

# Osteoarthritis and Cartilage



## Effectiveness of exercise therapy in patients with thumb carpometacarpal osteoarthritis: A multicenter, randomized controlled trial<sup>☆</sup>

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### ABSTRACT

**Objective:** To compare the effectiveness and costs of an orthosis + exercise therapy with only an orthosis on pain at 3 months and conversion to surgery < 1 year in patients with thumb carpometacarpal (CMC-1) osteoarthritis (OA).

**Design:** Multicenter, single-blinded, randomized controlled trial.

**Setting:** Eighteen outpatient hand surgery and therapy clinics in the Netherlands.

**Participants:** Adult patients with CMC-1 OA.

**Interventions:** Orthosis + exercise therapy versus orthosis-only.

**Primary outcome measures:** Pain at 3 months (Michigan Hand Outcomes Questionnaire pain subscale) and conversion to surgery < 1 year.

**Results:** We included 166 patients (81 orthosis + exercise, 85 orthosis-only). There was no difference between the orthosis + exercise group and the orthosis-only group in pain at three months (least mean square difference 3.7 [95% CI -1.0–8.3]). Conversion to surgery was 4.9% (n=4) in the orthosis + exercise group and 9.4% (n=8) in the orthosis-only group, which was not significantly different (risk difference 4.7% [-3.3–12.2%]) due to the low conversion to surgery rates. The total societal costs for orthosis + exercise were 37% (-€825 [-2072–421]) lower per patient than orthosis-only. The orthosis + exercise group had favorable outcomes in MHQ subscale activities of daily living scores (6mo), work ability (all time points), satisfaction with hand (3mo), the MHQ total score (3mo, 6mo), satisfaction with treatment results (all except 6mo), grip strength (6w), and illness perceptions (3mo).

**Conclusions:** In patients with CMC-1 OA, an orthosis + exercise therapy is preferred over orthosis-only because of the favorable secondary outcomes.

**Trial registration:** ClinicalTrials.gov: NCT05772715.

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## Introduction

Thumb carpometacarpal (CMC-1) osteoarthritis (OA) is a common disease with an estimated symptomatic prevalence of 2% in males and 7% in females aged > 50 [1]. The radiographic prevalence is strongly dependent on age and sex (odds ratio: 1.1 per increasing year of age, 1.3 for females [2]. Symptomatic CMC-1 OA causes pain, activities of daily life (ADL) limitations, reduced quality of life, and clinical features such as muscle wasting or deformity.

Current guidelines and reviews advise nonsurgical treatment before considering surgery [3–9]. Nonsurgical treatment may include orthoses, analgesics, intra-articular injections, joint protection programs, and exercise therapy. Exercise therapy typically targets the stability and positioning of the CMC-1, aiming for reduced loading, as joint overloading is related to pain and disease progression [6,10–20]. Orthoses often complement exercise therapy but are also used as a stand-alone treatment [3–9]. While widely used, strong evidence supporting exercise therapy in addition to an orthosis is lacking [3–9], and the results of comparative effectiveness studies are conflicting [13,14,16,18,19]. However, these studies combined multiple treatment modalities, and only one real-world evidence study directly compared an orthosis alone to its combination with exercise therapy, reporting positive effects of exercise therapy on pain [19]. Notably, this study was observational, and despite propensity score matching [21,22], confounding by indication may have influenced the findings. Furthermore, all aforementioned studies [13,14,16,18,19] had low sample sizes or short-term follow-up, and none investigated the costs of exercise therapy in addition to an orthosis.

Preventing surgery is an important treatment goal for patients with CMC-1 OA due to the long recovery, residual functional limitations, and limited satisfaction with treatment results after surgery [23,24]. Furthermore, the costs for surgery are high, especially when considering the postoperative treatment and productivity loss, as the median work absence is 12 weeks [25]. Previous studies reported that following any nonsurgical treatment, the conversion to surgery ranges from 13% to 29%, depending on follow-up duration (range 2–7 years) [19,20,26,27]. However, all these studies were observational, and it is unknown if additional exercise therapy compared to an orthosis alone reduces the conversion to surgery rate.

This multicenter randomized controlled trial compared the effectiveness of an orthosis combined with exercise therapy to an orthosis alone on pain at three months and conversion to surgery within one year in patients with CMC-1 OA. Secondary outcomes were costs, ADL, hand function, health-related quality of life, satisfaction with treatment results, return to work, grip and pinch strength, range of motion, patient-reported experience measurements, illness perceptions, anxiety, depression, and complications. As the present randomized controlled trial was performed in a very similar setting and with similar treatment arms as the aforementioned real-world evidence propensity score matching study [19], this study also allows investigation of how the similarities and differences in both designs and outcomes can complement or contradict each other. In that respect, this study also provides useful knowledge for designing future clinical studies on osteoarthritis treatment, especially given the advantages and disadvantages of observational research compared to RCTs and vice versa.

## Methods

### Trial design

This was a multicenter, single-blinded, randomized controlled trial using a parallel design with a 1:1 allocation ratio, reported following the Consolidated Standards of Reporting Trials statement [28]. Data were collected between September 2020 and December 2023 after

approval by the Erasmus MC institutional review board (reference: MEC-2019–0616). This study adhered to the Declaration of Helsinki and was pre-registered (ClinicalTrials.gov reference: NCT05772715).

### Participants, settings, and study procedures

Patients were included if they 1) were adults, 2) had Eaton [29] stage 2 (i.e., joint space narrowing, osteophytes < 2 mm, mild sclerosis and cysts, slight instability) or higher CMC-1 OA based on radiographs and/or clinical examination, and 3) were able to visit the treatment center for therapy sessions. Exclusion criteria were 1) secondary CMC-1 OA (e.g., due Bennet's fracture), 2) history of interventions or comorbidity interfering with treatment or outcome (e.g., trapeziectomy or De Quervain's tenosynovitis), 3) steroid injection in hand or wrist < 6 weeks before admission, 4) previous nonsurgical treatment for CMC-1 OA in one or both hands (including orthoses or hand therapy), and 5) Dutch or English language restrictions.

Recruitment took place at one of eighteen participating outpatient plastic or orthopaedic hand surgery clinics in the Netherlands. These were specialized clinics (Xpert Clinics), clinical teaching hospitals (Reinier Haga Orthopedisch Centrum, Franciscus Gasthuis en Vlietland, and Elisabeth-TweeSteden Ziekenhuis), and an academic hospital (Erasmus MC). If a patient was interested, the hand surgeon provided study materials, and a research assistant provided further study details and performed another eligibility check. After > 24 h of consideration, eligible and willing patients were formally included by a trained hand therapist, and written informed consent was obtained. After randomization (see below), the trained hand therapist scheduled the required appointments, after which the baseline measurements were performed.

All data were collected using GemsTracker [30], which is a secure web-based application for the distribution of questionnaires and forms during clinical research and quality registrations.

