Acute Ankle Sprains in Primary Care

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Acute Ankle Sprains in Primary Care

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Chapter 1

General introduction

INTRODUCTION

Of all injuries of the musculoskeletal system, 25% are acute lateral ankle sprains.[1] In the USA and the UK there are about 23,000 and 5000 ankle sprains, respectively, each day.[1,2] In the Netherlands approximately 600,000 people sustain an ankle injury each year, of those 120,000 occur during sport, of which 43,000 seek for medical care.[3,4] The latest statistics in the Netherlands show that general practitioners (GPs) see around 125,000 patients with an ankle sprain each year, with an incidence of eight per thousand patients per year.[5]

In the Netherlands, currently there are three clinical guidelines which deal with the diagnosis and treatment of acute lateral ankle injuries.[3,6,7] These guidelines roughly correspond with each other and recommend conventional treatment as the primary treatment modality of choice. Conventional treatment consists of early mobilizing, early weight bearing (as much as the pain will allow) combined with (or without) the use of an external support, e.g. tape, brace or bandage.

Acute lateral ankle ligaments injuries are treated in various ways. However, before being able to evaluate the effectiveness of therapeutic interventions, we need insight into the course of recovery after an acute lateral ankle injury. Beneficial effects or complications of different treatments may be considered against the background of this clinical course. In addition, the identification of relevant subgroups of patients with better or worse prognosis is also important. This may guide management decisions, give directions for future research, and is helpful when informing patients about the clinical course of their injury.

Therefore, we performed a systematic review to provide an overview of the literature evaluating the clinical course of conventionally treated acute lateral ankle sprains in adults, and possible prognostic factors for incomplete recovery of this injury.

Despite the large variety of treatments, several reviews and clinical guidelines indicate that conventional treatment (i.e. early mobilisation, including mobilisation instructions and early weight bearing combined with or without the use of external support) is the preferred treatment strategy and known as 'usual care'.[1-3,6,8-11] However, experimental studies examining ligamentous healing indicate that gradually increasing and functional load exercises, stimulate healing and increase the strength of ligaments after injury.[12-14] Therefore, a structured and supervised rehabilitation program after an ankle sprain might lead to better results concerning recovery or re-injuries. Nevertheless, different reviews report that there is no or only limited evidence for the effectiveness of supervised rehabilitation training or physiotherapy as a treatment strategy, and advise to conduct randomised controlled trials on this topic.[9,15,16] For that reason, we conducted a trial on the effectiveness of conventional treatment combined with supervised exercises in primary care patients with an acute lateral ankle sprain.

In clinical practice, ankle sprains are categorised according to the severity of the injury, and graded according to three levels: grade I (mild), grade II (moderate), and grade III (severe).[2,17] Despite this classification into grades, there is still some variation in the treatment applied within each severity group. Therefore, De Bie and colleagues introduced the 'Ankle Function Score' which allows to make a distinction between mild and severe ankle sprains at admission, and thereby for a distinction between patients who need specific physiotherapy treatment, or not.[18] Despite the fact that there are only indications that the function score can be used to make a distinction between mild and severe injuries, the 'Acute ankle injury' clinical guideline of the Royal Dutch Society of Physiotherapists proposes the use of that function score.[6] However, it remains unclear whether the Ankle Function Score can be used to evaluate recovery over time, and/or can be used to divide patients with ankle sprain injuries into those which need no treatment (mild) or need specific treatment (severe).

Whereas the Ankle Function Score is a specific tool to measure progress in recovery after an ankle sprain, in longitudinal research in musculoskeletal disorders we often make use of a single question to measure recovery.[19-21] As a consequence, an increased emphasis is placed on self-reported perceived recovery as an outcome measure. For the practicing clinician this question is a fundamental one, because it gives patient-relevant information on the effect of treatment and guides decision-making regarding the next step.[22] However a large variation in reported recovery exist. For example, patients with an acute ankle sprain experience no pain or functional disability, whereas they still report not to be recovered, or vice versa. More knowledge about what recovery means to patients who have suffered from a lateral ankle sprain will lead to better understanding of the patient in the aim to promote their recovery.

In addition, when patients do not recover it is important to explore the factors predicting persistent complaints after their initial ankle sprain. In 1965 Freeman et al.[23] investigated the effectiveness of coordination exercises on the occurrence of proprioceptive deficits and symptoms of 'giving way' in patients with a rupture of the lateral ligament of the ankle. Parallel to the positive results in their study, residual symptoms were reported after six to fourteen months follow-up. To our knowledge, since that time prognostic factors for residual symptoms have been evaluated in only one other study and, therefore, remain largely unknown.[24] This information would be helpful to inform patients about their expected clinical course, and to identify relevant subgroups of patients with a better or worse prognosis.

OUTLINE OF THIS THESIS

Chapter 2 presents a systematic review of the literature about the clinical course of conventionally-treated acute lateral ankle sprains in adults and its prognostic factors for incomplete recovery. **Chapter 3** describes the results of a randomised clinical trial evaluating the effectiveness of conventional treatment combined with supervised exercises compared with conventional treatment alone in primary care patients with acute ankle sprain. In **Chapter 4** a subgroup analysis is performed with the data of the trial in which patients are classified (based on the Ankle Function Score) according to the severity of the ankle sprain. The aim of **Chapter 5** is to find explanatory variables for recovery in adult patients with acute lateral ankle sprain. **Chapter 6** evaluates prognostic factors for incomplete recovery, and residual complaints during one-year follow-up, in patients who consulted primary care for acute ankle sprains. **Chapter 7** evaluates the evidence for conventional treatment combined with supervised exercises in patients with an acute ankle sprain, by reviewing the current literature. **Chapter 8** discusses the main results of the studies, the study limitations, and implications for future research and clinical practice.

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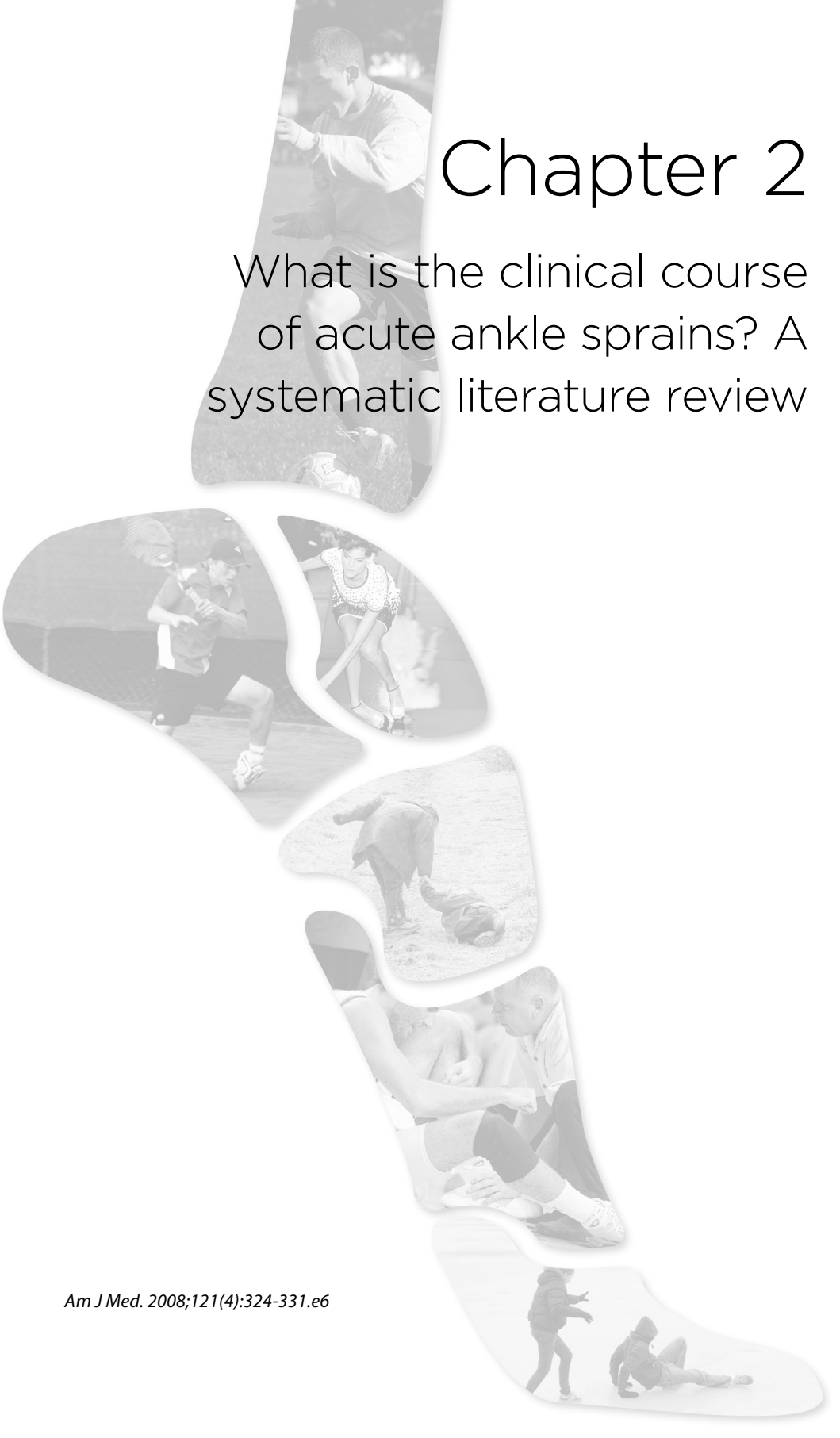

Chapter 2

What is the clinical course of acute ankle sprains? A systematic literature review

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ABSTRACT

Ankle sprains are one of the most common musculoskeletal injuries. In order to evaluate the effectiveness of therapeutic interventions and to guide management decisions it is important to have clear insight of the course of recovery after an acute lateral ankle injury and to evaluate potential factors for non recovery and re-sprains. The purpose of this study was to perform a systematic review of the literature regarding the clinical course of conventionally treated acute lateral ankle sprains in adults and its prognostic factors.

A database search was conducted in Medline, Cinahl, Pedro, Embase, and the Cochrane Controlled trial register. Included were observational studies and controlled trials with adult subjects who suffer from an acute lateral ankle sprain which was conventionally treated. One of the following outcomes had to be described: pain, re-sprains, instability or recovery. Two reviewers independently assessed the methodological quality of each included study. One reviewer extracted relevant data.

In total, 31 studies were included from which 24 studies were of high quality. Within the first two weeks there is a rapid decrease in pain reporting. 5% to 33% of the patients still experience pain after one year, while 36% to 85% reported full recovery within a period of three years. The risk of re-sprains ranged from 3% to 34% of the patients and re-sprain was registered in periods ranging from two weeks to 96 months post injury. There is a wide variation in subjective instability, ranging from 0% to 33% in the high quality studies and from 7% to 53% in the low quality studies. One study described prognostic factors and indicated that training more than three times a week is a prognostic factor for residual symptoms.

In conclusion, after one year of follow-up a high percentage of patients still experience pain and subjective instability, while within a period of three years as much as 34% of the patients reported at least one re-sprain. From 36% up to 85% of the patients reported full recovery within a period of three years.

INTRODUCTION

Ankle sprains are one of the most common musculoskeletal injuries. In the Netherlands an estimated 600,000 people sustain ankle injuries each year, with an incidence of 12.8 per 1,000 patients per year. Roughly half of these people visit a general practitioner or, on their own initiative, an emergency department.[1] In the USA and the UK there are 23,000 and 5,000 injuries of the ankle, respectively, each day.[2]

Recent reviews indicate that conventional treatment is the preferable initial treatment strategy[2-7]. Conventional treatment consists of early mobilisation with mobilisation instructions and early weight bearing, combined with or without the use of an external support (tape, bandage or brace). In order to evaluate the effectiveness of therapeutic interventions and to guide management decisions it is important to have clear insight of the course of recovery after an acute lateral ankle injury. Beneficial effects or complications of different treatments may be considered against the background of this clinical course. Besides, identification of relevant subgroups of patients with better or worse prognosis is also important. This may guide management decisions, give directions for future research and is helpful for informing patients about the clinical course of their injury. At present there is, however, no clear overview regarding the clinical course of acute lateral ankle sprains, and an evaluation of prognostic factors for incomplete recovery and re-sprains is missing.

Therefore, the purpose of this study was to perform a systematic review of the literature regarding the clinical course of conventionally treated acute lateral ankle sprains in adults and its prognostic factors.

METHODS

Literature search

One author (RvR) conducted a database search using MEDLINE (from 1966 to August 2006), CINAHL, PEDro, EMBASE (from 1984 to August 2006) and the Cochrane Controlled Trial Register (CCTR). The terms disorder, location and design were linked by the Boolean operator AND. For each of the terms, one or more synonyms were used (Table 1).

The selected studies had to fulfil the following criteria for inclusion in the review; (1) the adult subjects had to suffer from an acute lateral ankle sprain, (2) the study design had to be longitudinal i.e. observational (prospective as well as retrospective) or a controlled trial, (3) at least one of the following outcomes at follow-up had to be described: pain, re-sprains, subjective instability (feeling of insecurity, tendency for the foot to 'give way') or subjective recovery, (4) the treatment (or one of the arms in a trial) was conventional treatment. Conventional treatment involves early mobilisation, including

mobilisation instructions and early weight bearing combined with or without the use of an external support (tape, bandage or brace).

Table 1 Terms used for the database search

Term	Synonym
Disorder	inversion OR sprain OR strain OR rupture OR injur* OR distortion
Location	[ankle OR talocrural OR talofibular OR calcaneofibular] AND ligament
Design	prognos* OR predict* OR "disease course" OR case-control OR longitudinal OR cohort OR prospective OR retrospective OR follow-up OR randomized controlled trial OR controlled clinical trial OR randomized controlled trials OR random allocation OR double-blind method OR single-blind method

From title and abstracts, two reviewers (SB-Z and RvR) independently reviewed the literature searches to identify potentially relevant studies for full review. Abstracts for which full reports were not available and unpublished studies were not included. Based on the full text, two reviewers (SB-Z and RvR) independently selected studies for inclusion in this review. Relevant articles in the bibliographies of selected articles were also reviewed. The help of a native speaker was obtained for studies published in languages other than English, German or Dutch. Disagreements were resolved by consensus.

Methodological quality assessment

Methodological quality of the selected studies was assessed by two reviewers (PL and RvR) independently using a set of seven criteria (Table 2). In case of prognostic factors

Table 2 Criteria used for the quality assessment

	Criterion
1	Sample definition given (at least 3: age, gender, injury grade, and setting)
2	Baseline characteristics assembled within 2 weeks after injury
3	Participants selected by random selection or as consecutive cases
4	A prospective design used
5	Follow-up available from at least 80% of study population
6	Information on completers versus withdrawals available
7	The study provide raw data, percentages, survival rates, RRs, ORs or ES
8	*3 or more of the following prognostic determinants were measured (severity or injury grade, weight, BMI, activity level)*
9	*Independent assessment of outcome measurement (blinded for prognostic factors)*
10	*Crude estimates are given or can be calculated*
11	*Adjusted estimates are given or can be calculated*

RR = relative risk; OR = odds ratio; ES = estimate; BMI = body mass index. Items 8, 9, 10 and 11 are supplementary and are used for the quality assessment of prognostic studies.

the methodological quality assessment was expanded with four criteria. Each criterion was rated positive, negative or inconclusive (insufficient information presented). Disagreements were resolved by consensus. A total score for the methodological quality of each study was calculated by summing the number of positive criteria (range 0-7 or range 0-11). Studies with five (eight in case of prognostic factors) or more positive criteria were considered to be of 'high quality'.

Data extraction

One reviewer (RvR) extracted relevant data from the publications. Study characteristics extracted were target population (setting, gender, and age), sample size, duration of follow-up, prognostic factors (severity, weight, length, BMI, activity level), and outcome measures. Outcome data extracted were pain, subjective instability (feeling of giving way), re-sprain, subjective recovery (restored to pre-injury state, free from residual symptoms, cured), swelling (ankle girth) and range of motion (ROM).

For the association between prognostic factors and the outcome measures we extracted odd ratios (OR) or relative risks (RR). When not given, and sufficient data were available, for each study the association (OR) with 95% confidence intervals was calculated.

Data synthesis

The inter-observer reliability of the overall quality assessment was derived by Kappa statistics. Following the suggestions of Fleiss[8], kappa coefficients greater than 0.75 are considered to represent excellent agreement, values between 0.75 and 0.4 fair agreement, and values lower than 0.4 represent poor agreement.

The study outcomes are statistically pooled if the studies are considered to be homogeneous. However, if the studies are considered to be heterogeneous we refrain from pooling and only describe the outcomes. When studies do not contain enough information about the association between prognostic factors and outcome we graphically present the obtained data of the course subdivided by the pre-assumed prognostic factors.

RESULTS

Characteristics of identified studies

Our search strategy resulted in 1652 potentially relevant articles. From title and abstract we identified 120 relevant articles. Reviewing the full text 29 publications met our selection criteria. After screening the reference lists, another two studies were included,

resulting in 31 relevant articles (Figure 1). Information regarding these 31 studies is presented in Table 3.

Four studies were retrospective and 27 were prospective. In these studies the follow-up period ranged from one day to eleven years. Patients were recruited in various settings including hospital emergency departments[9-33], primary care[29,34,35] and military health care centres[36,37].

Five studies evaluated the effect of early mobilisation instructions only[9,13,14,34,36], while in 26 studies early immobilisation instructions were combined with partial immobilisation [9,10,12,15-33,35,37,38]. In our analysis we do not differentiate between these differences in conventional treatment.

Two of the included publications did not evaluate pain, subjective instability, re-sprains, or subjective recovery[13,19] but only reported the ROM. Only one study reported on prognostic factors.[39]

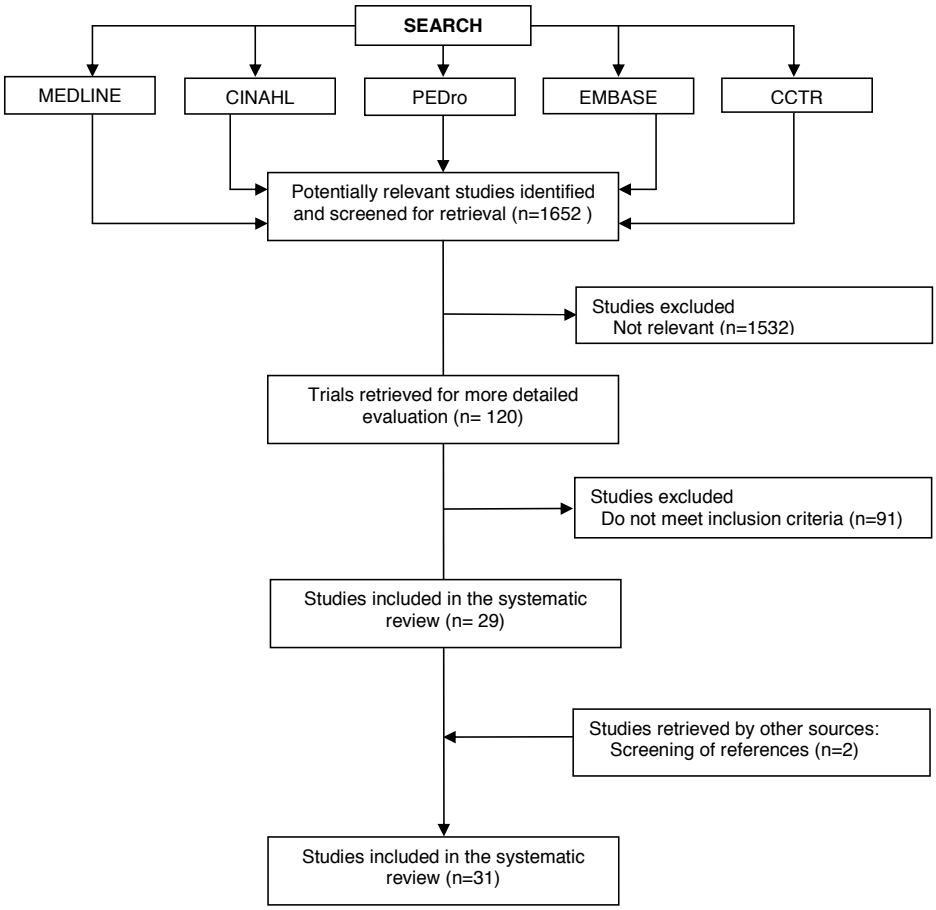

Figure 1 Flow chart of the selected studies

Table 3 Characteristics of the included studies

Study	Participants	Injury grade	Treatment	Outcomes	Results	Dropouts (n)
Allen et al., 1985[9]	n=19 ♀: 5 (26%) ♂: 14 (74%) Mean age: 31 yr Mean weight: 73.6 kg	Uncomplicated inversion injuries of the lateral ligament of the ankle joint	Rest with elevation for 24 hours, followed by gradually mobilisation	At 10 days follow-up: Pain *(severe + moderate)* ROM *(full plantar flexion to full dorsiflexion, % of uninjured ankle)*	*10 days:* Pain: 63% (24% - 91%) ROM: 72%	11
	n=20 ♀: 3 (15%) ♂: 17 (85%) Mean age: 28 yr Mean weight: 69.6kg		Rest with elevation for 24 hours, followed by gradually mobilisation and elastic bandage	At 10 days follow-up: Pain ROM *(% of uninjured ankle)*	*10 days:* Pain: 77% (46% - 95%) ROM: 75%	7
	n=18 ♀: 7 (39%) ♂: 11 (61%) Mean age: 32.5 yr Mean weight: 74.8 kg		Rest with elevation for 24 hours, followed by gradually mobilisation and taping	At 10 days follow-up: Pain ROM *(% of uninjured ankle)*	*10 days:* Pain: 58% (28% - 85%) ROM: 78%	6
Anandacooma-rasamy et al., 2005[29]	n=19 ♀: 7 (37%) ♂: 12 (63%) AL: range from elite level sportsmen and women to recreational athletes	Inversion ankle injury; no fracture with or without dislocation or with or without complete rupture	RICE and early controlled mobilization	At 29 months follow-up: Pain *(residual)* Subj. instability Re-sprain Swelling	*29 months:* Pain: 47% Subj. instability: 47% Re-sprain: 42% Swelling: 37%	0
De Bie et al., 1997[11]	n=35 ♀: 13 (37%) ♂: 22 (63%) Mean age: 28±10 yr	Lateral ankle sprain injury. Patients with fractures, severe injuries demanding operative interventions and patients with open wounds were excluded	Pressure bandage until swelling was reduced or until an ankle dorsiflexion of 90° was possible, followed by tape	At 2, 4 weeks follow-up: Pain *(spontaneous)* Re-sprain Swelling	*2 weeks:* Pain: 91% (76% - 98%) Re-sprain: 27% (13% - 46%) Swelling: 94% *4 weeks:* Pain: 87% (70% - 96%) Re-sprain: 29% (14% - 48%) Swelling: 97%	2
Boyce et al., 2005[30]	n=25 ♀: 6 (35%) ♂: 11(65%) Mean age: 35.3 yr	Moderate or severe lateral ligament sprain after an ankle inversion injury	Elastic support bandage with standardised advice of RICE	At 10 days follow-up: Pain *(0 –10 VAS)* Swelling *(circumferential measurement of ankle)*	*10 days:* Pain: 2.9 Swelling: 14.4 mm	8
	n=25 ♀: 11 (44%) ♂: 14(56%) Mean age: 32.6 yr		Aircast ankle brace with standardised advice of RICE	At 10 days follow-up: Pain *(0 –10 VAS)* Swelling *(circumferential measurement of ankle)*	*10 days:* Pain: 1.8 Swelling: 8.5 mm	7

Table 3 (continued)

Study	Participants	Injury grade	Treatment	Outcomes	Results	Dropouts (n)
Cetti et al., 1984[10]	n=65	Acute sprain of the ankle with positive stress radiograms indicating rupture of the fibular ankle ligaments	Semi-rigid ankle support (Mobile Pliton-80 bandage) during 6 weeks	At 8, 24 weeks follow-up: Re-sprain Subj. instability Swelling	*8 weeks:* Re-sprain: 3% (0% - 11%) Subj. instability: 6% (2% - 15%) Swelling: 15% *24 weeks:* Re-sprain: 9% (3% - 19%) Functional instability: 9% (3% - 19%) Swelling: 3%	0
Chaiwanichsiri et al., 2005[36]	n=17 ♂: 17 (100%) Mean age: 16.9 yr Mean weight: 60.0 kg Mean height: 170.7 cm BMI = 20.59 AL: athletes of armed forces academies preparatory school	Grade II ankle sprain	Conventional physical therapy: - Superficial heat - Ultrasound therapy - Range of motion exercise Stretching exercise Strengthening exercise	At 3 months follow-up: Re-sprain	*3 months:* Re-sprain: 12%	0
Els et al., 1996[12]	n=133 ♀: 48 (36%) ♂: 85 (64%) Mean age: 28 yr	Injury of the lateral capsule-ligamentous structures of the ankle	Lace-up ankle support for 6 weeks	At 18 months follow-up: Re-sprain	*18 months:* Re-sprain: 15%	
Green et al., 2001[13]	n=19 ♀: 7 (37%) ♂: 12 (63%) Mean age: 24.9±1.6 yr	An acute ankle sprain with sufficient severity to require assisted ambulation	RICE	At 2, 4,6 days follow-up: ROM *(pain free dorsiflexion, Pretreatment→posttreatment)*	*2 days:* ROM: 7.2° → 8.1° *4 days:* ROM: 13.0° → 15.0° *6 days:* ROM: 17.5° →16.4°	0
Gronmark et al., 1980[38]	n=30	Diagnosis of rupture of the lateral ligament	RICE and strapping for 6 weeks	At 17 months follow-up: Subjective recovery	*17 months:* Subjective recovery: 77%	0

Table 3 (continued)

Study	Participants	Injury grade	Treatment	Outcomes	Results	Dropouts (n)
Holme et al., 1999[14]	n=42 ♀: 15 (36%) ♂: 27 (64%) mean age: 27.4±4.6 yr AL: recreational athletes	Grade I (n=16), II (n=22) and III (n=4) ankle sprains	Standard treatment information regarding early ankle mobilization, including strength, mobility, balance exercises	At 12 months follow-up: Re-sprain	*12 months:* Re-sprain: 16%	4
Kerkhoffs et al., 2004[31]	n=721 age: 16 – 53 year weight: 40-160 kg	Acute lateral ankle sprain, with pain on walking and scored pain as > 30 mm on VAS (0 - 100 mm) and a clinically swollen ankle	10 days placebo and from day 4 until day 14 each patient had a Caligamed brace applied around the ankle	At 4, 7, 14 days follow-up: Pain *(0 –100 VAS)* Swelling *(volume of ankle)* ROM *(sum of dorsal- and plantar flexion)*	*4 days:* Pain: 30 Swelling: 2590 ROM: 40° *7 days:* Pain: 12.5 Swelling: 2545 ROM: 45° *14 days:* Pain: 2.5 Swelling: 2490 ROM: 52°	47
Klein et al., 1991[15]	n=27 ♀: 9 (33%) ♂: 18 (67%) median age: 22 (16-45) yr	Positive stress radiogram (talar tilt ≥ 7° and/or anterior drawer test ≥ 7mm AND difference between injured and uninjured ankle in: talar tilt ≥ 5° and/or anterior drawer test ≥ 5mm)	10 days RICE protocol and 6 weeks use of semi-rigid ankle support (Aircast leg brace)	At 15 months (median) follow-up Re-sprain Pain *(extensive load)* Subj. instability	*15 months* Re-sprain: 30% (14% - 50%) Pain: 33% (17% - 54%) Subj. instability: 33% (17%- 54%)	0
Konradsen et al., 2002[16]	n=648 ♀: 272 (42%) ♂: 376 (58%) median age:29 (16-67) yr AL: moderate ankle straining work and occasional jogging on uneven terrain.	Swelling and tenderness in the area of the lateral aspect of the ankle following an inversion mechanism injury. No fractures apart from avulsions < 5 mm at ligament insertion sites	RICE treatment and written instructions explaining mobilization exercises and early weight bearing	At 7 yr follow-up: Pain *(rest, activity)* Swelling *(occasional, constant)* Re-sprain *(3 or more)*	*7 years:* Pain: 16% Swelling: 22% Re-sprain: 19%	0

Table 3 (continued)

Study	Participants	Injury grade	Treatment	Outcomes	Results	Dropouts (n)
Korkala et al., 1987[17]	n=50	The anterior drawer sign exceeded 6 mm and the difference between injured and uninjured ≥ 3mm. The talar tilt more than 15° and the difference between injured and uninjured ≥ 10°.	Semi-elastic bandage during 1 week, additional 1-3 weeks elastic bandage. Immediately full weight-bearing	At 2 yr follow-up: Re-sprain Subj. instability	*2 years:* Re-sprain: 17% (6% - 33%) Subj. instability: 53% (25% - 53%)	14
Leanderson et al., 1995[19]	n=39	Grade II and grade III	Air-Stirrup ankle brace for 3 weeks with instructions to attempt early motion and weight bearing	At 3-5 , 2, 4, 10 wk follow-up: ROM *(max. dorsal flexion to max. plantar flexion, % of uninjured ankle)*	*3-5 days:* ROM: 65% *2 weeks:* ROM: 77% *4 weeks:* ROM: 84% *10 weeks:* ROM: 95%	15 (whole population)
	n=34		Compression bandage for 3 weeks with instructions to attempt early motion and weight bearing	At 3-5 , 2, 4, 10 wk follow-up: ROM *(max. dorsal flexion to max. plantar flexion, % of uninjured ankle)*	*3-5 days:* ROM: 58% *2 weeks:* ROM: 77% *4 weeks:* ROM: 86% *10 weeks:* ROM: 87%	

Table 3 (continued)

Study	Participants	Injury grade	Treatment	Outcomes	Results	Dropouts (n)
Leanderson et al., 1999[18]	n=39	Grade II and III	Air-Stirrup ankle brace for 3 weeks with instructions to attempt early motion and weight bearing	At 3-5 days, 2, 4, 10 wk follow-up: ROM *(active e- and inversion)* Pain *(Borg scale 0-10)*	*3-5 days (both groups)* ROM: 48° Pain: 1.3 *2 weeks (both groups)* ROM: 60° Pain: 1.6 *4 weeks (both groups)* ROM: 66° Pain: 1.1 *10 weeks (both groups)* ROM: 72° Pain: 0.3	
	n=34		Compression bandage for 3 weeks with instructions to attempt early motion and weight bearing	At 3-5 days, 2, 4, 10 wk follow-up: ROM *(active e- and inversion)* Pain *(Borg scale 0-10)*		
Linde et al., 1986[39]	n=137 ♀: 53 (39%) ♂: 84 (81%) median age: 28 yr AL: 58% athlete, 22% top athlete (training ≥ 3/week)	Lesion following an inverting injury, with swelling and pain at the lateral ankle joint. No fractures.	Foot elevated during first 24 hours, then start doing motion exercise and weight bearing according to ability. No fixation of the ankle	At 1 year follow-up: Pain Re-sprain Subj. instability	*1 year:* Pain: 14% Re-sprain: 4% Subj. instability: 7%	0
Mazieres et al., 2005[34]	n=82 ♀: 35 (43%) ♂: 47 (57%) mean age: 34.4 yr BMI: 24.7	Symptomatic lateral ankle sprain with spontaneous pain ≥ 50 mm on a 0-100 VAS, benign nature (grade I or II).	A placebo Topical Delivery System (TDS) patch every day for 2 wk	At 3-4, 7, 14 days follow-up: Pain *(0-100 VAS)* Swelling *(circumference of the ankle, injured vs. uninjured)*	*3-4 days* Pain: 40 mm Swelling: 4.0% *7 days* Pain: 28 mm Swelling: 3.5% *14 days* Pain: 20 mm Swelling: 2.2%	0
Moller-Larsen et al., 1988[20]	n=65 median age: 23 yr	Acute ankle sprain. Rupture of ATFL, isolated or combined with rupture of the CFL.	Rest with leg elevated for 5 days. Then tape bandage for 4 wk, weight bearing was allowed.	At 1 year follow-up: Subj. instability Swelling *(during activity)* Subjective recovery	*1 year:* Subjective instability: 14% Swelling: 14% Subjective recovery: 82%	0

Table 3 (continued)

Study	Participants	Injury grade	Treatment	Outcomes	Results	Dropouts (n)
Munk et al., 1995[21]	n=16 ♀: 5 (31%) ♂: 11 (69%) mean age: 25	Hematoma and tenderness in the AFTL and/or CFL and severe pain inhibiting walking. No fractures	Elastic bandage until absence of pain and then early mobilization	At 11 years follow-up: Subj. instability ROM *(dorsiflexion)* ROM *(plantar flexion)*	*11 years:* Subj. instability: 6% ROM (dorsiflexion): 12° ROM (plantar flexion): 39°	0
Nilsson, 1983[22]	n=29 AL: No top athletes	No rupture (arthrographically verified)	Elastic wrapping, 1day rest followed by weight bearing as much as pain would allow	At 1,7 d and 4, 36 mth follow-up: Pain *(constant, when walking)* At 1, 7 days follow-up: Swelling *(volume)* At 4 and 36 months follow-up: Re-sprain Subj. instability Subjective recovery	*1 day:* Pain: 100% (88% - 100%) Swelling: 45 ml *7 days:* Pain: 45% (26% - 64%) Swelling: 30 ml *4 months:* Pain: 21% (8% - 40%) Re-sprain: 7% (1% - 23%) Subj. instability: 24% (10% - 44%) Free from residual symptoms: 76% *36 months:* Pain: 12% (3% - 31%) Re-sprain: 16% (5% - 36%) Subj. instability: 20% (7% - 41%) Subjective recovery: 56%	4 (at 36 months)
	n=30 AL: No top athletes	Arthrographically verified ruptures	Elastic wrapping, 1day rest followed by weight bearing as much as pain would allow	At 1,7 d and 4, 36 mth follow-up: Pain *(constant, when walking)* At 1, 7 days follow-up: Swelling *(volume)*	*1 day:* Pain: 100% (88% - 100%) Swelling: 113 ml *7 days:* Pain: 83% Swelling: 75 ml	4 (at 36 months)

Table 3 (continued)

Study	Participants	Injury grade	Treatment	Outcomes	Results	Dropouts (n)
				At 4 and 36 months follow-up: Re-sprain Subjective instability Subjective recovery	*4 months:* Pain: 43% (25% - 63%) Re-sprain: 10% (2% - 27%) Subj. instability: 17% (6% - 35%) Subjective recovery: 47% *36 months:* Pain: 19% (7% - 39%) Re-sprain: 19% (7% - 39%) Subj. instability: 15% (4% - 35%) Subjective recovery: 58%	
	n=21 AL: No top athletes	No rupture (arthrographically verified)	Cold pack was applied for 45 minutes and afterwards replaced by a 2 cm thick foam rubber pad. Compression effect was secured by elastic wrapping	At 1,7 d and 4, 36 mth follow-up: Pain *(constant, when walking)* At 1, 7 days follow-up: Swelling *(volume)* At 4 and 36 months follow-up: Re-sprain Subjective instability Subjective recovery	*1 day:* Pain: 95% Swelling: 53 ml *7 days:* Pain: 48% Swelling: 23 ml *4 months:* *Pain: 24%* Re-sprain: 9.5% Subjective instability: 19% Subjective recovery: 71% *36 months:* Pain: 5% Re-sprain: 20% Subj. instability: 15% Subjective recovery: 75%	1 (at 36 months)

Table 3 (continued)

