KCE REPORT 197C

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

ANKLE SPRAINS: DIAGNOSIS AND THERAPY

KCE REPORT 197C
GOOD CLINICAL PRACTICE

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ANKLE SPRAINS: DIAGNOSIS AND THERAPY

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COLOPHON

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AGREE	Appraisal of guidelines for research and evaluation
AE	Adverse events
ATFL	Anterior talofibular ligament
CEBAM	Belgian Centre for Evidence-Based Medicine/Belgian Branch of the Dutch Cochrane Centre
CFL	Calcaneofibular ligaments
CBIP-BCFI	Belgian Centre for Pharmacotherapeutic Information
ED	Emergency department
GP	General practioner
HA	Hyaluronic acid
KNGF	Royal Dutch Society for Physical Therapy/Koninklijk Nederlands Genootschap voor
MA	Meta-analysis
MeSH	Medical Subject Headings
MRI	Magnetic Resonance Imaging
NNT	Number needed to treat
NSAID	Nonsteroidal anti-inflammatory drug
OAR	Ottawa Ankle Rules
PTFL	Posterior talofibular ligament
RCT	Randomized clinical trial
RICE	Rest, Ice, Compression, Elevation
ROM	Range of motion
RR	Relative risk
SR	Systematic review
US	Ultrasound scan
TENS	Transcutaneous electrical nerve stimulation
VAS	Visual analog scale
VSG	Vereniging voor Sportgeneeskunde/Dutch association for sport medicine
WMD	Weighted mean difference

SCIENTIFIC REPORT

1 INTRODUCTION

1.1 Ankle sprain: a frequent problem

Ankle sprains cover lesions of variable severity: from the mild sprain to the complete rupture of one or more ligaments supporting the ankle. The incidence reported in the general population is fairly limited. In the nineties, the estimation was about 300 ankle sprains per 10 000 inhabitants in three countries (6 000 per day in France, 5 000 per day in the UK and 1640 per day in the Netherlands).[1-3]

Not all sprains lead to a health care encounter and only a part of them are a reason for encounter in emergency departments (ED). In the UK, the annual incidence of ankle sprain diagnosed in ED ranged from 50 to 61 per 10 000.[4] In the US, a study using data from the National Electronic Injury Surveillance System found an incidence rate in EDs of 21.5 per 10 000 person per year.[5] According to the same study, nearly half of all ankle sprains (49.3%) occurred during athletic activity and the peak incidence of ankle sprain (72 per 10 000 person-years) concerned the 15-19 years age group.[5]

1.2 Controversies on the need for radiography

The likelihood of a fracture in an ankle injury varies from 1-4% in general practice to 15% in emergency departments.[6] Despite this relatively low probability, most patients undergo X-ray[7] with the risk of being exposed to unnecessary radiation in addition to a longer waiting time before treatment. In order to decrease the number of unnecessary radiographies, the Ottawa Hospital Research Institute published in 1992 a set of guidelines “The Ottawa ankle rules” to assist physicians in deciding whether a X-ray after ankle injury is needed.[8]

In Belgium, the Ottawa ankle rules were included in 2001 in a clinical practice guideline published by the former “Wetenschappelijke Vereniging Voor Huisartsen” (currently “Domus Medica”), the scientific association of Dutch-speaking general practitioners.[9] In practice however, it appeared that litigation risks, policies of insurance companies (e.g. work injuries or sport accidents) or patient expectations often jeopardize the applicability of these rules.[6]

Radiography is not the only controversial issue in the management of ankle injuries. Several questions have been raised on the utility of some therapeutic modalities including external support (e.g. braces, taping, elastic bandage, cast) and other treatment strategies (e.g. medications, physiotherapy).

1.3 Objective of this report

The aim of this project is to offer an overview of the current evidence on diagnosis and treatment of ankle sprain and to formulate recommendations to health care providers who manage patients who suffer from these injuries, in primary care or emergency settings (at least general practitioners, emergency nurses, emergency physicians, radiologists, physiotherapists, sport physicians). This guideline will assist physicians confronted with the uncertainty of medico-legal consequences in case of missed fracture for example.[10]

1.4 Anatomy and classification of ankle sprains

1.4.1 Anatomy of the ankle

Understanding the anatomy of the ankle is crucial to diagnose correctly ankle sprain. The ligaments of the ankle can be divided in 3 groups:[11]

