Ankle sprain prevention; from evidence, via practice, to the athlete
GENERAL DISCUSSION

The aim of this thesis was to assess the effects of interventions for preventing ankle ligament injuries. Prevention of ankle sprains could preserve health in people who participate in high-risk sports and in those who have suffered a previous ankle ligament injury. Chapter 2 of this thesis summarizes all the available evidence on the effectiveness of measures to prevent ankle sprains in athletes. Based on the available evidence, neuromuscular (NM) training and bracing were considered the two main secondary preventive interventions for further research. Subsequently, chapter 3 to 5 present the design and results of the first RCT that evaluated, following usual care, the (cost-)effectiveness of combined bracing and NM training, versus stand-alone bracing, versus the use of NM training, with recurrences of ankle sprain as the primary outcome. Chapter 6 provides a secondary analysis of the compliance with these interventions to reveal potential predictors of this compliance. In chapter 7 a user survey of three different ankle braces in soccer, volleyball and running describes subjective factors that can influence the acceptability of ankle brace use by athletes. The first part of this general discussion highlights the main findings from this thesis and puts those findings in a broader perspective. Methodological strengths and shortcomings of this thesis are discussed and implications and recommendations for ankle sprain prevention and future research are given in the second part of this last chapter 8.

Main findings
When discussing the main findings of this thesis the modified Van Mechelen model (van Tiggelen 2008) provides a framework on how the work described in this thesis replicates, reinforces, or fills gaps in knowledge on ankle sprain prevention (Fig. 1).
The proposed modification to Van Mechelen’s model involves the addition of a process to step 4, which in the original model appraises the effectiveness of a preventive measure. Van Tiggelen states that there are two major perspectives to take into account when addressing effective sports injury prevention: on the one side there are the stakeholders (e.g., government agencies, sports federations, team manager, advertisers) for whom the efficiency of the prevention program is of major concern, and on the other side there is the athlete (and often the coach) whose compliance and risk-taking behavior are of major importance. In this case efficiency refers to the effect of the intervention in the specific setting of the stakeholders wherein this intervention is introduced. Thus the needed economic investment must be balanced against a realistic reduction of injury risk and performance impact. In contrast, compliance and risk-taking behavior refer to the consequences of the implementation of the intervention for the individual athlete. Compliance is defined as the extent to which the athlete follows the
prescribed intervention (or not). Risk-taking behaviour refers to modification of attitude and behaviour in the growing awareness of injury risk by the athlete. Before implementing any preventive measure, the respective processes in relation to these two parallel but related sides should be assessed. The modified Van Mechelen model (by Van Tiggelen) is shown in Figure 1.

With regard to ankle sprains there is an abundance of knowledge on step 1 (incidence of ankle sprains)\(^1\)–\(^2\), and a vast knowledge on steps 2, 3 and 4 (causation, intervention development, effectiveness\(^3\)–\(^5\) and cost-effectiveness\(^6\)). However, knowledge on step 5 & 6 (efficiency, compliance and risk taking behavior) is lagging behind. Finally, implementation knowledge and program evaluation is almost completely lacking. Van Tiggelen states that "In reality, external pressures and individual interpretations have a significant impact on the uptake of a measure, and it is by understanding these that an accurate evaluation of the implementation of a preventive measure can be assessed."

**Preventing recurrent ankle sprains: what works, and what doesn’t?**

The link from this thesis to the modified Van Mechelen model (figure 1) starts in step 7, by referring to the results from the Cochrane review presented in Chapter 2. In this review the effectiveness of interventions are summarized for ankle ligament sprains. On the basis of a systematic review performed by Verhagen & Bay\(^7\) both braces as well as NM training were postulated to be equally effective for prevention of ankle sprains. They argued that both measures individually would account for an approximated overall 50% reduction in ankle sprain rate. One of the reasons to perform an update of the Cochrane review by Handoll et al\(^8\) on prevention of ankle ligament injuries was to verify the effectiveness of these two interventions and of other available interventions. The new Cochrane review (Chapter 2) contained a total of 47 trials, including 27,022 participants. Although the interventions were heterogeneous, and outcomes varied, the data from 29 trials could be pooled for the primary outcome ‘incidence of ankle ligament injury’. Overall, the risk of bias in the pooled studies was low to moderate. Most participants were high school athletes, recreational athletes (age mainly 18 to 35 years) or military recruits. The interventions tested in the included trials could be categorized into five main preventive strategies: footwear, taping, bracing, NM training, or multifaceted exercise programs. The duration of most trials was only one year, or one season, while a substantial part of the reported injuries concerned recurrent injuries. Proper studies with a longer follow-up were scarce, while a higher risk of subsequent injury could become manifest in the next playing season, and therefore an underestimation of the risk of subsequent injury was likely. The overall quality of the evidence included in this review was moderate. In contradiction to our hypothesis that bracing and NM training would prove to be equally effective when applied as an individual secondary preventive measure, bracing proved to be more effective than NM training (OR 0.22, 95% CI 0.13 to 0.35 versus OR 0.54, 95% CI 0.41 to 0.71). Furthermore, taping and multifaceted exercise programs proved to be effective in reduction of total ankle sprains (primary + secondary prevention; OR 0.44, 95% CI 0.24 to 0.79 and OR 0.55, 95% CI 1.43 to 0.71 respectively). Unfortunately, data were of insufficient detail to determine the effectiveness of taping and multifaceted exercise programs in prevention of recurrent sprains. Thus, strong evidence was found for NM training and ankle bracing, but optimal duration of these interventions is still to be determined. No evidence was found that
high-top shoes, stretching and insoles prevent ankle sprains. Furthermore, adequate monitoring and reporting of compliance are required in future investigations.

