Original Investigation

Rehabilitation After Immobilization for Ankle Fracture
The EXACT Randomized Clinical Trial

Anne M. Moseley, PhD; Paula R. Beckenkamp, BPhysio; Marion Haas, PhD; Robert D. Herbert, PhD; Chung-Wei Christine Lin, PhD; for the EXACT Team

IMPORTANCE The benefits of rehabilitation after immobilization for ankle fracture are unclear.

OBJECTIVES To determine the effectiveness of a supervised exercise program and advice (rehabilitation) compared with advice alone and to determine if effects are moderated by fracture severity or age and sex.

DESIGN, SETTING, AND PARTICIPANTS The EXACT trial was a pragmatic, randomized clinical trial conducted from December 2010 to June 2014. Patients with isolated ankle fracture presenting to fracture clinics in 7 Australian hospitals were randomized on the day of removal of immobilization. Of 571 eligible patients, 357 chose not to participate and 214 were allocated to rehabilitation (n = 106) or advice alone (n = 108), with 194 (91%) followed up at 1 month, 173 (81%) at 3 months, and 170 (79%) at 6 months. There were no withdrawals attributed to adverse effects. Recruitment terminated early on December 31, 2013 (planned enrollment, 342; actual, 214), because funding was exhausted.

INTERVENTIONS Supervised exercise program and advice about self-management (rehabilitation) (individually tailored, prescribed, monitored, and progressed) or advice alone, both delivered by a physical therapist.

MAIN OUTCOMES AND MEASURES Primary outcomes were activity limitation assessed using the Lower Extremity Functional Scale (score range, 0-80; higher scores indicate better activity), and quality of life assessed using the Assessment of Quality of Life (score range, 0-1; higher scores indicate better quality of life), measured at baseline and at 1, 3 (primary time point), and 6 months.

RESULTS Mean activity limitation and quality of life at baseline were 30.1 (SD, 12.5) and 0.51 (SD, 0.24), respectively, for advice and 30.2 (SD, 13.2) and 0.54 (SD, 0.24) for rehabilitation, increasing to 64.3 (SD, 13.5) and 0.85 (SD, 0.17) for advice vs 64.3 (SD, 15.1) and 0.85 (SD, 0.20) for rehabilitation at 3 months. Rehabilitation was not more effective than advice for activity limitation (mean effect at 3 months, 0.4 [95% CI, −3.3 to 4.1]) or quality of life (−0.01 [95% CI, −0.06 to 0.04]). Treatment effects were not moderated by fracture severity or age and sex.

CONCLUSIONS AND RELEVANCE A supervised exercise program and advice did not confer additional benefits in activity limitation or quality of life compared with advice alone for patients with isolated and uncomplicated ankle fracture. These findings do not support the routine use of supervised exercise programs after removal of immobilization for patients with isolated and uncomplicated ankle fracture.

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Author Affiliations: The George Institute for Global Health and Sydney Medical School, University of Sydney, Sydney, Australia (Moseley, Beckenkamp, Lin); Centre for Health Economics Research and Evaluation (CHERE), University of Technology Sydney, Sydney, Australia (Haas); Neuroscience Research Australia, Sydney, Australia (Herbert).

Group Information: Members of the EXACT Team are listed at the end of this article.

Corresponding Author: Anne M. Moseley, PhD, The George Institute for Global Health and Sydney Medical School, University of Sydney, PO Box M201, Missenden Road NSW 2050, Australia (amoseley@georgeinstitute.org.au).

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Ankle fracture is a common injury.[1] The annual incidence is at least 5 per 10 000 persons but is higher among older women (16 to 20 per 10 000 persons per year) and younger men (13 to 28 per 10 000 persons per year).[2] Ankle fracture is treated with reduction (realignment), sometimes with surgical fixation, followed by a period of immobilization while the fracture heals.[3] Although recovery from ankle fracture is initially rapid, the recovery slows with time and can be incomplete 2 years after fracture.[4]

Rehabilitation addresses the detrimental effects of the ankle fracture and the subsequent immobilization. A Cochrane systematic review[5] identified 5 studies evaluating rehabilitation after the removal of immobilization. Paraffin wax baths did not reduce pain.[6] Adding manual therapy or passive stretch to an exercise program did not confer benefits compared with exercise alone.[7-9] A supervised exercise program did not improve outcomes compared with usual care (n = 110).[10] The latter study may have underestimated the effects of exercise, as 78% of the usual-care group received physical therapy. The study provided preliminary evidence of an interaction between the effects of rehabilitation and age. It is possible that older women (who are more likely to experience osteoporosis[11] and decrements in physical performance[12] and physical activity[13] associated with aging) or people with more severe fracture (who have poorer outcomes[14]) may benefit more from rehabilitation.

Because the effects of rehabilitation following immobilization for ankle fracture remain unclear, we conducted a trial with primary objectives to (1) determine the effectiveness and cost-effectiveness of a supervised exercise program and advice about self-management (rehabilitation) compared with advice alone, and (2) determine if these effects were moderated by fracture severity (more vs less severe) or age and sex (women aged >50 years; women aged ≤50 years and all men). Secondary objectives were to compare rehabilitation with advice for 17 secondary outcomes (exploratory analyses) and safety.

Methods

Study Design and Eligibility Criteria

The EXACT (Exercise or Advice After Ankle Fracture) trial was a two-group, pragmatic, randomized clinical trial. Ethics approval was obtained from Hawkesbury Human Research Ethics Committee of Northern Sydney Central Coast Health. The protocol has been published.[15] A statistical analysis plan was ratified before the data were analyzed. The protocol and statistical analysis plan are also available in Supplement 1.

