care apart from disease activity.

4.2 INTRODUCTION

The primary clinical manifestation of Rheumatoid Arthritis (RA) is inflammation of the peripheral joints resulting in swelling, stiffness and pain. However, a wider range of symptoms can be present, including functional impairment and constitutional manifestations such as fatigue as well as global health impact.¹ This symptom heterogeneity may hinder easy diagnosis but also the evaluation of changes in disease status, which may complicate the management of RA patients (beyond modulating disease activity). In RA, unlike other diseases such as hypertension or diabetes, the severity or level of disease activity cannot be evaluated by a single clinical or laboratory measurement. Which is why, currently, the response to treatment is determined by evaluation of composite scores like the disease activity score in 28 joints (DAS28) or the simplified disease activity index (SDAI) being among the most commonly used in Europe.²

The level of disease activity in these scores is measured via clinical evaluation, Patient (PaGH) and physician (PhGH) assessments of global health in relation to RA disease activity rating from 0-10 or 0-100 on a visual analogue scale (VAS), as well as laboratory parameters of inflammation such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). The clinical evaluation includes the examination of tender (TJC) and swollen joints (SJC).¹ To facilitate the use of disease activity measures, thresholds of meaning have been defined, distinguishing: remission, low, moderate and high disease activity. Active disease is a predictor of damage and physical disability, and consequently with reduced health-related quality of life, increased costs and mortality.³ On this line, treating to a target (T2T) of remission or at least low disease activity (LDA) is widely advocated for RA.⁴

When evaluating comprehensively the impact of disease in clinical practice, physicians and patients are confronted with the difficulty to make an unambiguous distinction between aspects related to remaining disease activity requiring adaptation of pharmacological treatment and aspects requiring optimization of complementary forms of care. Unfortunately, even in patients in remission or LDA under current T2T treatment strategies, unmet needs or residual symptoms may persist and should be further explored. Among the most commonly reported remaining problems are pain, fatigue, morning stiffness, sleep disturbances, functional disability, impairment in mental health, work productivity and quality of life.⁵ Moreover, when patients are asked to define remission, pain, fatigue and independence have been identified as the most important factors.^{6,7} We hypothesized that including patient reported outcomes could capture some of these additional aspects of the disease experience independent from traditionally measured disease components. Therefore, we explored the possibility of integrating pain, fatigue and physical function into the evaluation of disease status, in addition to the standard components of composite disease activity scores, in early RA patients treated intensively and to target.

4.3 PATIENTS AND METHODS

Study population

Care in early Rheumatoid Arthritis (CareRA) was a 2-year open-label investigator-initiated pragmatic superiority trial (EudraCT number: 2008-007225-39, Clinical trials NCT01172639) conducted in 13 Flemish rheumatology centres (2 academic centres, 7 general hospitals and 4 private practices) in Belgium. The study was approved by the leading Ethics Committee of the University Hospitals Leuven after consulting the medical ethics committee of each

participating centre (ref s51411), and all study participants gave their written informed consent before inclusion.

Patients with recently diagnosed RA (≤ 1 year) were included and stratified into a high- or low-risk group based on classical factors of poor prognosis (erosions, rheumatoid factor (RF) and/or anti-citrullinated cyclic peptide (ACPA) positivity and baseline DAS28CRP > 3.2) and then randomized into four different treatment strategies. High-risk patients were randomized to methotrexate (MTX) 15mg weekly with a step-down glucocorticoid (GC) scheme (COBRA-Slim) or to this combination together with either sulphasalazine (COBRA-Classic) or leflunomide (COBRA-Avant-Garde). Low-risk patients were randomized to a step-up treatment of MTX monotherapy without GC (Tight Step-Up) or to COBRA-Slim.

For patients who did not respond sufficiently to the initial medication scheme, the protocol specified two subsequent treatment adaptation steps and afterwards treatment was left at the discretion of the treating rheumatologist. Details on patient eligibility criteria, randomization process, study design and treatment intensifications have been published.⁷ Overall, around 70% of the patients achieved a status of disease control after 2 years (DAS28CRP < 2.6).⁷

Study assessments

Clinical outcomes

Patients were assessed at screening, baseline and then followed-up at week 8, 16, 28, 40, 52, 65, 78, 91 and 104. Optional visits, if clinically required, could be performed. An electronic trial record (eCRF) was filled out and was routinely monitored. Clinical, patient and laboratory parameters were collected at every visit: SJC, TJC, PaGH -"Assuming all the ways your life is affected by your rheumatism, how did you feel on average over the past week?"-

, PhGH, CRP or ESR, health assessment questionnaire (HAQ), pain and fatigue each on a VAS of 0-100.

Statistical analyses

All randomized patients having taken at least one medication dose were considered for analysis. The data were considered hierarchical because the same patients were measured at different time points. To deal with this type of data, exploratory factor analysis for hierarchical data (EFA-HD) was performed. EFA-HD allows obtaining a general view of the factor structure of the variables, using data from all time points simultaneously while also avoiding violating the assumption of independent observations. The method described by Lovik, et al. was used.⁸ The EFA-HD consists of four steps: imputation, outputation, exploratory factor analysis (EFA), and combination of the analyses via congruence factor matching. A step by step flow-chart describing this methodology can be found in Figure 4-1.

Imputation

Missing data were assumed to be missing at random and were imputed with multiple imputation (classification and regression trees) by chained equations.⁹ Treatment strategy, the centre of recruitment, age, gender, presence of comorbidities, RF, ACPA, erosions at baseline and completion of the 2 year-trial were also taken into account when applying multiple imputation. Based on Bodner (2008), the number of imputed sets was set to 15, equal to the missing data percentage.¹⁰ Results of the 15 analyses were pooled using Rubin's rules.¹¹

Outputation

To obtain samples with independent observations, which is a requirement for exploratory factor analysis, multiple outputation (MO) was performed.^{12,13} MO was used for randomly selecting one observation from each visit from each patient, thereby creating a subset where all observations are independent of each other. To minimize loss of information, the technique was repeated 1000 times on each of the 15 multiply imputed datasets. Each of the 15000 datasets was analysed separately using exploratory factor analysis.

Exploratory factor analysis

EFA uncovers the fact that multiple observed variables have similar patterns of responses because they are all associated with a latent, not directly observable, variable. Direct oblimin rotation was selected because the factors were correlated. Rotation in factor analysis is needed because the factor solutions are not unique (several different mathematically equivalent solutions exist), and the rotation allows us to choose the one that is the easiest to interpret. The rotated factor loadings show the association between the variable and the latent factor.

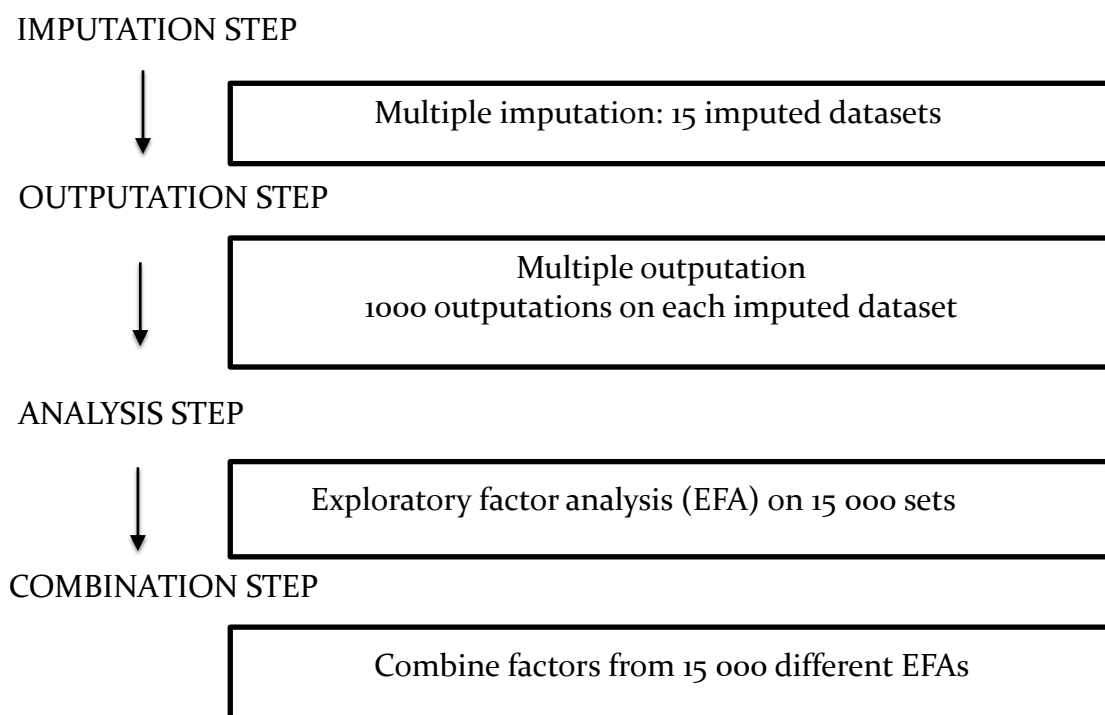
Combination of the results.

The 15 000 factor analytic results were then combined after re-ordering the factors by maximizing Tucker's factor congruence coefficient.¹⁴ Factor matching is a step in which congruent factors – factors with the same meaning in different analyses – are combined.⁸ The same analysis was performed on the standard components of disease activity scores only (SJC, TJC, PaGH, PhGH, CRP, ESR) and with the addition of pain, fatigue and physical function (HAQ). We also examined the possibility to leave out PaGH as standard patient derived component of disease activity scores in exchange of pain, fatigue and physical

function. Tucker's factor congruence coefficient was also used for estimating the similarity between factors that have been derived in different factor analyses to compare the final analytical results.¹⁴

On the 15 imputed datasets, Pearson correlations were also calculated to assess the strength of the association between all pairs of variables.

Figure 4-1: Flow chart of the different steps performed in exploratory factory analysis for hierarchical data.



Sensitivity analysis

A sensitivity analysis of EFA per visit without MO was also performed. In the sensitivity analysis, EFA was performed per time point (10 visits) on the variables that are standard components of composite scores only (SJC, TJC, PaGH, PhGH, CRP, ESR) and when including three extra variables: pain, fatigue and HAQ. These ten EFAs provide only information about the latent factors per time point, and obviously they are not useful to obtain a time-independent view of the disease status evaluation over the course of the disease process. All analyses were performed with R (version 3.5.3) and SAS 9.4.

4.4 RESULTS

In total, 379 patients with a mean (SD) age of 53.9 (13.0), 77% positive to RF or ACPA and 69% women, were included in CareRA of which 289 were stratified to high-risk and 90 to low-risk. The different EFAs based on the standard components of disease activity measurement instruments supported the traditional approach of composite scores extracting two factors with no substantial cross-loadings (<0.3) of the same variable on more than one factor (Table 4-1). This 2-factor model explained about 80% of the variance of the construct representing "disease activity" in the sense of the biological inflammatory process in peripheral joints.

Table 4-1: Exploratory factor analysis extracting 2-factor model with composite scores variables.

F1: Clinical	F2: Laboratory
PaGH: 0.72	CRP: 0.88
SJC28: 0.82	ESR: 0.77
TJC28: 0.87	
PhGH: 0.90	

Factor loadings presented (correlation between the observed score and the latent score). Cross-loadings were negligible (<0.3) -not presented. The factor order is by % of variance explained. F: factor, PaGH: Patient's global health assessment, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, SJC28: 28 swollen joint count, TJC28: 28 tender joint count, PhGH: physician's global health assessment

Still, pain (0.83), fatigue (0.65) and HAQ (0.59) were strongly correlated with PaGH (Table 4-2). When rerunning the EFAs including also these variables, the 2-factor model had substantial cross-loadings (≥ 0.3), meaning that the same variable was loading on more than one factor with variables also changing the factors in which they had primarily loaded (data not shown due to high number -1000- analyses).

Table 4-2: Pearson correlations of all measured variables after combining 15 000 datasets.

	CRP	ESR	SJC28	TJC28	PhGH	PaGH	Fatigue	Pain	HAQ
CRP	1								
ESR	0.464	1							
SJC28	0.292	0.319	1						
TJC28	0.247	0.271	0.756	1					
PhGH	0.228	0.293	0.680	0.679	1				
PaGH	0.204	0.231	0.403	0.470	0.564	1			
Fatigue	0.144	0.145	0.236	0.312	0.385	0.650	1		
Pain	0.193	0.219	0.394	0.465	0.570	0.834	0.632	1	
HAQ	0.209	0.263	0.407	0.464	0.492	0.588	0.430	0.572	1

Moderate (0.3-0.7) and strong (>0.7) correlations in **bold**

CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, SJC28: 28 swollen joint count, TJC28: 28 tender joint count, PaGH: Patient's global health assessment, PhGH: physician's global health assessment, HAQ: health assessment questionnaire

However, when a third factor clearly emerged, the so-called Patient's assessment factor, a straightforward interpretation was obtained. This first factor, extracted via principal component analysis, explained most of the variance. It included PaGH and the three new variables (pain, fatigue, HAQ), all being patient reported outcomes, so we designated it the Patient factor. Factor 2 contained SJC, TJC and PhGh, all being evaluated by the clinician, which we designated as the Clinical factor, and Factor 3 with CRP and ESR which we referred to as the Laboratory factor, for obvious reasons (Table 4-3). The three factors explained about 76% of the variance of the broader concept of "disease activity" which could also be called "disease burden" alluding to all the ways in which the disease process affects the patient.

Table 4-3: Exploratory factor analysis extracting 3-factor model with extended set of variables.

F1: Patient	F2: Clinical	F3: Laboratory
Fatigue: 0.90	SJC28: 0.92	CRP: 0.87
Pain: 0.86	TJC28: 0.89	ESR: 0.78
HAQ: 0.57	PhGH: 0.76	
PaGH: 0.87		

Factor loadings presented (correlation between the observed score and the latent score). Cross-loadings were negligible (<0.3) -not presented. The factor order is by % of variance explained.

F: factor, PaGH: Patient's global health assessment, HAQ: health assessment questionnaire, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, SJC28: 28 swollen joint count, TJC28: 28 tender joint count, PhGH: physician's global health assessment

While it is impossible to directly compare the factor analyses, the Tucker's congruence coefficient showed that the laboratory (0.99) and clinical assessment (0.87) factors were invariant -measure the same- for the six variables included in traditional disease activity composite scores.

The sensitivity analysis of EFAs per visit with the extended set of variables also showed high cross-loadings in the 2-factor model (Table 4-4). Again, if a 3-factor model emerged, there were no substantial cross-loadings over time (Supplemental Table 4-1). The cross-loadings were probably due to the lack of a simple factor structure in the 2-factor model with the extended set of variables. The 2-factor model, with only the standard components of composite disease activity scores, had no substantial cross-loadings over time (Supplemental Table 4-2).

We investigated the possibility to leave PaGH out of the model to evaluate to what extent this would decrease the explained variation in disease burden. Leaving out PaGH however destabilized the factor structure as HAQ was loading on both the Clinical and Patient factor (Supplemental Table 4-3).

Table 4-4: Exploratory factor analysis per time point extracting a 2-factor model with extended set of variables.

Timepoint	Week 0		Week 8		Week 16		Week 28		Week 40	
Variables	Clinical assessment	Laboratory assessment	Clinical assessment	Laboratory assessment	Clinical assessment	Laboratory assessment	Clinical assessment	Laboratory assessment	Clinical assessment	Laboratory assessment
CRP	-0.11	0.74	0.02	0.84	-0.03	0.70	0.01	0.80	-0.07	0.72
ESR	-0.05	0.71	-0.01	0.85	-0.06	0.55	0.04	0.76	-0.01	0.74
SJC28	0.07	0.80	0.60	0.11	-0.07	0.87	0.64	-0.23	0.41	0.19
TJC28	0.14	0.73	0.74	-0.04	0.13	0.70	0.79	-0.25	0.60	0.07
PaGH	0.90	0.04	0.87	-0.03	0.93	-0.01	0.82	0.20	0.85	0.09
Fatigue	0.85	-0.14	0.65	-0.01	0.81	-0.12	0.57	0.27	0.74	-0.04
PhGH	0.48	0.50	0.79	0.04	0.36	0.60	0.78	-0.86	0.60	0.26
Pain	0.94	-0.04	0.83	0.01	0.91	0.02	0.79	0.23	0.85	0.08
HAQ	0.62	0.26	0.74	-0.06	0.62	0.26	0.64	0.20	0.54	0.32
Timepoint	Week 52		Week 65		Week 78		Week 91		Week 104	
Variables	Clinical assessment	Laboratory assessment	Clinical assessment	Laboratory assessment	Clinical assessment	Laboratory assessment	Clinical assessment	Laboratory assessment	Clinical assessment	Laboratory assessment
CRP	-0.05	0.69	-0.01	0.84	-0.04	0.45	0.34	0.52	-0.05	0.65
ESR	-0.13	0.66	0.02	0.83	-0.19	0.55	0.05	0.54	-0.14	0.59
SJC28	0.10	0.72	0.61	0.98	0.15	0.70	0.11	0.40	0.07	0.74
TJC28	0.39	0.46	0.72	0.07	0.34	0.54	0.22	0.46	0.19	0.64
PaGH	0.90	0.03	0.84	-0.07	0.88	-0.01	0.86	0.06	0.87	0.34
Fatigue	0.83	-0.18	0.75	-0.12	0.82	-0.17	0.75	0.01	0.86	-0.15
PhGH	0.46	0.41	0.70	0.02	0.45	0.55	0.44	0.28	0.39	0.49
Pain	0.92	-0.10	0.84	-0.08	0.89	-0.02	0.83	0.87	0.85	0.07
HAQ	0.65	0.15	0.72	0.09	0.62	0.18	0.66	0.14	0.69	0.05

Factor loadings presented (correlation between the observed score and the latent score). Substantial cross-loadings (>0.3) have been highlighted in bold. The factor order is by % of variance explained. PaGH: patient's global health assessment, HAQ: health assessment questionnaire, CRP: c-reactive protein, ESR: erythrocyte sedimentation rate, SJC28: 28 swollen joint count, TJC28: 28 tender joint count, PhGH: physician's global health assessment.

4.5 DISCUSSION

By including relevant PROs to the standard measurements included in composite scores for evaluating disease activity in RA, a better understanding of the disease burden in terms of Patient's perceptions was obtained in this study. A 3-factor model including the new factor "patient perception" on top of "clinical assessment" and "laboratory assessment" gave the best representation of the disease status based on the extended set of variables. Because the original two factors remain in this 3-factor model, additional information is gained without losing the well-established Clinical and Laboratory factors.

Evaluating all the variables included in composite scores contributes to a more comprehensive evaluation than the classical question at an outpatient visit "how are you". The PaGH is put forward as a crucial component of composite disease activity scores, as it gives voice to the Patient, but it is also not unambiguous nor all-encompassing in this respect. However, there has been much debate about its interpretation and reliability.¹⁵ Adding to this controversy is the inconsistent phrasing of the question referring to this outcome, either all-encompassing global health or more specific disease activity related aspects.¹⁵ It could be argued that "Patient Global(PG)", "Patient Global Health(PaGH)" or "Patient Global Assessment (PGA) of disease activity" are not interchangeable. In CareRA, the question asked to patients alluded to the broad definition of patients' "global assessment".

The PaGH has been found to be influenced by factors not strictly related to disease activity such as pain, fatigue, and physical function.¹⁶ Pain was indeed strongly correlated to PaGH (0.83) in our cohort, similar as in other cohorts (0.86).¹⁷ PaGH, as an overarching evaluation of wellbeing by the patient, was more strongly correlated with pain, fatigue and HAQ respectively than these patient-reported outcomes were among each other, pairwise. This could indicate that PaGH, containing an objective judgement but also a personal and psychosocial appraisal, might act like a glue holding other patient reported variables in place within the model, possibly explaining the destabilizing effect of leaving out PaGH. Moreover, pain, fatigue and functional independence have been identified as the most critical factors when patients were asked to define remission.⁶ A clear understanding of what PaGH is measuring is key for accurate interpretation of the composite scores, including this outcome, appreciating its value but also its limitations.

By considering this as a separate factor along with other patient-important aspects such as pain, fatigue and physical function, we could demonstrate that PaGH indeed represents a different latent concept than the other two latent factors in our three-factor model, clinical evaluation and laboratory tests. The first latent factor was referring to what we could call the Patient's perception of "disease burden" alluding to all the ways in which the disease process affects the patient's perceived functioning and health and the latter two more directly to "disease activity" in the sense of the biological inflammatory process in peripheral joints.

While the 2-factor EFA focusses on aspects of "disease activity" the 3-factor EFA covers the more global "disease burden". A direct comparison of the 2- and 3-factor EFAs is not possible, but both analyses showed very clear factor structures with no relevant cross-loadings and very high primary-loadings. From a statistical perspective, both factor analytic models were satisfactory. Moreover, the 3-factor remained optimal when EFAs were performed per visit.

Based on the 3-factor analysis, a broader perspective of the patients' self-evaluation could be taken into account, including patient-important outcomes like pain, fatigue and physical function, while preserving the validity of the existing scale. This was demonstrated with the congruence coefficient, which indicates near-perfect congruence for the laboratory factor (0.99) and good congruence for the clinical factor (0.87). These factors thus have the same meaning in the 3-factor model as they do in the 2-factor and thus the information measured by these variables remains the same.