A crucial step for the athletic and physically active population in benefiting from (cost-) effective interventions is the implementation of these interventions in practice. To facilitate implementation in practice, these results should be included in updated clinical guidelines on prevention of ankle sprains. The characteristics of these guidelines need to be carefully considered as they are likely to affect actual use\textsuperscript{9}. Brief and concise guidelines that are easy to understand, can easily be tried out, and do not require specific resources have a greater chance of implementation\textsuperscript{10}. As previous research showed that appropriateness of diagnoses and treatment decisions improved when mobile devices were used\textsuperscript{11}, we suggest to implement the updated guideline in a mobile app for sports medicine practitioners.

**Design; a three instead of a four-arm RCT**

For discussing the rationale of the design of our three-arm RCT we move on to step 4 and 5 (efficacy & efficiency) of the modified Van Mechelen model. There is ample evidence for a twofold risk for sustaining a recurrent ankle injury in the first year after an index sprain\textsuperscript{12–14}. Up to 40\% of all recurrences lead to disability and chronic pain or instability, requiring prolonged medical care\textsuperscript{15}. This increased ankle sprain recurrence risk persists even after medical treatment\textsuperscript{16}. For this reason, use of secondary preventive measures is essential. In 2009 the Royal Dutch Society for Physical Therapy (KNGF) guideline on acute ankle injuries advocated both NM training and bracing for prevention of recurrences\textsuperscript{17}. However, a direct prospective head-to-head comparison of effectiveness between these interventions had not been performed when this recommendation was drawn. Therefore, the RCT described in this thesis was initially designed\textsuperscript{18} as a four-arm randomized controlled trial, comparing NM training versus bracing versus the combined intervention versus a control group or ‘no measure’ group. Even so, the medical ethics committee of the VU University Medical Centre (VUmc) reasoned that all three intervention modalities were proven effective and that adding a control group would therefore be unethical. Although we agreed that all three interventions were proven efficacious, the ruling usual care at the time did not necessarily include a preventive advise, which supported the inclusion of a control group. However, for practical and time-management reasons we could not to challenge the decision of the medical ethical committee and the control group was excluded from our final study design. In addition, without the control group the trial was still able test our hypothesis of comparable effectiveness of these measures. Thus now our trial had only three arms, i.e. the combined intervention versus NM training, versus bracing.

**Brace beats balance board**

The results of this three-arm RCT, presented in Chapter 3\textsuperscript{19} and 4\textsuperscript{20}, were not in accordance with our hypothesis. Our hypothesis was that bracing and NM training would prove to be equally efficacious and that the combination of both might prove to be most efficacious. Based on the outcome of the trial we concluded that bracing was superior to NM training in reducing the incidence of self-reported recurrences (OR 0.53, 95\% CI 0.29 to 0.97). This makes this result the first randomized controlled trial to confirm the superiority of bracing over NM training as secondary preventive measure, as suggested by the results from the Cochrane review described in chapter 2. In the literature only one trial is available for direct comparison, which was performed by
Schroter et al. in Germany. It concerned a quasi-randomized controlled trial in basketball for ankle sprain prevention of bracing versus NM training versus a control condition. A total of 334 active basketball players of all classes participated in the study. The training program consisted of 6 NM exercises, comparable to the balance board program in our RCT, performed with and without use of a basketball. The program was introduced by a physical therapist and subsequently performed coach-controlled before every training during warm-up, during the basketball season. The exercises increased in difficulty twice during the season. Over this season all injuries were recorded sustained during training and games. Of the total of 108 registered injuries, 54% were ankle sprains. Of those ankle sprains 66% were recurrent injuries. The incidence rate in the control group was highest, with 3.26 ankle sprains per 1000 units of sports participations. In the training group it concerned 1.97 ankle sprains per 1000 units of sports participations. The lowest incidence rate of 0.5 ankle sprains per 1000 units of sports participations was recorded in the brace group, which was significantly (p = 0.04) lower than in the control group. The design, which included a control group, allowed calculation of Numbers Needed to Prevent (NNP). In the brace group 6 players were needed to prevent one ankle sprain during one season (based on 70 units of sport participation per player per season) versus a NNP of 11 in the training group. Although in this trial the training was group-based instead of home-based, several different brace types were used, and the registered ankle sprains in this trial concerned both new and recurrent sprains, these results are in line with the results from our randomized controlled trial described in chapter 4, which also found bracing to be more efficacious than NM training for the prevention recurrent ankle sprain.

**Bracing: primary and secondary preventive effect?**

The most obvious explanation for the superiority of bracing over NM training is that bracing creates both a primary and secondary preventive effect, as opposed to a solely secondary preventive effect of NM training. The Cochrane review in chapter 2 provides the first early incomplete evidence for this explanation, namely a significant primary preventive effect of bracing (OR 0.45, 95% CI: 0.33-0.60; 6 studies, n = 3849; quality evidence: low) versus a non-significant primary preventive effect of NM training (OR 0.55, 95% CI 0.29-1.02; 2 studies, n = 709; quality evidence: very low). In an attempt to provide a theory for the dual preventive effect of bracing we need to go back to step 2 (etiology and mechanisms of the injury) in the modified Van Mechelen model. In the literature the etiology of ankle sprains has focused on the most common mechanism of injury; inversion and forceful plantar flexion of the ankle. Most mentioned precipitating mechanisms of ankle sprain include tripping, landing from a jump on a shoe, landing from a fall, stepping off a platform and going down stairs 22-25. Consequently, isolated injury to the anterior talofibular ligament (ATFL) accounts for 66% of the ruptures, where the calcaneofibular ligament (CFL) ruptures occur in another 20% of cases. While numerous researchers studied the effect of an ankle sprain on passive (mechanical) stability of the ankle joint, only recently more studies have been performed on the dynamic stability (and proprioception) of the ankle joint in case of ligament injury.