Study	Participants	Injury grade	Treatment	Outcomes	Results	Dropouts (n)
	n=38 AL: No top athletes	Arthrographically verified ruptures	Cold pack was applied for 45 minutes and afterwards replaced by a 2cm thick foam rubber pad. Compression effect was secured by elastic wrapping	At 1,7 d and 4, 36 mth follow-up: Pain *(constant, when walking)* At 1, 7 days follow-up: Swelling *(volume)* At 4 and 36 months follow-up: Re-sprain Subjective instability Subjective recovery	*1 day:* Pain: 100% Swelling: 78 ml *7 days:* Pain: 55% Swelling: 40 ml *4 months:* Pain: 34% Re-sprain: 11% Subjective instability: 26% Subjective recovery: 55% *36 months:* Pain: 12% Re-sprain: 15% Subj. instability: 6% Subjective recovery: 85%	5 (at 36 months)
O'Hara et al., 1992[35]	n=118	Acute ankle injury unassociated with bony injury or major ligamentous damage	Malleotrain ankle support	At 2 weeks follow-up: Pain at rest Pain at night Pain at activity Subjective recovery	*2 weeks:* Pain at rest: 7.5% Pain at night: 8% Pain at activity: 14% Subjective recovery: 56%	0
	n=102		Advice on resting the affected joint and a simple support (Tubigrip)	At 2 weeks follow-up: Pain at rest Pain at night Pain at activity Subjective recovery	*2 weeks:* Pain at rest: 16% Pain at night: 14% Pain at activity: 21% Subjective recovery: 36%	
Pijnenburg et al., 2003[32]	n=189	Painful ankle caused by an indirect supination injury	Functional treatment: wearing a non weight bearing cast for 5 days followed by elastic bandaging or taping for six weeks.	At 8 yr (median) follow-up: Pain *(residual)* Swelling Subj. instability Re-sprain	*8 years* Pain: 25% Swelling: 14% Subj. instability: 32% Re-sprain: 34%	31

Table 3 (continued)

Study	Participants	Injury grade	Treatment	Outcomes	Results	Dropouts (n)
Povacz et al., 1998[23]	n=88	Acute injury of the collateral ligaments of the ankle. Arthrographically verified rupture with a talar tilt ≥ 5°	3-7 days elastic wrapping, ice and elevation. Followed by 6 weeks ankle brace and weight bearing as tolerated and exercise instructions (ROM, proprioceptive, isometric)	At 27 (24-31) mth follow-up: Pain *(severe, mild)* Subj. instability Re-sprain Swelling	*27 months:* Pain: 23% (14% - 35%) Subj. instability: 15% (8% - 25%) Re-sprain: 25% (15% - 36%) Swelling: 8%	15
Pugia et al., 2001[37]	n=29 ♀: 9 (31%) ♂: 20 (69%) mean age: 30.88 ±11.37	Acute lateral ankle sprain with tenderness and swelling over the lateral ankle ligaments	RICE	At baseline: Swelling *(figure of eight measurement, injured vs. uninjured)*	*Baseline:* Swelling: 1.77 cm	
Schaap et al., 1989[24]	n=617	Grade I; no demonstrable sign of instability	Compression with bandages	At 9 months follow-up: Pain Subj. instability Swelling	*9 months:* Pain: 28% Subj. instability: 32% Swelling: 26%	126
	n=319	Grade II; mild or incomplete instability present	Partial immobilization by means of tape	At 9 months follow-up: Pain Subj. instability Swelling	*9 months:* Pain: 27% Subj. instability: 28% Swelling: 30%	56
Sommer et al., 1987[25]	n=40 ♀: 8 (20%) ♂: 32 (80%) mean age: 28.6 ±7.6	Arthrographically verified rupture: talar tilt ≥100° and leakage of contrast fluid	2 weeks elastic strapping followed by 4-6 weeks tape, weight bearing as tolerated	At 6 wks and 3-8 mth follow-up: Pain	*6 weeks:* Pain: 0% *3-8 months:* Pain: 0%	5
Sommer et al., 1989[26]	n=40 ♀: 8 (20%) ♂: 32 (80%) mean age: 26.1 ±7.3 AL: No competitive sportsmen	Arthrographically verified rupture: talar tilt ≥100° and leakage of contrast fluid	2 weeks elastic strapping followed by a bandage for a further 6 weeks. Weight bearing as tolerated.	At 6 wks and 1 yr follow-up: ROM Subj. instability	*6 weeks:* ROM: full movement Subj. instability: 0% *1 year:* ROM: full movement Subj. instability: 0%	13

Table 3 (continued)

Study	Participants	Injury grade	Treatment	Outcomes	Results	Dropouts (n)
Sommer et al., 1993[27]	n=40 ♀: 13 (33%) ♂: 27 (67%) mean age: 24.9 ±8.6	Arthrographically verified rupture: talar tilt ≥100º and leakage of contrast fluid	Immediate mobilization and weight bearing as tolerated, 6 weeks semi-rigid ankle support	At 6 months follow-up Re-sprain Pain Subj.instability	*6 months* Re-sprain: 3% (0% - 14%) Pain: n=0 Subj. instability: 3% (0% - 14%)	3
	n=40 ♀: 15 (38%) ♂: 25 (62%) mean age: 24.5 ±5.5		Immediate mobilization and weight bearing as tolerated, 2 weeks bandage, 4 weeks tape	At 6 months follow-up Re-sprain Pain Subj. instability	*6 months* Re-sprain: 6% (1% - 20%) Pain: n=0 Subj. instability: 9% (2% - 24%)	7
Wester et al., 1996[28]	n=24 AL: All active in sports for at least 2hr a week	Grade II, without positive anterior drawer sign or talar tilt	2 days elevation and immobilization, 1 week compression bandage, mobilisation based on pain sensations	At 1, 6, 12 weeks follow-up: Pain at sports Pain at rest Pain at walking Swelling *(volume, injured vs. uninjured)* At 230 days follow-up: Re-sprain Subj. instability	*1 week* Pain at sports: 96% (79% - 100%) Pain at rest: 29% Pain at walking: 83% Swelling: 65 ml *6 weeks* Pain at sports: 75% (53% - 90%) Pain at rest: 0% Pain at walking: 21% Swelling: 22 ml *12 weeks* Pain at sports: 29% (13% - 51%) Pain at rest: 4% Pain at walking: 4% Swelling: 10 ml *230 days* Re-sprain: 54% (33% - 74%) Subj. instability: 25% (10% - 47%)	

Table 3 (continued)

Study	Participants	Injury grade	Treatment	Outcomes	Results	Dropouts (n)
Zammit et al., 2005[33]	n=12	Grade I and II injuries	Ice and Tubigrip for 2 weeks and exercises depending on response of the patient	At 1, 8, 15, 22 days follow-up: Pain *(VAS 0 – 10)* Swelling *(figure of eight measurement)* ROM *(dorsiflexion and plantarflexion)*	*1 day* Pain: 4.9 Swelling: 54.8 cm ROM (dorsiflexion): 2.1° ROM (plantarflexion): 41° *8 days* Pain: 2.9 Swelling: 54.5 cm ROM (dorsiflexion): 6.5° ROM (plantarflexion): 45° *15 days* Pain: 1.6 Swelling: 54 cm ROM (dorsiflexion): 8.1° ROM (plantarflexion): 48° *22 days* Pain: 0.7 Swelling: 53.7 cm ROM (dorsiflexion): 7.6 ROM (plantarflexion): 51°	3

ROM = range of motion; AL = activity level; RICE = rest, ice, compression, elevation; VAS = visual analogue scale; BMI = body mass index; ATFL = Anterior talofibular ligament ; CFL = calcaneofibular ligament.

Quality assessment

Table 4 presents the results of the methodological quality assessment of the included studies. Of the 31 studies, 24 are deemed to be of high quality (i.e. having a score of at least five or eight). The following concerns, however, are noteworthy:

- In 23% (7 out of 31) of the studies there was a loss to follow-up of 20% or more of the initial study population.
- In 68% (21 out of 31) of the studies a comparison of completers versus non-completers at follow-up was missing.

The initial agreement of the two reviewers on the total quality assessment of the included trials was 87% (189 of 217 items) and the Kappa value was 0.65, which is considered as a fair agreement. All initial disagreements were solved in a consensus meeting.

Pain

Eighteen studies measured pain. Fourteen studies[9, 11, 15, 16, 22-25, 27-29, 32, 35, 39] presented pain as the percentage of patients who still experience pain, and four studies[30, 31, 33, 34] presented pain by means of the VAS score. Thirteen studies are of high quality and four of low quality. Figure 2 shows data on eight high quality studies[9, 11, 15, 22, 23, 25, 27, 35] with a follow-up period of three years or less. Five high quality studies[11, 22, 25, 31, 34] and two low quality studies[28, 33] had more than one follow-up moment. In these studies the number of patients who still experience pain decreased rapidly within the first two weeks after injury. This

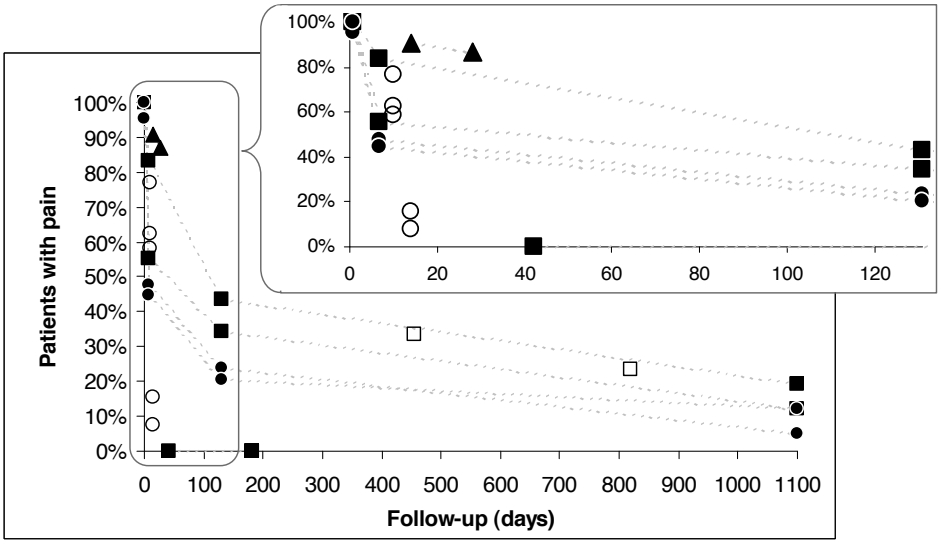

Figure 2 Percentage of patients in high quality studies who still experienced pain at follow-up. Eight studies (fifteen treatment groups) with a follow-up ≤ 3 years are presented. Severity of sprains in studies with one follow-up moment: □ rupture, ○ no rupture, △ mixed or unknown. Severity of sprains in studies with more than one follow-up moment: ■ rupture, ● no rupture, ▲ mixed or unknown

Table 4 Quality scores of the included studies

Authors	1	2	3	4	5	6	7	score	quality
Allen, et al.[9]	–	+	+	+	+	+	+	6	High
Anandacoomarasamy, et al.[29]	+	–	+	–	+	–	+	4	Low
De Bie, et al.[11]	+	+	+	+	+	+	+	7	High
Boyce, et al.[30]	+	+	+	+	–	+	+	6	High
Cetti, et al.[10]	+	+	+	+	+	–	+	6	High
Chaiwanichsiri, et al.[36]	+	–	+	+	+	–	+	5	High
Els, Niggli, et al..[12]	+	–	–	+	–	–	+	3	Low
Green, et al.[13]	+	+	+	+	+	+	+	7	High
Grønmark, et al.[38]	–	–	+	+	+	–	+	4	Low
Holme, et al.[14]	+	+	+	+	+	+	+	7	High
Kerkhoffs, et al.[31]	–	+	+	+	+	–	+	5	High
Klein, et al.[15]	–	+	+	+	+	–	+	5	High
Konradsen, et al.[16]	+	+	+	–	+	–	+	5	High
Korkala, et al.[17]	–	–	+	+	–	–	+	3	Low
Leanderson, et al.[19]	+	+	+	+	–	–	+	5	High
Leanderson, et al.[18]	+	+	+	+	–	–	+	5	High
Linde, et al.[39]	–	+	–	+	+	–	+	4*	Low*
Mazières, et al.[34]	+	+	+	+	+	+	+	7	High
Moller-Larsen, et al.[20]	+	+	+	+	+	–	+	6	High
Munk, et al.[21]	+	+	+	+	–	–	+	5	High
Nilsson[22]	+	+	+	+	+	+	+	7	High
O'Hara, et al.[35]	+	+	+	+	+	–	+	6	High
Pijnenburg, et al.[32]	+	+	+	+	+	+	+	6	High
Povacz, et al.[23]	+	+	+	+	+	+	+	6	High
Pugia, et al.[37]	+	+	–	+	+	–	+	5	High
Schaap, et al.[24]	–	–	–	–	+	+	+	3	Low
Sommer, et al.[26]	+	+	+	+	–	–	+	5	High
Sommer, et al.[25]	+	+	+	+	+	–	+	6	High
Sommer, et al.[27]	+	–	–	+	+	+	+	5	High
Wester, et al.[28]	–	+	+	+	–	–	+	4	Low
Zammit, et al.[33]	+	+	+	+	–	–	+	5	High

+ indicates the criterion was clearly satisfied; - indicates that the criterion was not satisfied or it was not clear if it was satisfied. * adding the criteria for prognostic factors, the quality score was six (low).

decrease continued after this first phase, although more slowly. Corresponding to this course are the results of the studies with one follow-up moment. Conversely, in six studies[15,16,22,23,32,39] the proportion of patients who reported to experience pain after a follow-up period of one year or longer still ranged from 5% to 33%. Even after three years follow-up 5% to 25% of patients still experienced pain.[16,22,32]

Re-sprains

Re-sprain was measured in fifteen studies.[10-12, 14-17, 22, 23, 27-29, 32, 36, 39] Of these, ten are of high quality and five of low quality. Figure 3 shows eight high quality studies[10, 11, 14, 15, 22, 23, 27, 36] with a follow-up period of three years or less. Re-sprains were registered within periods ranging from two weeks to 96 months after the injury. The occurrence of a re-sprain ranges from 3% to 34% of the patients. Only Wester et al.[28] and Anandacoomarasamy et al.[29] (both low quality studies) reported in, respectively, 54% and 42% of the patients a re-sprain, after 230 and 882 days follow-up.

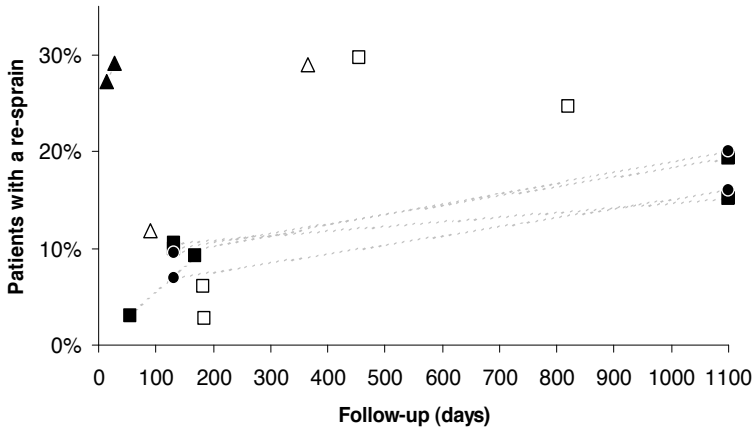

Figure 3 Percentage of patients in high quality studies who reported at least one re-sprain at follow-up. Eight studies (twelve treatment groups) with a follow-up ≤ 3 years are presented. Severity of sprains in studies with one follow-up moment: □ rupture, ○ no rupture, △ mixed or unknown. Severity of sprains in studies with more than one follow-up moment: ■ rupture, ● no rupture, ▲ mixed or unknown

Subjective instability

Fourteen studies assessed the occurrence of subjective instability[10, 15, 17, 20-24, 26-29, 32, 39]. Of these, nine are of high quality and five of low quality. Figure 4 shows data on seven high quality studies[10, 15, 20, 22, 23, 26, 27] with a follow-up period of three years or less. There is a large variation in the reported occurrence of subjective instability ranging from 0% to 33% in the high quality studies, and from 7% to 53% in the low quality studies. Nilsson[22] reported a decrease in subjective instability at 36.2 months compared to 4.3 months after injury in patients with arthrographically verified ruptures as well as in patients without a rupture. In contrast, Cetti et al.[10] reported an increase, from 6% to 9%, in subjective instability after 24 weeks compared to eight weeks after spraining an ankle. In general, the occurrence of subjective instability in patients seems higher in studies of low methodological quality[17, 24, 28, 29, 39] (Table 3).

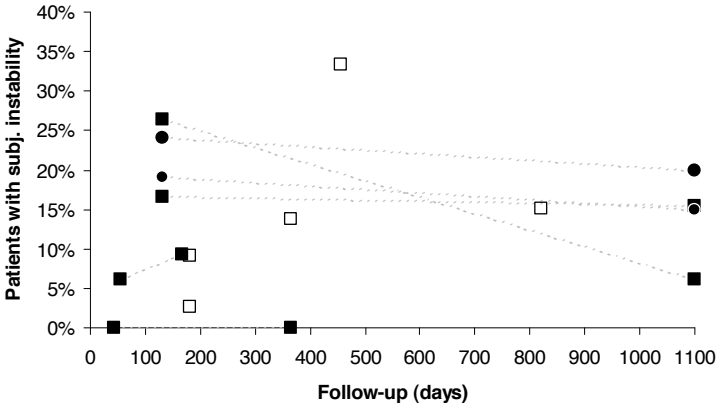

Figure 4 Percentage of patients in high quality studies who reported instability at follow-up.
Seven studies (eleven treatment groups) with a follow-up ≤ 3 years are presented. Severity of sprains in studies with one follow-up moment: □ rupture, ○ no rupture, △ mixed or unknown. Severity of sprains in studies with more than one follow-up moment: ■ rupture, ● no rupture, ▲ mixed or unknown

Subjective recovery

Three high quality studies presented the patients' judgement of full recovery as being restored to pre-injury state[20], completely free from symptoms[22], and cured on a six-point scale of improvement[35]. Besides, one low quality study[38] reported full recovery as being free from symptoms. One study[22] had more than one follow-up moment; in three out of four groups that were examined, the percentage of patients who reported full recovery was increased after 36 months compared to four months. Ranging from two weeks to 36.2 months follow-up, 36% to 85% of all patients reported full recovery (Figure 5).

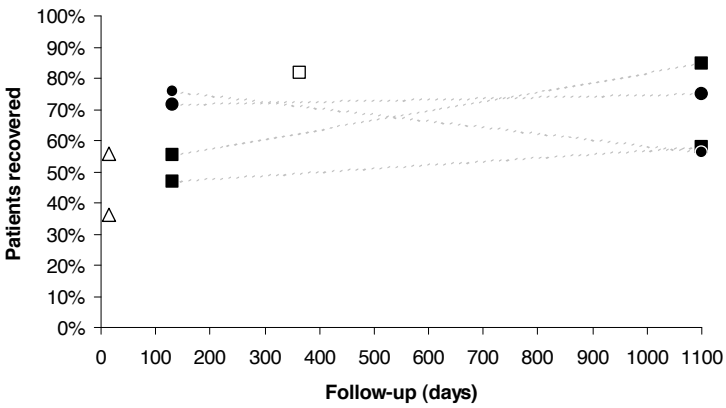

Figure 5 Percentage of patients in high quality studies who reported full recovery at follow-up.
Three studies (seven treatment groups) with a follow-up ≤ 3 years are presented. Severity of sprains in studies with one follow-up moment: □ rupture, ○ no rupture, △ mixed or unknown. Severity of sprains in studies with more than one follow-up moment: ■ rupture, ● no rupture, ▲ mixed or unknown

Prognostic factors

One study[39] evaluated prognostic factors for incomplete recovery and re-sprains. Sports activity at a high level (training ≥ 3 times a week) was a significant prognostic factor for residual symptoms compared to sports activity at a low level (training < 3 times a week) and no sports activity. However, only percentages and p-values were reported. Further, men had an increased risk of residual symptoms compared to women for which we calculated an OR of 4.78 (95% CI 1.36 – 16.61), but this difference may be due to the fact that the percentage of athletes among men was greater than among women.

We assessed prognostic factors indirectly according to study population characteristics. The only possible prognostic factor which was frequently described as a study population characteristic in the included studies was injury grade. When we plotted the outcome of high quality studies according to this characteristic we saw no clear difference in recovery rates or re-sprains.

DISCUSSION

This review summarizes the results on the course of pain, re-sprain, subjective instability and subjective recovery in patients with an acute lateral ankle sprain. Within two weeks, a rapid improvement of pain experience was seen in the majority of patients with acute ankle sprains. Further improvement occurred after these two weeks, although more slowly. Re-sprains occurred within periods ranging from two weeks to 96 months after the initial injury and ranges from 3% to 34% of the patients. The occurrence of subjective instability ranged from 0% to 33% in the high quality studies and from 7% to 53% in the low quality studies. Full recovery was reported by 36% to 85% of the patients at two weeks to 36.2 months follow-up. These results seem to be independent of the severity of the initial sprain. After three years follow-up some patients still report residual symptoms (pain, subjective instability) and thus no total recovery. Only one study reports on prognostic factors[39]; the authors found that sports activity at a high level compared to sports activity at a low level and no sports activity is a risk factor for residual symptoms. Furthermore, men had an increased risk of residual symptoms compared to women. Although the authors attributed this latter association to the fact that the percentage of athletes among men was greater than among women, the real association is not clear without multivariable analyses.

The methodological quality according to our criteria appeared to be high for most of the studies. The most prevalent methodological shortcoming was no available information on completers versus non-completers. A potential limitation of the present review might be the literature search in that our search was limited to indexed journals. Therefore, unpublished studies and studies in non-indexed journals have been missed.

However, this is the first time that the course of conventionally treated ankle sprains in adults has been described. Surprisingly, information about potential prognostic factors is rare; future studies on this topic are warranted.

As shown in the included studies, conventional treatment is performed in various ways. Conventional treatment is often combined with partial immobilisation, which can be offered by a broad spectrum of devices. In a systematic review, Kerkhoffs et al.[5,40] compared the effectiveness of different partial immobilising devices (semi-rigid ankle support, lace-up ankle support, tape, or elastic bandage) in the treatment for acute lateral ankle ruptures. Their results show, within six weeks follow-up, that there might be some difference in persistency of swelling, time to return to work and sport, and subjective instability when using different external supports.

Although the conventional treatments in the included studies are performed in various ways, the small differences, as found by Kerkhoffs et al.[5,40], might explain the large heterogeneity of the outcomes in this review. However, more obvious for the heterogeneity of the results is the difference in how the outcomes are measured and the differences between the study population in the included studies. Linde et al.[39] concluded that athletes had an increased risk of residual symptoms and that residual symptoms occurred in 32% of top athletes after one year. Because of this it would have been informative to classify the included studies according to the activity level of their included patient groups; the activity level might have explained some of the heterogeneity of the outcomes of the studies. However, only eight of the included studies provide some information about the activity level of their study population, and this was insufficient to classify the studies in a reasonable way. Besides, the studies did not report enough data to investigate the influence of age, gender, body weight and BMI on the occurrence of pain, re-sprains, subjective instability and subjective recovery.

As mentioned before, after three years follow-up some patients still have residual symptoms. The factors contributing to persistent complaints are largely unknown. For the time being, injury grade (rupture or no rupture) does not seem to be a strong predictor for the course of lateral ankle sprains. Figures 2-5 show that there are no differences towards the outcome measures. Furthermore, only Linde et al.[39] evaluated prognostic factors for residual symptoms. Therefore, more research is needed to evaluate prognostic factors for poor recovery and occurrence of re-sprains. This will allow determining which population is at risk for non recovery or for re-sprains. Such a high risk population might especially benefit from a specific treatment added to conventional treatment.

In conclusion, this review presents the clinical course of pain, objective and subjective instability and subjective recovery of adult patients with conventionally treated ankle sprains. During the first two weeks there is a rapid decrease in pain, after which it continues to improve more slowly. After three years follow-up some patients still have residual symptoms of their initial sprain. There is a wide variation in reported subjective

instability, re-sprains and subjective recovery between the different studies. A risk factor for residual symptoms might be sports activity at a high level, but more studies evaluating prognostic factors in patients with acute ankle sprains are needed.

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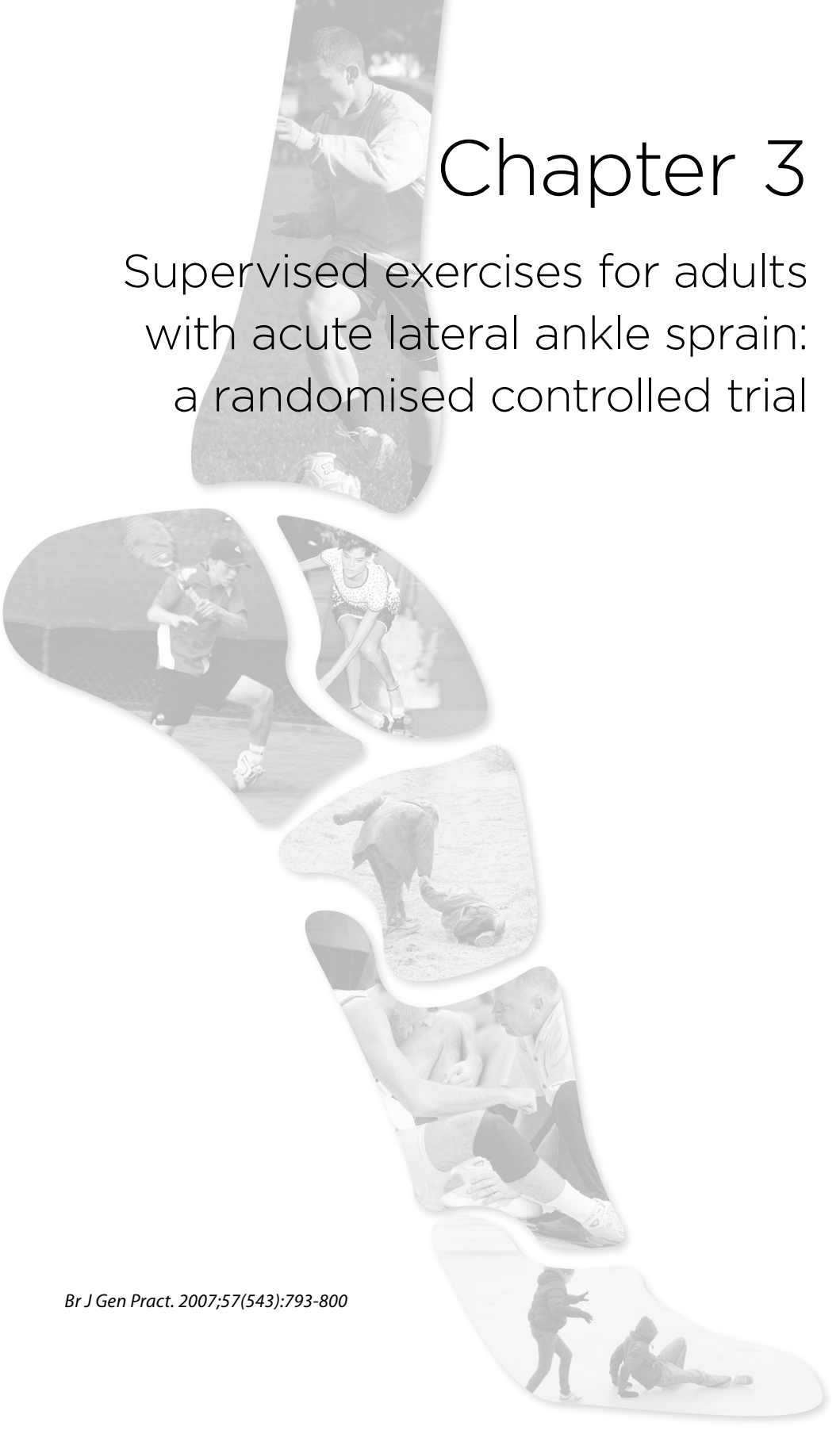

Chapter 3

Supervised exercises for adults with acute lateral ankle sprain: a randomised controlled trial

Br J Gen Pract. 2007;57(543):793-800

ABSTRACT

During the recovery period after acute ankle sprain, it is unclear whether conventional treatment should be supported by supervised exercises. Therefore we evaluate the short- and long-term effectiveness of conventional treatment combined with supervised exercises compared with conventional treatment alone in patients with an acute ankle sprain.

Adults with an acute lateral ankle sprain consulting general practices or the hospital emergency department were randomised to either conventional treatment combined with supervised exercises or conventional treatment alone. Primary outcomes were subjective recovery (0–10 point scale) and the occurrence of a re-sprain. Measurements were carried out at intake, four weeks, eight weeks, three months, and one year after injury. Data were analysed using intention-to-treat analyses.

A total of 102 patients were enrolled and randomised to either conventional treatment alone or conventional treatment combined with supervised exercise. There was no significant difference between treatment groups concerning subjective recovery or occurrence of re-sprains after three months and one year of follow-up.

In conclusion, conventional treatment combined with supervised exercises compared to conventional treatment alone during the first year after an acute lateral ankle sprain does not lead to differences in the occurrence of re-sprains or in subjective recovery.

INTRODUCTION

Ankle sprains are one of the most common musculoskeletal injuries. In the Netherlands an estimated 600,000 people sustain ankle injuries each year. Roughly half of these people visit general practitioners or, on their own initiative, emergency departments.[1] In Dutch general practice there is an incidence of 12.8 per 1,000 patients per year. Experimental studies of ligamentous healing indicate that gradually increasing and functional load exercises stimulate healing and increase the strength of ligaments after injury.[2-4] While injury to the ligaments may result in decreased mechanical stability of the ankle, neuromuscular deficits are also likely to occur due to injury to the nervous and musculo-tendinous tissue.[5-7] This may also result in an unstable ankle, which can lead to re-injuries and a feeling of "giving way". Balance training as part of rehabilitation may restrict the occurrence of functional instability and improve postural control after ankle sprains.[8-10]

Several reviews indicate that conventional treatment (early mobilisation, including mobilisation instructions and early weight bearing combined with or without the use of an external support) is the preferred treatment strategy.[11-16] External support used is tape, bandage or a brace, but never a plaster cast. At present, this conventional treatment is known as usual care. Systematic reviews of Ogilvie-Harris and Gilbart[14], and Kerkhoffs et al.[11] report that there is no existing evidence for effectiveness of physiotherapy as a treatment strategy for acute ankle sprains. Even more precise is the conclusion of a systematic review by van Os et al.[17], which reports that there is limited evidence from randomised controlled trials that conventional treatment combined with supervised rehabilitation training may be superior to conventional treatment alone as a treatment for acute injuries of the lateral ligament complex of the ankle. It is unclear whether conventional treatment should be supplemented with supervised functional exercises to decrease the feeling of 'giving away' and more importantly to decrease re- sprains in the long-term. All three systematic reviews advice to conduct a randomised controlled trial on this topic.[11,14,17] Therefore, the present prospective randomised study compared the short- and long-term effect of conventional treatment alone with those of conventional treatment combined with supervised functional exercises in the treatment of an acute ankle sprain in adults.

METHOD

Patients

Patients who had an acute injury of the lateral collateral ligaments of the ankle and who presented themselves to one of the 32 participating general practitioners or at the

emergency department of the local hospital in the same district between March 2002 and December 2003 were asked for informed consent to participate in the trial. Patients with a lateral ankle sprain were eligible for the study if they were aged between 18 and 60 years and their first visit to the physician was within one week of injury. Patients were excluded if they had a history of an injury of the same ankle during the previous two years or when they had a fracture of the same ankle.

Study design

The GP or physician working in an accident and emergency department carried out a standardised clinical examination. Occurrence of swelling, haematoma, location of the sprain, and anterior drawer sign were reported. In addition, the physician estimated the severity of the injury. Categorising severity was based on clinical findings (stability, intensity and location of swelling, pain, and haemorrhage),and graded according to three levels: grade I mild, grade II moderate and grade III severe.[18,19] If considered necessary based on the Ottawa ankle rules[20], radiological examination was performed to confirm the absence of bone injury.

After informed consent and after acquiring baseline information (questionnaire and clinical findings), each patient was randomised by a blinded and independent research assistant, making use of sealed envelopes which contained computer-generated randomisation cards, into either the conventional treatment group or the physical therapy group. Randomisation was stratified for setting (general practice vs. emergency department) and severity of the injury (grade I and grade II vs. grade III) with a block size of six.

Treatment

All participants in both groups received the same conventional treatment from their physician who was not aware of whether the patient undertook additional supervised exercises. Conventional treatment incorporated information about early ankle mobilisation, including advice for home exercises (for which patients received written instructions) and early weight bearing. Participants were encouraged to start these activities as early as possible, and to increase their activity level gradually. In general practice the ankle was protected by a tape or bandage if considered necessary by the physician, and in the emergency department with a brace (Active Ankle® - trainer, Louisville, USA).

Patients in the physical therapy group participated in an individual and progressive training program supervised by a physiotherapist, using a standardised protocol (see Appendix), which was based on the guideline of the Royal Dutch Society of Physiotherapists.[21] This programme existed of a maximum of nine half hour sessions, within a period of three months, and included balance exercises, walking, running and jumping.

Outcome assessment

The primary outcome measures were subjective recovery and occurrence of re-sprains at three months and one year follow-up. Secondary outcome measures were patients' appreciation of the received treatment, tested and reported instability and range of motion (ROM) of the ankle joint at three months' follow-up and reported instability at one year follow-up.

Questionnaires were administered at baseline at four weeks, eight weeks, three months and at one year after injury. Information was asked about: subjective recovery on a 0 – 10 point scale (0 represents no recovery and 10 full recovery); re-sprain; the patient's appreciation of the received treatment (no, partial, or full appreciation) and reported instability. Treatment preference before randomisation (physical therapy, physician, or no preference at all) was measured at baseline only.

Three months after injury a blinded assessor performed a standardised clinical examination. The un-injured ankle was tested first, during all tests and in all patients. All tests were performed barefooted. This examination included two functional stability tests (a modification of Romberg's test,[8] and the one-leg hop test[8, 22]), and an active ROM test of the ankle.[22]

Tested instability was assessed by patients standing on one leg for a maximum of one minute with eyes open, and standing on one leg for a maximum of 30-seconds with eyes closed. Balance time (the time patients could stand on one leg) was noted and patients were asked if they experienced the same feeling of stability in both legs. If not, they were asked to indicate which leg felt less stable.[8]

A one-leg hop test (forward jumping and landing on the same foot five times with each leg) was performed to assess functional stability. Patients were asked if they experienced the same feeling of stability in both legs; if not, they were asked to indicate which leg they judged as less stable.

For the active ROM test an electronic digital inclinometer was used (Cybex EDI 320, New York, USA). Sitting with the knees in 0 degrees and the ankle in maximal plantar flexion, participants performed a maximal dorsal flexion in the ankle. Differences between the sprained and not-sprained ankle scores were calculated.

Sample size

The study initially aimed at enrolling 158 patients during an inclusion period of one year, divided over two treatment groups of 79 persons each. This sample size was calculated to detect a 20% difference (a suspected decrease from 45% to 25%) between both groups in the occurrence of re-sprains after three months' follow-up, with a power of 80% (1-β) and a one-tailed level of significance (α) of 5%.

The 20% difference was based on a study by Wester et al.[23] which reported a difference of 29% in occurrence of re-sprains between a training group and no training group after

a mean follow-up of 230 days (standard deviation [SD] 62.9). Their population seemed comparable to the population in the current study. All patients with an acute lateral ankle sprain were recruited from the local casualty department, were given the usual conventional treatment and randomised into either a training group or a no- training group.

