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Five-year treat-to-target outcomes after methotrexate induction therapy with or without other csDMARDs and temporary glucocorticoids for rheumatoid arthritis in the CareRA trial

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Key messages

What is already known about this subject?

- The COBRA-Slim strategy, initiating methotrexate with glucocorticoid bridging and applying treat-to-target, , is a clinically and health-economically very effective approach for patients with early RA up to 2 years of follow up.

What does this study add?

- in RA patients with poor-prognostic factors, starting with COBRA-Slim led to similar and sustained effectiveness profiles over 5 years as starting with csDMARD combinations and glucocorticoid bridging.
- In RA patients without a poor prognosis, starting a COBRA-Slim scheme led to better effectiveness over 5 years than a conservative step-up from methotrexate without glucocorticoids.
- Only about 1 in 6 patients ever used glucocorticoids chronically for >6 months and about 1 in 5 patients initiated biologicals over 5 years.

How might this impact on clinical practice or future developments?

- The COBRA-Slim scheme can serve as an effective initial treatment option for all types of patients with early RA, avoiding chronic glucocorticoid use in a large majority and reserving more intensive treatment combinations for insufficient responders only.

Abstract

Objectives

To compare outcomes of different treatment schedules from the Care in early RA (CareRA) trial over 5 years.

Methods

RA patients completing the 2-year CareRA RCT were eligible for the 3-year observational CareRA-plus study. 5-year outcomes after randomization to initial MTX monotherapy with glucocorticoid bridging (COBRA-Slim) were compared to MTX step-up without glucocorticoids or csDMARD combination with glucocorticoid bridging, per prognostic patient group. Disease activity (DAS28-CRP) and functionality (HAQ) were compared between treatment arms using longitudinal models; safety and drug use were detailed.

Results

Of 322 eligible patients, 252 (78%) entered CareRA-plus, of which 203 (81%) completed the study. Treatments for high-risk patients resulted in comparable DAS28-CRP (p=0.539) and HAQ scores over 5 years (p=0.374). Low-risk patients starting COBRA-Slim had lower DAS28-CRP (p<0.001) and HAQ scores (p=0.041) than those starting only on MTX. At study completion, 114/203 (56%) patients never had their original DMARD therapy intensified, with comparable rates between all treatments. Safety was comparable between treatments in high-risk patients. In low-risk patients, there were 18 adverse events in 10 COBRA-Slim and 36 in 17 patients treated with initial MTX monotherapy (p=0.048). Over 5 years, 22% of patients initiated biologics, 25% took glucocorticoids for >3 months and 17% for >6 months outside the bridging period.

Conclusions

All intensive treatments with glucocorticoids bridging demonstrated excellent 5-year outcomes. Initiating COBRA-Slim was comparably effective as more complex treatments for high-risk early RA patients and more effective than initial MTX monotherapy for low-risk patients with limited need for biologics and chronic glucocorticoid use.

Keywords:

- DMARDs
- effectiveness
- rheumatoid arthritis
- glucocorticoids
- Initial treatment strategy

Introduction

It is recommended to treat patients with early rheumatoid arthritis (RA) immediately, intensively and to a predefined target to rapidly control disease activity, and to avoid joint damage and functional decline [1,2]. Methotrexate (MTX) forms the core of initial RA therapy. The CareRA study was designed to investigate whether MTX should be combined with an additional conventional synthetic (cs) DMARD and/or with glucocorticoid bridging to induce a rapid, stable clinical response in patients with early RA. We demonstrated that MTX monotherapy with glucocorticoid bridging (COBRA Slim) in a treat-to-target setting had a better effectiveness in patients with poor prognostic factors over 2 years, with similar efficacy but a better safety profile, compared to csDMARD combinations and glucocorticoid bridging [3–5]. Moreover, COBRA Slim showed benefit over a tight-step-up with MTX monotherapy in RA patients without poor prognosis markers [5,6]. The COBRA Slim regimen also proved to be more cost-effective and was endorsed in the updated EULAR recommendations of 2019 to treat RA [7,8].

As EULAR recommendations emphasize the importance of sustained remission or at least low disease activity, long-term evaluation of treatment effectiveness is necessary. The 11 year follow-up of the original COBRA trial showed reassuring long-term efficacy and safety of early intensive csDMARD combination therapy, even without a strict treat-to-target approach [9]. More recently, the 10 year follow-up of the BeSt trial, incorporating the tight control principle, confirmed the importance of early intensive combination therapy and demonstrated that drug-free remission and normalized mortality rates have become realistic outcomes [10]. Despite all evidence above, current guidelines are still debated, especially the early use of glucocorticoids [11]. Therefore, our objective was to study the long-term effectiveness of the initial treatment schemes used in CareRA within the 3-year observational CareRA-plus follow-up study. We compared patients according to their original treatment arms in terms of sustained disease control, use of csDMARDs, glucocorticoids and biologic (b)DMARDs, as well as safety over 5 years.

Methods

Study design

CareRA-plus was a 3-year observational follow-up study of the investigator-initiated, multicentre, pragmatic, 2-year CareRA RCT. In CareRA, we included 379 patients with early RA (<1 year), naïve to and without contraindications for csDMARDs or glucocorticoids. Participants completing CareRA were eligible for inclusion in CareRA-plus, which was conducted in 10 Belgian rheumatology centres (1 academic centre, 6 general hospitals and 3 private practices). The ethics committee (EC) of University Hospital Leuven approved the CareRA-plus protocol after consultation of the local ECs and all patients re-consented.

Initial and subsequent treatments in CareRA and CareRA-plus

Before randomization in CareRA, patients were stratified into a high-risk or low-risk group based on the presence of classical prognostic factors, including RF / ACPA positivity, high baseline disease activity (DAS28-CRP>3.2) and X-ray erosions. Patients in the high-risk group were randomized to one of three remission induction schemes: COBRA Classic (initial combination of methotrexate (MTX) and sulfasalazine), COBRA Slim (MTX monotherapy) or COBRA Avant-Garde (initial combination of MTX and leflunomide). All COBRA schemes included an initial step-down scheme of oral prednisone, started at a high or moderate dose, and tapered weekly over 6 or 7 weeks to a low maintenance dose which was discontinued at week 28. The schemes combining two csDMARDs were tapered to csDMARD

monotherapy at week 40 in case patients achieved low disease activity (DAS28-CRP≤3.2). Patients in the low-risk group were randomized to one of two schemes: the same COBRA Slim scheme as in high-risk or Tight Step-up (MTX monotherapy without oral glucocorticoids). During follow-up the treat-to-target principle was applied. When a target of low disease activity was not reached, treatment was adjusted according to two predefined steps, from week 8 onwards during the initial study year. During the second year, treatment was at the discretion of the rheumatologist. The protocol was described in detail in previous publications [4,5]. In CareRA-plus, further application of the treat-to-target principle was recommended but was left to the shared decision of rheumatologists and patients.

Assessments and outcomes in CareRA-plus

During CareRA-plus, participants were assessed every 6 months for 3 years. Disease activity (DAS28-CRP and Simplified Disease Activity Index (SDAI)), clinical parameters and functionality measured by the Health Assessment Questionnaire (HAQ) were registered. All (serious) adverse events ((S)AEs) considered to be relevant according to the investigators, and all DMARD and glucocorticoid use was recorded. Demographic variables, including comorbidities were registered at baseline of CareRA.

We assessed DMARD changes from baseline CareRA and over 5 years, resulting in 3 possible trajectories: Patients adding or switching csDMARDs, patients initiating a bDMARD and patients who never had an intensification. In the latter trajectory, patients stayed on csDMARD monotherapy from week 40 onwards in COBRA Classic and COBRA Avant-Garde, and from baseline in COBRA Slim till year 5 or alternatively, discontinued all DMARD therapy. We assessed glucocorticoid use by the cumulative dose of all systemic glucocorticoids and by chronic use (>3 or >6 months) of oral glucocorticoids outside of the initial prednisone step-down periods.

Yearly radiographs of hands and feet were read chronologically from baseline CareRA till year 5 using the Sharp van der Heijde (SvdH) score by one blinded reader [12]. This reader was trained by an experienced reader who scored previously all radiographs of the original CareRA trial in the same manner. This training was validated by calculating an intra-class correlation coefficient, using radiograph scores from baseline till year 2 of both readers, indicating a good inter-reader reliability (ICC=0.83 (95% CI: 0.81 to 0.85)). Radiographic progression was analysed by the change in the total SvdH score from baseline CareRA till year 5 as well as the evolution of the SvdH scores over time, and visualized by a cumulative probability plot in completers,.