From biomechanical studies, it was concluded that when mechanical stability is not restored, increased laxity could lead to further mechanical adaptations (i.e. greater laxity and/or altered joint alignment), deficits in neuromotor control (i.e. impaired balance and/or altered movement patterns) and recurrent injury as a maladaptive
compensation of the changes in joint laxity and/or sensorimotor control. Accordingly, the first generation preventive external ankle supports were designed as robust mechanical stabilizers of the ankle. The most convincing experiment of inversion restriction by 10 commercially available ankle braces was performed by Eils et al. (n = 25). A trapdoor, in combination with a goniometer system, measured hind foot inversion inside the shoe. Inversion was subdivided into a free fall and a maximum inversion phase. Their results showed that all braces restricted inversion significantly between 15% and 51%, compared to the no-brace condition. They concluded that the main function of (semi-rigid) ankle braces is to restrict inversion during the free fall phase and not at the extremes of motion. The restriction of inversion is probably the most logical mechanical explanation for the primary preventive effect of bracing.

Other studies showed that the mechano-protective effect of bracing is limited. Ashton-Miller et al measured the maximal isometric eversion force under full weight bearing, in 20 healthy adult basketball players with their ankles in 15 degrees of inversion, with and without a brace. Biomechanical calculations in this study suggested that at 15 degrees of inversion the fully active ankle evertor muscles isometrically developed a force more than three times larger than that developed passively when the athlete has tape or a brace worn inside a high-top shoe. Consequently, they concluded that strong ankle evertor muscles at footstrike are the best protection for a close to-maximally inverted ankle. In our opinion this finding pleas for NM training as secondary preventive measure, as weakness of the evertor muscles is one of the consequences of an ankle sprain.

**Passive external support with a dynamic effect?**

Ample research has been performed on the compensatory response in humans to perturbations of balance while walking. The body is programmed to maintain the centre of mass over the feet via a system of reflexes. For example, when tripping with one foot on uneven terrain rapid muscle contractions of the contra lateral side occur to prevent falling. This contraction against gravity is reported to be the most effective means for generating proprioceptive feedback. Receptors located in muscles, tendons, joints, and other tissues provide proprioceptive sensory input. Joint receptors only fire at extremes of range and are not the major source of proprioception. Muscles spindles detect dynamic and static stretch and both are critical to determine the location of body and limbs in space. Various studies evaluated the neuromuscular response in the lower leg muscles with respect to lateral ankle sprains. Konradsen et al. tested ten subjects without ankle instability, who had to walk and stand on a trap door, able to abruptly invert the foot to 30 degrees. Peroneal reaction time, measured through EMG, was 54 milliseconds. When the foot was placed in inversion the reaction time was significantly faster versus placement in eversion, before abrupt inversion. An explanation was that the peroneal reflex seemed to rely more on peripheral receptors in the tendons or muscles. That external support can effect this process was shown by Karlsson et al. who studied peroneal reaction times in subjects with chronic lateral ankle instability. The reaction time was significantly shorter in stable ankles, compared to unstable ankles (68.8 milliseconds vs. 84.5 milliseconds, p < 0.001). Interestingly, when the unstable ankles were taped, the reaction time improved significantly (p < 0.05). Not all ankles responded the same to tape; the most unstable ankles responded best. Therefore, it
seems that taping augments the reaction time in unstable ankles. This process is mainly controlled by stimulation of cutaneous mechanoreceptors, specifically on the plantar surface of the foot, which provide essential proprioceptive feedback under influence of gravity. It is likely that this effect is also true for bracing, at least when the brace provides compression to the plantar surface of the foot and the ankle. In other words, the compression properties of the brace possibly shorten the peroneal reaction time in unstable ankles only, providing an additional preventive effect. As bracing seems to improve the dynamic defence mechanism of the ankle this could provide a possible explanation for the secondary preventive effect of bracing.

**Braces: more bang for your buck**

Measures that prevent ankle sprains have a substantial public health effect, considering the high incidence of ankle sprains, their long-term consequences, and their associated costs. In the modified Van Mechelen model Van Tiggelen et al. describe that once an efficacious technique has been identified for the prevention of an injury, in step 4 the financial implications of the introduction of this intervention need to be determined in step 5 (efficiency). While recently published guidelines recommend the combined use of bracing and NM training after rehabilitation, our RCT in chapter 4 ascertained that bracing provides a more effective and less expensive measure as single intervention. It is important to emphasize that the results from the current study only evaluated the incremental costs and effects of braces or NM training as separate measures, against their combined use. Consequently, from the current results alone, no conclusions can be drawn on the effectiveness and cost-effectiveness of each of the measures separately.

To translate the cost-effects of bracing and NM training to a population level, VeiligheidNL, the Dutch Consumer Safety Institute, designed a business case ‘Prevention of ankle sprains in athletes’, taking into account the results from the Cochrane review described in chapter 2 and the ‘Dutch situation’ on ankle injury incidence and prevention. In doing so, it became possible to predict cost reductions by implementing bracing or NM training on a large scale. In the Netherlands every year 680,000 ankle sprains are sustained, of which 50% are sustained by athletes. At least 150,000 of these ‘athletic’ sprains are treated by a physical therapist, a GP, or a medical specialist (like a sports physician). In 31% of these ankle sprains it concerns a recurrent sprain. In the business case VeiligheidNL focused on prevention of recurrent sprains in athletes, with an assumption that 20% of athletes with an ankle sprain can be reached by this intervention via an App, resulting in 30,000 athletes reached in the Netherlands yearly. The preventive effect of bracing on recurrent ankle sprains on a population level could then be calculated as: 20% of medically treated athletes for ankle sprain reached * 31% recurrent ankle sprains * 78% (95%CI: 65-87%) secondary preventive effect of bracing = prevention of a recurrence in 4.8% of medically treated athletes. For NM training this preventive effect on recurrent ankle sprains was: 20% * 31% * 46% (95%CI: 39-59%) = prevention of a recurrence in 2.9% of medically treated athletes. VeiligheidNL then applied their ‘Letsellastmodel’, i.e. a model for calculating costs of healthcare and sick leave in case of an injury. In this model the estimated medical costs that could be prevented by bracing were €10,600,000 per year. For NM training this was calculated to be €6,200,000 per year. In addition, calculated reduction in sick leave costs where €16,000,000 for bracing and €9,400,000 for NM training. Finally, the assumption
was made that the costs of an ankle brace are €50 and costs of a home-based NM training equals €27,50 per athlete. This led to a total calculated cost reduction (direct and indirect costs) of €18,800,000 for preventive bracing versus €11,200,000 for NM training per year in the Netherlands.