Participants were recruited from 7 public hospitals in Sydney, Australia: Royal North Shore Hospital, Royal Prince Alfred Hospital, Blacktown Mount Druitt Hospital, Prince of Wales Hospital, Ryde Hospital, Mona Vale Hospital, and Hornsby Ku-ring-gai Hospital. Although patients were screened at Hornsby Ku-ring-gai Hospital, no participants were recruited from this site. Each site conducted fracture clinics staffed by a multidisciplinary team (orthopedic surgeons, nurses, and physical therapists) and provided outpatient physical therapy services. Physical therapists in the fracture clinics were responsible for applying and removing immobilization (casts, backslabs, and braces) and also provided assistive devices, exercise, education, and, if required, referrals to outpatient physical therapy services.

The inclusion criteria were isolated ankle fracture treated with immobilization (with or without surgical fixation), immobilization removed on the day of recruitment, approval received from the orthopedic surgeon to bear weight as tolerated or bear partial weight, reduced ankle dorsiflexion range of motion (at least 30 mm less motion compared with the nonfractured leg, using the weight-bearing lunge method),[16] ankle pain at least 2 of 10 when 50% of body weight was borne through the affected leg, completed skeletal growth (no evidence of epiphyseal cartilage in the tibia in radiographs taken for fracture management), no concurrent pathologies (eg, symptomatic osteoarthritis, stroke, other fractures) that would affect the ability to perform everyday tasks or the measurement procedures used in this trial, and written informed consent.

Randomization and Blinding

Randomization was concealed using a central telephone-based randomization service provided by the Australian National Health and Medical Research Council Clinical Trials Centre. Allocation was stratified by site and blocked within strata using random permuted blocks (block size 4, 6, and 8), with an allocation ratio of 1:1. Enrollment of participants, allocation of participants to interventions, and assessments were conducted by trained assessors with entry-level qualifications in physical therapy or medicine. Blinding of participants and physical therapists was not possible because of the nature of the intervention. Assessors were blinded to group allocation by having different assessors assign participants to groups and conduct follow-up assessments. However, the primary outcomes were self-reported by the unblinded participants. Assessor beliefs about allocation were evaluated at the end of each follow-up assessment. The assessor was asked if he or she was unblinded and, if not, to guess group allocation. These data were converted to a 4-point scale: (1) knows the participant received advice; (2) guesses the participant received advice; (3) guesses the participant received rehabilitation; (4) knows the participant received rehabilitation.

Interventions

Participants were randomly allocated to either a supervised exercise program and advice (rehabilitation group) or to advice alone (advice group). Participants in the advice group were provided with a single session of self-management advice about exercise and return to activity. The advice was given by a physical therapist in the fracture clinic after removal of immobilization. Exercise involved ankle movement in non-weight-bearing positions. Participants were given a handout summarizing this advice with text and illustrations (eAppendix in Supplement 1). Participants in the rehabilitation group received the same advice in the fracture clinic and also participated in a supervised exercise program individually tailored, prescribed, moni-

tored, and progressed by a physical therapist in the hospital outpatient physical therapy service (eAppendix in Supplement 1). These participants were encouraged to perform the exercises at home.

Three types of exercises were prescribed in the supervised exercise program: (1) ankle mobility and strengthening exercises, (2) stepping exercises, and (3) weight-bearing and balancing on the affected leg. Exercise cards were provided to participants. Participants also received gait training and advice about returning to usual work and leisure activities. The number of physical therapy consultations and timing of discharge were not mandated by the protocol, but the suggested schedule was 2 sessions in week 1 and a single session in each of weeks 2 to 4. All physical therapists providing the advice and supervised exercise program were registered to practice in Australia, employed by the participating sites, and trained in the trial procedures. The interventions were not modified during the trial. Treatment fidelity was monitored by unblinded investigators (A.M.M., C.-W.C.L.) who discussed the intervention provided to each participant in the rehabilitation group with the treating physical therapist.

Data Collection and Outcome Measures

Outcomes were assessed at baseline (prior to randomization) and at 1, 3, and 6 months of follow-up. The primary outcomes were activity limitation, measured by the Lower Extremity Functional Scale (range, 0 to 80; higher scores denote better activity; minimal clinically important difference, 9),[17] and quality of life, measured by the Assessment of Quality of Life[18] instrument and expressed as utility in terms of quality-adjusted life-years (QALYs; range, 0 to 1; higher scores denote better quality of life). An algorithm was used to calculate utility.[19] The primary end points were the primary outcomes measured at 3 months, as prespecified in the published protocol[15] and statistical analysis plan (Supplement 1).

The secondary outcomes were (1) number of days to pain-free walking; (2) number of days to return to full prefracture work; (3) percentage return to prefracture work; (4) percentage return to prefracture leisure activities; (5) ankle dorsiflexion range of motion[16]; (6) pain during equal weight bearing and (7) pain during stair descent, both measured using a numerical rating scale (range, 0 to 10; higher scores denote more pain); (8) speed of walking unaided over 10 m; (9) physical activity level,[20] dichotomized as low (low) or high (moderate or vigorous); (10) physical activity in metabolic equivalent (MET) minutes per week[20]; (11) global perceived effect of treatment (range, −5 to 5, higher scores denote larger perceived effects of treatment); and 6 health-related quality of life domains from the Assessment of Quality of Life[18]; (12) total score (range, 0 to 45; higher scores denote better quality of life); (13) illness; (14) independent living; (15) social relationships; (16) physical senses; and (17) psychological well-being (range, 0 to 9 for each domain; higher scores denote better quality of life). All secondary outcomes were assessed at baseline, 1, 3, and 6 months, except for ankle dorsiflexion range of motion and speed of walking (assessed at baseline and 1 month only) and global perceived effect of treatment (assessed at 1, 3, and 6 months only). The time frame for the Assessment of Quality of Life (primary outcome plus secondary outcomes 12-17) and International Physical Activity Questionnaire–Short (outcomes 9-10) was the week prior to the assessment, so the baseline scores include some of the immobilization period.

