Arthritis Care & Research
Vol. 69, No. 6, June 2017, pp 807–816
DOI 10.1002/acr.23013

ORIGINAL ARTICLE

Efficacy of Tailored Exercise Therapy on Physical Functioning in Patients With Knee Osteoarthritis and Comorbidity: A Randomized Controlled Trial

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Objective. **To evaluate the efficacy on physical functioning and safety of tailored exercise therapy in patients with knee osteoarthritis (OA) and comorbidities.**

Methods. **In a randomized controlled trial, 126 participants were included with a clinical diagnosis of knee OA and at least 1 of the following target comorbidities: coronary disease, heart failure, type 2 diabetes mellitus, chronic obstructive pulmonary disease, or obesity (body mass index ≥30 kg/m^2), with severity score ≥2 on the Cumulative Illness Rating Scale. The intervention group received a 20-week, individualized, comorbidity-adapted exercise program consisting of aerobic and strength training and training of daily activities. The control group received their current medical care for knee OA and were placed on a waiting list for exercise therapy. Primary outcome measures were the Western Ontario and McMaster Universities Osteoarthritis Index, subscale physical functioning (WOMAC-pf), and the 6-minute walk test (6MWT). Measurements were performed at baseline, after 20 weeks (directly posttreatment), and at 3 months posttreatment.**

Results. **Statistically significant physical functioning differences over time were found between the intervention and control group (WOMAC: B = −7.43 [95% confidence interval (95% CI) −9.99, −4.87], $P < 0.001$; and 6MWT: B = 34.16 [95% CI 17.68, 50.64], $P < 0.001$) in favor of the intervention group. At 3 months followup, the mean improvements in the intervention group were 33% on the WOMAC scale and 15% on the 6MWT. These improvements are of clinical relevance. No serious adverse events occurred during the intervention.**

Conclusion. **This is the first study showing that tailored exercise therapy is efficacious in improving physical functioning and safe in patients with knee OA and severe comorbidities.**

INTRODUCTION

Exercise therapy is a key intervention in the management of knee osteoarthritis (OA) and recommended in international guidelines on knee OA management (1,2). It is an effective intervention to improve physical functioning and to reduce joint pain in patients with knee OA (3). However, the presence of comorbid diseases interferes with the application of exercise therapy (4), contributes to nonadherence (5), and may affect the outcome of exercise therapy.

Comorbidity is present in 68–85% of patients with OA (6–8). Frequently, more than 1 comorbid disease is present (8). Common comorbidities in knee OA are cardiovascular diseases, type 2 diabetes mellitus, chronic obstructive pulmonary disease (COPD), and obesity (9). Comorbidity limits exercise tolerance, depending on the type, number, and

Dutch trial registration: NTR3027.

Supported by the Royal Dutch Society for Physical Therapy and Merck Sharp & Dohme.

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Dr. Haverkamp has received grants from Mathys, Implantcast, Arthrex, and Carbylan (less than $10,000 each), and has received grants and/or honoraria from Citera and Imove (less than $10,000 each). Dr. Dekker has received a grant from Merck Sharp & Dohme (less than $10,000).

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Submitted for publication March 30, 2016; accepted in revised form August 9, 2016.

Significance & Innovations

- Exercise therapy is a key intervention in the management of knee osteoarthritis. Comorbidity is highly prevalent in knee osteoarthritis and interferes with the application of exercise therapy, contributing to nonadherence. This is the first randomized controlled trial investigating the efficacy and safety of exercise therapy tailored to comorbidity.
- The results showed that tailored exercise therapy is efficacious in improving physical functioning and safe in patients with knee osteoarthritis and severe comorbidities. The mean improvements in the intervention group on physical functioning were 33% on the Western Ontario and McMaster Universities Osteoarthritis Index scale and 15% on the 6-minute walk test at 3 months followup. These improvements are of clinical relevance. No serious adverse events occurred during the intervention.
- The results should encourage clinicians to consider exercise therapy as a treatment option for patients with knee osteoarthritis, even in the presence of severe comorbidity.

severity of the comorbid disease. For example, comorbid heart failure or COPD may limit exercise capacity and may lead to exercise-induced adverse effects, such as decompensation in patients with heart failure, or desaturation in patients with COPD.

The effect of exercise therapy in patients with knee OA and severe comorbidity is not known. Patients with unstable medical conditions, precluding safe participation in an exercise program, are excluded from clinical trials (10–13), because of the high risk of comorbidity-induced adverse events. One study investigated the outcome of exercise therapy in a subgroup of patients with knee OA and comorbidity compared to patients without comorbidity (14). Beneficial effects of exercise therapy were found in both groups. However, patients with severe medical conditions, such as congestive heart failure or insulin-dependent diabetes mellitus, were excluded.

Guidelines on knee OA do not provide guidance on tailoring exercise therapy to the presence of comorbidity (1,2,15,16). In clinical practice, comorbidity is a frequent reason to exclude patients from exercise therapy (17). If accepted into an exercise program, both therapists and patients tend to reduce exercise intensity to a level that is unlikely to be effective, because of fear of aggravating symptoms of the comorbid disease (18,19).

We hypothesize that patients with severe comorbidity can exercise safely if certain precautions are taken and adequate adaptations to the exercise program are made. We have previously developed a treatment protocol to tailor exercise therapy for knee OA to comorbid diseases (20). The purpose of the present study was to evaluate the efficacy on physical functioning and safety of tailored exercise therapy in patients with knee OA and comorbidity.