This does not necessarily mean that bracing should be the measure of choice for ankle sprain prevention. The business case of VeiligheidNL only ascertained the cost-effectiveness of bracing for the prevention of recurrent ankle sprains. As we explained in chapters 3 and 4, in our RCT it concerned self-reported recurrences and costs. Other clinical and athlete consequences of ankle sprains were not taken into account. These may include, among others; persisting pain, feeling of giving way, return to sport and performance in sport, chronic ankle instability (CAI) and eventually osteoarthritis. These clinical and athlete consequences (secondary outcomes) were insufficiently reported in the RCT’s included in the Cochrane review described in chapter 2 to draw meaningful conclusions.

**Compliance; more is less, except for comfort...**

When translating evidence-based preventive interventions into daily practice in sports, important issues to address are compliance and risk taking behavior, as shown in step 6 of the modified Van Mechelen model. In sports injury prevention research, compliance is a term used to indicate the athlete’s correct execution of the prescribed intervention. Compliance could be explained as a marker of an unmeasured factor that predisposes participants to a better outcome, such as personality or self-efficacy. A more extreme interpretation is that the content of the intervention is irrelevant; it is the application of intervention by the athlete to his or her situation that produces the outcomes. In the RCT presented in chapter 3, compliance to the interventions was self-reported on a monthly basis. In the first two months self-reported compliance to home-based NM training and bracing during sports was comparable (45% vs. 48%, respectively), while the combination of the two interventions decreased compliance substantially (28%). To our knowledge this is the first time that this effect has been described in a head-to-head comparison of sports injury prevention measures. If this finding of ‘more is less’ is consistent with interventions in sports injury prevention needs to be confirmed. Moreover, after one year only 23% of participants in the bracing group were fully compliant with bracing during training and competition. In an evaluation of the intervention (unpublished data) 56% of the athletes provided a reason for the decision to stop brace usage before ending the intervention period. The main reason for discontinuation of the intervention during sport as experienced by 46% of those athletes was sub-optimal comfort of the study brace (i.e. semi-rigid DJO Aircast A60). Other studies confirmed that subjective factors, like perceived comfort, are an important barrier for active brace use. Sports medicine practitioners should therefore be aware that brace comfort is an important selection criterion in ankle brace prescription.

**Is compliance to training and bracing predictable?**

Verhagen suggested that factors associated with compliance need to be explored before interventions can effectively be applied in the real world. Therefore, in chapter 6 a secondary analysis of the compliance with bracing and NM training and the combination (data from our main RCT) was performed to provide potential predictors of compliance. In short we found that having had a previous ankle injury, i.e. before the index ankle...
General Discussion

sprain, increased the likelihood of a higher compliance with any of the interventions (OR 1.72; 95% CI 1.09-2.70). Furthermore, participants playing a high-risk sport (volleyball, korfbal, soccer, basketball) had an increased probability of being more compliant with any of the interventions (OR 1.53; 95% CI 1.02-2.29). For the NM training group having had previous experience with NM training was associated with a higher compliance. In contrast, participating in a high-risk sport was associated with a lower compliance. Athletes without a history of previous ankle sprains and athletes who had not previously performed home-based NM training were substantially less likely to comply with NM training. For the bracing and the combination groups participating in a high-risk sport was associated with a higher compliance to bracing.

As explained in chapter 6, one of the main theoretical approaches to predict compliance with sport injury rehabilitation and prevention is the “protection motivation theory”52. Confirming this theory, Taylor and May 53 showed that athletes with higher perceptions of susceptibility to re-injury were more likely to comply with their rehabilitation program.53 In line with these results is our finding, that having had a previous ankle injury significantly increased overall compliance with the preventive measures. In other words, these athletes were probably more compliant, because they were aware of their higher risk for a re-injury. However, this theory does not account for habitual behaviors, nor does it include a role for social and environmental factors.

Is compliance influenced by psychological factors?

A more integrated model of psychological response to the sport injury and rehabilitation process, analogous to the Attitude - Social influence - self Efficacy (ASE) model54, was introduced by Weise-Bjornstal and colleagues (Figure 2)55. This model showcases practical points of application for improving compliance with injury prevention measures, by explaining the cognitive appraisal process in athletes post injury, such as perceptions about the cause of injury, recovery status, and availability of social support. Intrinsic and extrinsic influences on cognitive appraisal by athletes are suggested to account for, and eventually lead to, a behavioral response via positive or negative emotions. Coping style, believes and attributions of the athlete concerning the risk of (re-)injury are central items in the cognitive appraisal of injury, and subsequently create a window of opportunity for injury prevention. From the evaluation of the interventions in our RCT (unpublished data) it became clear that an important obstructing belief on the use of preventive bracing is that wearing a brace during sport could weaken the lateral ankle ligaments. From the participants who had received a brace 38% was convinced of this common prejudice. Contrary to this believe, Cordova et al. 56 showed that consistent ankle brace use did not change the latency to inversion of the peroneus longus, i.e. the most important stabilizer of the ankle, particularly against inversion. Despite the evidence that this is indeed a misbelieve, in a user survey on preventive ankle brace use in soccer players, 69% of players was convinced that wearing an ankle brace would weaken their ankle ligaments49. In the same survey sports medicine practitioners were asked also what they considered to be the main reason for soccer players not to wear ankle braces. The most mentioned reason was the perception of lack of comfort of the ankle brace by athletes. The second most mentioned reason was again the misbelieve in athletes of weakening their ankle ligaments by bracing. One could conclude that if practitioners and preventive programs strive for long term compliance with preventive bracing this misbelieve should at least be replaced by a proper understanding of the effects of preventive bracing. Therefore, every brace prescription should start with the explanation that braces won’t weaken the lateral ankle ligaments.
or cause them to ‘get lazy’ and stop working. Braces actually provide stability to a weakened ankle and protect the ankle during high-risk activities, like sport participation, for sustaining an ankle sprain.