The perspective of the economic evaluation was that of the health system and the patient. Costs were measured in terms of direct costs to the health system and out-of-pocket costs to the participants over 6 months. Costs were estimated for visits to the hospital physical therapist (recorded by the treating physical therapists for the rehabilitation group) plus visits to hospital or private physical therapists, medical specialists, primary care physicians, community services or alternative or complementary health practitioners, emergency department visits and hospital admissions, medications, and equipment (collected from participants in a questionnaire at the 1, 3, and 6-month follow-up assessments). Data on number of days away from paid work and unpaid activities (eg, household duties) were collected in the same questionnaire.

Safety was evaluated at the 6-month follow-up by asking participants to describe the negative effects, if any, of the trial treatment. To assess adherence, participants completed a calendar to indicate each day on which they performed the trial exercises, and the treating physical therapist completed a discharge form for each participant allocated to rehabilitation detailing the number of sessions scheduled and attended, date and reason of discharge, specific exercises, and treatment implemented.

The frequency of prescription of each specific exercise and the frequency of use of other treatments were calculated. An independent person categorized the reasons for discharge and treatment implemented. The credibility of the intervention was assessed at the 6-month follow-up by asking participants to report how satisfied they were with the trial treatment on a 5-point Likert scale ranging from 1 (“extremely dissatisfied”) to 5 (“extremely satisfied”).

Statistical Analysis

A sample of 76 participants would provide an 80% probability of detecting a mean difference between groups of 10 points on the 80-point Lower Extremity Functional Scale (assuming an SD of 15 points)[7,8] and a mean difference between groups of 2.75 points on the 45-point Assessment of Quality of Life scale (assuming an SD of 4 points),[7] assuming an α of .05 and allowing 5% loss to follow-up. To power the study for the 2 subgroup analyses, the sample size was inflated to 342, assuming less severe fractures were twice as frequent as more severe fractures and there were about twice as many women 50 years or younger and men as there were women older than 50 years.[21] On May 14, 2013, a decision was made (without reference to the data, which remained blinded) to terminate recruitment on December 31, 2013, because funds would be exhausted at that time. Consequently, 214 participants were randomized.

All analyses were conducted by intention-to-treat using Stata version 13.1 (StataCorp). Interpretation was blinded to allocation and focused on the size of estimated effects. Hypothesis tests were 2-tailed and used a 5% significance level. Between-group comparisons of continuous variables were conducted using longitudinal mixed models. Time was treated as a categorical variable. The models included group, time, and baseline scores as fixed covariates, as well as the group × time interactions. Random intercepts for participants accounted for the dependence of repeated measures. The primary conclusions about effectiveness were based on between-group comparisons of activity limitation and quality of life at 3 months, estimated with the appropriate contrasts from the longitudinal model.

Five sensitivity analyses (2 preplanned and 3 post hoc) were conducted for the primary outcomes. One obtained percentile bootstrap confidence intervals to evaluate sensitivity to the distributions of the outcome data. A second sensitivity analysis used multiple imputation to evaluate sensitivity to missing data under the assumption that data were missing at random. An iterative Markov chain Monte Carlo method was used to simulate 20 imputed values from the posterior predictive distribution of a multivariate normal model. Point and interval estimates were obtained using Rubin rules[22] to combine the imputed observations. Three post hoc sensitivity analyses evaluated whether out-of-trial physical therapy could have diluted the estimates of treatment effect: for the as-treated analysis, participants in the advice group who received out-of-trial physical therapy were analyzed as if they had been allocated to rehabilitation; for the per-protocol analysis, participants in the advice group who received out-of-trial physical therapy were omitted from the analysis; and for the analysis of local average treatment effect, effect of rehabilitation was estimated using propensity score matching on prerandomization variables to exclude observations from participants in the advice group who received out-of-trial physical therapy and the matched participants in the rehabilitation group.

Additional analyses examined if the effects of intervention were moderated by 2 subgroups: fracture severity or age and sex. Unimalleolar fracture without dislocation was classified as a "less severe" fracture and unimalleolar fracture with dislocation or bimalleolar or trimalleolar fracture was classified as "more severe."[14] For the age and sex moderator, participants were divided into women older than 50 years and women 50 years or younger and all men. For the analysis of the moderating effect of fracture severity, additional terms were included in the longitudinal mixed model to investigate the interaction between group membership, fracture severity, and time. Similarly, for the analysis of the moderating effect of age and sex, terms for the interaction between group membership, age and sex, and time were included in the model. The primary conclusions about whether fracture severity or age and sex moderate the effectiveness of intervention were based on the interactions between these factors and effects of group (rehabilitation or advice) at 3 months, estimated with the appropriate contrasts from the longitudinal model.

Exploratory analyses, with no adjustment for multiple comparisons, were undertaken for the 17 secondary outcomes. Fourteen secondary outcomes were continuous variables; they were analyzed with longitudinal mixed models. For time-to-event outcomes (number of days to pain-free walking; number of days to return to full prefracture work), survival analysis was used. Survival curves were constructed on the basis of the dates participants returned to full prefracture work and could walk pain-free for 10 m. Kaplan-Meier survival probability estimates were used to describe both return to pain-free walking and full prefracture work. The effect of intervention was quantified with hazard ratios estimated using Cox regression. For the binary outcome (physical activity level), the ratio of the odds of being classified as having low physical activity was estimated at 1, 3, and 6 months using mixed-effects logistic regression models.

To evaluate safety of rehabilitation compared with advice, an independent person grouped the negative effects into categories and the number of participants with each category of negative effects in each group was reported. The relative risk of reporting a negative effect during the 6-month follow-up was evaluated using Fisher exact test.

