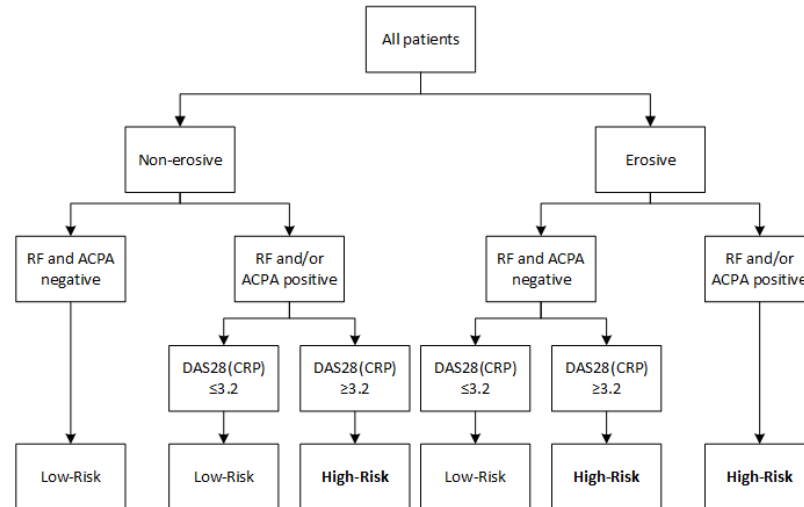


Supplemental Figure 1: Stratification scheme: Classification of patients in high or low-risk according to poor prognostic factors



RF= Rheumatoid Factor, ACPA= Anti-Citrullinated Protein Antibody, DAS28 (CRP) = 28 joint disease activity score calculated with C-reactive protein.

Supplemental Table 1: Adjusted p-values with the Holm-Bonferroni method to account for multiple testing.

Comparison	Values (COBRA Slim vs TSU)	Statistical test	p-value	Adjusted p-value
<i>Proportion of patients taking analgesics at any timepoint</i>	26/43 vs 43/47	Chi-square	0.0005091	0.004050
<i>Proportion of patients on chronic analgesics</i>	9/43 vs 25/47	Chi-square	0.001615	0.004050
<i>Proportion of patients on chronic NSAIDs</i>	6/43 vs 19/47	Chi-square	0.005099	0.0091782
<i>Proportion of patients on analgesics before the start of the trial</i>	33/43 vs 32/47	Chi-square	0.3596	0.4623429
<i>Proportion of patients on analgesics at baseline</i>	18/43 vs 28/47	Chi-square	0.0931	0.139650
<i>Baseline VAS pain (mean ± SE)</i>	48±6 vs 52±4	ANOVA	0.50394	0.5669325
<i>Baseline DAS28CRP (mean ± SE)</i>	4.5±0.3 vs 4.6±0.2	ANOVA	0.885941	0.885941
<i>Survival to time of first chronic analgesic intake (mean ± SE)</i>	85.8±5.5 vs 54.0±7.2	Log-rank Gehan-Breslow	0.0018 0.0010	0.004050 0.004050

NSAIDs: non-steroidal drugs, VAS: visual analogue scale, DAS28CRP: disease activity score in 28 joints with C-reactive protein, SE: standard error

Supplemental Table 2: Demographic and clinical characteristics at baseline per treatment scheme.

	COBRA Slim	Tight-Step-Up
	n=43	n=47
Demographic variables		
Age, years	51 (14)	51 (14)
Women, n (%)	33 (77)	38 (81)
Smokers, n smoked ever (%)	21 (49)	18 (38)
Current work n (%)	22 (51)	27 (57)
Clinical variables		
Body mass index, kg/m ²	25 (4)	27 (4)
Symptom duration, weeks; median (IQR)	21 (14-35)	19 (13-33)
RF positive, n (%)	11 (26)	11 (23)
Anti-CCP positive, n (%)	12 (28)	11 (23)
Erosive disease, n (%)	1 (2)	0 (0)
DAS28-CRP	4.50 (2.25)	4.55 (1.63)
Pain, mm (0-100)	48 (31)	52 (23)
Fatigue, mm (0-100)	39 (28)	46 (22)
HAQ score (0-3)	0.81 (0.85)	0.85 (0.72)

Data are presented as mean and standard deviation (SD) unless otherwise specified.