PATIENTS AND METHODS

Trial design. This was a single-blind, randomized, controlled trial, conducted in a secondary outpatient rehabilitation center. Measurements were performed at baseline, at 10 weeks (midtreatment), 20 weeks (posttreatment), and 32 weeks (3 months posttreatment). The study was conducted in accordance with the Declaration of Helsinki principles (21). The study protocol was approved by the Medical Ethical Review Board (Reade/Slotervaart Hospital, number 1148). All participants gave written informed consent.

Participants. Participants were recruited from December 2011 to January 2014 through regular referral by general health practitioners, rheumatologists, rehabilitation physicians, and orthopedic surgeons, or from advertisements in local newspapers. Participant eligibility was assessed by a short online screening questionnaire, a telephone screening by the researcher (MdR), and subsequently by a rheumatologist and a rehabilitation physician. The final decision on inclusion or exclusion of a participant was made by the rehabilitation physician.

Inclusion criteria were diagnosis of knee OA according to the clinical criteria of the American College of Rheumatology (22), and presence of at least 1 of the target comorbidities (coronary disease, heart failure, type 2 diabetes mellitus, COPD, or obesity [body mass index (BMI) $\geq$30 kg/m^2]), all diagnosed by a medical specialist, with severity score $\geq$2 for the comorbidity on the Cumulative Illness Rating Scale (23), indicating that the comorbidity has an impact on daily activities and the patient was receiving regular care for the comorbid disease. Confirmation of the medical diagnosis was obtained by medical history taking and medication prescription. If there was any doubt about the diagnosis, the medical specialist or general practitioner was consulted by the rehabilitation physician. Inclusion criteria also required that the primary treatment goal was related to knee OA (instead of comorbidity related).

Exclusion criteria were an absolute contraindication for exercise therapy (e.g., myocardial infarction within last 3 months), total knee arthroplasty (TKA) or planned TKA in the near future, participation in exercise therapy for knee OA within the preceding 3 months, insufficient comprehension of the Dutch language, psychological distress necessitating treatment, dementia (Mini-Mental State Examination score $>$24), significant physical limitations that would prohibit the participant from following exercise therapy, an expectation of being lost for followup (e. g., because of a planned change of residency), and refusal to sign informed consent.

Randomization, treatment allocation, and blinding. Participants were randomly assigned to the intervention group or the control group by the web-based program MagMin (24). This program uses a minimization algorithm based on the Pocock and Simon method (25), balancing the comorbid diseases (coronary disease, heart failure, diabetes mellitus type 2, COPD, BMI [BMI $<$30, 30–35, or $>$35]) and pain severity (numeric rating scale [NRS] scores of 1–5 and 6–10). Comorbid diseases were weighted 2, while pain severity was weighted 1. Participants were randomized by an independent staff member who had no

other involvement in the trial. Randomization, treatment allocation, and statistical analyses were performed blindly. The assessors (in total 3) were blinded for treatment allocation. Participants and physiotherapists (PTs) were not blinded for treatment allocation.

Intervention. *Exercise therapy.* Exercise therapy comprised a 20-week individualized (tailored) knee OA exercise program, with 2 sessions of 30–60 minutes per week under the supervision of a PT. The exercise therapy provided in the present study was based on the protocol developed by Knoop et al (12) and consisted of muscle-strength training of the lower extremity, aerobic training, and training of daily activities (1,2,12,16). Flexibility and stability exercises of the lower extremity were added on indication. See Supplementary Appendix A (available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23013/abstract) for an overview of the content of the exercise therapy. Comorbidity-related adaptations were made to the diagnostic phase and the intervention phase (20) (see Supplementary Appendix B, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23013/abstract). In the diagnostic phase, comorbidity-related contraindications and restrictions were identified by history taking and physical examination in an extensive 1-hour intake procedure. Absolute contraindications were defined as conditions that would lead to the immediate exclusion of the participant from exercise therapy (e.g., unstable angina). Restrictions (or relative contraindications) were defined as impairments that limit the application of exercise therapy (e.g., dyspnea in patients with COPD).

In the intervention phase, knee OA exercises as described by Knoop et al (12) (see Supplementary Appendix A, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23013/abstract) were adapted to the comorbid disease, taking into account restrictions. Exercise therapy was adapted by changing frequency, intensity, timing, and type (FITT) factors of the exercises or by adding educational (e.g., providing comorbidity-related information on exercise therapy) or coaching strategies (e.g., coaching for reducing body weight or coaching for fear of exertion). Third, during every training session, comorbidity-related symptoms and clinical parameters were monitored, and exercise was adapted if required. The specific adaptations to the OA exercises were based on principles described in comorbidity-specific exercise guidelines (e.g., cardiac rehabilitation) (26) and were listed in the protocol (20) (see Supplementary Appendix B, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23013/abstract). The training intensity was monitored with the Borg Rate of Perceived Exertion scale (range 6–20) (27) and on the heart rate reserve, if indicated (28). In addition to the supervised exercise sessions, education on knee OA was provided, and participants were encouraged to perform exercises at home at least 5 times a week.

Control intervention. Participants randomized to the control intervention received their current medical care for knee OA and comorbid disease. They were placed on a waiting list for a period of 32 weeks, and thereafter the comorbidity-adapted exercise intervention was offered.