Because the trial was stopped early and there were no significant effects of the intervention on primary outcomes (see Results), conditional power was assessed after the trial was completed to test the possibility that significant effects would have been detected if the target number of participants had been recruited. Two estimates of conditional power were obtained: a "trend" estimate that assumed the true effect in the additional participants was the point estimate from the primary analysis and a "design" estimate that assumed the true effect in the additional participants was the effect specified in the power calculations.[23]

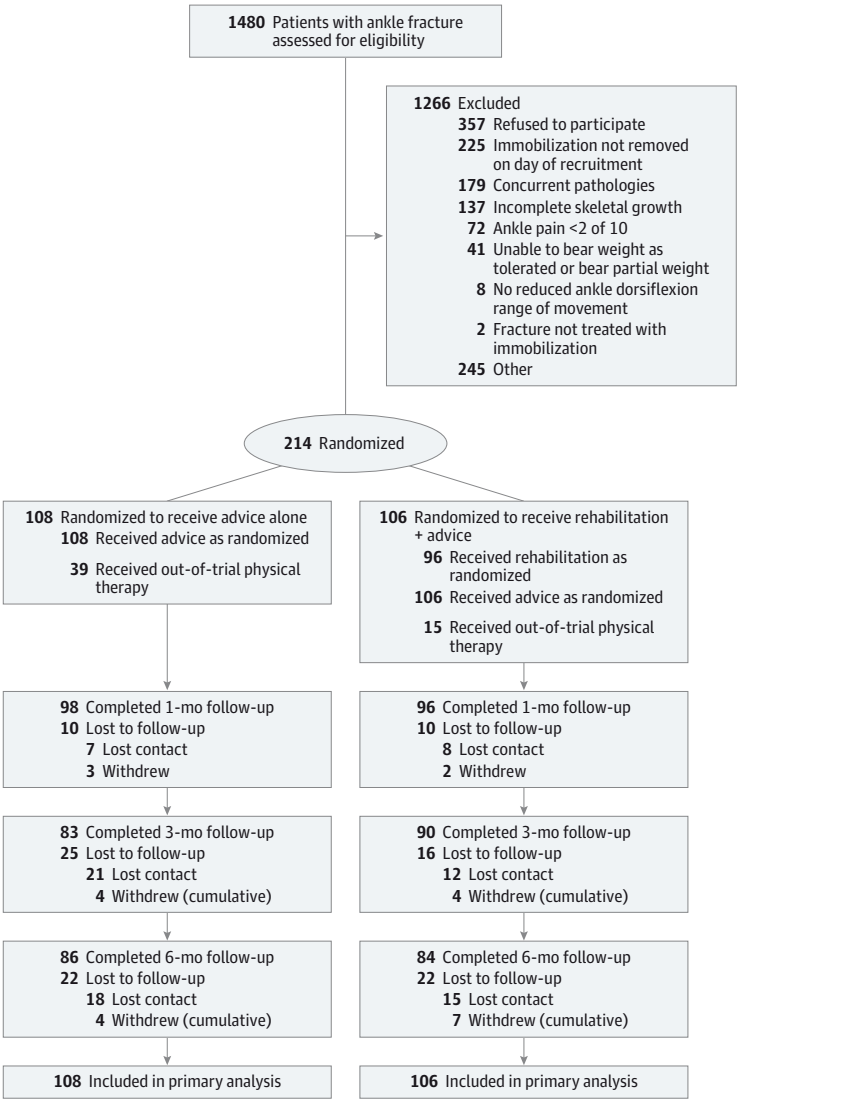
Economic Evaluation

Cost-effectiveness analysis was contingent on demonstration of between-group differences in the primary outcomes. Resources used were valued using published sources (eTable 2 in Supplement 2) or as reported by the participants, and missing utilization and cost data were replaced by multiple imputation. Bias-corrected bootstrapping (1000 replications) was used to obtain 95% confidence intervals for mean between-group differences in utilization and costs, and 4 sensitivity analyses were conducted. Costs were reported in 2013 Australian dollars (A $1 = US $0.87 = £0.46).[24] Number of days away from paid work and unpaid activities were reported as descriptive data only.

Results

Recruitment occurred between December 7, 2010, and December 24, 2013. Follow-up assessments were completed on June 6, 2014. **Figure 1** illustrates the flow of participants through the trial. The main reasons for exclusion were refused participation (n = 357), other reasons (n = 245, mainly because the person lived outside the hospital catch-

Figure 1. Flow of the EXACT Randomized Clinical Trial



ment area [n = 111] or was not available for the follow-up period [n = 63]), or because the immobilization was not removed on the day of recruitment (n = 225, people who removed their immobilization prior to attending the fracture clinic appointment). Of the 214 participants randomized, 194 (90.7%) were followed up at 1 month, 173 (80.8%) at 3 months, and 170 (79.4%) at 6 months.

On average the participants were middle-aged; there were more women than men, and more participants had less severe fractures. At baseline, participants had significant activity limitation (mean of 30 on the 0-80 Lower Extremity Functional Scale) and low quality of life (mean of 0.5 on the 0-1 measure of quality of life). The groups were similar on all demographic and clinical variables and outcomes at baseline (**Table 1**).

The primary analyses showed that rehabilitation did not provide a significant benefit over advice. Mean activity limitation increased from 30.1 (SD, 12.5) at baseline to 64.3 (SD, 13.5) at 3 months for the advice group and from 30.2 (SD, 13.2) to 64.3 (SD, 15.1) for the rehabilitation group. Mean quality of life increased from 0.51 (SD, 0.24) at baseline to 0.85 (SD, 0.17) at 3 months for advice and from 0.54 (SD, 0.24) to 0.85 (SD, 0.20) for rehabilitation. At 3 months, the primary time point, the rehabilitation group had a mean of 0.4 points less activity limitation (95% CI, −3.3 to 4.1) and 0.01 points lower quality of life (95% CI, −0.06 to 0.04) compared with the advice group (**Table 2**). Similar results were observed at 1 and 6 months (Table 2) and with the sensitivity analyses (eTable 1 in Supplement 2).

