EDITORIALS

Parachutes and Preferences — A Trial of Knee Replacement

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The term parachute trial entered the medical lexicon to depict studies of treatments everyone already assumes to be effective. (In other words, do we need a trial to show that parachutes save the lives of persons who jump from airplanes?[1]) The parachute trial has been invoked to decry randomized trials of total joint replacement as senseless. After all, joint replacements are among the most significant advances of the 20th century; don't we already know they are successful?

Nearly 1 million elective total knee and hip replacements are performed annually in the United States; rates of total knee replacement tripled in the past 20 years and are projected to increase further.[2,3] More than 90% of total knee replacements are performed for knee osteoarthritis, which affects approximately 14% of adults in the United States in their lifetimes.[4] Prior to the introduction of total knee replacement in the 1970s, patients with advanced knee osteoarthritis frequently became housebound; now such patients can remain mobile. By all accounts, total knee replacement is a game changer. So why subject it to a randomized, controlled trial?

First, total knee replacement poses risks. About 0.5 to 1% of patients die during the 90-day postoperative period. The risks of deep venous thrombosis, pulmonary embolus, deep prosthetic infection, and periprosthetic fracture range from 0.1 to 1.0%,[5-7] with higher risks among older persons and those with a higher number of coexisting conditions.[5,7] Second, the procedure is not universally successful; approximately 20% of patients who undergo total knee replacement have residual pain 6 or more months after the procedure.[8] Third, there are alternatives. Clinical trials have shown that physical therapy (including exercises and manual therapies) can diminish pain and improve functional status in patients with advanced knee osteoarthritis.[9-11] Until now, we have lacked rigorously controlled comparisons between total knee replacement and its alternatives.

Finally, an ideal treatment for one patient may not be right for the next. Patients with knee osteoarthritis differ in the importance they attach to pain relief, functional improvement, and risk of complications. Therefore, treatment decisions should be shared between patients and their clinicians and anchored by the probabilities of pain relief and complications and the importance patients attach to these outcomes.

These considerations set the stage for the carefully designed and executed trial by Skou et al., whose results are reported in this issue of the *Journal*.[12] In this randomized, controlled trial, involving 100 patients with symptomatic knee osteoarthritis, patients were assigned to undergo total knee replacement followed by a rigorous 12-week nonsurgical-treatment regimen (total-knee-replacement group) or to receive only the nonsurgical treatment (nonsurgical-treatment group), which consisted of supervised exercise, education, dietary advice, use of insoles, and pain medication. Total knee replacement proved markedly superior to nonsurgical treatment alone in terms of pain relief and functional improvement. The percentage of patients who had an improvement of at least 15% (a clinically important difference) in the score for pain after 1 year was 85% in the total-knee-replacement group and 68% in the nonsurgical-treatment group. In

fact, 26% of patients in the nonsurgical-treatment group elected to undergo total knee replacement before the 12-month follow-up, and more patients are likely to cross over as follow-up extends further.

However, it is noteworthy that more than two thirds of the patients in the nonsurgical-treatment group had clinically meaningful improvements in the pain score and that this group had a lower risk of complications. In the total-knee-replacement group, several severe adverse events occurred, including three episodes of deep venous thrombosis, one deep infection, one supracondylar fracture, and three episodes of stiffness requiring manipulation of the knee while the patient was anesthetized. The nonsurgical-treatment group had one episode of stiffness requiring manipulation of the knee while the patient was anesthetized and none of the other complications. In short, although total knee replacement was clearly superior in terms of pain relief, these findings suggest that the decision for treatment with total knee replacement is no parachute at all. Patients face choices that are associated with different levels of symptomatic improvement and risk: as compared with nonsurgical treatment, total knee replacement is associated with a higher level of improvement and a higher risk of adverse events. Each patient must weigh these considerations and make the decision that best suits his or her values.

As with all good studies, this randomized, controlled trial answers some questions and raises others. Sham-controlled trials have suggested that both surgical therapy and physical therapy can have a potent placebo effect.[13,14] In the absence of an untreated control group, some of the improvement that was seen in both groups may be attributable to placebo effects. Also, we do not know whether the benefit of nonsurgical treatment will be sustained over time. Finally, the study by Skou et al. was too small to examine the efficacy of total knee replacement in relevant subgroups, such as patients with mild baseline pain and dysfunction.

The trial by Skou et al. provides the first rigorously controlled data to inform discussions between patients and their physicians about whether to undergo total knee replacement or rigorous nonsurgical therapy. For most patients, the dramatic pain relief associated with total knee replacement provides a compelling rationale to choose surgery. Other patients, particularly those who are more risk-averse, may prefer nonsurgical care. Since patients vary considerably in their preferences, physicians should present the relevant data to their patients and then listen carefully.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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A Randomized, Controlled Trial of Total Knee Replacement

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ABSTRACT

BACKGROUND

More than 670,000 total knee replacements are performed annually in the United States; however, high-quality evidence to support the effectiveness of the procedure, as compared with nonsurgical interventions, is lacking.