Therapists and participant characteristics. Exercise therapy was applied by 7 qualified PTs, with 3–25 years of work experience. The PTs were trained to work with the protocol and to provide treatment in accordance with the protocol. Booster sessions were provided every 12 weeks. Participant characteristics were obtained at baseline, i.e., age, sex, educational level, duration of knee symptoms, BMI, unilateral or bilateral knee OA, Kellgren/Lawrence (K/L) grade (29), Cumulative Illness Rating Scale (23), use of pain medication, use of walking devices, and malalignment of the knee.

Outcomes. *Primary outcome measures.* Physical functioning was assessed with the Western Ontario and McMaster Universities Osteoarthritis Index, subscale physical function (WOMAC-pf, Dutch translation), (30) and the 6-minute walk test (6MWT) (31). An extended description of these measures is available in Supplementary Appendix C (available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23013/abstract).

Secondary outcome measures. Serious adverse events related to treatment and testing procedures were reported to the researcher by the treating PT or clinimetric assessors. Knee-pain severity during the previous week was scored on an NRS (32) and with the pain subscale of the WOMAC (30). Physical functioning was measured using self-reported physical function questionnaires (subscale of the 36-item Short Form health survey [SF-36] [33], patient-specific functioning scale [34], walking questionnaire [WQ35] [35], climbing stairs questionnaire [CSQ15] [36], rising and sitting down questionnaire [R&SDQ39] [37]), and 2 physical performance tests (i.e., get-up-and-go test [GUG] [38] and time walking up-down stairs [39]). The Longitudinal Aging Study Amsterdam Physical Activity Questionnaire (LAPAQ) was used to assess the moderate-intensity physical activity (40). Fatigue was assessed with the NRS scale. Isokinetic muscle strength and proprioceptive accuracy (41) were assessed as described in Supplementary Appendix A (available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23013/abstract). Psychological functioning was assessed with the Hospital Anxiety and Depression Scale (HADS) (42). The Evaluative Frailty Index for Physical activity was used to measure the level of frailty (43).

Global perceived effect was assessed directly posttreatment (week 20) in the intervention group, on a 9-point Likert scale, and dichotomized as improved (score 1–4) or not improved (score 5–10) (44). An extended description of the secondary outcome measurements is available in Supplementary Appendix C (available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23013/abstract).

For knee-specific variables (K/L grade, muscle strength, proprioceptive accuracy), we used data from 1 knee per person (index knee). Index knees were determined by the clinical diagnosis of knee OA according to the ACR criteria. In case of a clinical diagnosis of knee OA in both knees, a knee was chosen at random.

Process outcome measures. PTs assessed patient-perceived training intensity on a Borg scale (27) after each session, and pain severity (NRS) (32) once a week during the preceding week. In addition, PTs completed training