Furthermore, post hoc sensitivity analyses indicate that out-of-trial physical therapy did not dilute the estimates of effects. For activity limitation, the as-treated, per-protocol, and local average treatment effect estimates of effects at 3 months were 0.3 (95% CI, −4.0 to 4.5), 0.6 (95% CI, −3.3 to 4.6), and 0.9 (95% CI, −4.0 to 5.7), respectively. The corresponding values for quality of life were −0.01 (95% CI, −0.07

Table 1. Baseline Characteristics of the Trial Participants

Characteristic	No. (%) Advice (n = 108)	Rehabilitation (n = 106)
Sex		
Men	51 (47.2)	43 (40.6)
Women	57 (52.8)	63 (59.4)
Age at fracture, mean (SD), y	41.3 (15.2)	43.1 (16.5)
Height, mean (SD), cm	169.8 (9.2)	168.7 (8.5)
Weight, mean (SD), kg	79.1 (17.5)	78.1 (16.7)
Ankle fractured		
Left	50 (46.3)	56 (52.8)
Right	58 (53.7)	50 (47.2)
Cause of fracture		
Road traffic incident		
Pedestrian or bicycle	1 (0.9)	1 (0.9)
Car or motorbike	7 (6.5)	3 (2.8)
Fall	67 (62.0)	72 (67.9)
Sporting injury	23 (21.3)	23 (21.7)
Other	10 (9.3)	7 (6.6)
Fracture severity[a]		
Less severe	60 (55.6)	64 (60.4)
More severe	48 (44.4)	42 (39.6)
Open reduction and internal fixation	51 (47.2)	47 (44.3)
Length of immobilization, mean (SD), d	47.9 (13.2)	45.3 (11.2)
Type of immobilization used		
Backslab	92 (85.2)	81 (76.4)
Cast	66 (61.1)	56 (52.8)
Brace	50 (46.3)	55 (51.9)
Annual household income per year before tax, A$		
0 to 51 999	18 (16.7)	27 (25.5)
≥52 000	60 (55.6)	42 (39.6)
Did not wish to answer or missing	30 (27.8)	37 (34.9)
Private health insurance		
Yes	51 (47.2)	40 (37.7)
No	47 (43.5)	56 (52.8)
Did not wish to answer or missing	10 (9.3)	10 (9.4)
Home ownership		
Renting/boarding or buying (paying loan)	72 (66.7)	58 (54.7)
Owner (outright) or rent/board free	26 (24.1)	37 (34.9)
Did not wish to answer or missing	10 (9.3)	11 (10.4)
Lower Extremity Functional scale (0-80), mean (SD)	30.1 (12.5)	30.2 (13.2)
Assessment of Quality of Life[b]		
Utility (0-1), mean (SD)	0.51 (0.24)	0.54 (0.24)
Total (0-45)		
Mean (SD)	10.4 (5.3)	9.9 (5.2)
Median (IQR)	10.0 (7.0-14.0)	10.0 (6.0-13.0)
Illness (0-9)		
Mean (SD)	3.0 (2.3)	2.9 (2.3)
Median (IQR)	3.0 (1.0-5.0)	3.0 (1.0-4.0)
Independent living (0-9)		
Mean (SD)	3.3 (2.2)	2.7 (2.2)
Median (IQR)	3.5 (2.0-5.0)	2.0 (1.0-4.0)
Social relationships (0-9)		
Mean (SD)	1.5 (1.4)	1.5 (1.4)
Median (IQR)	1.0 (0.0-2.0)	1.0 (0.0-2.0)
Physical senses (0-9)		
Mean (SD)	0.3 (0.6)	0.4 (0.7)
Median (IQR)	0.0 (0.0-1.0)	0.0 (0.0-1.0)
Psychological well-being (0-9)		
Mean (SD)	2.3 (1.7)	2.4 (1.7)
Median (IQR)	2.0 (1.0-3.0)	2.0 (1.0-4.0)
Return to amount of prefracture work, %		
Mean (SD)	39.3 (42.8)	41.9 (44.8)
Median (IQR)	10.0 (0.0-87.5)	20.0 (0.0-100.0)
Return to amount of prefracture sport, leisure, or recreation, %		
Mean (SD)	3.7 (12.0)	2.2 (8.6)
Median (IQR)	0.0 (0.0-0.0)	0.0 (0.0-0.0)
International Physical Activity Questionnaire		
MET min/wk[c]		
Mean (SD)	455.1 (852.7)	427.4 (723.3)
Median (IQR)	132.0 (0.0-594.0)	99.0 (0.0-495.0)
Activity[c]		
Low[d]	88 (81.5)	75 (70.8)
Moderate or high[d]	19 (17.6)	28 (26.4)
Pain		
Standing with equal weight on both legs (0-10)		
Mean (SD)	3.8 (1.9)	4.0 (1.8)
Median (IQR)	3.0 (2.0-5.0)	3.0 (3.0-5.0)
Walking down stairs (0-10)		
Mean (SD)	4.4 (3.1)	4.8 (3.0)
Median (IQR)	4.0 (2.0-6.0)	4.0 (3.0-7.0)
Unaided walking speed, m/s		
Mean (SD)	0.5 (0.4)	0.4 (0.5)
Median (IQR)	0.5 (0.0-0.8)	0.4 (0.0-0.8)
Ankle dorsiflexion range of motion, mean (SD), mm[e]	−49.1 (55.9)	−45.3 (47.4)

Abbreviations: IQR, interquartile range; MET, metabolic equivalents.

[a] Less severe = 1 malleoli fractured; more severe = 2 or 3 malleoli fractured or the presence of dislocation regardless of the number of malleoli fractured.

[b] Higher Assessment of Quality of Life scores indicate better quality of life.

[c] Data are missing for 1 participant in advice and 3 participants in rehabilitation.