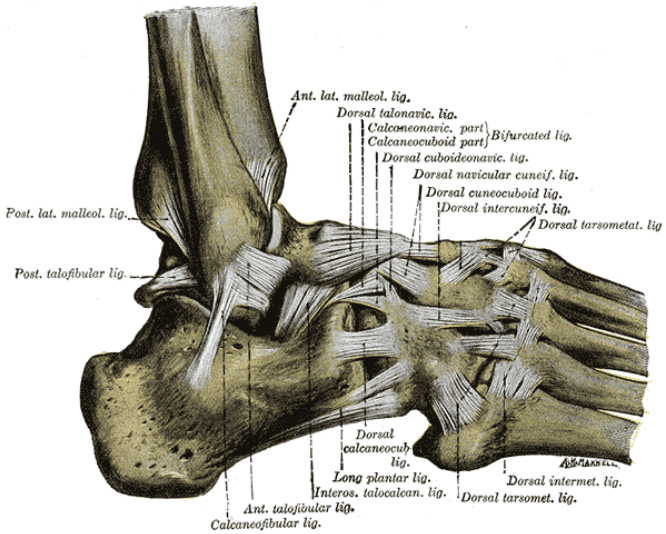
- The lateral group which connects the 3 bones of the ankle joint (tibia, fibula and talus). These ligaments are: the anterior talofibular (ATFL), posterior talofibular (PTFL) and calcaneofibular (CFL) ligaments.
- The medial group with 4 ligaments called the deltoid ligament.
- The ligaments of the syndesmosis which connect the tibia and the fibula in their inferior part (in the high level of the ankle). They include the anterior-inferior, the posterior-inferior and the transverse tibiofibular ligaments as well as interosseous structures (ligaments and membrane).

1.4.2 Ligaments hit in ankle sprains

The most frequent mechanism in an ankle injury is inversion (supination and adduction of the plantar-flexed foot).[11] This movement commonly hits the lateral collateral ligaments and more specifically the anterior talofibular ligament. The isolated injury of this ligament concerns more than 60% of the ankle sprains. Less often, the calcaneofibular ligament is also hit with combined tears of both ligaments in 20% of the cases. An isolated rupture of the calcaneofibular ligament is very rare. The injury of the posterior talofibular ligament occurs in rare cases of frank dislocation of the ankle.[11]

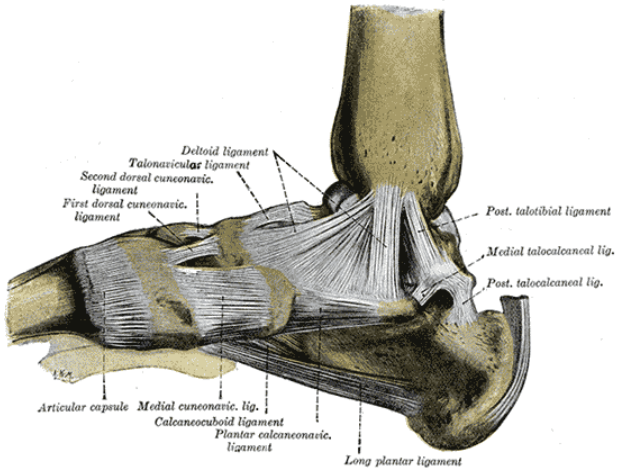
Although lateral ligament sprains are the most common ankle injury, several other lesions can occur after a trauma as peroneal tendon tears, deltoid tears, osteochondral lesion or fracture of any bone concerned in the joint.[12, 13] These lesions are out of the scope of this guideline. Nevertheless, they will be mentioned as differential diagnosis in chapter 4.

Figure 1 – Ligaments of the foot from the lateral aspect



Source: Henry Gray (1825–1861). Anatomy of the Human Body. 1918

Figure 2 – Ligaments of the medial aspect of the foot



Source: Henry Gray (1825–1861). Anatomy of the Human Body. 1918

1.4.3 Classification of ankle sprains

Different classifications of the severity of the ankle sprain exist.

- The classical classification is based on the **importance of the tear of the ligament**: microscopic, macroscopic stretching or complete rupture. However this classification focuses on the ATFL and ignores injuries of either the CFL or the PTFL.
- Grading systems taking into account **the number of ligaments injured** were proposed by some authors but with the difficulty to assess objectively each injury.
- A third classification system makes use of the **clinical severity** of the ankle injury e.g. the classification from the American College of Foot and Ankle Surgeons[14] (Table 1).

Table 1 – Classification of ankle sprains

Grade	Signs and symptoms
I: partial tear of a ligament	Mild tenderness and swelling Slight or no functional loss (i.e., patient is able to bear weight and ambulate with minimal pain) No mechanical instability (negative clinical stress examination)
II: incomplete tear of a ligament, with moderate functional impairment	Moderate pain and swelling Mild to moderate ecchymosis Tenderness over involved structures Some loss of motion and function (i.e., patient has pain with weight-bearing and ambulation) Mild to moderate instability (mild unilateral positivity of clinical stress examination)
III: complete tear and loss of integrity of a ligament	Severe swelling (more than 4 cm about the fibula) Severe ecchymosis Loss of function and motion (i.e., patient is unable to bear weight or ambulate) Mechanical instability (moderate to severe positivity of clinical stress examination)

Source: Wolfe M. et al. 2001.[14]

2 SCOPE

This guideline focuses on diagnosis and treatment of acute lateral ankle sprain in **adults and youngsters** (16 years and over). Ankle injuries in children are out of scope. The specificities of athletes' injuries are not analyzed.