### Interventions

Participants were randomly assigned to the orthosis-only group or the orthosis + exercise group. No analgesics were prescribed, but usage was allowed and monitored. The treatment duration was 3 months in both groups. To standardize treatment in both treatment groups as much as possible, we selected, trained, and instructed therapists to adhere to a detailed treatment guideline (Appendix 1). The research assistant regularly visited all treatment centers to discuss the treatment content and monitor standardization. Treatment adherence was measured at six weeks and three months using the Therapy Adherence Assessment Tool (TAAT). The TAAT evaluates adherence to doing exercises, changing activities as instructed, using splints/orthoses, putting effort into therapy, and completing home therapy on a 5-point scale (range: not at all – always) [31].

#### Orthosis-only group

The orthosis-only group received a custom-made thermoplastic orthosis immobilizing the CMC-1 into extension-abduction and the first metacarpophalangeal joint in slight flexion. Participants were instructed to use the orthosis 24/7 in the first two weeks. Usage during light activities was reduced from 2 weeks onwards, and from 6 weeks onwards, usage was only prescribed during heavy activities if necessary. Two appointments took place: one for orthosis fabrication and a checkup one week later. The therapists were instructed not to provide any additional exercises, therapy sessions, or joint protection principles.

#### Orthosis + exercise group

The orthosis + exercise group received the same orthosis and wearing instructions as the orthosis-only group. The exercise

therapy included a maximum of 12 weekly 25–30-minute physical therapy sessions. Sessions included education on thumb positioning, functional training, and home exercise instructions to improve CMC-1 stability during pinch in extension-abduction. The first phase (wk 0–6) comprised coordination exercises for the thumb intrinsics (except the adductor pollicis), extensor pollicis brevis, and first dorsal interosseous. The second phase (wk 7–3 mo) comprised thenar muscle strengthening exercises (except adductor pollicis). The home exercise program contained a predefined set of exercises, including instructions on exercise frequency and intensity.

## Outcomes

### Primary outcomes

There were two primary outcomes: pain at 3 months, measured using the pain subscale of the Michigan Hand outcomes Questionnaire (MHQ) [32,33], and conversion to surgery within one year after treatment initiation.

The MHQ has six subscales, high internal validity and consistency, and acceptable reliability (range: 0–100; we converted the pain subscale so that higher scores indicate better performance for each subscale) [34]. The MHQ subscale and total scores were secondary outcomes. The minimal important change of the MHQ pain subscale is 7.2 for patients with CMC-1 OA treated nonsurgically [35]. We used the mean score of both hands in bilateral CMC-1 OA, as the MHQ evaluates both hands in bilateral cases. We chose 1 year as the conversion to surgery endpoint since, in our previously published cohort study that reported a 15% conversion to surgery rate, 75% of the operated patients underwent surgery within 1 year [26]. To represent daily care, conversion to surgery was a shared decision by the patient and surgeon. Standard follow-up with the surgeon took place at 3 months to evaluate the therapy and allow the patient and surgeon to jointly consider surgery if deemed necessary. Conversion to surgery was recorded in several ways to prevent missingness, namely 1) therapist-reported, 2) patient-reported through the iMTA Medical Consumption Questionnaire (iMCQ), and 3) by a research assistant calling participants if information was lacking.

### Secondary outcomes

Costs were calculated based on healthcare consumption and productivity losses. Healthcare consumption (including the number of therapy visits; we report the number until three months) was retrieved from direct therapist registration and the iMCQ. Productivity losses were measured by the iMTA Productivity Cost Questionnaire (iPCQ). These data were complemented by a return to work questionnaire containing seven items on working status (currently working, usual/modified work, hours/week, time point returned to work, confidence) [36].

HRQoL was measured using the 5-level EuroQoL-5 Dimension (EQ-5D); utility scores were derived using the Dutch tariff (range 0(death)–1(perfect health)) [37].

We evaluated satisfaction with treatment results on a 7-point scale (range: extremely dissatisfied to extremely satisfied), willingness to undergo the treatment again under similar circumstances (yes/no), and whether the patient recommends the treatment to friends and family (yes/no) [36,38].

Complications were measured using the ICHOM Complications in Hand and Wrist conditions tool (ICHAW) [36,39–41]. Grade 0 defines no complication. Grade 1 includes any deviation from the normal treatment course without surgical, endoscopic, and radiological interventions (e.g., additional analgesics/hand therapy/splinting/casting). Grade 2 includes antibiotics, steroid injections, or pharmacological treatment not in Grade 1. Grade 3 includes complications requiring minor (3A) or major (3B) surgery or Complex Regional Pain Syndrome (3C).

Grip and pinch strength were measured in kilograms following the reliable and valid methods described by Mathiowetz et al. [42–44]. ROM measurements included goniometry of thumb joints (degrees) following the American Society of Hand Therapists recommendations [45], the Kapandji score (range 0–10), and intermetacarpal distance (IMD) during palmar abduction (mm) [46,47].

We used the Patient-Reported Experience Measurement (PREM) physical therapy questionnaire, a validated Dutch tool to evaluate patient experiences and the quality of care [48].

We used the valid and reliable Brief Illness Perception Questionnaire (B-IPQ) to measure illness perceptions [49]. The B-IPQ has eight separate domains, and a total score can be calculated (range 0–80, higher scores indicate worse illness perceptions).

Depression and anxiety were measured using the Patient Health Questionnaire (PHQ-9, range 0–27, higher scores indicate more depressive symptoms) and the Generalized Anxiety Disorder Questionnaire (GAD-7, range 0–21, higher scores indicate more anxiety), which are both well-validated instruments [50,51].

### Other variables

Other variables measured at baseline included sex (F/M), age, level of education (nine options), type of work (unemployed or light, moderate, or heavy physical labor), additional physiotherapy insurance (yes/no), comorbidity (yes/no), BMI, second opinion (i.e., whether patients consulted a hand surgeon before for the same issue, yes/no), hand dominance (left/right/ambidexter), affected hand (left/right/both), duration of symptoms (months), smoking status (daily/irregular/weekly/never, but former smoker), pain catastrophizing (Pain Catastrophizing Scale, range 0–52, higher scores indicate more pain catastrophizing [52]), and treatment outcome expectations and credibility (Credibility and Expectancy Questionnaire, range 3–27 per subscale, higher scores indicate higher credibility/expectations [53]). All were patient-reported, except type of work and affected hand, which were classified using prespecified categories by the hand therapist conducting the measurements.

Measures took place at baseline, 6 weeks, and 3, 6, 9, and 12 months; Appendix 2 displays the measurements at each time point.