METHODS

In this randomized, controlled trial, we enrolled 100 patients with moderate-to-severe knee osteoarthritis who were eligible for unilateral total knee replacement. Patients were randomly assigned to undergo total knee replacement followed by 12 weeks of nonsurgical treatment (total-knee-replacement group) or to receive only the 12 weeks of nonsurgical treatment (nonsurgical-treatment group), which was delivered by physiotherapists and dietitians and consisted of exercise, education, dietary advice, use of insoles, and pain medication. The primary outcome was the change from baseline to 12 months in the mean score on four Knee Injury and Osteoarthritis Outcome Score subscales, covering pain, symptoms, activities of daily living, and quality of life ($KOOS_4$); scores range from 0 (worst) to 100 (best).

RESULTS

A total of 95 patients completed the 12-month follow-up assessment. In the nonsurgical-treatment group, 13 patients (26%) underwent total knee replacement before the 12-month follow-up; in the total-knee-replacement group, 1 patient (2%) received only nonsurgical treatment. In the intention-to-treat analysis, the total-knee-replacement group had greater improvement in the $KOOS_4$ score than did the nonsurgical-treatment group (32.5 vs. 16.0; adjusted mean difference, 15.8 [95% confidence interval, 10.0 to 21.5]). The total-knee-replacement group had a higher number of serious adverse events than did the nonsurgical-treatment group (24 vs. 6, P=0.005).

CONCLUSIONS

In patients with knee osteoarthritis who were eligible for unilateral total knee replacement, treatment with total knee replacement followed by nonsurgical treatment resulted in greater pain relief and functional improvement after 12 months than did nonsurgical treatment alone. However, total knee replacement was associated with a higher number of serious adverse events than was nonsurgical treatment, and most patients who were assigned to receive nonsurgical treatment alone did not undergo total knee replacement before the 12-month follow-up. (Funded by the Obel Family Foundation and others; MEDIC ClinicalTrials.gov number, NCT01410409.)

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Total knee replacement is considered to be an effective treatment for end-stage knee osteoarthritis.[1] The number of total knee replacements performed each year in the United States has increased dramatically, from 31.2 per 100,000 person-years during the period 1971–1976 to 220.9 during the period 2005–2008.[2] In 2012, more than 670,000 total knee replacements were performed in the United States alone, with corresponding aggregate charges of $36.1 billion.[3] The number of total knee replacements is expected to increase as the average age of the population increases,[4] which highlights the associated future economic burden.

Despite the large number of procedures performed annually, we are not aware of any high-quality randomized, controlled trials that have investigated the effectiveness of total knee replacement, as compared with nonsurgical interventions, as treatment for knee osteoarthritis.[5] Recent research has provided substantial evidence to suggest moderate effectiveness of nonsurgical treatments for knee osteoarthritis,[6,7] which has prompted an increase in early use of nonsurgical treatment.[8] On the basis of the available evidence, clinical guidelines recommend a core treatment program that consists of exercise, education, dietary advice, biomechanical interventions such as insoles, and pharmacologic treatment.[6,7] We conducted this randomized, controlled trial, involving patients with knee osteoarthritis who were eligible for unilateral total knee replacement, to investigate whether total knee replacement followed by a 12-week nonsurgical-treatment program that consists of exercise, education, dietary advice, use of insoles, and pain medication[9] provides greater pain relief and improvement in function and quality of life than does nonsurgical treatment alone.

Methods

Participants

We followed the guidelines for reporting parallel-group, randomized, controlled trials.[10] From September 12, 2011, through December 6, 2013, we enrolled 100 patients with radiographically confirmed knee osteoarthritis (i.e., a score of ≥2 on the Kellgren–Lawrence scale, with scores ranging from 0 to 4 and a score of ≥2 indicating definite osteoarthritis[11]) who were eligible for total knee replacement. Eligibility for total knee replacement was determined by one of nine experienced orthopedic surgeons at one of two specialized, public outpatient clinics at Aalborg University Hospital, Denmark (Frederikshavn and Farsoe clinics); 50 patients from each clinic were enrolled. Major exclusion criteria were a previous total replacement of the same knee, previous simultaneous total replacements of both knees, and knee pain during the previous week that the patient rated at higher than 60 mm on a 100-mm visual-analogue scale (with higher scores indicating worse pain).

Study Treatments

Patients were randomly assigned in a 1:1 ratio to undergo total knee replacement followed by 12 weeks of nonsurgical treatment (total-knee-replacement group) or to receive only the 12 weeks of nonsurgical treatment (nonsurgical-treatment group). Total knee replacement was performed in accordance with standard methods[12] for insertion of a total cemented prosthesis with patellar resurfacing (NexGen CR-Flex or LPS-Flex Fixed Bearing Knee, Zimmer).