Symptom duration= number of weeks between onset of symptoms and start of treatment; RF= Rheumatoid factor; Anti-CCP= Anti cyclic citrullinated protein; DAS28= Disease activity score on 28 joints; CRP= C-reactive protein; HAQ= Health Assessment Questionnaire

Supplemental Table 3: Evolution over time of pain, DAS28CRP, patient's global health assessment, and CRP per treatment group and chronicity of NSAID/analgesic use:

VAS pain (0-100 scale)

Treatment group	Analgesic use	Visit weeks			
		0	8	52	104
COBRA Slim	Chronic (n=9)	63.3±6.7	36.4±6.6	27.4±6.0	26.0±6.2
	Non-chronic (n=34)	37.4±5.8	21.2±4.8	19.8±5.1	19.6±5.1
Tight-Step-Up	Chronic (n=25)	53.7±3.7	36.0±3.4	24.8±3.4	25.5±3.5
	Non-chronic (n=22)	45.1±8.5	25.9±5.3	27.4±9.5	31.9±9.1

Disease activity score in 28 joints with C-reactive protein (DAS28CRP)

Treatment group	Analgesic use	Visit weeks			
		0	8	52	104
COBRA Slim	Chronic (n=9)	5.1±0.4	3.0±0.3	2.4±0.3	2.2±0.2
	Non-chronic (n=34)	4.1±0.3	2.3±0.2	2.0±0.2	1.9±0.2
Tight-Step-Up	Chronic (n=25)	4.4±0.3	3.5±0.2	2.3±0.1	2.2±0.2
	Non-chronic (n=22)	5.0±0.6	2.7±0.4	2.2±0.2	2.2±0.3

Patients global health assessment (0-100 scale)

Treatment group	Analgesic use	Visit weeks			
		0	8	52	104
COBRA Slim	Chronic (n=9)	63.9±6.9	34.0±6.9	27.7±6.3	21.8±5.5
	Non-chronic (n=34)	37.6±5.4	22.9±4.8	18.6±4.6	17.9±4.3
Tight-Step-Up	Chronic (n=25)	50.7±3.7	40.8±3.9	27.2±3.4	27.5±3.2
	Non-chronic (n=22)	46.4±8.5	23.9±5.7	25.4±8.3	29.3±5.7

C-reactive protein (mg/L)

Treatment group	Analgesic use	Visit weeks			
		0	8	52	104
COBRA Slim	Chronic (n=9)	34.8±13.0	8.0±3.0	2.9±1.3	5.2±2.4
	Non-chronic (n=34)	9.6±3.3	6.2±2.2	5.4±1.9	3.2±1.9
Tight-Step-Up	Chronic (n=25)	13.5±3.2	8.7±2.6	5.6±1.2	7.2±1.9
	Non-chronic (n=22)	13.6±4.2	7.0±5.1	4.5±2.2	3.7±3.8

Data presented as mean and standard error

Supplemental Table 4: Number of patients with drug intake of the different types of analgesics: acetaminophen, NSAIDs, opioids (weak and strong), and antidepressants (as neuropathic pain drugs) at every visit week during the 2-year CareRA trial between COBRA Slim and Tight-Step-Up patients. Patients can be counted in more than one type of medication when taken in combination.

COBRA Slim (n=43)