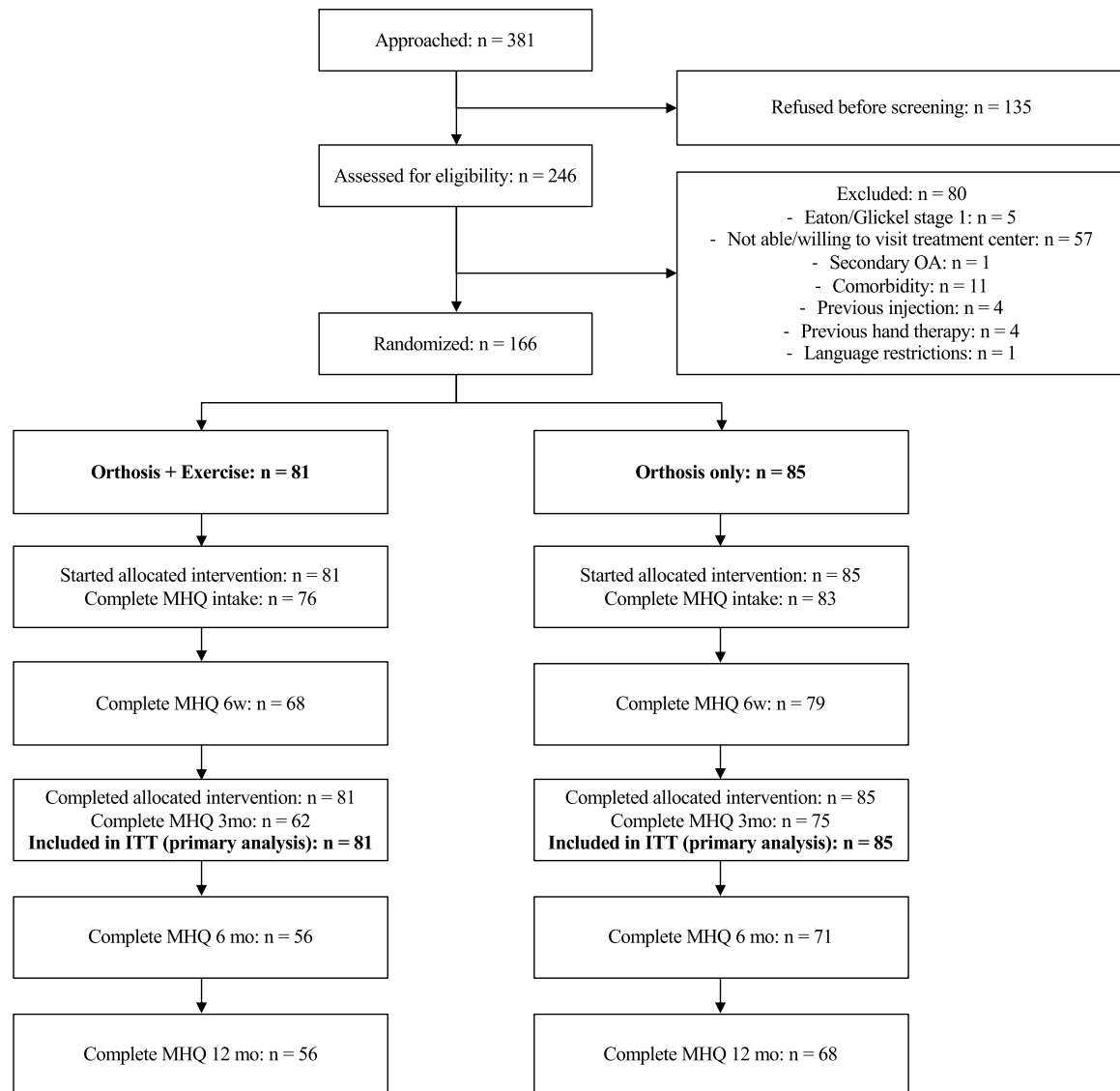
### Sample size

We estimated the sample size based on the primary outcome (pain at 3 months). We used G\*Power [54] and based our sample size on the ANOVA: Repeated Measures, Within-Between Interaction option to estimate power for the group×time interaction, corresponding to the main effect of interest in this trial. For a repeated measures design with five measures, a power of 0.80, alpha=0.025, and a conventional small [55] effect size *f* of 0.10, we needed 144 participants. We enlarged the sample by 10% to account for loss to follow-up, resulting in a final sample of 159 patients.

We assumed 10% conversion to surgery in the orthosis + exercise group and 20% in the orthosis-only group, based on the 15% conversion to surgery from the study by Tsehaie et al. [26]. We initially aimed for 532 participants based on logistic regression, a power of 0.80, and alpha=0.025, accounting for a 10% loss to follow-up. However, we had to revise our statistical analysis due to low inclusion rates and needed 104 participants to perform a Chi-square test with the same parameters. Thus, a sample of 159 patients would be sufficient.

### Randomization and blinding

Randomization occurred on a 1:1 ratio and was centrally executed using a built-in randomization module in GemsTracker. This module used a computer-generated list created by an independent researcher. As such, randomization was safeguarded

**Fig. 1**

Flow chart of the study. OA = Osteoarthritis, MHQ = Michigan Hand Outcomes Questionnaire, ITT = intention to treat.

and independent, and the treatment allocation was not accessible to the therapists and participants until after inclusion and randomization. The randomization took place at the patient level using block randomization at the location level, with random block sizes (range: 6–10). The final statistical analyses were performed on a blinded dataset. Blinding of clinicians carrying out the treatment and measurements (e.g., grip strength or range of motion) and patients was not possible.

#### Statistical methods and cost analysis

Pain was analyzed using mixed-effects models and the proportion of patients converting to surgery using a chi-square test, following intention-to-treat principles. We initially planned a logistic regression analysis for conversion to surgery, but revised our statistical analysis due to low inclusion rates.

Continuous secondary outcomes were also analyzed using mixed-effect models. In all mixed-effects models, we adjusted for the baseline score. We analyzed MHQ Pain (and other secondary continuous outcomes), with Group, Time, and their interaction (Group×Time) included as fixed effects. Time was modeled as a categorical variable with levels corresponding to specific time points (baseline/6w/3mo/6mo/12mo). Participant ID was included as a random intercept to account for within-subject correlations across repeated measures. All inferential results from mixed-effects models are reported based on least squares means. We used cumulative link mixed models for ordinal data and report these outcomes using odds ratios, except for complications, which were analyzed using Chi-square tests due to the low number of events. The significance level was set at 0.025 to account for two primary outcomes.

Extensive measures were taken to prevent missing data. We performed Little's test [56–58] to test the null hypothesis that missing data were not missing completely at random.

The cost analysis was conducted from a societal and healthcare perspective following Dutch guidelines [59]. Costs were categorized into healthcare costs, patient and family costs (e.g., travel costs), and costs outside the healthcare sector (e.g., productivity costs due to work absenteeism). Costs were converted to 2022 Euros and calculated by multiplying healthcare consumption volumes with prices per unit. The prices of healthcare consumption were primarily derived from Dutch costing research guidelines [59] and secondarily from financial registrations of the participating centers. Productivity costs were calculated using the friction cost method. Missing cost data were imputed using 40 imputations and 10 iterations using the Mice package in R and we applied Rubin's rules.