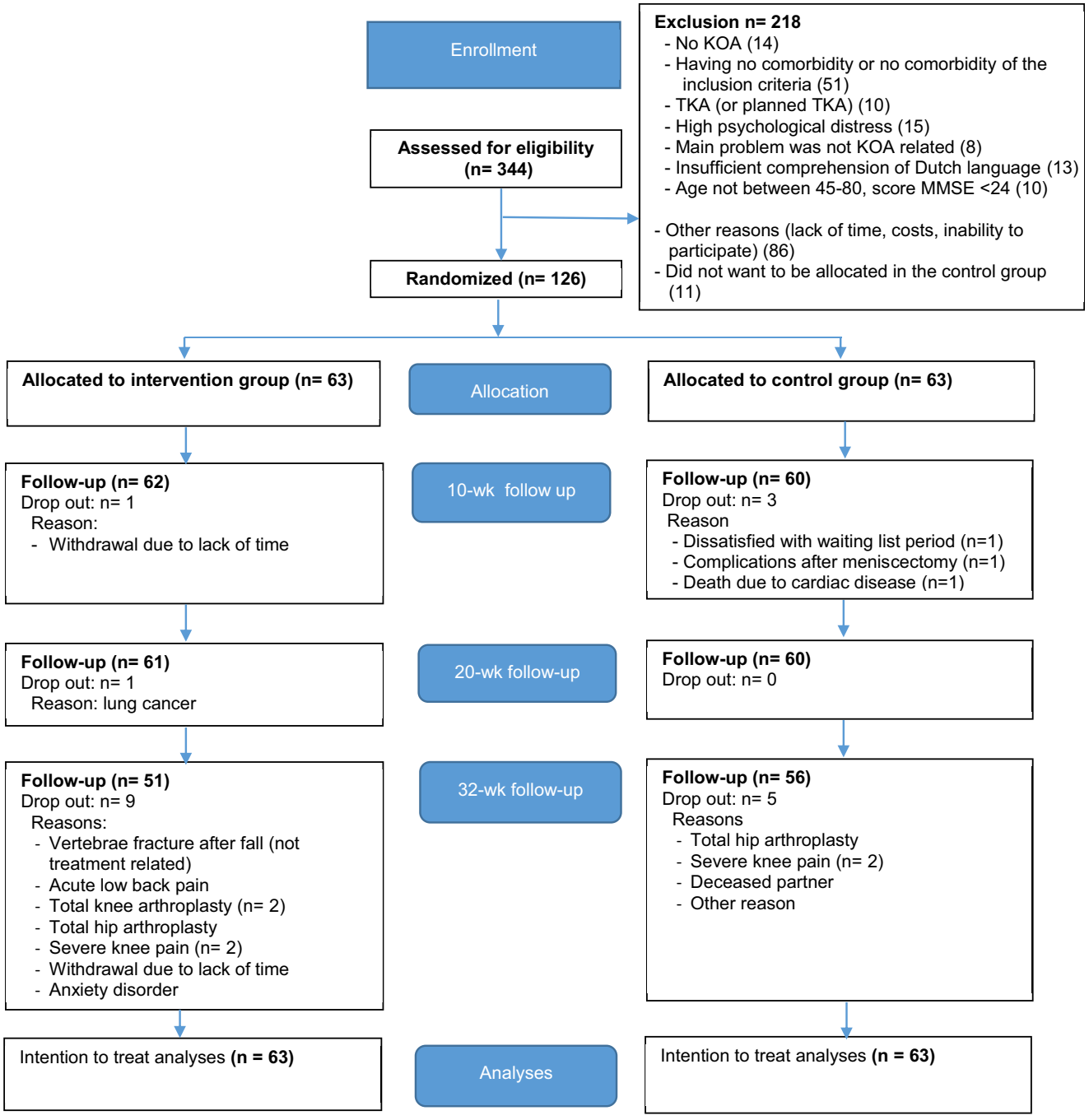

Figure 1. Participant flow chart. KOA = knee osteoarthritis; TKA = total knee arthroplasty; MMSE = Mini-Mental State Examination score. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.23013/abstract.

diaries and registration forms to record specific adaptations to the exercise program (e.g., FITT factors and other adjustments to the exercise program).

Sample size. The a priori power calculation was based on the WOMAC physical function subscale, with an expected effect size of 0.4 between intervention and control group at the 20-week followup, 4 time points of measurement (baseline and 3 followup moments), expected autocorrelation between the repetitions of 0.5, significance level of 0.05, and desired power of 0.80. Given these parameters, a total sample size of 122 participants was needed. Allowing for a dropout rate of 20% during the study, we aimed to include 154 patients (i.e., 77 patients in each group). However, due to a low dropout rate of only 3% during the study, we adjusted our sample size to 126 patients (i.e., 63 patients in each group).

Statistical analysis. Descriptive statistics for baseline participant characteristics were tabulated as means ± SDs or medians (interquartile range) or percentages if data did not have a

Table 1. Participant characteristics*

Characteristics	Intervention group (n = 63)	Control group (n = 63)
Demographics		
Age, years	63.2 ± 8.4	63.9 ± 12.4
Female, no. (%)	49 (77.8)	46 (73.0)
Education, no. (%)		
Primary	12 (19.0)	12 (19.0)
Secondary	29 (46.0)	32 (50.8)
College/university	21 (33.3)	19 (30.2)
Missing	1 (1.6)	
Clinical variables		
Duration of knee symptoms, years	8.59 ± 8.6	9.4 ± 9.3
BMI, kg/m^2	36.0 ± 6.8	35.0 ± 7.6
Clinical diagnosis of knee OA, no. (%)		
Unilateral	12 (19.0)	12 (19.0)
Bilateral	51 (81.0)	51 (81.0)
Radiographic severity of knee, K/L grade, no. (%)		
0/1	26 (41.3)	23 (36.5)
2	19 (30.2)	17 (27.0)
3	10 (15.9)	9 (14.3)
4	8 (12.7)	14 (22.2)
Total number of comorbidities (CIRS score ≥2; range 0–12), no. (%)		
1	31 (49.2)	24 (38.1)
2	17 (27.6)	21 (33.3)
≥3	15 (23.8)	18 (28.6)
Comorbidities of inclusion, no. (%)		
Cardiac diseases	24 (38.1)	21 (33.3)
Diabetes mellitus type 2	10 (15.9)	9 (14.3)
COPD	20 (31.7)	19 (30.2)
Obesity (BMI ≥30)	41 (65.1)	36 (57.1)
Use of pain medication (including NSAIDs), no. (%)	50 (79.4)	48 (76.2)
Use of walking device, no. (%)	23 (36.5)	18 (28.6)
Malalignment of knee, ≥5° varus or valgus, no. (%)†	49 (77.8)	43 (68.3)
Physical functioning		
WOMAC physical functioning (0–68)	35.1 ± 11.9	31.0 ± 12.3
6-minute walk test, meters	406.3 ± 107.6	406.4 ± 116.9
SF-36 physical functioning (0–20)	18.4 ± 4.1	18.8 ± 4.1
Get-up-and-go test, median (IQR) seconds	12.1 (10.4–14.5)	12.4 (10.4–15.4)
Stair climbing test, median (IQR) seconds		
Ascend	7.5 (5.7–11.4)	7.7 (6.3–9.9)
Descend	8.3 (6.0–13.2)	8.5 (6.6–12.5)
LAPAQ total activity (moderate activity), median (IQR)	57.9 (23.6–101.4)	45.7 (23.9–64.3)
Upper leg muscle strength, Nm/kg†	0.65 ± 0.29	0.62 ± 0.34
Pain		
NRS knee pain severity (0–10)	6.4 ± 1.8	5.9 ± 2.1
WOMAC pain (0–20)	10.1 ± 3.4	9.4 ± 3.5
Frailty		
EFIP (0–1)	0.3 ± 0.1	0.2 ± 0.1
Psychological functioning		
HADS depression and anxiety (0–21)	11.3 ± 6.6	10.0 ± 6.8