Statistical analysis

Data were analysed with researchers being unaware of participants' group assignment, using both an intention-to-treat analysis and a per-protocol analysis (that is, analysis based only on patients who complete the entire treatment protocol). For patients with incomplete datasets or who were lost to follow-up, the last available data were carried forward.

Patients' appreciation of the received treatment was dichotomised (full appreciation versus no or partial appreciation). Multivariable logistic regression was used to analyse relationships between dichotomous outcomes (re-sprain, appreciation of the received treatment and dichotomised recovery) and treatment (conventional treatment alone or combined with supervised exercises). Multivariable logistic regression produced odds ratios (OR) as outcome dimensions; therefore, results are presented as ORs with a 95% confidence interval (CIs). Risk differences with CIs were also added, as these are easier to interpret. Multivariable linear regression was used to analyse relationships between continuous outcome measures (subjective recovery and ROM) and treatment.

Potential confounders were age, sex, body mass index, injury grade, treatment received as preferred, ankle load during work and ankle load during leisure time at baseline. Variables that affected the univariate relationship (more than 10% change of the slope or β) were entered the multivariate model. Data are presented at a two-tailed level of significance (α) of 5%.

RESULTS

A total of 107 patients were randomised during the inclusion period. Five of these patients (three from the physical therapy group, two from the conventional treatment group) were randomised too early. Although they reported to have sent the baseline questionnaire at the time they were randomised, researchers never received it; therefore, these five patients could not be included in our analyses. During the trial another five patients (four from the physical therapy group, one from the conventional treatment group) were lost to follow-up, but their last available data were carried forward in the analyses, Figure 1.

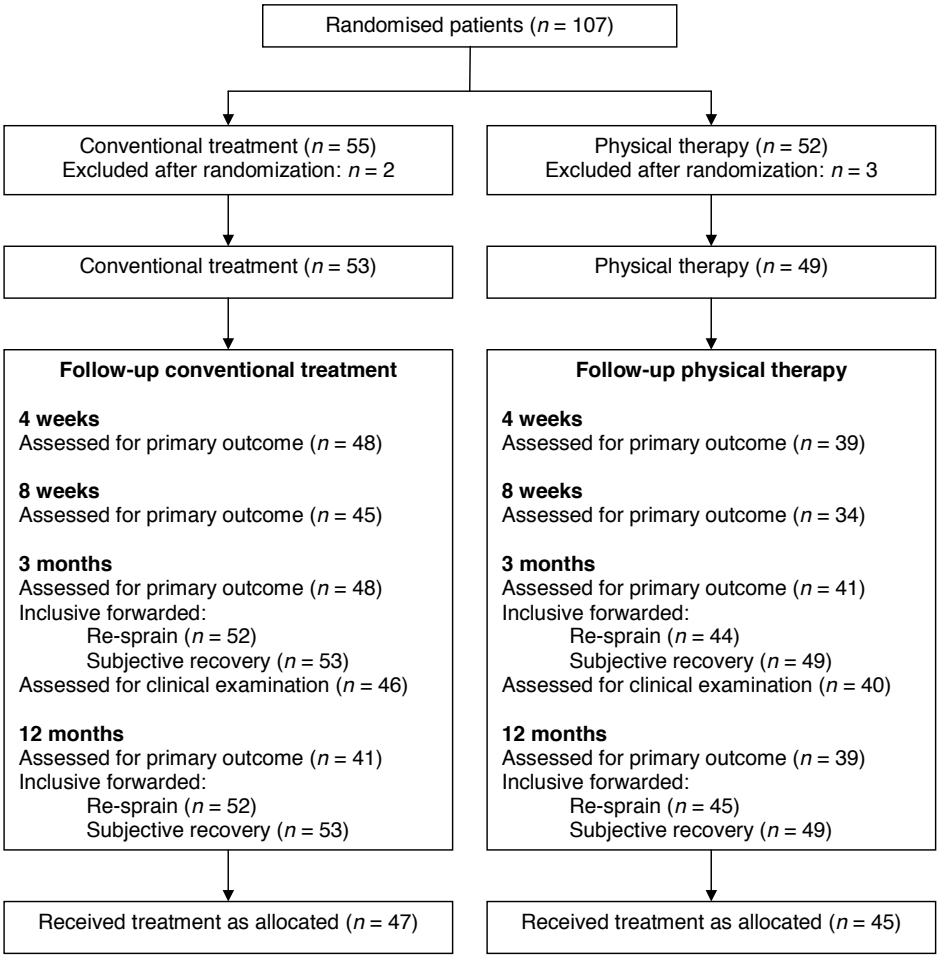

Figure 1 Flow of participants through the trial

Patients in the physical therapy group received a mean of 6.1 (SD=3.0) treatment sessions (median = 7). As some participants did not receive the treatment as initially allocated or crossed over and visited a physiotherapist during the trial, the treatment received was not 100% as initially allocated. Those who did not receive the physical therapy as allocated (n=4) never attended the physical therapy practice. 11% (n=6) crossed over and visited a physiotherapist during follow-up (all within the three months' follow-up period). All patients, in both groups, received instructions on home exercises as part of the conventional treatment at the initial examination. In the group with additional supervised exercises, 74% (n=28) of the patients reported to have done their home exercises regularly. Most patients in the group with conventional treatment alone (82%; n=36), reported that in the first three weeks after injury they rarely or never did their home exercises

Participants' baseline characteristics (Table 1) indicate that both groups are well balanced regarding their demographic and clinical variables.

After twelve months' follow-up there were five patients (one from the conventional treatment group and four of the physical therapy group) who only filled in their baseline questionnaire. Therefore, outcome measures could not be carried forward.

Table 1 Baseline characteristics of the study population

Characteristic	Conventional treatment (n=53)	Physical therapy (n=49)
Age *(yr)*, mean (SD)	37.0 (11.9)	37.0 (11.9)
Body mass index *(kg/m²)*, mean (SD)	25.4 (4.2)	25.1 (3.8)
Interval between injury and baseline *(days)*, mean (SD)	4.6 (2.4)	4.8 (2.3)
Gender, n (%)		
• Female	22 (42)	21 (43)
• Male	31 (59)	28 (57)
Injury grade, n (%)		
• I	23 (43)	20 (41)
• II	18 (34)	23 (47)
• III	1 (2)	3 (6)
• Unknown	11 (21)	3 (6)
Patient preference, n (%)		
• No preference	8 (15)	15 (31)
• Conventional treatment	30 (57)	23 (47)
• Physical therapy	9 (17)	10 (20)
• Unknown	6 (11)	1 (2)
Ankle affected, n (%)		
• Left	26 (49)	22 (45)
• Right	27 (51)	27 (55)
Setting, n (%)		
• General practitioner	33 (62)	31 (63)
• First-aid physician	20 (38)	18 (37)
Ankle protection, n (%)		
• Tape or bandage	31 (58)	26 (53)
• Brace	8 (15)	10 (20)
Ankle load during work, n (%)		
• No	14 (26)	11 (22)
• Light	20 (38)	20 (41)
• Heavy	14 (26)	17 (35)
• Unknown	5 (9)	1 (2)
Ankle load during sports or hobby, n (%)		
• No	13 (25)	8 (16)
• Light	10 (19)	16 (33)
• Heavy	25 (47)	22 (45)
• Unknown	5 (9)	3 (6)

For the per-protocol analysis, six patients of the conventional treatment group and four patients of the physical therapy group who did not adhere to the treatment protocol were excluded.

Treatment effect after three months

For all outcomes after three months no confounders were identified. Data for the primary and secondary outcomes at three months' follow-up are given in Table 2. No significant difference was found between treatment groups for subjective recovery (Figure 2), occurrence of re-sprains (Figure 3), tested instability, reported instability (Figure 4) and ROM.

A significant difference was observed in the appreciation of the received treatment in favour of the supervised exercises: 68% of the patients from the conventional treatment group and 91% of the patients from the physical therapy group fully appreciated the received treatment. OR for appreciation of the received treatment was 4.69 (95% CI = 1.41 to 15.5) in favour of the physical therapy group.

When subjective recovery is dichotomised (ten representing full recovery versus a score below ten) 19% of the patients from the conventional treatment group and 33%

Table 2 Outcomes after 3 and 12 months' follow-up with univariate analysis.[a]

Outcome (follow-up)	Conventional treatment	Physical therapy	Univariate analysis	Risk Difference
	n (%)	n (%)	OR (95% CI)	AR (95% CI)
Re-sprain (3 months)	*14 (27)*	*10 (23)*	*0.80 (0.31 – 2.03)*	*-4.2% (-21.5% - 13.1%)*
Re-sprain (12 months)	*16 (31)*	*13 (29)*	*0.91 (0.38 – 2.19)*	*-1.8% (-20.1% – 16.4%)*
Reported instability (3 months)	34 (64)	32 (65)	1.05 (0.47 – 2.37)	1.2% (-17.4% – 19.7%)
Reported instability (12 months)	30 (57)	26 (53)	0.87 (0.40 – 1.89)	-3.5% (-22.9% – 15.8%)
Tested instability (3 months)	26 (57)	18 (45)	0.63 (0.27 – 1.48)	-11.5% (-32.6% – 9.5%)
Full treatment appreciation (3 months)	32 (68)	40 (91)	4.69′ (1.41 – 15.5)[b]	22.8% (7.0% – 38.7%)
	mean ± SD	**mean ± SD**	**Mean diff (95% CI)**	**Effect size (95% CI)**
Recovery (3 months)	*7.8 ± 2.4*	*8.2 ± 2.4*	*0.33 (-0.60 - 1.27)*	*0.14 (-0.25 - 0.54)*
Recovery (12 months)	*8.6 ± 1.9*	*8.3 ± 2.8*	*- 0.28 (-1.22 - 0.66)*	*- 0.12 (-0.51 - 0.28)*
ROM difference (3 months)[c]	3.7 ± 8.0	1.9 ± 6.1	- 1.82 (-4.96 - 1.32)	- 0.25 (-0.69 - 0.18)

[a] Primary outcomes in Italic; [b] $p \leq 0.05$; [c] injured ankle versus non-injured ankle. ROM = range of motion; AR = absolute risk.

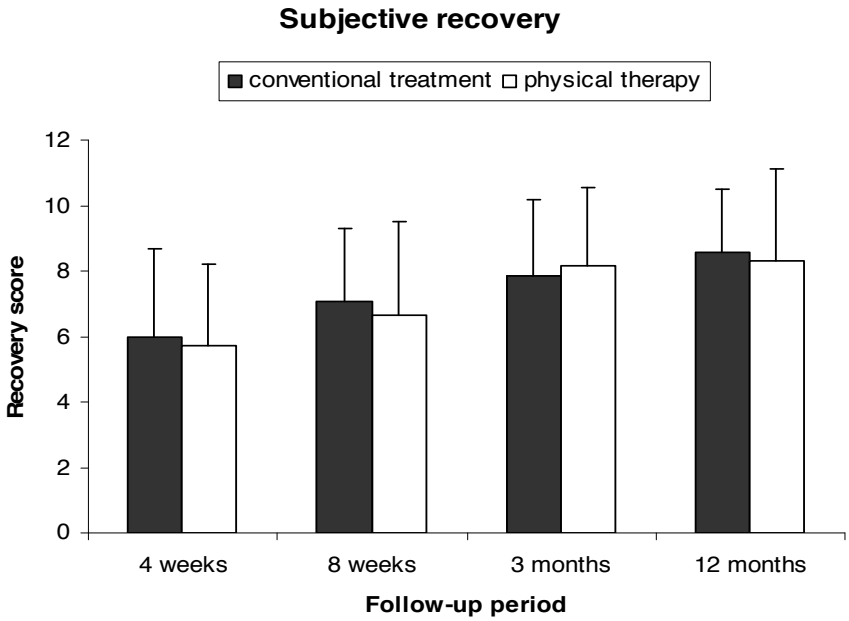

Figure 2 Mean ± SD recovery score (range 0-10) at 4 weeks, 8 weeks, 3 months, and 1-year follow-up

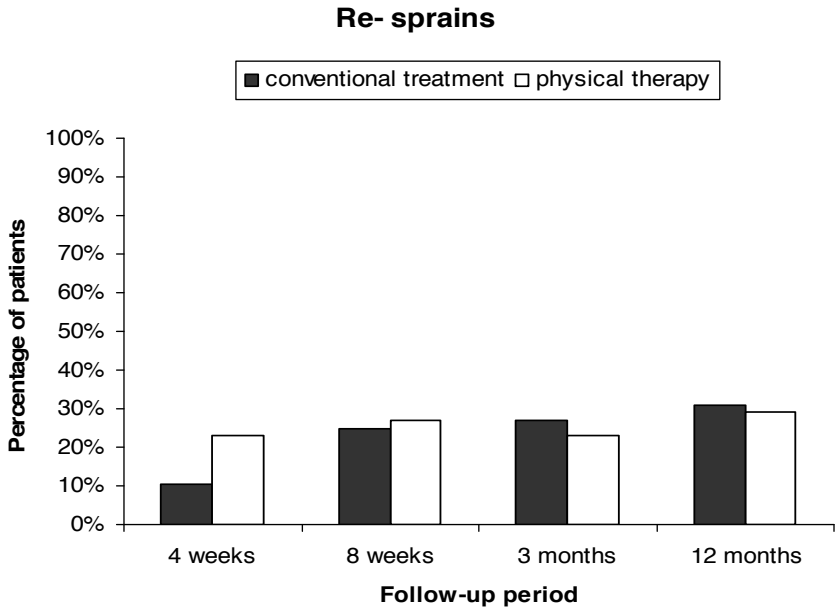

Figure 3 Percentage of patients who reported a re-sprain within 4 weeks, 8 weeks, 3 months, and 1 year follow-up

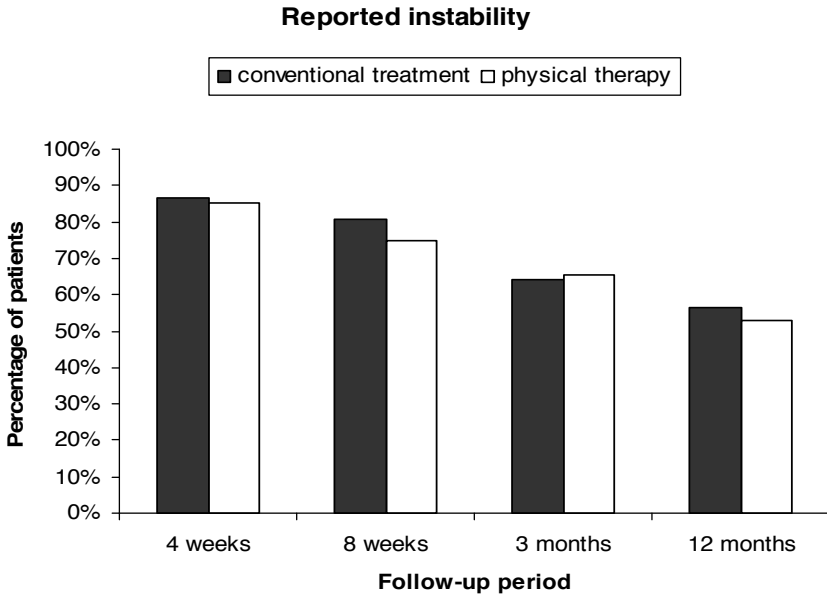

Figure 4 Reported instability at 4 weeks, 8 weeks, 3 months, and 1-year follow-up

from the physical therapy group reported full recovery. OR of full recovery was 2.09 (95% CI = 0.84 to 5.18). When nine was used as cut off score instead of ten, 60% of the patients from the conventional treatment group and 59% from the physical therapy group reported full recovery, with an OR of 0.95 (95% CI = 0.43 to 2.10).

Using per- protocol analysis the mean subjective recovery score (possible range from 0 to 10) for the conventional treatment group was 8.1 (SD 2.2) and for the physical therapy group was 8.4 (SD 2.0); mean difference was -0.34 (95% CI = -1.21 to 0.54). OR for re-sprains was 0.99 (95% CI = 0.37 to 2.65). Similar to the intention- to- treat analysis, a significant difference was found in the appreciation of the received treatment with an OR of 3.48 (95% CI = 1.01 to 12.0). Tested and reported instability between both groups showed no significant difference; ORs were 0.66 (95% CI = 0.27 to 1.61) and 1.02 (95% CI = 0.44 to 2.37) respectively.

Treatment effect after one year

For all outcomes after one year no confounders were identified. Data for the primary and secondary outcomes at twelve months' follow-up are given in Table 2. No significant difference was found between both groups in subjective recovery (Figure 2), occurrence of re-sprains (Figure 3), or reported instability (Figure 4).

Forty-two per cent of patients from the conventional treatment group and 53% from the physical therapy group reported full recovery when a score of ten on a eleven-point

scale represents full recovery. OR of full recovery was 1.59 (95% CI = 0.73 to 3.49). If a score of nine or ten represents full recovery, 72% of the patients from the conventional treatment group and 74% patients from the physical therapy group reported full recovery, with an OR of 1.20 (95% CI = 0.51 = 2.84).

Similar to the intention- to- treat analysis, no significant difference was found using the per- protocol analysis. Mean difference for subjective recovery was 0.13 (95% CI = -0.79 to 1.04); OR for re-sprains was 1.10 (95% CI = 0.44 to 2.74); OR for reported instability was 0.84 (95% CI = 0.37 to 1.91).

DISCUSSION

Summary of main findings

This study showed that usual care combined with supervised exercises compared with usual care alone at three months and one-year follow-up after an acute lateral ankle sprain did not indicate clinically- meaningful differences in the occurrence of re-sprains or in subjective recovery in patients consulting a GP or the emergency department. However, due to the large CI of the risk difference for re-sprains after three months' follow up, there is a slight possibility that usual care combined with supervised exercises is the preferred treatment option for this population. In support of this approach, patients' appreciation of the received treatment was higher for those who consulted the physiotherapist for supervised exercises than those who received usual care.

Strength and the limitations of this study

A few limitations of the present study should be noted. Due to financial- and time restrictions, researchers had to finish the (already extended) inclusion period before 158 patients were included. Nevertheless, this trial is still one of the largest in the field of ankle sprains to study the effect of supervised rehabilitation training. Sample size calculation was based on a 20% decrease (45% to 25%) in occurrence of re-sprains, as found by Wester et al. who had a comparable population to the current study.[23] The occurrence of re-sprains in the conventional treatment group was lower than expected (27% after three months, 31% after twelve months). Compared with the control group only, an additional decrease of 4% after three months and only a decrease of 2% after twelve months in occurrence of re- sprains was seen in the group receiving supervised exercises. The magnitude of this difference indicates that adding supervised exercises to conventional treatment does not lead to clinically- relevant improvements. From the 95% CI of the difference (-21.5% to 13.1%) it may conclude that a true population difference of 20% is not very likely with this intervention.

Comparison with existing literature

The main findings in the present study are concordant with several other studies.[24-27] These studies found no difference in occurrence of re-sprains or subjective instability between groups. Nilsson[26] examined elastic wrapping alone versus elastic wrapping combined with supervised exercises in patients who consulted the emergency department after 4.3 months and three years' follow-up. Oostendorp[27] compared plaster bandage alone with plaster bandage combined with a standardised exercise program in patients who were injured during high risk sport and referred to a physiotherapist after three months. Eiff et al.[24] conducted their trial at a military centre, and Konradsen et al.[25] treated 80 patients with grade III lateral ligament ruptures: both studies compared early mobilized and immobilised patients after twelve months' follow-up.

Other studies reported more positive results. Holme et al.[28] and Reinhardt et al.[29] reported diminished re-sprains and less instability in the training group after three months' follow- up. However, the participants in these studies were, respectively, recreational athletes and recruits and professional soldiers. Patients in the intervention group of Holme et al.[28] participated in a supervised-exercises group for one hour twice weekly, compared with the current study which conducted a maximum of nine half-hour sessions within a period of three months. Oostendorp[27] reported, in contrast to the results after three months' follow-up, a significant difference in 'fear of the ankle giving away' after six months follow-up. The 24 participants included in Oostendorp's study exclusively had a grade I or II sprain, were aged between fifteen and 30 year and were injured during volleyball, basketball, handball or soccer.

Wester et al.[23] and Holme et al.[28] reported fewer re-sprains after twelve months' follow-up. Wester et al. also reported less instability after twelve months in the 48 patients who completed the study. All were active in sports for at least two hours a week, patients with clinically demonstrable ankle instability were excluded and the treatment only consisted of wobble-board training. The differences in outcome between the current study and these studies could be due to the smaller number of patients in those trials[8, 23, 28, 29], specific patient groups[23, 27-29], different settings[27, 29] and different interventions[23, 27, 28].

These latter studies demonstrate that specific patient groups (people involved in sport) may benefit from early ankle mobilisation combined with supervised exercises. In line with these studies is the study of Verhagen et al.[30] which found that a proprioceptive balance-board training program does not have a primary preventive effect. Instead, the programme was thought to have a rehabilitative effect, as the training program led to a lower incidence of ankle sprains for volleyball players with a history of ankle sprains.

To demonstrate benefits for a specific patient group in the current study, subgroup analyses are needed. For example, subgroups classified by injury grade or level of sport practice at baseline. Such subgroup analyses did not lead to any significant differences.

These analyses were explorative and were based on very small numbers. Therefore, no meaningful conclusions can be made based on subgroup analysis in this study.

Furthermore, it is known that the Dutch conventional treatment as defined in the current study (early ankle mobilisation, including home exercises and early weight bearing) differs from the conventional treatment in other countries, which is much less involved. In the current study the difference in treatment between conventional treatment and intervention is less extreme compared with other studies. Therefore, this could explain why no difference was found between conventional treatment and intervention, while other studies have found a difference.

Implications for future research or clinical practice

This study was not large enough to perform meaningful subgroup analyses. However, a trial such as this in a specific subgroup would be of value. This study showed that after one year follow-up, some patients still had complaints relating to their initial injury. Factors causing persistent complaints are largely unknown. Therefore, a study to evaluate prognostic factors for poor recovery and occurrence of re-sprains is needed. The information derived from such a study could be used to determine a high-risk population for non recovery or re-sprain. Such a group may be a subgroup of interest for specific interventions.

Until further research is carried out, results from this and previous studies suggest that there is no strong indication that conventional treatment should be accompanied by supervised rehabilitation training.

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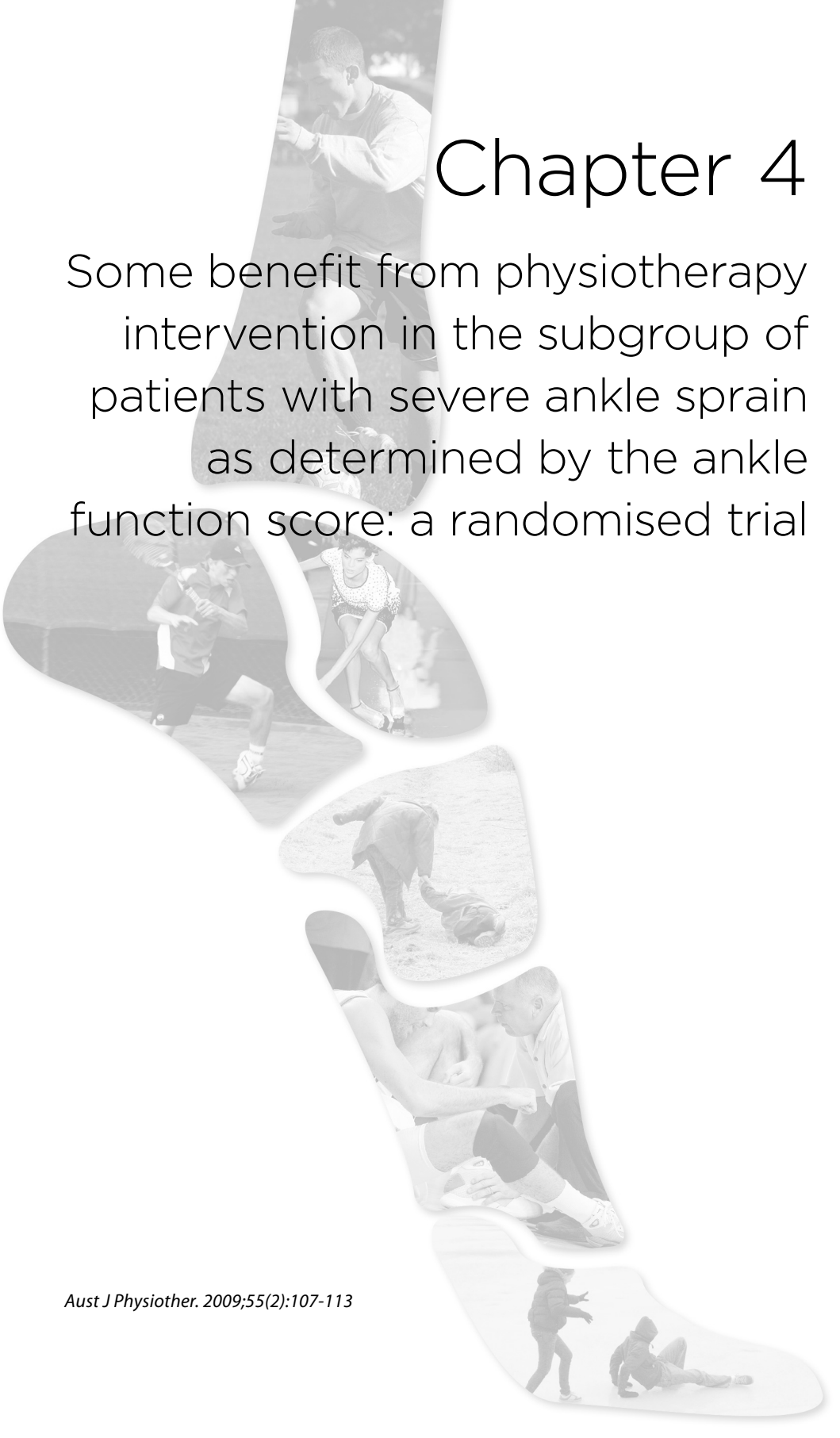
Appendix Guideline for physical therapy used in this study

Progression	**Low** (level I)		→		**High** (level VI)	
Stability	Isolated isometric exercises Standing on 2 legs: with → without support of the hands	Standing broad → small base Standing on 2 legs on an unstable base	Standing on 2 legs on an unstable base with distraction One leg standing on a stable base	One leg standing on a stable base with distraction One leg standing on an unstable base	One leg standing on an unstable base with distraction Walking and exercises on a small and/or unstable base	
Walking/running	Walking with → without crutches	walking with changes in direction broad → small base (e.g. walking on toes or heels, walking as on a tightrope)	Jogging in a straight line	jogging with changes in direction jogging → running in a straight line	Running with sudden changes in direction and speed	Sports
Jumping	Jumping on the place with → without support of the hands stable → unstable base	Forward and backward jumping with 2 legs together (stable → unstable base)	sideward jumping with 2 legs together (stable → unstable base) foreward jumping with 2 legs together and progression in height and distance (stable → unstable base)	forward jumps from one leg to the other (stable → unstable base) skate jumps (stable → unstable base)	Jumping on one leg	
Additional	barefooted (proprioceptive development) daily use of tape on the lateral side of the injured lower leg daily home exercises during a minimum of 6 weeks also training the uninjured leg					



Chapter 4

Some benefit from physiotherapy intervention in the subgroup of patients with severe ankle sprain as determined by the ankle function score: a randomised trial

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ABSTRACT

The objective of this study was to investigate if the baseline Ankle Function Score (AFS) could be used to predict recovery in patients with an acute lateral ankle sprain, if there was a difference in treatment effect of added supervised exercise in patients classified by the baseline AFS, and if there was evidence for an association between self-reported recovery and a follow-up AFS >75.

This study was conducted with the data obtained by our RCT. Outcomes were an AFS which consists of five categories in which a number of points can be summed to a maximum overall score of 100, recovery, pain and giving way all measured using a 0-10 visual analogue scale, and incidence of re-sprain. Measurements were carried out at baseline, four and eight weeks, three and twelve months after injury. Patients were divided into subgroups according to the baseline AFS; severe sprain (AFS ≤40) versus mild sprain (AFS >40).

At four weeks follow-up, patients with a mild injury had significantly less pain during walking and reported less feeling of giving way compared to patients with severe injuries. There was no difference in effect of added supervised exercises in those with a severe injury compared with a mild injury at eight weeks or twelve months. However, there was a beneficial effect of supervised exercises in patients with severe injuries according to pain and feeling of giving way when walking compared to patients who received conventional treatment alone. Correlations between subjective recovery and the AFS at follow-up ranged from 0.48 to 0.79.

In conclusion, the results of this study only partially support the recommendations regarding the use of the ankle function score in the 'Acute Ankle Injury' guideline of the Royal Dutch Society of Physiotherapists.

INTRODUCTION

In the Netherlands an estimated 600,000 people sustain ankle injuries each year and half of these acute ankle injuries occur during sport. In the USA there are 23,000 ankle injuries each day and in the UK there are 5,000.[1,2] The second Dutch national survey of general practice (conducted by the Netherlands Institute for Health Services Research; NIVEL), showed that general practitioners in the Netherlands see 210,000 ankle injuries each year, ie, an incidence of thirteen per thousand patients per year.[1,3] The most recent data available shows that in 1995 about 25% of the patients with an ankle injury were referred to a physiotherapist.[4] The 'Acute ankle injury' clinical guideline of the Royal Dutch Society of Physiotherapists proposes the use of an ankle function score.[5] The ankle function score was developed by de Bie and colleagues and was adapted for ankle sprain injuries from the Lysholm score for knee injuries.[6,7] It allows for a distinction between mild and severe injuries. Patients with a baseline ankle function score >40 out of 100 are described as having a mild injury, while those with a score ≤ 40 are described as having a severe injury. De Bie and colleagues report that patients with a mild injury are able to perform normal activities of daily living two weeks after injury.[6] Sensitivity and specificity for recovery at two weeks after injury were 97% and 100% respectively. Thus, the distinction between a mild and severe injury, based on the ankle function score, should enable physiotherapists to predict short-term recovery.

The guideline also states that patients with a mild injury (baseline ankle function score >40) do not need specific physiotherapy intervention whereas patients with severe injuries (baseline ankle function score ≤40) do. However, several investigators have shown that physiotherapy intervention does not lead to an improvement in recovery or a reduction in instability or the incidence of re-injury compared with conventional intervention.[8-12] Furthermore, we have previously shown in an exploratory subgroup analysis that classifying patients by injury does not lead to a difference in outcome.[12] Nevertheless, no study has evaluated the efficacy of physiotherapy intervention in patients who are classified as having mild versus severe injuries as determined by the ankle function score.

De Bie et al. reported that patients who obtain more than 75 points on the ankle function score are considered to be recovered.[6] Van der Wees et al, investigating adherence to the 'Acute Ankle Injury' guideline, reported that the ankle function score can distinguish between mild and severe injuries.[13] However, it remains unclear whether the ankle function score predicts recovery over time. Therefore, the specific research questions for this study were:

1. Do patients with a severe injury (baseline ankle function score ≤40) do less well in the short-term than patients with a mild injury (score >40)?

2. Does physiotherapy intervention have more effect on patients with a severe injury than a mild injury in the short- or long-term?
3. Is self-reported recovery related to ankle function score over time?

METHOD

Design

Data collected in a randomised trial were used to perform a subgroup analysis.[12] In this trial, participants with an acute lateral ankle sprain attending a general practice or a hospital emergency department were allocated to an experimental group or a control group via concealed allocation. The experimental group received physiotherapy intervention (consisting of supervised exercises) as well as conventional intervention while the control group received conventional intervention alone. Outcomes were self-reported recovery, pain, instability (feeling of giving way), and incidence of re-sprain, so collection was unblinded. They were collected at baseline, four weeks, eight weeks, three months, and one year after injury. There were no statistically-significant differences between the groups for any outcome at any time.

Participants

Patients with a lateral ankle sprain were eligible for inclusion if they were aged between 18 and 60 years and their first visit to the physician was within one week of injury. They were excluded if they had a history of an injury to the same ankle during the previous two years, or if they had a fracture of the same ankle. Participants were divided into two subgroups according to baseline ankle function score (≤40 and >40). The ankle function score (Table 1) consists of five categories: pain, instability, weight bearing, swelling, and gait pattern; each category is summed to a score out of 100 where 0 represents the worst possible function and 100 represents the best possible function.[6]

Intervention

The experimental group received individually-tailored and progressed exercises, supervised by a physiotherapist using a standardised protocol of exercises, based on the guideline of the Royal Dutch Society of Physiotherapists.[5] This was in addition to conventional intervention delivered by a medical practitioner which included information about early ankle mobilisation, including advice for home exercises (for which they received written instructions) and early weight bearing. The control group received conventional intervention only.

Table 1 Ankle function score where 0 represent the worst possible function and 100 represent the best possible function.[6]

Category	Item	Score
Pain	None	35
	during sports	30
	during running on non-level surface	25
	during running on level surface	20
	during walking on non-level surface	15
	during walking on level surface	10
	while carrying load	5
	Constant pain	0
Instability	None	25
	Sometimes during sports (less than once a day)	20
	Frequently during sports (daily)	15
	Sometimes during ADL (less than once a day)	10
	Frequently during ADL (daily)	5
	Every step	0
Weight bearing	Jumping	20
	Standing on toes of injures leg	15
	Standing on injured leg	10
	Standing on two legs	5
	None	0
Swelling	None	10
	Light	6
	Mild	3
	Severe	0
Gait pattern	Running	10
	Normal gait	6
	Mild limp	3
	Severe limp	0

Outcome measures

Outcomes were self-reported recovery, pain, instability (feeling of giving way) and incidence of re-sprain collected using a questionnaire. Recovery, pain and instability were measured on 10-point visual analogue scales; for recovery 0 represented no recovery and 10 full recovery, for pain 0 represented no pain and 10 intolerable pain, and for instability 0 represented never experiencing a feeling of giving way and 10 a continuous feeling of giving way.

Data analysis

Mean (SD) or number (%) were calculated for patient characteristics at baseline and outcome measures at all time points for the experimental and control groups divided into the two subgroups (ankle function score ≤40 and >40). To reduce bias and improve efficiency, missing values were multiply imputed.[14] We generated five imputed datasets using chained equations in the R routine of Multivariate Imputation by Chained Equations.[15] To answer the question 'Do patients with a baseline ankle function score ≤40 do

less well in the short-term than patients with a score >40?' the mean difference (95% CI) between subgroups at four weeks and eight weeks for all outcomes were calculated.

To answer the question 'Does physiotherapy intervention have a different effect on patients with a baseline ankle function score ≤40 than a score >40?', the mean difference or odds ratio (95% CI) between the experimental and control groups between subgroups (ankle function score ≤40 and >40) for all outcomes in the short-term (eight weeks) and the long-term (twelve months) were calculated.[16]

To answer the question 'Is self-reported recovery related to ankle function score over time?', we calculated the Pearson's correlation coefficient (r) between ankle function score and self-reported recovery at all time points. In addition, we calculated sensitivity and specificity of the ankle function score, when full recovery was defined as 10 out of 10.

RESULTS

Flow of participants through the study

A total of 102 patients participated in this study. At baseline, 61 participants (60%) completed the ankle function score. However, seven participants (7%) did not fill in the ankle function score at all, and eleven (11%) failed to fill in one category, twelve (12%) failed to fill in two categories, seven (7%) failed to fill in three categories, and four (4%) failed to fill in four categories. At baseline, 56 patients (55%) had a baseline ankle function score ≤40 and 46 patients (45%) had a baseline ankle function score > 40. Table 2 shows the baseline characteristics of the participants.