**Figure 2** Integrated model of psychological factors associated with the sport injury and rehabilitation process (adapted from Weise-Bjornstal et al.).

Which brace fits best?

In recent years lace-up and semi-rigid braces have been proven efficacious for ankle sprain prevention\(^4\, 8\, 21\). While we know that these braces work for some sports, like basketball and volleyball, comfort of these brace-types might be sub-optimal for sports like soccer and running\(^49\). An alternative, soft compression brace, is mainly used in the acute phase after an ankle sprain\(^57\). Advanced, yet comfortable, compression braces with some form of heel lock are now offered also for preventive use. They promise to offer reasonable stability with optimal comfort. In the modified Van Mechelen model Van Tiggelen et al. stress that selection of a specific intervention for a specific athlete or specific sport requires decisions to be carefully thought through, owing to the financial and performance impact of their introduction in step 5 (efficiency) and 6 (compliance & behavior). As noted before, there is evidence that subjective factors, like perceived comfort, are important barriers for active brace use\(^49\, 51\). Furthermore, an evaluation of the semi-rigid study brace from our RCT in chapter 3 showed that the main reason for discontinuation of brace use was experienced sub-optimal comfort (unpublished data). Very few studies have compared subjective aspects of different brace types, while previous examples make it seem obvious that knowledge of these subjective aspects could assist athletes and practitioners in selecting an optimal brace for the needs of the individual athlete.

Therefore, in the user-survey in chapter 7, we tested three different types of braces (i.e. compression brace, lace-up brace and semi-rigid brace), in three types of sports (i.e. soccer, running and volleyball). Overall, the three brace types received high (>3.5 out of
1 to 5) mean scores for perceived ease of use and quality. Accordingly, the tested modern ankle braces seemed acceptable on the basis of their look & feel and user friendliness. More contrasting results were obtained for perceived comfort, perceived stability, perceived hindrance, overall satisfaction and willingness to buy the tested brace. Overall, the compression brace was best appraised on perceived comfort, perceived hindrance and overall satisfaction compared to the alternatives. The exception was the appraisal of perceived stability; on this factor the lace-up brace was rewarded significantly higher, compared to the compression brace. Remarkably, the perceived stability of the compression brace was rewarded significantly higher than the perceived stability of the semi-rigid brace, i.e. the former standard in preventive bracing. For specific sports it was concluded that: soccer players gave the compression brace significantly higher scores over the semi-rigid brace; volleyball players gave the lace-up brace significantly higher scores over the semi-rigid brace; runners gave the compression brace significantly higher scores over the semi-rigid brace (only for perceived comfort). If still in doubt, the willingness of the athletes to buy the tested brace provided a clear order of preference; of the soccer players 56% was willing to buy the compression brace, versus lace-up brace 27% and semi-rigid brace 13%; of the volleyball players 58% was willing to buy the lace-up brace versus compression brace 21% and semi-rigid brace 33%; of the runners 57% was willing to buy the compression brace versus lace-up brace 39% and semi-rigid brace 22%. To our knowledge this is the first study to quantify these subjective factors of brace use in a direct comparison. Although it remains to be proven that the compression & figure-of-eight-strap brace is efficacious for prevention, on the basis of the positive subjective characteristics of this brace even a small preventive effect would make this intervention successful at a population level. In other words, if an athlete throws away a highly efficacious, but uncomfortable brace after one training, and then decides to wear a minimally efficacious but comfortable brace for one year during all exposures, the latter will most likely still be a winner at a population level.

**METHODOLOGICAL CONSIDERATIONS**

The main RCT in this thesis described in chapters 3, 4 and 5 had several shortcomings. These have been discussed in the respective chapters, but the most important ones are highlighted here.

**Power**

Our main RCT was designed as a cost-effectiveness evaluation, conducted alongside the clinical trial. In this case the sample size calculation should consider both the clinical evaluation as well as the economic analysis. However, issues surrounding the nature of cost data hinder power calculations with incremental costs as the outcome measure. Cost data are skewed, i.e. a large part of the participants make no or low costs, and consequently have a greater variance than clinical effects. “Normal” sample size calculations are based on an expected difference between groups of normally distributed data. As a consequence, sampling in cost-effectiveness studies is often based on clinical outcomes alone. However, in the current study, the analyses were powered based on expected cost differences alone, as we assumed comparable effectiveness of the interventions based on the literature. We decided to only account for a priori known and fixed cost differences between groups, i.e. differences in intervention costs,
to bypass the mentioned issues around power calculations based on costs. Accordingly, as our power calculations were not based on an expected difference in injury incidences between groups, there is a somewhat higher chance of a type 1 error, i.e. falsely rejecting the null hypothesis of our clinical trial. We found only one comparable trial on preventive bracing versus NM training versus a control condition in basketball with results that were in line with our study\textsuperscript{21}. Therefore, it is important that our results are replicated in future research.