Statistical analysis

Each analysis compared the outcomes between the originally allocated treatment arms of the CareRA trial. Potential differences in clinical outcomes, were examined by Chi-square, ANOVA or Kruskal-Wallis, independent t-test or Mann-Whitney U test, when appropriate.

Proportions of patients in low disease activity or in remission according to DAS28-CRP or SDAI were calculated based on observed data and on an 'intention-to-treat' analysis including all patients consenting to participate to CareRA-plus. For the latter, missing data of components of the disease activity indices were imputed with multiple imputation by chained equations, resulting in 100 datasets. Each dataset was analysed separately and results were pooled using Rubin's rules [7,13].

The changes in DAS28-CRP, SDAI and HAQ were analysed over 5 years using linear mixed models (LMM). Remission and low disease activity rates over 5 years were analysed by generalized linear mixed models (GLMM). These mixed models incorporated a random intercept and a random slope for time with an unstructured covariance matrix. This method accounts for the repeated observations within a patient and allows the estimation of a different regression line for each patient with a different baseline value and rate of change over time. SvdH scores over time were compared using a generalized estimating equations (GEE) analysis with a negative binomial working distribution to address skewness

of these data. For each model, treatment and time were used as determinants and it was tested whether there was an interaction between treatment and time. The numbers of AEs occurring during CareRA-plus were compared using Poisson regression. Significance level was set at 0.05. Analyses were carried out using SPSS version 26 and R version 4.0.1.

Results

Participants

Of 322 patients who completed the 2-year CareRA study, 252 (78%) re-consented to be enrolled in CareRA-plus. We compared patients according to their originally allocated treatment in the high-risk group: COBRA Slim (n=75) versus COBRA Classic (n=69) or COBRA Avant-Garde (n=59) and in the low-risk group: COBRA Slim (n=23) versus tight-step-up (n=26). In both risk groups, treatment arms were well balanced in terms of demographic and clinical characteristics, registered at baseline CareRA (table 1). Patients entering CareRA-plus had similar demographics and clinical characteristics at the final 2-year visit of the CareRA trial compared to patients not entering the follow-up study. CareRA-plus patients were enriched for being ACPA positive, compared to non-participants, but ACPA status did not differ between treatment groups (supplement 1). In total, 203 (81%) participants in CareRA-plus completed the extra 3-year follow up, with similar frequencies or reasons for discontinuation between original treatment arms (figure 1). The 49 patients not completing the study, were followed-up during a median of 19 months (Interquartile range: 13 to 26) in CareRA-plus and 29 (59%) of them were in remission based on their last registered DAS28-CRP.

Disease activity over time

Disease activity improved rapidly during the first 16 weeks in CareRA and remained stable over the following 5 years among patients of the high-risk group (figure 2). There were no differences in DAS28-CRP or SDAI scores over time between treatment arms (LMM: respectively p=0.539 and p=0.431 for overall comparison; supplement 2A). In the low-risk group, disease activity (DAS28-CRP) over 5 years was lower in patients starting COBRA Slim compared with those initiating tight-step-up (LMM: β=-0.46; CI [-0.63 to -0.29]; p<0.001). Accordingly, SDAI scores over 5-year follow-up were also lower with the COBRA Slim strategy (LMM: β=-2.46; CI [-3.87 to -1.04]; p=0.001; supplement 2B).

Remission and low disease activity states

Based on available data of CareRA-plus participants who completed the 5-year follow-up since treatment initiation, overall, 89% had low disease activity (DAS28-CRP≤3.2), and 74% were in remission (DAS28-CRP<2.6) at year 5. Low disease activity measured by SDAI≤11 was achieved by 89% of all patients and remission (SDAI≤3.3) by 40% of patients. The proportion with a DAS28-CRP<2.6 at year 5 in high-risk patients was 72%, 77% and 64% for the Classic, Slim and Avant-Garde group respectively (p=0.403). In the low-risk population, 83% of patients in the Slim and 82% in the tight-step-up arm had a DAS28-CRP<2.6 at year 5 (p=0.945). Remission rates at year 5 based on an intention-to-treat analysis with imputation of missing data were comparable (supplement 3). Remission and low disease activity rates are shown over time in figure 3/supplement 4. Occurrence of remission over time assessed by DAS28-CRP or SDAI was similar between treatments in the high-risk group (GLMM: respectively p=0.798 and p=0.224 for overall comparison; supplement 2A). In the low-risk group, patients on COBRA Slim had higher odds of achieving remission over time, compared to patients started on tight-step-up (GLMM: OR=2.62 CI [1.43 to 4.81]; p=0.002 for DAS28-CRP remission, OR=3.27 CI [1.35 to 7.91]; p=0.009 for SDAI remission) (supplement 2B).

Functionality

In the high-risk group, mean HAQ scores over 5 years were comparable between treatment arms (LMM: p= 0.374 for overall comparison; supplement 2A). Among patients of the low-risk group, those treated initially with COBRA Slim had lower HAQ scores and thus better functionality over 5 years (LMM: β= 0.21 CI [-0.41 to -0.01]; p=0.041; supplement 2B).

Radiographic progression

After 5 years, radiographic progression, measured as increase in SvdH score, in patients completing the study was limited and comparable between treatment arms in the high-risk population. More specifically, 3 patients in Classic, 3 in Slim high-risk and 1 in Avant-garde had an increase in SvdH score >5. There were 11 patients in Classic, 9 in Slim and 5 in Avant-Garde who had an increase in SvdH score >0.5 (p= 0.399). In the low-risk group there were no patients with a change in SvdH > 5, and there was 1 Slim patient with a change >0.5 (p=0.283). A cumulative probability plot is shown in supplement 5. Longitudinal analyses demonstrated that the mean change in SvdH score over 5 years was similar between treatment arms in the high-risk and the low-risk group (GEE: p= 0.524 and p=0.928 for overall comparison respectively; supplement 2).

Treatment intensifications

At the year 5 visit, 71%, 61% and 50% of high-risk patients were on csDMARD monotherapy (mostly MTX) in the Classic, Slim and Avant-Garde arm respectively. In the low-risk group, 65% in the COBRA Slim and 62% in the tight-step-up arm were taking a single csDMARD. All treatment schemes showed similar trajectories of changes in csDMARD or bDMARD use over the 4 years following the protocolized first year of the trial (figure 4). Of all patients completing the study, 56% never had their DMARD therapy intensified for 5 years. More specifically, 64%, 58% and 48% of high-risk patients in the Classic, Slim and Avant-Garde arm reached year 5 without DMARD intensifications. In the low-risk group, 50% of Slim low-risk and 52% of tight-step-up patients never had an intensification in their DMARD therapy. During the 5 study years, biologics were initiated in 22% of all participants consenting to CareRA plus: 23% of Classic, 23% of Slim high-risk, 25% of Avant-Garde, 17% of Slim low-risk, and 15% of tight-step-up patients. At the year 5 visit, only 9% of all participants were using oral glucocorticoid therapy for >3 months at a median dose of 5.0 mg prednisone equivalent. The cumulative glucocorticoid dose taken by patients was comparable between treatment arms in both risk groups from year 2 onwards (figure 5). Throughout the entire 5-year study, chronic glucocorticoid use of > 3 or >6 months outside of the initial prednisone schemes was limited to respectively 25% or 17% of all patients (Supplement 6).

Safety

In high-risk patients, the total numbers of AEs throughout the 3-year follow-up in CareRA-plus, were 70 in 36 Classic, 95 in 48 Slim and 80 in 36 Avant-Garde patients (p=0.182). In the low-risk group, there were 18 AEs in 10 Slim and 36 in 17 tight-step-up patients (β=-0.571 CI [-1.136 to -0.005]; p=0.048) (Table 2 and supplement 2).