* Values are the mean ± SD unless indicated otherwise. BMI = body mass index; OA = osteoarthritis; K/L = Kellgren/Lawrence; CIRS = Cumulative Illness Rating Scale; COPD = chronic obstructive pulmonary disease; NSAID = nonsteroidal antiinflammatory drug; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; SF-36 = Short Form 36 health survey; IQR = interquartile range; LAPAQ = Longitudinal Aging Study Amsterdam Physical Activity Questionnaire; NRS = numeric rating scale; EFIP = Evaluative Frailty Index for Physical activity; HADS = Hospital Anxiety and Depression Scale.
† Data from the index knee.

normal distribution. All outcome measures were normally distributed, except for proprioceptive accuracy, GUG test, stair climbing test, WQ35, R&SDQ39, HADS, and LAPAQ. A logarithmic transformation was applied for the non-normally distributed variables, by log10 (for proprioceptive accuracy, GUG test, stair climbing test, HADS, and LAPAQ) or square

root (for WQ35 and R&SDQ39). Comorbidity-related adaptations to the exercise program were described in percentages.

Analyses were based on the intention-to-treat principle, in which data of all participants were analyzed according to group assignment. Generalized estimating equation analysis was used to estimate the average group differences over time, and the group differences at the different time points. For the latter, time (treated as a categorical variable and represented by dummy variables) and the interaction between group and time were added to the model. Both analyses were adjusted for the baseline value of the outcome measure (45). Prior to the regression analysis, the assumptions for linear regression were checked. An exchangeable correlation structure was used to account for the within-subject correlations. The between-group standardized mean difference (SMD) was calculated (46). A sensitivity analysis was performed using the participants who fulfilled at least two-thirds of the training sessions, and with adaptations of the exercise program for FITT factors. Statistical significance was set at P values less than 0.05. Analyses were performed with SPSS software, version 22.0.

RESULTS

Study population. The participants' flow chart is presented in Figure 1. Of the 344 potential participants, 218 (63%) were not eligible or did not wish to participate. In total, 126 participants were randomized and allocated to the intervention (n = 63) or the control group (n = 63). One participant of the intervention group and 3 participants of the control group were lost before the first followup measurement.

Baseline characteristics of the intervention and control groups are presented in Table 1. The groups were well balanced and similar on entry to the trial in terms of age, sex, BMI, K/L grade, comorbid diseases, and outcome measures. Blinding for treatment allocation was successful. Group allocation was guessed correctly by the assessor in 64% of the participants (Cohen's $\kappa = 0.03$, $P = 0.4$).

Compliance and co-interventions. A total of 54 of the 63 participants (86%) in the intervention group received at least two-thirds of the exercise sessions (≥27 of 40 sessions). Of the 9 participants who did not complete the program, 2 participants did not because of severe knee pain and 7 participants due to other reasons (unrelated to the intervention). Nine of the participants (17%) performed the exercise program at a low training intensity (Borg scale ≤11), 40 participants (74%) reached a moderate training intensity (Borg scale 12–14), and 5 participants (9%) reached a high training intensity (Borg scale ≥15). On average, participants performed their home exercises 4 times per week (SD 1.1) during the trial. In the intervention group, 3 participants received a corticosteroid injection for their knee symptoms; 2 of these participants subsequently received a TKA. In the control group, 2 participants received a corticosteroid injection, 1 participant received a TKA, and 11 participants received treatment from a PT (the reason for consulting a PT is unknown).

Adaptations to the intervention. Comorbidity-related adaptations to the exercise program are described in Table 2.

Table 2. Comorbidity-related adaptations to the exercise program*

Adaptations	%
General comorbidity-related adaptations	100
Extended intake procedure: identification of comorbidity-related contraindication and restrictions for exercise therapy by history taken and physical examination	
Extended training program of 20 weeks (as opposed to 12 weeks, which is regular in our center)	
During and after every training session, therapists monitored symptoms and clinical parameters related to comorbidity and adapted the exercise program when required	
Exercise program: adaptations of FITT factors	76
Frequency (number of repetition per exercise set)	15
Intensity of exercises (exercise load)	76
Time (duration of exercise session)	17
Type of exercises	52
Additions to exercise program	96
Coaching on body weight reduction	76
Coaching on fear of exertion	20
Education related to the comorbid disease and exercise	69
Other adaptations	
Consulting a medical specialist or GP about the comorbid disease (e.g., medication or high blood pressure or trainability of the patient)	24
Monitoring blood glucose levels before and after the training and in the evening in patients with diabetes mellitus	7.4
Postponement of the training session (e.g., high blood pressure, pain on the chest, dyspnea)	17
Referred to a dietician	13

* FITT factors = frequency, intensity, time, type; GP = general practitioner.

In addition to the general adaptations, FITT factors were tailored to the restrictions posed by the comorbid disease in 76% of the participants. In 96% of the participants, additional educational or coaching strategies were provided (e.g., coaching on body weight reduction in participants with obesity, or coaching on fear of exertion). For 80% of the participants, a combination of adjustment of FITT factors and education or coaching strategies was provided, while for 17% of the participants, only educational or coaching strategies were provided.