The lesions considered are **acute lateral ankle sprains** only. The following are out of the scope of these guidelines:

- Tendinopathy and non-traumatic ankle pain including the diagnosis and treatment of patients with chronic ankle instability;
- Other acute injuries of the ankle (see differential diagnosis chapter 4).

Conservative treatment is the focus of the therapeutic aspects discussed in these guidelines. Surgery is out of scope.

No search was made about the specific cost-effectiveness aspects in the management of ankle sprain.

3 METHODOLOGY

Several steps were followed to elaborate this guideline. Firstly, clinical questions were developed and the inclusion and exclusion criteria were defined in collaboration with the stakeholders. Secondly a literature review was made (including search for recent, high quality guidelines). Thirdly, on the basis of the results of the literature review, recommendations were formulated and graded according to the GRADE approach.

3.1 Stakeholder and expert involvement

3.1.1 Stakeholders

A group of stakeholders was formed at the start of the project. Each association of health care professionals involved in the management or treatment of ankle sprain was identified and invited to contribute to this guideline (maximum 2 representatives per association). Two face-to-face meetings were organized (stakeholders were invited to provide their comments by email if they could not attend the meeting). The list of the identified professional associations is presented in Table 2. The names of the stakeholders are available in the colophon page of this guideline.

The roles assigned to the stakeholders group were:

- The definition of the clinical questions, in close collaboration with the team of researchers;
- The feedback on the content of the guideline;
- The validation and scoring of the recommendations (see Chapter 3.4);
- The preparation of the implementation of the guideline (see Chapter 8).

Table 2 – List of Professional Associations included in the stakeholders groups

Name	Category
ABP (Association Belge des podologues)	Podiatrists
AFIU (Association Francophone des Infirmier(e)s d'Urgence)	Emergency nurses
Axxon, Physical Therapy in Belgium	Physiotherapists
BeSEDIM (Société belge de Médecine d'Urgence)	Emergency physicians
BFAS (Belgian Foot and Ankle Society)	Orthopedists
BBOT-UPBTO (Belgische Beroepsvereniging voor Orthopedische Technologieën-Union Professionnelle Belge des Technologies Orthopédiques)	Professionals specialized in bandaging
Domus Medica v.z.w.	General practitioners
FBP (Federatie van Belgische Podologen - Fédération Belge des Podologues)	Podiatrists
SSMG (Société scientifique de Médecine Générale)	General practitioners
RBRS (Royal Belgian Society of Radiology)	Radiologists
RIZIV-INAMI	Public authorities
VVVS v.z.w (Vlaamse Vereniging Verpleegkundigen Spoedgevallenzorg)	Emergency nurses
Federal Public Service of health, Food Chain Safety and Environment	Public authorities

No patients were included in this group because of a lack of representative patient associations dedicated specifically to this problem in Belgium.

3.1.2 Experts

A group of experts was formed at the beginning of this project and was consulted during 3 face-to-face meetings. It encompassed radiologists, emergency physician, orthopedists, physiotherapist, methodologist, physical medicine physician, sport physician and general practitioner. The aim of this group was to assess the literature search strategy and the comprehensiveness of the results and to suggest improvement when necessary. They were also invited to participate in the elaboration of recommendations, together with the stakeholders group at the end of the process to form the above-mentioned panellist group. The names of the experts are available in the colophon page of this guideline.

3.2 Clinical questions

3.2.1 General questions

The following clinical questions were formulated by the researchers' team with the collaboration of stakeholders.

- Related to the diagnosis:
  - Which diagnostic procedures are used in the clinical assessment of ankle sprain?
  - What is the accuracy and reliability of these diagnostic procedures?
  - Which criteria are used to exclude a fracture in ankle sprain?
  - What is the accuracy of these criteria?
- Related to the treatment:
  - Which treatments are used in an acute ankle sprain?
  - What is the efficacy and efficiency of these treatments?
- Which clinical recommendations can be formulated for the management of an acute ankle sprain in terms of diagnosis and treatment?