Table 1: Demographic and clinical characteristics of patients enrolled in CareRA-plus per original treatment arm, as recorded at baseline CareRA

	High-risk			Low-risk	
	COBRA Classic n=69	**COBRA Slim n=75**	**COBRA Avant-Garde n=59**	**COBRA Slim n=23**	**Tight Step Up n=26**
Demographic variables					
Age, years	54 (12)	52 (13)	53 (13)	53 (14)	51 (13)
Body mass index, kg/m²	26 (4)	27 (4)	27 (4)	25 (4)	28 (4)
Women, n (%)	43 (62)	53 (71)	39 (66)	16 (70)	20 (77)
Smokers, n smoked ever (%)	41 (59)	43 (57)	38 (64)	13 (57)	11 (42)
Median (IQR) symptom duration	22 (13-44)	23 (14-38)	27 (14-52)	23 (16-36)	19 (10-30)
RF positive, n (%)	52 (75)	62 (83)	46 (78)	8 (35)	6 (23)
ACPA positive, n (%)	53 (77)	60 (80)	52 (88)	10 (43)	6 (23)
Erosive disease, n (%)	25 (36)	24 (32)	18 (31)	0 (0)	0 (0)
Comorbidity present, n(%)	31 (45)	41 (55)	30 (51)	10 (43)	8 (31)
RDCI	0.8 (1.0)	1.0 (1.1)	0.9 (1.1)	1.0 (1.3)	0.6 (1.3)
Clinical variables					
DAS28-CRP	5.0 (1.1)	4.8 (1.1)	4.7 (1.2)	4.4 (1.9)	4.5 (1.6)
Tender Joint Count (0-68)	14 (9)	14 (9)	14 (8)	13 (13)	13 (8)
Swollen Joint Count (0-66)	11 (7)	11 (7)	10 (6)	11 (8)	8 (7)
PGA, mm (0-100)	62 (20)	55 (22)	55 (24)	48 (32)	44 (23)
Pain, mm (0-100)	60 (22)	57 (20)	58 (24)	45 (31)	48 (23)
Fatigue, mm (0-100)	50 (24)	48 (22)	50 (24)	39 (28)	41 (21)
PhGA, mm (0-100)	52 (17)	52 (18)	49 (17)	46 (19)	43 (24)
ESR, mm/h	34.6 (24.8)	33.2 (24.0)	26.0 (18.8)	32.4 (31.1)	25.3 (18.1)
CRP, mg/L	18.8 (25.5)	24.0 (35.9)	13.8 (18.3)	27.3 (50.9)	13.6 (18.5)
HAQ score (0-3)	1.2 (0.7)	0.9 (0.7)	1.0 (0.6)	1.0 (1.0)	0.9 (0.7)

Values reported are means (standard deviation) unless specified otherwise. Symptom duration= weeks elapsed between onset of symptoms and start of treatment; IQR= Inter Quartile Range; RF= Rheumatoid factor; ACPA= Anti-Cyclic Citrullinated Protein; RDCI= Rheumatic Diseases Comorbidity Index; Comorbidity present= presence of at least 1 comorbidity as selected by the RDCI; DAS28= Disease activity score based on 28 joints; CRP= C-reactive protein; PGA= Patient's global assessment; PhGA= Physician's global assessment; ESR= Erythrocyte sedimentation rate; HAQ= Health assessment questionnaire. Comparisons of variables between treatment groups performed via ANOVA or Kruskal-Wallis test, unpaired t-test or Mann-Whithey U test, or Chi² test when appropriate. There were no significant differences in characteristics between treatment arms in high- or in low-risk groups.

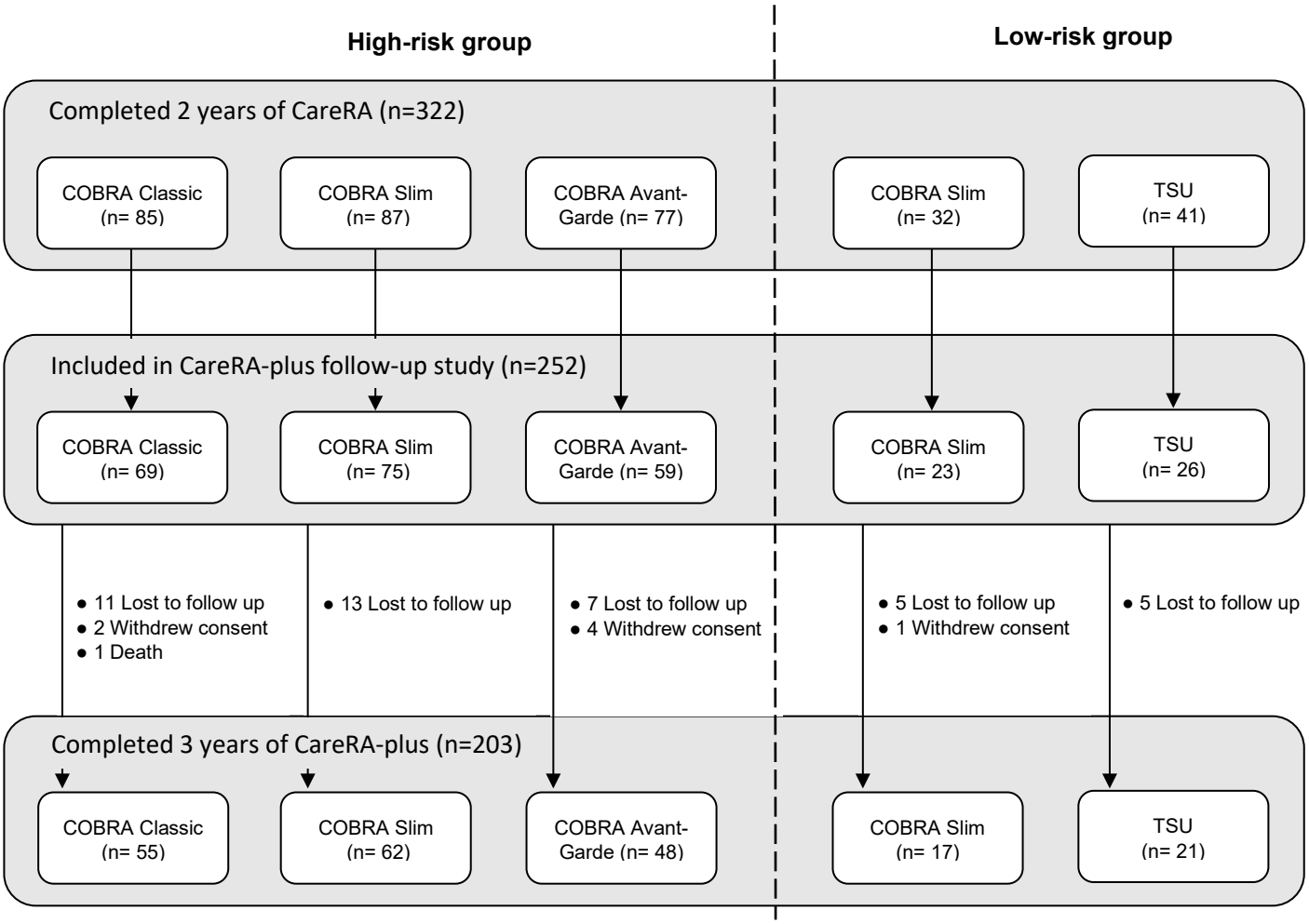

Figure 1: Flow chart of participants during the 3-year observational CareRA-plus study.
TSU= Tight Step Up