The 12-week nonsurgical-treatment program consisted of five interventions: exercise, education, dietary advice, use of insoles, and pain medication. To ensure proper standardization and to reduce the number of crossovers, the nonsurgical treatment was delivered to the two groups separately but identically, at the same facility, by specially trained physiotherapists and dietitians. This nonsurgical-treatment program has previously been shown to be more effective than usual care (which consisted of two leaflets with information and treatment advice) in a population of patients with knee osteoarthritis of a severity similar to that seen in our study participants.[13] Further details about the nonsurgical-treatment program are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Exercise

The neuromuscular exercise training program, which has previously been shown to be feasible in patients with moderate-to-severe knee osteoarthritis who are eligible for total knee replace-

ment,[14] was administered in 1-hour, group-based, supervised sessions twice weekly for 12 weeks. The goal of the exercise program was to restore neutral, functional alignment of the legs by building compensatory functional stability and improving sensorimotor control.[14,15] Neutral, dynamic alignment was emphasized, and each patient was monitored individually for exercise quality. Pain level was used to guide progression.[14] After the 12-week training program, the patients underwent an 8-week transitional period, during which the exercise program was performed increasingly at home, to improve long-term adherence. To support adherence to exercise, a physiotherapist contacted the patients monthly by telephone until the 12-month follow-up assessment.

Education

The patients participated in two 1-hour educational sessions that focused on disease characteristics, treatments, and self-help strategies. The sessions actively engaged patients in the treatment of their knee osteoarthritis.

Dietary Advice

Patients with a body-mass index (the weight in kilograms divided by the square of the height in meters) of 25 or higher at baseline participated in a 12-week dietary weight-loss program, which was administered in four 30-to-60-minute sessions. The goal of the program was to reduce body weight by at least 5% and maintain the lower weight.[16] The intervention included motivational interviewing, with instructions and guidance relevant to the individual participant.[17] A dietitian contacted the patients by telephone for 30 minutes at weeks 26 and 39 after the initiation of the nonsurgical treatment to support adherence to the dietary program.

Insoles

The patients received individually fitted, full-length insoles with medial arch support (Formthotics Original Dual Medium [perforated], Foot Science International). Furthermore, a four-degree lateral wedge was added to the insoles of patients who were classified as having a knee-lateral-to-foot position; in such patients, the knee moves over, or lateral to, the fifth toe in three or more out of five trials of the single-limb mini-squat test.[18]

Pain Medication

The patients were offered pain medication if an orthopedic surgeon considered it to be necessary for participation in the exercise program. A prescription (reassessed every 3 weeks) was provided for acetaminophen (1 g four times daily), ibuprofen (400 mg three times daily), and pantoprazole (20 mg daily), to be used as needed.

FOLLOW-UP ASSESSMENTS

Follow-up assessments were performed at 3, 6, and 12 months after the initiation of nonsurgical treatment. The assessments were performed at Aalborg University Hospital, Denmark, by a specially trained assessor who was not affiliated with the treatment sites and who was unaware of the treatment assignments. Before meeting with the assessor, all patients were instructed to cover the index knee from 15 cm above to 15 cm below the patella with three layers of white elastic tape to hide a potential scar after total knee replacement.

OUTCOMES

Primary Outcome

The prespecified primary outcome was the between-group difference in change from baseline to 12 months in the mean score on four Knee Injury and Osteoarthritis Outcome Score (KOOS) subscales, covering pain, symptoms, activities of daily living, and quality of life ($KOOS_4$). Each subscale consists of multiple items scored on a 4-point Likert scale[19,20]; the $KOOS_4$ ranges from 0 (worst) to 100 (best). KOOS is a valid, reliable, responsive measure of patient-reported outcomes during short-term and long-term follow-up for knee osteoarthritis and total knee replacement.[21]

Secondary Outcomes

We also assessed the change from baseline to 12 months in five prespecified secondary outcomes. The first was the scores on all five KOOS subscales, including the $KOOS_4$ subscales plus a fifth subscale covering function in sports and recreation (with scores on all subscales ranging from 0 [worst] to 100 [best]), to assist in the clinical interpretation of the primary outcome.[22]

The second was the time on the timed up-and-go test[23] — which measures the time (in seconds) taken to rise from a chair, walk 3.1 m (10 ft), return, and sit down — and the mean time on two 20-m walk tests; for both tests, a shorter time indicates better mobility.[24] The third is the results of a general health assessment with the three-level version of the EuroQol Group 5-Dimension Self-Report Questionnaire (EQ-5D), including both the score on the EQ-5D descriptive index (ranging from −0.59 to 1.00) and the score on the EQ-5D visual-analogue scale (ranging from 0 to 100)[25,26]; higher scores indicate better quality of life. The descriptive index is based on a Danish "time trade-off" value set, a method used to evaluate the relative amount of time patients would be willing to sacrifice to avoid a certain poor health state. The fourth was weight (in kilograms), measured with the patient wearing no shoes or outerwear, at the same time of the day, with the use of the same digital scale (model 813, Seca). The fifth was the type, dose, and quantity of pain medication taken during the previous week; data on medication intake was recorded as "yes" or "no" for analytic purposes.

Adverse events and serious adverse events that occurred before the 12-month follow-up were identified in three ways: in hospital records, by self-report at follow-up visits, and by the physiotherapist. Adverse events were categorized as involving the index knee or sites other than the index knee, and serious adverse events were identified according to the definition established by the U.S. Food and Drug Administration.[27]

STUDY OVERSIGHT

The study complied with the principles of the Declaration of Helsinki and was approved by the local ethics committee of the North Denmark Region (N-20110024). The study protocol (available at NEJM.org) has been published previously.[9] None of the sponsors of this study were involved in the design or conduct of the study, the data analysis, or the writing of the manuscript. Foot Science International provided the insoles but was not otherwise involved in the study. The first author takes responsibility for the integrity and accuracy of the reported data and for the fidelity of the study to the protocol.