**Recruitment**

Between April 2010 and June 2011 384 participants were recruited and randomised to one of the three intervention groups. Almost all eligible athletes were recruited via the study website www.anklesbackincontrol.nl. Calls for participants were mainly effective via a hyperlink from www.sportzorg.nl. This website is maintained by the Dutch Association for Sports Medicine and presents comprehensive information on treatment and prevention of sports injuries. A recent survey concluded that internet-based recruitment is the number one source for health-related information (87.7\% score) in the Netherlands, followed closely by information provided by health care professionals (71.1\% score)\textsuperscript{62}. This method of recruitment resulted in a sample of participants from a wide spectrum of different activities, sports and ages. However, selection bias may have been introduced by the fact that individuals seeking medical information on the internet probably represent a population with a more active coping strategy (56\% of participants were highly educated). Therefore, we assume that our study sample represents the part of the population with a higher motivation for self-treatment than the general public, potentially leading at the level of the entire Dutch population to an overestimation of the differences between the interventions.

**Participation bias**

The athletes’ inclusion protocol is described in detail in Chapter 3. From the 454 eligible athletes, 70 were excluded for several reasons. Thirty of these athletes did not meet our inclusion criteria: 25 had a non-recent ankle sprain (injury > 2 months before inclusion) and 5 had other accompanying injuries, like a fracture. In addition, 21 eligible athletes did not return our baseline questionnaire. Unfortunately, we were not always able to collect the reason why a potential participant did not complete this questionnaire. Many of them stated that they were not willing to be randomly allocated to one of the interventions, thus actually not willing to provide informed consent. Other reasons were: wanting to follow the advice from their treating practitioner (mostly physical therapists); expressing a specific preference for one of the interventions; and ongoing diagnostic imaging of their ankle. After three attempts to contact the potential participant for handing in the baseline questionnaire, exclusion followed. The remaining reasons for exclusion were: still undergoing treatment (9), no informed consent (8) and other reasons (2). Besides the mentioned barriers, in general potential participants were very willing to enter the study. This was caused probably by the fact that the preventive interventions were available free from charge. Therefore, positive participation bias may have influenced our results.

**Randomisation**

Participants were randomly assigned to one of three intervention groups, after the baseline questionnaire and the informed consent were received. Forty-four participants did not commence their intervention. Most of these participants did not receive their
intervention timely, probably due to a coinciding strike of Dutch Mail. Eventually, 340 participants were included in the study. Randomisation was stratified for care received (i.e. medical vs. non-medical primary care). Stratification created a lower percentage medically treated participants for the brace group (medically treated; NM training 69%; brace 58%; combination 68%). Although this was not a significant difference, this difference could have influenced our results. Furthermore, only 50% of the athletes in the general population seek medical care. An earlier comparable RCT from our group showed that proprioceptive training was specifically beneficial in athletes whose index sprain was not medically treated. Although we were not able to replicate this finding in the current study, we did see a trend for such an effect in the combination group. In chapter 3 we showed that in non-medically treated athletes for combined bracing and NM training the point estimate suggested a 77% reduction in recurrent sprains leading to costs, versus the training group. However, this finding was not significant (relative risk 0.23; 95% CI 0.04 to 1.25). One could argue that a stronger combined effect of braces and NM training exists for the prevention of recurrent sprains that lead to costs. Randomisation did not influence this effect as the training and combination group had comparable percentages non-medically treated athletes.

**Performance and detection bias**

The consequence of using injury registration forms was that only 65% of the participants had a clinical diagnosis of lateral ankle sprain at inclusion, as diagnosed by the treating practitioner. Misclassification of index ankle sprains was minimized by verification of the diagnosis on the basis of the injury registration form and an interview by telephone with a sports physician. The injury registration form has been used successfully in two comparable studies on the same topic. Only after the participants had completed the baseline questionnaire and had provided written informed consent, a blinded research assistant allocated the participant numbers and performed randomization to one of the three interventions. Participants individually applied the allocated intervention. Therefore, it is plausible that outcomes were not influenced by participants’ allocation to one of the three interventions. As recurrences were reported on a monthly basis during follow-up via the mentioned injury registration form, recall bias was not likely. Blinding was only broken when a more specific diagnosis was warranted. For example in case the injury registration form did not lead to a recurrent ankle sprain diagnosis. In this case a sports physician via a phone call verified the diagnosis with the participant. The primary investigator was not concealed for the allocation to the three intervention groups during conduction of the analyses. This could have introduced detection bias. However, a second investigator independently performed the same analyses and confirmed the results. Therefore, the risk for detection bias is considered to be low.

**Attrition bias**

Once participants had started the intervention, they were included in the analysis. Only 22 patients (6% from 340) were lost to follow-up (NM training group 5, brace group 10 and combination group 7). Comparable numbers of participants were lost to follow-up for unknown reasons (NM training 5, brace 8, combination 6). Therefore, we assume that the risk of attrition bias was low, limiting threat to internal validity.
Generalisability
As explained in chapter 3, participants were recruited through the internet. Information on the study and a call for participation were available on the website: www.anklesbackincontrol.nl. We deliberately decided not to recruit participants via the hospital setting. A previous study by our group showed that internet recruiting was far more successful. This method of recruitment resulted in a sample of participants from a wide spectrum of sports. The mean hours of sport participation in our study population was 2.1 hours weekly. In the Netherlands 59% of the population participates in sport on a weekly basis, on average twice a week. Therefore, with respect to exposure, the study population was considered a valid sample of the athletic population in the Netherlands.

RECOMMENDATIONS AND IMPLICATIONS
Implementation of the interventions
After step 7, once an effective intervention has been established, the implementation of the interventions needs to be discussed. Community uptake of bracing and NM training is still lagging behind. In an attempt to bridge this implementation gap VeiligheidNL developed a freely available interactive App (‘Strengthen your ankle’, translated in Dutch as: ‘Versterk je enkel’; available for iOS and Android) that contains the proven cost-effective NM training program and also preventive brace advice. The brace advise was based on this thesis and was implemented in an updated version of the ‘Versterk je Enkel’ App that previously only offered the NM training program. This app is downloaded 80 times a day in the Netherlands, creating about 30,000 users annually.