In turn, the 3-factor model could result in a more adequate estimation of the remaining disease burden, despite optimal control of disease activity, by evaluating the patient-important outcomes separately from the laboratory factor and the clinical factor and providing an opportunity for more appropriate personalized treatment according to Patient's needs. Complementary care options other than drug adaptations could be suggested to patients whose disease burden does not seem to be directly related to disease activity, for instance when the Patient-derived factor is clearly incongruent with the clinical as well as the laboratory factor. A more tailored or perhaps even dual-target might be needed for addressing the complete disease burden, making a distinction

between aspects directly related to inflammatory disease activity and impact of disease not directly related to disease activity.¹⁸

4.6 CONCLUSION

By including patient-relevant outcomes such as pain, fatigue and physical function besides PaGH to the standard components of disease activity scores, a more patient-centred estimation of the disease burden could be obtained and should be further explored as a target for care, in view of the further development of a more holistic care strategy without compromising accurate disease activity measurement needed for pharmacological targeting.

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SUPPLEMENTAL MATERIAL

Supplemental Table 4-1: Exploratory factor analysis per time point extracting a 3-factor model.

	Timepoints (weeks)									
	0	8	16	28	40	52	65	78	91	104
Variables	Factor 1:									
	Patient's assessment									
Fatigue	0.86	0.89	0.83	0.92	0.87	0.87	0.91	0.87	0.85	0.88
Pain	0.93	0.84	0.88	0.85	0.88	0.88	0.86	0.89	0.86	0.85
HAQ	0.59	0.61	0.61	0.58	0.52	0.64	0.50	0.56	0.65	0.63
PaGH	0.90	0.88	0.92	0.86	0.88	0.87	0.86	0.87	0.85	0.89
	Factor 2:									
	Clinical assessment									
SJC28	0.93	0.93	0.88	0.89	0.93	0.88	0.89	0.87	0.85	0.90
TJC28	0.93	0.86	0.86	0.81	0.73	0.75	0.76	0.80	0.82	0.83
PhGH	0.64	0.67	0.72	0.73	0.65	0.76	0.78	0.66	0.62	0.54
	Factor 3:									
	Laboratory assessment									
CRP	0.89	0.84	0.73	0.85	0.83	0.83	0.87	0.80	0.84	0.77
ESR	0.89	0.85	0.90	0.87	0.84	0.85	0.86	0.81	0.81	0.86

Factor loadings presented (correlation between the observed score and the latent score).

Cross-loadings were negligible (<0.3) -not presented. The factor order is by % of variance explained.

PaGH: patient's global health assessment, HAQ: health assessment questionnaire, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, SJC28: 28 swollen joint count, TJC28: 28 tender joint count, PhGH: physician's global health assessment

Supplemental Table 4-2: Exploratory factor analysis per time point extracting a 2-factor model with only composite score variables.

Variables/ Timepoints (weeks)	Factor 1: Clinical assessment										Factor 2: Laboratory assessment									
	0	8	16	28	40	52	65	78	91	104	0	8	16	28	40	52	65	78	91	104
CRP											0.90	0.83	0.77	0.87	0.83	0.80	0.86	0.79	0.84	0.76
ESR											0.87	0.86	0.89	0.85	0.83	0.85	0.84	0.79	0.79	0.87
SJC28	0.83	0.81	0.69	0.75	0.79	0.68	0.79	0.74	0.71	0.77										
TJC28	0.86	0.89	0.84	0.87	0.82	0.80	0.81	0.79	0.76	0.80										
PaGH	0.65	0.67	0.65	0.68	0.64	0.69	0.70	0.64	0.57	0.65										
PhGH	0.89	0.86	0.88	0.84	0.80	0.81	0.81	0.82	0.76	0.72										

Factor loadings presented (correlation between the observed score and the latent score). Cross-loadings were negligible (<0.3) -not presented. The factor order is by % of variance explained.

PaGH: patient's global health assessment, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, SJC28: 28 swollen joint count, TJC28: 28 tender joint count, PhGH: physician's global health assessment

Supplemental Table 4-3: Exploratory factor analysis extracting 3-factor model with extended set of variables, but without patient's global health assessment.

Variables	Factor 1: Clinical assessment	Factor 2: Patient's assessment	Factor 3: Laboratory assessment
HAQ	0.32	0.55	0.04
Pain	0.20	0.79	0.01
TJC 28	0.88	0.05	-0.01
SJC 28	0.94	-0.12	0.04
CRP	-0.11	0.04	0.90
PhGH	0.77	0.21	-0.03
Fatigue	-0.14	0.93	0.02
ESR	0.19	-0.03	0.75

Factor loadings presented (correlation between the observed score and the latent score). Substantial cross-loadings (>0.3) have been highlighted in bold.

PaGH: patient's global health assessment, HAQ: health assessment questionnaire, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, SJC28: 28 swollen joint count, TJC28: 28 tender joint count, PhGH: physician's global health assessment.

B. Traditional treatment response measures do not necessarily match patient reported improvement, even in early Rheumatoid Arthritis.*

4.1 ABSTRACT

Objective: To test if co-evaluation of 3 separate aspects of disease status –patient-reported (PRF), clinical (CF) and laboratory (LF) factors- could facilitate multidimensional evaluation of treatment response and prediction of future disease impact in early RA.

Methods: Patients from the 2-year CareRA trial were included. Three factors representing disease status were previously identified using exploratory factor analysis (EFA): PRF (Patients global health, pain, fatigue and HAQ), CF (Physician's global health, tender (TJC) and swollen (SJC) joint count), and LF (CRP and ESR). PRF, CF and LF scores were calculated by summing up their components. Differences in percentage (%) improvement (baseline-week(w)₁₀₄) and area under the curve (AUC) across time points per factor score were compared between patients achieving or not early and sustained (w₁₆-w₁₀₄) remission (DAS₂₈CRP <2.6) by ANOVA with Bonferroni correction. A discordance score between the PRF and the other two scores as a measure of the mismatch between patient-reported and other representations of disease impact was tested for associations with future health status using Spearman correlations, Kruskal-Wallis tests and mediation analysis.

Results: Patients with early RA were treated to target with COBRA-like schemes (n=332) or MTX monotherapy (n=47). PRF, CF and LF scores improved rapidly over the first 8 weeks. In patients achieving sustained remission (n=122) PRF score improved 59% with an

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AUC of 15.6, CF 90% (AUC 3.4) and LF 10% (AUC 4.8), compared to 33% (AUC 33.2), 78% (AUC 10.1) and 10% (AUC 7.2) respectively, in patients not achieving sustained remission (n=257) ($p<0.01$ for PRF and $p<0.001$ for CF score improvement, and $p<0.001$ for all AUC). The discordance score was associated with factor scores at later time points and had a mediating effect on the relation of DAS28CRP with any future PRF, but not with CF and inconsistent for LF.

Conclusions: PRF, CF and LF scores improved rapidly over time in patients achieving early and sustained disease control. However, overall, PRF seemed not to improve to the same extent as CF. Looking at the difference between the PRF score and CF/LF scores does provide further insight, potentially helpful for future treatment.

KEY MESSAGES

What is already known about this subject?

- Early and intensive RA drug-treatment using disease activity as a target allows rapid disease control and prevents joint destruction.

What does this study add?

- Including pain, fatigue and physical function to monitor patients with early RA broadens disease status evaluation and may suggest additional domains for specific interventions.

How might this impact on clinical practice or future developments?

- A better understanding of the broader disease impact from the patient's perspective could lead to effective interventions other than drug adjustments, specifically targeting aspects not directly related to disease activity.

4.2 INTRODUCTION

The primary clinical manifestation of Rheumatoid Arthritis (RA) is inflammation of the peripheral joints resulting in swelling, stiffness and pain.² However, more constitutional symptoms such as fatigue, pain, stiffness, restricted ability to work, and impact on other aspects of health related quality of life can be present.³ Symptom heterogeneity sometimes hinders timely diagnosis and complicates recognition of changes in disease status. Treating early to a target of remission or at least low disease activity is highly advocated,⁴ especially since this treatment strategy aims to improve long term patient outcomes.⁵

The guidelines from the European League Against Rheumatism recommend treatment aimed at reaching a target of sustained remission or low disease activity (LDA). Specific instruments are used to define remission or LDA.⁴ The ACR/EULAR Boolean remission criterion is stringent requiring swollen/tender joint counts (SJC/TJC) to be below or equal to 1, C-reactive protein (CRP) < or equal to 1mg/dL and Patient's global health (PaGH) < or equal to 1 (0-10 scale). When using this criterion for remission, it has been shown that one-third of RA patients fail to reach remission solely because of PaGH (near-remission).⁶ If the current treatment recommendations would be followed,⁴ this state of near-remission, could lead to an adaptation of immunosuppressive therapy, even if the PaGH reflects needs that are not related to inflammation. Hence, disease burden as reported by the patient might not only be mediated by disease activity. Unmet needs conceived in the PaGH and their relative importance should be uncovered when aiming to reduce the broader disease impact of RA.

Using factor analysis we previously showed on data from the CareRA trial that adding pain, fatigue, and physical function to the variables in composite disease activity scores, provides additional information about the broader disease impact on top of the assessment of

disease activity (Chapter 4.A)¹. We hypothesized that the co-evaluation of 3 separate aspects of the evolving disease status in early RA -patient-reported factors (PaGH, pain, fatigue and physical function), clinical factors (PhGH, TJC and SJC) and laboratory factors (CRP and ESR)- could lead to a more multidimensional evaluation of the early response to therapy, avoiding overestimation of remaining disease activity while at the same time quantifying other unmet needs potentially requiring complementary interventions. This broader view might also facilitate prediction of the future health status. We aimed to test this hypothesis in the CareRA population.

4.3 PATIENTS AND METHODS

CareRA was a 2-year open-label investigator-initiated pragmatic superiority trial (EudraCT number: 2008-007225-39) conducted in 13 Flemish rheumatology centres (2 academic centres, 7 general hospitals and 4 private practices).

Study population

Patients with recently diagnosed RA (≤ 1 year) were included and stratified into a high- or low-risk group based on classical factors of poor prognosis (erosions, rheumatoid factor (RF) and/or anti-citrullinated cyclic peptide (ACPA) positivity and baseline disease activity score in 28 joints with C-reactive protein (DAS28CRP) > 3.2) and then randomised into four different treatment arms. High-risk patients were randomised to methotrexate (MTX) 15mg weekly with a step-down glucocorticoid (GC) scheme or to this combination together with either sulphasalazine or leflunomide. Low-risk patients were randomised to a tight step-up treatment of MTX monotherapy without GC or to MTX with step-down GCs. Overall, around 70% of the patients achieved a status of good disease control after 2 years (DAS28CRP < 2.6) with a treat-to-target approach.⁷

Clinical outcomes

Clinical, patient and laboratory parameters were collected in an electronic case report form (eCRF) at every visit and routinely monitored: swollen (SJC28) and tender joint (TJC28) count in 28 joints, patient's global health assessment (PaGH), physician's global health assessments (PhGH), C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR), Health Assessment Questionnaire (HAQ), pain and fatigue each on a visual analogue scale (VAS) of 0-100. Assessments at baseline, week 16, 52, and 104 were used in this post-hoc analysis.

Statistical analyses

All randomised patients having taken at least one medication dose were considered for intention to treat (ITT) analysis. Missing data were assumed to be missing at random and were imputed with multiple imputation (classification and regression trees) by chained equations.⁸ Missing clinical variables used to estimate disease activity per time point were imputed as well as VAS pain. Besides the incomplete variables, treatment strategy, centre of recruitment, age, gender, presence of comorbidities, RF, ACPA, erosions at baseline and trial completion were included as predictors in the imputation matrix. Based on Bodner (2008), the number of imputed sets was set to 15, equal to the missing data percentage.⁹ Results of the 15 analyses were pooled using Rubin's rules.¹⁰

Factor derived scores

Previously, three factors representing the health status of early RA patients were identified using exploratory factor analysis (EFA) on nine variables (all standard components of disease activity scores plus pain, fatigue and HAQ), for more details see Pazmino *et al.*¹ The identified factors were: Patient-Reported factor (PRF; PaGH, pain, fatigue and HAQ), Clinical factor (CF; PhGH, TJC and SJC), and Laboratory factor (LF; CRP and ESR). In the

current study we explored if a quantitative co-evaluation of these three factors over time could facilitate a multidimensional evaluation of the early response to therapy in early RA. Factor loadings, which represent how strong a variable relates to its factor, from the EFAs were used as weights to correct for the relative contribution of individual variables to their corresponding latent factor. The scores of the individual variables were normalized to a 0-1 scale considering clinically feasible maximum and minimum. Afterwards, the normalized scores were multiplied -weighted- by the factor loadings to calculate PRF (PGA -0.86-, pain -0.86-, fatigue -0.90-, HAQ-0.50), CF (SJC28 -0.92-, TJC28-0.89-, PhGH-0.76-) and LF (CRP-0.87-, ESR-0.78-) scores (higher values suggesting more burden). Because the number of variables was different for each factor, the PRF, CF and LF factor scores were also re-scaled to 0-1. Thus, for each patient three factor scores per visit were obtained.

Rate of improvement

Next, the percentage (%) of improvement from baseline to week 104 and the area under the curve (AUC) across time points were calculated per score. Differences in % improvement and AUC were compared between patients not achieving and achieving early and sustained (week 16 to week 104) disease activity score remission (DAS28CRP <2.6) with ANOVA. Bonferroni correction was used for multiple testing. We chose to look at patients achieving early and sustained remission as a surrogate for “good responders” in whom we expected there would be less disease burden.^{11,12}

Discordance score

A discordance score for the PRF and CF/LF factor scores was calculated by subtracting the mean of the other two factor scores from the PRF score:

$$Discordance_score = Patientreportedfactor - \left(\frac{Clinicalfactor + Laboratoryfactor}{2} \right)$$

The higher this discordance score, the more the impact of disease as experienced by the patient is not addressed by traditional measures of disease activity. Correlations between all three factor-scores and their difference at baseline, week 16, 52, and 104 were calculated to evaluate if later scores for PRF, CF and LF could be estimated based on discordance scores at earlier time points. We chose to use the discordance scores because by looking at this difference we have the advantage of having one predictor instead of three. Besides, a discordance score accounts for intra-individual difference between factor scores and avoids collinearity. Basically, we expected the discordance score to allow us to predict future burden. Due to the skewed distribution of the factor scores, Spearman correlations were used. Since no clinically relevant cut-off was available yet for these factor scores, four equally large groups were created depending on the factor score quartile (Q) to facilitate comparisons over time.

To evaluate if the discordance score at an earlier visit would be significantly discrepant compared to the factor scores at the next visit, we used Kruskal-Wallis test. First, the discordance scores were calculated for baseline, week 16 and 52. With these results four equally large groups were created depending on their quartile (Q) per time point evaluated. Next, the factor scores at week 16, 52 and 104 were calculated. Kruskal-Wallis test was used for comparing the baseline discordance score to the factor scores at week 16. Further comparisons included the discordance score at week 16 in relation to factor scores at week 52 and 104, and finally the discordance score at week 52 compared to factor scores at week 104.

Sensitivity analysis

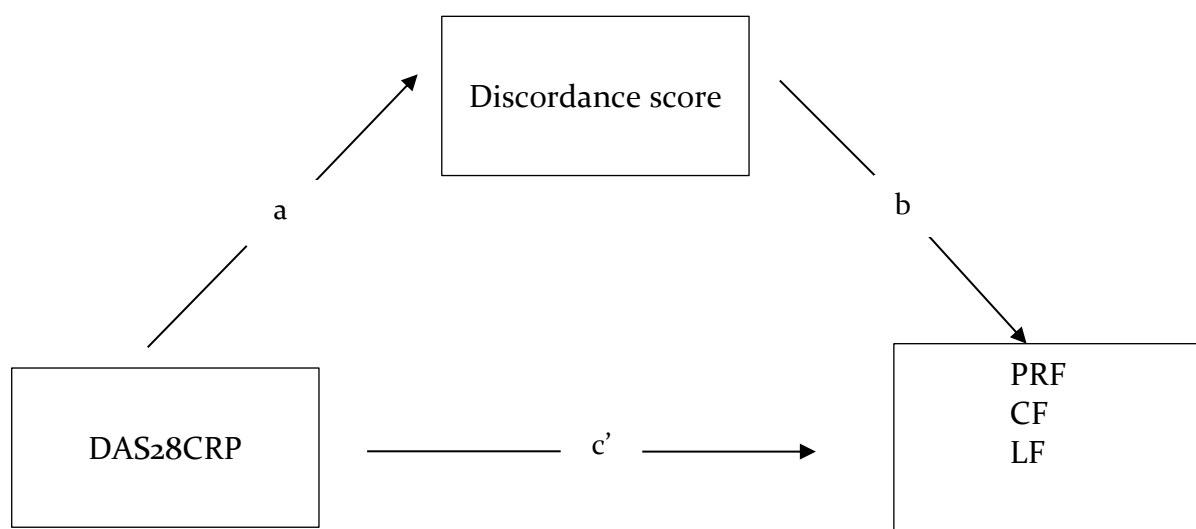
The evaluation of the relationship between the discordance score at an earlier time point with PRF, CF and LF at a later time point was also performed dividing the population into patients achieving or not sustained remission (DAS28CRP <2.6 from week 16 to week 104).

Mediation analysis

A regression is fitted for DAS28CRP at a previous time point being baseline, week 16 and 52 over PRF, CF and LF at a future time point being week 16, 52 and 104. Another regression is fitted between DAS28CRP and the discordance score and finally a multiple regression is fitted between the DAS28CRP and discordance score over PRF, CF and LF. This postulated mediation analysis is described in Figure 4-2. Confidence intervals were estimated via 1000 bootstraps.

All analyses were performed with R V.4.0.0 and SPSS 26.

Figure 4-2: Postulated Mediation Path Model.



DAS28CRP=disease activity score in 28 joints, PRF= Patient reported factor,
CF= Clinical factor, LF=Laboratory factor

4.4 RESULTS

Patients with early RA (n=379) were included with a mean (SD) age of 53.9 (13.0), 77% positive to RF or ACPA and 69% women of which 289 were stratified to the high-risk and 90 to low-risk group. PRF, CF and LF factor scores improved rapidly over the first 8 weeks (Figure 4-3a).

Rate of improvement

From baseline to week 104 the scores improved 41%, 78% and 10% for the PRF, CF and LF respectively in the entire population (n=379), 59%, 90% and 27% in patients achieving sustained remission (n=122), and 33%, 78% and 10% in patients not achieving sustained remission (n=257). There was a significant difference in PRF ($p<0.01$) and CF ($p<0.001$) but not for LF between patients in sustained and not sustained remission.

Patients in CareRA had an AUC of 27.4, 7.9 and 6.4 for PRF, CF, LF scores respectively in the overall population. Those who achieved sustained remission had an AUC of 15.6, 3.4 and 4.8 for the PRF, CR and LF scores respectively, compared to 33.2, 10.1, and 7.2 in participants not achieving sustained remission ($p<0.001$ for all improvements between patients in sustained and not sustained remission). (Figure 4-3b) As can be seen in Figure 4-3 and Table 4-5 the PRF score had higher values at all times, compared to its counterparts, the CF and LF scores, which were rather similar. There was a discrepancy in the evolution of the three factor scores which alludes to the rationale for using a discordance score.

Discordance score

The Spearman correlations, as illustrated in Figure 4-4, indicated a strong relationship between the discordance scores at an early stage and factor scores at a later time point,

suggesting that later scores could be estimated based on discordance scores at earlier time points.

The evaluation of the discordance score at an earlier visit as determinant of any of the factor scores at the next visit using Kruskal-Wallis test is presented in Table 4-6. The discordance scores at each of the previous visits, depending on the quartile, were statistically significantly different from the median PRF scores at the future time points ($p < 0.0001$ for all comparisons). For the CF, the difference was mostly in the first (Q₁) and fourth (Q₄) quartile of the discordance scores. Sensitivity analyses on the subgroups of patients who reached/did not reach sustained remission were similar and led to the same conclusions and were therefore not reported.

Mediation analysis

The mediation analysis showed that the discordance score mediated the effect of DAS28CRP on any future PRF. (Table 4-7). On the other hand, there was no mediation effect of the discordance score in the prediction of the CF and there was an inconsistent mediation effect when predicting the LF.

Figure 4-3: Mean factor score evolution over the 2-year CareRA trial for a. the entire population and b. divided in the ones achieving sustained remission or not ($DAS28CRP < 2.6$).