Short-term outcome by subgroup

Table 3 presents self-reported recovery, pain, instability and incidence of re-sprain in the short-term (four and eight weeks) for the two subgroups. Of the seven outcomes measured at four weeks, there was a statistically significant difference in three outcomes in favour of participants with a baseline ankle function score >40. At four weeks, participants with a baseline ankle function score ≤40 had 1.1 out of 10 (95% CI 0.1 to 2.0) more pain walking on the flat, 1.7 out of 10 (95% CI 0.5 to 2.9) more pain walking over rough ground, 1.8 out of 10 (95% CI 0.6 to 2.9) more instability when walking over rough ground than participants with a baseline ankle function score > 40. At eight weeks, there were no statistically significant differences between the subgroups for any of the seven outcomes.

Table 2 Baseline characteristics of participants

Characteristic	AFS ≤40 (n = 56)		AFS >40 (n = 46)	
	Exp (n = 28)	Con (n = 28)	Exp (n = 21)	Con (n = 25)
Age *(yr)*, mean (SD)	39.3 (12.7)	38.8 (13.3)	34.0 (10.4)	35.0 (10.0)
BMI *(kg/m²)*, mean (SD)	25 (4)	26 (4)	25 (4)	25 (4)
Gender, number (%)				
• Female	14 (50)	12 (43)	7 (33)	11 (44)
• Male	14 (50)	16 (57)	14 (67)	14 (56)
Injury grade, number (%)				
• I, mild	11 (39)	13 (46)	9 (43)	10 (40)
• II, moderate	14 (50)	8 (29)	10 (48)	9 (36)
• III, severe	3 (11)	1 (4)	0 (0)	0 (0)
• Unknown	0 (0)	6 (21)	2 (9)	6 (24)
Earlier injury, number (%)				
• No earlier injury	10 (36)	14 (50)	12 (57)	16 (64)
• Earlier injury	17 (61)	11 (39)	8 (38)	7 (28)
• Unknown	1 (3)	3 (11)	1 (5)	2 (8)
Setting, number (%)				
• General practitioner	21 (75)	18 (64)	10 (48)	15 (60)
• Emergency department	7 (25)	10 (36)	11 (52)	10 (40)
Pain *(VAS 0-10)*, mean (SD)				
• Rest	3.0 (2.1)	2.0 (2.0)	1.4 (2.0)	1.1 (1.1)
• Walking (flat)	5.1 (2.5)	4.7 (2.8)	2.3 (2.7)	2.2 (2.2)
• Walking (rough)	7.1 (2.2)	7.2 (2.4)	5.3 (2.5)	4.3 (2.6)
Giving way *(VAS 0-10)*, mean (SD)				
• Walking (flat)	3.5 (2.4)	3.9 (2.7)	1.6 (2.1)	1.4 (2.0)
• Walking (rough)	5.9 (2.3)	6.0 (2.8)	4.2 (2.1)	3.5 (2.9)

AFS = Ankle function score; Exp = Experimental group; Con = Control group; BMI = Body mass index; VAS = Visual analogue scale

Effect of intervention between subgroups

Table 4 presents self-reported recovery, pain, instability, and incidence of re-sprain in the short-term (eight weeks) and in the long-term (twelve months) for the experimental and control groups of the two subgroups. There was no statistically significant difference between the experimental and control groups between subgroups in the short-term or the long-term. At eight weeks, the experimental group of the subgroup of participants with a baseline ankle function score ≤40 had 1.4 out of 10 (95% CI 0.1 to 2.6) less pain walking over rough ground, 1.1 out of 10 (95% CI 0.4 to 1.8) less instability walking on the flat, 1.2 out of 10 (95% CI 0.2 to 2.2) less instability when walking over rough ground, than the control group of the same subgroup, with effect sizes of 0.62 (95% CI 0.05 to 1.18), 0.82 (95% CI 0.31 to 1.33), and 0.61 (95% CI 0.08 to 1.14) respectively.

Table 3 Mean (SD) or number (%) for outcomes of subgroups and mean differences or odds ratio (95% CI) between subgroups

Outcome		Subgroups		Difference between subgroups
		AFS ≤ 40 (n=56)	AFS > 40 (n=46)	AFS ≤ 40 minus AFS > 40
Recovery *(VAS 0-10)*, mean (SD)	4 wk	5.6 (2.4)	5.9 (2.8)	-0.3 (-1.5 ; 1.0)
	8 wk	6.9 (2.1)	7.3 (2.6)	-0.4 (-1.5 ; 0.6)
Pain *(VAS 0-10)*, mean (SD)				
• at rest	4 wk	1.1 (1.6)	0.5 (1.1)	0.6 (-0.2 ; 1.4)
	8 wk	1.0 (2.0)	0.4 (1.2)	0.6 (-0.2 ; 1.3)
• walking flat	4 wk	1.8 (2.2)	0.8 (1.3)	1.1 (0.1 ; 2.0)
	8 wk	0.9 (1.6)	0.4 (1.2)	0.6 (-0.1 ; 1.3)
• walking rough	4 wk	3.9 (2.5)	2.2 (2.3)	1.7 (0.6 ; 2.9)
	8 wk	2.4 (2.2)	1.3 (1.9)	1.1 (-0.1 ; 2.2)
Instability*(VAS 0-10)*, mean (SD)				
• walking flat	4 wk	1.5 (1.7)	0.7 (1.2)	0.8 (-0.3 ; 1.9)
	8 wk	0.9 (1.4)	0.6 (1.1)	0.3 (-0.3 ; 0.9)
• walking rough	4 wk	3.8 (2.6)	2.0 (2.1)	1.8 (0.6 ; 2.9)
	8 wk	2.3 (1.9)	1.4 (1.8)	0.8 (-0.1 ; 1.7)
Re-sprain, n (%)	4 wk	10 (18)	7(17)	0.90 (-3.88 ; 5.67)
	8 wk	16 (30)	9 (22)	0.61 (-0.45 ; 1.68)

AFS = ankle function score; VAS = visual analogue scale

Relation between recovery and ankle function score

Figure 1 shows the relation between self-reported recovery and the ankle function score over time. Recovery was correlated with ankle function score at four weeks ($r = 0.48$, $p < 0.01$), at eight weeks ($r = 0.66$, $p < 0.01$), at three months ($r = 0.67$, $p < 0.01$), and at 12 months ($r = 0.79$, $p < 0.01$). When 10 out of 10 was used to define full recovery, sensitivity ranged from 98–100%, indicating that almost all participants reporting 10 out of 10 for recovery had an ankle function score >75. Specificity ranged from 31% to 74%, indicating that a substantial number of participants with an ankle function score >75 did not report 10 out of 10 for recovery.

DISCUSSION

This study has shown that patients with a severe injury do worse on some outcomes than those with a mild injury at four weeks but not at eight weeks. At four weeks, patients with a severe injury reported more pain when walking on the flat and over rough ground and

Table 4 Mean (SD) or number (%) for outcomes of subgroups and mean differences or odds ratio (95% CI) between subgroups

Outcome		Groups				Difference between groups within subgroups		Difference between groups between subgroups
		AFS ≤ 40		AFS > 40		AFS ≤ 40	AFS > 40	AFS ≤ 40 minus AFS > 40
		Exp n=28	Con n=28	Exp n = 21	Con n = 25	Exp minus Con	Exp minus Con	Exp minus Con
Recovery *(VAS 0-10)*, mean (SD)	8 wk	7.2 (2.1)	6.6 (2.0)	7.0 (2.9)	7.7 (2.3)	0.6 (-0.6 ; 1.7)	-0.7 (-2.3 ; 1.0)	1.3 (-0.7 ; 3.3)
	12 mth	8.4 (2.4)	8.7 (1.6)	9.2 (1.9)	8.7 (2.1)	-0.3 (-1.5 ; 1.0)	0.5 (-0.9 ; 2.0)	-0.8 (-2.9 ; 1.3)
Pain *(VAS 0-10)*, mean (SD)								
• at rest	8 wk	0.5 (1.0)	1.5 (2.6)	0.2 (0.7)	0.6 (1.5)	-1.0 (-2.3 ; 0.3)	-0.4 (-1.3 ; 0.4)	-0.6 (-2.2 ; 1.0)
	12 mth	0.3 (0.9)	0.4 (0.8)	0.4 (0.9)	0.1 (0.6)	-0.1 (-0.6 ; 0.5)	0.2 (-0.6 ; 1.0)	-0.3 (-1.2 ; 0.6)
• walking flat	8 wk	0.6 (1.2)	1.2 (1.9)	0.3 (0.6)	0.5 (1.5)	-0.6 (-1.6 ; 0.4)	-0.2 (-1.1 ; 0.6)	-0.4 (-1.7 ; 1.0)
	12 mth	0.3 (1.0)	0.2 (0.7)	0.1 (0.5)	0.3 (0.8)	0.1 (-0.5 ; 0.7)	-0.1 (-0.7 ; 0.4)	0.2 (-0.7 ; 1.1)
• walking rough	8 wk	1.7 (1.9)	3.1 (2.4)	1.1 (1.7)	1.5 (2.3)	-1.4 (-2.6 ; -0.1)	-0.4 (-1.7 ; 0.8)	-1.0 (-2.7 ; 0.8)
	12 mth	0.9 (2.3)	1.0 (1.5)	1.0 (2.1)	0.8 (1.5)	-0.10 (-1.6 ; 1.4)	0.1 (-1.4 ; 1.7)	-0.2 (-2.8 ; 2.3)
Instability *(VAS 0-10)*, mean (SD)								
• walking flat	8 wk	0.3 (0.8)	1.4 (1.6)	0.4 (0.9)	0.7 (1.2)	-1.1 (-1.8 ; -0.4)	-0.4 (-1.0 ; 0.3)	-0.7 (-1.7 ; 0.3)
	12 mth	0.4 (1.6)	0.4 (0.8)	0.5 (1.5)	0.3 (0.7)	0.1 (-0.8 ; 0.9)	0.2 (-0.9 ; 1.3)	-0.1 (-1.8 ; 1.5)
• walking rough	8 wk	1.6 (1.6)	2.8 (2.1)	1.2 (1.4)	1.6 (2.1)	-1.2 (-2.2 ; -0.2)	-0.4 (-1.6 ; 0.8)	-0.8 (-2.4 ; 0.9)
	12 mth	1.4 (2.5)	1.4 (1.5)	1.5 (2.6)	0.7 (1.3)	0.0 (-1.4 ; 1.3)	0.7 (-1.6 ; 3.1)	-0.8 (-3.2 ; 1.7)
Re-sprain, number (%)	8 wk	6 (21)	10 (36)	7 (33)	2 (8)	0.50 (0.13 ; 1.86)	5.43 (0.49 ; 60.69)	0.09 (0.01 ; 1.36)
	12 mth	9 (32)	12 (43)	8 (38)	5 (20)	0.7 (0.20 ; 2.30)	2.3 (0.26 ; 19.52)	0.3(0.02 ; 3.65)

AFS = ankle function score; VAS = visual analogue scale; Exp = Experimental group; Con = Control group.

more instability when walking over rough ground compared with patients with a mild injury but no difference in recovery. Furthermore, although the ankle function score is recommended to distinguish patients who need physiotherapy intervention from those who do not, our findings showed that the effect of physiotherapy intervention was no different for those with a mild compared with those with a severe injury, either in the short- or long-term. Finally, self-reported recovery was related to ankle function score at all points in time. However, although almost all participants reporting a full recovery had a high ankle function score, a substantial number of participants with a high ankle function score did not report a full recovery.

In the present study, the distinction between mild and severe injuries was made by means of the ankle function score as described by the Royal Dutch Society of Physiotherapists in their 'Acute Ankle Injury' guideline. The guideline states that the ankle function score is determined by the physiotherapist. In the present study, however, the ankle function score was obtained from a questionnaire and is therefore self-reported by the patient. However, this is not likely to have had much impact on the results because exactly the same questions as the physiotherapist would have asked while determining the ankle function score were included in the questionnaire. In addition, even though not all categories of the ankle function score were completed, we used multiple imputation to account for the missing data since this is reported to be a reliable method to deal with missing values.[17] The guideline, as well as de Bie and colleagues, states that the ankle function score is an excellent predictor of outcome within two weeks.[6] The results of our study support this statement to some extent. We found more pain and feeling of giving way in patients with a severe injury compared with those with a mild injury at four weeks, although this difference had disappeared by eight weeks. There was no difference between subgroups in self-reported recovery at four weeks, although this result might to some extent be distorted by the 17% of participants who incurred a re-sprain. The guideline states that patients with an ankle function score ≤40 need physiotherapy intervention and those with an ankle function score >40 do not. In the present study, we could not show a difference in effect of physiotherapy intervention between these subgroups. However, although the mean differences were small and non-significant statistically, they were in favour of more benefit for the subgroup with a severe injury. Given that the experimental group of the severe subgroup had less pain walking over rough ground and less giving way walking on the flat and over rough ground than the control group of the same subgroup in the short-term, a randomised trial of physiotherapy intervention in patients with a severe injury is warranted.

Participants in the control group of the subgroup with a mild injury reported less re-sprain at eight weeks than the experimental group although this was not statistically significant. Since participants in the experimental group were more active earlier be-

cause of the nature of their intervention, they may have had a higher risk of re-spraining compared to those who received conventional intervention.

de Bie and colleagues considered recovery to have taken place with a score of more than 75 points out of 100 on the ankle function score.[6] However, in the 'Acute Ankle Injury' guideline this score is not introduced as an alternative outcome measure. In the present study, self-reported recovery predicted ankle function score and the strength of the prediction increased over time. However, if the ankle function score is to be useful in determining recovery from ankle injury, more responsiveness studies should be conducted, because we found that a substantial number of participants with a high ankle function score did not report a full recovery.

In conclusion, the results of this study only partially support the recommendations in the 'Acute Ankle Injury' guideline of the Royal Dutch Society of Physiotherapists. First, patients with a severe injury had only a few worse outcomes than those with a mild injury in the short-term. Second, the effect of physiotherapy intervention was not statistically different for those with a mild injury compared with a severe injury, either in the short- or long-term. However, given that the experimental group of the severe subgroup showed some benefits over the control group of the same subgroup in the short-term, a randomised trial of physiotherapy intervention in patients with a severe injury is warranted. Finally, self-reported recovery predicted ankle function score and the strength of the prediction increased over time.

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Chapter 5

Explanatory variables for patients' self reported recovery in adults after acute lateral ankle sprain

Physical Therapy; in press

ABSTRACT

Longitudinal research in musculoskeletal disorders often makes use of a single question to measure recovery; however, a large variation in reported recovery exists. After an acute ankle sprain patients may experience no pain or functional disability, whereas they report not to be recovered, or vice versa.

The objective of this study is to find explanatory variables for reporting recovery by analyzing to what extent different outcomes (e.g. pain intensity) are associated with recovery, and how baseline scores of different variables influence this association in adult patients after acute lateral ankle sprain.

This study was constructed within the framework of a randomized controlled trial. A total of 102 patients with an acute ankle sprain were included. Recovery, pain intensity, 'giving way', and Ankle Function Score were assessed at four and eight weeks, and three and twelve months post-injury. Mean differences were calculated between baseline and follow-up. Associations were calculated using linear mixed models; the influence of baseline scores on these associations was determined using linear regression with interaction.

Associations were found between recovery and the mean differences of pain during running on a flat and a rough surface (four and eight weeks, three months), and the mean difference of giving way during walking on a rough surface (eight weeks, three months).

In conclusion, this study is the first to find explanatory variables for reporting recovery in adults after ankle sprain. Pain intensity and giving way measured during high ankle load activities makes it easier to measure and to generalise recovery in this population and should be the primary outcome measure of interest. This study indicates the necessity of reaching consensus about primary outcome measures for research in patients who have sustained an ankle sprain.

INTRODUCTION

Nowadays, longitudinal research on musculoskeletal disorders often makes use of a single question to measure recovery.[1-4] Consequently, an increased emphasis is placed on self-reported perceived recovery as an outcome measure. For the practicing clinician this question is also a fundamental one, because it provides the patient with relevant information about the effect of treatment, and guides decision-making regarding the next step.[5]

Lateral ligament injuries of the ankle are among the most common injuries of the human musculoskeletal system. In the USA and the UK there occur about 23,000 and 5,000 ankle sprains, respectively, each day.[6] In the Netherlands, about 600,000 people sustain an ankle injury each year.[7] Recent data show that in the Netherlands (with about 7,300,000 athletes) a total of 120,000 ankle sprains were registered in the period 2000-2002 during sports, of which 43,000 injuries received medical treatment.[8]

A recent systematic review evaluated the clinical course of conventionally-treated acute ankle sprains and found that, at one-year follow-up, 5%-33% of the patients still experience pain and instability, that 34% of the patients report at least one re-sprain, and that 15%-64% report not to be fully recovered.[9] Similar results were found in studies on the effectiveness of functional treatment in patients after acute lateral ankle sprains, reporting that 9%-41% of the patients is still not fully recovered at one-year follow-up.[4, 10] The large variation in recovery might be explained by the variation in the outcome measures used, such as pain, giving way, and functional scores on the one hand, and self-reported recovery on the other. For example, after an acute lateral ankle sprain patients might experience no pain or functional disability during follow-up, whereas they may report not to be fully recovered, or vice versa.[11] More insight into what recovery means to patients who have sustained a lateral ankle sprain, may lead to better understanding and promote the patient's recovery process. In addition, this might enable to define relevant outcome measures.

Therefore, this study aimed to find explanatory variables for reporting recovery, by analyzing to what extent other outcomes (e.g. pain intensity, giving way, and Ankle Function Score) are associated with patients' self-reported recovery, and how baseline scores of different variables (e.g. patient characteristics, activity level) influence this association after an acute lateral ankle sprain.

METHODS

This study was constructed within the framework of a randomised clinical trial on the effectiveness of supervised exercises in patients after an acute lateral ankle sprain.[4] In

this trial patients who had an acute lateral ankle sprain and consulted general practice or the hospital emergency department were randomised to either conventional treatment combined with supervised exercises, or to conventional treatment alone. Primary outcomes were occurrence of re-sprains and recovery, both of which were measured at baseline, at four and eight weeks, and at three and twelve months after initial injury, using questionnaires. The trial showed that at one-year follow-up additional supervised exercises do not lead to a reduction of re-sprains or improved recovery. Therefore, the current study was interpreted and analysed as a cohort study.

Participants

Patients with a lateral ankle sprain were eligible for the study when they were aged between 18 and 60 years and their first visit to the physician was within one week of injury. Patients were excluded if they had a history of an injury of the same ankle during the previous two years, or when they had a fracture of the same ankle. After informed consent and after acquiring baseline information (self-reported questionnaire and clinical findings), each patient was randomised to either the conventional treatment group or the physical therapy group (conventional treatment plus supervised exercises).

Treatment

All participants received the same conventional treatment from their physician. Conventional treatment included information about early ankle mobilisation, including advice for home exercises (for which they received written instructions) and early weight bearing. Patients in the physical therapy group participated, in addition, in an individual and progressive training program supervised by a physical therapist using a standardized protocol of exercises. A detailed description of the treatment options is described elsewhere.[4]

Outcome measures

Questionnaires were completed at baseline, at four and eight weeks, and at three and twelve months follow-up. Outcome measures were recovery, pain intensity (at rest, during walking, during running), giving way (during walking), and Ankle Function Score (AFS). Recovery was measured on 0-10 visual analogue scale (VAS) (with 0 representing no recovery; 10 representing full recovery), pain was measured on 0-10 VAS (with 0 representing no pain; 10 representing intolerable pain), and giving way was measured on 0-10 VAS (with 0 representing never feeling of giving way; 10 representing continuous feeling of giving way).

The AFS consists of five categories: pain, instability, weight bearing, swelling, and gait pattern. In each category a number of points can be summed to a maximum overall score of 100 (indicating minimal severity).[12]

Data analysis

Patient characteristics were described using descriptive statistics. To reduce bias and improve efficiency, missing values were multiple imputed.[13] We generated ten imputed datasets using chained equations implemented in the R routine MICE[14], since a total of 18.4% of the data was missing. Percentages of missing data were: at baseline 9.5%, at four weeks 19.1%, at eight weeks 26.5%, at three months 15.3% and at twelve months 25.0%. Missing data were due to loss to follow-up of five patients (from four weeks), incomplete questionnaires, and questionnaires not received.

First, mean differences were calculated for the continuous outcome measures pain intensity, AFS, and giving way between baseline and the follow-up moments. Associations between recovery and these mean differences were calculated using a general linear model for correlated data which is often seen as a type of mixed model. However no random coefficients were used as the correlation matrix is modelled directly. Mean differences were used since these are relevant scores in relation to a relative score such as recovery, instead of absolute scores. Secondly, the influence of baseline variables on the association between recovery and the mean differences of the outcome measures were determined by adding an interaction term to the model. The results are presented as regression coefficients (β) with 95% confidence intervals (95% CI). All analyses were performed with the SPSS software package (version 15.0).

RESULTS

Study population

Tables 1 and 2 present the characteristics of the study population at baseline and at follow-up. Of the 102 patients who incurred an acute lateral ankle sprain, 64 (63%) consulted a GP, and 38 (37%) contacted the emergency department. At baseline, 75 (74%) and 80 (78%) patients reported to endure ankle load during work and sports/hobby, respectively. For more details concerning the flow of participants we refer to the trial publication.[4]

Association between recovery and mean differences of outcomes

Table 3 presents the association between recovery at follow-up and mean differences (follow-up vs. baseline) of pain intensity, AFS, and giving way. Significant associations were found (at almost all follow-up moments) between patients' self- reported recovery and mean differences for pain during running on a flat and a rough surface, with regression coefficients ranging from -0.42 (95% CI -0.58 to -0.25) to -0.25 (95% CI -0.50 to -0.01).

The mean differences for giving way during walking on a rough surface were significantly associated with self-reported recovery at eight weeks and three months follow-

Table 1 Baseline characteristics of the study population (n=102)

Characteristic	Baseline
Age *(yr)*, mean (SD)	37.0 (11.8)
BMI *(kg/m²)*, mean (SD)	25.2 (4.0)
Gender, number (%)	
• Female	43 (42)
• Male	59 (58)
Injury grade, number (%)	
• I, mild	43 (42)
• II, moderate	41 (40)
• III, severe	4 (4)
• Unknown	14 (14)
Earlier injury, number (%)	
• No earlier injury	51 (50)
• Earlier injury	44(43)
• Unknown	7 (7)
Setting, number (%)	
• General practitioner	64 (63)
• Emergency department	38 (37)
Treatment, number (%)	
• Conventional	53 (52)
• Physical therapy	49 (48)
Ankle load (work), number (%)	
• No	27 (26)
• Yes	75 (74)
Ankle load (sport / hobby), number (%)	
• No	22 (22)
• Yes	80 (78)

up: -0.26 (95% CI -0.50 to -0.02) and -0.25 (95% CI -0.47 to -0.03), respectively. Nearly no associations were found between recovery and the mean differences for pain at rest, pain during walking on a flat surface, pain during walking on a rough surface, AFS, and

Table 2 Outcome measures at baseline, 4 weeks, 8weeks, 3 months, and 12 months follow-up

Characteristics	Baseline	4 weeks	8 weeks	3 months	12 months
Pain *(VAS 0-10)*, mean (SD)					
• Rest	1.9 (2.0)	0.9 (1.6)	1.3 (2.5)	0.4 (1.1)	0.3 (1.0)
• Walking (flat)	3.7 (2.8)	1.5 (2.1)	1.2 (2.3)	0.4 (1.2)	0.2 (0.7)
• Walking (rough)	6.1 (2.7)	3.2 (2.7)	2.3 (2.8)	1.1 (1.7)	1.0 (2.1)
• Running (flat)	7.6 (2.7)	4.0 (3.3)	2.8 (3.0)	1.7 (2.4)	1.3 (2.6)
• Running (rough)	8.3 (2.2)	5.1 (3.4)	3.3 (3.2)	2.0 (2.7)	1.6 (2.8)
Giving way *(VAS 0-10)*, mean (SD)					
• Walking (flat)	2.7 (2.6)	1.2 (1.7)	1.1 (1.9)	0.6 (1.3)	0.5 (1.3)
• Walking (rough)	5.0 (2.8)	3.0 (2.7)	2.4 (2.7)	1.6 (2.1)	1.4 (2.3)
Ankle Function Score *(0-100)*, mean (SD)	39.4 (18.9)	65.8 (25.4)	75.8 (23.4)	83.0 (21.4)	87.3 (19.9)
Recovery *(VAS 0-10)*, mean (SD)	-	5.9 (2.7)	7.2 (2.2)	8.2 (2.2)	8.7 (2.1)

VAS = Visual analogue scale

giving way during walking on a flat surface. As an example, the association (with accompanying correlation coefficient) between recovery and mean differences for pain at rest and during running on a rough surface are presented in, respectively, Figure 1 and 2. Figure 1 shows a non- significant association with a far from optimal correlation coefficient (r = -0.17), whereas Figure 2 shows a significant association with a moderate correlation coefficient (r -0.60). These figures show that a better recovery score is accompanied by a decrease (negative mean difference) on the pain scores.

Table 3 Associations between recovery at follow-up and mean differences (follow-up vs. baseline) of pain intensity, ankle function score, and giving way. Associations are presented by means of a regression coefficient (ß) with corresponding 95% confidence interval

	Follow-up			
	4 weeks	**8 weeks**	**3 months**	**12 months**
Pain vs. recovery				
• at rest	-0.05 (-0.63 ; 0.53)	-0.15 (-0.38 ; 0.09)	-0.18 (-0.40 ; 0.04)	-0.13 (-0.40 ; 0.14)
• walking flat	-0.21 (-0.65 ; 0.23)	-0.20 (-0.51 ; 0.11)	-0.29 (-0.63 ; 0.05)	-0.20 (-0.58 ; 0.18)
• walking rough	-0.20 (-0.44 ; 0.05)	-0.21 (-0.45 ; 0.03)	**-0.33 (-0.51 ; -0.15)**	-0.28 (-0.58 ; 0.22)
• running flat	**-0.31 (-0.57 ; -0.05)**	**-0.25 (-0.50 ; -0.01)**	**-0.42 (-0.58 ; -0.25)**	-0.23 (-0.68 ; 0.22)
• running rough	**-0.25 (-0.45 ; -0.04)**	**-0.24 (-0.40 ; -0.08)**	**-0.38 (-0.55 ; -0.20)**	-0.24 (-0.57 ; 0.10)
AFS vs. recovery	0.03 (-0.01 ; 0.07)	0.03 (-0.01 ; 0.08)	0.04 (-0.01 ; 0.10)	**0.05 (0.02 ; 0.08)**
Giving way vs. recovery				
• walking flat	-0.05 (-0.35 ; 0.24)	-0.15 (-0.39 ; 0.08)	-0.12 (-0.31 ; 0.08)	-0.12 (-0.37 ; 0.12)
• walking rough	-0.23 (-0.50 ; 0.05)	**-0.26 (-0.50 ; -0.02)**	**-0.25 (-0.47 ; -0.03)**	-0.27 (-0.63 ; 0.09)

AFS = ankle function score

Influence of baseline variables on associations

Table 4 presents the interaction effect of baseline scores and patient characteristics on the association between recovery and the mean difference of outcomes at three months follow-up. Significant interaction effects were found between pain during walking on a rough surface at baseline and the association between recovery and the mean difference of pain during walking on a rough surface (0.05; 95% CI 0.00 to 0.09), and between pain during running on a rough surface and the association between recovery and the mean difference of pain during running on a rough surface (0.08; 95% CI 0.00 to 0.15).

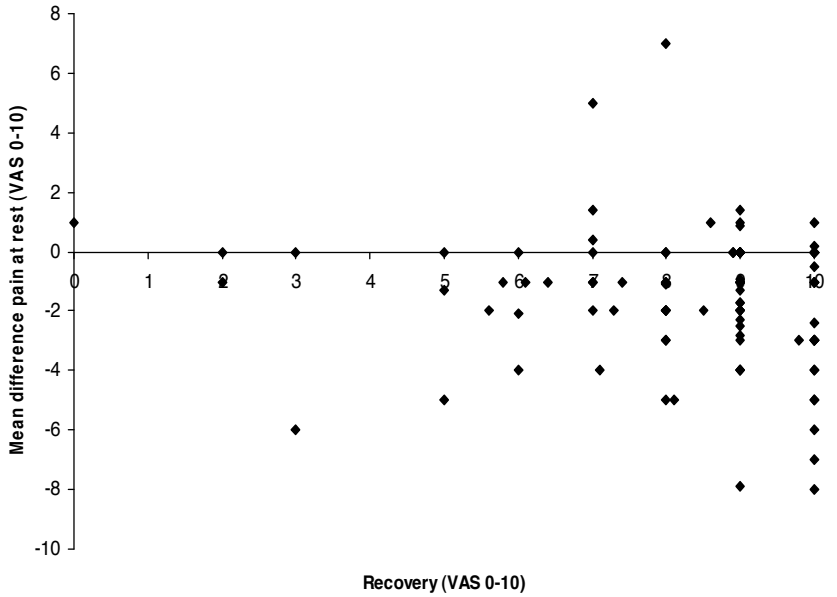

Figure 1 Association between recovery (3 months follow-up) and the mean difference of pain at rest (3 months vs. baseline). Every dot represent one patient with his/her recovery score (x axis) and his/her corresponding mean difference of pain at rest (y axis)

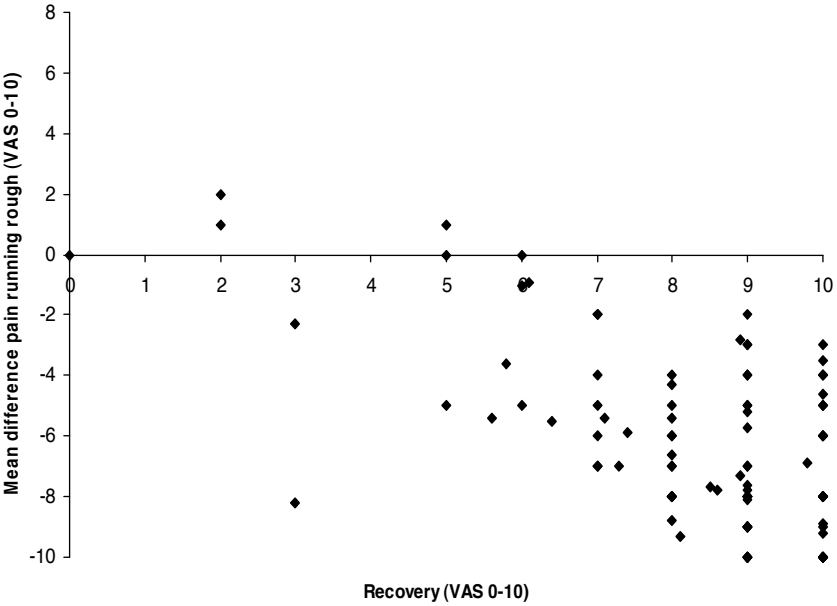

Figure 2 Association between recovery (3 months follow-up) and the mean difference of pain during running at a rough surface (3 months vs. baseline). Every dot represent one patient with his/her recovery score (x axis) and his/her corresponding mean difference of pain at rest (y axis)

Table 4 Interaction of baseline scores on the association between recovery (3 months) and mean differences (3 months vs. baseline) of pain intensity, giving way, and the ankle function score (AFS). Interaction effects are presented by means of a regression coefficient (ß) with corresponding 95% confidence interval

	Recovery – Pain (rest)	**Recovery – Pain (walking flat)**	**Recovery – Pain (walking rough)**	**Recovery – Pain (running flat)**	**Recovery – Pain (running rough)**	**Recovery – AFS**	**Recovery – Giving way (walking flat)**	**Recovery – Giving way (walking rough)**
Ankle load								
• Work	-0.16 (-0.72 ; 0.40)	-0.01 (-0.70 ; 0.67)	0.09 (-0.40 ; 0.59)	0.06 (-0.25 ; 0.36)	0.09 (-0.32 ; 0.49)	0.05 (-0.33 ; 0.43)	0.05 (-0.33 ; 0.43)	0.05 (-0.33 ; 0.43)
• Sport/hobby	-0.44 (-0.88 ; 0.01)	-0.36 (-0.98 ; 0.26)	-0.18 (-0.65 ; 0.29)	0.04 (-0.40 ; 0.48)	-0.03 (-0.54 ; 0.49)	-0.14 (-0.54 ; 0.26)	-0.14 (-0.54 ; 0.26)	-0.14 (-0.54 ; 0.26)
Re-sprain within 3 months	0.12 (-0.80 ; 1.04)	0.03 (-0.87 ; 0.94)	0.09 (-1.04 ; 1.22)	0.01 (-0.82 ; 0.83)	0.14 (-0.89 ; 1.16)	-0.03 (-0.13 ; 0.07)	0.14 (-0.62 ; 0.90)	0.32 (-0.92 ; 1.56)
Pain								
• rest	-0.04 (-0.13 ; 0.05)	-0.05 (-0.13 ; 0.03)	-0.02 (-0.10 ; 0.06)	-0.01 (-0.08 ; 0.06)	0.01 (-0.05 ; 0.07)	0.00 (-0.01 ; 0.01)	0.03 (0.07 ; 0.12)	0.03 (-0.04 ; 0.10)
• walking flat	-	-0.05 (-0.13 ; 0.03)	-	-	-	-	-	-
• walking rough	-	-	**0.05 (0.00 ; 0.09)**	-	-	-	-	-
• running flat	-	-	-	0.05 (-0.02 ; 0.11)	-	-	-	-
• running rough	-	-	-	-	**0.08 (0.00 ; 0.15)**	-	-	-
AFS	-	-	-	-	-	0.00 (0.00 ; 0.00)	-	-
Giving way								
• walking flat	-	-	-	-	-	-	0.01 (-0.08 ; 0.10)	-
• walking rough	-	-	-	-	-	-	-	0.03 (-0.02 ; 0.08)

No significant interaction effect was found between baseline scores and associations between recovery and mean differences at one year follow-up.

DISCUSSION

This study shows significant associations between patients' self-reported recovery and the mean differences of pain during running on a flat and a rough surface (at four weeks, eight weeks, three months), and mean difference of giving way during walking on a rough surface (at eight weeks, three months). At three months, the baseline scores of pain during walking and running on a rough surface increased the associations between recovery and, respectively, the mean difference of pain during walking on a rough surface, and mean difference of pain during running on a rough surface.

The significant associations between self-reported recovery and the mean differences were mainly found at on short-term follow-up and during activities that demand high ankle loads, e.g. walking on a rough surface, and running. These outcome measures, which are more related to activities of daily living, seems to be better explanatory variables for recovery than the outcomes measured during activities demanding low ankle loads. For that reason, it is plausible that the use of outcomes measured during activities with high ankle loads makes it easier to measure, and to generalise recovery in patients who have sustained an ankle sprain. Consequently, this result makes them the outcome measures of choice for future research in this specific population.

In addition, low baseline scores will generally result in small mean differences and, therefore, will contribute less to the extent patients report to be recovered or not, which is the case with outcomes measured during activities with low ankle loads. This assumption is supported by our findings of the influence of baseline scores on the associations between recovery and the mean differences of the different outcomes. Therefore, it is of interest to determine the required magnitude of these mean differences on which patients report to be recovered or not.