Primary outcome. The WOMAC-pf and 6MWT outcomes at week 10 (midtreatment), week 20 (directly posttreatment), and week 32 (3 months posttreatment) are illustrated in Figure 2. Significant differences over time between groups were found for WOMAC-pf (B = −7.43 [95% CI −9.99, −4.87], $P < 0.001$) and the 6MWT (B = 34.16 [95% CI 17.68, 50.64], $P < 0.001$) in favor of the intervention group (Table 3). At

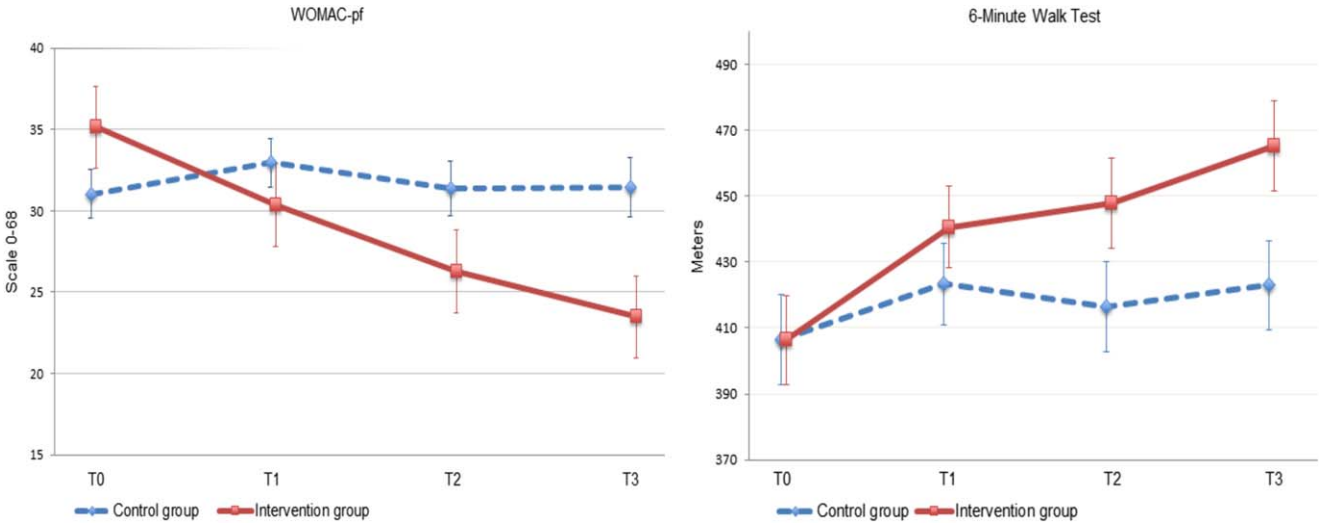

Figure 2. Mean and SE of Western Ontario and McMaster Universities Osteoarthritis Index, subscale physical functioning (WOMAC-pf), and 6-minute walk test at baseline (T0), week 10 (T1, midtreatment), week 20 (T2, directly posttreatment), and week 32 (T3, 3 months posttreatment).

each time point, a significant difference between groups was found (see Supplementary Appendix D, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23013/abstract). Directly posttreatment, between-group SMD for the intervention group was 0.9 and 0.6 for WOMAC-pf and 6MWT, respectively. At 3 months posttreatment, between-group SMD was 1.0 and 0.7 for WOMAC-pf and 6MWT, respectively.

Secondary outcome. No serious adverse events occurred that could be attributed to the exercise therapy provided. We found a significant difference over time between groups, in favor of the intervention group for pain and the majority of physical functioning measures (Table 3), as well as for fatigue, muscle strength, physical activity, and frailty (see Supplementary Appendix E, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23013/abstract). No significant differences between groups were found for physical functioning measured with WQ35 and CSQ15 (see Table 3), proprioceptive accuracy, psychological functioning, and BMI (see Supplementary Appendix E). A total of 97% of the participants in the intervention group reported improvement as a result of the intervention directly posttreatment, and 62.7% still reported improvement at 3 months followup (global perceived effect scale).

Sensitivity analyses. The results on the primary outcome measures directly after treatment and at 3 months followup were similar when restricted to participants who received less than two-thirds of the training sessions and in whom specific adaptations to the exercise program included adjustments in FITT factors (data not shown). In addition, we performed a subgroup analysis only including patients with obesity (BMI $\geq$30 kg/m^2). Similar results were found as compared to the results of the total group (data not shown).

DISCUSSION

This is the first study showing that a tailored exercise program for patients with knee OA and severe comorbidity is efficacious in improving physical functioning. Statistically significant improvements were found in the intervention group, compared to the control group, directly after treatment and at 3 months followup. With respect to physical functioning, the mean improvement in the intervention group was 11.6 points (33%) on the WOMAC-pf and 59 meters (15%) on the 6MWT at 3 months followup. For pain, the mean improvement in the intervention group was 1.7 points (27%) on the NRS pain scale at 3 months followup. These improvements are of clinical relevance (47,48). No treatment-related serious adverse events occurred and dropout during the intervention was low, which suggests that our intervention is safe and feasible. However, we do realize that our sample size, although adequate for measuring the effectiveness of treatment, was small with respect to serious adverse events.

In comparison to other exercise trials in patients with knee OA and comorbidity, we included patients with more severe comorbidity (10,12,13,49). Our study population had more activity limitations at baseline, had on average more pain, and had lower muscle strength in comparison to the baseline characteristics of patients in other exercise trials (10,12,13,49). We selected patients if they had a severity score $\geq$2 for the comorbidity on the Cumulative Illness Rating Scale (23), indicating that the comorbidity had an impact on daily activities, and the patient was receiving regular care for the comorbid disease.