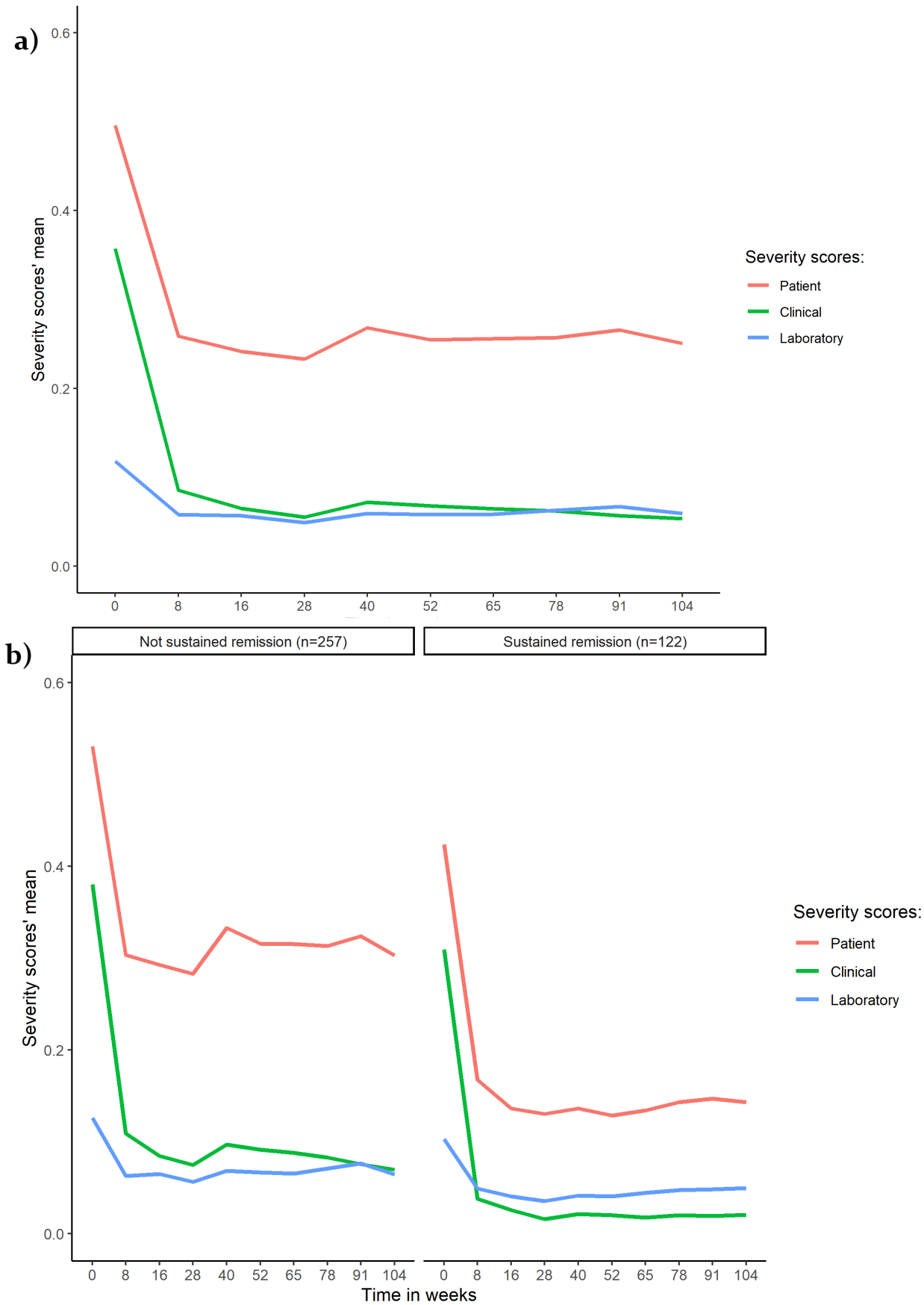
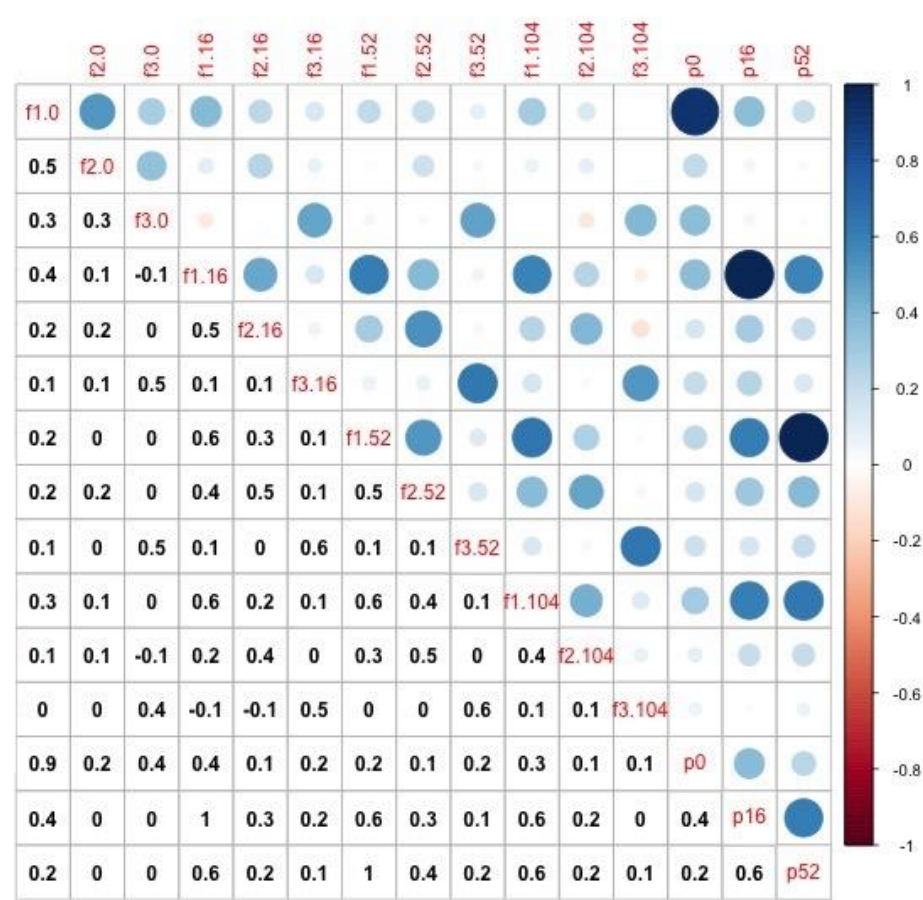


Table 4-5: Mean factors per time point on the total population and in the patients achieving and not sustained remission (DAS28CRP<2.6 from week16 to week 104).

CareRA population (n=379)										
Factor	Week									
	0	8	16	28	40	52	65	78	91	104
Patient	0.50	0.26	0.24	0.23	0.27	0.25	0.26	0.26	0.27	0.25
Clinical	0.36	0.09	0.07	0.06	0.07	0.07	0.06	0.06	0.06	0.05
Laboratory	0.12	0.06	0.06	0.05	0.06	0.06	0.06	0.06	0.07	0.06
Discordance score	0.26	0.19	0.18	0.18	0.21	0.19	0.20	0.20	0.21	0.20
Non-sustained remission (n=257)										
Factor	Week									
	0	8	16	28	40	52	65	78	91	104
Patient	0.53	0.30	0.29	0.28	0.33	0.32	0.32	0.31	0.32	0.30
Clinical	0.38	0.11	0.08	0.07	0.10	0.09	0.09	0.08	0.08	0.07
Laboratory	0.13	0.06	0.06	0.06	0.07	0.07	0.07	0.07	0.08	0.06
Discordance score	0.28	0.22	0.22	0.22	0.25	0.24	0.24	0.24	0.24	0.24
Sustained remission (n=122)										
Factor	Week									
	0	8	16	28	40	52	65	78	91	104
Patient	0.42	0.17	0.14	0.13	0.14	0.13	0.13	0.14	0.15	0.14
Clinical	0.31	0.04	0.03	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Laboratory	0.10	0.05	0.04	0.04	0.04	0.04	0.04	0.05	0.05	0.05
Discordance score	0.22	0.13	0.11	0.10	0.11	0.10	0.10	0.11	0.12	0.11

Figure 4-4: Spearman correlations of the factor scores at baseline, week 16, 52, and 104 and the discordance scores.



f1: Patient-reported factor .0: baseline
f2: Clinical factor .16: week 16
f3: Laboratory factor .52: week 52
p: discordance score .104: week 104

The color scheme for the correlations goes from -1 (red) to +1 (blue) and is a colored representation of the strength of each correlation, same as with the size of the mark.

Table 4-6: Pairwise comparisons of Patient Reported, Clinical and Laboratory Factor scores based on the quartile of discordance scores at previous visits with non-parametric Kruskal-Wallis test.

Factor scores	Test statistic Kruskal-Wallis test	p-value	Significant pairwise differences (correcting for multiplicity)
Week 16 factor score		←	Baseline discordance score quartile
Patient reported	51.317	p < 0.0001	Q1-Q3, Q1-Q4, Q2-Q3, Q2-Q4
Clinical	8.895	p = 0.031	Q1-Q4
Laboratory	18.086	p < 0.0001	Q1-Q4, Q2-Q4
Week 52 factor score		←	Week 16 discordance score quartile
Patient reported	134.058	p < 0.0001	Q1-Q2, Q1-Q3, Q1-Q4, Q2-Q3, Q2-Q4, Q3-Q4
Clinical	38.835	p < 0.0001	Q1-Q3, Q1-Q4, Q2-Q3, Q2-Q4
Laboratory	8.645	p = 0.034	None
Week 104 factor score		←	Week 16 discordance score quartile
Patient reported	126.368	p < 0.0001	Q1-Q2, Q1-Q3, Q1-Q4, Q2-Q3, Q2-Q4
Clinical	16.863	p = 0.001	Q1-Q3, Q1-Q4
Laboratory	6.779	p = 0.079	None
Week 104 factor score		←	Week 52 discordance score quartile
Patient reported	133.901	p < 0.0001	Q1-Q2, Q1-Q3, Q1-Q4, Q2-Q3, Q2-Q4
Clinical	15.515	p = 0.001	Q1-Q4
Laboratory	7.912	p = 0.048	None

Q1= first quartile, Q2= second quartile, Q3= third quartile, Q4= fourth quartile

Table 4-7: Mediation analysis (* $p < 0.05$)

Timepoint	Predictor variables	Effect	95% CIs	R squared	Mediation effect of discordance factor score
Patient reported factor					
Week 16	DAS28CRP at baseline	-0.0091	-0.0240, 0.0058	0.1450	Present
	Discordance score at baseline	0.0246*	0.0169, 0.0331	0.1784	
Week 52	DAS28CRP at week 16	0.0215*	0.0010, 0.0419	0.3394	Partial
	Discordance score at week 16	0.0580*	0.0442, 0.0739	0.2749	
Week 104	DAS28CRP at week 16	0.0101	-0.0102, 0.0305	0.2798	Present
	Discordance score at week 16	0.0528*	0.0396, 0.0686	0.2749	
	DAS28CRP at week 52	0.0260*	0.0067, 0.0454	0.3558	Partial
	Discordance score at week 52	0.0577*	0.0429, 0.0754	0.3732	
Clinical factor					
Week 16	DAS28CRP at baseline	0.0153*	0.0074, 0.0232	0.0599	Absent
	Discordance score at baseline	0.0019	-0.0010, 0.0048	0.1784	
Week 52	DAS28CRP at week 16	0.0365*	0.0267, 0.0463	0.1944	Absent
	Discordance score at week 16	0.0034	-0.0031, 0.0095	0.2749	
Week 104	DAS28CRP at week 16	0.0115*	0.0024, 0.0207	0.0409	Absent
	Discordance score at week 16	0.0033	-0.0019, 0.0089	0.2749	
	DAS28CRP at week 52	0.0243*	0.0154, 0.0333	0.0947	Absent
	Discordance score at week 52	-0.0019	-0.0087, 0.0037	0.3732	
Laboratory factor					
Week 16	DAS28CRP at baseline	0.0063*	0.0015, 0.0111	0.0634	Partial
	Discordance score at baseline	0.0030*	0.0012, 0.0050	0.1784	
Week 52	DAS28CRP at week 16	0.0003	-0.0063, 0.0068	0.0305	Present

Week 104	Discordance score at week 16	0.0051*	0.0012, 0.0096	0.2749	
	DAS28CRP at week 16	-0.0007	-0.0079, 0.0064	0.0014	
	Discordance score at week 16	0.0013	-0.0019, 0.0046	0.2749	Absent
	DAS28CRP at week 52	0.0067	-0.0004, 0.0139	0.0149	Absent
	Discordance score at week 52	0.0001	-0.0045, 0.0046	0.3732	

4.5 DISCUSSION

The Patient Reported, Clinical- and Laboratory Factor scores improved rapidly over time in a treat-to-target setting. However, overall, Patient reported disease burden seemed not to improve to the same extent as Clinically evaluated impact. In fact, Patient reported factor scores remained in most cases higher than either Clinical or Laboratory factor scores in nearly all patients. The discordance score, which reflects the difference between the PRF score and CF/LF scores, was strongly associated with the health impact measured at later visits, especially for PRF scores. This relationship means that assessing the discordance may be used as a warning system for the clinician since it predicts the future Patient reported and Clinically evaluated health status. However, for the Clinically evaluated disease burden, the difference was mostly in what could be considered the “low discordance” (Q1) and “high discordance” (Q4) quartiles of this score. It appears that only the absence of or extreme discrepancy between PRF and CF/LF is predictive of the future health status as evaluated clinically

In this analysis, we chose to cut the patients into four approximately equal groups based on their discordance scores, in other words, we did not use optimal cut-off points. Despite this limitation, we found significant differences between these groups with regards to their factor scores at later time points. Generally speaking, belonging to a group with higher

difference between the Patient reported and the other factor scores is associated with higher patient reported disease burden at later time points. A limitation of this current study is the lack of effect size estimation. Due to the unusual distribution of the factor scores (Supplemental Figure 4-1), simple regression models could not be used to predict them. Both the definition of optimal cut-offs and finding an appropriate prediction model requires further research. However, the mediation analysis showed that the discordance score had a mediating effect for PRF, when using the DAS28CRP for predicting future burden of PRF, CF and LF. Ultimately the impact of addressing these findings should be further explored in a properly designed prospective study.

4.6 CONCLUSION

Patient's unmet needs in terms of pain, fatigue, physical function and overall well-being should be given more attention, even in patients in sustained remission. Looking at the difference between the Patient factor score and the Clinical and Laboratory scores does provide further insights allowing to broaden the future scope of treating-to-target, potentially to non-pharmacological interventions.

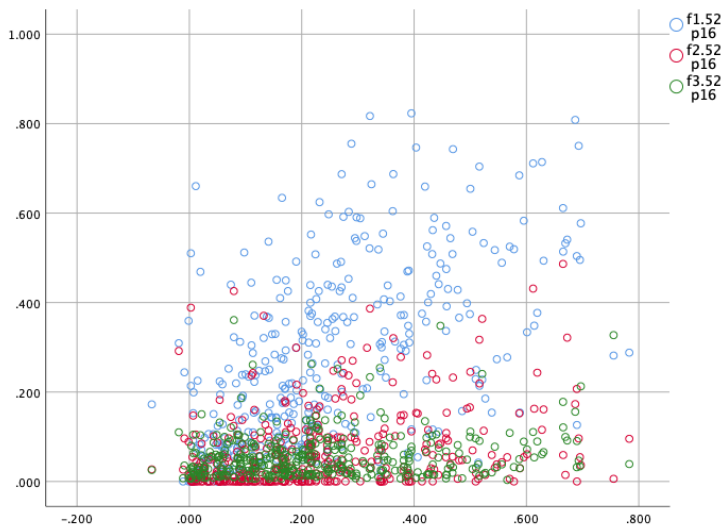
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SUPPLEMENTAL MATERIAL

Supplemental Figure 4-1: Scatterplots of the relationship between factor scores (Patient-reported, Clinical and Laboratory) and the discordance score for the Patient-reported minus the Clinical/Laboratory factor scores at later versus earlier time points.



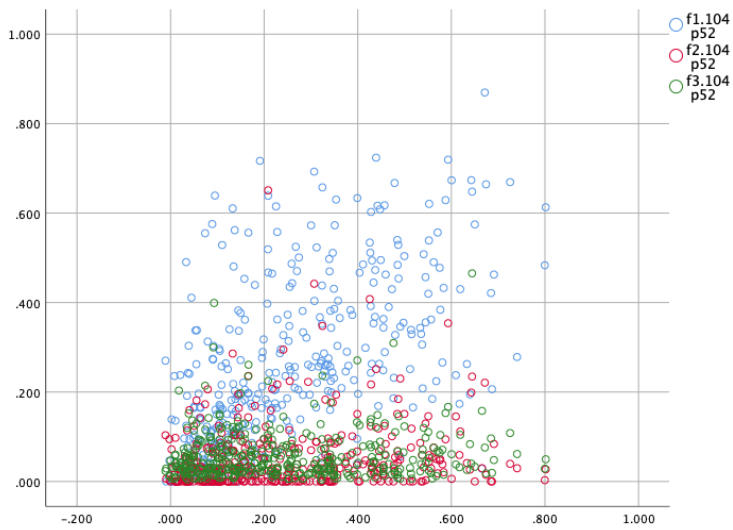


f1.52: Patient-reported score at week 52

f2.52: Clinical score at week 52

f3.52: Laboratory score at week 52

p16: discordance score at week 16



f1.104: Patient-reported score at week 104

f2.104: Clinical score at week 104

f3.104: Laboratory score at week 104

p52: discordance score at week 52

Chapter 5.

Painful RA

A. Is there a window of opportunity for optimal pain management in RA: lessons from the CareRA trial?.*

5.1 ABSTRACT

Objective: To explore chronic analgesic use on top of a remission induction scheme in early Rheumatoid Arthritis (RA)

Methods: Patients (n=379) from the 2-year CareRA trial with early RA (≤ 1 year) were included, all treated to target with different csDMARD combinations with or without prednisone. Chronic intake (≥ 90 days) of narcotic and non-narcotic analgesics, and antidepressants specifically prescribed for musculoskeletal pain as daily intake were considered. Patterns in drug intake, reported pain (VAS) and disease activity (DAS28CRP; ACR/EULAR Boolean remission with or without patient global assessment) were detailed and compared with non-chronic users.

Results: Of 379 patients included in the CareRA trial, 336 were at any point using an analgesic with any duration and 283 for musculoskeletal pain. Chronic use of analgesics for musculoskeletal pain was documented in 105 patients. These had a statistically higher (33.07 vs 25.38 mm) VAS pain (0-100) and (2.64 vs 2.32) disease activity (DAS28CRP) 2-year area under the curve compared to non-chronic users (n=274) (both $p < 0.001$). The values at baseline and at 2-year were similar between users. The difference seemed to occur in the early stages (week 16: pain 30.31mm vs 22.25mm and DAS28CRP 2.65 vs 2.18, $p < 0.01$). Chronic analgesic users reached less frequently Boolean remission (14% vs 31%, $p < 0.05$) at

* **This subchapter to be submitted as:** Sofia Pazmino, Annelies Boonen, Diederik De Cock, Veerle Stouten, Johan Joly, Delphine Bertrand, René Westhovens, Patrick Verschueren. Is there a window of opportunity for optimal pain management in RA: lessons from the CareRA trial?

year 2, had more csDMARD adaptations (25% vs 18%) and were started more frequently a biological DMARD (23% vs 12%, $p < 0.05$) over 2 years.

Conclusions: Patients using chronically analgesics at the early stages of RA behave differently in pain and disease activity parameters but also had more DMARD adaptations. They might benefit from a differential focus on pain, broadening the scope of treating-to-target, also to non-pharmacological interventions.

KEY MESSAGES

What is already known about this subject?

- Pain has been indicated by patients with rheumatoid arthritis as their highest priority for improvement.
- Pain of non-inflammatory origin seems to exist in some well-treated patients with RA, despite early and ongoing DMARD treatment.

What does this study add?

- Insight into prescription of chronic analgesics in a population with early RA receiving early and intensive treatment.
- Patients on chronic analgesics seem to evolve differently in terms of pain and disease activity parameters at the early stages of the disease.

How might this impact on clinical practice or future developments?

- More attention should be given to analgesic prescription behaviour in response to complaints of chronic pain in patients with early RA.
- Alternative multimodal approaches might be considered for managing non-inflammatory remaining pain in patients with early RA.

5.2 INTRODUCTION

The primary clinical manifestation of Rheumatoid Arthritis (RA) is inflammation of the peripheral joints resulting in swelling, stiffness and pain.¹ Pain related to RA, in an early stage, is traditionally attributed to inflammation (nociceptive), and is expected to improve by rapid suppression of disease activity with disease-modifying anti-rheumatic drugs (DMARDs). With the inflammation gone, the improvement of pain should follow. However, recent studies have reported a subgroup of early RA patients suffer from remaining pain that seems to be non-inflammatory mediated pain.²⁻⁴

Patients usually indicate pain as their primary reason to seek medical attention.⁵ Moreover, pain remains their highest priority for improvement alongside fatigue and regaining functionality.^{6,7} Pain is one of the most debilitating RA symptoms⁸ and closely related to functionality and quality of life.⁹

We aim to explore in detail how patients with recently diagnosed RA who have been chronically (≥ 90 days) using analgesics behave in terms of pain and disease activity parameters during their first 2-year follow up compared with non-chronic users.

5.3 PATIENTS AND METHODS

CareRA was a 2-year open-label investigator-initiated pragmatic superiority trial (EudraCT number: 2008-007225-39) conducted in 13 Flemish rheumatology centres (2 academic centres, 7 general hospitals and 4 private practices).