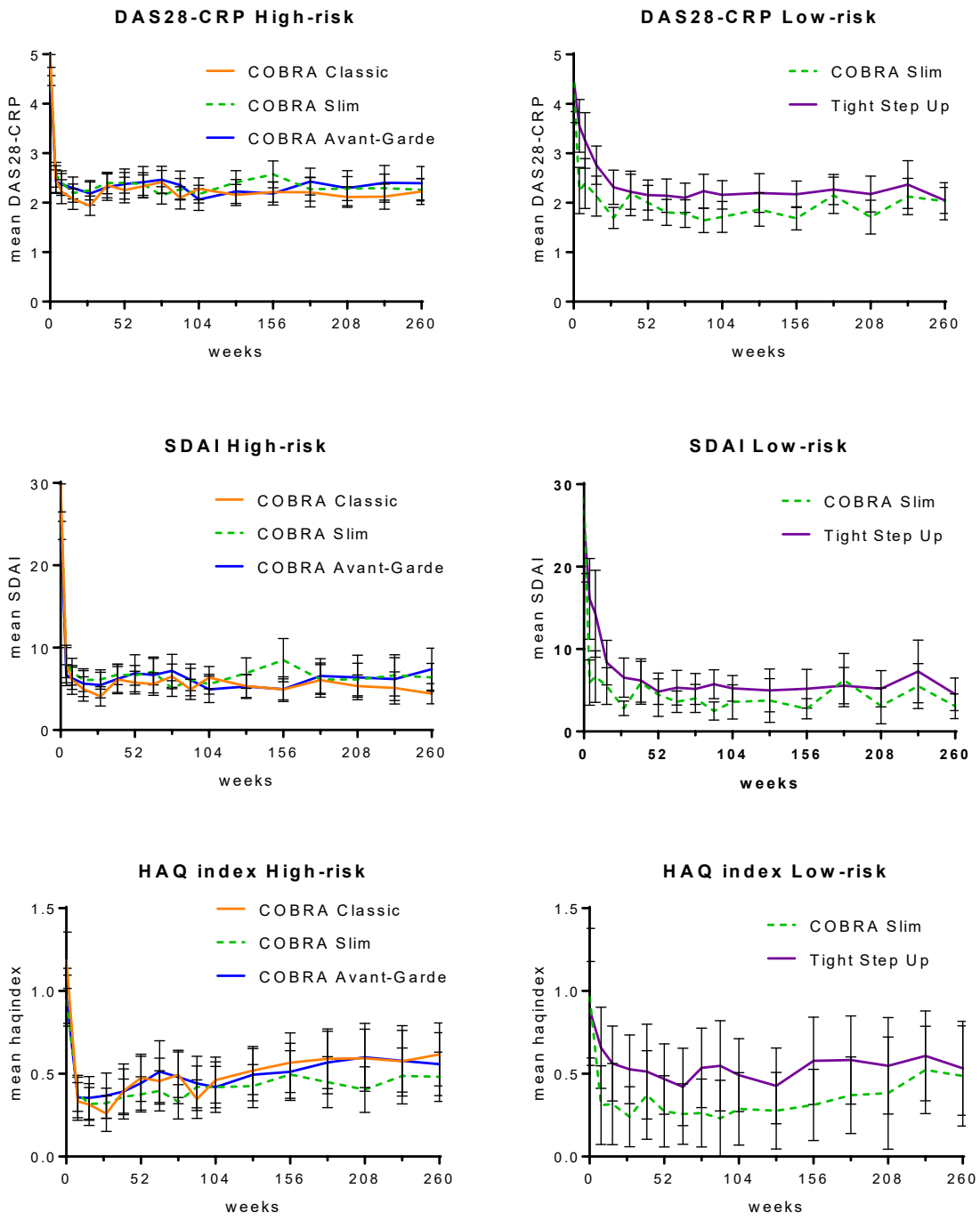

Figure 2: Disease activity and physical functioning during 5 years of follow up

Data are shown as observed, based on patients still in follow-up at each time point. Error bars indicate the 95% confidence intervals. DAS28-CRP= Disease activity score based on 28 joints calculated with C-reactive protein; SDAI= Simplified Disease Activity Index; HAQ= Health assessment questionnaire.

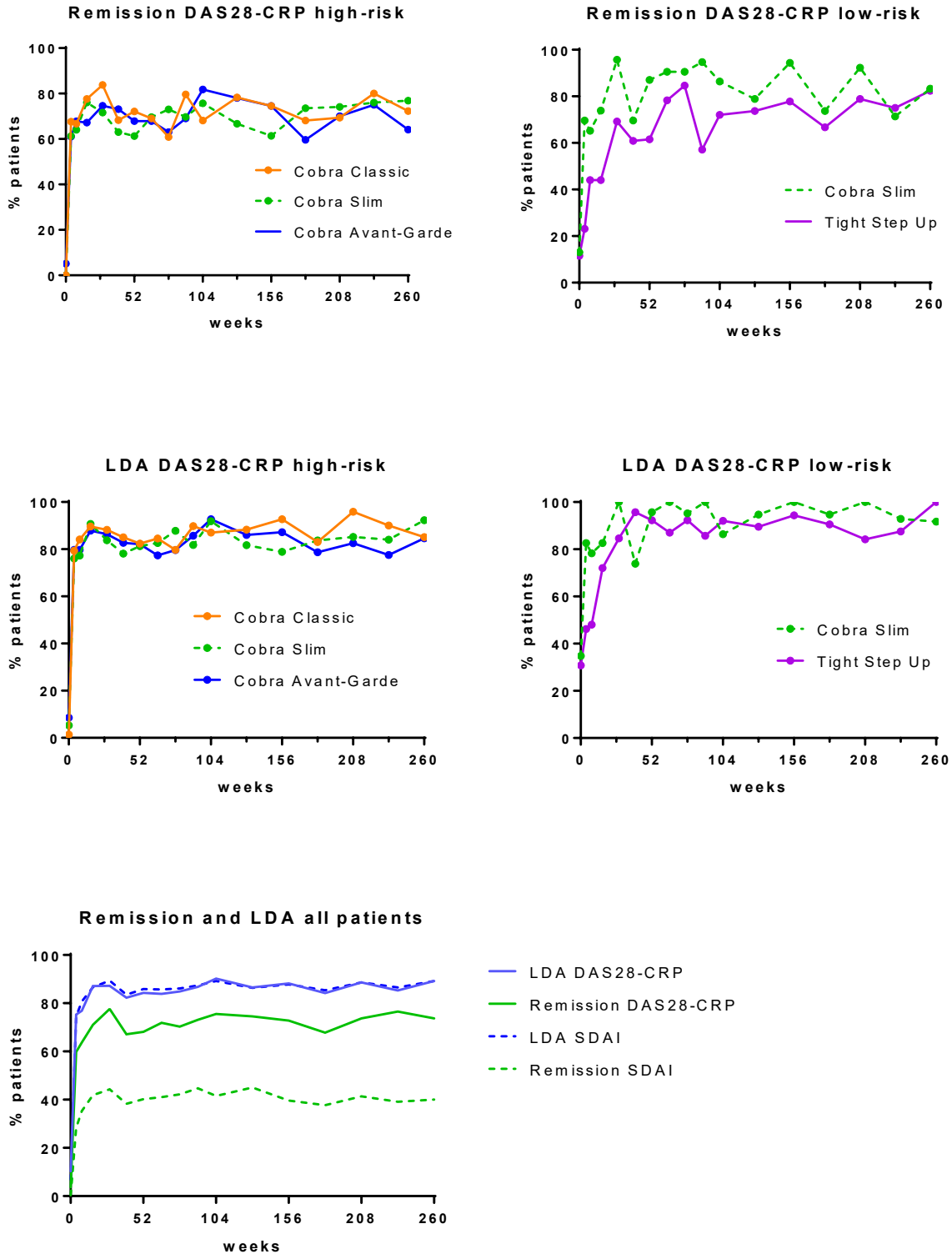

Figure 3: Remission and low disease activity rates during 5 years of follow up

Data are shown as observed, based on patients still in follow-up at each time point; DAS28-CRP= Disease activity score based on 28 joints calculated with C-reactive protein; LDA= low disease activity; Remission DAS28-CRP<2.6; LDA DAS28-CRP≤3.2; SDAI= Simplified Disease Activity Index; Remission SDAI ≤3.3; LDA SDAI ≤11.