[d] High cutpoints: 3 or more days of vigorous-intensity activity achieving 1500 MET min/wk or more or 7 days of walking, moderate-intensity, or vigorous-intensity activities achieving 3000 MET min/wk or more. Moderate cutpoints: 3 or more days of 20 minutes or more vigorous-intensity activity, or 5 or more days of 30 minutes or more moderate-intensity activity or walking, or 5 or more days of walking, moderate-intensity, or vigorous-intensity activities achieving 600 MET min/wk or more. Low cutpoint: not "moderate" or "high."

[e] As per the weight-bearing lunge method,[16] negative values represent the distance between the knee and the wall; positive values represent the distance between the great toe and the wall.

Table 2. Primary Outcomes for the Advice and Rehabilitation Groups at 1, 3, and 6 Months

	Mean (95% CI)								
	1 mo			3 mo[a]			6 mo		
Variable	Advice	Rehabilitation	Difference	Advice	Rehabilitation	Difference	Advice	Rehabilitation	Difference
Lower Extremity Functional Scale (0-80)	54.8 (51.7 to 58.0)	54.4 (51.5 to 57.2)	0.4 (−3.9 to 3.2)	64.3 (61.3 to 67.2)	64.3 (61.1 to 67.4)	0.4 (−3.3 to 4.1)	69.9 (67.3 to 72.5)	69.9 (67.4 to 72.5)	0.2 (−3.4 to 3.9)
Assessment of Quality of Life (utility; 0-1)	0.78 (0.74 to 0.83)	0.75 (0.71 to 0.80)	−0.04 (−0.09 to 0.01)	0.85 (0.81 to 0.89)	0.85 (0.81 to 0.89)	−0.01 −0.06 to 0.04)	0.89 (0.85 to 0.92)	0.89 (0.86 to 0.93)	−0.01 (−0.06 to 0.04)

[a] Primary time point.

to 0.05), −0.01 (95% CI, −0.06 to 0.05), and 0.00 (95% CI, −0.06 to 0.07). The conditional power estimates (trend estimates: 0% for both activity limitation and quality of life; design estimates: 12% for activity limitation and 2% for quality of life) indicate there was little possibility of obtaining statistically significant effects on primary outcomes had the target sample size been recruited.

Because between-group differences were not found in the primary outcomes, a cost-effectiveness analysis was not conducted. Resource use and costs for each group were calculated. There was little difference between groups in terms of health service resource use (eTable 2 in Supplement 2), except participants in the rehabilitation group had more consultations with hospital physical therapists (as dictated by the protocol) and sought fewer consultations with private physical therapists. The rehabilitation group incurred a higher cost to the health care system, but there were no significant between-group differences in out-of-pocket or total costs (health care system plus out-of-pocket costs) (eTable 3 in Supplement 2). Sensitivity analyses showed similar results (eTable 4 in Supplement 2).

Treatment effects were not moderated by fracture severity or age and sex (**Figure 2**). Even though recruitment was stopped early, so that the actual sample size was less than that expected to be necessary to adequately power the analysis of the interactions, the estimates of interactions were sufficiently precise to rule out clinically important effects in the trial populations and in the subpopulations represented by the prespecified subgroups.

There were no significant between-group differences for any of the exploratory analyses of the secondary outcomes. With the exception of physical activity, the mean between-group differences were close to zero and the 95% confidence intervals did not include clinically important differences (eTable 5 in Supplement 2). The confidence intervals for physical activity included a clinically important difference of 600 MET min/wk in favor of the advice group. The survival curves are illustrated in eFigure in Supplement 2. The between-group differences in pain-free walking (hazard ratio, 0.87 [95% CI, 0.65 to 1.16]) and return to full prefracture work (hazard ratio, 0.87 [95% CI, 0.61 to 1.22]) were not statistically significant. However, we could not rule out a clinically important difference in these 2 outcomes in favor of the advice group, as the median times for return to pain-free walking were 27 days for advice and 31 days for rehabilitation, and the median times for return to full prefracture work were 23 days and 32 days, respectively.

Negative effects were recorded for 9 participants in the advice group compared with 2 in the rehabilitation group. Although this difference nears statistical significance (relative risk, 0.23 [95% CI, 0.05 to 1.02]; $P = .057$ by Fisher exact test), most negative effects were dissatisfaction with treatment dose (5 advice, 0 rehabilitation), dissatisfaction with treatment outcomes (1 advice, 1 rehabilitation), or dissatisfaction with treatment costs (1 advice, 0 rehabilitation). Safety concerns were few: there were 2 cases of pain (1 advice, 1 rehabilitation) and 1 case of deep venous thrombosis (1 advice, 0 rehabilitation).

There was good adherence to the trial protocol (eTable 6 in Supplement 2), but a significant proportion of participants received out-of-trial physical therapy (15/106 [14%] in the rehabilitation group and 39/108 [36%] in the advice group), which was usually in the private sector (Figure 1 and eTable 2 in Supplement 2). Participants completed their exercises on 78.8% and 79.8% of the days between the baseline and 1-month assessment for the advice and rehabilitation groups, respectively. Participants in the rehabilitation group attended an average of 5 physical therapy consultations. Participants in both groups were generally satisfied with the intervention they received. With the exception of the 1-month assessment, for which assessors reported they knew the allocations of 16 of 98 participants in the advice group (16.3%) and 43 of 96 participants in the rehabilitation group (44.8%), assessors were generally unaware of group allocation. The number of days away from paid work and unpaid activities did not appear different between groups.