The first author, an experienced clinical researcher in health sciences with a strong focus on biostatistics and data analysis, conducted the analysis. An experienced health economist performed the cost analysis.

## Results

After applying the eligibility criteria, we included 166 patients: 81 in the orthosis + exercise group and 85 in the orthosis-only group (Fig. 1, Table 1). The mean number of exercise therapy visits was 7.4 ( $\pm 2.9$ ) in the orthosis + exercise therapy group and 0.3 ( $\pm 0.9$ ) in the orthosis-only group. There was no crossover between the groups. A non-significant Little's test ( $p=0.353$ ) suggested that missing data were missing completely at random. Supplementary Table 1 indicates the patient-reported treatment adherence.

### Primary outcomes

Both the orthosis + exercise and orthosis-only group demonstrated a significant within-group improvement in the MHQ pain subscale at three months (least-squares mean difference 13.9 [standard error  $\pm 1.9$ ] and 10.5 [ $\pm 1.8$ ], respectively, both  $p < 0.001$ ). However, there was no difference in MHQ pain scores at three months between the orthosis + exercise group and the orthosis-only group (least mean square difference 3.7 [95% CI  $-1.0$ – $8.3$ ], Fig. 2A).

The conversion to surgery rate within one year was 4.9% ( $n=4$ ) in the orthosis + exercise group and 9.4% ( $n=8$ ) in the orthosis-only group. This difference was not significant due to the low number of events (risk difference 4.7% [ $-3.3$ – $12.2\%$ ], Fig. 2B), and a post hoc analysis indicated that with these conversion to surgery rates, a total sample size of 362 would have been needed to demonstrate a significant difference for a chi-square test and 90 converted patients for a log-rank test.

### Secondary outcomes

Table 2 demonstrates that the orthosis + exercise group had favorable secondary outcomes at various time points, that is, in the MHQ subscales ADL, work ability, satisfaction with hand, the MHQ total score, satisfaction with treatment results, grip strength, and illness perceptions. There were no other between-group differences in secondary outcomes (Table 2).

### Costs

Table 3 provides an overview of the mean costs until 12 months per patient for both groups. In the intention-to-treat analysis, the total societal costs of the orthosis + exercise group were 37% (between group difference:  $-\text{€}825$  [ $-2072$ – $421$ ]) lower compared to the orthosis-only group. This difference was mainly explained by lower productivity costs in the orthosis + exercise group ( $\text{€}476$  [ $-280$ – $1233$ ] versus  $\text{€}1214$  [ $\text{€}467$ – $1961$ ]). Despite the large absolute difference,

Variable	Orthosis + exercise group (n = 81)	Orthosis-only (n = 85)
Age, mean (SD)	63.9 (8.1)	63.3 (8.0)
Male sex, n (%)	30 (37.0)	30 (35.3)
Location inclusion, n (%)		
Elisabeth-TweeSteden Orthopaedics dept.	1 (1.2)	0 (0.0)
Erasmus MC Orthopaedics dept.	2 (2.5)	0 (0.0)
Franciscus Plastic Surgery dept.	7 (8.6)	5 (5.9)
Reinier Haga Orthopaedic Center	6 (7.4)	9 (10.6)
Xpert Clinics Hand and Wrist care	65 (80.2)	71 (83.5)
No additional in insurance for physical therapy, n (%)	8 (9.9)	7 (8.3)
Type of work, n (%)		
Unemployed (e.g., state pension, retired)	32 (39.5)	35 (41.7)
Unemployed (volunteer)	6 (7.4)	3 (3.6)
Light physical labor	24 (29.6)	23 (27.4)
Moderate physical labor	13 (16.0)	17 (20.2)
Heavy physical labor	6 (7.4)	6 (7.1)
Hand affected, n (%)		
Left	33 (40.7)	31 (36.5)
Right	28 (34.6)	30 (35.3)
Both	20 (24.7)	24 (28.2)
Eaton Glickel stage, n (%)		
Stage 2 (joint space narrowing, osteophytes < 2 mm, mild subchondral sclerosis and cysts, slight instability may be present)	31 (50.0)	35 (47.3)
Stage 3 (osteophytes > 2 mm, pronounced subchondral sclerosis and cysts, no scaphotrapeziotrapezoid OA)	25 (40.3)	38 (51.4)
Stage 4 (presence of scaphotrapeziotrapezoid OA)	6 (9.7)	1 (1.4)
Dominant hand, n (%)		
Ambidextrous	4 (5.3)	2 (2.4)
Left	11 (14.7)	14 (16.9)
Right	60 (80.0)	67 (80.7)
BMI, mean (SD)	26.9 (4.7)	26.2 (5.3)
Comorbidity = yes, n (%)	58 (71.6)	55 (64.7)
Educational level, n (%)		
Primary education	2 (2.7)	2 (2.4)
Basic/Vocational Track Secondary Education, Entry-Level Vocational Training	11 (14.7)	5 (6.0)
Lower General Secondary Education	2 (2.7)	1 (1.2)
Intermediate Vocational Education Level 2–3	8 (10.7)	9 (10.8)
Intermediate Vocational Education Level 4	13 (17.3)	20 (24.1)
Senior General Secondary / Pre-University	10 (13.3)	12 (14.5)
University of Applied Sciences / Research University Bachelor's	18 (24.0)	22 (26.5)
University of Applied Sciences / Research University Master's	9 (12.0)	10 (12.0)
Doctorate / PhD	2 (2.7)	2 (2.4)
Smoking status, n (%)		
Yes, daily smoker	6 (8.0)	12 (14.5)
Yes, irregularly smoker	1 (1.3)	0 (0.0)
Yes, weekly smoker	0 (0.0)	1 (1.2)
No, never smoked	20 (26.7)	34 (41.0)
No, but former smoker	48 (64.0)	36 (43.4)
Duration of symptoms in months, mean (SD)	40.3 (72.0)	42.1 (88.3)
Not coming for a second opinion, n (%)	70 (93.3)	76 (91.6)
Pain (MHQ pain subscale range 0–100)), mean (SD)	51.3 (19.0)	50.8 (18.3)
Anxiety (GAD-7 [range 0–21]), mean (SD)	2.0 (3.2)	1.9 (3.2)
Depressive symptoms (PHQ-9 [range 0–27]), mean (SD)	2.3 (3.0)	2.6 (3.4)

(continued on next page)



Table 1 (continued)

Variable	Orthosis + exercise group (n = 81)	Orthosis-only (n = 85)
Illness perceptions (B-IPQ [range 0–80]), mean (SD)	32.0 (11.7)	33.1 (11.3)
Pain catastrophizing (PCS [range 0–52]), mean (SD)	8.7 (8.9)	9.7 (8.7)
Treatment outcome expectations (CEQ expectancy [range 3–27]), mean (SD)	20.9 (5.1)	20.0 (4.4)
Treatment credibility (CEQ credibility [range 3–27]), mean (SD)	18.1 (4.9)	17.5 (4.6)

SD = Standard Deviation, BMI = Body Mass Index, MHQ = Michigan Hand Outcomes Questionnaire, GAD-7 = Generalized Anxiety Disorder-7, PHQ-9 = Patient Health Questionnaire-9, B-IPQ = Brief Illness Perception Questionnaire, PCS = Pain Catastrophizing Scale, CEQ = Credibility/Expectancy Questionnaire.