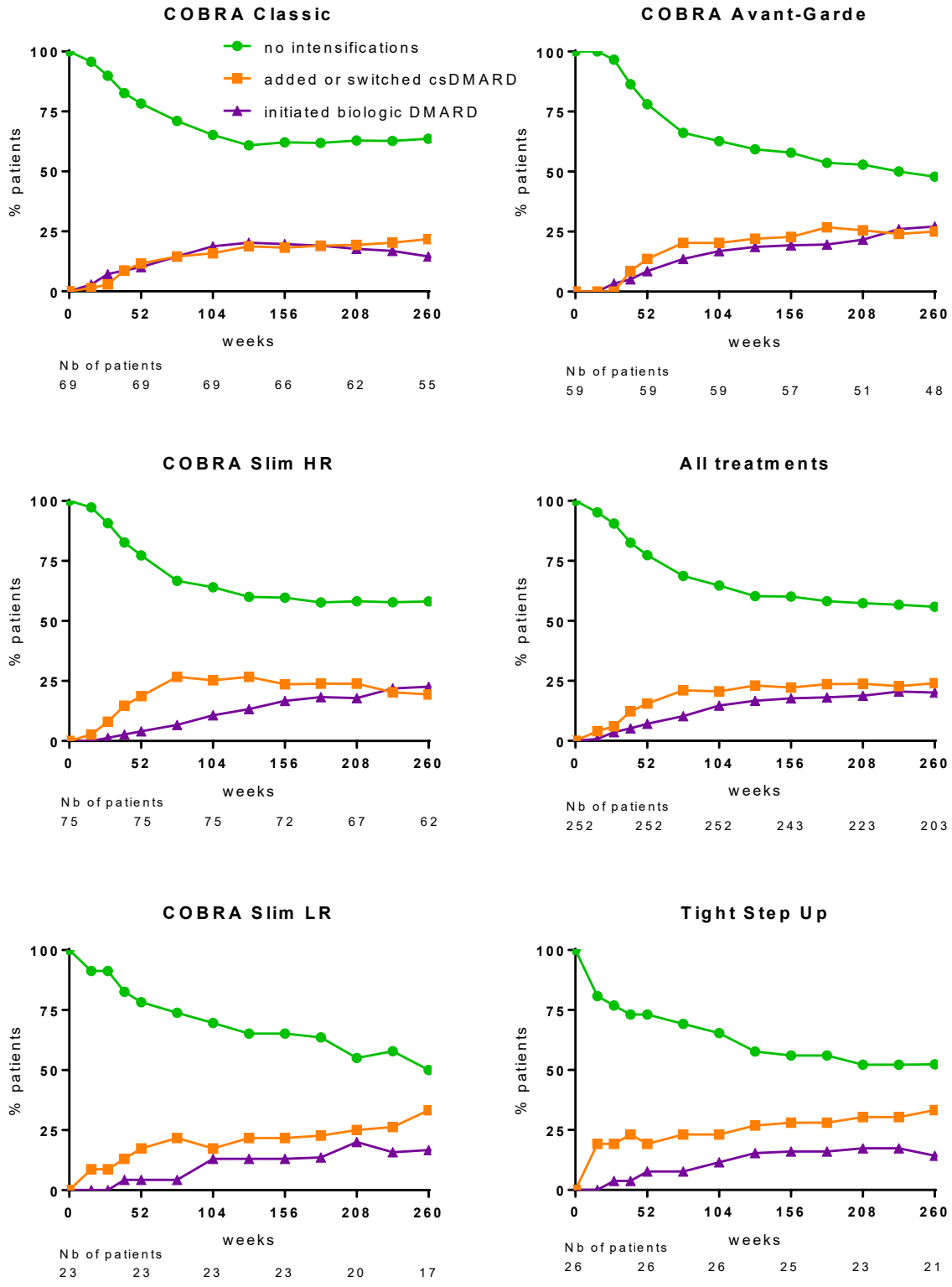

Figure 4: Medication profiles taken by participants during 5 years of follow up in each treatment arm

No intensifications = participants who did not have to intensify their DMARD treatment; Added or switched csDMARD = participants who added or switched a csDMARD; Initiated biologic = participants who initiated biologic DMARD(s); Percentages are calculated on patients still in follow up at each time point; Nb= Number; csDMARD= conventional synthetic disease modifying anti-rheumatic drug; HR= high-risk; LR= low-risk.

	High-risk			Low-risk	
	COBRA Classic n=69	**COBRA Slim n=75**	**COBRA Avant-Garde n=59**	**COBRA Slim n=23**	**Tight Step Up n=26**
Total Nb of AE	70	95	80	18	36
Patients with AE	36 (52%)	48 (64%)	36 (61%)	10 (43%)	17 (65%)
Total Nb of SAE	9	20	11	3	6
Patients with SAE	7 (10%)	15 (20%)	11 (19%)	2 (9%)	6 (23%)
Severe infection	16	18	17	1	6
Orthopedic intervention	6	10	10	1	4
Fracture	6	3	8	1	6
Severe cardiovascular problem	0	5	5	2	1
Malignancy	1	5	1	0	1
Diabetes Mellitus	2	1	0	0	0
RA related extra-articular disease	1	0	1	0	0
Vasculitis	1	1	0	0	0

Table 2: Safety analysis from year 2 till year 5 within the observational CareRA-plus follow-up study
Data are presented as absolute numbers (percentages); (S)AE = All (Serious) Adverse Events considered to be clinically relevant by investigators were reported

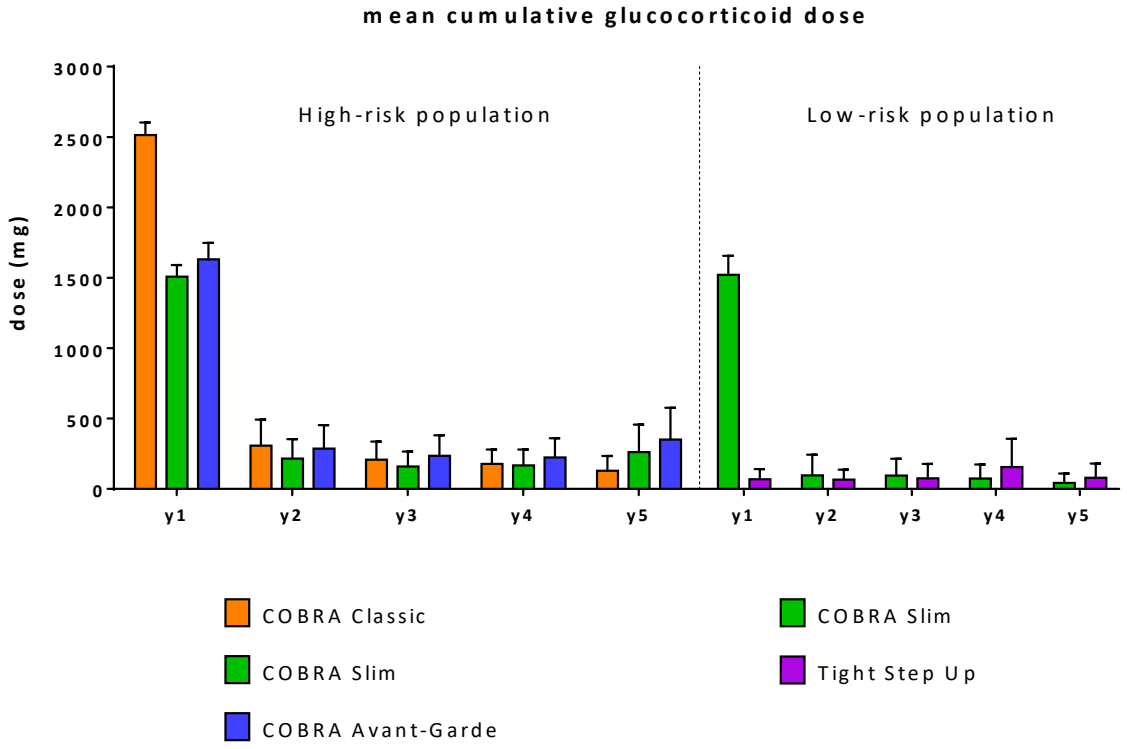

Figure 5: Mean cumulative glucocorticoid dose per treatment arm and per year of follow-up.

All systemic glucocorticoids taken, including the initial step-down prednisone schemes, and all other oral, intramuscular or intra-articular glucocorticoids were considered; The mean cumulative dose of prednisone equivalent in each year is depicted, calculated on patients still in follow-up; y=year.

Discussion

Initial intensive treatment with csDMARDs and bridging glucocorticoids in CareRA, followed by treatment adaptation to a target of low disease activity, resulted in sustained control of disease activity over 5 years in a large majority of RA patients with markers of poor prognosis. Additionally, these treatment schedules led to a sustained improvement in functionality and very limited progression in joint damage over 5 years. During the 3-year follow-up in CareRA-plus with further targeted treatment, safety data were reassuring and comparable between the schemes. The simplified COBRA-Slim scheme, starting MTX monotherapy with glucocorticoid bridging and, if needed, adapting treatment to a realistic disease activity target, can lead to comparable sustained treatment responses on the long term as more complex combination schemes and is an effective initial treatment option.

Patients without markers of poor prognosis who started COBRA-Slim had better disease control and functionality over 5 years than patients starting MTX without glucocorticoids and no more safety issues on the long-term. Suppression of joint damage progression over 5 years was comparable with both treatment schemes. Therefore, our results confirm the benefit of combining initial csDMARD treatment with bridging glucocorticoids also in patients without presumed markers of poor prognosis [14,15].

Remarkably, 56% of all patients never had their DMARD therapy intensified during the first 5 years of treatment, and many patients were on DMARD monotherapy at year 5, without differences between treatment schemes. Hence, the simplified COBRA-Slim scheme did not lead to a higher need for DMARD intensifications on the long-term compared to the initial combinational regimens. Additionally, contrary to the common perception, the chronic use of glucocorticoids was limited, with the vast majority of patients being able to stop glucocorticoids after the induction phase. Moreover, chronic glucocorticoid use was comparable in low-risk patients who did or did not initiate a bridging scheme of prednisone. Further, overall bDMARD use was limited, with 22% of participants having ever taken a bDMARD over 5 years. These results indicate not only a sustained long-term effectiveness of the studied treatment schemes including glucocorticoids but also confirm our earlier findings on the feasibility of these regimens in clinical practice [16].