Study population

Patients with recently diagnosed RA (≤ 1 year) were included and stratified into a high- or low-risk group based on classical factors of poor prognosis (presence of erosions, positivity to rheumatoid factor or anti-citrullinated peptide antibodies and moderate disease activity) and then randomised into four different treatment arms. High-risk patients were randomised to methotrexate (MTX) 15mg weekly with a step-down glucocorticoid (GC) scheme or to this combination together with either sulfasalazine or leflunomide. Low-risk patients were randomised to a tight step-up treatment of MTX monotherapy without GC or to MTX weekly with step-down GCs. Overall, around 70% of the participants achieved a status of excellent disease control after 2 years (DAS28CRP < 2.6) with a treat-to-target approach.¹⁰

Clinical outcomes

Patients were assessed at screening, baseline and then followed-up at week 8, 16, 28, 40, 52, 65, 78, 91 and 104. Optional visits, if clinically required, could be performed. An electronic trial record (eCRF) was filled out and was routinely monitored. Comorbidities, including amongst other depression, were recorded at baseline. Clinical, patient and laboratory parameters were collected at every visit: swollen joint count (SJC), tender joint count (TJC), patient's global health assessment (PaGH), physician's global health assessments (PhGH), C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR), Health Assessment Questionnaire (HAQ), pain and fatigue each on a visual analogue scale (VAS) of 0-100.

Analgesic recording

Analgesics recorded in the eCRF were categorized per type of medication and indication for intake. For this analysis, all recorded analgesics will be referred to as 'prescribed'. Chronic intake (≥ 90 consecutive days) of analgesics such as NSAIDs, acetaminophen, or opioids including tramadol, as well as other neuropathic pain drugs such as antidepressants prescribed for musculoskeletal (MSK) pain as daily intake were considered. Opioids were divided in strong (oxycodone, methadone, fentanyl and sufentanil) and weak (tramadol, codeine, meperidine, tilidine, dextropropoxyphene and piritramide). A diagnosis of depression was considered if the patient had depression recorded as comorbidity in the eCRF or had a recorded antidepressant for the indication of depression in the eCRF.

Pain and disease activity outcomes

VAS pain (0 to 100 mm) at each time point, as well as the presence of refractory pain, was taken into account. Refractory and non-inflammatory pain was defined as a report of pain >40 mm as described by Tubach et al.¹¹ with $\text{CRP} \leq 10 \text{ mg/L}$ and $\text{SJC} \leq 1$.⁴ Disease activity evolution as measured by the DAS28CRP throughout the trial, and cross-sectionally at week 104, ACR/EULAR Boolean remission as defined by $\text{SJC} \leq 1$, $\text{TJC} \leq 1$, $\text{CRP} \leq 10 \text{ mg/L}$ and $\text{PaGH} \leq 10 \text{ mm}$; and ACR/EULAR Boolean near remission with only $\text{PaGH} > 10 \text{ mm}$ were calculated.

Treatment (DMARD) adaptations

Low disease activity ($\text{DAS28CRP} \leq 3.2$) was used for steering treatment adaptations. Pre-specified treatment adaptations were protocolized for the first year and left at

the discretion of the treating rheumatologist for the second year. The first adjustment was an increase in the weekly MTX dose to 20mg, in all treatment schemes. Next, the dose of the other csDMARD was increased in the combination arms (COBRA Classic and COBRA Avant-Garde) or 10mg LEF was added in the non-combination arms (COBRA Slim and TSU). Further treatment changes could include bDMARD initiation according to Belgian reimbursement rules.¹²

Statistical analyses

All randomised patients having taken at least one medication dose from the trial treatment arms, were considered for analysis, intention to treat (ITT). Missing data were assumed to be missing at random and were imputed with multiple imputation (classification and regression trees) by chained equations.¹³ Missing clinical variables used to estimate disease activity per time point were imputed as well as VAS pain. Besides the incomplete variables, treatment strategy, centre of recruitment, age, gender, presence of comorbidities, RF, ACPA, erosions at baseline and trial completion were included as predictors in the imputation matrix. Based on Bodner (2008), the number of imputed sets was set to 10, equal to the missing data percentage.¹⁴ Results of the 10 analyses were pooled using Rubin's rules.¹⁵

Comparisons

Patients with and without chronic use of analgesics were compared for VAS pain and disease activity (DAS28CRP) evolution as area under the curve (AUC), as well as medication adaptations performed during the 2-years and reaching Boolean remission at year 2. Comparisons were performed with pooled ANOVA and chi-

square when appropriate. Multiple testing was corrected with Benjamini-Hochberg's method.

Survival analysis

Survival analysis using Kaplan Meier was employed for time to the first recorded use of a chronic analgesic. Differences in analgesic curves were estimated with a log-rank test.

All analyses were performed with R V.4.0.0.

5.4 RESULTS

Of the 379 patients included in the CareRA trial, 336 were at any point during the trial used an analgesic for any indication and with any duration, 284 for musculoskeletal pain as indication. Chronic analgesic (≥ 90 days) use for musculoskeletal (MSK) pain as daily intake was present in 106/284 (37%) patients.

For acetaminophen, 7 out of 145 prescribed patients had a chronic daily intake of only this analgesic. For NSAIDs, 71 out of 244, for opioids 8 out of 69 and for antidepressants used for MSK pain 4 out of 9 users, and 16 users had a combination of analgesics chronically as daily intake. A graphical representation of recorded use patterns can be found in Figure 5-1.

Analgesic use and pain evolution

Patients with chronic intake of analgesics ($n=106$) had over the 2-year trial a statistically higher (33.07 vs 25.38 mm) VAS pain (0-100) area under the curve (AUC) in comparison to non-chronic users ($n=273$) ($p<0.001$). Notwithstanding, chronic users did not have a statistically significant higher baseline VAS pain (59.93 vs

54.44mm) in comparison to non-chronic users ($p=0.07$). The difference in AUC seemed to be made at the early stages (week 16: 30.0 vs 22.30mm for chronic and non-chronic users respectively $-p<0.01$), and no differences were noted by the end of the 2-year trial (week 104: 28.32 vs 24.99mm $-p=0.32$). (Figure 5-2a and b) The percentage of patients with refractory non-inflammatory pain was numerically higher between week 8 till week 52 in those with a chronic use of analgesics. (Figure 5-2 c)

Analgesic use and disease activity evolution

Patients with a chronic intake of analgesics ($n=106$) had over the 2-year trial a statistically higher (2.64 vs 2.32) DAS28CRP AUC in comparison to non-chronic users ($n=273$) ($p<0.001$). However, chronic users did not have a statistically significant higher baseline DAS28CRP (4.93 vs 4.71) in comparison to non-chronic users ($p=0.17$). Again, the difference seemed to be made in the early stages (week 16: 2.65 vs 2.18 for chronic and non-chronic users respectively $-p<0.001$) and was no longer there by the end of the 2-year trial (2.20 vs 2.15 $-p=0.61$). (Figure 5-3)

Chronic users had statistically significant different DMARD treatment trajectories ($p<0.05$): 52% (55/106) maintained the original treatment scheme, compared to 70% (191/273) of non-chronic users. About 25% (27/106) of chronic analgesic users had a csDMARD adaptation in comparison to 18% (48/273) non-chronic users, and 23% (24/106) vs 12% (34/273) were started a bDMARD.

Chronic users statistically reached Boolean remission less frequently ($p<0.05$), 14% (15/106) vs 31% (84/273), at week 104. However, 44% (47/106) had a near Boolean remission (because of an elevated PGA) in comparison to 37% (100/273) of non-chronic analgesic users.

Patients considered to have depression (n=29) did not differ significantly from the chronic users (10/106) to the non-chronic users (19/273 ($p=0.60$)).

Recorded use behaviour and survival analysis

Figure 5-4a and Table 5-1 represent the chronic analgesics recorded use behaviour. For 39 patients, it started at baseline and the last 4 patients were started at week 91. Half of the patients' (n=53) chronic use took place in the first 8 weeks and then a new increase was seen by week 40. The different curves of medication per type of analgesic were not significantly different, no differences between type of analgesics or combination (Figure 5-4) The patients (n=16) taking a combination of analgesics chronically include a combination of 2 analgesics in 12 patients either opioid with acetaminophen (n=7), or with an antidepressant (n=1) acetaminophen with NSAID (n=3) or with an antidepressant (n=1). Furthermore, 4 patients had 3 analgesics as combination: acetaminophen +NSAID +opioid. The majority of recorded use again occurred at early stages. (Table 5-2). A more detailed way of chronic use for acetaminophen, NSAIDs, opioids and antidepressants is depicted in Supplemental Figure 5-1. When prescribing acetaminophen, the mean \pm standard deviation of VAS pain was 55.96 ± 24.24 , for NSAIDs 48.47 ± 26.31 , for opioids 58.70 ± 23.78 , and for antidepressants 67.67 ± 23.18 .

Figure 5-1: Graphic representation of the chronic drug intake of Acetaminophen, NSAIDs, Opioids, and other neuropathic pain drugs (antidepressants) at every visit week during the 2-year CareRA trial. Each mark is a prescribed analgesic per patient, per time point.

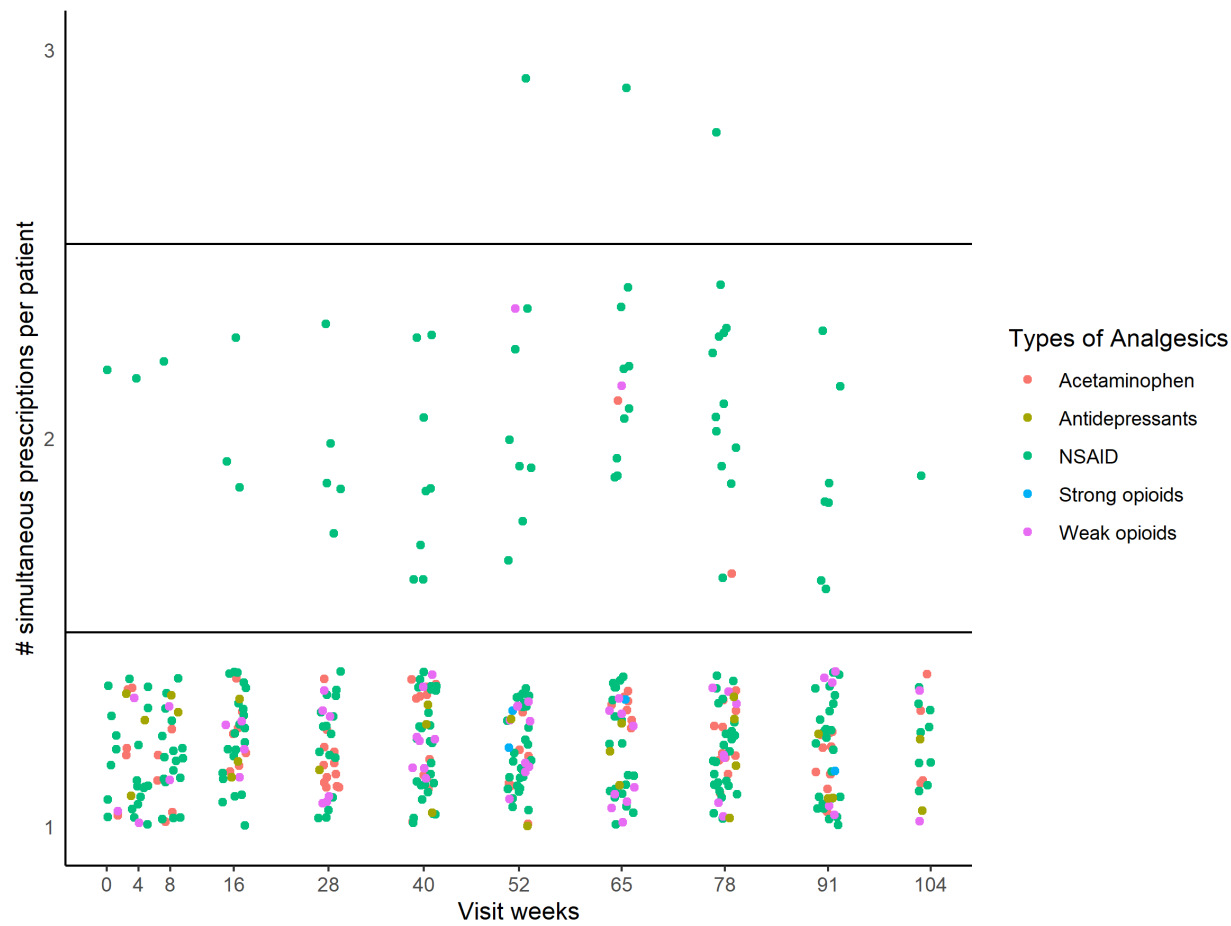


Figure 5-2: Evolution of pain on a) visual analogue scale (0-100mm), b) distribution as a violin plot, and c) the percentage of refractory pain over the 2-year trial in patients with and without chronic intake of analgesics.

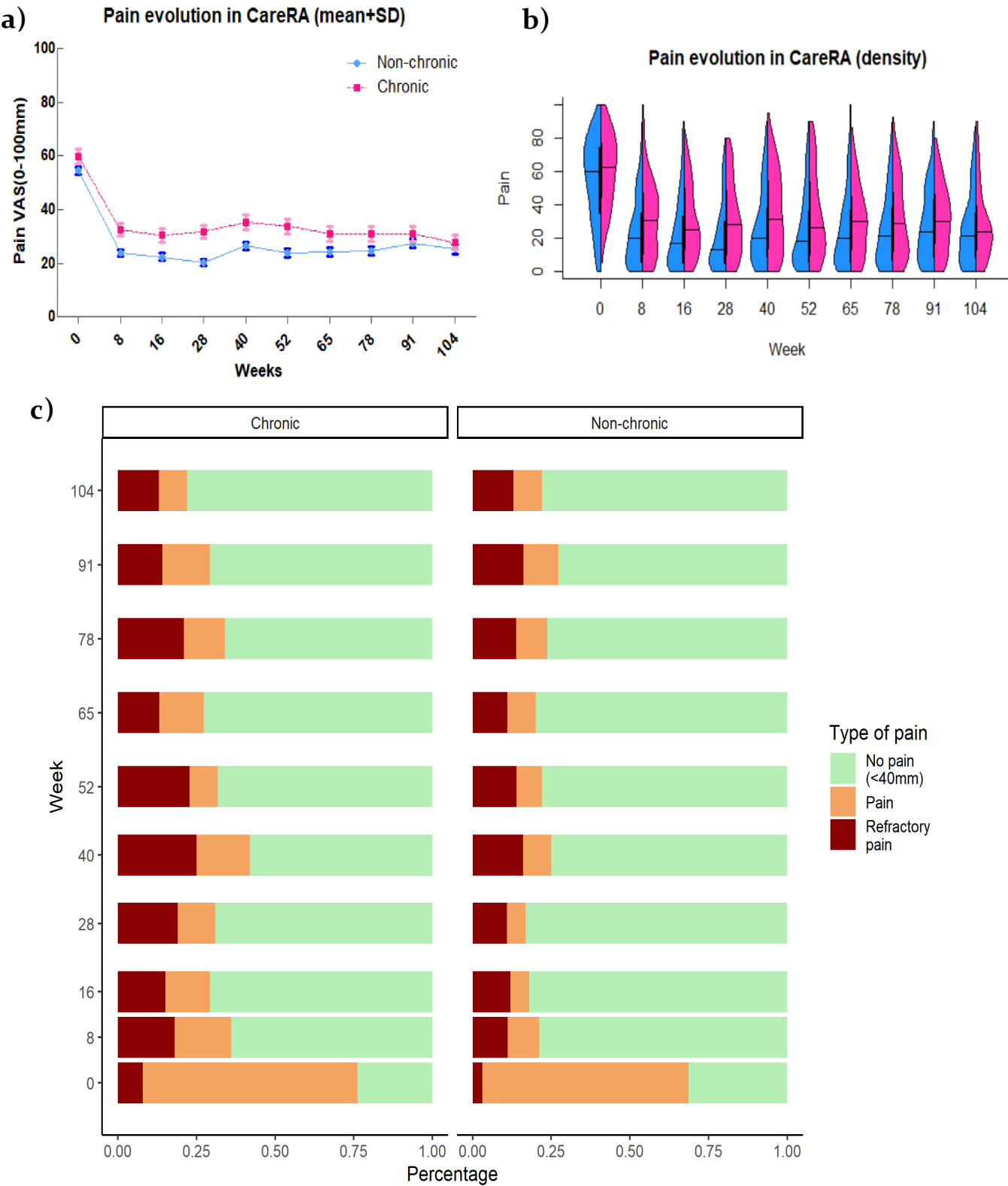


Figure 5-3: Evolution of disease activity (DAS28CRP) and its components swollen joint count (SJC), tender joint count (TJC), C-reactive protein and patient (PaGH) and physician's global health assessment (PhGH) and their distribution as a violin plot over the 2-year trial patients with and without chronic intake of analgesics.

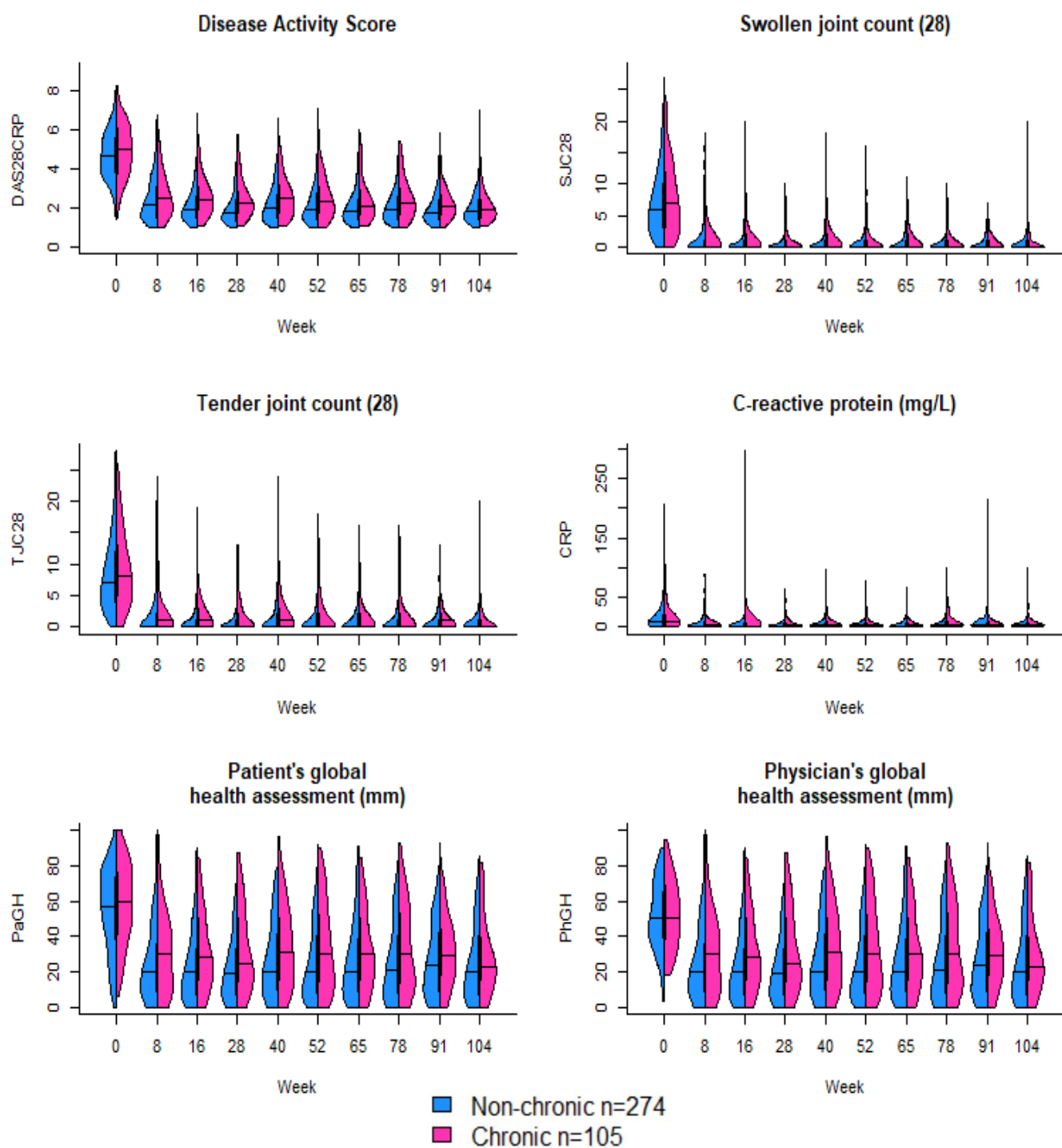


Figure 5-4: Survival analysis of time to the first prescription of chronic analgesics with Kaplan Meier in a. the total population b. comparison on chronic users between the single and combination analgesics.