STATISTICAL ANALYSIS

A detailed statistical analysis plan was made publicly available before follow-up was completed and any analyses were performed.[28] An independent statistician who was unaware of the group assignments performed all the analyses. To reduce the risk of bias during interpretation, blinded results from the analyses (with study groups labeled as group A and group B) were presented to all the authors, who agreed in writing on two alternative interpretations.[29] Thereafter, the data manager broke the randomization code (see the Supplementary Appendix).

For $KOOS_4$ and the KOOS subscale scores, a minimal clinically important difference of 10 is recommended and commonly used.[30] We calculated that a sample size of 41 patients in each group would give the study 90% power to detect a 10-point greater improvement in $KOOS_4$ and the KOOS subscale scores in the total-knee-replacement group than in the nonsurgical-treatment group (with a standard deviation of 14) at a two-sided significance level of 0.05. To account for possible crossovers before the 12-month follow-up and for missing data, 100 patients were enrolled.

The primary prespecified analysis was an intention-to-treat analysis; the intention-to-treat population included all 100 patients who underwent randomization. We also performed a prespecified per-protocol analysis; the per-protocol population included patients in both groups who had attended at least 75% of the supervised exercise sessions (≥18 of 24 sessions) and excluded patients in the nonsurgical-treatment group who underwent total knee replacement before the 12-month follow-up and those in the total-knee-replacement group who received only nonsurgical treatment.

Between-group comparisons of treatment effect for all primary and secondary outcomes, except for pain-medication use and adverse events, were performed with the use of a mixed-effects model, with patient as a random effect and time of assessment (baseline and 3, 6, and 12 months), study group (total-knee-replacement group or nonsurgical-treatment group), clinic (Frederikshavn or Farsoe), and baseline values of the outcome as fixed effects. Interaction between time of assessment and study group was also included in the model. Crude analyses