Remarkably, we found a large between-group effect size for self-reported physical functioning (SMD 0.9) directly after ending treatment, and even further improvement during the following 3 months (SMD 1.0). In a recently published Cochrane review, the magnitude of the treatment effect of exercise therapy on physical functioning in patients with knee OA was found to be moderate (SMD 0.5) (immediate posttreatment) to small (SMD 0.15) (2–6 months posttreatment) (3). This finding suggests that tailoring exercise therapy

Table 3. Outcome measures by group at different time points and group differences over time (intention-to-treat)*

Outcomes	Baseline		10-week followup		20-week followup		32-week followup		Differences over time B (95% CI)†
	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	
Primary									
WOMAC-pf (0–68)	35.1 ± 11.9 (n = 63)	31.0 ± 12.3 (n = 63)	30.4 ± 11.6 (n = 60)	32.9 ± 11.2 (n = 55)	26.3 ± 12.7 (n = 59)	31.4 ± 13.4 (n = 59)	23.5 ± 13.1 (n = 51)	31.4 ± 12.6 (n = 56)	−7.43 (−9.99, −4.87)‡
6-minute walk test, meters	406.3 ± 107.6 (n = 63)	406.4 ± 116.9 (n = 63)	440.6 ± 96.7 (n = 61)	423.4 ± 115.5 (n = 53)	448.0 ± 102.5 (n = 56)	416.5 ± 116.9 (n = 58)	465.3 ± 93.9 (n = 48)	423.0 ± 114.8 (n = 55)	34.16 (17.68, 50.64)‡
Secondary									
NRS pain week (0–10)	6.4 ± 1.8 (n = 63)	5.9 ± 2.1 (n = 63)	5.3 ± 1.9 (n = 60)	5.7 ± 2.3 (n = 55)	4.3 ± 2.0 (n = 59)	5.8 ± 2.2 (n = 59)	4.7 ± 1.9 (n = 51)	6.2 ± 2.1 (n = 56)	−1.41 (−1.87, −0.95)‡
WOMAC pain (0–17)	10.1 ± 3.4 (n = 63)	9.4 ± 3.5 (n = 63)	8.4 ± 3.0 (n = 60)	9.1 ± 3.6 (n = 55)	6.9 ± 3.4 (n = 59)	8.8 ± 4.2 (n = 59)	6.6 ± 3.6 (n = 51)	8.6 ± 3.6 (n = 56)	−1.78 (−2.65, −0.91)‡
GUG, seconds	13.6 ± 5.6 (n = 63)	13.5 ± 5.5 (n = 63)	12.0 ± 3.4 (n = 61)	12.9 ± 4.3 (n = 55)	11.9 ± 3.6 (n = 56)	13.0 ± 4.4 (n = 58)	11.4 ± 3.0 (n = 48)	12.8 ± 3.7 (n = 55)	−1.35 (−2.16, −0.55)§
Stair climbing up, seconds	10.1 ± 6.9 (n = 63)	9.2 ± 4.7 (n = 63)	8.6 ± 6.7 (n = 61)	11.4 ± 14.7 (n = 55)	7.7 ± 4.3 (n = 55)	8.7 ± 4.4 (n = 58)	7.4 ± 3.8 (n = 47)	10.0 ± 9.6 (n = 55)	−2.41 (−4.40, −0.43)¶
Stair climbing down, seconds	10.7 ± 7.2 (n = 63)	11.0 ± 6.6 (n = 63)	9.6 ± 8.0 (n = 61)	11.6 ± 12.5 (n = 55)	8.3 ± 4.4 (n = 55)	9.8 ± 5.5 (n = 58)	7.6 ± 3.8 (n = 47)	9.7 ± 4.9 (n = 55)	−1.64 (−3.18, −0.91)¶
SF-36 subscale pf (score 0–20)	18.4 ± 4.1 (n = 63)	18.8 ± 4.1 (n = 63)	NA	NA	20.8 ± 4.5 (n = 59)	18.9 ± 5.0 (n = 59)	21.4 ± 4.5 (n = 50)	18.9 ± 4.7 (n = 55)	2.19 (1.10, 3.28)‡
PSFL (performance of activities 0–10)#	6.7 ± 1.4 (n = 63)	6.6 ± 1.3 (n = 63)	NA	NA	4.2 ± 2.1 (n = 57)	5.8 ± 1.7 (n = 58)	4.1 ± 2.2 (n = 50)	5.9 ± 1.8 (n = 55)	−1.59 (−2.19, −0.99)‡
WQ35 (0–100)	40.2 ± 23.3 (n = 61)	39.76 ± 23.2 (n = 63)	NA	NA	30.9 ± 25.2 (n = 59)	38.4 ± 24.1 (n = 58)	29.9 ± 25.4 (n = 51)	34.9 ± 22.5 (n = 55)	−6.84 (−14.94, 1.26)**
CSQ15 (0–100)	51.4 ± 17.9 (n = 51)	51.2 ± 16.7 (n = 56)	NA	NA	42.7 ± 20.3 (n = 52)	48.8 ± 18.2 (n = 50)	40.3 ± 22.6 (n = 47)	48.1 ± 18.1 (n = 46)	−6.10 (−13.41, 1.21)††
R&SDQ39 (0–100)	51.6 ± 27.2 (n = 56)	45.5 ± 22.8 (n = 61)	NA	NA	39.2 ± 26.1 (n = 55)	45.9 ± 25.7 (n = 52)	38.5 ± 26.7 (n = 48)	43.8 ± 25.7 (n = 52)	−10.20 (−15.48, −4.92)§