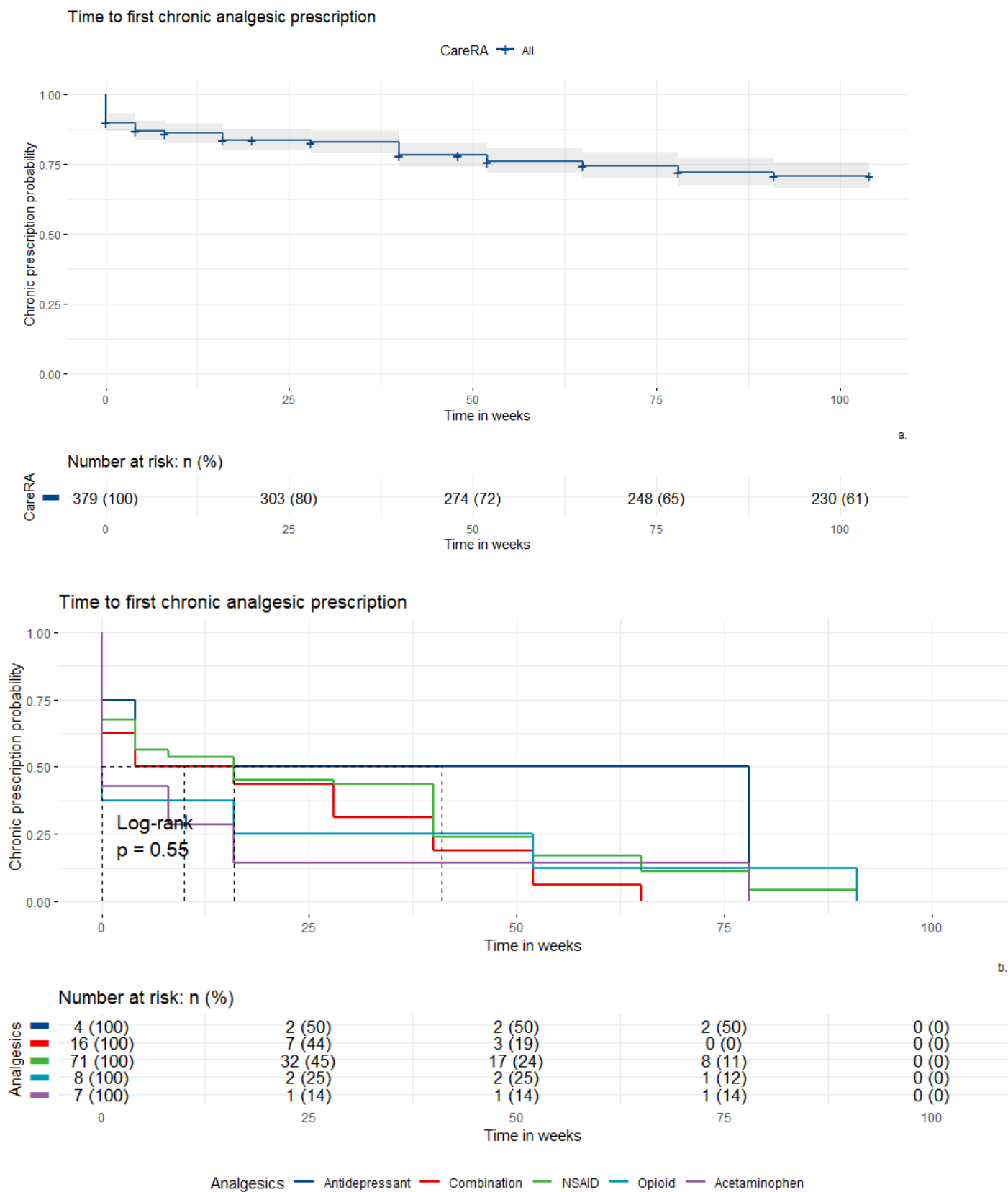


Table 5-1: Survival analysis of time to the first recorded use of chronic analgesics with Kaplan Meier in a. the total population b. comparison on chronic users between the single and combination analgesics.

Time	Number at risk	Number of events	Survival	Standard error	Lower 95% CI	Upper 95% CI
0	379	39	0.897	0.0156	0.867	0.928
4	334	11	0.868	0.0175	0.834	0.902
8	322	3	0.859	0.0179	0.825	0.895
16	317	9	0.835	0.0192	0.798	0.873
28	303	3	0.827	0.0195	0.789	0.866
40	295	16	0.782	0.0215	0.741	0.825
52	274	8	0.759	0.0223	0.717	0.804
65	256	5	0.744	0.0228	0.701	0.790
78	248	8	0.720	0.0236	0.675	0.768
91	236	4	0.708	0.0240	0.663	0.757

Table 5-2: Cumulative events of chronic analgesic use as daily intake during the entire 2-year trial per different type of analgesic.

Acetaminophen						
Time	Number at risk	Number of events	Survival	Standard error	Lower 95% CI	Upper 95% CI
0	7	4	0.429	0.187	0.1822	1.000
8	3	1	0.286	0.171	0.0886	0.922
16	2	1	0.143	0.132	0.0233	0.877
78	1	1	0.000	-	-	-

NSAIDs						
Time	Number at risk	Number of events	Survival	Standard error	Lower 95% CI	Upper 95% CI
0	71	23	0.6761	0.0555	0.5755	0.794
4	48	8	0.5634	0.0589	0.4591	0.691
8	40	2	0.5352	0.0592	0.4309	0.665
16	38	6	0.4507	0.0590	0.3486	0.583
28	32	1	0.4366	0.0589	0.3352	0.569
40	31	14	0.2394	0.0506	0.1582	0.362
52	17	5	0.1690	0.0445	0.1009	0.283
65	12	4	0.1127	0.0375	0.0587	0.216
78	8	5	0.0423	0.0239	0.0140	0.128
91	3	3	0.0000	-	-	-

Opioid

Time	Number at risk	Number of events	Survival	Standard error	Lower 95% CI	Upper 95% CI
0	8	5	0.375	0.171	0.1533	0.917
16	3	1	0.250	0.153	0.0753	0.830
52	2	1	0.125	0.117	0.0200	0.782
91	1	1	0.000	-	-	-

Antidepressants

Time	Number at risk	Number of events	Survival	Standard error	Lower 95% CI	Upper 95% CI
0	4	1	0.75	0.217	0.426	1
4	3	1	0.50	0.250	0.188	1
78	2	2	0.00	-	-	-

Combination

Time	Number at risk	Number of events	Survival	Standard error	Lower 95% CI	Upper 95% CI
0	71	23	0.6761	0.0555	0.5755	0.794
4	48	8	0.5634	0.0589	0.4591	0.691
8	40	2	0.5352	0.0592	0.4309	0.665
16	38	6	0.4507	0.0590	0.3486	0.583
28	32	1	0.4366	0.0589	0.3352	0.569
40	31	14	0.2394	0.0506	0.1582	0.362
52	17	5	0.1690	0.0445	0.1009	0.283
65	12	4	0.1127	0.0375	0.0587	0.216
78	8	5	0.0423	0.0239	0.0140	0.128
91	3	3	0.0000	-	-	-

5.5 DISCUSSION

In this post-hoc analysis of a randomised trial, patients with early RA who were prescribed for more than 90 days an analgesic had a different evolution in terms of pain and disease activity parameters compared to non-chronic users. However, there seemed to be a window during which these differences are present. At baseline and around the end of the 2-year trial, the differences were not there, but the chronic use remained, which is not without danger. Although an opioid epidemic is not yet seen in Europe the consumption of opioids in Belgium is more frequent compared to most other European countries.¹⁶⁻¹⁹

Pain being one of the most important symptoms for patients, its management is a crucial topic in RA, primarily since it is closely related to quality of life. Health status improved after the start of intensive treatment strategies.²⁰ The Oslo Rheumatoid Arthritis Register showed that despite a change in treatment strategy that already improved VAS pain levels from 46mm in 1994 to 35.8mm in 2001, pain has remained the area of the highest priority for improvement in patients with RA.²⁰ Moreover, Heiberg *et al.* report a 45.2% use of NSAIDs in 1994 compared to 37.1% in 2001.²⁰ In CareRA about 1 in every 4 patients ended up with a chronic analgesic recorded use of more than 90 days that can even be of a narcotic (opioid). Despite evidence not supporting prescription of weak or strong opioids for longer than 6 weeks in RA.²¹ NSAIDs overuse or misuse, both prescribed or over the counter, account for 39.5% of RA patients.²² However, without complete certainty of the actual intake due to no recording of a measure of compliance of the analgesic or specifically if the intake was on the prescription of a GP/rheumatologist or over the counter intake but only recorded use of analgesics, caution must be applied when interpreting these findings.

Chronic analgesic users reached less frequently Boolean remission (14% vs 31% - $p < 0.05$) at year 2, had more csDMARD adaptations (25% vs 18%) and were started more frequently a biological DMARD (23% vs 12% - $p < 0.05$) over 2 years. An interesting finding in our study

is that more patients (7% more) who were chronic analgesic users had a near Boolean remission status (without PaGH that might be linked to VAS pain) compared to non-chronic users. PaGH and PhGH (see violin plots) showed the same patterns over time, with worse scoring in chronic users and apparently physicians following patients in their reported pain despite CRP and swollen joints counts being similar and very low in both patient groups. This raises questions about the one-dimensional capability of these measures. This seems important as apparently influences prescription of DMARDs also. Awareness should also be given to the prescription behaviour of all stakeholders involved, not only the treating rheumatologist but also general practitioner.¹⁸

Furthermore, a qualitative-interview study performed with CareRA participants by Van der Elst *et al.* confirms that patients after 1 year of follow up still feared their initial pain experience and remembered its impact on daily life explaining why pain relief, especially the intolerable pain related to flares and its impact on sleep quality, remained a highly preferred outcome, despite perceived disease control.⁷ Hence, demonstrating the importance of appropriate shared-decision making. The European League Against Rheumatism (EULAR) also in its recommendations for pain management has as an overarching principle of patient-centred care.²³ Our findings urge health professionals to pay specific attention to pain also in the early RA disease course, to evaluate personal patient factors involved and to search for the best therapeutic options that might be other than analgesics and certainly opioid drugs. We suggest further study and adding pain as a specific focus in the management of early RA where patients might benefit from a broader scope of Treating-to-Target (T2T) separate from disease control as recently suggested.²³ Also, unnecessary DMARD adaptation based mainly on pain reporting should be avoided. Nevertheless, this early disease period could probably be a separate window of opportunity for pain management and especially for critically assessing chronic analgesic prescription.

5.6 CONCLUSION

Adding pain in a separate and additional early T2T approach in early RA is important.

Avoiding chronic analgesic use might have an early window of opportunity that should not be missed.

A critical reflection about evaluation of disease activity and DMARD adaptation is also needed in patients expressing persistent pain in the early disease phase.

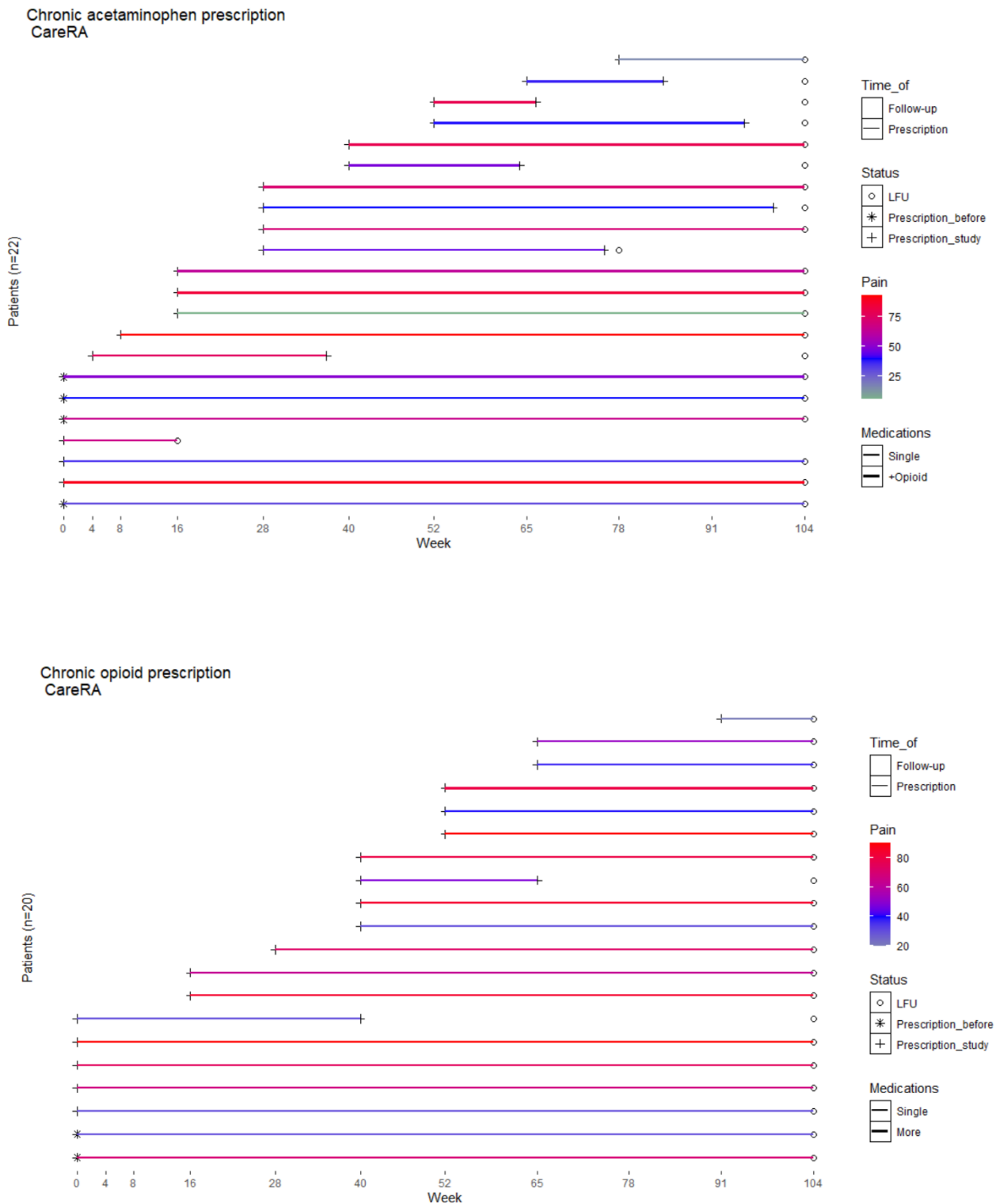
5.7 REFERENCES

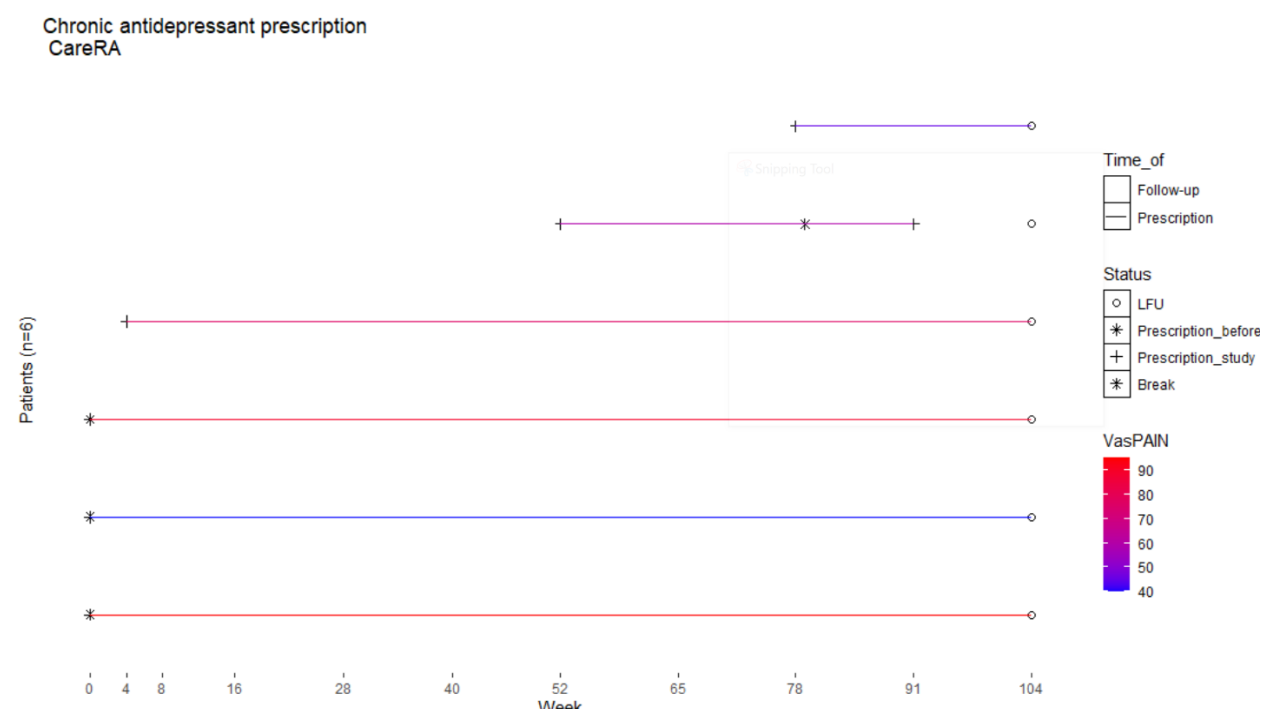
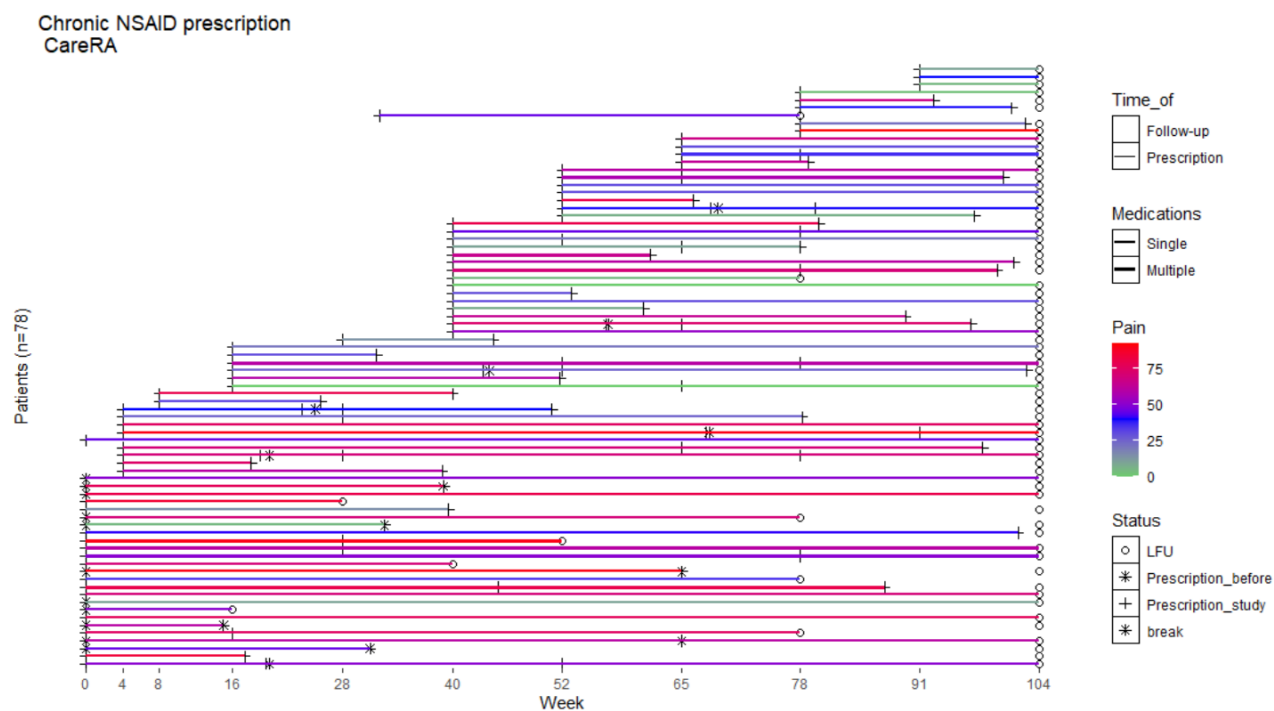
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SUPPLEMENTAL MATERIAL

Supplemental Figure 5-1: Graphic representation of the recorded use behaviour of Acetaminophen, NSAIDs, Opioids, and other neuropathic pain drugs (antidepressants) during the 2-year CareRA trial.





B. Bridging with glucocorticoids reduces the risk of chronic analgesic use among early rheumatoid arthritis patients with favourable prognosis: sub analysis of the CareRA randomized trial *

5.1 ABSTRACT

Objective: To explore analgesic use in early Rheumatoid Arthritis (eRA) patients with a favourable risk profile initiating methotrexate with or without glucocorticoid bridging.

Methods: Patients with eRA (≤ 1 year) and a favourable risk profile (no erosions, negative rheumatoid factor and anti-citrullinated protein antibodies, low disease activity) in the 2-year CareRA trial were randomized to methotrexate (MTX) 15mg with a step-down glucocorticoid (GC) scheme (COBRA-Slim), or MTX Tight-Step-Up-(TSU) without oral GCs. Prescribed analgesics were recorded, including frequency, start/end date and indication. Chronic intake (≥ 90 consecutive days in trial) of NSAIDs, acetaminophen, or opioids including tramadol, and antidepressants indicated for musculoskeletal (MSK) pain was considered.

