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Blinded Interpretation of The Primary Endpoint Results From The Study:

'Total Hip Arthroplasty Versus Progressive Resistance Training in Patients With Severe Hip Osteoarthritis (The PROHIP Trial): A Randomized Controlled Trial'

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Clinical trial registration: ClinicalTrials.gov (NCT04070027)

ABBREVIATIONS

30s-CST	30 seconds Chair Stand Test
40m-FPWT	40 meter Fast Paced Walk Test
HOOS	Hip disability and Osteoarthritis Outcome Score
MCII	Major clinically important improvement
MIC	Minimal important change
MID	Minimal important difference
OHS	Oxford Hip Score
OMERACT-OARSI	Outcome Measures for Rheumatology Committee and Osteoarthritis Research Society International Standing Committee for Clinical Trials Response Criteria Initiative
OPEN	Odense Patient data Explorative Network
PRT	Progressive Resistance Training
REDCap	Research Electronic Data Capture
THA	Total Hip Arthroplasty
UCLA	University of California Los Angeles

BLINDED INTERPRETATION PROCEDURE

This document presents the blinded results and the blinded interpretation of the intention-to-treat analysis from our randomized controlled trial evaluating the effectiveness of total hip arthroplasty (THA) followed by standard care compared with 12 weeks of progressive resistance training (PRT) followed by 12 weeks of optional non-supervised PRT, on change in patient-reported hip pain and function measured using the Oxford Hip Score (OHS), from baseline to the primary endpoint at 6 months follow-up in patients with severe hip osteoarthritis. The statistical analyses and blinded interpretation were previously described in the trial protocol[1] and the statistical analysis plan[2] published before any analyses commenced.

Before patient enrollment started on September 2, 2019, the two treatment arms were coded 'Group A' and 'Group B' by the Database Manager (David Hass), otherwise unrelated to the trial, from Odense Patient data Explorative Network (OPEN) in Research Electronic Data Capture (REDCap).

The principal investigator (Thomas Frydendal) prepared and delivered the blinded data set for the statistical analyses. The blinded biostatistician (Sabrina Mai Nielsen), otherwise unrelated to the trial, then performed the descriptive statistics on the baseline characteristics and intention-to-treat analyses on the primary outcome and key secondary outcomes from baseline to 6 months follow-up in accordance with statistical analysis plan[2]. This also included the predefined sensitivity analysis using a single-step non-responder imputation (i.e. missing data was replaced by baseline observation carried forward). After completing these analyses, the biostatistician presented the results to the trial group. Finally, the trial group (identical to the authors signing this document) conducted a blinded interpretation of the results before the treatment codes was disclosed. Interpretation version 1 assumes that Group A received THA, while interpretation version 2 assumes that Group A received PRT.

To ensure the blinding of group allocation, no analyses were performed on serious adverse events, treatment crossovers (i.e. number of patients declining surgery in the THA group after randomization and number of patients undergoing THA surgery in the PRT group), per protocol population, and as treated population in preparation for this blinded interpretation. These predefined analyses will be commenced after this document has been made publicly available, and the results will be taken into account for the overall interpretation of the trial results.

RESULTS FROM THE INTENTION-TO-TREAT ANALYSES

Primary outcome

The least squares mean (±standard error) changes in OHS from baseline to 6 months follow-up were 4.5 ± 1.0 in Group A and 15.9 ± 1.0 in Group B, corresponding to a statistically significant greater improvement in OHS in Group B compared to Group A with a mean group difference of -11.4 points (95% CI -14.0 to -8.9). As the mean difference between the groups and lower limit of the 95% confidence interval are above the predefined minimal important difference (MID) of 5 points[3], the true difference in change between the two treatments is considered clinical significant in favor of Group B (Table 2). The multiple sensitivity analyses also supports this finding (Appendix Table 2).

Key secondary outcomes

Group B had statistically significant greater improvements in all five HOOS subscales compared with Group A at 6 months with mean group differences of -24.2 points (95% CI -30.2 to -18.2) for HOOS pain, -25.7 points (95% CI -31.8 to -19.5) for HOOS symptoms, -20.8 points (95% CI -26.3 to -15.2) for HOOS ADL, -31.8 points (95% CI -38.8 to -24.9) for HOOS

quality-of-life, and -32.7 points (95% CI -40.4 to -25.0) for HOOS sport/recreation. As the mean differences between the groups and lower limits of the 95% confidence intervals are above the MID of 10 points for all five HOOS subscales[4], the true differences in change between the two treatments are considered clinical significant in favor of Group B. (Table 2). Group B had statistically significant greater improvements in the UCLA activity score and 40m-FPWT compared with Group A at 6 months with a mean group difference of -0.7 points (95% CI -1.3 to -0.1) and median group difference of -0.10 m/s (95% CI -0.17 to -0.03), respectively. There was no statistically significant between-group difference in change from baseline to 6 months follow-up in the 30s-CST as the median group difference was 0.0 repetitions (95% CI -2.0 to 1.0). As the mean or median differences between the groups and upper limits of the 95% confidence intervals were below the MID of 2 points for the UCLA activity score[5], major clinically important improvement (MCII) of 0.2 m/s for the 40m-FPWT[6], and MCII of 2.1 repetitions for the 30s-CST[6], the true differences in change between the two treatments are considered not clinically significant (Table 2). The results for all key secondary outcomes were not changed in the sensitivity analyses (Appendix Table 2).