After completing the ABrCt study a new grant was rewarded to the Department of Public and Occupational Health and the EMGO+ institute to evaluate the effectiveness of the ‘Strengthen your ankle’ App, as compared to the usual practice of providing injured athletes with written materials. The results of this study showed that both the App and the written advises had a good compliance (73% versus 77%) and that there was no significant difference in the number of recurrent sprains. Though, an earlier study, that evaluated the implementation effectiveness of the previous version of the ‘Versterk je Enkel’ App, had disappointing results. The App reached only 2.6% of the projected target population. User ratings for the App’s relevancy, clarity, usefulness, appeal, information and reliability were high (>80% of participants scored at least 5 out of 6 on a Likert scale). Contradictory to the good compliance in the more recent study, reach and adoption of the App were low. It is important to remark that the reach and adoption of the written materials are unknown. An explanation for the suboptimal reach and adoption of the App can be found in the fact that the implementation of the App followed an ecological approach. The researchers described that “Regular dissemination channels of the Dutch Consumer Safety Institute were followed, resulting not so much in an ‘implementation’ strategy but more so in a ‘marketing’ strategy to promote the App within the target population.” To improve the reach and adoption of the App it was advised to make the App consistent with an athlete’s training regime and treatment and rehabilitation process. More specific, it was suggested to have the App personally recommended by professionals in sports and medicine. These so-called influential opinion leaders, i.e. trainers and coaches, physical therapists, sports physicians, orthopaedic surgeons, and general practitioners could provide a valuable dissemination pathway to promote proper usage of the App by the target population.
General Discussion

Knowledge Transfer Group ‘Ankle’

As shown, evidence of effectiveness does not equal successful implementation. To progress the field, practical tools are needed to bridge the gap between research and practice and to truly unite effectiveness and implementation evidence\(^6\), in fact an addition of an 8h step to the modified Van Mechelen model is needed. To support this process the Dutch Association for Sports Medicine developed a Knowledge Transfer Scheme (Figure 3), integrating existing implementation research frameworks into a tool which has been developed specifically to bridge the gap between knowledge derived from research on the one side and evidence-based usable information and tools for practice on the other\(^6\).

![Figure 3](image)

**Figure 3** Five-step Knowledge Transfer Scheme adapted from Verhagen et al. \(^6\)

We applied this scheme to interventions preventing ankle ligament injury. Step 1 in the transfer scheme is to describe the problem in practice. In this case the main RCT in the present thesis was the trigger for the Dutch Association for Sports Medicine to update preventive advises to athletes. The Knowledge Transfer Group (KTG) determined the following problem as a starting point: ‘How can we help an athlete looking for information on ankle sprain prevention find valid and comprehensible preventive products applicable to his or her individual situation at home or on the field?’ In step 2 the results from Chapters 2, 3 and 4 were used to provide evidence synthesis and description for interventions preventing ankle sprains. In step 3 the KTG organized a meeting with key stakeholders: athletes who had sustained an ankle sprain and experienced practitioners who treated ankle sprains on a regular basis. During the second meeting athletes’ experiences and needs for information on ankle sprain prevention were explored and summarized in a focus group conversation. This resulted in the following participants: 3 athletes who had sustained an ankle sprain, 2 sports physical therapists experienced in ankle sprain treatment, an expert sports physician / researcher (author of this thesis), a KTS process manager and an independent chair to guide the discussion. In the third meeting the athlete experiences and needs were discussed with the key stakeholders: i.e. 2 athletic trainers, a physical education trainer,
a sports injury prevention implementation specialist, a general practitioner, a sports physician / researcher, a KTS process manager and an independent chair. In step 4 the information from the third meeting was restructured by a sports physician, a sports physical therapist and a media expert from the Dutch Association for Sports Medicine, and developed into a preventive product. The goal of the product was to provide the individual athlete with a compact, yet comprehensive and integrated evidence based advise on treatment and prevention of ankle sprains in sports, because the athletes did not see treatment and prevention as two separate products. An infographic was considered the most appropriate way to present this integrated preventive advice. The infographic is shown in figure 4. An implementation strategy for the integrated advise on treatment and prevention of ankle sprains, wherein the infographic is the main product, is currently developed by the Dutch Association for Sports Medicine. Step 5, the evaluation of the product through the RE-AIM framework, is to be continued.
Enkelverstuiking

Een enkelverstuiking betreft in 85% van de gevallen de buitenste enkelbanden

- 33% is een recidief
- 66% is een eerste verstuiking

Infographic: Sportarts@KasperJanssen

Tijdlijn

Een acute enkelverstuiking vraagt meteen aandacht vanwege pijn en zwelling. Maar wist je dat het risico op een tweede verstuiking nog een jaar lang dubbel zo hoog is?!