Treatments were compared using Chi-square and ANOVA with Holm's correction for multiple testing.

Results: In total, 43 patients were randomized to COBRA Slim and 47 to TSU. At study inclusion, 33/43 (77%) of patients in the COBRA Slim and 32/47 (68%) in the TSU arm had been using analgesics ($p=0.5$). During the trial, 67 analgesic were indicated for MSK pain

* **This subchapter was submitted as:** Sofia Pazmino, Annelies Boonen, Diederik De Cock, Veerle Stouten, Johan Joly, Delphine Bertrand, René Westhovens, Patrick Verschueren. Bridging with glucocorticoids reduces the risk of chronic analgesic use among early rheumatoid arthritis patients with favourable prognosis: sub analysis of the CareRA randomized trial. *Arthritis Rheumatology* (2020).

in 26/43 (60%) COBRA Slim patients of which 9/43 (21%) daily chronically (DC), while 107 analgesics were indicated in 43/47 (92%) TSU patients, of which 25/47 (53%) DC. The total number of patients on analgesics at any time during the study ($p < 0.001$) and chronically ($p < 0.01$) was significantly different between treatment arms. Number of patients on DC NSAIDs was also significantly different ($p < 0.05$) between COBRA Slim 6/43 (14%) and TSU 19/47 (40%).

Conclusion: In eRA patients considered to have a favourable prognosis, initial oral GC bridging resulted in lower chronic analgesic consumption.

KEY MESSAGES

What is already known about this subject?

- Early and intensive RA treatment using disease activity as a target for treatment adaptation allows rapid disease control and prevents joint destruction.
- MTX with glucocorticoid (GC) bridging is recommended by EULAR as first-line treatment for all RA patients. However, in clinical practice there is still discussion if this intensive approach is also necessary in patients lacking classical markers of poor prognosis.

What does this study add?

- Early RA patients considered to have a favourable prognosis, and receiving initial MTX monotherapy had a significantly higher risk of analgesic consumption, even chronically, than those treated with MTX and glucocorticoid bridging.

How might this impact on clinical practice or future developments?

- Early initial intensive treatment should incorporate GC bridging, even in patients considered to have a favourable prognosis.

5.2 INTRODUCTION

Early, intensive, treat-to-target strategies have improved the clinical outcomes for patients with Rheumatoid Arthritis (RA).¹⁻³ However, there is evidence that even achieving the target of remission is sometimes insufficient to normalise patients' quality of life, and persistent complaints such as pain remain a challenge.² Despite European guidelines recommending as first treatment strategy the initiation of disease modifying anti-rheumatic drug (DMARD) such as methotrexate (MTX) with a short-term glucocorticoid (GC) course³, it is debated if this intensive approach is also necessary in patients lacking classical markers of poor prognosis.⁴ In the CareRA trial we demonstrated that also in patients without erosions, being seronegative or having low disease activity, the speed of response was more rapid when starting MTX with a step-down-bridge GC scheme compared to MTX therapy without GC, while long-term treat-to-target results were comparable.^{5,6} However, the potential advantage of intensive therapy on patient important outcomes such as pain and the concomitant use of analgesics deserves more detailed study in relation to the clinical response to a treat-to-target approach, taking into account the cumulative need but also the evolution over time.

Therefore, we aim to compare both the extent and dynamics of analgesic use in patients with early RA considered to have a favourable prognosis and were treated to target with or without initial GC bridging during the first 2 years in the Care in early RA (CareRA) trial.

5.3 PATIENTS AND METHODS

CareRA was a 2-year open-label investigator-initiated pragmatic superiority trial (EudraCT number: 2008-007225-39) conducted in 13 Flemish rheumatology centres (2 academic centres, 7 general hospitals and 4 private practices).

Study population

Patients with recently diagnosed RA (≤ 1 year) were included and stratified into a low- versus a high-risk group based on classical factors of poor prognosis. This study focuses on the low-risk patients, who had to fulfil at least 2 of the following 3 criteria: absence of erosions, negativity for both, rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA), or low disease activity score -DAS28CRP ≤ 3.2 . Patients in this low-risk group were randomised to either a Tight Step-Up (TSU) treatment of MTX monotherapy 15mg/weekly without GC or to COBRA Slim (MTX 15mg/weekly with step-down GCs, starting with prednisone 30mg followed by tapering to 5mg over 6 weeks and stopping at 34 weeks). From week 8 onwards treatment had to be adjusted in case of insufficient disease control (DAS28CRP > 3.2). Overall, around 70% of the participants achieved a status of excellent disease control (DAS28CRP < 2.6) after 2 years with a treat-to-target approach.⁶

Clinical outcomes

Patients were assessed at screening, baseline and during followed-up at week 8, 16, 28, 40, 52, 65, 78, 91 and 104. Optional visits, if clinically required, could be performed. An electronic case report form (eCRF) was filled out and was routinely monitored. Clinical, patient and laboratory parameters were collected at every visit: swollen joint count (SJC), tender joint count (TJC), patient's global health assessment (PaGH), physician's global health assessments (PhGH), C- reactive protein (CRP) or erythrocyte sedimentation rate (ESR), health assessment questionnaire (HAQ), pain and fatigue each on a visual analogue scale (VAS) of 0-100.

VAS pain (0 to 100 mm) and disease activity (DAS28CRP) evolution throughout the trial were calculated as area under the curve (AUC).

Analgesic recording

Analgesics recorded in the eCRF were categorized per type of medication and indication. For this analysis, recorded analgesics will be referred to as 'prescribed'. NSAIDs, acetaminophen, or opioids including tramadol, as well as other neuropathic pain drugs such as antidepressants indicated for musculoskeletal (MSK) pain for any time period of at least 90 consecutive days for which daily intake of a certain analgesic was documented, was considered 'chronic analgesic use'. Opioids were divided in strong (e.g. oxycodone, methadone, fentanyl and sufentanil) and weak (e.g. tramadol, codeine, meperidine, tilidine, dextropropoxyphene and piritramide). No formal evaluation of patient compliance (e.g. pill count, questionnaire) was performed, but registration of current medication intake was part of the routine evaluation during follow up, as in daily clinical practice.

Treatment adaptations

In both treatment arms, low disease activity ($\text{DAS28CRP} \leq 3.2$) was used for steering treatment adaptations. Per-protocol adaptations were specified for the first trial year while the second-year adaptations were left at the discretion of the treating rheumatologist. The first adjustment was an increase in the weekly MTX dose to 20mg for both arms. Next, 10mg leflunomide could be added. Further treatment changes could include bDMARD initiation. More details on adaptations has been published elsewhere.⁶

Statistical analyses

All randomised patients having taken at least one study medication dose were considered for intention to treat (ITT) analysis. Missing data were assumed to be missing at random and were imputed with multiple imputation (classification and regression trees) by chained equations. Missing clinical variables used to estimate disease activity per time point were

imputed as well as VAS pain. Besides the incomplete variables, treatment strategy, centre of recruitment, age, gender, presence of comorbidities, RF, ACPA, erosions at baseline and trial completion were included as predictors in the imputation matrix. The number of imputed datasets was fixed to 100, each dataset was analysed and the results were pooled using Rubin's rules. No imputation was done for recorded medication.

Comparison of clinical outcomes in patients with or without GC bridging

Comparisons for VAS pain and DAS28CRP evolution during the 2-years between treatment arms were performed using repeated measures ANOVA and chi-square when appropriate. Multiple testing was corrected with Holm's method.

Survival analyses of analgesics

To assess differences between treatment arms from time of diagnosis to the initiation of an analgesic for ≥ 90 days within the trial, survival curves were computed and differences tested using both the Gehan-Breslow-Wilcoxon method, which gives more weight to events at early time points, and the log-rank test which gives equal weight to all time points. To estimate the independent role of the initial treatment strategy (MTX with or without GC), previous analgesic use and VAS pain at baseline on chronic analgesic use, a Cox regression analysis was performed.

All analyses were performed with R V.4.0.0.

5.4 RESULTS

Of the 90 patients recruited in the low-risk group of the CareRA trial, 43 were randomized to COBRA Slim and 47 to TSU. Before the start of the study 33/43 (77%) of patients in the COBRA Slim and 32/47 (68%) in the TSU arm reported to have been taking analgesics

($p=0.5$). Cross-sectionally at baseline, 18/43 (42%) patients starting COBRA Slim and 28/47 (60%) starting TSU used analgesics ($p=0.14$). During the trial, 26/43 (60%) COBRA Slim patients were recorded a total of 67 analgesics for MSK pain of which 9/43(21%) daily chronically (DC) and a total of 107 analgesics recorded use in 43/47 (92%) TSU patients of which 25/47(53%) DC. The total number of patients on analgesics at any time during the study ($p<0.001$) and chronically ($p<0.01$) was significantly different between treatment arms. Figure 5-5a shows the analgesic intake at every visit during the trial. Patients on TSU were prescribed more analgesics, especially early in the disease course, compared to patients on COBRA-Slim. Number of patients on NSAIDs was also significantly different between COBRA-Slim and TSU for daily chronic intake (6/43=14% vs 19/47=40%; $p<0.05$) (Figure 5-5b and Supplemental Figure 5-2) as well as for non-chronic intake (12/43=28% vs 35/47=75%; $p<0.001$) (Figure 5-5c).

Pain and disease activity evolution

Patients starting COBRA Slim had a baseline VAS pain of 48 compared to 52 for TSU ($p=0.51$). In terms of disease activity (DAS28CRP), COBRA Slim patients had a baseline DAS8CRP of 4.5, compared to 4.6 for TSU ($p=0.89$) (Figure 5-6). The ANOVA of repeated measures corrected for baseline pain ($p=0.004$) or DAS28CRP ($p=0.0000275$) respectively, demonstrated a significant difference for pain and DAS28CRP over the 2 treatment years between treatment groups.

Analgesic use at different time points and survival analysis

At baseline, 13 (28%) patients in TSU and 3 (7%) patients in the COBRA Slim group started using an analgesic that was continued daily and chronically (≥ 90 days). The time to first use of any chronic analgesic (Figure 5-7 and Supplemental Table 5-1) as well as specifically

chronic NSAID use was significantly different between treatment arms (Supplemental Figure 5-3). After correcting for before the trial chronic analgesic use and VAS pain at baseline, when fitting a Cox regression, between group differences remained. Initiating COBRA Slim (HR 0.17, 95%CI 0.07-0.41, $p < 0.001$) and having had no previous chronic analgesic use before the trial (HR 0.11, 95%CI 0.05-0.29, $p < 0.001$) were associated with a longer time to initiation of chronic use of analgesics (TTCUA) during the trial. Baseline VAS pain was not significantly associated with TTCUA (HR 1.02, 95%CI 0.98-1.04, $p < 0.01$). Overall, this model had a good fit ($p < 0.001$).

Figure 5-5: a) Drug intake of Acetaminophen, NSAIDs, Opioids (weak and strong), and other neuropathic pain drugs (antidepressants) at every visit week during the 2-year CareRA trial between COBRA Slim and TSU patients. Each mark is a prescribed analgesic per patient, per time point. b) Percentage of patients on daily chronic analgesics per type of analgesic and per treatment group and c) non-chronic analgesic intake with any frequency of intake over the 2-year trial.

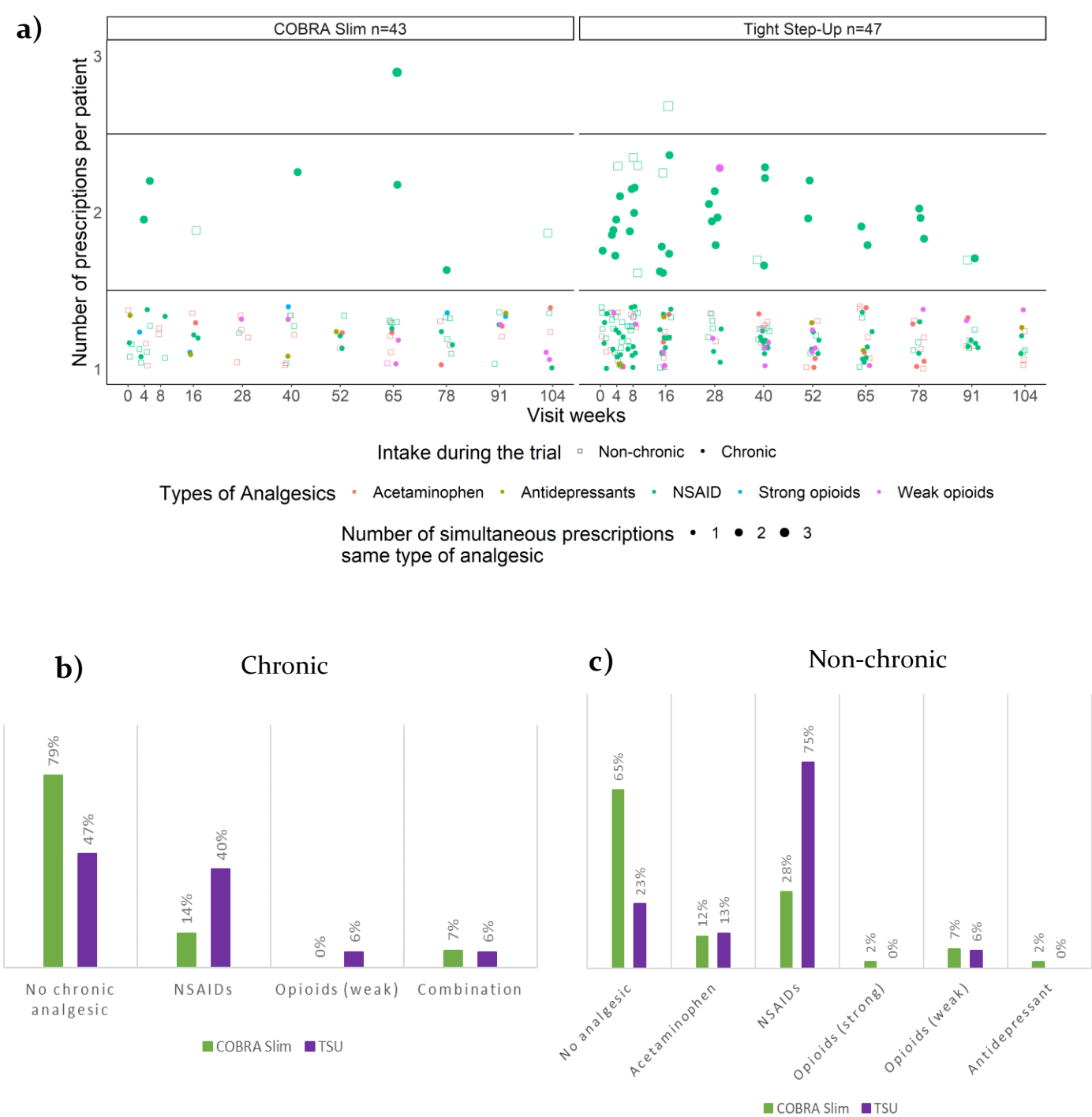


Figure 5-6: Pain and disease activity (DAS28CRP) evolution over the 2-year trial per treatment group.

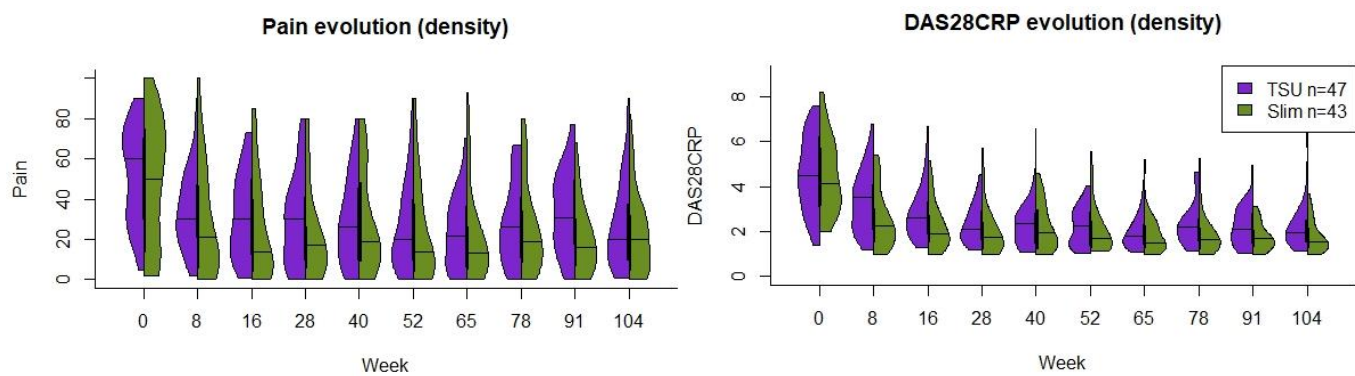
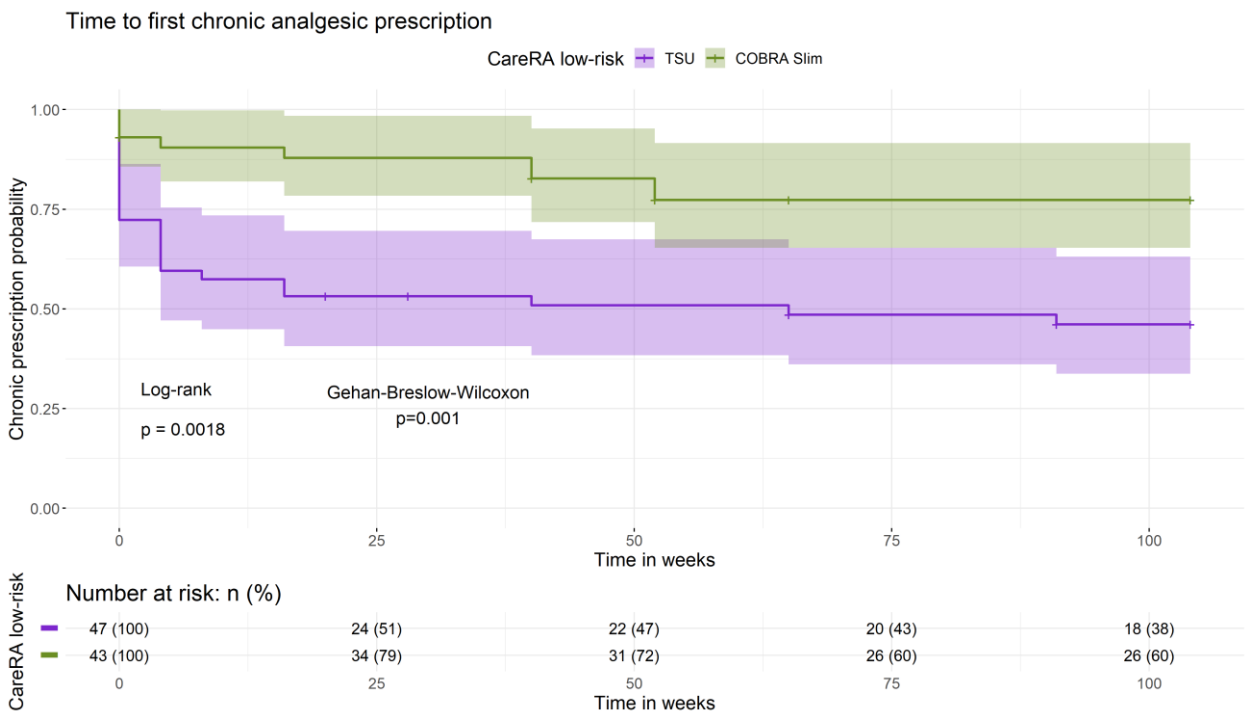


Figure 5-7: Survival analysis of time to the first recorded use of chronic analgesics with Kaplan Meier.



5.5 DISCUSSION

In this post-hoc analysis of the randomised CareRA trial, patients with early RA perceived as having a favourable risk profile who were not initially treated with step-down GC, had a significantly higher use of analgesics (92% vs 60%), being chronic for a significant proportion of them (53% vs 21%) compared to patients treated with step-down GC. Even when correcting for previous chronic analgesic use and baseline pain, patients treated with MTX and step-down GCs had an 83% lower hazard of using a daily chronic analgesic.