Table 1

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Baseline demographic characteristics of the study participants.

multiple imputation-pooled uncertainty (Rubin's rules), skewed cost distributions, and missing data produced wide confidence intervals that included zero, making the difference not statistically significant (Table 3). As there were no significant between-group differences in our primary outcomes (pain and conversion to surgery), the pre-planned cost-effectiveness and cost-utility analyses were not performed following standard practice [59].

## Discussion

Both the orthosis + exercise therapy and an orthosis alone improved pain in patients with CMC-1 OA, but there were no between-group differences. Conversion to surgery was low in both groups and lowest in the orthosis + exercise group, but there was insufficient statistical power to detect a significant difference due to the low number of conversions to surgery. The orthosis + exercise group outperformed the orthosis-only group in various secondary outcomes, including ADL, work ability, satisfaction with hand, MHQ total score, satisfaction with treatment results, grip strength, and illness perceptions. Also, the societal costs of orthosis + exercise were 37% lower than those of an orthosis only. Based on the much lower costs and better secondary outcomes, we recommend the combination of an orthosis and exercises.

Our findings confirm previous positive outcomes of non-surgical treatment, but there are also differences [13,14,16,18,19]. For example, this randomized controlled trial confirms the earlier reported low conversion to surgery rate, underlining the importance of a stepped-care approach in CMC-1 OA. However, while both studies report pain decrease in both treatment arms, our previous real-world evidence study using propensity score matching [19] found more pain reduction in the orthosis + exercise group, a finding not confirmed by the present study. One difference between both studies is the primary outcome (Visual Analogue Scale for Pain versus the MHQ pain subscale). Additionally, the difference may have occurred because the previous study [19] was observational and, despite propensity score matching, confounding by indication may

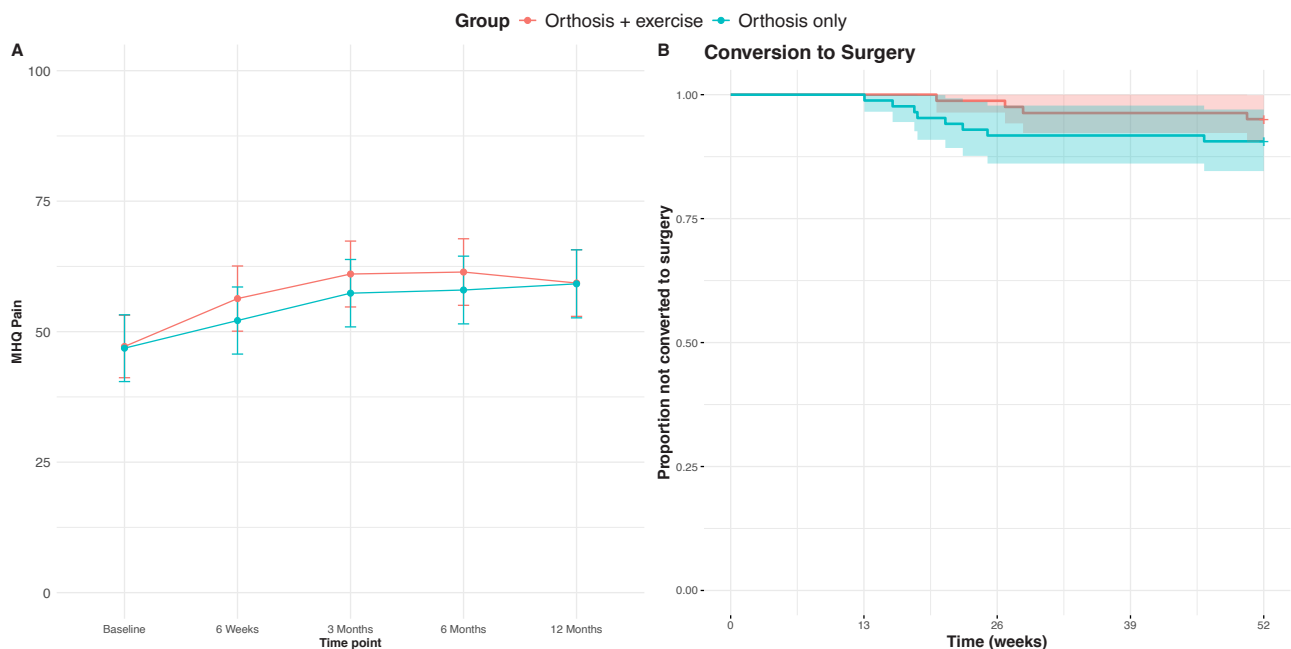


Fig. 2

## Osteoarthritis and Cartilage

A-B. A) The effect of orthosis + exercise compared to orthosis-only on the Michigan Hand Outcomes Questionnaire (MHQ) pain subscale over 12 months. Higher scores indicate less pain. There was no between-group difference in pain at 3 months - the co-primary outcome in this trial (least mean square difference 3.7 [95% CI -1.0–8.3]). The results were estimated using linear mixed-effects models with Group, Time, and their interaction (Group × Time) included as fixed effects. Time was modeled as a categorical variable with levels corresponding to specific assessment points (i.e., baseline, 6 weeks, 3 months, 6 months, and 12 months). Participant ID was included as a random intercept to account for within-subject correlations across repeated measures. The error bars display the 95% confidence intervals. B) Conversion to surgery within 12 months for both groups. The observed difference was not significant due to the low number of events, i.e., the low conversion to surgery rate ( $p=0.416$ ).