3.2.2 Specific questions

- Related to the diagnosis
  - What is the accuracy and reliability of history taking in the diagnosis of acute lateral ankle sprain?
  - What is the accuracy and reliability of physical examination in the diagnosis of acute lateral ankle sprain?
  - What is the accuracy and reliability of the Ottawa ankle rules in the diagnosis of acute lateral ankle sprain?
  - What is the accuracy and reliability of functional test other than Ottawa ankle rules in the diagnosis of acute lateral ankle sprain?
  - What is the accuracy and reliability of X-ray in the diagnosis of acute lateral ankle sprain?
  - What is the accuracy and reliability of ultrasonography in the diagnosis of acute lateral ankle sprain?
  - What is the accuracy and reliability of magnetic resonance imaging in the diagnosis of acute lateral ankle sprain?
  - What is the accuracy and reliability of computer assisted tomography in the diagnosis of acute lateral ankle sprain?
  - Which criteria are used to exclude a fracture in ankle sprain?
  - What is the accuracy of these criteria?
- Related to the treatment:
  - What is the efficacy and efficiency of oral medication (paracetamol, anti-inflammatory drug…) in the treatment of acute lateral ankle sprain?
  - What is the efficacy and efficiency of topical medication in the treatment of acute lateral ankle sprain?
  - What is the efficacy and efficiency of rest, ice, compression and elevation in the treatment of acute lateral ankle sprain?
  - What is the efficacy and efficiency of ultrasound in the treatment of acute lateral ankle sprain?
  - What is the efficacy and efficiency of laser in the treatment of acute lateral ankle sprain?
  - What is the efficacy and efficiency of ankle supports (cast, brace, tape…) in the treatment of acute lateral ankle sprain?
  - What is the efficacy and efficiency of exercice therapy in the treatment of acute lateral ankle sprain?

3.3 Literature review

The clinical questions were translated into in- and exclusion criteria using the P.I.C.O. (Participants–Interventions–Comparator–Outcomes) framework.

3.3.1 Participants

- Inclusion criteria
  - Adults and youngsters (16 years and over)
  - Inversion sprain (including acute inversion sprain among patients with chronic ankle instability)
- Exclusion criteria
  - Children (age younger than 16)
  - Tendinopathy
  - Acute and chronic non traumatic ankle pain
  - Chronic ankle instability
  - Other ankle trauma

3.3.2 Intervention

- Inclusion criteria

a. Diagnostic and/or prognostic evaluation

  - Anamnesis
  - Clinical examination: physical examination and functional assessment (including Ottawa rules)
  - Imaging (X-ray, ultrasonography, magnetic resonance imaging, computer assisted tomography)

b. Management and treatment

  - Information or education programs
  - Drug therapy (oral, topical, intraarticular injection)
  - "RICE": Rest, Ice, Compression, Elevation
  - Electrophysical therapy (ultrasound, laser)
  - Ankle support (casting, bracing, orthosis…)
  - Physiotherapy (mobilisation, exercise therapy)

- Exclusion criteria:
  - Prevention
  - Surgical interventions

3.3.3 Comparator

Comparators are either no treatment or alternative diagnostic tests and management/treatment procedures (gold standard or usual procedures).

- Inclusion criteria were the following:
  - Reference diagnostic evaluation versus other diagnostic evaluation;
  - Reference management and treatment versus other management and treatment;
  - Diagnostic evaluation and/or management and treatment versus no intervention, no treatment.

3.3.4 Outcome

- Inclusion criteria
  - Diagnostic accuracy of procedures (e.g. false positive, false negative, sensitivity, specificity, positive and negative predictive values);
  - Patients' outcomes (until 1 year):
    - Symptoms: pain, swelling for example;
    - Side effects, adverse events of treatments or diagnostic procedures;
    - Functional capacity (disability measures) and return to work or sport activities related measures;
    - Relapse and complications such as fractures, ruptured syndesmosis and osteochondral lesions;
    - Quality of life.
- Exclusion criteria: none.

3.3.5 Study design

- Inclusion criteria for the study design:
  - Diagnostic studies: systematic reviews, guidelines, meta-analyses, RCTs, prospective studies;

  - Therapeutic studies: systematic reviews, guidelines, meta-analyses, RCTs.
- Only studies with a sample size of at least 30 participants in each (sub)group were included. Articles in Dutch, English, French and German were included.
- Exclusion criteria for study design
  - Narrative review
  - Cadaver studies
  - Case reports
- A hierarchical approach was followed:
- First the analysis focused only on recently published systematic reviews and meta-analyses (SR/MA) published since 2000.
- Second, the selected evidence synthesis was updated by a search for all relevant primary studies (RCTs and prospective studies) published after the search date of the selected SR/MA.
- In the absence of high quality SRs/MAs, clinical guidelines of high quality were considered as a stating point.