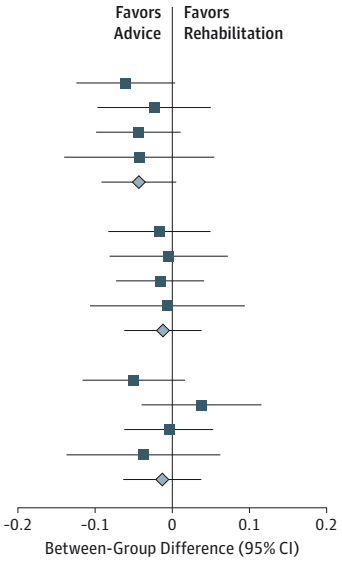
Discussion

The EXACT trial provides robust evidence that a supervised exercise program and self-management advice (rehabilitation) did not improve activity limitation or quality of life compared with advice alone after removal of immobilization in patients with isolated ankle fracture. In addition, the trial shows that treatment effects were not associated with fracture severity or age and sex. Rehabilitation was more costly to the health care system but did not influence out-of-pocket costs to the individual or total costs. Although we could not completely rule out a clinically important effect in favor of advice for the secondary outcomes of physical activity, time to pain-free walking, and time to return to full prefracture work, there were no statistically significant effects at any point in the exploratory analyses of the 17 sec-

Figure 2. Treatment Effects of Intervention for the Assessment of Quality of Life (Utility) and Lower Extremity Functional Scale, Overall and by Age, Fracture Severity, and Sex

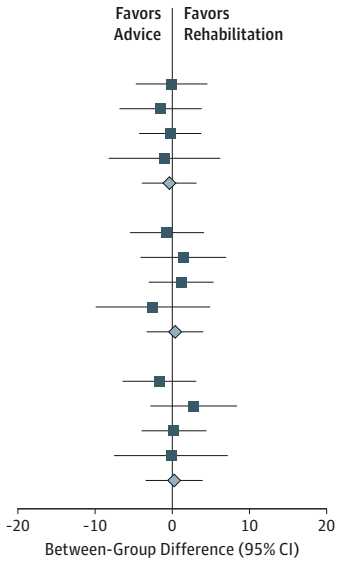
A Assessment of Quality of Life (utility)

	No. of Patients		Assessment of Quality of Life, Mean (95% CI)		Between-Group Difference (95% CI)
	Advice	Rehabilitation	Advice	Rehabilitation	
1 Month					
Not a severe fracture	52	57	0.81 (0.76-0.87)	0.77 (0.71-0.83)	-0.06 (-0.12 to 0.00)
Severe fracture	45	39	0.75 (0.68-0.82)	0.73 (0.66-0.80)	-0.02 (-0.10 to 0.05)
Women ≤50 y and men	73	73	0.82 (0.77-0.86)	0.78 (0.73-0.83)	-0.04 (-0.10 to 0.01)
Women >50 y	24	23	0.69 (0.59-0.79)	0.66 (0.55-0.78)	-0.04 (-0.14 to 0.05)
All participants	97	96	0.78 (0.74-0.83)	0.75 (0.71-0.80)	-0.04 (-0.09 to 0.01)
3 Months					
Not a severe fracture	45	54	0.86 (0.81-0.90)	0.85 (0.79-0.90)	-0.02 (-0.08 to 0.05)
Severe fracture	38	36	0.84 (0.78-0.90)	0.85 (0.78-0.91)	-0.00 (-0.08 to 0.07)
Women ≤50 y and men	60	70	0.88 (0.85-0.92)	0.86 (0.82-0.91)	-0.02 (-0.07 to 0.04)
Women >50 y	23	20	0.76 (0.66-0.86)	0.79 (0.69-0.89)	-0.01 (-0.11 to 0.09)
All participants	83	90	0.85 (0.81-0.89)	0.85 (0.81-0.89)	-0.01 (-0.06 to 0.04)
6 Months					
Not a severe fracture	48	50	0.92 (0.89-0.95)	0.88 (0.83-0.93)	-0.05 (-0.12 to 0.02)
Severe fracture	38	33	0.84 (0.77-0.90)	0.92 (0.89-0.95)	0.04 (-0.04 to 0.12)
Women ≤50 y and men	63	62	0.91 (0.87-0.95)	0.92 (0.88-0.95)	-0.00 (-0.06 to 0.05)
Women >50 y	23	21	0.82 (0.75-0.89)	0.82 (0.73-0.92)	-0.04 (-0.14 to 0.06)
All participants	86	83	0.89 (0.85-0.92)	0.89 (0.86-0.93)	-0.01 (-0.06 to 0.04)



B Lower Extremity Functional Scale

	No. of Patients		Lower Extremity Functional Scale, Mean (95% CI)		Between-Group Difference (95% CI)
	Advice	Rehabilitation	Advice	Rehabilitation	
1 Month					
Not a severe fracture	52	57	57.7 (53.6-61.8)	58.3 (54.8-61.8)	-0.1 (-4.7 to 4.6)
Severe fracture	46	39	51.6 (46.7-56.5)	48.6 (44.1-53.2)	-1.5 (-6.8 to 3.8)
Women ≤50 y and men	74	73	55.9 (52.2-59.6)	56.0 (52.7-59.3)	-0.2 (-4.3 to 3.8)
Women >50 y	24	23	51.5 (45.3-57.8)	49.1 (43.4-54.9)	-1.0 (-8.2 to 6.2)
All participants	98	96	54.8 (51.7-58.0)	54.4 (51.5-57.2)	-0.4 (-3.9 to 3.2)
3 Months					
Not a severe fracture	45	53	66.2 (62.8-69.5)	65.8 (61.8-69.9)	-0.7 (-5.5 to 4.1)
Severe fracture	38	36	62.0 (56.9-67.1)	62.0 (56.7-67.3)	1.4 (-4.1 to 7.0)
Women ≤50 y and men	60	69	65.4 (62.2-68.5)	65.9 (62.5-69.4)	1.2 (-3.0 to 5.4)
Women >50 y	23	20	61.4 (54.4-68.4)	58.7 (50.9-66.4)	-2.5 (-9.9 to 4.9)
All participants	83	89	64.3 (61.3-67.2)	64.3 (61.1-67.5)	0.4 (-3.3 to 4.1)
6 Months					
Not a severe fracture	48	51	72.4 (69.6-75.2)	69.4 (65.7-73.0)	-1.7 (-6.4 to 3.1)
Severe fracture	38	33	66.8 (62.1-71.4)	70.8 (67.1-74.6)	2.8 (-2.8 to 8.4)
Women ≤50 y and men	63	63	71.4 (68.7-74.2)	71.4 (68.6-74.3)	0.2 (-4.0 to 4.5)
Women >50 y	23	21	65.8 (59.5-72.0)	65.5 (59.5-71.5)	-0.2 (-7.5 to 7.2)
All participants	86	84	69.9 (67.3-72.5)	69.9 (67.4-72.5)	0.2 (-3.4 to 3.9)