The results of the additional 3-year follow-up in CareRA-plus confirm and extend on the conclusions after 2 years in the CareRA trial. Moreover, these results support findings regarding the sustained effectiveness of COBRA schemes from the original COBRA, the BeSt and the COBRA-Light trial [9,10,17,18]. Results of the BeSt trial showed that initial combination therapy of MTX, SSZ and prednisone resulted in sustained clinical improvement over 10 years. Similarly as in CareRA, most patients in BeSt were able to taper their combinational DMARD treatment to monotherapy and glucocorticoid use was very limited by the end of the follow-up [10]. Also the COBRA-light trial demonstrated that MTX with prednisolone bridging had similar efficacy and safety outcomes over 4 years compared with a combination of MTX, SSZ and prednisolone bridging [18]. However, this protocol prescribed the addition of a bDMARD (preferably etanercept) in case DAS44<1.6 was not achieved, which resulted in higher proportions of patients having ever initiated a bDMARD (67% versus 22% in CareRA) Additionally, in the COBRA-Light trial more patients used glucocorticoids for > 3 months during follow-up (42% versus 25% in CareRA) [19]. Our data are also fully in line with 5y IMPROVED data [20] and both confirm again the EULAR recommendations and contradict the recent draft of the

2020 revision of the ACR recommendations for the management of RA, advising to minimize the use of bridging glucocorticoids [21].

Our study population is close to a daily practice early RA population. We included patients with diverse disease characteristics in terms of severity, autoantibody positivity, erosive or comorbidity status, from different types of practices, and followed them regularly for a long period. These features support the external validity of our results and are indicative for a good applicability of such intensive treatment in daily practice.

The vast majority of patients completing the preceding CareRA study, re-consented to participate in CareRA-plus. Enrolled patients, did not differ in demographics, nor in clinical characteristics from patients not enrolled into CareRA-plus, except for being more ACPA positive. This enrichment for ACPA positivity might have resulted in an underestimation of treatment effect since ACPA is assumed to be a prognostic factor of poor outcome [22]. However, ACPA positive patients were well distributed between treatment arms, so no selection bias influenced group comparison.

In conclusion, we demonstrated that all intensive treatment strategies using bridging steroids showed excellent long-term clinical outcomes without chronic glucocorticoid use in the majority of patients. Initial COBRA Slim therapy with MTX and bridging prednisone demonstrated comparable 5-year effectiveness as more complex combination schemes in high-risk early RA patients and a better effectiveness than conservative step-up MTX monotherapy in low-risk patients.

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Disclosures
All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work other than those listed above; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Author Contributions
PV, JJ and RW designed the study protocol in collaboration with the CareRA study group. Investigators of the CareRA study group, including PV and RW recruited and enrolled patients and were responsible for daily patient management. PV, VS and JJ were responsible for coordination of the trial and of collection of data. VS was responsible for data analysis. All authors contributed to interpretation of the data. Furthermore, VS, PV, DDC and RW drafted the manuscript. SP, KVdE, DB and JJ revised it critically for important intellectual content. All authors have approved the final draft for publication. PV and VS are the guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Ethical approval
The CareRA plus study was approved by the leading Ethics Committee of the University Hospitals Leuven after consulting the medical ethics committee of each participating centre (ref s53336) and all study participants gave their written informed consent before inclusion.

Data sharing
The authors commit to making the relevant anonymized patient level data available for a specified purpose approved by the institution and the principal investigator of the CareRA plus study and with a signed data access agreement.

Disclaimer
Patrick Verschueren and Veerle Stouten affirm that this manuscript is an honest, accurate, and transparent account of the study being reported.

Patient involvement
The pragmatic CareRA protocol was strongly inspired by daily interactions of the investigators with RA patients in daily clinical practice. Results of this research will be disseminated to study participants, all stakeholders and the general public in collaboration with patient organisations and the Belgian patient partners program (trained patients who educate physicians, medicine students and other health care professionals in collaboration with a rheumatologist).

Supplemental material

Supplement 1: Demographic characteristics at baseline and clinical characteristics at the final year 2 visit of CareRA, comparing patients participating or not in the follow-up CareRA-plus study

	Participating in CareRA-plus n=252	**Not participating in CareRA-plus n=70**	**p-value**
Demographic variables			
Age, years	53 (13)	52 (13)	0.826
Body mass index, kg/m²	27 (4)	26 (5)	0.662
Women, n (%)	171 (68)	46 (66)	0.735
Smokers, n smoked ever (%)	146 (58)	32 (46)	0.069
Median (IQR) symptom duration	23 (14-43)	22 (13-32)	0.357
RF positive, n (%)	174 (69)	43 (61)	0.229
ACPA positive, n (%)	181 (72)	34 (49)	<0.001
Erosive disease, n (%)	67 (27)	19 (27)	0.926
Clinical variables			
DAS28-CRP	2.1 (0.8)	2.2 (1.1)	0.558
Tender Joint Count (0-28)	1 (2)	1 (3)	0.593
Swollen Joint Count (0-28)	1 (1)	1 (3)	0.357
PGA, mm (0-100)	26 (22)	24 (22)	0.418
Pain, mm (0-100)	26 (22)	24 (25)	0.261
Fatigue, mm (0-100)	30 (23)	26 (25)	0.139
PhGA, mm (0-100)	10 (13)	15 (18)	0.122
ESR, mm/h	15.4 (12.2)	18.3 (19.7)	0.958
CRP, mg/L	4.8 (7.1)	6.8 (15.7)	0.113
HAQ score (0-3)	0.4 (0.6)	0.4 (0.5)	0.514

Values reported are means (standard deviation) unless specified otherwise. Symptom duration= weeks elapsed between onset of symptoms and start of treatment; RF= Rheumatoid factor; Anti-CCP= Anti cyclic citrullinated protein; DAS28= Disease activity score based on 28 joints; CRP= C-reactive protein; PGA= Patient's global assessment; PhGA= Physician's global assessment; ESR= Erythrocyte sedimentation rate; HAQ= Health assessment questionnaire. Comparisons performed via independent t-test, Mann-Whitney U test, or Chi² test when appropriate.

Supplement 2A: Test statistics of the longitudinal analyses of evolution in efficacy and safety outcomes between treatment arms in the high-risk population

Linear Mixed Model Analyses		**β**	**95% CI**	**p-value**
HAQ	COBRA Classic vs COBRA Slim	0.06	-0.03 to 0.15	0.218
	COBRA Avant-Garde vs COBRA Slim	0.06	-0.04 to 0.15	0.246
	Time in weeks	0.00	-0.03 to 0.03	0.997
	(constant)	0.44	0.38 to 0.51	<0.001
DAS28-CRP	COBRA Classic vs COBRA Slim	-0.06	-0.18 to 0.05	0.270
	COBRA Avant-Garde vs COBRA Slim	-0.02	-0.14 to 0.09	0.695
	Time in weeks	0.00	0.00 to 0.00	<0.001
	(constant)	2.73	2.65 to 2.81	<0.001
SDAI	COBRA Classic vs COBRA Slim	-0.45	-1.31 to 0.42	0.312
	COBRA Avant-Garde vs COBRA Slim	-0.54	-1.44 to 0.36	0.237
	Time in weeks	-0.03	-0.03 to -0.02	<0.001
	(constant)	10.06	9.40 to 10.72	<0.001
Generalized Linear Mixed models		**OR**	**95% CI**	**p-value**
DAS28-CRP<2.6	COBRA Classic vs COBRA Slim	1.14	0.77 to 1.69	0.502
	COBRA Avant-Garde vs COBRA Slim	1.06	0.71 to 1.58	0.778
	Time in weeks	1.01	1.00 to 1.01	<0.001
	(constant)	1.25	0.95 to 1.64	0.108
SDAI <3.3	COBRA Classic vs COBRA Slim	1.61	0.93 to 2.77	0.087
	COBRA Avant-Garde vs COBRA Slim	1.36	0.77 to 2.40	0.290
	Time in weeks	1.00	1.00 to 1.00	0.024
	(constant)	0.29	0.19 to 0.43	<0.001
Generalized Estimating Equations		**β**	**95% CI**	**p-value**
Total SvdH scores	COBRA Classic vs COBRA Slim	0.32	-0.56 to 1.19	0.481
	COBRA Avant-Garde vs COBRA Slim	0.57	-0.42 to 1.56	0.256
	Time in weeks	0.00	0.00 to 0.00	0.002
	(constant)	-0.45	-1.21 to 0.32	0.250
Poisson regression		**β**	**95% CI**	**p-value**
Number of adverse events	COBRA Classic vs COBRA Slim	-0.22	-0.53 to 0.09	0.159
	COBRA Avant-Garde vs COBRA Slim	0.07	-0.23 to 0.37	0.654
	(constant)	0.24	0.04 to 0.44	0.021

Coefficients or odds ratios stem from longitudinal models with either HAQ, DAS28-CRP, SDAI, remission rate according to DAS28-CRP or SDAI, or total SvdH score as dependent variable; For each model, treatment and time were used as determinants and it was tested whether there was an interaction between treatment and time, which was not observed for any of the outcomes. HAQ= Health Assessment Questionnaire; DAS28-CRP= Disease Activity Score using 28 joints and C-reactive Protein; SDAI= Simplified Disease Activity Index; SvdH= Sharp van der Heijde score; CI= confidence intervals. OR= odds ratio.