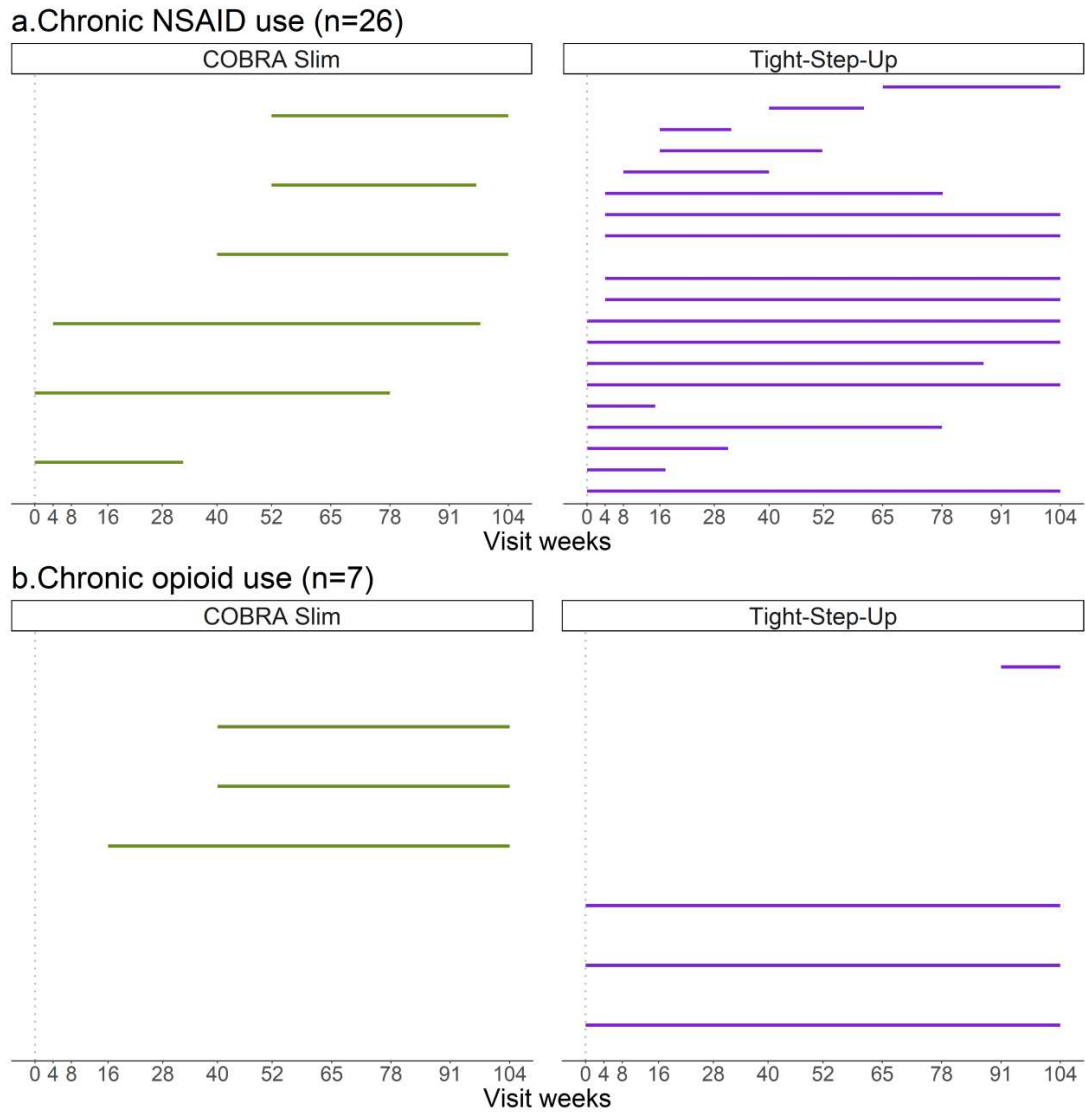
Medication	Trial weeks										
	0	4	8	16	28	40	52	65	78	91	104
Acetaminophen	5 (12)	3 (7)	3 (7)	5 (12)	5 (12)	6 (14)	6 (14)	6 (14)	5 (12)	7 (16)	6 (14)
NSAIDs	16 (37)	8 (19)	6 (14)	6 (14)	7 (16)	7 (16)	10 (23)	9 (21)	10 (23)	8 (19)	7 (16)
Opioids (strong)	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)
Opioids (weak)	2 (5)	-	-	1 (2)	1 (2)	2 (5)	2 (5)	3 (7)	2 (5)	2 (5)	2 (5)
Antidepressants	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)

Tight-Step-Up (n=47)

Medication	Trial weeks										
	0	4	8	16	28	40	52	65	78	91	104
Acetaminophen	7 (15)	9 (19)	9 (19)	8 (17)	10 (21)	11 (23)	8 (17)	9 (19)	10 (21)	10 (21)	11 (23)
NSAIDs	25 (53)	35 (74)	32 (68)	30 (64)	25 (53)	22 (47)	21 (45)	19 (40)	19 (40)	20 (43)	19 (40)
Opioids (strong)	-	-	-	-	-	-	-	-	-	-	-
Opioids (weak)	3 (6)	4 (9)	4 (9)	3 (6)	4 (9)	5 (11)	4 (9)	3 (6)	3 (6)	3 (6)	3 (6)
Antidepressants	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)

Data presented as number of patients and between brackets the percentage of them from their treatment strategy total

Supplemental Figure 2: Graphic representation of the use of a) NSAIDs and b) opioids in patients taking these drugs daily and chronically during the 2-year CareRA trial. Each line represents the time window of DC NSAID/opioid use in one patient. One patient of the Tight-Step-Up arm is not represented (on combination of acetaminophen + antidepressant).