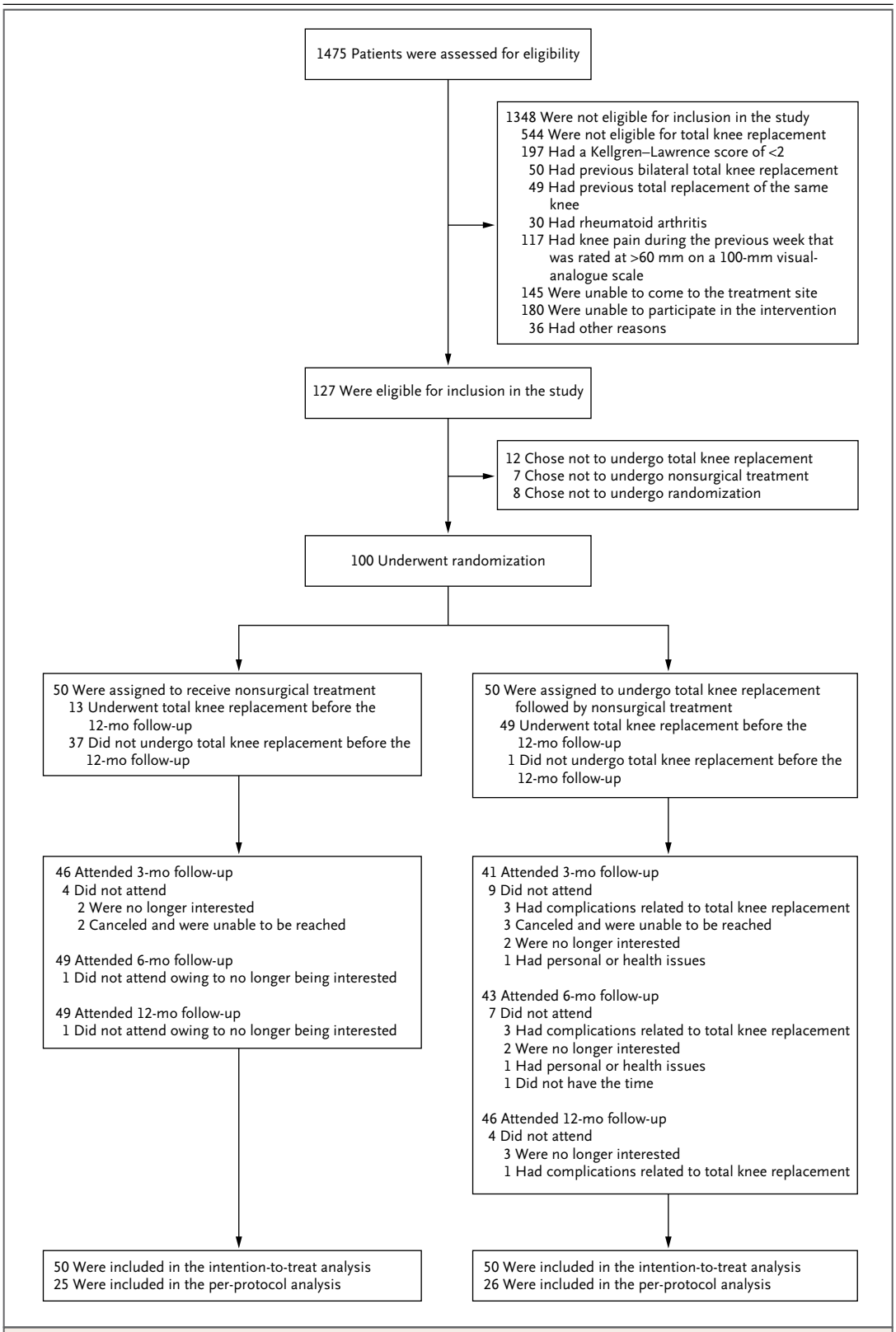

Figure 1. Enrollment, Randomization, Treatment, and Follow-up.

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Nonsurgical-Treatment Group (N=50)	Total-Knee-Replacement Group (N=50)
Female sex — no. (%)	30 (60)	32 (64)
Age — yr	67.0±8.7	65.8±8.7
Body-mass index†	32.0±5.8	32.3±6.2
Kellgren–Lawrence score — no. (%)‡		
2	5 (10)	7 (14)
3	21 (42)	21 (42)
4	24 (48)	22 (44)
KOOS scores§		
$KOOS_4$	48.5±11.4	47.4±13.4
Pain	49.5±13.1	48.6±17.5
Symptoms	58.3±15.2	54.0±15.0
Activities of daily living	53.5±14.2	55.0±17.0
Quality of life	32.7±13.3	32.3±15.3
Sports and recreation	16.7±15.1	18.0±14.7
Time on the timed up-and-go test — sec	8.6±2.1	9.4±2.4
Time on the 20-m walk tests — sec	12.2±2.6	13.4±3.7
EQ-5D scores¶		
Descriptive index	0.681±0.147	0.661±0.156
Visual-analogue scale	66.8±16.5	66.3±19.1
Used pain medication in the past week — no. (%)	29 (58)	33 (67)‖

* Plus–minus values are means ±SD. No significant differences between groups in the reported characteristics were found at baseline. For a complete table of baseline characteristics, see the Supplementary Appendix.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Scores on the Kellgren–Lawrence scale range from 0 to 4, with a score of 2, 3, or 4 indicating definite osteoarthritis and higher scores indicating more severe disease.
§ Scores on the Knee Injury and Osteoarthritis Outcome Score (KOOS) subscales range from 0 (worst) to 100 (best). $KOOS_4$ is the mean score on the pain, symptoms, activities of daily living, and quality of life subscales.
¶ The three-level version of the EuroQol Group 5-Dimension Self-Report Questionnaire (EQ-5D) includes both the EQ-5D descriptive index (with scores ranging from –0.59 to 1.00) and the EQ-5D visual-analogue scale (with scores ranging from 0 to 100); higher scores indicate better quality of life.
‖ In the total-knee-replacement group, a total of 49 patients responded to the question about use of pain medication.

and analyses adjusted for time of assessment, clinic, baseline values of the outcome, and the interaction between time of assessment and study group were performed. To assess for superiority, mean between-group differences in changes from baseline and two-sided 95% confidence intervals were calculated.

We used a Poisson regression model, with robust error variance for the confidence intervals, to perform between-group comparisons of the relative risks associated with use of pain medication and the occurrence of adverse events.[31] We also performed an as-treated analysis using a mixed-effects Poisson regression model, with patient as a random effect and robust error variance for the confidence intervals, to assess the relative risks associated with the occurrence of adverse events.[31] In addition, we performed an exploratory analysis to estimate the number needed to treat with total knee replacement for one person to have a 15% improvement[32,33] in $KOOS_4$ and the KOOS subscale scores from baseline to 12 months.

A two-sided P value of less than 0.05 was considered to indicate statistical significance. All analyses were performed with the use of Stata software, version 13.0 (StataCorp).

RESULTS

ENROLLMENT AND FOLLOW-UP

A total of 100 patients underwent randomization (Fig. 1); 49 of 50 patients (98%) in the nonsurgical-treatment group and 46 of 50 patients (92%) in the total-knee-replacement group completed the 12-month follow-up assessment. In the nonsurgical-treatment group, 13 of 50 patients (26%) had a total knee replacement before the 12-month follow-up (mean time after the initiation of nonsurgical treatment, 6.9 months; range, 2.6 to 11.5). In the total-knee-replacement group, 1 of 50 patients (2%) decided not to undergo total knee replacement and received only the nonsurgical treatment. All 100 patients were included in the intention-to-treat analysis, whereas 25 of 49 patients (51%) in the nonsurgical-treatment group and 26 of 46 patients (57%) in the total-knee-replacement group were included in the per-protocol analysis. The mean follow-up time after the initiation of nonsurgical treatment was 12.4 months in the nonsurgical-treatment group and 12.1 months in the total-knee-replacement group.