3.3.6 Databases and date limits

The following databases were included in the literature search:

- The Cochrane Database of systematic reviews (http://www.cochrane.org)
- Medline (http://www.ncbi.nlm.nih.gov/pubmed)
  Embase (http://www.embase.com/)
- Pedro search database (http://www.pedro.fhs.usyd.edu.au/redirect.html)
- CINAHL (http://www.cinahl.com)
- Medion for diagnostic studies (http://www.mediondatabase.nl)

For the guidelines the search engines were:

- G.I.N. guideline resource (http://www.g-i-n.net)
- NEHL guidelines finder (http://www.library.nhs.uk/GuidelineFinder/)
- National Guideline Clearinghouse (http://www.guideline.gov/)
- New Zealand Guidelines (http://www.nzgg.org.nz/)
- NICE guidelines (http://www.nice.org.uk)
- SIGN guidelines (http://sign.ac.uk/)

The electronic search for systematic reviews, meta-analyses and guidelines covered the period from **01/01/2000 to 06/12/2011.**

3.3.7 Search strategy

The search combined 3 groups of words with “OR” inside the groups and “AND” between the groups (see details of the search strategy in appendix 1 et 2).

- Pathology: **ankle sprain OR ankle injury OR ankle trauma;**
- Field of search (intervention): **diagnosis / treatment**, according to the 2 research questions.
  - For diagnosis in Medline, a broad filter was used in order not to miss any articles about the Ottawa ankle rules. In Embase, the search was built on specific Emtree terms.
  - For treatment, searches were similar in both databases with an adaptation of MeSH to Emtree terms.
- Type of reference (study design) included: **(systematic) reviews OR meta-analyses OR guidelines OR RCT’s OR diagnostic trials OR controlled clinical trials**

The number of articles by database is provided in appendix 3.

Studies were screened on **title and abstract** by a group of two researchers (T.W. & P.R. and R.DR. & P.R.) with the P.I.C.O. in- and exclusion criteria. In a second step, the remaining papers were screened on a **full-text** basis by the same researchers. The flowchart below shows the amount of studies finally included and the main reasons for exclusion. Hand searching of additional articles was performed on the basis of reference list in all the selected studies.

Figure 3 – Flow chart of the final results of the screening of the literature for diagnosis