Treatment response

The proportion of patients who improved by 8 points (minimal important change [MIC] = 8 points)[3] or more in the OHS was 38% in Group A and 75% in Group B, corresponding to a risk difference of -0.38 (95% CI -0.55 to -0.21). The proportion of patients who were responders to treatment (OMERACT–OARSI criteria)[7] was 38% in Group A and 77% in Group B, corresponding to a risk difference of -0.40 (95% CI -0.57 to -0.23).

INTERPRETATION VERSION 1. 'Group A received THA'

Among patients aged 50 years or above with clinical and radiographic hip osteoarthritis considered eligible for THA, PRT is clinically significant more effective than THA in improving patient-reported hip pain and function, symptoms, quality-of-life, and function in sports and recreation at 6 months. PRT also led to statistically but not clinically significant greater improvements in patient-reported physical activity level and functional performance in gait speed, while there was no additional improvement in performance based sit-to-stand function compared with THA. Patients who performed PRT are considerably more likely to experience a clinically relevant improvement in hip pain and function than those who received a THA.

This is the first randomized controlled trial to investigate the effectiveness of THA compared with PRT. The results of this trial provide direct evidence that PRT is superior to THA in improving almost all of the assessed patient-reported outcomes after 6 months in patients with severe hip osteoarthritis. This may be used to facilitate the shared decision making process between clinicians and patients with hip osteoarthritis in clinical practice to reach a decision about treatment based on both evidence and on the patient's individual preferences and values.

As the results are in favor of PRT, our primary hypothesis (described previously in the trial protocol[1] and statistical analysis plan[2]) cannot be confirmed, suggesting that current guideline recommendations for the referral to THA need to be discussed and revised in the management of hip osteoarthritis.

INTERPRETATION 2. 'Group A received PRT'

Among patients aged 50 years or above with clinical and radiographic hip osteoarthritis considered eligible for THA, THA is clinically significant more effective than PRT in improving patient-reported hip pain and function, symptoms, quality-of-life, and function in sports and recreation at 6 months. THA also led to statistically but not clinically significant greater improvements in patient-reported physical activity level and functional performance in gait speed, while there was no additional improvement in performance based sit-to-stand function compared with PRT. Patients who received a THA are considerably more likely to experience a clinically relevant improvement in hip pain and function than those who performed PRT.

This is the first randomized controlled trial to investigate the effectiveness of THA compared with PRT. The results of this trial provide direct evidence that THA is superior to PRT in improving almost all of the assessed patient-reported outcomes after 6 months in patients with severe hip osteoarthritis. This may be used to facilitate the shared decision making process between clinicians and patients with hip osteoarthritis in clinical practice to reach a decision about treatment based on both evidence and on the patient's individual preferences and values.

As the results are in favor of THA, this confirms our primary hypothesis described previously in the trial protocol[1] and statistical analysis plan[2]. This supports current guideline recommendations in the management of hip osteoarthritis, in which THA should be considered for patients with pain and functional impairments that substantially impacts quality-of-life when first-line treatment is ineffective or inappropriate.

Table 2. Change from Baseline in Primary and Key Secondary Outcomes at 6 months in the Intention-To-Treat Population.[a]

Outcome	Change from Baseline to 6 Months		Between-Group Difference in Mean Improvement	
	Group A (N=56)	Group B (N=53)	Adjusted Mean Difference (95% CI)	*P* value
Primary Outcome				
OHS score (range 0-48)	4.5 (1.0)	15.9 (1.0)	-11.4 (-14.0 to -8.9)	<.001
Key Secondary Outcomes				
HOOS subscale scores (range 0-100)				
Pain	15.0 (2.3)	39.2 (2.4)	-24.2 (-30.2 to -18.2)	<.001
Symptoms	13.6 (2.4)	39.3 (2.5)	-25.7 (-31.8 to -19.5)	<.001
Function in activities of daily living	12.1 (2.1)	32.9 (2.2)	-20.8 (-26.3 to -15.2)	<.001
Hip-related quality of life	9.2 (2.7)	41.0 (2.8)	-31.8 (-38.8 to -24.9)	<.001
Function in sports and recreation	10.7 (3.0)	43.5 (3.1)	-32.7 (-40.4 to -25.0)	<.001
UCLA activity score (range 1-10)	0.5 (0.2)	1.2 (0.2)	-0.7 (-1.3 to -0.1)	.018
Gait speed in the 40 meter fast-paced walk test, m/s[b]	0.06 [-0.05;0.19]	0.15 [0.05;0.33]	-0.10 (-0.17 to -0.03)	.009
Number of repetitions in the 30-second chair stand test[b]	1.0 [0.0;3.0]	1.0 [0.0;4.0]	0.0 (-2.0 to 1.0)	.361
Response to Treatment				
OHS minimal important change criteria, no. (%)[c]	21 (38)	40 (75)	-0.38 (-0.55 to -0.21)	
OMERACT-OARSI criteria, no. (%)[d]	21 (38)	41 (77)	-0.40 (-0.57 to -0.23)	