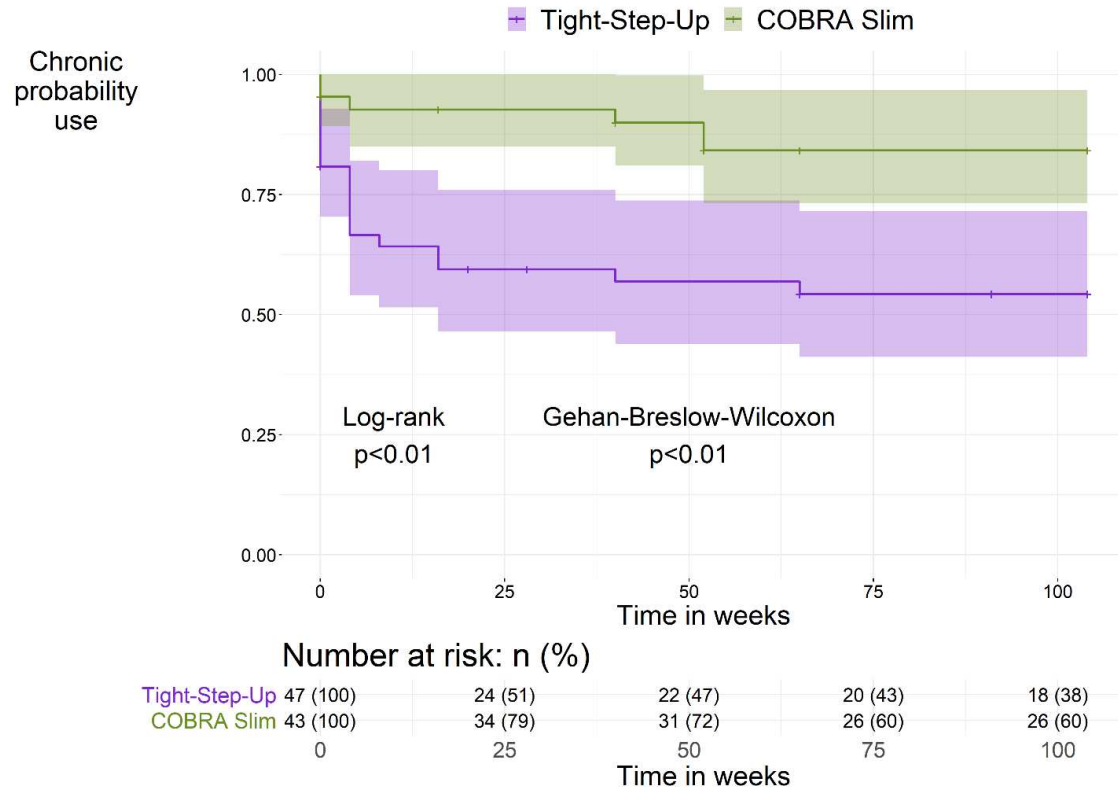
Supplemental Table 5: Dose, duration, and number of patients per analgesic in the case of chronic use, per treatment group.

Medication	Tight-Step-Up			COBRA Slim		
	Mean daily dose	Mean duration of use in days	# of patients	Mean daily dose	Mean duration of use in days	# of patients
Acetaminophen	2.3g	670.0	3	650mg	543.5	2
NSAIDs	-	327.9	20	-	346.3	6
Ibuprofen	1.2g	432.0	1	1.2g	444.0	2
Diclofenac	127.5mg	272.0	6	150mg	199.5	3
Meloxicam	11.25mg	433.0	2	15mg	316.0	1
Naproxen	950mg	174.3	5	-	-	-
Piroxicam	20mg	299.8	6	-	-	-
Etoricoxib	101.5mg	483.3	4	-	-	-
Indomethacin	125.0mg	339.3	3	-	-	-
Aceclofenac	150.0mg	418.5	2	-	-	-
Proglumetacin	-	-	-	450.0mg	133.0	1
Phenylbutazone	-	-	-	200.0mg	247.0	1
Oxaprozin	-	-	-	1.2g	729.0	1
Opioids	-	347.7	3	-	521.7	3
Tramadol	133.3mg	347.7	3	75.0mg	552.5	2
Methadone	-	-	-	30.0mg	460.0	1
Antidepressants	60mg	723.0	1	37.5mg	381.7	1
Duloxetine	60mg	723.0	1	-	-	1
Nortriptyline	-	-	1	37.5mg	381.7	1

Supplemental Table 6: Analgesics and NSAIDs specifically prescribed for RA with chronic daily intake per treatment group. Each row corresponds to a patient. Some patients had either a combination of different analgesics/NSAIDs or consecutive courses of the same analgesic/NSAID.

Treatment group	Medication	Total daily dosage	Total time of intake in days	Week of start within the trial
COBRA Slim	Meloxicam	15mg	315	52
	Diclofenac	150mg	228	Baseline
	Oxaprozin	1200mg	561	Baseline
Tight-Step-Up	Piroxicam	20mg	137	Baseline
	Piroxicam	20mg	244	4
	Naproxen	1000mg	121	Baseline
	Meloxicam	7.5mg	146	40
	Naproxen	500mg	105	Baseline
	Naproxen	1000mg	353	28
	Diclofenac	150mg	179	78
	Meloxicam	15mg	718	4
	Naproxen	1000mg	250	16
	Naproxen	1000mg	90	65
	Acetaminophen	2g	501	28
	Celecoxib	200mg	217	Baseline
	Acetaminophen	3g	783	Baseline
	Tramadol	200mg	783	Baseline
	Etoricoxib	90mg	744	4
	Etoricoxib	90mg	721	Baseline
Diclofenac	150mg	277	Baseline	

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



Supplemental Table 7: Cumulative events in time to first chronic analgesic use for COBRA Slim and Tight-Step-Up 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