Supplement 2B: Test statistics of the longitudinal analyses of evolution in efficacy and safety outcomes between treatment arms in the low-risk population

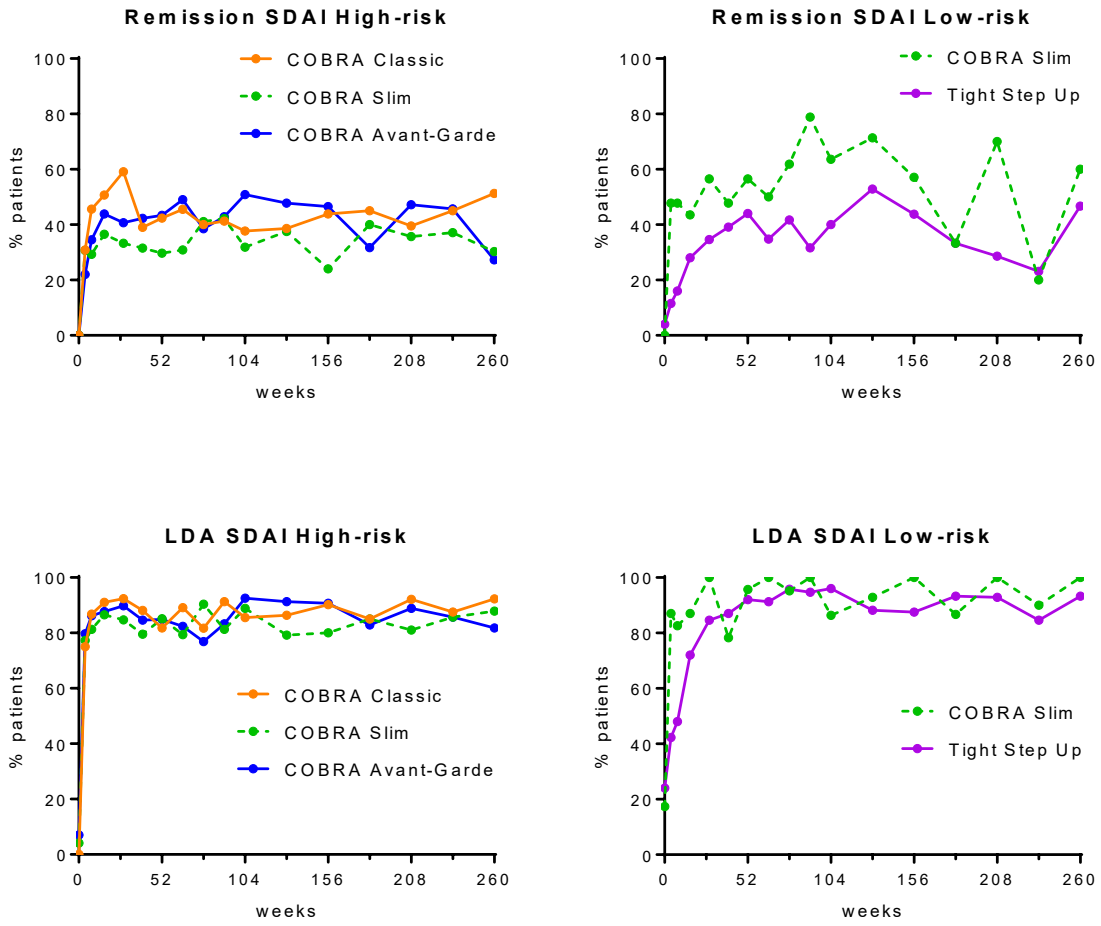
Linear Mixed Model Analyses		**β**	**95% CI**	**p-value**
HAQ	COBRA Slim vs Tight Step-Up	-0.21	-0.41 to -0.01	0.041
	Time in weeks	0.00	-0.09 to 0.09	0.991
	(constant)	0.61	0.47 to 0.75	<0.001
DAS28-CRP	COBRA Slim vs Tight Step-Up	-0.46	-0.63 to -0.29	<0.001
	Time in weeks	0.00	-0.01 to 0.00	<0.001
	(constant)	2.92	2.78 to 3.06	<0.001
SDAI	COBRA Slim vs Tight Step-Up	-2.46	-3.87 to -1.04	0.001
	Time in weeks	-0.04	-0.05 to -0.03	<0.001
	(constant)	11.50	10.26 to 12.74	<0.001
Generalized Linear Mixed models		**OR**	**95% CI**	**p-value**
DAS28-CRP<2.6	COBRA Slim vs Tight Step-Up	2.62	1.43 to 4.81	0.002
	Time in weeks	1.01	1.01 to 1.02	<0.001
	(constant)	0.70	0.43 to 1.15	0.155
SDAI <3.3	COBRA Slim vs Tight Step-Up	3.27	1.35 to 7.91	0.009
	Time in weeks	1.01	1.00 to 1.01	0.023
	(constant)	0.23	0.12 to 0.44	<0.001
Generalized Estimating Equations		**β**	**95% CI**	**p-value**
Total SvdH scores	COBRA Slim vs Tight Step-Up	-0.07	-1.68 to 1.53	0.928
	Time in weeks	0.00	0.00 to 0.01	0.856
	(constant)	-0.50	-1.94 to 0.93	0.491
Poisson regression		β	95% CI	p-value
Number of adverse events	COBRA Slim vs Tight Step-Up	-0.57	-1.14 to -0.00	0.048
	(constant)	0.33	0.00 to 0.65	0.051

Coefficients or odds ratios stem from longitudinal models with either HAQ, DAS28-CRP, SDAI, remission rate according to DAS28-CRP or SDAI, or total SvdH score as dependent variable; For each model, treatment and time were used as determinants and it was tested whether there was an interaction between treatment and time, which was not observed for any of the outcomes. HAQ= Health Assessment Questionnaire; DAS28-CRP= Disease Activity Score using 28 joints and C-reactive Protein; SDAI= Simplified Disease Activity Index; SvdH= Sharp van der Heijde score; CI= confidence intervals. OR= odds ratio.

Supplement 3: Percentages of patients in low disease activity or in remission according to different criteria, per time point and per treatment arm