No associations between recovery and mean differences were found at one year follow-up, and the influence of baseline scores on these associations was not significant. This might be due to the long recall period over which recovery is measured. Another explanation is that it might be attributable to the occurrence of a re-sprain during follow-up. However, no effect was found of the occurrence of a re-sprain, within three months of the initial injury, on the different associations between recovery and mean differences during follow-up. In this respect, it might be reasoned that recovery is not only reflected in changes in the state of the disorder but also in an adjustment of life to work around the disorder (re-adjustment), or an adaptation to living with the disorder (re-definition).[5] Similar to the absence of studies evaluating the meaning of recovery in

patients after an acute lateral ankle sprain, studies on recovery related to other physical conditions are also limited. For example, in patients with low back pain the meaning of recovery is highly individualized, as determined by assessment of the impact of symptoms on the ability to perform meaningful daily activities, as well as on social factors and factors related to physical and psychological health.[15] In line with these findings is the study by Williams et al. in which low back patients said that, for them, recovery meant '*getting back to the way I was before injury*'.[16]

One limitation of the present study is that our questionnaire did not include questions concerning readjustment, redefinition and possible hindrance due to injury. Moreover, we do not have information about time to return to pre-injury activity level, time to return to sport, or time to return to work. These latter outcomes reflect the demands and activity level of the patients and it would be worthwhile to see whether or not these are associated with recovery. Also, because the data were obtained at fixed time points, we were unable to establish the exact date when patient's changed from 'non-recovered' to 'recovered'. Finally, we used a 0-10 VAS to measure recovery instead of the frequently used 4, 6 or 7-point Likert scales. Despite that these dichotomized scales make it easier to establish 'recovered' patients, we used a continuous scale which resulted in less loss of information.

In conclusion, this study is the first to find explanatory variables for reporting recovery in adults after an acute lateral ankle sprain. An association was found between the mean differences of pain intensity and giving way during high ankle load activities and recovery at short-term follow-up. This means that it is not useful to measure pain and giving way during low ankle load activities, and that pain intensity and giving way during high load ankle activities should probably be the primary outcome measures of interest. However, more research is needed to gain more insight into the underlying meaning of recovery in patients after an acute lateral ankle sprain; for example, by means of qualitative research. Finally, the present study also reveals a need to reach consensus about primary outcome measures for research in patients who have sustained an acute lateral ankle sprain.

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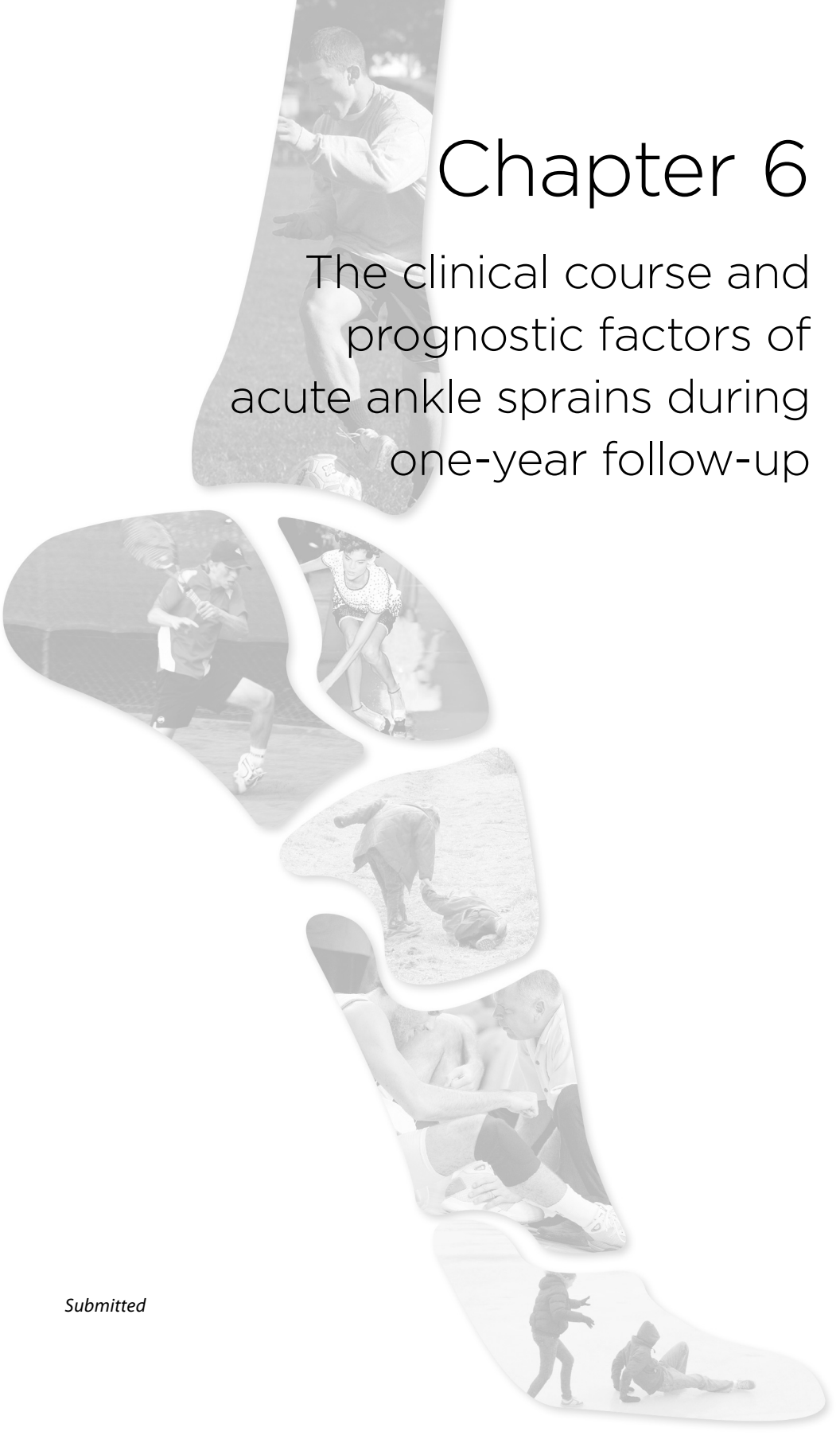

Chapter 6

The clinical course and prognostic factors of acute ankle sprains during one-year follow-up

Submitted

ABSTRACT

During the first two months after an acute lateral ankle sprain there is a rapid decrease in pain, after which it continues to improve more slowly. The factors predicting persistent complaints from ankle sprains are largely unknown.

Therefore, the objective of this study is to evaluate prognostic factors for incomplete recovery, instability, pain intensity and re-sprains during one year follow-up in patients who consulted primary care for acute ankle sprains.

A total of 102 patients consulting their general practitioner or a first aid department for an acute ankle sprain were included in this prospective study. Possible prognostic factors were assessed at baseline and at three months follow-up. Outcome measures assessed at one year follow-up were self-reported recovery, re-sprains, instability and pain intensity.

At three months follow-up 65% of the patients reported instability and 23% reported one or more re-sprains. At one year follow-up, 27.5% still reported instability and more than 50% regarded themselves as not completely recovered. At three months follow-up, for the non-recovered patients no prognostic factors from the physical examination were identified. However, re-sprains and self-reported pain at rest at three months follow-up were related to incomplete recovery at one year for the non-recovered patients at three months follow-up.

We concluded that a physical examination at three months follow-up for the non-recovered patients with an ankle sprain seems to have no additional value for predicting outcome at one year follow-up. However, self-reported pain at rest and re-sprains during the three months follow-up seem to have a prognostic value for recovery at one year follow-up.

INTRODUCTION

In the Netherlands an estimated 600,000 people sustain ankle injuries each year, an incidence of 12.8 per 1000 patients per year. About 50% of these people visit a general practitioner (GP) or, on their own initiative, a hospital emergency department.[1] In the USA, more than 23,000 people per day, including athletes and non-athletes, require medical care for ankle sprains.[2]

Several studies have investigated pain intensity during one year follow-up of patients with acute ankle sprains. During the first two months there is a rapid decrease in pain, after which it continues to improve more slowly. A recent systematic review showed that the proportion of patients who reported to experience pain at one year follow-up or later ranges from 16% to 33%.[3]

So far, there is no clear evidence that interventions such as (supervised) exercise will lead to benefits related to the occurrence of re-sprains, subjective recovery, instability or pain intensity.[4-7] In order to evaluate the effectiveness of therapeutic interventions and to guide management decisions, clear insight on the course of recovery after ankle sprain is needed. This information is helpful to inform patients about the expected clinical course, and to identify relevant subgroups of patients with a better or worse prognosis.

The factors predicting persistent complaints from ankle sprains are largely unknown.[3] Until now, only one study has evaluated prognostic factors for incomplete recovery and re-sprains. Sport activity at a high level was found to be a prognostic factor for residual symptoms.[8] However, that study showed methodological shortcomings, and the full range and impact of residual complaints was not investigated.[8-11]

Therefore, the first objective of the present prospective study was to evaluate baseline prognostic factors for incomplete recovery, re-sprains, instability and pain intensity during one year follow-up in adult patients who consulted primary care for an acute lateral ankle sprain. Because of the clinical course of ankle sprains, outcomes and factors at short-term follow-up could have a predictive value for the long-term outcome in a subgroup of non-recovered patients. Therefore, the second objective of this study was to analyse possible prognostic factors for the non-recovered patients at three months follow-up for the outcome at one year follow-up.

MATERIALS AND METHODS

Patient selection

The data used for this study were derived from a randomised clinical trial (RCT) investigating the effectiveness of supervised exercises in primary care.[7] Patients who had an

acute injury of the lateral collateral ligaments of the ankle and who presented themselves to one of the 32 participating GPs, or at the emergency department of the local hospital in the same district, between March 2002 and December 2003 were considered for inclusion. Patients with a lateral ankle sprain were eligible for this study if they were aged between 18 and 60 years and their first visit to the physician was within one week of the injury. Patients were excluded if they had a history of an injury of the same ankle during the previous two years, or when they had ever had a fracture of the same ankle.

The first-aid physician or GP carried out a standardised clinical examination, which was especially developed and conducted for the present study. Occurrence of swelling, haematoma, location of the sprain, and anterior drawer sign were reported. In addition, the physician estimated the severity of the injury. Based on clinical findings (stability, intensity and location of swelling, pain and haemorrhage), the injuries were graded from I to III (grade I mild, grade II moderate, and grade III severe).[12]

After acquiring baseline information, each patient was randomised to either the usual care group or the physical therapy group. In both groups, the total 102 participating subjects received the same standard treatment from their physician. This included general information about early ankle mobilisation, including advice for home exercises and early weight bearing (if necessary, based on the physician's experience, protected by a tape, bandage, or brace). Subjects were encouraged to start these activities as early as possible and to gradually increase their activity level. Patients in the physical therapy group participated, in addition, in an individual and progressive training program supervised by a physical therapist using a standardised protocol.

For the present study, the data of the RCT are analysed as a cohort study because the study results showed no differences between the usual care group and the physical therapy group.[7] Nevertheless, in the present study the interventions were also considered to be potential prognostic factors.

The Medical Ethics committee of the Erasmus MC Rotterdam approved the protocol, and all participants provided written informed consent.

Data collection

All participants were asked to complete a baseline questionnaire with questions on potential prognostic factors. At baseline, the following prognostic factors were taken into consideration to evaluate recovery, the occurrence of re-sprains, instability, and pain during walking at one year follow-up: 1) demographic factors, i.e. age, gender and body mass index (BMI), 2) clinical factors, e.g. setting, baseline intervention, injury grade, self-reported swelling and Ankle Function Score (AFS)[11], and 3) ankle load factors, e.g. ankle load during work and during hobby/sports ('Are your working/sport tasks aggravating for your ankle?' answered by 'no' (score=0) or 'yes' (light/heavy score=1)).

Potential prognostic factors in the group of non-recovered patients at three months follow-up were demographic factors (age, gender, BMI), clinical factors (setting, intervention at baseline), and outcome measures at three months follow-up (pain at rest, walking, running, re-sprains, AFS, and recovery).

Subjective recovery was measured on an 11-point numerical rating scale (range 0-10; where 0 represents no recovery and 10 full recovery).

Instability was measured with six questions about instability and a feeling of giving way, and included the following items: 1) the degree of a feeling of giving way during walking on a flat underground, 2) walking on uneven underground, 3) hill walking ascending, 4) hill walking descending, 5) sport activities (all rated on an 11-point scale ranging from 0-10), and 6) instability (rated on a 6-point scale ranging from 'never a feeling of giving way' to 'a feeling of giving way with every step'). Thereafter, stability was dichotomised into 'feeling of instability' (at least one of the answers positive) or 'no feeling of instability' (negative answers on all the questions).

Pain intensity was measured on an 11-point numerical rating scale (range 0-10, where 0 represents no pain and 10 unbearable pain).

The AFS consists of five categories: pain, instability, weight bearing, swelling, and gait pattern. In each category, the points can be summed to a maximum overall score of 100 (indicating minimal severity).[11]

One assessor, blinded for the intervention, conducted a standardized physical examination procedure at three months follow-up. This examination included pressure thresholds (tenderness of palpation: yes or no) of the ventral, distal and dorsal malleoli lateralis, an active range of motion (ROM) test and a passive stability test. These possible prognostic factors were taken into consideration for a subgroup analysis of the non-recovered patients at three months follow-up for the outcome at one year follow-up. The cut-off value for non-recovery was a score of 9 or lower on the 0-10 point scale, where 10 is full recovery.

The outcome measures of the study, assessed at one year, were recovery, the occurrence of re-sprains, subjective instability and pain intensity.

Statistical analysis

To reduce bias and improve efficiency, missing values were multiple imputed. We generated ten imputed datasets using chained equations implemented in the R routine MICE.[13] Linear (outcomes recovery, pain and ankle function) and logistic regression models (outcomes instability and re-sprains) were constructed for the total population using the potential prognostic factors from baseline, and separately for the non-recovered subjects at three months follow-up using the prognostic factors from the physical examination and the questionnaire completed at three months. For analyses of the

physical examination, only data of the subjects who underwent a physical examination at three months follow-up were included in the analyses.

First, a univariate model was constructed for each of the prognostic factors separately. Second, factors with a p-value ≤ 0.15 on the Wald test in univariate models were entered into a backward multivariate selection model. The variables with the highest p-value were removed one-by-one (Wald test), until all the remaining variables had a p-value < 0.10.Linear regression models were constructed for the potential prognostic factors at baseline and three months follow-up for the outcome measures recovery and pain during running. Logistic regression models were constructed for the use of baseline and three months variables for the outcome measures instability and re-sprains.

The results of the linear regression are presented as betas (β) with 95% confidence intervals (95%CI) and the results of the logistic regression are presented as odds ratios (OR) with 95% CI. All analyses were corrected for baseline values, and were performed with the SPSS software package (version 15.0, 2006).

RESULTS

Study population

Table 1 presents the patient characteristics and potential prognostic factors of the study population at baseline. Of the 102 patients, 64 (62.7%) contacted a GP and 38 (37.3%) a first aid physician. A total of 49 (48%) patients visited a physical therapist in addition to usual care, and 53 (52%) patients received usual care only. Nine of these patients were lost at the three months and one year follow-up periods. These nine patients did not differ significantly from patients who completed the one year study period regarding their injury grade, re-injuries and subjective recovery at the earlier follow-up moments.

Outcomes

Table 2 presents data on recovery, re-sprains, instability and pain intensity at baseline, three months and one decreased to about 50% at one year. In total 23.5% of the patients reported at least one re-injury during the first three months compared with 28.4% during the one year follow-up. At one year, 27.5% of the patients still reported a feeling of instability. About 15% of all patients experienced pain during rest at three months follow-up, decreasing to 9.8% at one year. After one year, 7.8% of the patients still experienced pain during walking, while 21.6% still experienced some pain during running at one year follow-up.

Table 1 Baseline characteristics and potential prognostic factors (n = 102)

Characteristic	Number of patients (%)
Age *(yr)*	
• < 35	53 (52%)
• ≥ 35	49 (48%)
Gender	
• Female	43 (42.2%)
• Male	59 (57.8%)
Injury grade	
• I	43 (42.2%)
• II or III	45 (44.1%)
• Unknown	14 (13.7%)
Body Mass Index	
• < 25 kg/m2	50 (49.0%)
• ≥ 25 kg/m2	42 (41.2%)
• Unknown	10 (9.8%)
Treatment	
• Usual care	53 (52.0%)
• Physical therapy	49 (48.0%)
Setting	
• General practitioner	64 (62.7%)
• Emergency department	38 (37.3%)
Earlier injury *(>2 yrs ago)*	
• No earlier injury	51 (50.0%)
• Earlier injury	44 (43.1%)
• Unknown	7 (6.9%)
Ankle load during work	
• No or light	65 (63.7%)
• Heavy	31 (30.4%)
• Unknown	6 (5.9%)
Ankle load during sports or hobby	
• No or light	47 (46.1%)
• Heavy	47 (46.1%)
• Unknown	8 (7.8%)
Self-reported swelling	
• No to light	30 (29.4%)
• Moderate to severe	65 (63.7%)
• Unknown	7 (6.9%)

Prognostic factors from baseline questionnaire

The AFS (β 0.024; 95%CI -0.01; 0.05) was univariately associated with recovery at one year follow-up, but did not reach significance (Table 3). The setting (emergency department) was univariately associated with both subjective instability and pain during running at one year follow-up; OR 2.05 and β 1.16; respectively. However, in both analyses, significance level was not reached. The occurrence of re-sprains at one year follow-up was univariately not associated with any of the ten possible prognostic factors.

Table 2 Outcomes at 3 and 12 months follow-up of the 102 patients with acute ankle sprain

Outcome	Baseline	3 months	12 months
	n(%)	*n(%)*	*n(%)*
Re-sprains *(yes/no)*	-	24 (23.5%)	29 (28.4%)
Subjective instability *(yes/no)*	91 (89.2%)	66 (64.7%)	56 (27.5%)
	Mean (SD)	*Mean (SD)*	*Mean (SD)*
Recovery *(0-10)*	-	8.33 (2.00)	8.93 (1.81)
Pain at rest *(0-10)*	1.92 (1.96)	0.35 (1.06)	0.26 (0.79)
Pain during walking *(0-10)*	3.67 (2.84)	0.37 (1.11)	0.23 (0.78)
Pain during running *(0-10)*	7.63 (2.60)	1.61 (2.29)	0.88 (1.68)

Table 3 Univariate regression analyses for subjective recovery, reported instability, resprain and pain during running after 12 months, β(Beta) or OR with 95% Confidence Intervals (95%CI)

Baseline variable	Subjective recovery (β, 95%CI)	Instability (OR, 95%CI)	Resprain (OR, 95%CI)	Pain during running (β, 95%CI)
Age	-0.01 (-0.05 ; 0.04)	1.00 (0.97 ; 1.04)	0.98 (0.94 ; 1.01)	0.02 (-0.04 ; 0.08)
Gender	-0.00 (-1.03 ; 1.03)	0.80 (0.36 ; 1.75)	1.11 (0.44 ; 2.80)	-0.06 (-1.46 ; 1.35)
BMI	-0.00 (-0.11 ; 0.11)	1.03 (0.92 ; 1.14)	0.95 (0.84 ; 1.08)	0.03 (-0.21 ; 0.28)
Randomisation	0.08 (-0.82 ; 0.97)	1.15 (0.53 ; 2.51)	0.89 (0.33 ; 2.36)	0.06 (-1.20 ; 1.32)
Setting	-0.97 (-4.06 ; 2.12)	2.05* (0.89 ; 4.71)	1.77 (0.73 ; 4.31)	1.16* (-0.30 ; 2.62)
Injury grade	-0.04 (-1.04 ; 0.97)	0.79 (0.38 ; 1.63	0.80 (0.31 ; 2.10)	0.34 (-1.03 ; 1.72)
Swelling	-0.35 (-2.32 ; 1.62)	2.14 (0.48 ; 9.58)	0.80 (0.13 ; 5.00)	0.04 (-2.89 ; 2.98)
Function score	0.02* (-0.01 ; 0.05)	0.98 (0.95 ; 1.01)	0.98 (0.96 ; 1.01)	-0.02 (-0.05 ; 0.02)
Workload	0.15 (-0.99 ; 1.30)	1.49 (0.60 ; 3.78)	1.23 (0.43 ; 3.56)	0.13 (-1.61 ; 1.88)
Sport load	-0.27 (-1.34 ; 0.80)	1.25 (0.48 ; 3.25)	0.94 (0.30 ; 2.92)	0.24 (-1.24 ; 1.72)
Pain during walking	-0.13 (-0.38 ; 0.12)	1.12 (0.91 ; 1.38)	0.57 (0.22 ; 1.51)	0.18 (-0.20 ; 0.56)

CI = Confident interval; * = $p < 0.15$; BMI = Body mass index

Prognostic factors in non-recovered patients at 3-months follow-up

A total of 75 patients (73.5%) regarded themselves as not being recovered at three months follow-up. Seven of the potential prognostic factors were univariately associated with the outcome recovery at one year. The final model (Table 4) included the variables

Table 4 Univariate and multivariate regression analyses for subjective recovery, instability, re-sprain and pain during running

3 months variable	Subjective recovery (β, 95%CI)		Instability (OR, 95%CI)		Re-sprain (OR, 95%CI)		Pain during running (β, 95%CI)	
	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate
Age	-0.01 (-0.05 ; 0.04)		0.99 (0.95 ; 1.03)		0.97 (0.91 ; 1.04)		0.01 (-0.05 ; 0.08)	
Gender	-0.02 (-1.17 ; 1.12)		0.78 (0.29 ; 2.12)		1.18 (0.29 ; 4.77)		-0.15 (-1.67 ; 1.38)	
BMI	0.00 (-0.13 ; 0.14)		0.99 (0.87 ; 1.13)		0.97 (0.81 ; 1.15)		0.01 (-0.26 ; 0.29)	
Randomisation	0.12 (-1.12 ; 1.37)		0.95 (0.35 ; 2.59)		0.44 (0.09 ; 2.10)		0.09 (-1.75 ; 1.92)	
Setting	-0.45 (-1.68 ; 0.77)		1.90 (0.66 ; 5.47)		2.69 (0.69 ;10.42)		1.21* (-0.22 ; 2.64)	1.11 (-0.53 ; 2.76)
Re-sprain	-0.20* (-2.16 ; 1.76)	-1.64# (-3.11 ; -0.16)	4.95 (0.52 ; 47.47)		1.06 (0.12 ; 9.13)		1.83 (-1.00 ; 4.66)	
Pain *(rest)*	-0.74* (-1.21 ; -0.27)	-0.69# (-1.08 ; -0.29)	1.80 (0.76 ; 4.26)		1.26 (0.81 ; 1.96)		0.39 (-0.25 ; 1.03)	
Pain *(walking)*	-0.72* (-1.12 ; -0.32)		213682109.72 (0 ; ∞)		1.27 (0.79 ; 2.04)		0.50 (-0.15 ; 1.15)	
Pain *(running)*	-0.34* (-0.60 ; -0.08)		1.72* (1.15 ; 2.54)	1.48 (0.99 ; 2.23)	1.12 (0.88 ; 1.44)		0.35* (0.01 ; 0.68)	
Ankle Function Score (AFS)	0.04* (0.01 ; 0.06)		0.95* (0.91 ; 0.99)		0.99 (0.95 ; 1.02)		-0.04* (-0.08 ; 0.00)	-0.05# (-0.09 ; -0.01)
Recovery	0.33* (0.03 ; 0.63)		0.34* (0.14 ; 0.80)		0.97 (0.70 ; 1.36)		-0.40* (-0.84 ; 0.04)	
Instability	-0.95* (-2.21 ; 0.32)		16.61* (4.02 ; 68.72)	6.89 (0.30 ; 159.17)	2.47 (0.29 ; 20.73)		1.31 (-0.45 ; 3.07)	

CI = Confident interval, * = $p < 0.15$, # = $p < 0.05$

having re-sprains during three months follow-up (β -1.64; 95%CI -3.11; -0.16) and having pain at rest at three months follow-up (β -0.69; 95%CI -1.08; -0.29). Subjective instability at one year follow-up was univariately associated with four potential prognostic factors (pain during running, AFS, recovery, and instability at three months follow-up). After backward selection, the final multivariate model included pain during running [OR 1.48 (95%CI 0.99; 2.23)] and instability [OR 6.89 (95%CI 0.30; 159.17)] at three months follow-up. However, these factors did not reach significance.

Pain during running at one year follow-up was univariately associated with four potential prognostic factors (setting, pain during running, AFS, and recovery at three months follow-up). The AFS at three months follow-up [β -0.05 (95%CI -0.09; -0.01)] and setting [β 1.11 (95%CI -0.53; 2.76)] were included in the final multivariate model; however, only the AFS was significantly associated with pain during running at one year follow-up [β -0.05 (95%CI -0.09; -0.01)].

Of the 75 patients who were not fully recovered at three months follow-up, 63 (84%) underwent the physical examination at three months follow-up. The patients who did not show up at the physical examination were on average younger (36.5 vs 34.8), had a higher BMI (25.5 vs. 26.5) and were more often treated with physical therapy (40% vs 70%). There was no univariate association with one of the five possible prognostic factors from the physical examination at three months follow-up for subjective recovery at one year follow-up. Pain during running and the occurrence of re-sprains were both univariately associated with the pressure threshold of the ventral malleoli lateralis. The univariate association for both outcomes was, however, not significant: [β 0.75 (95%CI 0.21;1.30)] and [β 0.54 (95%CI -0.09; 1.16)], respectively.

Finally, reported instability at one year follow-up was univariately associated with the pressure thresholds of the ventral, distal and dorsal malleoli lateralis. The final multivariate model included the pressure thresholds of the ventral [OR 2.03 (95% 0.99; 4.15)] and dorsal malleoli lateralis [4.26 (95%CI 1.14; 15.96)]; only the association with the dorsal malleoli lateralis was significant (p=.035).

DISCUSSION

In the present study, 51% of the patients with a lateral ankle sprain were not fully recovered at one year follow-up. The regression analyses of possible prognostic factors at baseline for persistent complaints showed that there is no strong predictor for the outcome at one year follow-up.

The second analyses for the prognosis in the subgroup of non-recovered patients at three months follow-up, showed that factors from the three month questionnaire can

better predict the outcome compared to the factors from the physical examination at three months.

At one year, 28.4% of the patients reported at least one re-injury, which is in line with earlier studies reporting that 29% [14] and 54% [15] of the subjects receiving usual care sustained a re-injury at approximately twelve months follow-up. In our study, 49% of the patients were regarded as recovered at one year. This is comparable with the outcome of a recent systematic review showing that 36%-85% of the patients reported full recovery at two weeks to 36.2 months follow-up after ankle sprain injuries.[3]

Several studies have investigated pain after a lateral ankle sprain.[16-18] The proportion of patients experiencing pain after at least one year ranged from 5-33%.[3] Our study results are similar to these findings, but only 7.8% of our patients reported pain during walking while 21.6% still experienced some pain during running at one year follow-up.

We found no prognostic factors at baseline for the prediction of outcome at one year follow-up. None of the possible prognostic factors were univariately associated with one of the primary or secondary outcome measures. The fact that we did not find any significant association could be related to the small number of subjects included in the analyses. Further, other prognostic factors, not included in our analyses, might predict the outcome at one year follow-up. To our knowledge, the study of Linde et al. is the only one evaluating prognostic factors for incomplete recovery and re-sprains.[8] In their study, sports activity at a high level (training ≥3 times a week) was a significant prognostic factor for residual symptoms compared with sports activity at a low level (training <3 times a week), and no sports activity. Unfortunately, our questionnaire did not include detailed questions about sports activities of the patients. Although we did ask subjects if the ankle was loaded during sport activities, this factor does not appear to have a positive or negative influence on recovery, re-sprains, or pain of the subjects.

Because there might be factors during the one year follow-up that can predict the outcome at one year, we analyzed the three monthly data with respect to subjective and objective prognostic factors. These analyses showed that a low AFS at three months predicts a high score on pain during running at one year follow-up. Further, a positive association was found between re-sprains during three months follow-up and subjective recovery at one year. About 24% of the patients had a re-sprain during the first three months of follow-up. Of these, 37% regarded themselves as being recovered at one year. Additionally, only 30% of the subjects with a re-sprain during one year follow-up regarded themselves as recovered at one year follow-up. Therefore, it seems that the occurrence of a re-sprain predicts the subjective feeling of recovery. Because of this, we tested the association between re-sprains occurring between months three and twelve, and recovery at one year follow-up, in both the total study population and for the non-recovered patients at three months follow-up. These analyses showed a strong significant association between re-sprains and recovery [β -3.12 (95%CI -4.86; -1.37) and

β -2.97 (95%CI -4.43; -1.51), respectively]. Therefore, studies focusing on the prevention of re-sprains after an ankle sprain might interfere with this relationship and might have a positive effect on subjective recovery of ankle sprain patients.[19]

The physical examination at three months follow-up does not appear to have an additional value in the prediction of recovery at one year. Only one factor from the physical examination at three months follow-up appeared to predict the outcome at one year follow-up, i.e. the pressure threshold on the dorsal malleoli lateralis is positively associated with subjective instability of the ankle at one year. The fact that we hardly found an association with any of the factors from the physical examination could be related to the small number of patients included in the analysis. Moreover, because in-depth data on the physical examination were lacking, we could only include five possible prognostic factors in the analyses. However, from the available data, we conclude that the physical examination performed at three months follow-up does not offer any additional value on the prediction of the outcome at one year follow-up.

Limitations

Our sample of patients was studied prospectively and can be considered as a cohort of patients with acute ankle sprains in which the interventions were regarded as potential prognostic factors. The interventions studied in the RCT were strictly protocolised, which resulted in less treatment heterogeneity than in most other population-based cohort studies. Physical therapy treatment was considered to be a prognostic factor, but no significant treatment effect was found.[7]

Because the data used in this study were derived from an RCT investigating the effectiveness of supervised exercise in primary care, some selection bias of patients might have occurred. Also, a selection bias might have occurred in the patient group who underwent the physical examination compared to the total study population.

The severity of the injury was dichotomised into grade I versus grade II, III. This dichotomisation was made because only four of the 102 patients who presented themselves to the GP (n=2) or emergency department (n=2) had a grade III ankle sprain. However, the same results were derived in the analyses when excluding the patients with injury grade III.

Both the possible prognostic factors from the baseline questionnaire and the outcomes are self-reported and, therefore, subjective. However, since there are no validated objective outcome measures available for patients with an acute lateral ankle sprain, the use of validated subjective outcome measures seems appropriate. Nevertheless, some factors and outcomes may not be completely reliable because of their subjective nature.

Finally, this study evaluates the possible association of prognostic factors from the baseline questionnaire, the three month questionnaire and physical examination with recovery, re-sprains, instability and pain intensity. Because of the relatively small number

of subjects included in this RCT we could not evaluate more (possibly prognostic) factors. In addition, because this study was not primarily designed to evaluate prognostic factors, we could have missed some factors (e.g. sports participation) that might be associated with poor recovery. The final model could have been over-fitted because of the number of subjects in our three month analyses, and the number of possible prognostic factors included in the model.

Implications for practice

This study shows that re-sprains sustained during the first three months after the initial sprain, and pain at rest at three months follow-up, are related to incomplete recovery after one year. Additional data from Linde et al.[8] show that sports activity at high level is a prognostic factor for residual symptoms compared to sports activity at low level and no sport. A GP or physical therapist should take these factors into account when advising a patient about treatment options and possible preventive measures. More active people can be advised to support their ankle with semi-rigid braces during high-risk activities or to perform proprioceptive training, as there is evidence that this can prevent sprains, especially in patients with previous ankle sprains.[19,20]

In conclusion, our predictive model has very few implications for clinical practice. Of the patients reporting persistent complaints at three months follow-up, 51% still report persistent complaints at one year follow-up. Unfortunately, we did not find any clear predictive factors from the three month evaluation for the outcome at one year follow-up. Only re-sprains can predict a negative recovery outcome at one year follow-up. Therefore, we have to conclude that more research is needed to evaluate prognostic factors for poor recovery, re-sprains and residual pain. The prognosis might be improved by use of additional diagnostic tests, such as MRI and X-ray. A large cohort study may be helpful to identify patients at risk and to evaluate the consequences of these persistent complaints.

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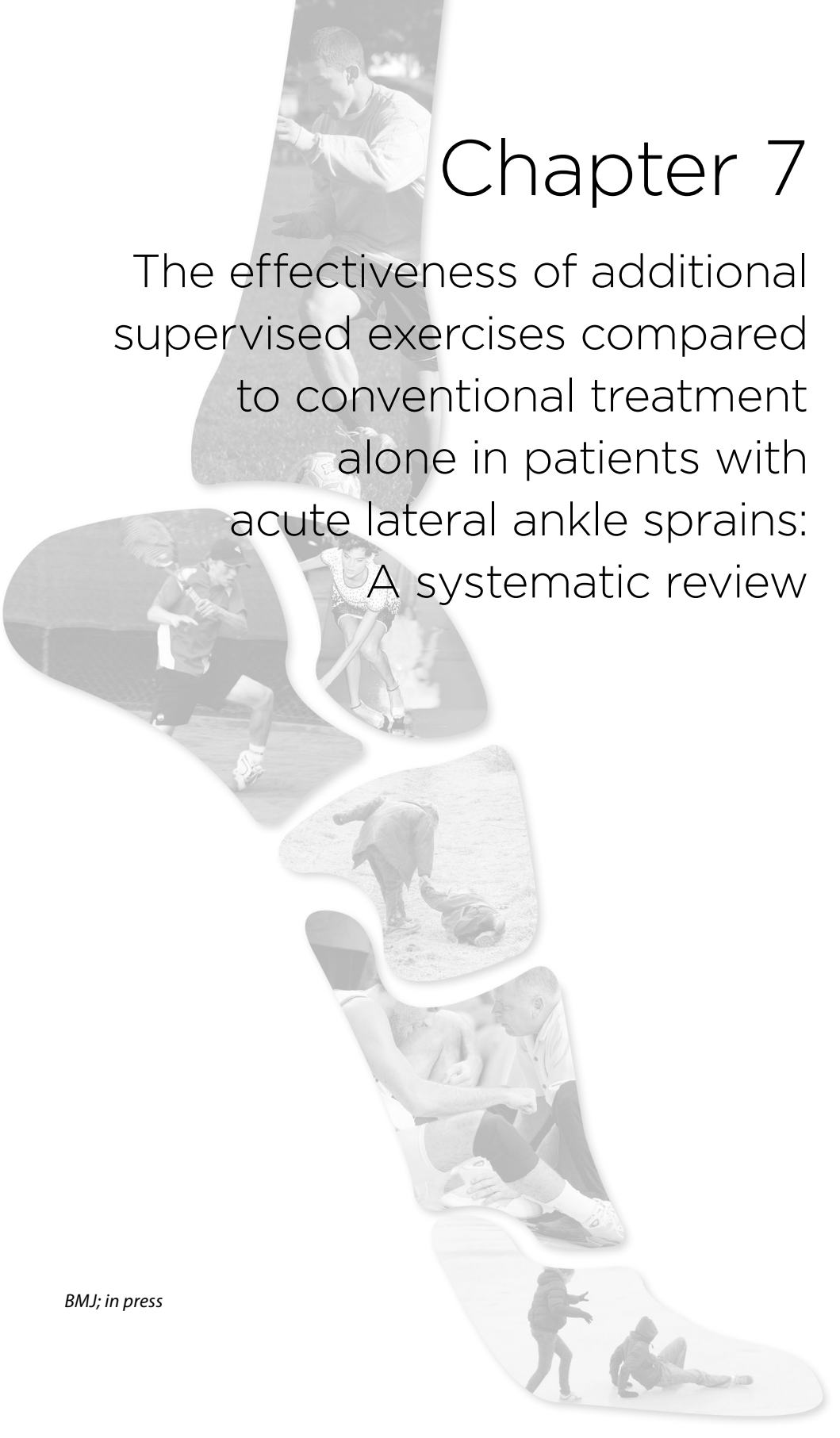

Chapter 7

The effectiveness of additional supervised exercises compared to conventional treatment alone in patients with acute lateral ankle sprains: A systematic review

BMJ; in press

ABSTRACT

The effectiveness of supervised exercises as supplied by a physical therapist is uncertain. Therefore, the objective of this study is to summarise the available evidence for the effectiveness of supervised exercises in addition to conventional treatment, compared with conventional treatment alone, in patients with an acute lateral ankle sprain.