Outcome measure	Score range	Time point		Between group comparisons <sup>†</sup>								
		6 weeks		3 months		6 months		1 year				
		Orthosis + Exercise	Orthosis only	Orthosis + Exercise	Orthosis only	Orthosis + Exercise	Orthosis only	Orthosis + Exercise	Orthosis only			
<i>Primary outcomes</i>												
Michigan Hand Outcomes Questionnaire Subscale Pain, least square mean (95% CI)	0–100 ↑	56.3 (50.1 to 62.6)	52.1 (45.7 to 58.6)	61.0 (54.7 to 67.4)	57.4 (50.9 to 63.8)	61.4 (55.0 to 67.8)	58.0 (51.5 to 64.5)	59.3 (52.9 to 65.7)	59.2 (52.6 to 65.7)	3.7 (–1.0 to 8.3)	3.4 (–1.4 to 8.2)	0.2 (–4.7 to 5.0)
Converted to surgery, n (%)	-	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.2)	7 (8.2)	4 (4.9)	8 (9.4)	-	p = 0.081	p = 0.416
<i>Secondary outcomes</i>												
EuroQoL–5-Dimension–5-levels, least square mean (95% CI)	0–1 ↑	0.74 (0.69 to 0.80)	0.72 (0.66 to 0.77)	0.76 (0.70 to 0.81)	0.73 (0.67 to 0.78)	0.74 (0.68 to 0.79)	0.72 (0.66 to 0.78)	0.75 (0.69 to 0.80)	0.76 (0.71 to 0.82)	0.02 (–0.02 to 0.01)	0.02 (–0.03 to 0.07)	–0.02 (–0.06 to 0.03)
Index utility score		72.7 (65.5 to 80.0)	71.3 (63.9 to 78.6)	70.1 (62.7 to 77.6)	70.6 (63.2 to 78.0)	75.9 (68.3 to 83.4)	74.7 (67.3 to 82.2)	71.1 (63.6 to 78.6)	74.2 (66.8 to 81.7)	1.5 (–4.0 to 7.0)	–0.5 (–6.3 to 5.4)	1.1 (–4.9 to 2.9)
VAS General Health	0–100 ↑											
<i>Michigan Hand Outcomes Questionnaire, least square mean (95% CI)</i>												
ADL		70.5 (64.6 to 76.3)	68.2 (62.3 to 74.2)	75.2 (69.3 to 81.2)	71.8 (65.8 to 77.8)	76.1 (70.1 to 82.1)	69.4 (63.4 to 75.4)	76.9 (70.9 to 82.9)	74.7 (68.7 to 80.8)	2.3 (–2.2 to 6.7)	3.4 (–1.2 to 8.0)	2.2 (–2.6 to 7.0)
Hand function		62.2 (56.7 to 67.6)	61.8 (56.3 to 67.3)	62.6 (57.1 to 68.2)	63.7 (58.2 to 69.3)	65.0 (59.4 to 70.6)	61.3 (55.7 to 66.8)	65.4 (59.8 to 71.0)	61.7 (56.1 to 67.3)	0.4 (–3.9 to 4.6)	–1.1 (–5.4 to 3.2)	3.8 (–0.8 to 8.3)
Aesthetics		78.2 (71.9 to 84.5)	74.9 (68.5 to 81.4)	82.0 (75.6 to 88.3)	78.3 (71.9 to 84.7)	81.8 (75.4 to 88.2)	77.0 (70.5 to 83.4)	81.0 (74.6 to 87.4)	79.9 (73.4 to 86.4)	3.3 (–1.5 to 8.0)	3.7 (–1.2 to 8.6)	1.1 (–0.4 to 2.6)
Work ability		69.9 (62.6 to 77.2)	66.2 (58.8 to 73.7)	77.5 (70.1 to 84.9)	70.1 (62.6 to 77.6)	80.2 (72.7 to 87.7)	71.9 (64.4 to 79.5)	79.7 (72.2 to 87.2)	72.4 (64.8 to 79.9)	3.7* (1.8 to 9.2)	7.4* (1.7 to 13.1)	73* (1.3 to 13.3)
Satisfaction with hand		59.8 (51.7 to 68.0)	54.1 (45.8 to 62.4)	65.4 (57.2 to 73.7)	54.7 (46.4 to 63.0)	65.3 (56.9 to 73.7)	58.8 (50.4 to 67.1)	64.1 (55.8 to 72.5)	60.5 (52.0 to 68.9)	5.8 (–0.5 to 12.0)	10.8* (4.4 to 17.2)	3.7 (–3.0 to 10.4)
Total score		66.4 (61.7 to 71.2)	62.9 (58.0 to 67.7)	70.9 (66.1 to 75.7)	66.0 (61.2 to 70.9)	71.9 (67.1 to 76.7)	66.2 (61.3 to 71.1)	71.2 (66.4 to 76.1)	67.7 (62.8 to 72.6)	3.6 (0.0 to 7.1)	4.9* (1.3 to 8.5)	3.5 (–0.3 to 7.3)
<i>Satisfaction with Treatment Result Questionnaire, n (%)</i>												
How satisfied are you with your treatment result so far?	-											
Extremely dissatisfied		1 (1.2)	2 (2.4)	1 (1.2)	3 (3.5)	4 (4.9)	0 (0)	2 (2.5)	3 (3.5)			
Very dissatisfied		5 (6.2)	9 (10.6)	3 (3.7)	4 (4.7)	4 (4.9)	2 (2.4)	3 (3.7)	3 (3.5)			
Somewhat dissatisfied		5 (6.2)	10 (11.8)	3 (3.7)	11 (12.9)	2 (2.5)	4 (4.7)	2 (2.5)	6 (7.1)			
Neither satisfied/dissatisfied		8 (9.9)	17 (20)	7 (8.6)	15 (17.6)	7 (8.6)	14 (16.5)	6 (7.4)	19 (22.4)			
Somewhat satisfied		21 (25.9)	22 (25.9)	14 (17.3)	24 (28.2)	8 (9.9)	21 (24.7)	10 (12.3)	11 (12.9)			
Very satisfied		24 (29.6)	15 (17.6)	24 (29.6)	12 (14.1)	19 (23.5)	23 (27.1)	23 (28.4)	22 (25.9)			
Extremely satisfied		4 (4.9)	4 (4.7)	9 (11.1)	2 (2.4)	10 (12.3)	6 (7.1)	9 (11.1)	4 (4.7)			
Missing data		13 (16)	6 (7.1)	20 (24.7)	14 (16.5)	27 (33.3)	15 (17.6)	26 (32.1)	17 (20)			
Would you undergo the treatment again under similar circumstances?												
Yes		60 (74.1)	59 (69.4)	54 (66.7)	51 (60.0)	47 (58.0)	56 (65.9)	43 (53.1)	49 (57.6)	4.2* (1.1 to 15.6)	4.8* (1.2 to 18.4)	1.9 (0.5 to 6.5)
No		8 (9.9)	20 (23.5)	7 (8.6)	20 (23.5)	7 (8.6)	14 (16.5)	12 (14.8)	19 (22.4)			
Missing data		13 (16.0)	6 (7.1)	20 (24.7)	14 (16.5)	27 (33.3)	15 (17.6)	26 (32.1)	17 (20.0)			
Would you recommend this treatment to friends and family?												
Yes		63 (77.8)	61 (71.8)	56 (69.1)	56 (65.9)	50 (61.7)	58 (68.2)	44 (54.3)	50 (58.8)	9.8* (1.8 to 52.3)	5.5* (1.1 to 27.3)	2.7 (0.6 to 11.2)
No		5 (6.2)	18 (21.2)	5 (6.2)	15 (17.6)	4 (4.9)	12 (14.1)	11 (13.6)	18 (21.2)			
Missing data		13 (16.0)	6 (7.1)	20 (24.7)	14 (16.5)	27 (33.3)	15 (17.6)	26 (32.1)	17 (20.0)			