PATIENT CHARACTERISTICS

Baseline characteristics were similar in the two study groups (Table 1). The mean length of stay in the hospital after total knee replacement was 4.6 days in Frederikshavn and 3.1 days in Farsoe.[34] Adherence to the nonsurgical-treatment program was moderate to high in both groups (Table S8 in the Supplementary Appendix). The

Table 2. Outcomes at 12 Months.

Outcome	Total No. of Assessments*		Mean Improvement in Outcome from Baseline to 12 Mo (95% CI)		Between-Group Difference in Mean Improvement (95% CI)	
	Nonsurgical-Treatment Group	Total-Knee-Replacement Group	Nonsurgical-Treatment Group	Total-Knee-Replacement Group	Crude	Adjusted†
Primary outcome						
$KOOS_4$	179	193	16.0 (10.1 to 21.9)	32.5 (26.6 to 38.3)	16.5 (10.2 to 22.7)	15.8 (10.0 to 21.5)
Secondary outcomes						
KOOS subscale scores						
Pain	180	194	17.2 (10.4 to 24.1)	34.8 (28.1 to 41.5)	17.6 (10.1 to 25.1)	17.1 (10.4 to 23.8)
Symptoms	179	194	11.4 (4.4 to 18.4)	26.4 (21.5 to 31.4)	15.0 (8.3 to 21.7)	12.7 (6.6 to 18.8)
Activities of daily living	180	193	17.6 (11.4 to 23.9)	30.0 (22.7 to 37.2)	12.3 (5.5 to 19.2)	12.9 (6.8 to 19.1)
Quality of life	180	194	17.8 (11.2 to 24.4)	38.2 (30.6 to 45.8)	20.4 (12.8 to 27.9)	20.2 (13.2 to 27.1)
Sports and recreation	177	193	19.3 (10.8 to 27.7)	34.5 (27.9 to 41.0)	15.2 (6.7 to 23.7)	15.6 (7.3 to 23.9)
Time on the timed up-and-go test (sec)	163	185	−1.2 (−1.8 to −0.6)	−2.4 (−3.1 to −1.6)	1.2 (0.4 to 1.9)	0.9 (0.2 to 1.6)
Time on the 20-m walk tests (sec)	163	185	−1.0 (−1.5 to −0.4)	−2.9 (−3.8 to −1.9)	1.9 (0.9 to 2.8)	1.5 (0.7 to 2.4)
EQ-5D scores						
Descriptive index	178	194	0.115 (0.063 to 0.166)	0.206 (0.141 to 0.270)	0.091 (0.026 to 0.155)	0.078 (0.023 to 0.132)
Visual-analogue scale	180	193	10.2 (4.6 to 15.7)	15.0 (8.6 to 21.5)	4.9 (2.2 to 12.0)	4.4 (1.8 to 10.6)
Weight (kg)‡	134	160	−2.6 (−3.9 to −1.4)	0.1 (−1.5 to 1.7)	2.8 (1.4 to 4.1)	2.8 (1.4 to 4.1)

* There were 200 possible assessments for each study group (50 each at baseline and at 3, 6, and 12 months).
† The results were adjusted for time of assessment (baseline and 3, 6, and 12 months), clinic (Frederikshavn or Farsoe), baseline values, and the interaction between time of assessment and study group.
‡ Data are presented only for patients with a body-mass index of 25 or higher at baseline (43 patients in the nonsurgical-treatment group and 39 patients in the total-knee-replacement group).

number of treatments or consultations with practitioners other than those given in the study was similar in the two groups (Table S9 in the Supplementary Appendix).

OUTCOMES

In the intention-to-treat analysis, the total-knee-replacement group had a significantly greater improvement in the $KOOS_4$ score than did the nonsurgical-treatment group, with a crude mean difference of 16.5 (95% confidence interval [CI], 10.2 to 22.7) and an adjusted mean difference of 15.8 (95% CI, 10.0 to 21.5). In the nonsurgical-treatment group, the increase in the $KOOS_4$ from baseline to month 12 was 16.0 (95% CI, 10.1 to 21.9), whereas in the total-knee-replacement group, the increase was 32.5 (95% CI, 26.6 to 38.3) (Table 2 and Fig. 2). Furthermore, as compared with the nonsurgical-treatment group, the total-knee-replacement group had significantly greater improvements in the scores on all five KOOS subscales, the times on the timed up-and-go test and 20-m walk tests, and the scores on the EQ-5D descriptive index (Table 2, and Fig. S1 in the Supplementary Appendix). (Additional results, including those related to the use of pain medication, are provided in the Supplementary Appendix.)

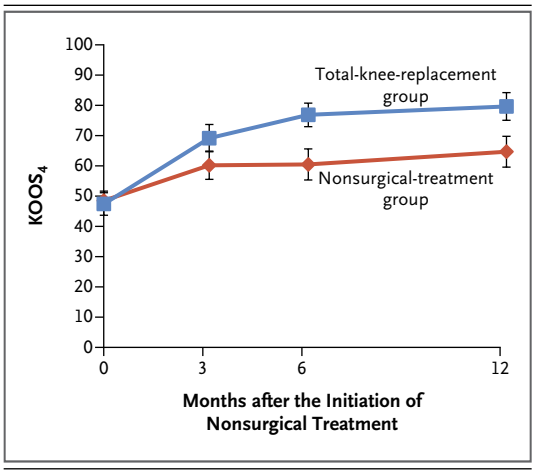

Figure 2. Primary Outcome.
The graph shows the mean score on four Knee Injury and Osteoarthritis Outcome Score subscales, covering pain, symptoms, activities of daily living, and quality of life ($KOOS_4$), for groups randomly assigned to undergo total knee replacement followed by 12 weeks of nonsurgical treatment (total-knee-replacement group) or to receive only the 12 weeks of nonsurgical treatment (nonsurgical-treatment group), which consists of exercise, education, dietary advice, use of insoles, and pain medication. The $KOOS_4$ ranges from 0 (worst) to 100 (best). I bars indicate 95% confidence intervals.