Behandeld & Belast

- Na een verstuiking ontstaan vaak een zwelling en een bloeduitstorting. Een teken dat je enkelbanden zijn ingescheurd.
- Koelen en paracetamol helpen tegen de pijn
- Geef je enkel rust totdat de pijn gezakt is
- Probeer je enkel zo snel mogelijk weer te belasten

Belast & Bescherm

- Wanneer je enkel weer belastbaar is, is het slim je verzwalde enkelbanden te beschermen met een brace of sporttape.
- Voordelen brace:
  - Is snel aangelegd, op de lange termijn goedkoper en geeft minder huidinitiatie dan sporttape

Train & Tape of Brace

- Eindelijk weer lekker trainen!
- Maar pas op! Tijdens sportloop je nog zeker één jaar lang een dubbel zo hoog risico op een tweede verstuiking!
- Balanstraining verminderd de kans op een recidief met 40%
- Braces verminderen de kans op een recidief met 80%
- Tapen is een beetje ouderwets, maar helpt ook

Infographic: Ankle SPRain INtervention Timeline (SPRINT)
Recommendations and implications for athletes and practitioners

The present thesis showed that bracing is superior to NM training in reducing the incidence of self-reported recurrences, but not the severity. Bracing is associated with an added 47% reduction in risk of recurrence, versus NM training. Although the current clinical guidelines are vague on the prescription of NM training and bracing, our study results support the prescription of bracing as single secondary preventive measure for the prevention of self-reported recurrences. In addition, bracing provides not only a more effective measure as a single intervention, but also a less expensive one. As in our study bracing was shown to be effective when prescribed during sports for 12 months, the prescription period of brace use in athletes needs to be extended, instead of being phased out. In the first 2 months full compliance to NM training and bracing as individual home-based interventions was 45% and 48%, respectively. However, when the interventions were combined the compliance dropped to 28%. Combined prescription of these interventions is therefore discouraged, unless carefully considered by the treating practitioner for ‘additional’ purposes other than prevention of recurrences, like persisting pain, feeling of giving way, return to sport and performance in sport, or chronic ankle instability (CAI). It is important to remark that the superiority of bracing over NM training with respect to prevention of recurrences does not imply that NM training is obsolete for ankle sprain prevention. Firstly, the superiority of bracing over NM training is only valid on a population level. When it comes to preventive advise to an individual athlete, intrinsic, extrinsic, situational and psychological factors are to be incorporated. Secondly, the mentioned ‘additional’ purposes also apply to NM training prescription and should be valued individually.

The current work demonstrated that a major factor to account for when prescribing measures for ankle sprain prevention is compliance. Having had a previous ankle sprain, i.e. before the index ankle sprain, increases the likelihood of a higher compliance with any of the interventions. Athletes without a history of previous ankle sprain and athletes who did not previously perform NM training are substantially less likely to comply with NM training. In contrast, athletes who participate in a sport that is high-risk for sustaining an ankle sprain, like soccer, basketball, and volleyball, are substantially more likely to comply with wearing a brace during sports. For these reasons, practitioners prescribing preventive NM training or bracing should take into account “history of previous ankle sprains”, “history of experience with NM training”, and “high- or low-risk sport participation” for sustaining an ankle sprain, to optimize compliance with these interventions.

Finally, it was shown that modern ankle braces-types all score high on perceived ease of use and perceived quality. However, the brace types significantly differ with respect to subjective evaluation of comfort, stability, hindrance, overall satisfaction and willingness to buy the brace. Soccer players and runners prefer a compression brace over a semi-rigid brace, while volleyball players prefer a lace-up brace over a semi-rigid brace. These results need to be disseminated in athletes, sporting clubs, coaches and practitioners, thus promoting selection of an optimal ankle brace for individual ankle sprain prevention. Other studies have shown that prescribing an App-based preventive NM training program is a valid option, when compared to written advice. If brace advise is also efficacious if given via an App remains to be proven.
Following the current trend for patient centered-care, preventive advice should take into account individual needs and preferences of the athlete. Athletes should have the opportunity to make informed decisions about their treatment and preventive interventions, if applicable, in partnership with their (sports medicine) practitioner or coach. Introducing the knowledge transfer scheme for use in ankle sprain prevention by the Dutch Association of Sports Medicine created a compact, but comprehensive and integrated, advice on treatment and prevention of ankle sprains in sport, for use by individual athletes. In a focus group meeting athletes concluded that preventive advise needs to be linked to treatment advise for ankle sprains to create a window of opportunity for initiation of preventive behaviour. An ankle SPRain INtervention Timeline (SPRINT) infographic was developed to present this integrated preventive advice to athletes via social and other media. GP’s, sports medicine practitioners, coaches and sporting clubs can use this timeline to inform and guide an informed decision for preventive bracing, NM training, or even taping.

**Challenges for future research**
The results of this thesis create new insights in the effectiveness and cost-effectiveness of bracing, versus NM training, versus a combination of these two interventions. Furthermore, this thesis presents new potential predictors for compliance with NM training and brace use and quantifies subjective factors that may help to enhance adoption of bracing. Nevertheless, this thesis also displays new challenges for future research. I recommend the following for future research:

- To perform more randomized controlled trials on bracing versus NM training for prevention of ankle sprain recurrences to support our findings, including clinical and athlete consequences of ankle sprains, like persisting pain, feeling of giving way, return to sport and performance in sport, chronic ankle instability (CAI) and osteoarthritis.
- To design a practitioner-centred App to guide brace, tape and NM training prescription, and to evaluate effects on preventive ankle sprain advice, linked to initial treatment of the index sprain.
- To adequately monitor and report compliance in future investigations on NM training and bracing.
- To perform an implementation study on interventions preventing ankle sprains (bracing, NM training and taping) with an athlete-centered approach, wherein the informed athlete is allowed to select the intervention.
- To determine optimal duration of ankle bracing for secondary prevention of ankle sprains in sport. Specifically, long term follow-up is necessary to determine if life-long preventive bracing is necessary in high-risk sports.
- To establish the pathway through which bracing reduces the risk of ankle sprain occurrence and recurrence.
- To confirm the value of potential predictors of compliance to bracing and NM training in different sports.
- To evaluate the effect of a compression & figure-of-eight strap brace on the risk of ankle sprain recurrences in different sports (for example soccer and running).
- To perform a RE-AIM analyses of the reach of educational material on ankle sprain prevention (like the Ankle SPRINT infographic), for example testing the influence of the material on the misbelieve of ‘weakening ankle ligaments by bracing’.
References


General Discussion

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