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Table 2 (continued)

Outcome measure	Score range	Time point				Between group comparisons†			
		6 weeks		3 months		6 months		1 year	
		Orthosis + Exercise	Orthosis only	Orthosis + Exercise	Orthosis only	Orthosis + Exercise	Orthosis only	Orthosis + Exercise	Orthosis only
Patient Reported Experience Measure, n (%)									
To what extent have your symptoms changed since the start of treatment?	-	0 (0.0)	1 (1.2)	0 (0.0)	0 (0)	-	-	-	-
Very much worsened		2 (2.5)	1 (1.2)	4 (4.9)	2 (2.4)				
Slightly worsened		4 (4.9)	7 (8.2)	4 (4.9)	8 (9.4)				
No change		11 (13.6)	23 (27.1)	4 (4.9)	18 (21.2)				
Slightly improved		28 (34.6)	20 (23.5)	23 (28.4)	26 (30.6)	-	-	-	-
Much improved		17 (21.0)	13 (15.3)	15 (18.5)	12 (14.1)				
Very much improved		4 (4.9)	3 (3.5)	7 (8.6)	2 (2.4)				
Missing data		15 (18.5)	17 (20)	24 (29.6)	17 (20)				
To what extent has your ability to perform activities changed since the start of treatment? (activities include self-care, household activities, work, hobbies or sports)									
Very much worsened		0 (0)	0 (0)	1 (1.2)	0 (0)				
Much worsened		0 (0)	2 (2.4)	1 (1.2)	1 (1.2)				
Slightly worsened		6 (7.4)	6 (7.1)	5 (6.2)	6 (7.1)				
No change		19 (23.5)	25 (29.4)	10 (12.3)	34 (40)				
Slightly improved		22 (27.2)	25 (29.4)	19 (23.5)	19 (22.4)				
Much improved		18 (22.2)	6 (7.1)	17 (21)	7 (8.2)				
Very much improved		0 (0)	3 (3.5)	4 (4.9)	1 (1.2)				
Missing data		16 (19.8)	18 (21.2)	24 (29.6)	17 (20)				
ICHO Modified Clavien-Dindo Classification, n (%)									
Grade 1	-	-	-	-	-	-	-	-	p = 0.135
Grade 2									
Grade 3A									
Grade 3B									
Grade 3 C									
Patient Health Questionnaire-9, least square mean (95% CI)	0-27 ↓	-	-	2.3 (1.6 to 3.0)	2.2 (1.6 to 2.9)	-	-	0.1 (-0.4 to 0.6)	-
General Anxiety Disorder-7, least square mean (95% CI)	0-21 ↓	-	-	1.7 (1.0 to 2.4)	1.7 (1.0 to 2.4)	-	-	0.0 (-0.5 to 0.5)	-
Brief Illness Perception Questionnaire, least square mean (95% CI)	0-80 ↓	-	-	30.8 (27.9 to 33.6)	33.6 (30.7 to 36.7)	-	-	-2.8* (-4.9 to -0.7)	-

†Least square mean difference with 95% confidence interval for continuous outcomes, odds ratios with 95% confidence intervals for ordinal outcomes

(i.e., satisfaction with treatment results and patient reported experience measure). For conversion to surgery, we only report the p-value for the Chi-square test due to the low number of events. (Least square mean difference with 95% confidence interval for continuous outcomes, odds ratios with 95% confidence intervals for ordinal outcomes)

<sup>\*\*</sup>  $p < 0.025$ 

↓ higher scores indicate worse performance.

↑ higher scores indicate better performance.

ADL = activities of daily living, VAS = visual analogue scale, MCP-1 = first carpometacarpal joint, MCP-1 = first metacarpophalangeal joint, IP-1 = first interphalangeal joint, ICHOM = International Consortium for Health Outcomes Measurement

## Table 2

Primary and secondary outcomes for both groups at each time point.

	Costs per unit in €	Orthosis + Exercise group	Orthosis-only group	Mean difference (95% CI)
<b>Healthcare costs</b>				
Referral and primary orthosis application <sup>a</sup>	Varying <sup>a*</sup>	85.80 (22.50)	91.50 (17.90)	-5.65 (-11.86 to 0.56)
Additional orthosis and injections <sup>b</sup>	Varying <sup>b*</sup>	36.80 (122.29)	67.80 (172.16)	-30.99 (-64.05 to 2.05)
Medical specialist care <sup>c</sup>	123.75 per visit <sup>c</sup>	82.53 (119.46)	79.00 (167.54)	3.53 (-18.93 to 26.00)
Occupational therapy	41.54 per visit <sup>c</sup>	106.67 (64.64)	147.10 (78.97)	-40.43 (-49.42 to 31.44)
Physical therapy	59.51 per visit <sup>c</sup>	363.88 (146.70)	167.92 (122.91)	195.95 (179.16 to 212.75)
General practitioner	40.32 per visit <sup>c</sup>	147.69 (128.85)	175.19 (140.77)	-27.50 (-51.84 to 3.16)
Other healthcare professionals <sup>d</sup>	Varying <sup>c</sup>	34.02 (131.91)	26.29 (105.48)	7.73 (-9.41 to 24.86)
Home care <sup>e</sup>	Varying <sup>c</sup>	24.73 (120.50)	82.60 (441.62)	-57.88 (-105.61 to 10.14)
Medication usage <sup>f</sup>	Varying <sup>g</sup>	4.72 (9.54)	5.82 (17.84)	-1.11 (-3.34 to 1.13)
Surgery (trapeziectomy) <sup>g</sup>	2.967.11 per surgery <sup>h</sup>	145.09 (636.69)	280.62 (871.45)	-135.53 (-230.78 to -40.29)
<b>Total healthcare costs (95% CI)<sup>h</sup></b>		<b>946.12 (743.79 to 1148.46)</b>	<b>1032.35 (834.98–1229.71)</b>	<b>-87.16 (-209.44 to 35.11)</b>
<b>Patient and family costs</b>				
<b>Total patient and family costs (95% CI)<sup>h</sup></b>	<b>0.19 per kilometer<sup>e</sup> for traveling costs</b>	<b>6.57 (4.27 to 8.85)</b>	<b>8.23 (6.01–10.45)</b>	<b>-1.66 (-4.84 to -1.42)</b>
<b>Costs outside healthcare and productivity costs</b>				
<b>Total costs outside healthcare and productivity costs (95% CI)<sup>h</sup></b>	<b>42.46 per hour<sup>e</sup></b>	<b>476.37 (-279.87 to 1232.62)</b>	<b>1213.90 (467.28 to 1960.52)</b>	<b>-742.01 (-1866.73 to 213.49)</b>
<b>Total societal costs (95% CI)<sup>h</sup></b>		<b>1429.07 (541.06 to 2317.07)</b>	<b>2254.47 (1379.27 to 3129.68)</b>	<b>-825.41 (-2072.04 to 421.22)</b>

Costs are based on the year 2022 and are expressed as mean (SD) unless otherwise stated. Following intention to treat principles, we imputed missing data. Data on costs at 12 months were missing in 42% for the orthosis + exercise group and 34% for the orthosis-only group.