Table 3. Serious Adverse Events.*

Events	Nonsurgical-Treatment Group	Total-Knee-Replacement Group	P Value
	no. of events		
Overall	6	24	0.005
Involving sites other than the index knee	5	16	0.04
Musculoskeletal	0	4	
Skin	1	0	
Gastrointestinal	0	3	
Other	4	9	
Involving the index knee	1	8	0.05
Occurred during total knee replacement	0	0	
Occurred after total knee replacement			
Stiffness requiring brisement forcé†	1	3	
Deep infection	0	1	
Deep venous thrombosis requiring anticoagulation	0	3	
Supracondylar femur fracture	0	1	

* This table includes all serious adverse events that occurred before the 12-month follow-up but were not necessarily caused by the treatment. Serious adverse events include adverse events that have the potential to compromise the clinical outcome, result in disability or incapacity, or require hospital care or adverse events that are considered to prolong hospital care, to be life-threatening, or to result in death. For a complete table of adverse events that occurred in this study, see the Supplementary Appendix.
† Brisement forcé is manipulation of the knee while the patient is under anesthesia to improve range of motion.

Serious adverse events were more common in the total-knee-replacement group than in the nonsurgical-treatment group (8 vs. 1 involving the index knee [P=0.05], and 24 vs. 6 overall [P=0.005]) (Table 3). In the total-knee-replacement group, the two most common serious adverse events involving the index knee were deep venous thrombosis (in 3 patients) and stiffness requiring brisement forcé (in 3 patients).

The per-protocol analysis also showed that the total-knee-replacement group had a significantly higher increase in the $KOOS_4$ than did the nonsurgical-treatment group (Table S3 in the Supplementary Appendix). The per-protocol analysis of the secondary outcomes yielded results similar to those of the intention-to-treat analysis, except that there was a significant between-group difference in the scores on the EQ-5D visual-analogue scale and not in the scores on the KOOS symptoms subscale (Table S3 in the Supplementary Appendix).

In the as-treated analysis of adverse events, serious adverse events were more likely to occur after total knee replacement had been performed than before (9 vs. 0 involving the index knee [P<0.001], and 24 vs. 6 overall [P=0.02]) (Table S7 in the Supplementary Appendix). The number needed to treat with total knee replacement for a 15% improvement from baseline to 12 months in $KOOS_4$ was 5.7 in the intention-to-treat analysis (Table S2 in the Supplementary Appendix) and 6.0 in the per-protocol analysis (Table S6 in the Supplementary Appendix).

DISCUSSION

This randomized, controlled trial showed that total knee replacement followed by nonsurgical treatment is more efficacious than nonsurgical treatment alone in providing pain relief and improving function and quality of life after

12 months in patients with knee osteoarthritis who are eligible for unilateral total knee replacement. However, clinically relevant improvements were noted in both groups, and patients who underwent total knee replacement had a higher number of serious adverse events.

We are not aware of any previous or ongoing randomized trials investigating the effectiveness of total knee replacement, despite its wide and increasing use.[2,5] Previous reports on the effects of total knee replacement have been case series, without a control group for comparison.[5]

Both groups in our study had substantial improvement with respect to most outcomes, and only 26% of the patients who were assigned to receive nonsurgical treatment alone underwent total knee replacement in the following year. Previous reports have suggested a benefit of nonsurgical treatment in patients with moderate-to-severe knee osteoarthritis who are eligible for total knee replacement.[33,35] Even for patients progressing to surgery, participation in supervised exercise before surgery has been associated with a faster postoperative recovery.[36] The benefits and harms of the respective treatments underscore the importance of considering patients' preferences and values during shared decision making about treatment for moderate-to-severe knee osteoarthritis.[37]

Our study has limitations. We did not include a sham-surgery control group; since surgery and, to a lesser extent, nonsurgical treatments are associated with placebo effects,[38] the findings in this study may overestimate effects attributable to the specific treatments and to surgery in particular. The scores on the KOOS pain subscale that were obtained before surgery were similar to those obtained in previous studies of total knee replacement[39,40] and indicated mild-to-severe pain during activities, but it is not known whether our results are generalizable to patients with more severe pain. The intensity of nonsurgical treatment may have differed between groups owing to differences in clinical status at the time treatment was initiated. However, the intervention was standardized and administered in both groups by the same physiotherapists and dietitians. Since all patients received multimodal nonsurgical treatment, it is not possible to separate the effects of the individual modes of treatment. The combination of nonsurgical treatments that we administered complies with international recommendations on the treatment of knee osteoarthritis,[6,7] which increases the generalizability of the results.