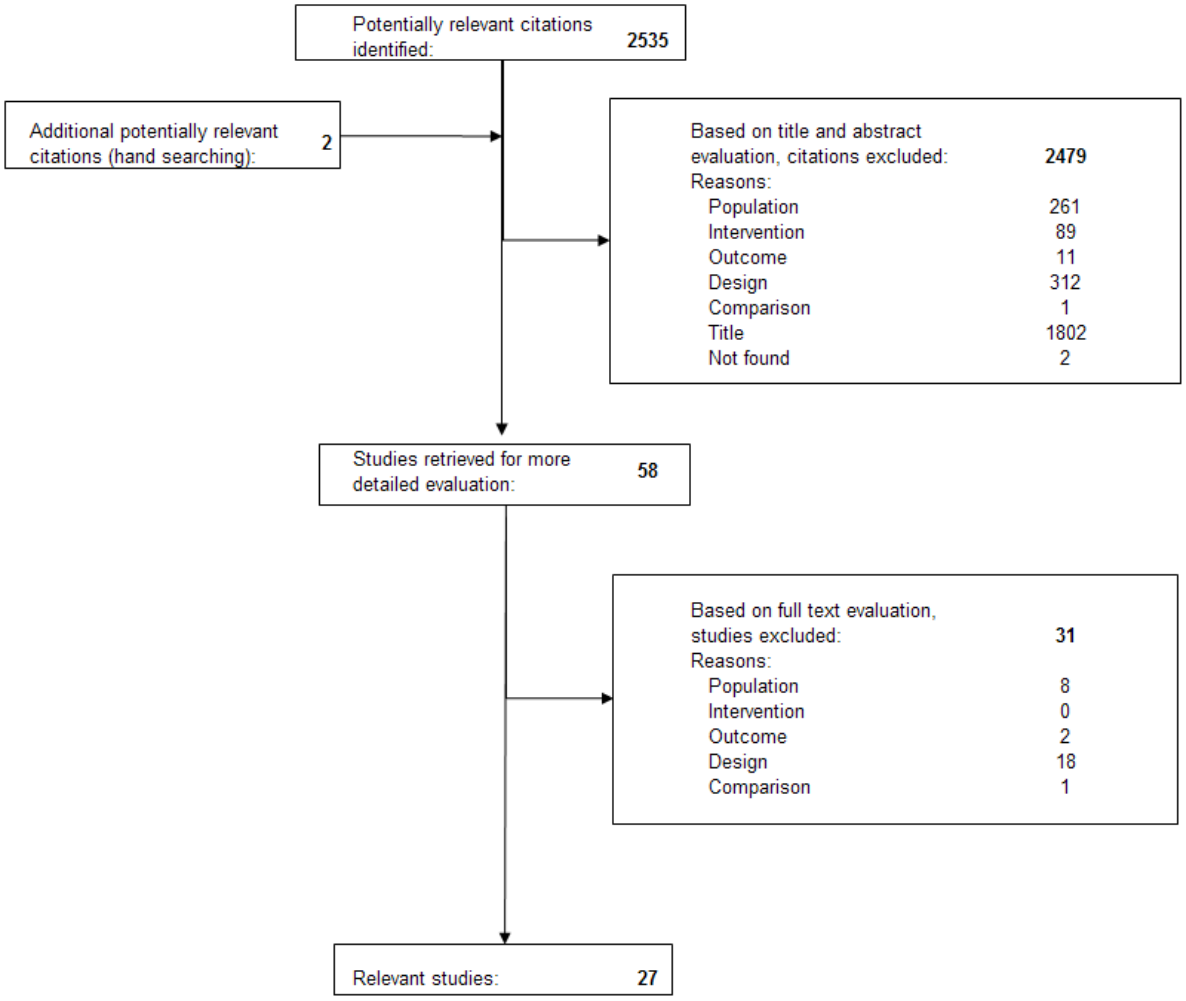
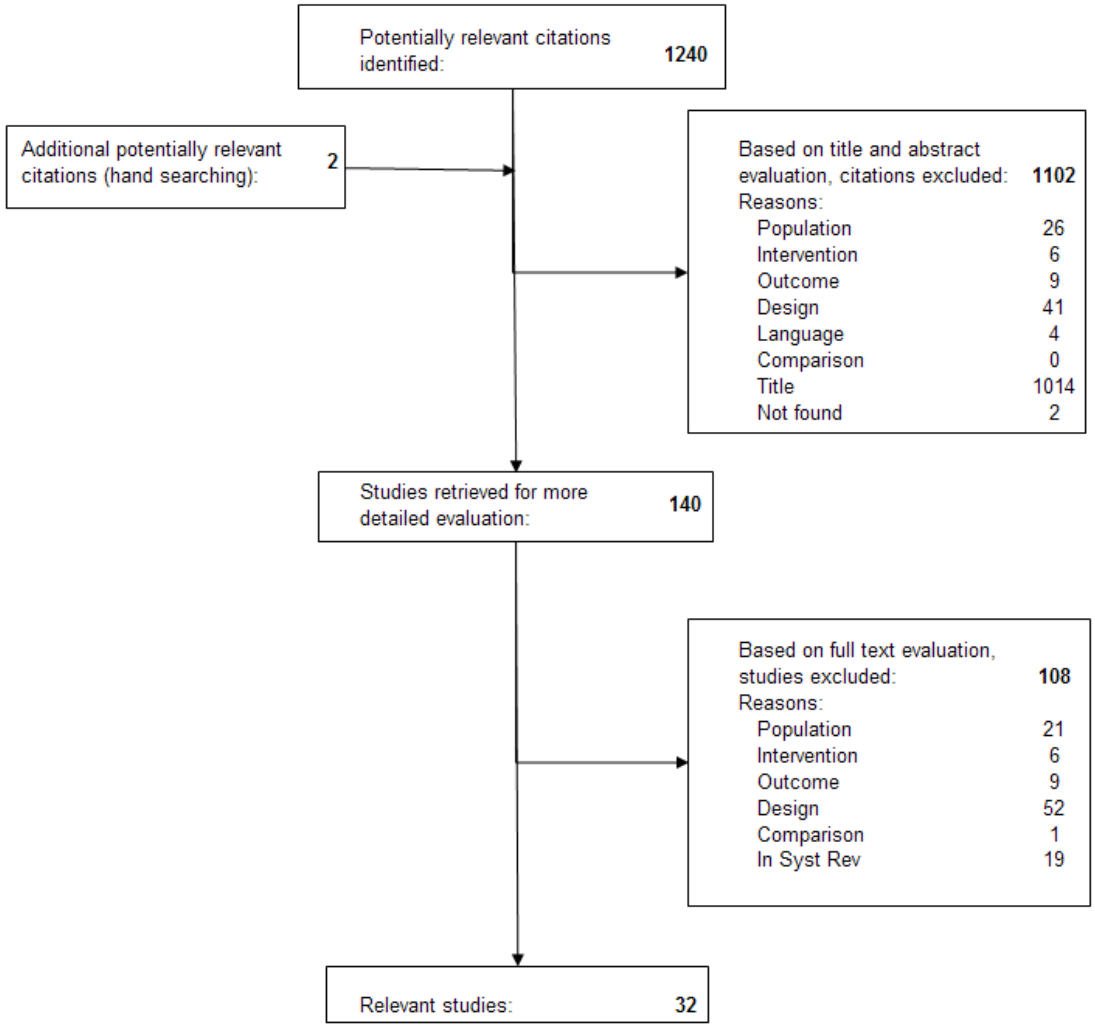


Figure 4 – Flow chart of the final results of the screening of the literature for therapy



The screening of the **guidelines** was performed on title and abstract by a group of two researchers (T.W. & P.R. and R.DR. & P.R.) based on the P.I.C.O. in- and exclusion criteria. Four guidelines were selected.[3, 9, 15, 16]

3.3.8 Quality appraisal

The quality appraisal was performed by three researchers (T.W., R.DR., P.R.) previously trained in order to obtain consensus for appreciation of the publications. Another group of researchers (K.H., L.S., P.J.) double checked the quality appraisal performed.