Chronic pain and analgesic consumption is a major health issue throughout the world and a huge economic burden for nations.⁷ In a cohort of 70,929 patients with RA, data collected from Medicare (United States) from 2006 to 2014 showed that in the average rheumatologist's practice, 40% of RA patients used opioids regularly. In almost half of the patients, at least some opioid prescriptions were written by a rheumatologist, and 14% received opioids that were co-prescribed concurrently by more than 1 physician.^{8,9} Awareness should also be given to the prescription behaviour of all stakeholders involved, not only the treating rheumatologist but also the general practitioner.¹⁰

Regular intake of analgesics both narcotic and non-narcotic comes with risks. NSAIDs are considered fast-acting and help to relieve pain and decrease inflammation.¹¹ Associated side effects can be reduced by gradually tapering doses as a patient's condition improves. However, GCs are a more potent anti-inflammatory medication than NSAIDs, and contrary to NSAIDs they also have immunomodulatory effects and they have been shown to prevent structural damage.¹² Keeping this in mind, we observed patients on TSU had more analgesic use, especially NSAIDs and specifically early in the disease course, compared to

patients on COBRA Slim. In contrast, the analgesic consumption before entering the trial was comparable between groups. This suggests that in TSU, analgesics were used instead of GC as bridging therapy in the first few months to alleviate the symptoms of RA. In terms of analgesic and total strategy cost, we have previously published that it was significantly different between treatment arms, in favour of COBRA Slim along with an increased quality of life.¹³

EULAR guidelines recommend as a first treatment strategy, in early RA, the combination of MTX with short-term GCs. It is feasible to reach high remission rates and stop GCs completely in the vast majority of patients after induction with GC-based schedules like COBRA Slim as shown in CareRA after 2 years.⁶ In addition, patients considered to have a good-prognosis (RF and ACPA negative, no erosions, low disease activity) benefit equally well from GC-bridging compared to poor-prognosis patients. In the current post-hoc study, we demonstrated a higher use of analgesics if the initial scheme does not include GCs, despite the expected good prognosis. However, with a small sample size and without complete certainty of the actual intake but only recorded use of analgesics, caution must be applied when interpreting these findings.

What is more, we should explore and understand the hurdles and opportunities for patients,¹⁴ rheumatologists¹⁵ and other health professionals,¹⁶ in the early management of RA with intensive strategies including GCs,¹⁷ especially in the context of shared-decision making with the patient. The early disease period could probably be a separate window of opportunity for pain management and especially for avoiding chronic analgesic use. The choice of initial treatment strategy might influence pain management on the long run, even in patients considered to have a good prognosis.

5.6 CONCLUSION

Almost every patient in the TSU group used an analgesic for MSK pain compared to 60% in the group treated with MTX and a step-down GC scheme (COBRA Slim). Chronic analgesic use was more than double in TSU. It is remarkable that even in patients considered to have a favourable risk profile, when the initial treatment did not include oral GC bridging, there was a significant use of analgesics becoming chronic for a significant proportion of patients. To benefit maximally from the window of opportunity for treating early RA, intensive remission induction strategies using GCs should be applied even in patients without traditional factors of poor prognosis.

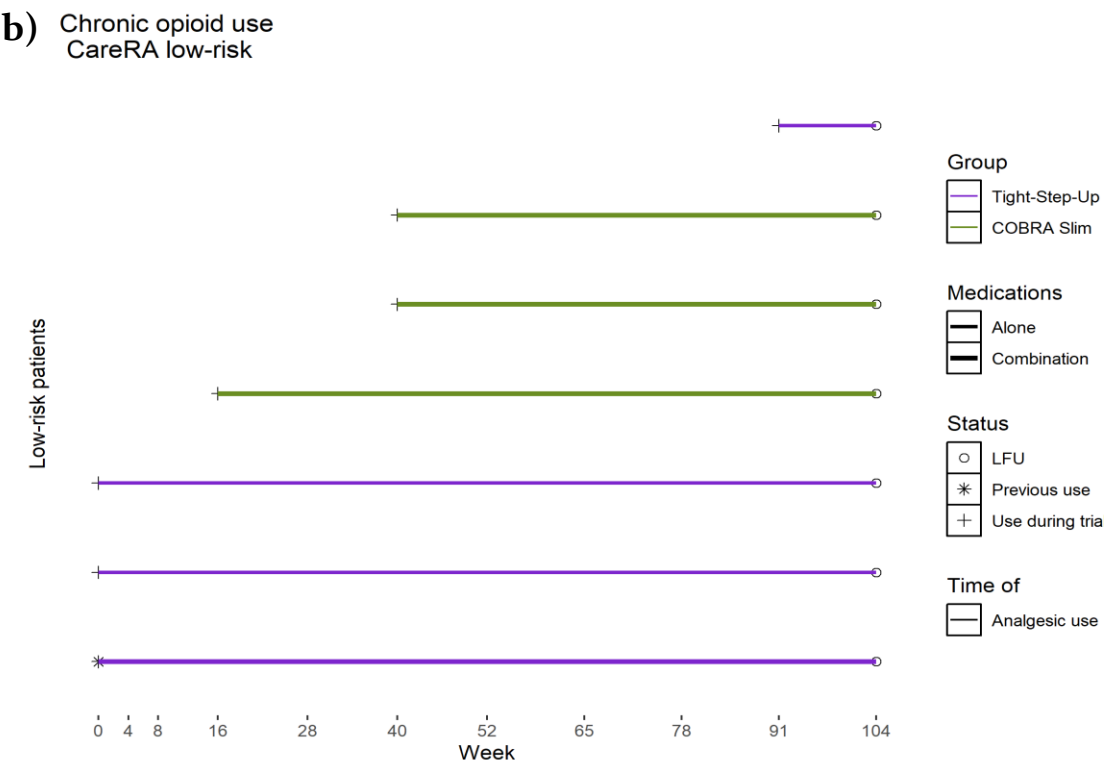
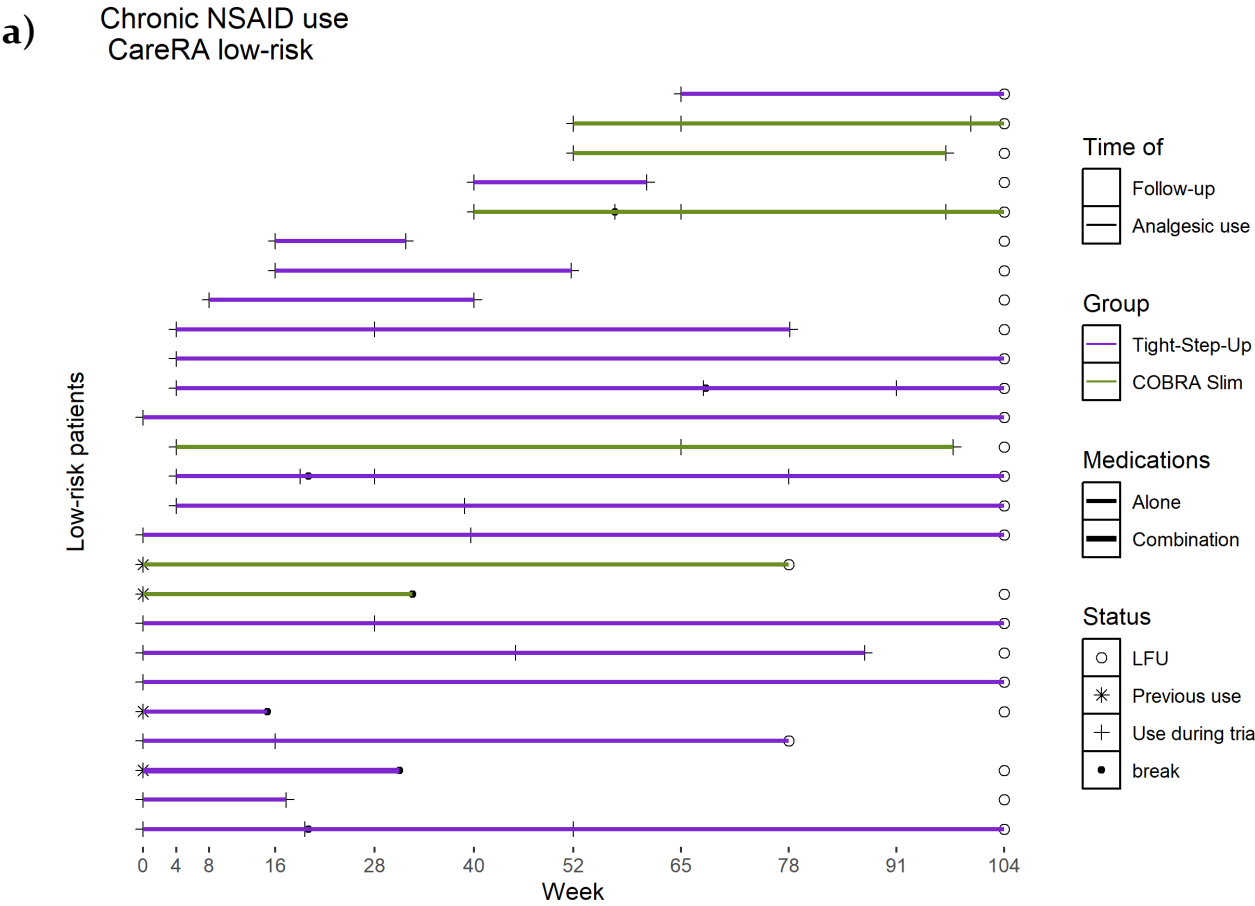
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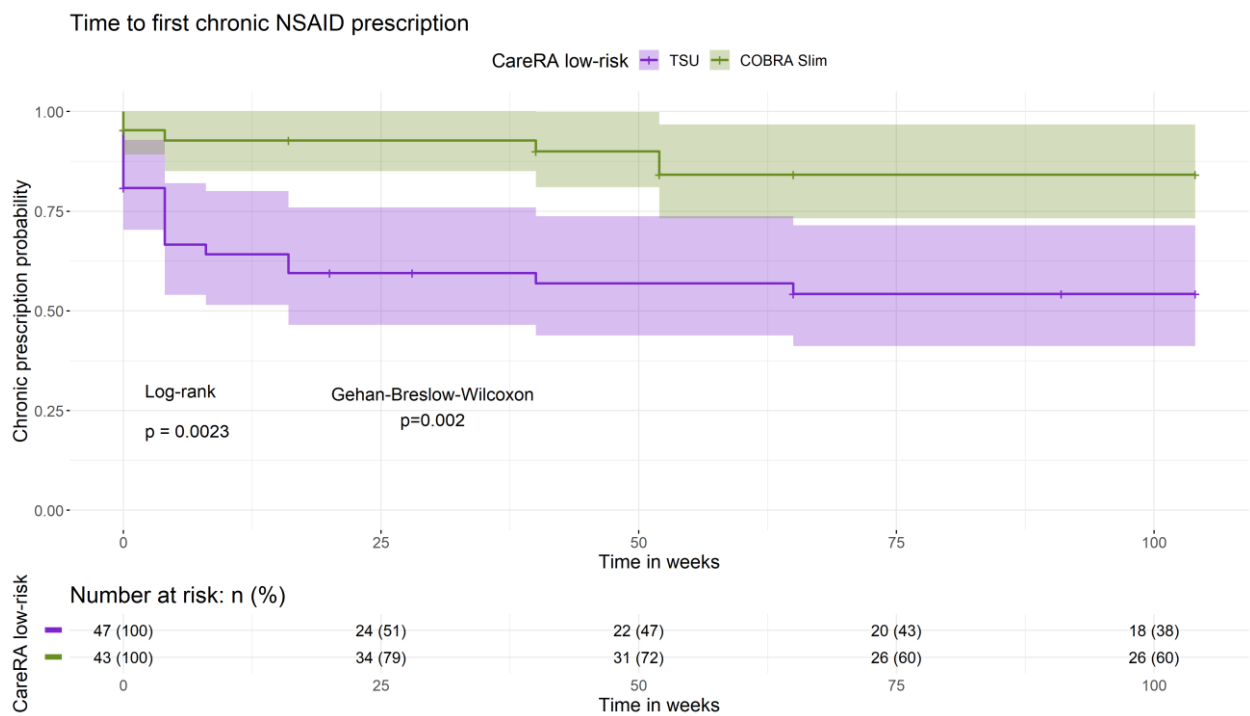
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SUPPLEMENTAL MATERIAL

Supplemental Figure 5-2: Graphic representation of the use of a) NSAIDs and b) opioids during the 2-year CareRA trial (LFU=lost to follow-up). One patient of TSU not represented (on combination of acetaminophen + antidepressant).



Supplemental Figure 5-3: Survival analysis of time to the first recorded use of chronic NSAID with Kaplan Meier.



Supplemental Table 5-1: Cumulative events in time to first chronic analgesic use for COBRA Slim and TSU patients.

COBRA Slim						
Time	Number at risk	Number of events	Survival	Standard error	Lower 95% CI	Upper 95% CI
0	43	3	0.930	0.0388	0.857	1.000
4	36	1	0.904	0.0456	0.819	0.998
16	35	1	0.879	0.0511	0.784	0.985
40	34	2	0.827	0.0597	0.718	0.953
52	31	2	0.774	0.0667	0.653	0.916
Tight-Step-Up						
Time	Number at risk	Number of events	Survival	Standard error	Lower 95% CI	Upper 95% CI
0	47	13	0.723	0.0652	0.606	0.863
4	34	6	0.596	0.0716	0.471	0.754
8	28	1	0.574	0.0721	0.449	0.735
16	27	2	0.532	0.0728	0.407	0.696
40	23	1	0.509	0.0732	0.384	0.675
65	22	1	0.486	0.0734	0.361	0.653
91	20	1	0.461	0.0737	0.337	0.631

Chapter 6.

General discussion and overall conclusion

Overview of key findings

In this PhD project we have evaluated several **unmet needs** in patients with early RA that are being treated to target focusing on economic impact and patient centeredness. We have performed an in-depth analysis of the economic impact of intensive conventional early RA treatment and how it affects disease control and quality of life. Furthermore, we have investigated if these findings also count for a subgroup of patients without rheumatoid factor and anti-citrullinated peptide antibodies as classical markers predictive of poor prognosis. We have taken a closer look at the measurement instruments used to steer therapy and how they measure disease activity and burden. Finally, the patient's most important outcome -pain- has been investigated with chronic analgesic recorded use as a proxy.

In this final chapter we will discuss our research findings in relation to the available literature. This general discussion contains the following sections:

1. The cost-effectiveness of different treat to target treatment schemes in early RA
2. The response of patients with seronegative RA to intensive treatment strategies
3. The interpretation of disease activity markers and the estimated comprehensive disease burden in early RA
4. Chronic consumption of analgesics in early RA as a proxy for remaining pain

6.1 The price tag of RA: how we piggybacked CareRA

The cost-effectiveness of different treat-to-target treatment schemes in early RA

Our economic analysis showed that for high-risk early RA patients, csDMARD combination schemes with GCs (COBRA Classic and COBRA Avant-Garde) were not cost-effective or were even dominated in the first 2 years when compared to MTX monotherapy together with a moderate-dose step-down GC bridging scheme (COBRA Slim). In the low-risk group COBRA Slim dominated the traditional MTX monotherapy without GC in patients with early RA treated-to-target.

This study's results were comparable to other cost-effectiveness analyses of early RA strategy trials. In the BeSt trial, the COBRA-Classic-like treatment had a total cost of k€9.2 of which k€5.0 were direct medical costs (calculated from US dollars; exchange rate of 1:0.90),¹ comparable to our cost of k€6.086 in COBRA-Classic. In the COBRA-light trial, using treatment schedules comparable to COBRA-Classic and Slim, the total costs were k€9.7 and k€5.6, respectively and differences in QALYs comparable to CareRA.² The robust comparability with previous trials reinforces our message that COBRA-Slim seems a cost-saving strategy. Over the years, several trials have demonstrated increased efficacy of initial csDMARD combinations over monotherapy,^{3,4} but good evidence is lacking for the superiority of combining csDMARDs within strategies including a step-down-bridge GC scheme.⁵ CareRA has broadened the available data in this context.

Pragmatic trials are attractive for economic analysis since they reflect what may happen in clinical practice, while the gold standard for assessing the efficacy of interventions is the randomised controlled trial.⁶ In this sense, CareRA being a randomised controlled trial rooted in daily clinical practice has two key elements for an economic assessment. It also

had less stringent in- and exclusion criteria, hence the study population may represent a typical day-to-day health care population with no artificially enhanced compliance, using strategies already in place in clinical practice. However, this post-hoc study of an RCT, provided no data on indirect costs nor direct non-medical costs. There might also be direct medical costs missing when it comes to general practitioner appointments and use of paramedical or alternative therapies.

The present study has confirmed that using GCs instead of expensive biological DMARDs as agents for rapid remission induction in combination with MTX allows to optimise relatively cheap conventional DMARDs^{7,8} without compromising disease control in the sense of sustained remission nor quality of life. The COBRA Slim scheme had less adverse events and hence less disutility. It is a scheme sustainable for society and the patient. Some limit on the freedom to prescribe bDMARDs, as Belgian reimbursement rules propose (failure to two csDMARDs and DAS28>3.7)⁹, may be favourable to sustainability of rheumatological care without compromising patient care. Even in the sensitivity analysis, when replacing the biological originator by less costly biosimilar, the overall health economic picture did not change.

In general, COBRA Slim is a cost-effective initial scheme for patients with early RA which endorses EULAR recommendations.¹⁰ EULAR recommends treatment to a target of sustained remission or at least low disease activity as an end goal. However, the level of disease activity used for steering treatment adaptations is a different story. More tightly steered treatment might lead to medication overconsumption. A recent systematic review on the economic burden of RA¹¹ has found that drug costs comprise up to 87% of direct costs which is a finding in line with results from CareRA, COBRA Slim is cost saving since it delays the initiation of bDMARDs without compromising disease control nor quality of

life. Moreover, the COBRA light study¹² showed that steering based on a threshold of early remission instead of LDA leads to relatively high bDMARD use at the risk of overtreatment and also to protocol violations by treating physicians overruling the indication to change treatment based on their clinical judgement of sufficient response. Furthermore, rheumatologist's adherence to a disease activity score (DAS) steered treatment protocol in the BeSt and IMPROVED studies demonstrated that adherence to DAS-steered protocols appears to depend on the target level and on physician's perception of DAS reflecting RA activity or not.¹³

Further research is needed to fully understand if an early and short-term bDMARD course would be more effective but also cost-effective in comparison to csDMARDs with initial step-down GC schemes and subsequent DMARD adaptations in a treat-to-target approach. Moreover, having a bDMARD as first-line treatment immediately after diagnosis has not shown a clear benefit. The NORD-STAR trial has revealed that 24 weeks after treatment initiation, active conventional therapy based on MTX with GCs was non-inferior to certolizumab or tocilizumab.¹⁴ Furthermore, from an economical point of view, costs to achieve a better quality of life are too high using infliximab with MTX (BeSt trial) for initial remission induction. Theoretically, infliximab costs could be compensated by productivity savings; however, the 2 year cost-utility analysis of the BeSt trial did not prove this.¹⁵ Combination with GCs should be preferred.¹⁶ The CareRA study group has started the CareRA 2020 trial (EudraCT # 2017-004054-41) examining the cost-effectiveness of accelerated but temporary bDMARD access after failing to MTX monotherapy with a GC bridging scheme. Since baseline prognostic markers are still insufficiently effective, in this study the selection of patients with early RA for an upgrade to bDMARD therapy is based on currently the most effective predictor of the long-term disease course, being the early response to an intensive conventional remission induction regimen, COBRA Slim.

6.2 Seronegative RA, the sometimes-underestimated stepsister

The response of patients with seronegative RA to intensive treatment strategies

Seronegative rheumatoid arthritis patients have been historically undertreated and their good prognosis as having a milder disease course has been overestimated.^{17–20} Current EULAR recommendations focus on treating early, intensively and to a target of sustained remission or at least low disease activity. They also expand the concept of poor prognosis to include more than just seropositivity for RF and/or ACPA. Today, treatment decisions should be based on disease activity, safety issues and other patient factors, such as comorbidities and progression of structural damage.¹⁰ We compared the disease course in seronegative and seropositive patients from the CareRA trial and demonstrated that inflammation can be even more difficult to control in early 'seronegative' disease, which certainly needs more attention in the future. Specific studies in these seronegative patients are mandatory also further exploring the clinical heterogeneity and particular etiopathogenesis of this disease group.

The population without these markers, accounts for approximately one in three to four RA patients. Therefore, most analyses on this small population in trials are secondary, and little has been defined about this subgroup.¹⁷ However, this post-hoc analysis in CareRA included 141 patients treated with the same treatment scheme making it an ideal context to evaluate clinical response without having to adjust for treatment. Delayed treatment response¹⁷ and more initial inflammation²¹ was shown in the ARCTIC trial as well as in CareRA for seronegative patients. In spite of this, clinicians might sometimes feel reluctant to start intensive strategies on seronegative patients due the importance given to autoantibodies as diagnostic and prognostic factors historically.²²

The importance of rapid disease control is increasingly recognised nowadays as shown also by our group demonstrating speed of response is an independent predictor of future reported health.²³ The traditional outcome of radiographic progression has become increasingly less important in this era of effective treat-to-target strategies.²² In CareRA we demonstrated a delay in response (first remission) in seronegative patients. On the other hand, early response (week 16) and not serological status, was the most important predictor for losing disease control, after having achieved a first remission. It seems that seronegative RA requires at least an equally intensive initial treat-to-target therapy as seropositive RA.

6.3 How to measure the unobservable

The interpretation of disease activity markers and the estimated comprehensive disease burden in early RA

In this analysis, we integrated patient-important outcomes like pain, fatigue and physical function into the standard measurements of disease activity in RA, which provided a better understanding of the disease burden as perceived by the patient. Patient's global health assessment (PaGH) together with pain, fatigue, and physical function represented a separate aspect of the disease burden, the "Patient Reported" assessment. The swollen, and tender joint counts together with the physician's global health assessment corresponded to the "Clinical" assessment and serum acute phase reactants, CRP and ESR represented the "Laboratory" assessment. This 3-factor model: Patient, Clinical and Laboratory gave a comprehensive representation of 'disease status'. Because the original components of traditional disease activity scores remain in this 3-factor model, additional Patient Reported information is gained without losing the well-established Clinical and Laboratory factors.