A database search was conducted using Medline, Embase, the Cochrane Central Register of Controlled Trials, and Cinahl. Besides, references of relevant articles were screened.

Studies were selected when: the design was a randomised clinical trial (RCT), a quasi-RCT, or a controlled clinical trial; patients were adolescents or adults with an acute lateral ankle sprain; one of the treatment options consisted of conventional treatment; or one of the treatment options consisted of conventional treatment combined with supervised exercises. Two reviewers independently assessed the risk of bias, and one reviewer extracted data. Due to clinical heterogeneity the data were analysed using a best-evidence synthesis.

A total of eleven studies were included. There is limited to moderate evidence to suggest that the addition of supervised exercises to conventional treatment leads to a faster and better recovery, and a faster return to sports at short-term follow-up, when compared to conventional treatment alone. In a specific population (athletes, soldiers and patients with severe injuries) this evidence was restricted to a faster return to work and sports only.

In conclusion, there is moderate or limited evidence for effectiveness in favour of additional supervised exercises compared to conventional treatment alone, according to the outcome measures recovery and return to sports at short-term follow-up. For none of the outcome measures strong evidence was found for effectiveness. In a more specific population, limited to moderate evidence for effectiveness was found. Most of the eleven studies had a high risk of bias and few had adequate statistical power to detect clinically relevant differences. These results suggest that further high-quality RCTs should be conducted to determine the effectiveness of additional supervised treatment, especially in specific populations such as athletes and patients with severe injuries.

INTRODUCTION

Lateral ligament ankle sprains are one of the most commonly encountered musculoskeletal injuries.[1] It is reported that up to 23,000 and 5000 acute lateral ligament injuries occur daily in the USA and the UK, respectively.[1,2] In the Netherlands about 600,000 people sustain an ankle injury each year, of which about 120,000 are the result of sporting injuries; of these, it is estimated that about 43,000 people present for medical care.[3,4] General practitioners (GPs) in the Netherlands see around 125,000 patients with an ankle sprain each year, with an incidence of eight per thousand patients per year.[5] A recent systematic review evaluated the clinical course of conventionally treated acute ankle sprains and found that at one year follow-up 5-33% of the patients still experienced pain and instability, that 34% of the patients reported at least one re-sprain, and that 15-64% reported that they had not recovered fully from their initial injury.[6] Despite the high incidence of acute ankle sprains and their associated burden to society, and considering the (often) poor clinical course, optimal treatment and rehabilitation for these injuries has yet to be established.

There are indications that balance training and coordination exercises as part of a formal rehabilitation protocol reduce proprioceptive deficits, symptoms of giving way and risk of re-injury, and improve postural control.[7-9] In addition, it is reported that: I) functional treatment of the ankle (defined as the use of an elastic bandage, tape, lace-up ankle support, or semi-rigid ankle support) results in a quicker return to sports and work compared to immobilisation, II) there is no evidence that surgery is better than functional treatment or immobilization, and III) a semi-rigid ankle support is preferable to the use of an elastic bandage or tape.[10-12]

Protection of the ankle by means of functional treatment is needed to avoid stress to the scar tissue in the inflammatory phase of tissue healing. In the subsequent proliferative and maturation phases, the emphasis is on the alignment and strengthening of the newly-formed collagen fibres.[13] Physical therapists use this knowledge on tissue healing to construct an exercise program for patients with an acute ankle sprain.[14] However, the effectiveness of supervised exercises as administered by a physical therapist remains uncertain.

Therefore, the aim of this systematic review is to compare the effectiveness of conventional treatment (non-surgical treatment: i.e. immobilization, non-supervised treatment involving exercise instructions or use of external support) combined with supervised exercises, with conventional treatment alone, for the rehabilitation of acute lateral ankle sprains. Since the effectiveness can differ between populations[15,16] and may depend on the type of conventional treatment used, or on the severity of the injury, or on the exposure to activities sustainable for a high-risk of (re-)sprains, we also evaluate the added

value of supervised exercises in specific populations, as well as the type of conventional treatment.

METHODS

Literature search

As a starting point for our review, we identified all included references of an earlier review by our group (Van Os et al.[17] which covered the same topic as the present review) who used a literature search up to March 2004. Their material was supplemented with a literature search in electronic databases (Medline, Embase, Cochrane Central Register of Controlled Trials, and Cinahl) covering the period from March 2004 through July 2010, using the same search strategy as reported by van Os et al. (Table 1).[17]

Table 1 Search strategy used for the present study

Studies	((randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial" [tw]) OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR ("latin square" [tw]) OR placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study[pt] OR evaluation studies[pt] OR follow-up studies [mh] OR prospective studies [mh] OR cross-over studies [mh] OR control* [tw] OR control[tw] OR controlled[tw] OR controled[tw] OR controls[tw] OR prospectiv* [tw] OR volunteer* [tw]) NOT (animal [mh] NOT human [mh]))
Location	(ankle OR talocrural OR (anterior AND talofibular AND ligament) OR (posterior AND talofibular AND ligament) OR (calcaneofibular AND ligament) OR (lateral AND ligament AND complex))
Injury	(ankle OR talocrural OR (anterior AND talofibular AND ligament) OR (posterior AND talofibular AND ligament) OR (calcaneofibular AND ligament) OR (lateral AND ligament AND complex)) AND (inversion OR sprain OR strain OR rupture OR injur* OR distortion)
Treatment	(training OR therapy OR treatment OR rehabilitation OR exercise OR physiotherapy OR (early AND mobilisation))

Two reviewers (RMvR and PAJL) independently selected the articles, initially based on title and abstract. For final inclusion the articles had to fulfil all of the following criteria: 1) the adolescent and adult subjects in the study had to have an acute lateral ankle sprain, 2) at least one of the treatment options consisted of a conventional treatment (defined as either immobilization, such as in a plaster cast, non-supervised treatment involving exercise instructions or use of external support), 3) at least one of the treatment options consisted of conventional treatment combined with supervised exercises, 4) the study design had to be either an RCT or a quasi RCT, or a controlled clinical trial.

Studies involving post-surgical treatment or treatment of recurrent ankle injuries or chronic instability were excluded.

The assistance of a native speaker was obtained for studies published in languages other than English, German or Dutch. A consensus method was used to resolve any disagreements. Finally, the references of all included studies were checked for possible relevant articles.

Assessment of risk of bias

Risk of bias of the included studies was assessed by pairs of reviewers (RMvR, JvO and MvM) independently, using the Cochrane collaboration's tool for assessing risk of bias (RMvR assessed all studies, except the study for which he is first author; RMvR was not involved in any decision regarding this trial).[18] This tool is adapted for the objective of this review and consists of five domains, with eleven items in total (Appendix I). Each item was rated as 'yes', 'no', or 'unsure'. Disagreements were resolved in a consensus meeting. Studies with six or more points on the risk of bias assessment were regarded as studies with a low risk of bias. The interpretation of the risk of bias tool was pre-tested using two studies that focused on the effectiveness of physical therapy treatment in patients with low back pain (a physical condition outside the scope of this review).

Data extraction

One reviewer (RMvR) extracted relevant data from the included studies. Study characteristics extracted were: information on target population (age, gender, setting, injury grade, sample size), treatment, outcome measures, and duration of follow-up. Outcome measures extracted (if present) were: pain, instability (feeling of 'giving way'), re-sprain, return to sport and work, recovery, and functional scores. In case of uncertainty about the extracted data from the included studies, a second reviewer (MvM) was consulted.

The core findings in each article were expressed as estimates, relative risks (RR) or effect sizes (ES), with corresponding 95% confidence interval (95% CI). Where possible, these measures were directly extracted from the article. For articles in which this information was not presented, these measures were calculated if enough data were available. Outcome measures were presented according to follow-up time, and therefore grouped into the following categories: 1) short term (within two weeks of randomization), 2) intermediate term (between two weeks and three months follow-up), and 3) long term (longer than three months follow-up).[6]

Data analysis

The main comparison in this review is of any conventional treatment versus conventional treatment with additional supervised exercises. A secondary objective was to evaluate the results of the main comparison in vulnerable populations with a high risk for (re-)

sprains or with increased risk for slower improvement. Athletes show an increased risk for (re-)sprains[15] and patients with a severe injury are reported to have slower improvement[16]. Therefore, we defined these populations as specific vulnerable populations. Finally, we present the results classified by type of conventional treatment.

Statistical pooling was performed when studies were clinically homogeneous concerning population, intervention and outcome measures. In case of clinical heterogeneity the data were analysed using a best-evidence synthesis.[19] This rating system consists of four levels of scientific evidence based on the quality of the studies: 1) strong evidence; provided by generally consistent findings in multiple RCTs assessed as having low risk of bias, 2) moderate evidence; provided by generally consistent findings in one RCT assessed as having low risk of bias, and one or more RCTs assessed as having high risk of bias or by generally consistent findings in multiple RCTs assessed as having high risk of bias, 3) limited or conflicting evidence; only one RCT (either assessed as having low or high risk of bias) or inconsistent findings in multiple RCTs, and 4) no available evidence; no RCTs.

RESULTS

Literature search

Our search resulted in 2,946 potentially relevant articles. From titles and abstract we identified 41 articles. Of these, three articles met our inclusion criteria after reviewing the full text.[20-22] Multiple publications were found reporting on the same data for Van Rijn et al.[16,22] Information from both these publications was used for the methodological quality assessment and data extraction, but only the first or most prominent publication was used for citation of these studies. In addition, we examined the original search results of an earlier review by Van Os et al.[17] on the same topic and found one additional article.[23] Combined with the articles already included in the review of Van Os et al.[17] a total of eleven articles were included in the present review (Figure 1).

Assessment of risk of bias

Figure 2 presents the overall assessment of the risk of bias, and Table 2 shows assessment of the risk of bias of the individual studies. The initial agreement of the reviewers on the total assessment of risk of bias was 80.2% (97 of 121 items). All the initial disagreements were solved in a consensus meeting. Ten studies were assessed as having high risk of bias[20,21,23-30] and one study was assessed as having low risk of bias.[22] The most prevalent shortcomings were found in the items on blinding (patient, care provider, outcome assessor), allocation concealment, and similarity of treatment groups at baseline.

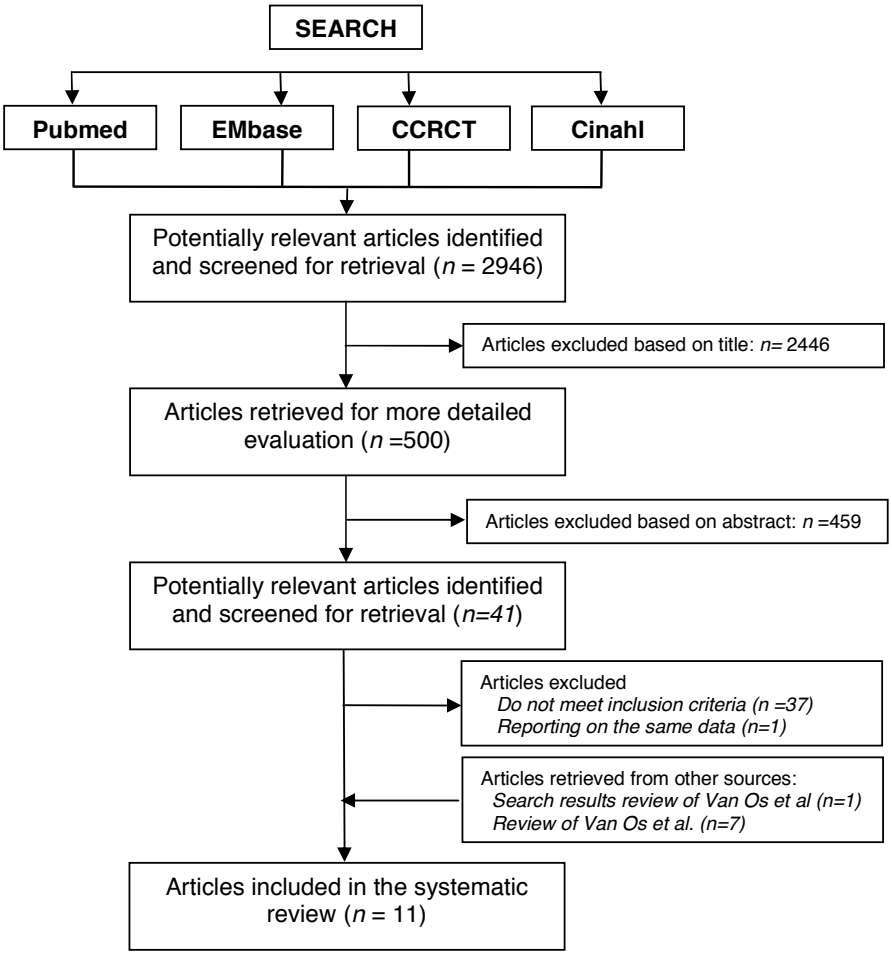

Figure 1 Flow chart of the selected articles. CCRCT = Cochrane Central Register of Controlled Trials

Description of included studies

Table 3 presents the characteristics of the included studies. Conventional treatment in the included studies consists of a variety of therapies, namely: no treatment, ice application, partial immobilisation (tape, brace, or bandage), complete immobilisation (plaster cast), a home exercise program, early ankle mobilization instructions, or a combination of these treatments. Supervised exercises consist of physical therapist visits in which the patients focused on strength, mobility and balance exercises whether or not combined with the use of a balance or wobble board.

The included studies were considered too heterogeneous to perform a meta-analysis. Therefore, we refrained from pooling and performed a best-evidence synthesis (Table 4). In addition, the contrast between the types of conventional treatments was too small to perform an analysis grouped by type of treatment. For that reason, we describe the

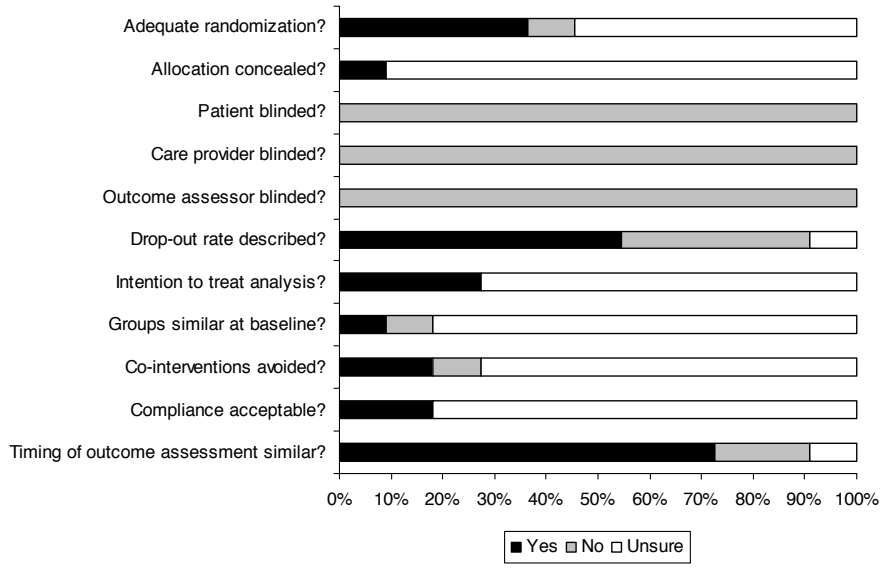

Figure 2 Results of risk of bias assessment. Frequency (%) of scores per item (yes, no, unsure)

Table 2 Results of the risk of bias assessment of the individual studies with scores per item.

Authors	1. Adequate randomization?	2. Allocation concealed?	3. Patient blinded?	4. Care provider blinded?	5. Outcome assessor blinded?	6. Drop-out rate described?	7. Intention-to-treat analysis?	8. Groups similar at baseline?	9. Co-interventions avoided?	10. Compliance acceptable?	11. Timing of outcome assessment similar?	Total score
Basset et al.[20]	+	?	-	-	-	+	?	-	?	+	?	3
Brooks et al.[24]	?	?	-	-	-	-	?	?	+	?	+	2
Holme et al.[25]	+	?	-	-	-	+	+	+	?	?	+	4
Hultman et al.[21]	-	?	-	-	-	-	?	?	?	?	+	1
Karlsson et al.[23]	?	?	-	-	-	+	?	?	?	?	-	1
Nilsson[26]	?	?	-	-	-	+	+	?	-	?	-	2
Oostendorp[27]	?	?	-	-	-	?	?	?	?	?	+	1
Reinhardt et al.[28]	?	?	-	-	-	+	?	?	?	?	+	2
Roycroft et al.[29]	?	?	-	-	-	-	?	?	?	?	+	1
Van Rijn et al.[22]	+	+	-	-	-	+	+	?	?	+	+	6
Wester et al.[30]	+	?	-	-	-	-	?	?	+	?	+	3

+ = yes; - = no; ? = unsure

Table 3 Characteristics of the 11 studies included in the present review

Author	Study population	Conventional treatment	Supervised treatment
Basset et al.[20]	47 (52) patients with an acute ankle sprain (first-time or recurrent) recruited from 4 physical therapy clinics in middle to low socioeconomic suburbs: 60% male; mean age 30±12.4 yr; injury grade: 38% mild, 51% moderate, 11% severe; re-sprain 55%	Home-based intervention program -Small home program of no more than 4 simple activities - Equipment such as strapping tape, Tubigrip for compression, Thera-band resistance bands, and wobble boards. - Treatment booklet; information about structure of the ankle, ankle sprains, diary grids, progress sheets, adherence enhancing, and the 3 treatment phases: 1. Acute (36-48 hr): RICE, and active ankle movements within the limits of pain 2. Mobilizing (10-14 days): mobilizing and strengthening exercises, calf and heel stretches, ankle strapping/taping 3. Strengthening (10-14 days): Thera-band resistance, body-weight resistance in standing, one-leg standing, standing on wobble board, weight bearing activities, ankle strapping	Clinic-based intervention program - Small home program of no more than 4 simple activities - Physical therapist treated symptoms, and supervised the activities/exercises of a 3-phase physical therapy program: 1. Acute (36-48 hrs): RICE, and active ankle movements within the limits of pain 2. Mobilizing (10-14 days): mobilizing and strengthening exercises, calf and heel stretches, ankle strapping/taping 3. Strengthening (10-14 days): Thera-band resistance, body-weight resistance in standing, one-leg standing, standing on wobble board, weight bearing activities, ankle strapping
Brooks et al.[24]	102 (241) patients with inversion injury, with a talar tilt <15°, who attended the local emergency department: age 12-65 yr	Treatment groups: 1. No treatment, no support or only a minimal bandage 2. Double Tubigrip support to wear during daytime and advised to remove in bed at night 3. Ankle completely immobilized in a below-knee plaster-of-Paris cast, but patients were encouraged to bear weight as soon as possible	First day or within 48 hr of presentation: - iced foot bath, mobilization, instruction in normal gait. Second or third visit: - wobble board exercises Treatment was considered complete when the patient could tolerate 10 min on the wobble board

Table 3 Continue

Author	Study population	Conventional treatment	Supervised treatment
Holme et al.[25]	71 (92) patients, all recreational athletes, with an ankle sprain sustained during sports who attended the local emergency department: 62% male; mean age 26.5 yr; injury grade: 30% mild, 53% moderate, 17% severe	Information regarding early ankle mobilization, including strength, mobility, and balance exercises	Information regarding early ankle mobilization, including strength, mobility, and balance exercises, combined with supervised group physical therapy rehabilitation (1 hr, twice weekly): - comprehensive balance exercises on both legs - figure-of-eight running - standing on a balance board and catching a ball - standing on the outside of the feet - standing on the inside of the feet with open and closed eyes
Hultman et al.[21]	65 (115) with an ankle sprain who attended emergency department: 54% male; mean age 35 (18-65) yr	Examination of the ankle, initial weight-unloading with crutches, elastic wrap, and verbal and/or written information from the attending physician or nurse about mobilization and early weight-bearing, followed by two visits to the physiotherapist (6 weeks, 3 months): - early range of motion training - weight-bearing on injured ankle - balance and strength training - instructions for home exercises	Examination of the ankle, initial weight-unloading with crutches, elastic wrap, and verbal and/or written information from the attending physician or nurse about mobilization and early weight-bearing, followed by 4 visits to the physiotherapist (baseline, 3 weeks, 6 weeks, 3 months): - early range of motion training - weight-bearing on injured ankle - balance and strength training - instructions for home exercises

Author	Study population	Conventional treatment	Supervised treatment
Karlsson et al.[23]	84 (86) consecutive patients, active in sports on recreational or competitive level, with ligament ruptures of the ankle: 66% male; mean age 22 (16-38) yr; injury grade: 59% moderate, 41% severe	Elastic wrapping, partial weight bearing and crutches until the pain subsided	Functional treatment - compression pads - early weight bearing Range of motion training - dorsal and plantar flexion - supination proprioceptive training - standing on one leg with eyes closed - walking along zig-zag lines Strength training - rubber cords - weight boots
Nilsson[26]	118 (180) patients with injury to the lateral ankle ligaments (classified as 'rupture' or 'no rupture'), occurred within the last 6 hr, who attended the local emergency department: 59% male; mean age 33.6 (15-66) yr	Elastic wrapping only (n=59)	Elastic wrapping and cryotherapy combined with physiotherapy starting on the 5th day after injury: - limbering exercises of the ankle - ultrasound treatment to the lateral side of the ankle - coordination exercises - strengthening exercises of the fibular muscles (n=59) Each session lasted 45 min, and was given daily until patient was symptom free or had received 10 treatments.
Oostendorp[27]	24 (24) patients with inversion injury of the ankle, sustained during volleyball, basketball, handball or soccer, who attended physical therapy practices: 67% male; mean age 22.1 (15-30) yr	Cryotherapy, compression bandage and minimal weight bearing followed by 6 wk tape bandage	Cryotherapy, compression bandage and minimal weight bearing followed by 6 wk tape bandage combined with a standardized progressive training program (3 physical therapy sessions a week, daily home exercises): stability exercises - disturbance in balance - variation in posture - visual control isometric strengthening exercises - manual resistance

Table 3 Continue

Author	Study population	Conventional treatment	Supervised treatment
Reinhardt et al.[28]	72 (80) patients, consisting of recruits and professional soldiers, with acute ankle sprain: mean age 22.6 yr	Early functional treatment: - Aircast brace - non-weight bearing - cryotherapy - elevation for 3-5 days	Early functional treatment: - Aircast brace - non-weight bearing - cryotherapy - elevation for 3-5 days 6 physical therapy sessions: - proprioceptive training (balance board, rough terrain) - limbering exercises - strengthening exercises - home exercises (n=47)
Roycroft et al.[29]	43 (98) patients with inversion injury of the ankle who attended the local emergency department: injury grade: 47.5% mild, 52.5% moderate	Wool and elastoplasts bandage or plaster of Paris back slab, non weight bearing (n=37)	Immediate active treatment (RICE) and full weight bearing, after 24 hr referred to physical therapy: - ultrasound - taping - tubigrip support - mobilization and rehabilitation (n=43)
Van Rijn et al.[22]	102 (107) patients with an acute lateral ankle sprain, who attended the GP or local emergency department: 58% male; mean age 37.0 yr; injury grade 42% mild, 40% moderate, 4% severe, 14% unknown	Early ankle mobilization, home exercises, early weight bearing, and tape, bandage or brace (n=53)	Early ankle mobilization, home exercises, early weight bearing, and tape, bandage or brace Progressive training program supervised by a physiotherapist (max. 9.5 hr sessions, within 3 months): - balance exercises - walking - running - jumping (n=49)
Wester et al.[30]	48 (61) patients, active in sports >2 hr/week, with a primary ankle sprain who attended the local emergency department: 60% male; mean age 25 (±7.2) yr; injury grade: moderate	Compression bandage for 1 wk, leg elevation and immobilization for 2 days, avoiding activities straining the lateral ligaments, and return to sports activities was not permitted until ADL were possible without pain.	Compression bandage for 1 wk, leg elevation and immobilization for 2 days, avoiding activities straining the lateral ligaments, and return to sports activities was not permitted until ADL were possible without pain, 12 wk training program (15 min/day), using a wobble board

Hr = hour, wk = week, yr = year, ADL = activities of daily living

Table 4 Results of the best-evidence synthesis

Outcome	Follow-up	Studies	Effectiveness #	Best-evidence synthesis
Pain	Short term	2 HR RCT[26,30]	No, No	Moderate evidence no effectiveness
	Intermediate term	2 HR RCT[27,30] 1 LR RCT[22]	Yes, No No	Conflicting evidence
	Long term	2 HR RCT[26,27] 1 LR RCT[22]	No, No No	Moderate evidence no effectiveness
Instability	Short term	-	-	No available evidence
	Intermediate term	2 HR RCT[27,28] 1 LR RCT[22]	No, No No	Moderate evidence no effectiveness
	Long term	3 HR RCT[26,27,30] 1 LR RCT[22]	No, No, Yes No	Conflicting evidence
Recovery	Short term	1 HR RCT[29]	Yes	Limited evidence effectiveness
	Intermediate term	1 LR RCT[22]	No	Limited evidence no effectiveness
	Long term	1 LR RCT[22]	No	Limited evidence no effectiveness
Function	Short term	2 HR RCT[20,21]	No, Yes	Conflicting evidence
	Intermediate term	-	-	No available evidence
	Long term	1 HR RCT[23]	No	Limited evidence no effectiveness
Re-sprain	Short term	-	-	No available evidence
	Intermediate term	1 HR RCT[28] 1 LR RCT[22]	No No	Moderate evidence no effectiveness
	Long term	3 HR RCT[25,26,30] 1 LR RCT[22]	Yes, No, No No	Conflicting evidence
Return to work	Short term	5 HR RCT[21,23,24,26,28]	No, Yes, NA, NA, Yes	Conflicting evidence
	Intermediate term	1 HR RCT[27]	No	Limited evidence no effectiveness
	Long term	1 HR RCT[27]	No	Limited evidence no effectiveness
Return to sport	Short term	2 HR RCT[23,28]	Yes, NA	Limited evidence effectiveness
	Intermediate term	1 HR RCT[27]	Yes, No*	Conflicting evidence
	Long term	1 HR RCT[27]	No	Limited evidence no effectiveness

HR = High risk of bias; LR = Low risk of bias; RCT = Randomised controlled trial; NA = Not applicable, due to incomplete data. # 'No' = No difference in effectiveness between treatment groups; 'Yes' = Effectiveness of conventional treatment combined with supervised exercises compared to conventional treatment alone. * One study described two follow-up moments (6 and 12 weeks) measuring 'return to sport' which are part of the intermediate-term follow-up. No differences between treatment groups were found at 6 weeks, whereas a significant difference was found at 12 weeks follow-up in favour of supervised exercises.

results of the main comparison per outcome measure but, where possible, evaluate the results by distinguishing between high-risk populations.

Six studies included a vulnerable population consisting of patients active in sports >2 h/week[30], patients who sustained an ankle sprain during sports[25,27], patients active in sports on a recreational or competitive level[23], recruits and professional soldiers[28], and patients with a severe injury[22]. Table 5 presents the results of the studies per outcome measure classified by duration of follow-up.

Effectiveness of supervised exercises

Pain

Four studies described pain as an outcome measure, of which three with high risk of bias[26,27,30], and one with low risk of bias.[22] Pain was measured using a visual analogue scale[22,27], or by presenting the number of patients reporting pain.[26,30] Two studies measured pain intensity on several occasions (e.g. at rest, during walking, and during sports)[22,30], whereas the other studies did not specify pain intensity. Conventional treatment corresponds roughly in three out of four studies. Oostendorp[27] used a more reserved policy in the first week of rehabilitation by prescribing cryotherapy, compression bandage and minimal weight bearing, whereas the other studies promote early ankle mobilization or early weight bearing. The effect of additional supervised exercises was assessed in the study of Oostendorp[27] at intermediate follow-up, whereas the other studies found no significant difference between treatment groups. Therefore, the evidence of effectiveness is conflicting. None of the studies describing pain as an outcome measure found a significant difference between treatment groups at short-term[26,30] and long-term[22,26,27] follow-up, resulting in moderate evidence of no effectiveness.

In a subgroup of studies with a population consisting of athletes, conflicting evidence for effectiveness (intermediate term), and moderate evidence for no effectiveness (short and long term), was found.[27,30] In contrast, there is limited evidence for effectiveness in patients with severe injuries at intermediate follow-up.[22]

Instability

Five studies, four with high risk of bias[26-28,30] and one with low risk of bias[22], presented instability as an outcome measure to evaluate the effectiveness of additional supervised exercises. Four studies measured instability or 'feeling of giving way' by using a questionnaire[22,26,28,30]; one study did not provide information on measuring instability[27]. All studies present the number of patients reporting instability. Conventional treatment corresponds roughly in three out of five studies.

In the studies of Oostendorp[27] and Reinhardt et al.[28], a more reserved policy in the first week of rehabilitation was used by prescribing cryotherapy, compression bandage

or aircast brace, and minimal weight bearing, whereas the other studies promote early ankle mobilization or early weight bearing as much as pain allowed.

From the study of Wester et al.[30] no relative risks could be calculated; however, a significant difference in the number of patients with instability was reported on the long-term follow-up. No differences were found in the other studies concerning instability.[22,26,27] Therefore, the evidence for effectiveness was conflicting at long-term follow-up. None of the studies describing instability as an outcome measure found a significant difference between treatment groups at intermediate-term follow-up [22,27,28], resulting in moderate evidence for no effectiveness.

In a subgroup of studies with a population consisting of athletes or soldiers, moderate evidence for no effectiveness (intermediate-term) and conflicting evidence for effectiveness (long term) was found.[27,28,30] In contrast, there is limited evidence for effectiveness in patients with severe injuries at intermediate follow-up.[22]

Re-sprain

Five studies, one with low risk of bias[22] and four with high risk of bias[25,26,28,30], reported the number of re-sprains sustained during intermediate and long-term follow-up. In three of these studies the study population consist of recreational athletes, patients who were active in sports >2 h/week, and recruits or professional soldiers.[25,28,30] Conventional treatment corresponds roughly in four out of five studies.

The studies of Van Rijn et al.[22], Holme et al.[25], Nilsson [26] and Wester et al.[30] promote early ankle mobilization or early weight bearing as much as pain allowed, whereas Reinhardt et al.[28] prescribed a more preserved policy (cryotherapy, compression bandage, minimal weight bearing). Holme et al.[25] found significantly fewer re-sprains in the group treated with early ankle mobilization combined with supervised balance exercises. The other studies found no difference between the treatment groups regarding the number of re-sprains, resulting in conflicting evidence for effectiveness at long-term follow-up.[22,26,30] None of the studies showed a difference between treatment groups in the number of re-sprains reported at intermediate follow-up. Hence, there is moderate evidence for no effectiveness.