In conclusion, our results show that total knee replacement followed by nonsurgical treatment is superior to nonsurgical treatment alone in providing pain relief and improving function and quality of life after 12 months in patients with moderate-to-severe knee osteoarthritis who are eligible for unilateral total knee replacement. However, total knee replacement is associated with a higher number of serious adverse events, and most patients who were assigned to receive nonsurgical treatment alone did not undergo total knee replacement before the 12-month follow-up and had clinically relevant improvements.

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contradict the results of the intention-to-treat analysis.

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Since publication of their article, the authors report no further potential conflict of interest.

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THE EDITORIALISTS REPLY: With respect to the comments by Schäfer and colleagues: we think that further investigation in this area is required, albeit with appropriate informed consent. There are at least two major unanswered questions. First, we do not know whether the results of the SERVE-HF trial were influenced by the specific adaptive servo-ventilation algorithm for adjustment of positive pressure. An ongoing trial (Effect of Adaptive Servo Ventilation on Survival and Hospital Admissions in Heart Failure [ADVENT-HF]; ClinicalTrials.gov number, NCT01128816) has different inclusion and exclusion criteria (it includes patients with both obstructive and central apneas) and uses a different adaptive servo-ventilation device with a less aggressive adjustment of positive pressure. The data and safety monitoring board for the ADVENT-HF trial has performed two interim analyses subsequent to the initial notification of the results of the SERVE-HF trial, and it has concluded that there are no safety concerns (Bradley TD: personal communication).

Second, we do not know whether the risks and benefits of adaptive servo-ventilation are different in specific subgroups of patients with sleep-disordered breathing and congestive heart failure. Thus, we continue to think that further investigation of this topic is required.

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A Randomized, Controlled Trial of Total Knee Replacement

TO THE EDITOR: In the study reported by Skou and colleagues (Oct. 22 issue),[1] patients were excluded if they had symptomatic knee osteoarthritis with pain scores higher than 60 mm on a visual-analogue scale (on which scores range from 0 to 100, with higher scores indicating worse pain). We are unclear as to the rationale for excluding patients with this level of pain, who are commonly seen in orthopedic practice. We agree with the conclusion that total knee replacement is superior to the nonsurgical regimen investigated. However, we are concerned that the exclusion of 117 of 244 otherwise eligible patients (48%) because of severity of symptoms may have led to substantial underestimation of the effect sizes of treatments in both groups, especially in the surgical group because of potentially increased crossover rates among the more severely symptomatic patients.

Reported serious adverse events (stiffness requiring manipulation of the knee while the patient was under anesthesia and deep venous thrombosis requiring anticoagulation) both occurred among 6% of patients in the total-knee-replacement group. These rates were higher than the respective rates (1.3%[2] and 1.5%[3]) reported elsewhere for much larger cohorts. The authors did not report the time-to-event end points, care

protocols (such as prophylaxis against deep venous thrombosis), and criteria for manipulation of the knee while the patient was under anesthesia. Collectively, these factors may lead to misinterpretation of the complications associated with total knee replacement.

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Dr. Lieberman reports receiving consulting fees and intellectual-property royalties from DePuy Synthes, holding stock options in Hip Innovation Technology, and receiving royalties and financial and material support from Elsevier. No other potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: We agree with Teuscher and Lieberman that our results cannot be generalized to patients with a pain-intensity rating higher than 60 mm on a 100-mm visual-analogue scale during the previous week. However, at baseline, 42% of the patients reported pain higher than 60 mm when asked about worst pain during the previous 24 hours, and 22% reported, on average, at least severe pain during activities of daily living in the previous week. As stated in our article, the mean baseline Knee Injury and Osteoarthritis Outcome Score pain subscale score of 49 (on a scale ranging from 0 to 100, with lower scores indicating more severe pain) was similar to previously reported scores in studies involving cohorts of patients who underwent total knee replacement.

In our study, patients who had severe knee stiffness during the rehabilitation period received manipulation of the knee while they were under anesthesia. A recent Danish multicenter study that included investigators from our department showed that among patients who underwent total knee replacement, 2.2% required manipulation of the knee while they were under anesthesia.[1]

At admission to the hospital, all patients in our study received prophylaxis against deep venous thrombosis with 10 mg of rivaroxaban orally once daily for 1 to 3 days. Cases of deep venous thromboses were diagnosed on day 2, day 3, and day 184 after total knee replacement (the third case of deep venous thrombosis occurred in a patient after surgery for femoral-neck fracture during the follow-up period). Our trial was too small to provide reliable rates of adverse events associated with total knee replacement.

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Since publication of their article, the authors report no further potential conflict of interest.

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DOI: 10.1056/NEJMc1514794

Pediatric Outcome after Maternal Cancer Diagnosed during Pregnancy

TO THE EDITOR: Amant et al. (Nov. 5 issue)[1] report on a study of outcomes in children exposed in utero to maternal cancer. Despite the importance of this study, we are concerned about some basic methodologic flaws.[2]

Although this study is presented as a "pro-