Patient's global health assessment (PaGH) has been found to be influenced by factors not strictly related to disease activity such as pain, fatigue, and physical function.²⁴ Pain was indeed strongly correlated to PaGH (0.83) in our cohort, similar as in other cohorts (0.86).²⁵ PaGH in a cross-sectional study of patients with early RA, has been accounted for 32.8% of the variation in pain intensity and 10.7 % of the variation in morning stiffness.²⁶ Moreover, pain, fatigue and functional independence have been identified as the most critical factors when patients were asked to define remission.²⁷ A clear understanding of what PaGH is measuring is key for accurate interpretation of the composite scores including this outcome.

The 3-factor model provides a comprehensive assessment of the impact of RA on patients' life. A more tailored or perhaps even dual target might be needed for addressing the complete disease burden, making a distinction between aspects directly related to inflammatory disease activity and impact of disease not directly related to disease activity.

Based on the 3-factor model, after normalizing to a 0-1 scale and weighting by the factor loadings (how strong a variable relates to its factor) we calculated Patient Reported, Clinical and Laboratory factor scores, as well as a discordance score between the Patient Reported and the other two scores. Looking at the difference between the Patient reported severity score and the Clinical and Laboratory scores does provide further insights in remaining unmet needs despite optimal disease control and would allow to broaden the future scope of treating-to-target, potentially to more holistic non-pharmacological interventions. This is highly needed even in patients under sustained disease control.

Furthermore, this research group has shown within the CareRA trial that a rapid and sustained response ($\text{DAS28CRP} < 2.6$) from week 16 until year 1 and not treatment type was associated with favourable patient reported health and illness perceptions at year 1.²³ Most patients with rapid and sustained disease control had patient reported outcomes in concordance with their well-controlled disease activity. However, one in five patients still reported not feeling well at year 1. These patients reported higher pain and fatigue.²⁸ Already early in the disease course, a more rapid recognition of such remaining complaints could provide opportunities for additional potentially non-pharmacological interventions.

6.4 Painful RA

Chronic consumption of analgesics in early RA as a proxy for remaining pain

Rheumatoid Arthritis (RA) commonly presents with painful joints. Pain is and remains for patients with RA, their highest priority for improvement. Pain management is a crucial topic, primarily since it is closely related to quality of life. RA has been associated with analgesic prescription, historically as a stand-alone drug and afterwards in conjunction with DMARDs. Patients with RA use analgesics for RA-related and non-related pain, intermittently for acute flares or chronically.²⁹ In this analysis we investigate the consumption of analgesics. In the CareRA trial, patients who were recorded for more than 90 days an analgesic had a different evolution in terms of pain and disease activity parameters compared to non-chronic users.

Up to now, the health status of most RA patients has much improved since the introduction of intensive treatment strategies.³⁰ Despite a change in treatment strategy that already improved VAS pain levels from 46mm in 1994 to 35.8mm in 2001 according to a population based Norwegian publication, pain has remained the area of the highest priority for improvement in patients with RA.³⁰ In the same publication, Heiberg *et al.* report a 45.2% use of NSAIDs in 1994 compared to 37.1% in 2001.³⁰ NSAIDs overuse or misuse, both prescribed or over the counter, accounts for 39.5% of patients with RA according to a study in an outpatient-clinic where patient's pattern for NSAID consumption were evaluated.^{31,32} In CareRA about 1 in every 4 patients took analgesics for 90 days or more, which could even be of a narcotic (opioid) despite evidence not supporting prescription of weak or strong opioids for longer than 6 weeks in RA.^{32,33}

Pain related to RA disease activity or structural damage is by definition nociceptive. However, remaining pain experienced in RA may have multimodal features of pain perception, including neuropathic and sensitisation elements,^{34,35} making it harder to measure it accurately. Pain reported by patients is unique to their own experience and thresholds for pain, making it difficult to generalise. Obviously, such pain deserves appropriate treatment. However, studies have shown that taking analgesics, especially opioids, is frequently not discontinued even after the source of pain has gone, but rather their consumption increases.^{36,37}

Furthermore, in the low-risk group of CareRA, 92% of the patients who were started on MTX with no oral GC (TSU), were at some point during the trial using analgesics for MSK pain compared to 60% in the group treated with MTX and a step-down GC scheme (COBRA Slim). Chronic analgesic intake was more than double in TSU. Even in patients considered to have a favourable risk profile, when the initial treatment did not include oral GC bridging, there was an important consumption of analgesics becoming chronic for a significant proportion of them. To benefit maximally from the window of opportunity for treating early RA, intensive remission induction strategies (with GCs) should be applied even in patients without traditional factors of poor prognosis.

Taken together, these results suggest that pain should be given more attention, even in early RA. Awareness should also be given to the prescription behaviour of all stakeholders involved, not only the treating rheumatologist but also the general practitioner.³⁸ Unnecessary DMARD adaptations based mainly on pain reporting should be avoided. However, special interest should be given to the choice of initial treatment strategy since we have shown that it might influence pain management on the long run, even in patients considered to have a good prognosis. We suggest further study and adding pain as a specific focus in the management of early RA where patients might benefit from a broader scope of treating-to-target, besides disease control.³⁹

COBRA Slim: across the board

The combination of MTX with a step-down GC (prednisone 30mg) scheme, COBRA Slim, has been proven to be cost-effective, and applicable for both seronegative and seropositive patients with RA. COBRA Slim is a well-balanced scheme both clinically and economically. Clinically, it takes advantage of the quick effect of GCs to give MTX time enough to have an effect on disease control. Economically, it balances the cost by delaying the too early initiation of a bDMARD, optimising less costly schemes while preserving quality of life by avoiding added disutility of adverse events which are more frequent in schemes with a combination of csDMARDs.

The CareRA trial was conducted in Belgium, which, as a country, has the advantage of a Bismarck-type health care system which guarantees health coverage to almost its entire population. Hence, treatment cost is a worry for the government and not so much for the patient. However, even under reversed circumstances like in Latin America with health care coverage that goes as low as 22%,⁴⁰ in which the patient would have to entirely pay for the treatment, COBRA Slim would remain the best available choice. Especially since the Latin American public health system has coverage of less than 10% for bDMARDs and in about half of the countries.⁴⁰

Latin America has inadequate access to specialists which in term delays diagnosis and treatment diminishing the probability to achieve remission. RA-related deformities that have become a thing of the past in developed countries can still be seen in Latin America. Moreover, the vast majority of rheumatologists work in urban areas, leaving the rural areas without any access.⁴² Furthermore, more accurate epidemiological data is missing for Latin America in terms of RA, in particular health seeking behaviour, patient-centred outcomes, and preferences.

In more challenging health care settings, such as sub-Saharan Africa , MTX and step-down GC has been proven to be effective in a study performed at the rheumatology unit of the University Hospital of Kinshasa.⁴¹ However, implementation of a regular follow-up is a major issue, more than one third of this study's patients were lost at follow-up.⁴¹ Clearly, further research is needed to better understand and tackle the different potential barriers for successful implementation of intensive conventional treatment regimens in more challenging health care circumstances.

Overall conclusion

Are all needs of patients with early RA being met with intensive treat-to-target strategies? The research performed during this PhD research demonstrates that despite a majority of patients achieving a status of disease control, remaining unmet needs are still present. These results point to a more tailored approach, which might be necessary for patients not responding to the proposed initial "one size fits all" strategy in order to provide them with long-term effectiveness in disease control and quality of life while also being applicable and economically sustainable for every patient in daily clinical practice.

In chapter 2 (RQ₁), we demonstrated that COBRA Slim, the combination of MTX with a GC bridging scheme is less expensive with comparable health utility than more intensive step-down combination strategies or a conventional step-up approach 2 years after initial treatment and even substantial gain for low-risk patients. Therefore, we consider COBRA Slim a good starting strategy for all patients with early RA, irrespective of prognostic markers, in a treat-to-target setting.

In chapter 3 (RQ₂), the findings shed new light to patients with seronegative RA. These patients in general had a higher initial disease activity and longer time to first treatment response (remission) but achieved comparable remission status as seropositive patients with COBRA Slim. It seems that seronegative RA requires an equally intensive initial treat-to-target therapy as seropositive RA.

In chapter 4 (RQ₃), our study revealed that patient's global health assessment together with pain, fatigue, and physical function represent a separate aspect of the disease burden of early RA patients. Moreover, the difference between so-called factor scores derived from Patient Reported (calculated from PaGH + pain + fatigue + HAQ), Clinical (SJC28 + TJC28 + PhGH) and Laboratory (CRP and ESR) outcomes, does provide further insights and would allow to broaden the future scope of treating-to-target, including patient-centred apart from disease-activity-targeted care.

In chapter 5 (RQ₄), we showed that patients using chronic analgesics at the early stage of disease behaved differently in pain and disease activity parameters but also had more

DMARD adaptations. A critical reflection about evaluation of disease activity and DMARD adaptation is also needed in patients expressing persistent pain in the early disease phase. Attention should be given to the choice of initial treatment strategy. Intensive remission induction strategies (with GCs) should be applied even in patients without classical factors of poor prognosis to maximize the benefit from the window of opportunity of early RA. Moreover, patients might further benefit from a future differential focus on pain, adapting a broader scope of Treating-to-Target. Avoiding chronic analgesic use might have an early window of opportunity that should not be missed.

Altogether, the findings of this PhD research confirm the value of an initial intensive treat-to-target strategy but provides also evidence that a more tailored approach might be necessary for patients not responding. Of special interest is the patient's voice represented by patient-important outcomes for improvement which should be given more attention since they are not always strictly related to the level of disease activity.

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Summary

Rheumatoid Arthritis (RA) is the most common inflammatory joint disease. Patients with rheumatoid arthritis diagnosed and treated early achieve in most cases a state of remission or absence of disease activity. However, about 30% of patients do not. Evidence suggests that the initial chosen treatment scheme and a correct implementation is of paramount importance for reaching early and sustained disease control. It is recommended to start with methotrexate and a short-term course of glucocorticoids as a first-line treatment. For patients, failing the first-line treatment there is still some debate if as second-line, other conventional synthetic disease modifying anti-rheumatic drug csDMARD or a biological (bDMARD) should be given.

My work has focused on cost-effectiveness, on the importance of rapid disease control in seronegative disease, which should no longer be perceived as 'benign' but also deserves optimal treatment implementation certainly in the early disease period, and on remaining complaints, in terms of pain, fatigue and physical function. A holistic approach correctly assessing different aspects of disease burden is important already in the early disease course. The correct understanding of all factors reported by patients that might be different from laboratory evaluations or clinical assessments by the treating physician is critical. A more detailed analysis of these issues will hopefully lead to differential steering of medical decisions.

Scientific acknowledgement

Chapter 1: General introduction

Chapter 6: General discussion and overall conclusion

I would like to express my deepest appreciation to my supervisor Prof. Patrick Verschueren and co-supervisors Prof. René Westhovens and Prof. Annelies Boonen for their continuous guidance and mentoring. I feel extremely grateful to have had your unconditional support during the development of my PhD. I have enjoyed very much working with you and value how you have steered me in the right direction and revising critically my draft version for the PhD thesis.

Chapter 2: The price tag of RA: how we piggybacked CareRA

Two-year Cost-effectiveness of different COBRA-like intensive remission induction schemes in early rheumatoid arthritis: a piggyback study on the pragmatic randomized controlled CareRa trial

The following authors were involved in this study: Sofía Pazmino (SP), Patrick Verschueren (PV), René Westhovens (RW), Annelies Boonen (AB), Diederik De Cock (DDC), Veerle Stouten (VS), Kristien Van der Elst (KV), and Johan Joly (JJ).

Study conception and design: SP, PV, RW, AB

Data analysis with R: SP

The manuscript was written by SP, PV, RW, AB, and DDC and subsequently revised critically by all the remaining co-authors. All authors were involved in data interpretation and approved the final version to be submitted for publication.

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Chapter 3: Seronegative RA, the sometimes-underestimated stepsister

Impact of being seronegative for rheumatoid factor and anti-citrullinated cyclic peptide on the response to early intensive rheumatoid arthritis treatment: data from the CareRA trial

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All authors were involved in the interpretation of the data, and critically reviewed the manuscript content during data sessions. SP, PV, RW and AB drafted the manuscript.

We wish to thank Steffen Fieuws and Anikó Lovik for providing statistical advice.

Chapter 4: How to measure the unobservable

A. Including pain, fatigue and physical function when assessing patients with early rheumatoid arthritis provides a comprehensive picture of disease burden

The following authors were involved in this study: Sofia Pazmino (SP), Anikó Lovik (AL), Patrick Verschueren (PV), René Westhovens (RW), Annelies Boonen (AB), Diederik De Cock (DDC), Veerle Stouten (VS), Kristien Van der Elst (KV), Delphine Bertrand (DB), and Johan Joly (JJ).

Study conception and design: SP, AL, PV, RW, AB

Data analysis with R and SAS: SP and AL

The manuscript was written by SP, AL, PV, RW, AB, and DDC and subsequently revised critically by all the remaining co-authors. All authors were involved in data interpretation and approved the final version to be submitted for publication.

B. Traditional treatment response measures do not necessarily match patient reported improvement, even in early Rheumatoid Arthritis

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Study conception and design: SP, AL, PV, RW, AB

Data analysis with R and SPSS: SP and AL

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Chapter 5: Painful RA

A. Is there a window of opportunity for optimal pain management in RA: lessons from the CareRA trial?

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Study conception and design: SP, PV, RW, AB

Data analysis with R: SP

All authors were involved in the interpretation of the data, and critically reviewed the manuscript content during data sessions. SP, PV, RW and AB drafted the manuscript.

We wish to thank Anikó Lovik for providing statistical advice.

B. Bridging with glucocorticoids reduces the risk of chronic analgesic use among early rheumatoid arthritis patients with favourable prognosis: sub analysis of the CareRA randomized trial

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We wish to thank Anikó Lovik for providing statistical advice.

Personal Contribution

The following section summarizes the contribution of Sofia Pazmino Lucio to this PhD thesis.

Chapter 1 and Chapter 6: I drafted the general introduction and the general discussion based on advice and feedback from my supervisors.

Chapter 2: I was involved in the data analysis and interpretation. I drafted and revised the manuscript based on feedback from the co-authors.

Chapter 3: I was involved in data interpretation and performed the statistical analysis after advice from a statistician. I drafted and revised the manuscript based on the feedback from my supervisors.

Chapter 4: I was involved in data interpretation and performed the statistical analysis in collaboration with Anikó Lovik. I was involved in data interpretation, and I drafted and revised the manuscript based on the feedback from the co-authors.

Chapter 5: I was involved in the design, collected data and performed the statistical analysis after advice from a statistician. I drafted and revised the manuscript based on the feedback from my supervisors.

Conflict of Interest

The authors have no conflicts of interest to disclose.

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None of the funding organizations have access to the study data, nor were they involved in the preparation of the manuscripts.

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- Basic knowledge of SAS and Python

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- Pazmino, S., Boonen, A., Stouten, V., De Cock, D., Joly, J., Van der Elst, K., Westhovens, R., Verschueren, P. (2020). Two-year cost-effectiveness of different COBRA-like intensive remission induction schemes in early rheumatoid arthritis: a piggyback study on the pragmatic randomised controlled CareRA trial. *Annals Of The Rheumatic Diseases*, Art.No. 2019-216874.R1. (Impact factor: 16.10)
- De Cock D., Brants L., Soenen I., Pazmino S., Bertrand D., Stouten V., Westhovens, R., Verschueren, P. (2020) A systematic review on the effect of DMARDs on fertility in rheumatoid arthritis. *Semin Arthritis Rheum* [Internet]. 2020 Aug 30 Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0049017220301992> (Impact factor: 5.02)

- Van der Elst, K., Verschueren, P., De Cock, D., De Groef, A., Stouten, V., Pazmino, S., Vriezekolk, J., Joly, J., Moons, P., Westhovens, R. (2020). One in five patients with rapidly and persistently controlled early rheumatoid arthritis report poor wellbeing after 1 year of treatment. *RMD Open* 2020; 6:e001146. doi: 10.1136/rmdopen-2019-001146 (Impact factor: 3.44)
- Verschueren, P., Stouten, V., Westhovens, R., De Cock, D., Pazmino, S. (2020). Comment on: what is the best treatment for early rheumatoid arthritis? *Rheumatology (Oxford)*. doi: 10.1093/rheumatology/keaa106 (Impact factor: 5.60)
- Stouten, V., Michiels, S., Westhovens, R., De Cock, D., Belba, A., Pazmino, S., Van der Elst, K., Joly, J., Verschueren, P. (2020). Effectiveness of maintenance therapy with methotrexate compared with leflunomide for patients with RA having achieved disease control with both these drugs: results of a predefined sub-analysis of CareRA, a pragmatic RCT. *Clin Rheumatol*. doi: 10.1007/s10067-020-05008-4 (Impact factor: 2.29)
- Stouten, V., Westhovens, R., Pazmino, S., De Cock, D., Van Der Elst, K., Joly, J., Verschueren, P. (2019) Effectiveness of different combinations of DMARDs and glucocorticoid bridging in early rheumatoid arthritis: two-year results of CareRA. *Rheumatology (Oxford)* /doi/10.1093/rheumatology/kez213/5522554. (Impact factor 5.60)
- Van der Elst, K., Verschueren, P., Stouten, V., Pazmino, S., De Groef, A., De Cock, D., Joly, J., Moons, P., Westhovens, R. (2019). Patient-Reported Outcome Data From an Early Rheumatoid Arthritis Trial: Opportunities for Broadening the Scope of Treating to Target. *Arthritis Care Res*; 71(12):1566–75. doi/abs/10.1002/acr.23900 (Impact factor 1.87)

Abstracts at Scientific Conferences

International Conferences

2020

- Pazmino, S., Boonen, A., Stouten, V., De Cock, D., Bertrand, D., Van der Elst, K., Joly, J., Westhovens, R., Verschueren, P. (2020). Patients with early Rheumatoid Arthritis considered to have a favourable risk profile and treated according to a step-up strategy have an increased risk of chronic analgesic consumption. American College of Rheumatology Congress. Washington, US, 5-9 November 2020. [**submitted**]
- Pazmino, S., Boonen, A., Stouten, V., De Cock, D., Bertrand, D., Van der Elst, K., Joly, J., Westhovens, R., Verschueren, P. (2020). Seronegative rheumatoid arthritis: mild no more. Panamerican League Against Rheumatism Congress. Miami, US, 17-20 September 2020. [**virtual poster**]
- Pazmino, S., Lovik, A., Boonen, A., Stouten, V., De Cock, D., Bertrand, D., Joly, J., Westhovens, R., Verschueren, P. (2020). Clinical treatment response still does not match patient reported improvement, even in early Rheumatoid Arthritis. European Congress of Rheumatology. Frankfurt, Germany, 3-6 June 2020. [**virtual poster**]

- Pazmino, S., Stouten, V., Verschueren, P., Mamouris, P., Westhovens, R., De Vlam, K., Bertrand, D., Van der Elst, K., Vaes, B., De Cock, D. Analgesic and anti-inflammatory drug use in patients with rheumatoid arthritis, psoriatic arthritis and spondyloarthritis versus controls in a Belgian General Practitioner registry. European Congress of Rheumatology. Frankfurt, Germany, 3-6 June 2020. [**virtual poster**]
- De Cock, D., Nooyens, A., Bertrand, D., Stouten, V., Pazmino, S., Joly, J., Westhovens, R., Verschueren, P. Early remission is associated with lower fatigue levels on the long term in patients with recent onset Rheumatoid Arthritis. European Congress of Rheumatology. Frankfurt, Germany, 3-6 June 2020. [**virtual poster**]
- De Cock, D., Nooyens, A., Pazmino, S., Bertrand, D., Stouten, V., Joly, J., Westhovens, R., Verschueren, P. Treating early and intensively is associated with lower fatigue levels on the long term, even in patients with early Rheumatoid Arthritis considered to have a favourable risk profile. European Congress of Rheumatology. Frankfurt, Germany, 3-6 June 2020. [**virtual poster**]
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Cover Page

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The two original paintings used for the cover of this thesis are the work of art of an ecuadorian painter Nelson Ramos Vinueza. The paintings were inspired on the work of the famous ecuadorian expresionist painter Oswaldo Guayasamín, who described his work as “My painting is to hurt, to scratch and strike at the hearts of the people”.

The author, Nelson Ramos Vinueza, gave written authorization to use and digitally modify the paintings.

Art is a tool that allows the human being to express an array of emotions. The pain and the suffering can be conveyed in a painting. In the same way, a painting can transmit joy, satisfaction, and overall well-being. This is the message being depicted with this two paintings.

For the first work of art, the painter was charged with capturing the pain and suffering of people with uncontrolled Rheumatoid Arthritis (RA). This painting is a painful reminder of a time when RA was truly a disabling disease.

In the second canvas, the painter represents tranquility and harmony, of a patient under control. Thus, calm and well-being are perceptible.





“Out of doom and misery, the most beautiful song may rise”

De mensen hebben hun gebreken. A. Van Duinkerken, 1958