- **Systematic reviews** were assessed using the AMSTAR checklist[17] (http://amstar.ca/Amstar_Checklist.php);
- **RCTs for diagnosis** were assessed with the QUADAS criteria;[18]
- **RCTs for treatment** were assessed with the Dutch Cochrane tool for assessing risk of bias (www.cochrane.nl);
- Appraisal of the **guidelines** was based on the AGREE II instrument (www.agreetrust.org).

The results of the quality appraisal are in appendix 4 for diagnosis and appendix 5 for therapy.

3.3.9 Data extraction

Two groups of independent reviewers (T.W. & P.R. and R.DR. & P.R.) extracted the data, using a standard KCE template for evidence tables (Appendices 6 and 7). The tables encompassed a description of the study type, its objective, the P.I.C.O., the results and the level of evidence.

Four categories of outcomes were defined to formulate the conclusion:

- Patients' symptoms: pain and swelling;
- Functional evaluation: Range of motion (ROM);
- Patients' return to sport or work activites;
- Relapse.

For each relevant outcome, a level of evidence was assigned to each conclusion using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (http://www.gradeworkinggroup.org/).

GRADE tables were produced by three researchers (K.H., L.S., P.J.) by means of internal discussion and consensus.

Table 3 – Levels of evidence according to the GRADE system[19]

Quality level	Definition	Methodological Quality of Supporting Evidence
High	We are very confident that the true effect lies close to that of the estimate of the effect	RCTs without important limitations or overwhelming evidence from observational studies
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies
Low	Our confidence in the effect estimated is limited: the true effect may be substantially different from the estimate of the effect	RCTs with important limitations or observational studies or case series
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect	

The quality of evidence was down- or upgraded based on predefined criteria (Table 4)

Table 4 – Down- or upgrading the evidence according to the GRADE system[20]

Study design	Quality of evidence	Lower if	Higher if
RCT	High	Risk of bias: -1 Serious -2 Very serious	Large effect: +1 Large +2 Very large
	Moderate	Inconsistency: -1 Serious -2 Very serious	Dose response: +1 Evidence of a gradient
Observational study	Low	Indirectness: -1 Serious -2 Very serious	All plausible confounding +1 Would reduce a demonstrated effect
	Very low	Imprecision: -1 Serious -2 Very serious	+1 Would suggest a spurious effect when results show no effect
		Publication bias: -1 Likely -2 Very likely	

Grade tables were done only for therapy and are available on appendix 8.

For diagnosis, there were too few data and a too broad clinical heterogeneity between the publications to produce a meta-analysis. The level of evidence for each conclusion was based on the quality appraisal and the numbers of primary studies or SR leading to this conclusion or on the level of evidence of the same conclusion provided by a guideline if any.

3.4 Elaboration of recommendation

On the basis of the available evidence from the literature review, several recommendations were drafted by a small working group (P.J., D.P., K.H., L.S.). An assessment of the strength of recommendation was made according to the GRADE system (Table 5 and 6).

Table 5 – Strength of recommendations according to the GRADE[21]

Grade	Definition
Strong	The desirable effects of an intervention clearly outweigh the undesirable effects *(the intervention is to be put into practice),* or the undesirable effects of an intervention clearly outweigh the desirable effects *(the intervention is not to be put into practice).*
Weak	The desirable effects of an intervention probably outweigh the undesirable effects *(the intervention probably is to be put into practice),* or the undesirable effects of an intervention probably outweigh the desirable effects *(the intervention probably is not to be put into practice).*

Table 6 – Factors that influence the strength of a recommendation[21]

Factor	Comment
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted.
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted.
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted.
Costs (resource allocation)	The higher the costs of an intervention – that is, the greater the resources consumed – the lower the likelihood that a strong recommendation is warranted.

The rating was then submitted by email to the panellist group gathering the stakeholders and the experts as described in the points 3.1.1 and 3.1.2. Panellists were asked to score each recommendation on a 5-point Likert-scale to indicate their agreement with the recommendation (Table 7 – Signification of the 5-point Likert-scale used to score recommendations). If panellists disagreed with a recommendation (score '1' or '2'), they were asked to provide the reasons as well as appropriate evidence that justifies their disagreement.