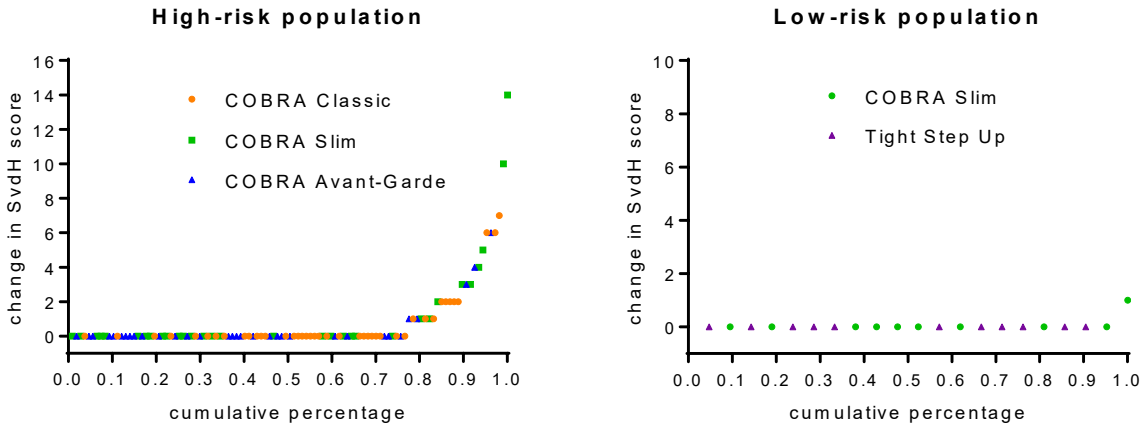
Treatment	Week 16	Year 1	Year 2	Year 3	Year 4	Year 5
COBRA Classic n=69						
LDA DAS28-CRP	88%	82%	87%	90%	89%	83%
LDA SDAI	90%	81%	86%	86%	87%	86%
Rem DAS28-CRP	77%	73%	68%	73%	66%	68%
Rem SDAI	49%	42%	38%	37%	36%	35%
COBRA Slim High-risk n=75						
LDA DAS28-CRP	91%	81%	91%	82%	87%	88%
LDA SDAI	87%	84%	89%	84%	85%	88%
Rem DAS28-CRP	76%	61%	75%	65%	75%	72%
Rem SDAI	38%	29%	33%	29%	37%	33%
COBRA Avant-Garde n=59						
LDA DAS28-CRP	88%	80%	93%	88%	83%	84%
LDA SDAI	88%	82%	93%	90%	88%	85%
Rem DAS28-CRP	68%	66%	83%	74%	71%	64%
Rem SDAI	45%	41%	52%	45%	43%	34%
COBRA Slim Low-risk n=23						
LDA DAS28-CRP	83%	96%	87%	98%	97%	91%
LDA SDAI	87%	96%	87%	99%	96%	91%
Rem DAS28-CRP	74%	87%	87%	89%	86%	80%
Rem SDAI	43%	57%	65%	50%	62%	50%
Tight Step Up n=26						
LDA DAS28-CRP	73%	92%	92%	89%	81%	99%
LDA SDAI	73%	92%	96%	87%	88%	93%
Rem DAS28-CRP	46%	62%	73%	67%	72%	80%
Rem SDAI	28%	42%	38%	34%	28%	37%

Values are percentages based on an intention-to-treat analysis. Missing data were imputed via multiple imputation resulting in 100 datasets. The imputation model included terms for observed disease activity, HAQ score, treatment randomization, demographics, classical prognostic factors, comorbidity status, treatment intensifications, and SvdH scores. Each dataset was analyzed separately and results were pooled using Rubin's rules. Percentages were compared between treatment arms in high- and low-risk separately using Chi^2 test. There were no significant differences observed after correction for multiplicity by Holm's test. LDA= low disease activity; Rem= remission; DAS28-CRP= disease activity score based on 28 joints calculated with C-reactive protein; LDA DAS28-CRP≤3.2; Remission DAS28-CRP<2.6; SDAI= Simplified Disease Activity Index; LDA SDAI ≤11; Remission SDAI ≤3.3.



Supplement 4: Remission and low disease activity rates during 5 years of follow up measured by SDAI

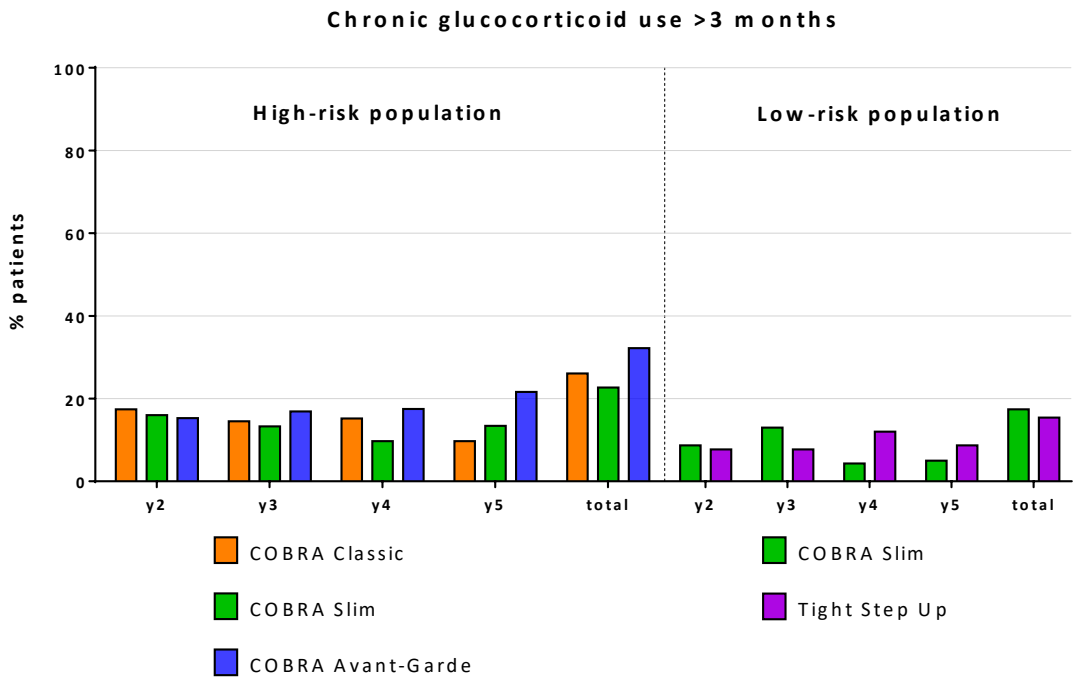
Data are shown as observed, based on patients still in follow-up at each time point; LDA= Low Disease Activity; SDAI= Simplified Disease Activity Index; Remission SDAI ≤3.3; LDA SDAI ≤11.



Supplement 5: Probability plots of radiographic progression defined by change in SvdH scores in patients completing the 5-year follow up.

SvdH score = Sharp van der Heijde score.

A



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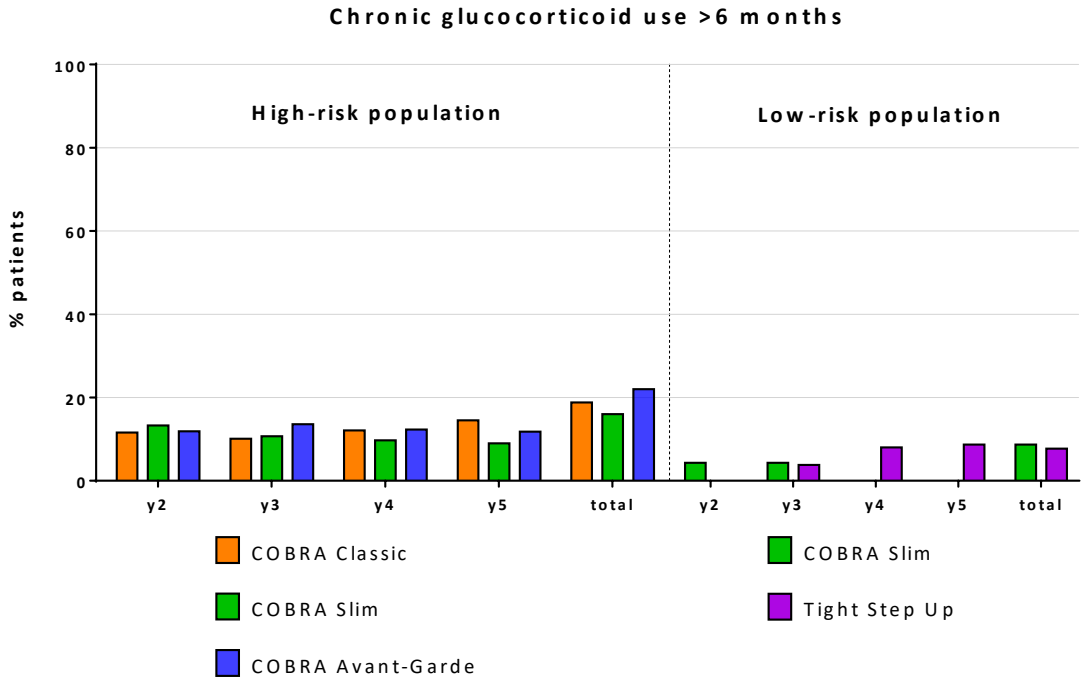

Supplement 6: Chronic glucocorticoids use per treatment arm and per year of follow-up.

All oral glucocorticoids taken outside of the initial step-down prednisone schemes were considered from baseline CareRA till year 5; Chronic glucocorticoid use was defined as either taken > 3 months consecutively **(A)** or as > 6 months consecutively **(B);** Percentages of patients are depicted per year, calculated on patients still in follow-up; y=year.