In a subgroup of studies with a population consisting of athletes or soldiers, moderate evidence for no effectiveness (intermediate term) and conflicting evidence for effectiveness (long term) was found.[25,28,30] Besides, there is limited evidence for no effectiveness of additional supervised exercises on the long-term follow-up regarding the number of re-sprains in patients with severe injuries.[22]

Recovery

Two studies described recovery as an outcome measure to determine the effectiveness of additional supervised exercises.[22,29] Recovery was measured using a visual analogue

Table 5 Results of the individual studies per outcome measure classified by duration of follow-up

First author	Outcome	Follow-up	Conventional treatment	Supervised treatment	RR *or* ES (95% CI)
Pain					
Short term					
Nillson[26]	Pain, *n (%)*	7 days	38 (64.4)	31 (52.5)	RR 0.82 (0.60-1.11)
Wester[30]	Pain, *n (%)*				
	At rest	1 wk	7 (29)	12 (50)	RR 1.71 (0.82-3.60)
	Walking	1 wk	20 (83)	20 (83)	RR 1.00 (0.78-1.29)
	Sports	1 wk	23 (96)	23 (96)	RR 1.00 (0.89-1.13)
Intermediate term					
Oostendorp[27]	Pain (VAS 0-100), *mean (SD)*	6 wk	25 (5)	18 (7)	ES 1.11 (0.25-1.97)*
		12 wk	15 (7)	9 (8)	ES 0.77 (-0.06-1.60)
Van Rijn[22]	Pain (VAS 0-10), *mean (SD)*				
	At rest[#]	3 mth	0.4 (1.0)	0.3 (1.2)	ES 0.14 (-0.28-0.56)
	Walking flat[#]	3 mth	0.4 (1.0)	0.4 (1.3)	ES 0.04 (-0.38-0.47)
	Walking rough[#]	3 mth	1.3 (1.7)	0.8 (1.3)	ES 0.30 (-0.13-0.72)
	Subgroup AFS≤40 (severe)				
	At rest	8 wk	1.5 (2.6)	0.5 (1.0)	ES 0.50 (-0.03-1.03)
	Walking flat	8 wk	1.2 (1.9)	0.6 (1.2)	ES 0.37 (-0.16-0.90)
	Walking rough	8 wk	3.1 (2.4)	1.7 (1.9)	ES 0.64 (0.10-1.17)*
	Subgroup AFS>40 (mild)				
	At rest	8 wk	0.6 (1.5)	0.2 (0.7)	ES 0.31 (-0.27-0.89)
	Walking flat	8 wk	0.5 (1.5)	0.3 (0.6)	ES 0.17 (-0.41-0.75)
	Walking rough	8 wk	1.5 (2.3)	1.1 (1.7)	ES 0.19 (-0.39-0.77)
Wester[30]	Pain, *n (%)*				
	At rest	6 wk	0 (0)	1 (4)	NA
		12 wk	1 (4)	0 (0)	NA
	Walking	6 wk	5 (21)	6 (25)	RR 1.20 (0.42-3.41)
		12 wk	1 (4)	1 (4)	RR 1.00 (0.07-15.08)
	Sports	6 wk	18 (75)	18 (75)	RR 1.00 (0.72-1.39)
		12 wk	7 (29)	4 (17)	RR 0.57 (0.19-1.70)

First author	Outcome	Follow-up	Conventional treatment	Supervised treatment	RR *or* ES (95% CI)
Long term					
Nillson[26]	Pain, *n (%)*	3-6 mth	19 (32.2)	18 (30.5)	RR 0.95 (0.56-1.62)
		3 yr	8 (15.7)	5 (9.4)	RR 0.60 (0.21-1.72)
Oostendorp[27]	Pain (VAS 0-100), *mean (SD)*	24 wk	10 (6)	6 (4)	ES 0.76 (-0.07-1.59)
Van Rijn[22]	Pain (VAS 0-10), *mean (SD)*				
	At rest[#]	12 mth	0.3 (0.8)	0.3 (0.9)	ES 0.02 (-0.44-0.48)
	Walking flat[#]	12 mth	0.2 (0.7)	0.3 (0.9)	ES -0.10 (-0.56-0.36)
	Walking rough[#]	12 mth	0.8 (1.4)	0.9 (2.1)	ES -0.05 (-0.51-0.41)
	Subgroup AFS≤40 (severe)				
	At rest	12 mth	0.4 (0.8)	0.3 (0.9)	ES 0.12 (-0.41-0.64)
	Walking flat	12 mth	0.2 (0.7)	0.3 (1.0)	ES -0.11 (-0.64-0.41)
	Walking rough	12 mth	1.0 (1.5)	0.9 (2.3)	ES 0.05 (-0.47-0.57)
	Subgroup AFS>40 (mild)				
	At rest	12 mth	0.1 (0.6)	0.4 (0.9)	ES -0.39 (-0.98-0.19)
	Walking flat	12 mth	0.3 (0.8)	0.1 (0.5)	ES 0.29 (-0.29-0.87)
	Walking rough	12 mth	0.8 (1.5)	1.0 (2.1)	ES -0.11 (-0.69-0.47)
Instability					
Intermediate term					
Oostendorp[27]	Fear of giving way, *n (%)*	6 wk	8 (67)	3 (25)	RR 0.38 (0.13-1.08)
		12 wk	5 (42)	2 (17)	RR 0.40 (0.10-1.67)
Reinhardt[28]	Instability, *n (%)*	3 mth	5 (15)	2 (4)	RR 0.28 (0.06-1.36)
Van Rijn[22]	Instability, *n (%)*	3 mth	32 (65)	34 (64)	RR 1.02 (0.76-1.36)

Table 5 Continue

First author	Outcome	Follow-up	Conventional treatment	Supervised treatment	RR *or* ES (95% CI)
	Instability (VAS 0-10), *mean (SD)*				
	Subgroup AFS≤40 (severe)				
	Walking flat	8 wk	1.4 (1.6)	0.3 (0.8)	ES 0.86 (0.31-1.40)*
	Walking rough	8 wk	2.8 (2.1)	1.6 (1.6)	ES 0.63 (0.10-1.17)*
	Subgroup AFS>40 (mild)				
	Walking flat	8 wk	0.7 (1.2)	0.4 (0.9)	ES 0.27 (-0.31-0.86)
	Walking rough	8 wk	1.6 (2.1)	1.2 (1.4)	ES 0.22 (-0.37-0.80)
Long term					
Nilsson[26]	Instability, *n (%)*	3-6 mth	12 (20.3)	14 (23.7)	RR 1.17 (0.59- 2.30)
		3 yr	12 (23.5)	7 (13.2)	RR 0.56 (0.24-1.31)
Oostendorp[27]	Fear of giving way, *n (%)*	24 wk	5 (42)	1 (8)	RR 0.20 (0.03-1.47)
Van Rijn[22]	Instability, *n (%)*	12 mth	26 (53)	30 (57)	RR 1.06 (0.75-1.52)
	Instability (VAS 0-10), *mean (SD)*				
	Subgroup AFS≤40 (severe)				
	Walking flat	12 mth	0.4 (0.8)	0.4 (1.6)	ES 0.00 (-0.52-0.52)
	Walking rough	12 mth	1.4 (1.5)	1.4 (2.5)	ES 0.00 (-0.52-0.52)
	Subgroup AFS>40 (mild)				
	Walking flat	12 mth	0.3 (0.7)	0.5 (1.5)	ES -0.17 (-0.75-0.41)
	Walking rough	12 mth	0.7 (1.3)	1.5 (2.6)	ES -0.39 (-0.98-0.19)
Wester[30]	Instability, *n (%)*	230 days	6 (25)	0 (0)	NA
Re-sprain					
Intermediate term					
Reinhardt[28]	Re-sprain, *n (%)*	3 mth	4 (12)	1 (2)	RR 0.18 (0.02-1.55)
Van Rijn[22]	Re-sprain, *n (%)*	3 mth	14(27)	10(23)	RR 0.86 (0.43-1.75)
	Subgroup AFS≤40 (severe)	8 wk	10 (36)	6 (21)	RR 0.60 (0.25-1.43)
	Subgroup AFS>40 (mild)	8 wk	2 (8)	7 (33)	RR 4.14 (0.97-17.95)

First author	Outcome	Follow-up	Conventional treatment	Supervised treatment	RR *or* ES (95% CI)
Long term					
Holme[25]	Re-sprain, *n (%)*	12 mth	11 (28.9)	2 (6.9)	RR 0.24 (0.06-0.99)*
Nilsson[26]	Re-sprain, *n (%)*	3-6 mth	5 (9)	6 (10)	RR 1.20 (0.39-3.72)
		3 yr	9 (18)	9 (17)	RR 0.96 (0.42-2.23)
Van Rijn[22]	Re-sprain, *n (%)*	12 mth	16(31)	13(29)	RR 0.94 (0.51-1.73)
	Subgroup AFS≤40 (severe)	12 mth	12 (43)	9 (32)	RR 0.75 (0.38-1.49)
	Subgroup AFS>40 (mild)	12 mth	5 (20)	8 (38)	RR 1.90 (0.73-4.95)
Wester[30]	Re-sprain, *n (%)*	230 days	13(54)	6(25)	RR 0.46 (0.21-1.01)
Recovery					
Short term					
Roycroft[29]	Mean recovery period (days)		18.6	11.9	NA
Intermediate term					
Van Rijn[22]	Recovery (VAS 0-10), *mean (SD)*	3 mth	7.8 (2.4)	8.2 (2.4)	ES 0.17 (-0.22-0.55)
	Subgroup AFS≤40 (severe)	8 wk	6.6 (2.0)	7.2 (2.1)	ES 0.29 (-0.24-0.82)
	Subgroup AFS>40 (mild)	8 wk	7.7 (2.3)	7.0 (2.9)	ES -0.27 (-0.85-0.32)
Long term					
Van Rijn[22]	Recovery (VAS 0-10), *mean (SD)*	12 mth	8.6 (1.9)	8.3 (2.8)	ES -0.13 (-0.51-0.26)
	Subgroup AFS≤40 (severe)	12 mth	8.7 (1.6)	8.4 (2.4)	ES -0.15 (-0.67-0.38)
	Subgroup AFS>40 (mild)	12 mth	8.7 (2.1)	9.2 (1.9)	ES 0.24 (-0.34-0.83)
Function					
Short-term					
Basset[20]	LLTQ recreational, *mean (SD)*	10-14 days	8.2 (7.2)	12.0 (10.1)	ES -0.43 (-1.02-0.17)
	LLTQ ADL, *mean (SD)*	10-14 days	1.8 (3.9)	2.3 (3.6)	ES -0.13 (-0.72-0.46)
	Motor activity scale, *mean (SD)*	10-14 days	5.7 (1.1)	5.1 (1.3)	ES 0.49 (-0.11-1.09)
Hultman[21]	FAOS	6 wk	NA	NA	NA

Table 5 Continue

First author	Outcome	Follow-up	Conventional treatment	Supervised treatment	RR *or* ES (95% CI)
Long term					
Karlsson[23]	Excellent functional results, *n (%)*	12-24 mth	34 (87)	41 (91)	RR 0.78 (0.23-2.70)
Return to work					
Short term					
Brooks[24]	Days off work (days), *n*		I 5.1/ II 7.5 / III 14.0	6.0	NA
Hultman[21]	Days off work (days), *mean (SD)*		6.1 (7.4)	4.6 (6.1)	ES 0.22 (-0.34-0.77)
Karlsson[23]	Mean sick leave (days), *mean (SD)*		10.2 (6.8)	5.6 (4.2)	ES 0.82 (0.37-1.27)*
Nilsson[26]	Mean sick leave (days)		12.7	11.5	NA
Reinhardt[28]	Return to work (days), *mean (SD)*		8.7 (3.1)	5.7 (3.1)	ES 0.96 (0.49-1.43)*
Intermediate term					
Oostendorp[27]	Return to work, *n (%)*	6 wk 12 wk	10 (85) 11 (88)	10 (86) 11 (91)	RR 1.00 (0.70-1.43) RR 1.00 (0.79-1.27)
Long term					
Oostendorp[27]	Return to work, *n (%)*	24 wk	11(91)	11(94)	RR 1.00 (0.79-1.27)
Return to sport					
Short term					
Karlsson[23]	Return to sports activity (days), *mean (SD)*		19.2 (9.5)	9.6 (4.8)	ES 1.29 (0.82-1.76)*
Reinhardt[28]	Return to sports (days)		13.8	11.7	NA
Intermediate term					
Oostendorp[27]	Return to sports training, *n (%)*	6 wk 12 wk	7 (62) 11(88)	4 (30) 5(43)	RR 0.57 (0.22-1.45) RR 0.45 (0.23-0.91)*
Long term					
Oostendorp[27]	Return to sports training, *n (%)*	24 wk	11(96)	9 (74)	RR 0.82 (0.57-1.18)

ES = effect size (ES>0 indicates beneficial effects of supervised treatment); RR = relative risk (RR<1.0 indicates beneficial effects of supervised treatment; NA = not applicable; * = p < .05; VAS = visual analogue scale; dgr = degrees; wk = week; mth = month, AFS = ankle function score, LLTQ = lower limb task questionnaire; ADL =

scale[22] or by calculating the mean period (in days) after which patients were recovered.[29] Conventional treatment differs between the studies, i.e. wool and elastoplast bandage or a plaster of Paris backslab with non-weight bearing[29] versus early ankle mobilization and early weight bearing with external protection with tape, bandage or brace.[22]

From the study of Roycroft et al., with high risk of bias, no effect size could be calculated.[29] However, patients receiving active treatment report a significantly shorter recovery period compared to patients receiving conservative treatment at short-term follow-up, i.e.11.9 days versus 18.6 days. At intermediate-term and long-term follow-up only one study (low risk of bias) reported recovery, but no differences were found between the treatment groups.[22] Hence, there is limited evidence for effectiveness at short-term follow-up and limited evidence for no effectiveness at intermediate-term and long-term follow-up.

Additionally, Van Rijn et al. performed a subgroup analysis in patients with severe injuries.[22] In this population there is limited evidence for effectiveness at short-term follow-up and limited evidence for no effectiveness at intermediate and long-term follow-up.

Function

In three studies, all with high risk of bias, some sort of functional score was measured to evaluate the effectiveness of additional supervised exercises.[20,21,23] Basset et al.[20] presented the results of two functional scores, namely the Lower Limb Task Questionnaire (LLTQ) and the motor activity scale. The LLTQ consist of two subscales, i.e. the recreational activity scale, which measures strenuous activities such as running, jumping and cutting, and the activities of daily living scale, which measures less demanding activities such as walking, getting up from a chair, and carrying. The motor activity scale measures motor performance on six activities that involve running, walking, and hopping. Karlsson et al.[23] present a scoring scale for functional results consisting of categories such as instability, pain, swelling, stiffness, work and sport activities, stair climbing, running and support. Hultman et al.[21] present the results of the Foot and Ankle Outcome Score (FAOS), which is a 42-item questionnaire consisting of five subscales: pain, symptoms, activities of daily living, sports and recreation function, and ankle-related quality of life. In this latter study, since treatment in both groups is standardised after six weeks, we only report the results up to six weeks follow-up.

In one study the study population consisted of patients who were active in sports on the recreational or competitive level.[23] Conventional treatment differs between the studies; RICE followed by mobilizing and strengthening exercises[20] vs. elastic wrapping, partial weight bearing and crutches until pain subsided.[21,23] At short-term follow-up, Basset et al. found no significant differences for both functional scales between the treatment groups.[20] From the study of Hultman et al.[21] no effect sizes could be calculated. However, patients receiving early physiotherapy treatment report significant improvements on all

subscales of the FAOS compared to patients receiving conventional treatment at short-term-follow-up. At long-term follow-up, Karlsson et al. found no difference in functional results between the two treatment groups.[23] Consequently, there is conflicting evidence on short-term follow-up, and limited evidence for no effectiveness on long-term follow-up.

The study of Karlsson et al., which is the only study with a population consisting of athletes, found no difference in the number of patients with excellent functional results between both treatment groups at long-term follow-up.[23] Therefore, in this population there is limited evidence for no effectiveness of additional supervised exercises at long-term follow-up.

Return to work

In six studies, all with high risk of bias, time to return to work was used as an outcome measure to evaluate the effectiveness of treatment.[21,23,24,26-28] In two of these studies, effect sizes could not be calculated due to insufficient data.[24,26] Conventional treatment differs between the studies. The studies of Oostendorp[27], Reinhardt et al.[28] and Karlsson et al.[23] prescribed a more reserved policy (cryotherapy, compression bandage, minimal weight bearing until pain subsided). The studies by Nilsson[26] and Hultman et al.[21] promote early ankle mobilization or early weight bearing as much as pain allowed. Besides, in the study of Hultman et al. this treatment was followed by two visits to the physiotherapist at six weeks and three months follow-up.[21] Conventional treatment in the study of Brooks et al. was divided into three groups; 1) no treatment or minimal bandage, 2) tubigrip, and 3) complete immobilisation in a below-knee plaster-of-Paris cast.[24]

Three studies included a more specific study population; patients who were active in sports on the recreational or competitive level[23,27], and recruits or professional soldiers[28]. The studies of Reinhardt et al.[28] and Karlsson et al.[23] demonstrate a faster return to work for patients receiving early functional treatment, and supervised balance and strengthening exercises, compared to patients receiving conventional treatment at short-term follow-up. In contrast, Hultman et al. found no difference between treatment groups at short-term follow-up concerning return to work.[21] One study evaluated time to return to work at intermediate and long-term follow-up, but found no difference between the treatment groups.[27] Therefore, there is conflicting evidence for effectiveness of supervised exercises at short-term follow-up in reducing the time to return to work, and limited evidence for no effectiveness at intermediate and long-term follow-up.

Return to sport

Time to return to sport was used in three studies, all with high risk of bias, as an outcome measure.[23,27,28] All studies included a more active population, e.g. athletes and soldiers,

which were more susceptible for sustaining an ankle sprain. Conventional treatment roughly corresponds in the three studies. All used a more reserved policy in the first week of rehabilitation by prescribing cryotherapy, compression bandage or aircast brace, and minimal weight bearing (with or without crutches).

At short-term follow-up, Karlsson et al. report that patients receiving functional treatment, range of motion and proprioceptive training return earlier to sports activity compared to patients receiving conventional treatment.[23] From the study of Reinhardt et al. no effect sizes could be calculated on short-term follow-up due to incomplete data.[28] Therefore, there is limited evidence for the effectiveness of additional supervised exercises at the short-term follow-up in shortening the time to return to sport.

A significant difference between treatment groups was found at twelve weeks follow-up (intermediate) in the study of Oostendorp.[27] However, this study failed to demonstrate differences on intermediate-term (six weeks) and long-term follow-up. Consequently, there is conflicting evidence for the effectiveness on the intermediate- term follow-up, and limited evidence for no effectiveness on the long-term follow-up.

DISCUSSION

This review summarizes evidence for the effectiveness of supervised exercises added to conventional treatment in patients who have sustained an acute lateral ligament ankle sprain. In general, this overview revealed only moderate or limited evidence in favour of added supervised exercises to conventional treatment compared to conventional treatment alone, according to the outcome measures recovery and return to sport at short-term follow-up. However, for none of the outcome measures was strong evidence found for the effectiveness of additional supervised exercises.

The aforementioned evidence for effectiveness of additional supervised exercises is based on only eleven studies, with a maximum of six studies per outcome measure. In these studies conventional treatment was defined as no treatment, ice application, partial or complete immobilisation, home exercise program, early ankle mobilization instructions, or a combination of these treatments. Since the effectiveness of additional supervised exercises may depend on the type conventional treatment we planned to present the results classified by type of conventional treatment. We also aimed to classify studies according to the type of treatment; however, considering the limited number of studies included and the somewhat overlapping types of conventional treatment, it was not possible to perform an analysis grouped by type of treatment.

The supervised treatment in the included studies was similar, and consisted of visits to the physical therapy department during which rehabilitation focused on strength, mobility and balance exercises, whether or not combined with the use of a balance

board. However, the number of visits and the duration of treatment follow-up differ between studies and varied from maximally nine 30-min sessions within three months, a twelve week training program, a six week training program with three sessions per week, maximally ten sessions of 45 min each, to a three phase training program during fourteen days.

In addition, heterogeneity among the studies was also apparent concerning the study populations, outcome assessment, and follow-up time. Besides, most of the studies (with the exception of one), were assessed as having high risk of bias. Therefore, we refrained form undertaking statistical pooling of the results of the individual studies and conducted a best-evidence synthesis.

The assessment of risk of bias resulted in 91% of the studies assessed as having high risk of bias. The threshold to differentiate between low and high risk of bias studies was based on a methodological study of Van Tulder et al.[31] in which they assessed the validity of the Cochrane Collaboration's tool for assessing risk of bias in trials of back pain interventions. In their study a threshold of 50% or less was associated with bias; therefore, we decided that a study with six or more points would be regarded as a study with a low risk of bias.

Critical items in the risk of bias assessment were the items on blinding (items 3, 4 and 5), allocation concealment (item 2), and similarity of treatment groups at baseline (item 8).

None of the studies scored positive on the items of blinding, which is devoted to the fact that the setting of physical therapy often does not allow blinding of patients or care providers. Besides, in all studies the patient was the outcome assessor. Therefore, when patients were not blinded for the intervention, the item on blinding of outcome assessor was automatically scored as negative. Of all studies, 91% and 82% scored 'unsure' on the items concerning allocation concealment and similarity of treatment groups at baseline, respectively. Hence, these studies are more susceptible for selection bias, and, consequently, will affect the generalisability of the results of this review. A critical note concerning the risk of bias assessment is that disagreements were resolved in a consensus meeting between the assessors. For more transparency and objectivity it might have been better to have consulted a third reviewer.

Although we only considered significant differences in the individual studies for evaluation of the evidence for the effectiveness of additional supervised exercises, also non-significant differences in favour of the supervised treatment were seen. In these studies, significant differences could easily be missed due to low power (small number of patients), i.e. 90% of the studies did not provide a power analysis. For example, in the study of Wester et al.[30], which included only 48 patients, no difference was found between treatment groups concerning the number of reported re-sprains. This resulted in a relative risk of 0.46 with a 95% CI of 0.21-1.01, implying that there is an effect in favour of additional supervised exercises which may become significant if this study had

been conducted with enough power in a larger population. To statistically confirm such an effect the sample size should be approximately doubled. Furthermore, Van Rijn et al. performed a subgroup analysis of a randomised trial, distinguishing between patients with a mild and a severe sprain based on the Ankle Function Score.[16,22] Significant differences in favour of the group receiving supervised exercises additional to usual care were found in patients with severe injuries. However, this subgroup analysis was explorative and not predefined. Moreover, because of the classification into mild and severe injuries the groups became relatively small, resulting in low power.

The limited evidence found for the effectiveness of additional supervised exercises in the present review corresponds with findings in studies comparing functional treatment with surgery and/or immobilisation. In 1965, Freeman demonstrated that external protection combined with mobilization resulted in a shorter mean duration to become symptom-free compared to immobilization and surgery after rupture of the lateral ligament of the ankle.[32] Recently, Bleakley et al. demonstrated that early therapeutic exercises during the first week after an ankle sprain improved ankle function compared to the current best treatment available (applying ice and compression).[33] In addition, Kannus et al. conclude that functional treatment, including protection by tape, bandage or brace, early weight bearing, ROM exercises and neuromuscular training, resulted in the quickest recovery to full ROM and faster return to work and physical activity after a grade III ankle sprain, compared to surgery or immobilization.[2] However, no differences were found for outcome measures such as pain and swelling. In a more recent review Kerkhoffs et al. demonstrated that functional treatment, which includes elastic bandage, soft-cast, tape or orthosis with associated coordination training, results in improved outcomes for patients compared to immobilisation alone.[11] However, no differentiation was made between supervised and non-supervised treatment, as was the case in the present review.

The effectiveness of additional supervised exercises in a more specific population is restricted to moderate or limited evidence, concerning the outcomes return to work and return to sport only. There are indications from the individual studies included in this review that more specific patient groups might benefit to a greater extent from participation in an additional supervised exercise program. Oostendorp reported significantly less pain, at six weeks follow-up, in favour of the supervised exercise group in a population who sustained their ankle sprain during volleyball, basketball, handball or soccer.[27] Besides, in the study of Holme et al., patients who sustained their ankle sprain during sports and received supervised treatment reported significantly less re-sprains at one year follow-up compared to the conventional treatment group.[25] Furthermore, in the study of Van Rijn et al., patients with a severe injury receiving additional supervised exercises showed significantly less instability at two months follow-up compared to the conventional treatment group.[22]

Thus, more high-quality RCTs are needed to evaluate the effectiveness of additional supervised exercises in more defined subgroups such as athletes and patients with severe injuries.

In conclusion, this review shows moderate or limited evidence for effectiveness in favour of additional supervised exercises compared to conventional treatment alone, according to the outcome measures recovery, and return to sports at short-term follow-up. Strong evidence was not observed for any of the outcome measures. In a more specific population (i.e. athletes and soldiers) there is limited to moderate evidence that supervised treatment leads to an earlier return to work and return to sports. Furthermore, there is limited evidence for effectiveness of supervised treatment additional to conventional treatment in patients with severe injuries.

However, only a few studies were included in this review, most studies were assessed as having high risk of bias, and most studies were lacking power. Therefore, we recommend conducting high-quality RCTs which concentrate on the effectiveness of additional supervised treatment in specific study populations, such as athletes and patients with severe injuries. In order to promote complete and transparent reporting of RCTs, future trials must comply with the CONSORT statement.[34]

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Appendix Sources of risk of bias

Item	Judgement
A) Sequence generation	
1. Was the method of randomization adequate?	Yes / No / Unsure
B) Allocation concealment	
2. Was the treatment allocation concealed?	Yes / No / Unsure
C) Blinding of participants, personnel and outcome	
Was knowledge of the allocated interventions adequately prevented during the study?	
3. Was the patient blinded to the intervention?	Yes / No / Unsure
4. Was the care provider blinded to the intervention?	Yes / No / Unsure
5. Was the outcome assessor blinded to the intervention?	Yes / No / Unsure
D) Incomplete outcome data	
Were incomplete outcome data adequately addressed?	
6. Was the drop-out rate described and acceptable?	Yes / No / Unsure
7. Were all randomised participants analysed in the group to which they were allocated?	Yes / No / Unsure
E) Other sources of potential bias	
8. Were the groups similar at baseline regarding the most important prognostic indicators?	Yes / No / Unsure
9. Were co-interventions avoided or similar?	Yes / No / Unsure
10. Was the compliance acceptable in all groups?	Yes / No / Unsure
11. Was the timing of the outcome assessment similar in all groups?	Yes / No / Unsure

Criteria for a judgment of 'yes' for the sources of risk of bias

1. Was the method of randomization adequate?

A random (unpredictable) assignment sequence. Examples of adequate methods are coin toss (for studies with two groups), rolling a dice (for studies with two or more groups), drawing of balls of different colours, drawing of ballots with the study group labels from a dark bag, computer-generated random sequence, pre-ordered sealed envelops, sequentially-ordered vials, telephone call to a central office, and pre-ordered list of treatment assignments.

Examples of inadequate methods are: alternation, birth date, social insurance/security number, date in which they are invited to participate in the study, and hospital registration number.

2. Was the treatment allocation concealed?

Assignment generated by an independent person not responsible for determining the eligibility of the patients. This person has no information about the persons included in the trial and has no influence on the assignment sequence or on the decision about eligibility of the patient.

Was knowledge of the allocated interventions adequately prevented during the study?
3. Was the patient blinded to the intervention?
This item should be scored "yes" if the index and control groups are indistinguishable for the patients or if the success of blinding was tested among the patients and it was successful.

4. Was the care provider blinded to the intervention?
This item should be scored "yes" if the index and control groups are indistinguishable for the care providers or if the success of blinding was tested among the care providers and it was successful.

5. Was the outcome assessor blinded to the intervention?
Adequacy of blinding should be assessed for the primary outcomes. This item should be scored "yes" if the success of blinding was tested among the outcome assessors and it was successful or:

for patient-reported outcomes in which the patient is the outcome assessor (e.g., pain, disability): the blinding procedure is adequate for outcome assessors if participant blinding is scored "yes"

for outcome criteria assessed during scheduled visit and that supposes a contact between participants and outcome assessors (e.g., clinical examination): the blinding procedure is adequate if patients are blinded, and the treatment or adverse effects of the treatment cannot be noticed during clinical examination

for outcome criteria that do not suppose a contact with participants (e.g., radiography, magnetic resonance imaging): the blinding procedure is adequate if the treatment or adverse effects of the treatment cannot be noticed when assessing the main outcome

for outcome criteria that are clinical or therapeutic events that will be determined by the interaction between patients and care providers (e.g., co-interventions, hospitalization length, treatment failure), in which the care provider is the outcome assessor: the blinding procedure is adequate for outcome assessors if item "E" is scored "yes"

for outcome criteria that are assessed from data of the medical forms: the blinding procedure is adequate if the treatment or adverse effects of the treatment cannot be noticed on the extracted data

Were incomplete outcome data adequately addressed?
6. Was the drop-out rate described and acceptable?
The number of participants who were included in the study but did not complete the observation period or were not included in the analysis must be described and reasons given. If the percentage of withdrawals and drop-outs does not exceed 20% for during

follow-up and does not lead to substantial bias a 'yes' is scored. (N.B. these percentages are arbitrary, not supported by literature).

7. Were all randomised participants analysed in the group to which they were allocated?
All randomised patients are reported/analyzed in the group they were allocated to by randomization for the most important moments of effect measurement (minus missing values) irrespective of non-compliance and co-interventions.

Other sources of potential bias:
8. Were the groups similar at baseline regarding the most important prognostic indicators?
In order to receive a "yes", groups have to be similar at baseline regarding demographic factors, severity of complaints, and value of main outcome measure(s).

9. Were co-interventions avoided or similar?
This item should be scored "yes" if there were no co-interventions or they were similar between the index and control groups.

10. Was the compliance acceptable in all groups?
The reviewer determines if the compliance with the interventions is acceptable, based on the reported intensity, duration, number and frequency of sessions for both the index intervention and control intervention(s). For example, physiotherapy treatment is usually administered over several sessions; therefore it is necessary to assess how many sessions each patient attended. For single-session interventions (for example: surgery), this item is irrelevant.

11. Was the timing of the outcome assessment similar in all groups?
Timing of outcome assessment should be identical for all intervention groups and for all important outcome assessments.

Note: These instructions are adapted from van Tulder 2003, Boutron et al., 2005 (CLEAR NPT) and the Cochrane Handbook of Systematic Reviews of Interventions.

Chapter 8

General discussion

INTRODUCTION

Currently, three Dutch clinical guidelines are available with respect to the diagnosis and treatment of acute lateral ankle injuries.[1-3] These guidelines roughly correspond with each other and recommend conventional treatment as the primary treatment modality of choice. Conventional treatment consists of early mobilizing, early weight bearing (as much as pain will allow) combined with, or without, the use of an external support (e.g. a tape, brace or bandage). However, additional treatment of acute injuries to the lateral ligament complex of the ankle remains a controversial topic. There are indications that balance training and coordination exercises, as part of the treatment, result in improved outcomes regarding symptoms of giving way, risk of re-injury, proprioceptive deficits, and postural control.[4-6]

Despite the fact that lateral ankle injuries are among the most common injuries of the musculoskeletal system, little is known about the clinical course and factors predicting possible persistent complaints.

Therefore, the overall aim of this thesis was to assess the effectiveness of supervised exercises, in addition to usual care, in primary care patients with an acute ankle sprain, to gain insight into the clinical course of ankle sprains and to determine factors for non-recovery.

In this chapter we summarize and discuss the most important findings from the work in this thesis, consider the implications for clinical practice, and make recommendations for future research

CLINICAL COURSE AND PROGNOSTIC FACTORS

Ankle sprains are one of the most common injuries of the human musculoskeletal system and can occur under many circumstances. However, most injuries occur during sports, with the ankle as the most injured body site and ankle sprains as the major injury.[7] Despite the number of sprains sustained and the total costs incurred, ankle sprains are still considered as 'innocent' lesions from which patients can recover without serious consequences.[8] However, our review presented in Chapter 2 revealed that after one year follow-up 5%-33% of the patients with an ankle sprain still experienced pain and instability, that 34% of the patients reported at least one re-sprain, and 15%-64% of the patients report not to be fully recovered. In fact, after three years follow-up some patients still experience residual symptoms of their initial ankle sprain. In addition, the results of our trial, in which we evaluate the effectiveness of supervised exercises in addition to usual care, compared to usual care alone, demonstrate that after twelve months follow-up

about 55% of the patients still report instability, 30% endure at least one re-sprain, and that about 53% of the patients report not be fully recovered. This indicates that an ankle sprain is not 'just a sprain' and that a patient who sustains an ankle sprain will not necessarily return to a pre-injury state of health within a short time period.

Although residual complaints appear frequently, the factors predicting these persistent complaints after an ankle sprain are largely unknown. From the literature we know that a higher level of sports activity (training ≥3 times a week) is a prognostic factor for residual symptoms compared to a low level (training <3 times a week) and no sports.[9] Moreover, after treatment, highly active patients report more instability and re-injuries compared to patients with a low activity.[10] In addition, the clinical course of recovery after an acute ankle sprain can be influenced by the type of treatment, the severity of the sprain, and may be complicated by sustaining a re-sprain.

To gain more insight into factors predicting residual symptoms we evaluated prognostic factors for incomplete recovery, re-sprains, instability, and pain intensity (Chapter 6). Potential prognostic factors at baseline were demographic, clinical and ankle load factors. The analysis showed that, at baseline, there is no strong predictor for the outcome after one year of follow-up. However, an analysis in a subgroup comprised of non-recovered patients at three months follow-up showed that re-sprains occurring during the first three months after the initial sprain, and pain at rest at three months follow-up, were related to incomplete recovery after twelve months follow-up. A supplementary analysis also revealed a strong and significant association between the occurrence of a re-sprain between three and twelve months after initial injury and patient-reported recovery at twelve months. These results are useful for general practitioners (GPs) and physical therapists, since this information can be used to adapt their rehabilitation program where possible, and to inform patients about their prognosis regarding recovery.

Severity of injury

It is noteworthy that the severity of the initial ankle sprain, classified as a mild (grade I), moderate (grade II) or severe (grade III) sprain, was not found to be a prognostic factor for residual complaints after one year follow-up. Although the available Dutch guidelines recommend treating severe sprains with additional treatment, the results of our review (Chapter 2) and our prognostic study (Chapter 6) give no indication that the severity of a sprain influences the clinical course of recovery after injury. In addition, in our trial (Chapter 3) we performed explorative subgroup analyses to reveal possible differential effects in patients classified by injury grade, i.e. mild (grade I), moderate (grade II) and severe (grade III). Classification was based on the results of a physical examination which determined the extent of the swelling, the formation of haematoma, localisation of pain on palpation, and the anterior drawer test. This analysis did not lead to any meaningful differences between treatment groups per subgroup. In line with our results are the

findings of Nilsson who concludes that treatment, in this case cryotherapy, administration of cortisone, elastic wrapping and walking as much as pain permits, can be given regardless of the severity of the sprain.[11] This may imply that severe injuries should not be treated differently from milder injuries.

However, we found indications that physiotherapy treatment added to usual care might be beneficial to patients with severe injuries when 'severity' is defined in a different way. In our subgroup analysis (Chapter 4) we divided patients into two subgroups (mild sprain vs. severe sprain) according to the baseline ankle function score. In this subgroup analysis we evaluated the difference in the effect of additional physiotherapy treatment between patients with a mild and a severe sprain by means of a test of interaction. In spite of no significant differences in the effect of additional physiotherapy between the two subgroups (mild vs. severe), all outcomes showed more beneficial effects for the subgroup with a severe sprain at baseline. Also, within this subgroup, less pain and less giving way when walking was reported by patients treated with additional physiotherapy. However, the findings of our subgroup analyses are still explorative and should therefore be interpreted with caution. Although, due to multiple testing, there is a high risk that an effect occurs by chance, the results do show an overall tendency. In addition, the trial was powered for the main effect and not to identify effects in the small subgroups. Therefore, our study lacks sufficient power to show an interaction effect equal or less to the overall treatment effect, since the sample size should then be increased approximately fourfold.[12] However, the results do raise the question as to whether the traditional grading method used (in which injuries are classified from grade I to III) is sufficiently valid and applicable to determine the severity of a sprain, and whether or not we should use the ankle function score instead of the traditional classification system.

Classification of severity

In the literature many different criteria are used to define the severity of a lateral ankle sprain. For example, sprains are grade I if a partial tear of the anterior talofibular ligament or calcaneofibular ligament is present with a negative or positive anterior drawer sign[13,14], or if minimal swelling, localised tenderness and minor functional deficit is present[15]; grade II if a complete tear of the talofibular ligament with a positive anterior drawer sign is present[13], or if a spectrum of significant pain, swelling haematoma formation, difficulty or inability to weight bear and degree of functional impairment is present[15], or there is decreased motion and some loss of function, a torn anterior talofibular ligament with an intact calcaneofibular ligament, some ligamentous instability, swelling, haemorrhage, and point tenderness[14]; and grade III if a complete tear of the anterior talofibular ligament and calcaneofibular ligament with a positive anterior drawer sign and talar tilt is present[13], or if there is almost total loss of function, diffuse swelling and haemorrhage,

extreme point tenderness, disruption of the ankle capsule, and a complete tear of the lateral ligament complex as evidenced by marked ligamentous instability[14]. Another problem associated with the physical examination is the large discrepancy in the interobserver agreement for physical findings of ankle injury patients.[16] Good agreement was only found for judging the ability to bear weight in the emergency department, while the agreement of other frequently used outcomes (e.g. judgement of range of motion, swelling and anterior drawer sign) ranged from poor to moderate. The complexity of classifying the severity of ankle sprains is also illustrated by the results of our trial (Chapter 3). An inconsistency was seen between the GP and the physician at the emergency department concerning the classification of the severity. The GP classified 51% of the ankle sprains as a grade I sprain versus 25% by the physician at the emergency department. In addition, 47% and 38% of the ankle sprains were classified as a grade II and III sprain by, respectively, the GP and the physician at the emergency department. A larger number of more severe sprains were seen by the GP whereas we expected that this would be the case at the emergency department - an situation which might be due to misclassifications.

To assess the validity of the different criteria we need to compare the results of physical examination with findings from more objective measurement tools, such as magnetic resonance imaging (MRI), arthrography, or arthroscopy. Van Dijk and colleagues determined the diagnostic accuracy of delayed physical examination (determination of swelling, haematoma, pain and anterior drawer test) four to seven days after injury to distinguish between a rupture and no rupture, and concluded that this methods compared favourably with findings at arthrography.[17] In a study by Frey et al., the accuracy of physical examination (pain on palpation, presence of swelling, positive anterior drawer or talar tilt test) was determined with MRI as the reference test. In that study, 100% accuracy was found if the diagnosis was a grade III injury, whereas an accuracy of 25% was found if the diagnosis was a grade II injury.[18] Despite the variation in accuracy found, we know of no other studies which have compared physical examination with findings derived from more objective measurement tools.

A relatively new tool to distinguish between mild and severe injuries is proposed in the clinical guideline 'Acute ankle injury' of the Royal Dutch Society of Physiotherapists; i.e. the ankle function score (AFS).[2] The AFS was developed by De Bie and colleagues[19] and was adapted for ankle injuries from the Lysholm score for knee injury.[20] De Bie et al. found that, by making a distinction between mild and severe injuries, the AFS is an excellent instrument to predict recovery at two weeks after injury (AFS of ≥75) with a sensitivity and specificity of 97% and 100%, respectively.[19] In a study by Van der Wees et al. (in press) the AFS was further validated by examining the prognostic validity, construct validity and responsiveness. The prognostic validity was moderate, with a sensitivity of 88% and a specificity of 57%. Mixed results were found concerning the

construct validity and responsiveness of the AFS. The results of our subgroup analysis (Chapter 4), in which we used the baseline AFS to classify patients by severity, support the findings of the above-mentioned studies concerning the predictive value of the AFS; i.e. patients with severe injuries do less well on outcomes concerning pain intensity and instability at short-term follow-up. In addition, we investigated the value of the AFS to assess recovery on the short and long-term follow-up. Self-reported recovery was associated with the AFS at all time points, with correlations ranging from 0.48 to 0.79. In addition, when 10 out of 10 was used to define full recovery, sensitivity ranged from 98% to 100% and specificity ranged from 31% to 74%. This indicates that a substantial number of patients with an AFS ≥75 did not report 10 out of 10 for self-reported recovery. Because the outcomes of our study only partially support the recommendations in the clinical guideline, and the other studies present only limited evidence for the AFS as a diagnostic and evaluative instrument, the AFS must be used with caution.