[a] All analyses was based on the Intention-To-Treat (ITT) population. For continues outcomes, repeated measures linear mixed effects models (with no imputation for missing data) were used for estimating least squares means (LSMeans) and standard errors (SE) difference between groups reported with 95% confidence intervals. For dichotomous outcomes, n (%) and risk differences (RD) were estimated with corresponding 95% confidence intervals using a conservative non-responder imputation.

[b] Median (IQR) and median differences with 95% confidence intervals are reported for these outcomes (with no imputation for missing data). For both outcomes, there were missing data on five patients in Group A and four patients in Group B.

[c] Patients was classified as having a minimal important change (MIC) if the OHS score improved by 8 points or more.[3]

[d] According to the criteria of the Outcome Measures for Rheumatology Committee and Osteoarthritis Research Society International Standing Committee for Clinical Trials Response Criteria Initiative (OMERACT–OARSI),[7] patients was classified as having a response if the OHS pain or function subscale score improved by 50% or more and by 20 or more points or if two of the following three findings was observed: an improvement in the OHS pain score by 20% or more and by 10 or more points on the subscale, an improvement in the OHS function score by 20% or more and by 10 or more points on the subscale, or an improvement in the OHS score by 20% or more and by 10 or more points. The OHS pain and function subscales range from 0 to 100, with higher scores indicating better disease status.[8]

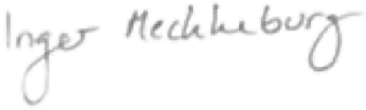
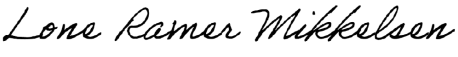
Appendix Table 2. Change from Baseline in Primary and Key Secondary Outcomes at 6 months in the Intention-to-Treat Population using a single-step non-responder imputation.[a]

Outcome	Change from Baseline to 6 Months		Between-Group Difference in Mean Improvement
	Group A (N=56)	Group B (N=53)	Adjusted Mean Difference (95% CI)
Primary Outcome			
OHS score (range 0-48)	4.0 (1.0)	14.7 (1.0)	-10.7 (-13.3 to -8.2)
Key Secondary Outcomes			
HOOS subscale scores (range 0-100)			
Pain	13.7 (2.3)	36.3 (2.4)	-22.7 (-28.7 to -16.6)
Symptoms	12.3 (2.4)	36.7 (2.4)	-24.4 (-30.5 to -18.3)
Function in activities of daily living	11.0 (2.1)	30.4 (2.2)	-19.4 (-24.9 to -13.9)
Hip-related quality of life	8.1 (2.7)	37.9 (2.8)	-29.8 (-36.7 to -22.8)
Function in sports and recreation	9.4 (3.0)	40.3 (3.0)	-30.9 (-38.5 to -23.6)
UCLA activity score (range 1-10)	0.5 (0.2)	1.2 (0.2)	-0.7 (-1.2 to -0.2)
Walking speed in the 40 meter fast-paced walk test, m/s[b]	0.05 [-0.03;0.19]	0.13 [0.03;0.29]	-0.09 (-0.16 to -0.02)
Number of repetitions in the 30-second chair stand test[b]	1.0 [0.0;3.0]	1.0 [0.0;3.0]	0.0 (-1.0 to 0.0)

[a] All analyses was based on the Intention-To-Treat (ITT) population. For continues outcomes, repeated measures linear mixed effects models (missing data is replaced by baseline observation carried forward) were used for estimating least squares means (LSMeans) and standard errors (SE) difference between groups reported with 95% confidence intervals.

[b] Median (IQR) and median differences with 95% confidence intervals are reported for these outcomes.

SIGNATURES OF THE TRIAL GROUP

Date	Name	Signature
Feb 09, 2023	Thomas Frydendal PT, MSc	
2023, Feb. 13	Robin Christensen PhD, Professor	
Feb 11, 2023	Inger Mechlenburg PT, PhD, DMSc, Professor	
Feb 13, 2023	Lone Ramer Mikkelsen, PT, PhD, Associate professor	
Feb 09, 2023	Sabrina Mai Nielsen, PhD, Postdoc	
Feb 09, 2023	Kim Gordon Ingwersen PT, PhD, Associate professor	
Feb. 11, 2023	Søren Overgaard MD, PhD, DMSc, Professor	

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