* Values are the mean ± SD unless indicated otherwise. 95% CI = 95% confidence interval; WOMAC-pf = Western Ontario and McMaster Universities Osteoarthritis Index, subscale physical functioning; NRS = numeric rating scale; GUG = get-up-and-go test; SF-36, subscale pf = Short Form 36, subscale physical functioning; NA = not applicable; PSFL = patient-specific functioning list; WQ35 = walking questionnaire; CSQ15 = climbing stairs questionnaire; R&SDQ39 = rising and sitting down questionnaire.

† 10-, 20-, and 32-week followup. Adjusted for baseline value of outcome variable difference.

‡ $P < 0.001$.

§ $P < 0.001$. Although the outcome measure was not optimally distributed, analysis of nontransformed data is reported, as this result is more easily interpretable and yielded similar results to analysis with transformed data.

¶ $P < 0.05$. Although the outcome measure was not optimally distributed, analysis of nontransformed data is reported, as this result is more easily interpretable and yielded similar results to analysis with transformed data.

Average score of 3 activities that were most relevant and problematic for the patient.

** $P > 0.05$. Overall, a lower score indicates an improvement in physical functioning or pain, with the exception of the 6-minute walk test and the physical functioning subscale of the SF-36. For all other secondary outcome measures, see Supplementary Appendix C (available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23013/abstract). Although the outcome measure was not optimally distributed, analysis of nontransformed data is reported, as this result is more easily interpretable and yielded similar results to analysis with transformed data.

†† $P > 0.05$. Overall, a lower score indicates an improvement in physical functioning or pain with the exception of the 6-minute walk test and the physical functioning subscale of the SF-36. For all other secondary outcome measures, see Supplementary Appendix C.

to the comorbid disease is highly effective. The beneficial results of the present study can be attributed not only to the high volume and frequency of the exercise, but also to the several adjustments to the exercise program. First, in order to tailor exercise therapy to the individual patient, an extensive intake procedure was conducted. Second, therapists were encouraged to consult colleagues or medical specialists to discuss the medical condition of the patient, which provided them with the information needed to adapt the exercise program. Third, all patients were scheduled to receive an extended training program of 20 weeks (as opposed to 12 weeks, which is regular in our center). Fourth, for more than two-thirds of the patients, exercises were adapted to the comorbid disease by changing FITT factors of the exercises. Fifth, in almost all patients, additional comorbidity-related education or coaching strategies were provided. Last, comorbidity-related symptoms were monitored during each training session, and exercise was adapted if required. We assume that all these factors contributed to exercise adherence in our treatment group.

Some methodologic issues should be considered. First, patients in the control group received their current medical care for knee OA and comorbid disease and were placed on a waiting list for exercise therapy. We included patients with a comorbidity severity score ≥ 2 on the Cumulative Illness Rating Scale, indicating that the comorbidity has an impact on daily activities and the patient was receiving regular care for the comorbid disease. Because of an increased risk of comorbidity-related serious adverse events, it was considered unethical to provide regular exercise therapy without tailoring to the comorbid disease. Thus, the study contrast concerns tailored exercise therapy versus current medical care. Second, we included patients with various comorbidities. With the current sample size, we cannot analyze the outcome of the exercise program in patients with specific comorbidities (except for patients with obesity, in whom we observed similar results). Third, we performed an efficacy trial to evaluate the effect of tailored exercise. The treatment was provided in a secondary care setting where PTs have advanced skills in treating patients with complex health conditions and have close collaboration with rehabilitation physicians and rheumatologists. More research is needed to evaluate the effectiveness of the protocol in primary care. In addition, the effect of tailored exercise in other highly prevalent comorbid diseases in knee OA (e.g., chronic pain or depression) (9,20,50) should be investigated. Fourth, a limitation of the present study is that we did not investigate the cost-effectiveness of the developed protocols to get insight as to whether the costs outweigh the benefits on health-related outcomes, medication use, hospital care, and outpatient care.

In conclusion, this is the first study showing that tailored exercise therapy is efficacious in improving physical functioning and is safe in patients with knee OA and severe comorbidities. The results should encourage clinicians to consider exercise therapy as a treatment option for patients with knee OA, even in the presence of comorbidity.

ACKNOWLEDGMENTS

The authors thank D. G. de Rooij, PhD, for advice and critical reading of the manuscript, the participants in this study, the therapists who provided the treatment, clinimetric assessors for performing measurements, and Prof. Dr. HongWei Cai for giving his support in using the minimization allocation system.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Ms de Rooij had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. de Rooij, van der Leeden, van der Esch, Häkkinen, Roorda, Vollebregt, Lems, Dekker.

Acquisition of data. de Rooij, Cheung, Haverkamp.

Analysis and interpretation of data. de Rooij, van der Leeden, Twisk, Dekker.

ROLE OF THE STUDY SPONSOR

Merck Sharp & Dohme had no role in the study design or in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by Merck Sharp & Dohme.

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