<sup>a</sup> Includes x-rays, costs associated with referral, and orthosis materials.

<sup>b</sup> Includes additional regular orthoses, sustainable orthoses (e.g., silver splints), and corticosteroid injections.

<sup>c</sup> Contact with orthopedic and/or plastic surgeon.

<sup>d</sup> Contact with a psychologist, occupational physician, and alternative healers.

<sup>e</sup> Includes household support, personal care, guidance, and nursing.

<sup>f</sup> Medication (including paracetamol, NSAIDs, and opioids).

<sup>g</sup> Trapeziectomy (including surgery, medical specialist visits, physical therapy, occupational therapy, and orthosis materials).

<sup>h</sup> Rubin's rules were applied to the imputed cost data and we computed group means and the associated confidence intervals using linear regression for each imputation and between-group differences using 5000 non-parametric bootstraps.

\* Dutch guideline for costing research; † Financial registration of study centers; ‡ Medication and Aid Information Project database (medicijnkosten.nl)

Table 3

Osteoarthritis and Cartilage

Overview of the mean costs for the study participants.

have occurred. In other words, there may still have been baseline between-group differences in unmeasured covariates that influenced pain outcomes. For example, there may be differences in treatment outcome expectations for one of both treatment arms, which in turn influences outcomes [60,61]. In the observational study, these expectations were not controlled for, and expectations may have influenced treatment allocation (i.e., the choice between orthosis only and orthosis combined with exercise by patients). However, in the trial, patients were randomized to a treatment arm, but they may still have had different expectations since the treatment allocation was not blinded. These differences underline that treatment allocation and outcomes in real-world CMC-1 OA care differ from the relatively artificial setting of a randomized controlled trial. Therefore, we suggest that both designs provide valuable but different insights, i.e., the real-world evidence study provides more insights into outcomes in actual daily care with less certainty about causal paths (i.e., effectiveness), while the present trial does provide more certainty about these causal paths but has a more artificial setting that is less representative of daily clinical care (i.e., efficacy). Future comparative effectiveness studies may thus consider both designs depending on the underlying research question.

Conversion to surgery was 4.9% (n=4) in the orthosis + exercise group and 9.4% (n=8) in the orthosis-only group, which is lower than previous studies (13–29%) [19,20,26,27]. As we based our sample size on higher conversion rates (10% and 20%, respectively) based on previous research [26], we had insufficient statistical power to demonstrate a significant difference. With these low conversion to surgery rates, a total of 362 participants would have been required to demonstrate a significant difference for a chi-square test and 90

converted patients to perform an adequate survival analysis, which would have been the preferred approach.

Several reasons may explain the lower conversion to surgery rate compared to previous studies. First, surgeons may be less inclined to operate based on the increasing evidence supporting nonsurgical treatment over time [14,16,19,20,26]. Also, our data collection happened during the COVID-19 pandemic. Healthcare production was scaled down in the Netherlands at that time, and patients may have been less inclined to seek care for a chronic condition in that situation. Therefore, we will evaluate the long-term conversion to surgery of trial participants to investigate if these rates increased over time. Lastly, the conversion to surgery may have been lower due to the setting of a trial; the patients participating in it may have done so to avoid surgery. Future work may explore this. Also, we recommend future prospective studies to aim for larger samples to draw more definitive conclusions on between-group differences in conversion to surgery.

This study has several limitations. Although inherent to research using patient-reported outcome measurements, one limitation is missing data. Following current standards, we used linear mixed models (which can handle missing data), and the non-significant Little's test suggested that the data were missing completely at random. Also, we downgraded our sample size due to disappointing inclusion rates. This had common reasons (e.g., specific treatment preferences or feasibility during outpatient clinic), but the COVID-19 pandemic also negatively affected our inclusion, as fewer patients with CMC-1 OA sought care at the time. Therefore, we were statistically underpowered to demonstrate a difference in conversion to surgery between the two groups. Furthermore, despite extensive

training of the hand therapists and monitoring treatment adherence, the actual treatment may have differed from our protocols. We did not perform a per-protocol analysis, and the effect of exercise therapy may have washed out due to low compliance, or patients in the orthosis-only group may have had some exercise therapy sessions (as indicated by the costs for physical therapy in this group). However, our intention-to-treat approach represents daily care and therefore appears more face-valid. Another limitation is that physical therapy reimbursement depends on the patient's additional insurance. This may have affected the number of therapy sessions.

We did not base our sample size on a minimal clinically important difference value because this value was unavailable for nonsurgically treated patients with CMC-1 OA when we designed the trial. This is relevant as we recently demonstrated that such clinically important outcome values strongly depend on diagnosis and treatment type (e.g., surgical versus nonsurgical) [35]. Therefore, although not ideal in terms of clinical relevance, we used conventional statistical effect sizes [55].

Lastly, a limitation is that we had to make assumptions about healthcare consumption for home care and productivity loss. Similarly, the healthcare and productivity costs associated with surgery were based on treatment guidelines and literature reviews and not on prospective data collection in the study participants who converted to surgery. This may have affected the reliability of the estimated healthcare and societal costs in both groups. Also, although orthosis + exercises yielded lower mean total societal costs, the pooled confidence intervals indicate substantial uncertainty. Therefore, the cost difference should be interpreted as potentially meaningful but is not statistically confirmed.

## Conclusions

Both an orthosis + exercise therapy and an orthosis alone provided clinically relevant pain relief, but there was no difference between the groups. Conversion to surgery was low and lowest in the orthosis + exercise group, but there was insufficient statistical power to demonstrate a significant difference. The orthosis + exercise group had better secondary outcomes and is, therefore, preferred.

## Ethical review committee statement

This study was performed in accordance with the ethical standards in the 1964 Declaration of Helsinki. The ethical review committee of Erasmus MC approved this study (MEC-2019-0616).

## Author contributions

Conception and design: RW, SBZ, JC, GV, RS. Analysis and interpretation of the data: RW, LEL, SH, SBZ, GK, JC, JMZ, GV, RS. Drafting of the article: RW. Critical revision of the article for important intellectual content: LEL, SH, SBZ, GK, JC, JMZ, GV, RS. Final approval of the article: RW, LEL, SH, SBZ, GK, JC, JMZ, GV, RS. Provision of study materials or patients: RW, LEL, GK, JC, JMZ, GV. Statistical expertise: RW, SH, RS. Obtaining of funding: RW, SBZ, JC, GV, RS. Administrative, technical, or logistic support: RW, LEL. Collection and assembly of data: RW, LEL, GK, JC, JMZ, GV, RS.

## Declaration of Competing Interest

All authors declare that they have no conflicts of interest related to the current study.

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## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.joca.2025.10.005.

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