Assessment of Quality of Life utility scale range, 0 to 1 (higher scores denote better quality of life). Lower Extremity Functional Scale range, 0 to 80 (higher scores denote better activity; minimal clinically important difference, 9).

ondary outcomes. These results can be generalized to people with isolated and uncomplicated ankle fracture.

This trial incorporated several features thought to reduce bias. Randomization was concealed. Follow-up rates were good at the 1-month (>90%) and acceptable at the 3- and 6-month (≈80%) assessments. The trial was prospectively registered and followed a prespecified protocol and statistical analysis plan. Blinding of participants, and therefore assessment of the primary outcomes, was not possible owing to the nature of the interventions, but data analysis and interpretation were conducted blinded to group allocation.

The effectiveness of a supervised exercise program for patients with ankle fracture has been assessed in a previous randomized trial that included only participants whose fractures were managed surgically.[10] Like us, Nilsson et al[10] found no overall difference in outcomes with exercise or usual care. Pooling data from EXACT and the study by Nilsson et al suggests there was no effect on activity limita-

tion of a supervised exercise program compared with usual care or advice only after ankle fracture (mean effect, −0.2 [95% CI, −4.3 to 3.8] on a 0-100 scale). Nilsson et al found that a subgroup of participants younger than 40 years (n = 40) had statistically significant effects at both 6 and 12 months, favoring those who received rehabilitation. It was not clear if the subgroup analysis was prespecified, and the trial was not adequately powered for subgroup effects. In contrast to Nilsson et al, we hypothesized that rehabilitation could potentially be more effective in older women (>50 years), but our results strongly suggest that the effect of rehabilitation was not moderated by age and sex or by fracture severity (Figure 2).

The limitations of the trial were that the advice group received out-of-trial physical therapy, the trial was terminated early, and the cost data may not generalize beyond the Australian setting. Nearly one-third of participants in the advice group received out-of-trial physical therapy. This potentially dilutes the observed effect. To evaluate this possibility, a series of sensitivity analyses were conducted. These included an as-treated analysis in which participants in the advice group who received out-of-trial physical therapy were analyzed as if they had been allocated to the rehabilitation group, a per-protocol analysis in which participants in the advice group who received out-of-trial physical therapy were omitted from the analysis, and an analysis in which propensity score matching was used to estimate the local average treatment effect in the population that did not receive out-of-trial physical therapy when allocated to receive advice only. All 3 sensitivity analyses yielded point and interval estimates similar to those from the primary analysis. Although the target sample size was not reached (214 recruited of the targeted 342 participants), the sample size had been inflated to accommodate the planned subgroup analyses. The results of all analyses, including the subgroup analyses, had sufficiently narrow confidence intervals to rule out important beneficial effects of a supervised exercise program.

We have previously shown that recovery of activity limitation after ankle fracture is rapid in the first 6 months[4] and that adding passive stretch[8] or manual therapy[7] to a supervised exercise program did not enhance the benefits of exercise alone. It is possible that the lack of treatment effect we observed in this trial is attributable to the fact that rehabilitation cannot accelerate this rapid recovery. These findings and the findings of the present trial suggest that routine care for patients after isolated ankle fracture should include self-management advice at the time of removal of immobilization but not a supervised exercise program.

Conclusions

A supervised exercise program did not confer additional benefits in activity limitation or quality of life compared with advice alone for patients with isolated and uncomplicated ankle fracture. These findings do not support the routine use of supervised exercise programs after removal of immobilization for patients with isolated and uncomplicated ankle fracture.

ARTICLE INFORMATION

Author Contributions: Drs Moseley and Herbert had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Moseley, Haas, Herbert, Lin.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Beckenkamp, Herbert, Lin.
Obtained funding: Moseley, Haas, Herbert, Lin.
Administrative, technical, or material support: Moseley, Beckenkamp, Haas, Lin.
Study supervision: Moseley, Haas, Lin.

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Group Information: The EXACT (Exercise or Advice After Ankle Fracture) Team: Patricia Evans, BAppSc (Physio) (Royal North Shore Hospital); Deborah Taylor, BAppSc (Physio) (Royal North Shore Hospital); Andrew Wines, FRACS (Orth) (Royal North Shore Hospital); Jeremy Hogan, BAppSc (Physio) (Royal Prince Alfred Hospital); Julie Penn, BAppSc (Physio) (Royal Prince Alfred Hospital); Mark Horsley, FRACS (Orth) (Royal Prince Alfred Hospital); Vanessa Abbott, BAppSc (Physio) (Blacktown Mount Druitt Hospital); Luke Elias, BAppSc (Physio) (Blacktown Mount Druitt Hospital); Bijoy Thomas, FRACS (Orth) (Blacktown Mount Druitt Hospital); Karen Lee, BAppSc (Physio) (Prince of Wales Hospital); Judy Chen, PhD (Prince of Wales Hospital); Julia Cameron, BAppSc (Physio) (Ryde Hospital); Michelle Appleby, BAppSc (Physio) (Mona Vale Hospital); Tyson Russell, BAppSc (Physio) (Mona Vale Hospital).

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