Re-sprains

It is known that enduring a re-sprain influences the clinical course of recovery after an acute lateral ankle sprain. Re-sprains sustained during the first three months after initial injury predict incomplete recovery at twelve months follow-up. This seems logical, but it remains unclear which factors actually cause a re-sprain.

In general, there is evidence that previous injury coupled with inadequate rehabilitation results in a higher risk for re-injury.[21] Inadequate rehabilitation can occur when patients start to return to pre-injury activity level too early. Applied to the topic of this thesis, patients with a mild sprain might think that their injury is less severe and start their activities too soon, whereas patients with a severe sprain take their injury more seriously and allow more time for the rehabilitation process. Patients are reported to be at higher risk for a recurrent sprain in the first year after their initial sprain.[22,23] Although this higher risk was determined in a group of athletes, it is plausible that this also applies to a general population consulting GPs or physical therapists.

The high risk of re-sprain might be explained by applying the dynamic model of aetiology in sport injury.[24] Incurring a first sprain induces an alteration of intrinsic factors resulting in an increased predisposition to re-sprain. An ankle sprain is thought to lead to damage to the ligamentous, nervous and musculotendinous tissue. As a consequence, joint laxity, decreased ankle strength, impaired balance, impaired cutaneous sensation, decreased dorsiflexion and reduced joint position sense are reported after an ankle sprain.[13,25] To what extent these impairments contribute to a re-sprain is not known. The alteration of intrinsic factors makes it difficult to determine which factors predict that a certain group of patients will endure a re-sprain. The patient is 'changed' after injury and will change again after incurring a re-sprain. It is also possible that one individual is

more susceptible to injury than another, and that an ankle sprain is just one of the many injuries that such a person will endure.

Furthermore, the problem with re-sprains is that every patient experiences a recurrent injury in a different individualistic way. Some patients might assess a moment of instability as a re-sprain, whereas others report a re-sprain when this is as severe as their initial sprain. Most research on the subject of ankle sprains used questionnaires, with one simple question on a binary scale (e.g. 'yes' or 'no'), to determine whether someone has suffered a re-sprain. Because of that, no information on the severity and the consequences of the re-sprain is available. Future research on the topic of ankle sprains should take into consideration that a re-sprain is interpreted differently by each patient; therefore, questions should ask for details about (at least) the severity of the re-sprain, possible hindrance after the recurrent injury, and the circumstances in which the re-injury occurred.

Limitations

Athletes at both a recreational and competitive level are vulnerable for incomplete recovery and are at increased risk to incur a re-sprain. Ideally, in our systematic review (Chapter 2), we would have preferred to classify the included studies according to the activity level of their populations; this would have allowed us to determine and reflect on the clinical course compared to other populations. Such information would be useful to inform patients, set-up appropriate treatment, and provide directions for future research. Unfortunately, because too few studies provided information on the activity level of their included population, it was not possible to classify them according to activity level in a meaningful way.

In our prognostic study (Chapter 6) we aimed to fill the gap of uncertainty about prognostic factors for incomplete recovery in patients with lateral ankle sprains. To our knowledge, only one study has reported on prognostic factors for incomplete recovery and found that sports activity at a high level, compared with sports activity at a low level and no sports activity, is a risk factor for incomplete recovery.[9] Our study was primarily designed to evaluate the effectiveness of supervised exercises in addition to usual care, and not to evaluate prognostic factors. Therefore, it is possible that we included a somewhat biased sample of patients and that we might have missed some factors, e.g. activity level. Moreover, only a limited number of possible prognostic factors could be evaluated because of the relatively small number of patients included in the study.

TREATMENT

In the Netherlands, two healthcare professions (i.e. GPs and physical therapists) have their own guidelines for the diagnosis and treatment of acute lateral ankle injuries.[1,2] These guidelines recommend conventional treatment, rather than immobilisation and surgery, for patients with acute lateral ankle sprains. Conventional treatment consists of 'rest, ice, compression and elevation' (RICE) in the acute phase after injury, followed by early mobilizing and early weight bearing (as much as pain will allow), with or without the use of an external support (e.g. tape, brace) to the ankle.

Furthermore, there is another Dutch guideline for lateral ankle injuries which contains consensus recommendations established by eleven medical specialties.[3] This guideline is currently undergoing an update, but a concept version is available. The recommendations in this concept guideline concerning the treatment of acute lateral ankle injuries do not differ from the issue published in 1999, i.e. RICE in the acute phase after injury followed by functional treatment is still the first treatment modality of choice. Here, functional treatment was defined as treatment strategies using an external support to the ankle such as elastic bandage/stocking, tape, lace-up ankle support or semi-rigid ankle support. However, which of these latter types of support is most effective (clinically as well as regarding cost-effectiveness) remains unclear.[26] More recent publications provide supplementary evidence that the use of a brace combined with, or without, elastic wrapping provides an earlier return to pre-injury function, a faster recovery and an improved ankle joint function compared to elastic wrapping or tubular compression bandage alone.[14,15,27] Lamb and colleagues even recommend a short period of immobilisation in patients with severe sprains, by means of a plaster cast.[27] However, the results of that study should be interpreted with caution, since the authors found no differences on other outcomes (such as self-perceived benefits), did not report the number of re-sprains in the different intervention groups, and were unable to determine the compliance with wearing the external supports.[28,29] Since these latter studies have been recently published, the Cochrane review on the efficacy of functional treatment strategies[26], which can be seen as the highest level of evidence, needs to be updated.

The use of an external support restricts the range of motion and enhances proprioception of the injured ankle[30,31], which would result in protection of the injured tissue and avoid stress of the scar tissue in the first phase of tissue healing, i.e. the inflammatory phase. This phase of tissue healing will be followed by the proliferative phase and the maturation phase. In these latter phases the emphasis is on alignment and strengthening of the newly-formed collagen fibres.[32] Physical therapists use this information as a starting point to construct their rehabilitation program for each patient with an acute ankle sprain.[2] Nonetheless, there is no, or only limited, evidence for the effectiveness of treatment by a physical therapist.[33-35] Therefore, we evaluated the short and long-term

effectiveness of conventional treatment combined with exercises supervised by a physical therapist, compared with conventional treatment alone, in primary care patients (Chapter 3). Conventional treatment comprised information on early ankle mobilisation, including advice for home exercises and early weight bearing. Supervised exercises consisted of an individual and progressive training program with emphasis on stability, walking, jumping and joint mobility. No differences were found between the treatment groups for the primary outcomes recovery and occurrence of re-sprains after three and twelve months follow-up. However, appreciation of the received treatment was higher in those who consulted the physiotherapist for additional supervised exercises than in those who received usual care alone. In contrast to our findings, studies from Wester et al.[36] and Holme et al.[13] demonstrate beneficial effects in favour of patients receiving early ankle mobilisation combined with supervised exercises. The differences in outcome might be due to difference in follow-up time, the inclusion of a specific patient group (athletes vs. general population), or to a different type of intervention.

Furthermore, it is known that usual care in the Netherlands (as defined in our trial) differs from usual care in other countries, which is much less focused on early mobilisation. The contrast between treatment groups is, therefore, less extreme compared to other studies. This may explain why no difference was found between the groups, whereas other studies did find a difference.

Nevertheless, our summary of the available evidence on the effectiveness of additional supervised exercises (Chapter 7), which also presents the results of our trial, shows some evidence that a supervised exercise program results in a better recovery, and an earlier return to work and sport at short-term follow-up (within two weeks of randomisation).

Treatment or prevention?

Since the incidence of recurrent ankle sprains is high, much research focuses on the effectiveness of preventive measures to prevent ankle sprain recurrences. From the literature there is evidence that semi-rigid orthoses or air-cast braces are effective in the prevention of ankle sprains during high-risk sporting activities.[37] The guidelines of the different healthcare professions recommend the use of tape and brace as prevention, because this decreases the risk of re-injury and leads to less severe sprains.[1-3] Moreover, a recent randomised trial showed that an unsupervised home-based proprioceptive training is effective in the prevention of self-reported re-sprains by athletes.[38]

Braces, tape and orthoses, as well as home based proprioceptive training, are defined as secondary prevention, which means that these interventions are given when a patient has finished treatment. Because we are still searching for the most optimal treatment modality, it is plausible to hypothesise that the beneficial effects are not due to the preventive measures but to prolonged treatment of the initial sprain. This assumption is strengthened by the fact that, for example, unsupervised home-based propriocep-

tive training is particularly effective in patients whose initial sprain was not medically treated.[38] In our opinion, prevention of recurrent sprains must be part of the treatment of initial sprains, as is aiming for a return to pre-injury activity level, reducing pain and feelings of giving way, restoring function and, eventually, recovery.

Limitations

Our trial initially aimed at enrolling 158 patients during an inclusion period of one year. Due to financial and time restrictions we had to finish the (already extended) inclusion period before 158 patients were included. According to Lasagna's law it is possible that we overestimated the number of patients available for this study.[39] Moreover, problems with patient recruitment might be due to the fact that we focus on incident cases (rather than prevalent cases) and that the GP or physician at the emergency department had to be alert during consultation. Both factors are associated with less successful recruitment of patients.[39] Despite the inclusion of 'only' 102 patients with an acute lateral ankle sprain, this is one the largest studies in its field.

Furthermore, in our trial it was impossible to perform blinding on either the patient or the caregiver level. This may result in some bias, since awareness of the type of treatment received may influence the response of the patient to that treatment. Therefore, it is not surprising that 91% of the patients receiving conventional treatment combined with supervised exercises fully appreciate their treatment, compared to 68% of the patients receiving conventional treatment alone.

In addition, recovery was measured using a 0-10 visual analogue scale instead of the frequently used 4, 6 or 7-point Likert scales. Despite that these dichotomized scales make it easier to establish recovered patients we used a continuous scale, which resulted in less loss of information. It is questionable whether recovery is the appropriate outcome to measure the effectiveness of treatment since, after an acute lateral ankle sprain, patients experience no pain or functional disability during follow-up, whereas they do report not to be fully recovered, or vice versa. Chapter 5 of this thesis showed that outcome measures that are more related to activities of daily living (ADL) seem to be better explanatory variables for recovery than the outcomes measured during activities demanding low ankle loads. Therefore, future research in patients who have incurred an ankle sprain should focus on these ADL outcome measures.

We did not perform a cost-effectiveness study of additional supervised exercises compared to conventional treatment alone in patients with an acute lateral ankle sprain, because no differences of treatment effect were found between the two groups. Combined with the fact that there was no difference with regard to absence from work between treatment groups at all follow-up moments, additional exercises supervised by a physiotherapist will obviously involve higher costs compared to conventional treatment alone.

Our review (Chapter 7) summarised the available evidence from the literature of additional supervised exercises and showed that the included studies were very heterogeneous with respect to the study populations, outcome assessment, and follow-up times. Further, most of the studies were assessed as having a high risk of bias. Critical items in the risk of bias assessment were the items on blinding, allocation concealment, and similarity of treatment groups at baseline. Because of these limitations it was not possible to draw firm conclusions about the efficacy of supervised exercises. However, there are indications that athletes might benefit from additional supervised exercises. Unfortunately, in our trial no information was available concerning the activity level or participation in sports of the included patients. It would have been informative to perform a subgroup analysis in patients classified by activity level to investigate whether this specific group indeed derives benefit from additional supervised exercises.

IMPLICATIONS FOR DAILY PRACTICE

This thesis shows that a high percentage of patients with an acute lateral ankle sprain, and treated according to the GP guideline, experience residual symptoms such as pain, instability and re-sprains one year after their initial sprain. Even at three years after an initial sprain some patients have residual complaints. This information from our systematic review (Chapter 2) can be used by clinicians to inform patients about the possible clinical course after injury, but should also be incorporated in future updates of the currently available guidelines. Moreover, from prognostic research we know that sports activity at a high level (training ≥3 times a week) is a prognostic factor for residual symptoms compared to sports activity at a low level (training <3 times a week) and no sports, and that re-sprains sustained during the first three months after the initial sprain, and pain at rest at three months follow-up, were related to incomplete recovery after twelve months follow-up. A GP or physical therapist should take these factors into account when advising a patient about treatment options and possible preventive measures. More active people can be advised to support their ankle with a semi-rigid brace during high-risk activities or to perform a proprioceptive training as this might prevent sprains, especially in patients with a previous ankle sprain.[37,38]

Based on the results of our trial (Chapter 3) assessing the effectiveness of supervised exercises additional to conventional treatment, there is no clear evidence to support the use of this treatment modality in patients with an acute lateral ankle sprain consulting in primary care. On the other hand, because supervised exercises do not harm the patient and since there is greater appreciation among patients receiving additional supervised exercises compared to patients receiving conventional treatment alone, it can be

considered as a treatment option for the GP. However, this higher level of perceived appreciation may well be associated with higher costs.

IMPLICATIONS FOR FUTURE RESEARCH

Knowledge on prognostic factors for incomplete recovery after an acute lateral ankle sprain is very limited. Our prognostic study was a first attempt to elucidate which factors are responsible for residual symptoms in primary care patients with an acute ankle injury. However, because we used data from our randomised trial (which was not primarily designed to evaluate prognostic factors) we might have missed some factors.

A large cohort study with an integrated case-control study is currently in progress, consisting of patients with persistent complaints six to twelve months after an ankle sprain, to gain more insight in these residual symptoms. This may allow to identify patients at risk, by means of patient characteristics, medical history, or outcomes on clinical examination, and to assess the impact of these complaints on activities of daily living. Moreover, associations between ankle abnormalities and persistent complaints will be investigated, since different studies report morphologic ligamentous abnormalities, osteochondral lesions and cartilage damage in patients with residual symptoms >2 months after incurring an ankle sprain.[40-42]

As already mentioned, a large variety of criteria (especially of physical examinations) are used to define the severity of an ankle sprain. Researchers should aim to reach consensus about criteria used during physical examination to classify ankle sprains according to the level of severity. Reliability studies comparing findings from physical examination with more objective measurement tools (such as MRI, CT, arthrography or arthroscopy) can be useful. In addition, it would be interesting to perform this kind of research using the ankle function score in comparison with findings from physical examination. The ankle function score has advantages over tools like imaging, surgery or physical examination, with regard to feasibility and reproducibility. However, before we can apply it broadly to research and clinical practice there must be sufficient evidence for the diagnostic and evaluative value of this particular measurement. A large prospective cohort study with patients included at the moment they sustained a lateral ankle sprain would be valuable. It will yield information on the reliability of physical examination and the ankle function score, on the course of ankle sprains and prognostic factors.

In addition, Chapter 5 of this thesis showed that outcome measures that are more related to activities of daily living seem to be better explanatory variables for recovery than outcomes measured during activities demanding low ankle loads. This result might make them the outcome measure of choice for future research in patients who have incurred an ankle sprain. Therefore, researchers should also focus on reaching consen-

sus about the choice of primary outcome measures for studies in patients who have sustained an acute lateral ankle sprain.

There is some evidence that conventional treatment should be accompanied by supervised exercises during rehabilitation after an acute ankle sprain, but no strong evidence was found. Also, the effect of additional supervised exercises in more specific patient populations (e.g. athletes and patients with severe injuries), based on the ankle function score, is largely unknown. For these topics we recommend high-quality randomised clinical trials with sufficient statistical power and a follow-up longer than one year. Another option to provide evidence for effectiveness of supervised exercises in specific patient populations is a meta-analysis of subgroups of individual trials. However, the characteristics of these subgroups must be similar and sufficient trials on this topic must be available, which is a problem when looking at the currently available literature.

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Summary

Of all injuries to the musculoskeletal system 25% are an acute lateral ankle sprain, making it one of the most common musculoskeletal injuries. However, the treatment of ankle sprains in primary care remains a controversial topic.

The overall aim of this thesis was to assess the effectiveness of supervised exercises in primary care patients with an acute ankle sprain, to gain insight into the clinical course of ankle sprains, and to determine factors for non-recovery.

In order to evaluate the effectiveness of therapeutic interventions and to guide management decisions it is important to have clear insight into the course of recovery after an acute lateral ankle injury, and to evaluate potential factors for non-recovery and re-sprains.

In **Chapter 2** we performed a systematic review of the literature regarding the clinical course of conventionally treated acute lateral ankle sprains in adults and its prognostic factors for incomplete recovery. A total of 31 studies were included, of which 24 studies were of high quality. The studies show that within the first two weeks there is a rapid decrease in reports of pain. About 5% to 33% of patients still experience pain after one year, and 15% to 64% of patients report not to be fully recovered within a period of three years. The risk of re-sprains ranged from 3% to 34% of the patients in a period ranging from two weeks to 96 months post-injury. Instability ranged from 0% to 33% in the high-quality studies and from 7% to 53% in the low-quality studies. One study described prognostic factors and indicated that training more than three times a week is a prognostic factor for residual symptoms.

Chapter 3 describes the results of the randomised controlled trial (RCT) that we performed to evaluate the short and long-term effectiveness of additional supervised exercises compared to conventional treatment alone, in patients with an acute ankle sprain. A total of 102 patients with acute lateral ankle sprain, consulting a general practitioner or the hospital emergency department, were enrolled and randomised to either conventional treatment combined with supervised exercises or to conventional treatment alone. Primary outcomes were recovery and the occurrence of a re-sprain. Measurements were carried out at intake, four weeks, eight weeks, three months, and at one year post-injury. There were no significant differences between both treatment groups concerning recovery and occurrence of re-sprains after three months and at one year follow-up. The conclusion of this study was that conventional treatment combined with supervised exercises, compared to conventional treatment alone, during the first year after an acute lateral ankle sprain does not lead to differences in the occurrence of re-sprains or in recovery.

The objective of **Chapter 4** was to investigate whether the baseline Ankle Function Score (AFS) could be used to predict recovery in patients with an acute lateral ankle sprain, if there was a difference in treatment effect of added supervised exercise in patients classified by the baseline AFS, and if there was evidence for an association between

self-reported recovery and a follow-up AFS of less than 75. This study was conducted with the data obtained from our RCT (as described in chapter 3). The outcome measures were the AFS (consisting of five categories in which points are summed to a maximum overall score of 100), as well as recovery, pain and giving way (measured using a 0-10 visual analogue scale), and the incidence of re-sprain. Measurements were carried out at baseline, and at four and eight weeks, and three and twelve months after injury. Patients were divided into subgroups according to the baseline AFS; severe sprain (AFS ≤40) versus mild sprain (AFS>40). At four weeks follow-up, patients with a mild injury had significantly less pain during walking and reported less feeling of giving way compared to patients with severe injuries. There was no difference in effect of added supervised exercises in those with a severe injury compared with a mild injury at eight weeks or one year. However, there was a beneficial effect of supervised exercises in patients with severe injuries according to pain and feeling of giving way when walking, compared to patients who received conventional treatment alone. Correlations between subjective recovery and the AFS at follow-up ranged from 0.48 to 0.79.

Longitudinal research in musculoskeletal disorders often makes use of a single question to measure recovery; however, a large variation in reported recovery exists. Patients with an acute ankle sprain who experience no pain or functional disability, often report not to be recovered, or vice versa. In **Chapter 5** we used the data of the RCT to find explanatory variables for recovery by analyzing to which extent different outcomes (e.g. pain intensity) were associated with recovery, and how baseline scores of different variables influence this association in adult patients with an acute lateral ankle sprain. Mean differences were calculated between baseline and follow-up scores. Associations were calculated using linear mixed models, and the influence of baseline scores on these associations was determined using linear regression with interaction. Associations were found between recovery and the mean differences of pain during running on a flat and on a rough surface (at four and eight weeks, three months), and the mean difference of instability during walking on a rough surface (at eight weeks, three months). In conclusion, this study was the first attempt to find explanatory variables for recovery in adults with ankle sprain. Pain intensity and instability measured during high ankle load activities makes it easier to measure and to generalise recovery in this population, and should be the primary outcome measures of interest. This study also indicates the urgent need to reach consensus about the primary outcome measures used for research in patients with an ankle sprain.

The aim of **Chapter 6** was to evaluate prognostic factors for incomplete recovery, instability, pain intensity and re-sprains during one year follow-up in patients who consulted primary care for an acute ankle sprain. Since no differences were found between treatment groups in our RCT, for the purpose of this study we analysed the data as a cohort study. Possible prognostic factors assessed at baseline and at three months

follow-up were demographic factors, clinical factors, ankle load factors and factors from the physical examination at three months follow-up. The main outcome measures were self-reported recovery, re-sprains, instability and pain intensity at one year follow-up. No baseline factors related to incomplete recovery at one year follow-up were found. Furthermore, no prognostic factors from the physical examination for the non-recovered patients at three months follow-up could be identified. However, re-sprains and self-reported pain at rest at three months follow-up were related to incomplete recovery at one year, for the non-recovered patients at three months follow-up. Thus, a physical examination at three months follow-up for the non-recovered patients seems to have no additional value for predicting outcome at one year follow-up. However, self-reported pain at rest and re-sprains during three months follow-up seem to have a prognostic value for recovery at one year follow-up.

Chapter 7 presents the results of a systematic review which summarises the available evidence for the effectiveness of additional supervised exercises compared to conventional treatment alone in patients with an acute lateral ankle sprain. The eleven included studies show limited to moderate evidence for effectiveness in favour of additional supervised exercises compared to conventional treatment alone, according to the outcome measures recovery and return to sport at short-term follow-up (within two weeks of randomisation). No strong evidence for effectiveness was found for any of the outcome measures. In a more specific sub-population, limited to moderate evidence for effectiveness was found. However, it is emphasised that only eleven studies were examined, most of which were assessed as having a high risk of bias and most of which were lacking statistical power. Therefore, we recommend conducting high-quality RCTs on the effectiveness of supervised treatment particularly in specific populations, such as athletes and patients with severe injuries.

Chapter 8 summarizes and reflects on the main findings emerging from this thesis. Results, limitations and implications for clinical practice are discussed and recommendations for future research are made.

Samenvatting

Vijfentwintig procent van alle letsels aan het bewegingsapparaat is een enkelverstuiking. Dit maakt het één van de meest voorkomende blessures aan het bewegingsapparaat. Echter, de behandeling van enkelverstuikingen in de eerstelijns gezondheidszorg is nog steeds onderwerp van controverse. Het doel van dit proefschrift is om de effectiviteit van oefentherapie onder begeleiding van een fysiotherapeut te onderzoeken bij patiënten met een enkelverstuiking, om inzicht in het klinisch beloop van enkelverstuikingen te verkrijgen, en factoren te bepalen voor onvolledig herstel.

Voor het opstellen van behandelplannen en het meten van de effectiviteit van therapeutische interventies bij enkelverstuikingen is het van belang om inzicht te hebben in het klinisch beloop van dit letsel en om potentiële factoren voor onvolledig herstel en recidief te evalueren. In **hoofdstuk 2** is een systematische review van de literatuur uitgevoerd waarin het klinisch beloop van conventioneel behandelde enkelverstuikingen bij volwassenen en eventuele prognostische factoren voor onvolledig herstel besproken worden. In totaal werden 31 studies geïncludeerd, waarvan 24 studies van hoge kwaliteit waren. In de eerste twee weken is een snelle afname te zien van het percentage patiënten dat pijn rapporteert. Verder zien we dat 5% tot 33% van de patiënten nog steeds pijn ervaart na één jaar, en dat 15% tot 64% van de patiënten rapporteert niet volledig hersteld te zijn in een periode van drie jaar. Het risico op een recidief varieert van 3% tot 34% van de patiënten in een periode variërend van twee weken tot 96 maanden na de eerste enkelverstuiking. Instabiliteit varieert van 0% tot 33% in de studies van hoge kwaliteit en van 7% tot 53% in de studies van lage kwaliteit. Slechts één studie beschrijft prognostische factoren; trainen meer dan drie keer per week is een voorspellende factor voor residuale symptomen.

Hoofdstuk 3 beschrijft de resultaten van de gerandomiseerde gecontroleerde trial waarin de korte- en langetermijneffecten van de standaardbehandeling van een acuut laterale enkelverstuiking bij volwassen patiënten vergeleken wordt met de standaardbehandeling gecombineerd met oefentherapie onder begeleiding van een fysiotherapeut. In totaal werden 102 patiënten met een acuut laterale enkelverstuiking, welke de huisarts of de spoedeisende hulp consulteerde, geïncludeerd en gerandomiseerd naar ofwel de groep met standaardbehandeling ofwel naar de groep die naast de standaardbehandeling oefentherapie onder begeleiding van een fysiotherapeut kreeg. Primaire uitkomstmaten waren herstel en het oplopen van een recidief. Metingen werden uitgevoerd op baseline, vier weken, acht weken, drie maanden, en één jaar na het letsel. Er werden geen significante verschillen tussen beide behandelgroepen met betrekking tot herstel en het oplopen van een recidief na drie maanden en één jaar follow-up gevonden. Daarom kan geconcludeerd worden dat tijdens het eerste jaar na een enkelverstuiking een standaardbehandeling gecombineerd met oefentherapie on-

der toezicht van een fysiotherapeut, vergeleken met alleen de standaardbehandeling, niet tot verschillen leidt in herstel en het oplopen van een recidief.

Het doel van **Hoofdstuk 4** was om te onderzoeken of 1) de baseline 'Ankle Function Score' (AFS) gebruikt kon worden om het herstel van patiënten met een acuut laterale enkelverstuiking te voorspellen; 2) of er tussen patiënten, ingedeeld op basis van de baseline AFS, een verschil in behandeleffect was van oefentherapie onder begeleiding, en 3) of er bewijs was voor een associatie tussen zelfgerapporteerd herstel en een follow-up AFS van >75. Deze studie werd uitgevoerd met de gegevens verkregen uit de RCT zoals beschreven in hoofdstuk drie. Uitkomstmaten waren de AFS, welke bestaat uit vijf categorieën waarbinnen punten gescoord worden waarna ze kunnen worden opgeteld tot een maximale totale score van 100; herstel, pijn en instabiliteit, alle gemeten met behulp van een 0-10 visuele analoge schaal (VAS); en de incidentie van recidieven. Metingen werden verricht op baseline, vier en acht weken, drie en twaalf maanden na het oplopen van een enkelverstuiking. Patiënten werden onderverdeeld in subgroepen op basis van de baseline AFS; ernstige verstuiking (AFS ≤ 40) versus lichte verstuiking (AFS> 40).

Na vier weken follow-up hadden patiënten met een lichte verstuiking significant minder pijn tijdens het lopen en rapporteerde ze minder instabiliteit in vergelijking met patiënten met een ernstige verstuiking. Er was geen verschil in effect wat betreft additionele oefentherapie onder begeleiding van een fysiotherapeut tussen patiënten met een ernstige verstuiking en patiënten met een lichte verstuiking na acht weken en twaalf maanden follow-up. Echter, bij patiënten met een ernstige enkelverstuiking was een gunstig effect te zien van additionele oefentherapie onder begeleiding van een fysiotherapeut wat betreft pijn intensiteit en instabiliteit tijdens het lopen. Correlaties tussen zelfgerapporteerd herstel en de AFS bij follow-up varieerde van 0,48 tot 0,79.

Longitudinaal onderzoek naar aandoeningen van het bewegingsapparaat maakt vaak gebruik van een enkele vraag voor het meten van herstel. Er bestaat echter een grote variatie in gerapporteerd herstel.

Patiënten met een acuut laterale enkelverstuiking ervaren bijvoorbeeld geen pijn of een functiebeperking terwijl ze niet rapporteren hersteld te zijn, of vice versa.

In **Hoofdstuk 5** gebruiken we de gegevens van onze RCT om verklarende variabelen te vinden voor herstel door te analyseren in welke mate de verschillende uitkomsten (bijv. pijn intensiteit) waren geassocieerd met herstel, en hoe baselinescores van de verschillende variabelen invloed hadden op deze associatie bij patiënten na een acuut laterale enkelverstuiking. De gemiddelde verschilscores werden berekend tussen baseline en follow-up. Associaties werden berekend met behulp van lineair mixed models, en de invloed van baselinescores op deze associaties werd bepaald met behulp van lineaire regressie met interactie.

Associaties werden gevonden tussen herstel en de gemiddelde verschilscore van pijn tijdens het hardlopen op een vlakke en oneffen ondergrond (op vier en acht weken, drie maanden), en de gemiddelde verschilscore van instabiliteit tijdens het lopen op een oneffen ondergrond (op acht weken, drie maanden).

Deze eerste aanzet tot het vinden van verklarende variabelen voor herstel bij volwassenen na een enkelverstuiking leidt er toe dat pijn intensiteit en instabiliteit gemeten tijdens de meer belastende activiteiten het makkelijker maken om herstel te meten en te generaliseren naar patiënten met een enkelverstuiking. Daaraanvolgend dienen deze uitkomstmaten in het vervolg als de primaire uitkomstmaten te worden beschouwd. Verder toont deze studie aan dat er enorme behoefte is aan consensus over de primaire uitkomstmaten voor onderzoek bij patiënten met enkel verstuikingen.

Het doel van **Hoofdstuk 6** was het evalueren van prognostische factoren voor onvolledig herstel, instabiliteit, pijn intensiteit en recidieven na één jaar follow-up bij patiënten met een acuut laterale enkelverstuiking welke de eerstelijns gezondheidszorg consulteerde. Aangezien er geen verschillen werden gevonden tussen de behandelgroepen in de RCT konden de gegevens, voor het doel van deze studie, geanalyseerd worden als een cohort studie. Mogelijke prognostische factoren vastgesteld op baseline en na drie maanden follow-up waren: demografische factoren, klinische factoren, enkel belastende factoren en factoren uit het lichamelijk onderzoek na drie maanden follow-up. De belangrijkste uitkomstmaten waren herstel, recidieven, instabiliteit en pijn intensiteit na twaalf maanden follow-up.

Er werden geen baseline factoren gevonden welke gerelateerd waren aan onvolledig herstel na twaalf maanden follow-up. Bovendien, prognostische factoren uit het lichamelijk onderzoek voor de niet-herstelde patiënten na drie maanden follow-up konden niet geïdentificeerd worden. Echter, recidieven opgelopen in de eerste drie maanden na de eerste verstuiking en pijn in rust na drie maanden follow-up waren gerelateerd aan onvolledig herstel na twaalf maanden voor de niet-herstelde patiënten na drie maanden follow-up.

We kunnen concluderen dat een lichamelijk onderzoek na drie maanden follow-up voor de niet-herstelde patiënten geen extra waarde lijkt te hebben voor het voorspellen van de uitkomst na twaalf maanden follow-up. Echter, pijn in rust en recidieven gedurende de eerste drie maanden van de follow-up lijken wel een prognostische waarde te hebben voor herstel na twaalf maanden follow-up.

Hoofdstuk 7 beschrijft de resultaten van een systematische review van de literatuur naar de effectiviteit van additionele oefentherapie onder begeleiding, in vergelijking met de standaard behandeling, bij patiënten met een acute laterale enkelverstuiking uit de eerstelijnszorg.

De elf geïncludeerde studies leverde beperkt tot matig bewijs op dat additionele oefentherapie onder begeleiding effectief is in vergelijking met alleen de standaard

behandeling betreffende de uitkomstmaten herstel en terugkeer naar sport op de korte termijn (binnen twee weken na randomisatie). Voor geen van de uitkomstmaten werd sterk bewijs gevonden dat additionele oefentherapie onder begeleiding effectief was. In een meer specifieke populatie werd beperkt tot matig bewijs gevonden voor de effectiviteit van oefentherapie onder begeleiding. Niettemin werden er in deze review slechts enkele studies geïncludeerd, waren de meeste studies van lage kwaliteit en waren in de meeste studies kleine patiënten aantallen geïncludeerd. Daarom wordt aangeraden om een hoogwaardige RCT uit te voeren naar de effectiviteit van oefentherapie onder begeleiding welke dan specifiek gericht is op een populatie bestaande uit sporters of patiënten met een ernstige enkelverstuiking.

Hoofdstuk 8 geeft een samenvatting van en reflecteert op de belangrijkste bevindingen van dit proefschrift. Tekortkomingen van de studies, implicaties voor de praktijk en aanbevelingen voor toekomstig onderzoek worden besproken.

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Rogier

Curriculum Vitae

Rogier van Rijn is op 12 september 1980 geboren te Rozenburg. Na het behalen van zijn VWO diploma aan het Interconfessioneel Makeblijde College te Rijswijk begon hij in 1999 aan de studie Bewegingstechnologie aan de Haagse Hogeschool. In 2003 studeerde hij af en startte in datzelfde jaar met de studie Gezondheidswetenschappen aan de universiteit van Maastricht. Tijdens zijn afstuderen deed hij onderzoek naar knijpkracht, krachtcoördinatie en vermoeid bij patiënten met een cerebrale parese. In augustus 2005 studeerde hij af in de richting Bewegingswetenschappen. Sinds januari 2006 werkt hij op de afdeling Huisartsgeneeskunde van het Erasmus MC, waar hij als onderzoeksassistent werd aangesteld op de TIS-studie; effectiviteit van corticosteroid injecties bij patiënten met trochantair pijnsyndroom. Daarnaast werkte hij aan de in dit proefschrift beschreven studies. Verder was hij betrokken bij de studie naar arbeidsgerelateerde factoren bij klachten aan de arm, nek en/of schouder, en bij de studie naar de diagnostische waarde van beeldvormende technieken bij lage rugklachten. Sinds juni 2010 werkt hij aan de CHECK data, een cohort dat vroege heup- en knieklachten bestudeert.

PhD Portfolio

Courses

2009, NIHES 'Prognostic research'	*1.4 ECTS*
2009, Basiscursus Regelgeving en Organisatie van Klinisch onderzoek (BROK)	*42 hours*
2007, NIHES 'Introduction to Clinical Research'	*0.9 ECTS*
2006, Methodologie van patiëntgebonden onderzoek en voorbereiding van subsidieaanvragen	*8 hours*

Conferences/Presentations

Annual conference of the Dutch College of General Practitioners (NHG)	
2009, Utrecht (poster presentation)	*16 hours*
2008, Rotterdam (poster presentation)	*16 hours*
2008, Rotterdam (oral presentation)	*20 hours*
Annual conference of the Royal Dutch Society for Physical Therapy (KNGF)	
2009, Amsterdam (oral presentation)	*20 hours*
2009, Amsterdam (oral presentation)	*20 hours*
Annual conference of the European College of Sport Science	
2009, Oslo (poster presentation)	*16 hours*
Annual conference of the Dutch society of Sport physicians (VSG)	
2009, Noordwijkerhout (oral presentation)	*20 hours*
2007, Noordwijkerhout (oral presentation)	*20 hours*
International Primary Care Musculoskeletal Research Congress (PRIMUS)	
2010, Rotterdam (poster presentation)	*16 hours*

Teaching activities

Supervising medical student, 2010	*80 hours*

Ankle sprains are one of the most common injuries of the human musculoskeletal system and can occur under many circumstances. However, we are still seeking for the most optimal treatment. Besides, little is known about the clinical course and factors predicting possible persistent complaints. Therefore, the overall aim of this thesis was to assess the effectiveness of supervised exercises, in addition to usual care, in primary care patients with an acute ankle sprain, to gain insight into the clinical course of ankle sprains and to determine factors for non-recovery.