Table 7 – Signification of the 5-point Likert-scale used to score recommendations

1	Completely disagree
2	Somewhat disagree
3	Unsure
4	Somewhat agree
5	Completely agree

An anonymous summary was performed with mean score, standard deviation and % of 'agree' scores (score 4 and 5). This summary is available in appendix 8. A face-to-face meeting was organized with the panellist group (stakeholders and experts) to present and discuss this summary and obtain a consensus about the wording of the recommendations. After the meeting, the stakeholders and the experts involved in this guideline received the modified recommendations.

3.5 Validation and updating the guideline

3.5.1 Validation process

The guideline was reviewed prior to its publication by 3 independent validators (cf. names in the colophon), making use of the Agree II checklist. The validation process was chaired by CEBAM. The validation of the report results from a consensus or a voting process between the validators. According to a proposal by the validators of this report, recommendations based on expert consensus were labeled as "Best practices".

3.5.2 Updating of the guideline

The KCE processes foresee that the relevance of an update would be yearly assessed for each published guideline by the authors. Decisions are made on the basis of new scientific publications on a specific topic (e.g. Cochrane reviews, RCTs on medications or interventions). Potential interest for groups of health practitioners is also considered in this process.

This appraisal leads to a decision on whether to update or not a guideline or specific parts of it to ensure the recommendations stay in line with the latest scientific developments.

3.6 Funding and declaration of interest

The KCE is a publicly funded federal scientific research institution; its mission is to provide independent scientific advice. KCE as an institution and all individual KCE collaborators declare to have no interests in commercial companies, health care organizations, professional interest groups or any other body on which the guidelines could have a positive or negative impact (financial or other). Every person having contributed to the elaboration of this guideline (as an expert, validators, stakeholder, …) has been requested to declare potentially conflicting interests. This information is published in the colophon pages of this guideline.

4 RESULTS FOR DIAGNOSIS

In clinical practice, ankle trauma is evaluated with careful history taking and physical examination (inspection, palpation, weight-bearing status and functional tests). The main purpose of the diagnostic procedures is to identify the anatomical structure injured and the severity of the lesion.

Several differential diagnosis may be evoked (non-exhaustive list) when confronted with an ankle injury.

Table 8 – Differential diagnosis of ankle injuries

Ligament partial or complete rupture	Fractures
Lateral ankle sprain	Osteochondral fracture (talar dome)
High ankle sprain or syndesmosis sprain	Anterior calcaneal process fracture
Deltoid ligament rupture	Lateral malleolar fracture Medial malleolar fracture
Achilles tendon rupture	Navicular fracture
Peroneal tendon subluxation or tear	First metatarsal base fracture
Subtalar joint instability	Fifth metarsal base fracture
	Lisfranc's fracture or dislocation
	Proximal fibular fracture associated with syndesmosis sprain (Maisonneuve fracture)

It is out of the scope of this guideline to review all the examinations needed to eliminate the differential diagnosis of ankle sprain. This guideline focuses on the injury of the ankle lateral ligaments: the examinations needed to distinguish between a partial and a complete rupture of the ligament or to exclude a fracture.

4.1 History taking

- Both the stakeholder and expert groups underlined the importance of a deep history taking in the context of ankle trauma. However, this topic is poorly studied in the literature. Some items as cracking sound heard and twisting mechanism have been analysed by Stiell in 1992[22] but given their poor correlation with fracture they were not retained for the Ottawa rules (see chapter 4.3).
- One guideline of low quality suggested questions to be part of the specific history taking on ankle sprain, without any reference to the literature.[9] These questions were also proposed by stakeholders and experts involved in the present guideline:
  - Mechanism of injury: for instance, a lateral ankle sprain is likely with a combination of plantar flexion and inversion; a syndesmotic sprain is associated to a dorsiflexion and eversion of the ankle with internal rotation of the tibia cause;[23]
  - Symptoms and evolution: even a few hours after the trauma, the symptoms can evolve towards diffuse ankle swelling and tenderness. It is therefore important to search information on the immediate symptoms and their evolution: swelling, colour, pain, hematoma, felt and heard crackling, possibility of weigh bearing or walking, insomnia due to pain;
  - Immediate response to the trauma: e.g. application of ice or use of oral antalgics;
  - Medical history: previous history of ankle injury, chronic disease, usual treatment, allergy.

Key message regarding the history taking

- **The history taking contribution in the assessment of acute ankle sprain is important according to experts, but poorly studied in the recent international literature.**
- **Questions on mechanism of injury, symptoms and evolution, immediate management, and medical history including previous history of ankle injury are suggested (expert consensus).**

4.2 Physical examination (Ottawa Ankle Rules excepted)

The examination performed by clinicians for assessing ankle trauma usually encompasses inspection, palpation and special functional tests. This section summarizes the content of the most recent guidelines and studies on these topics. The Ottawa Ankle Rules, which combine inspection and palpation are studied in the next chapter.

4.2.1 Inspection and palpation

- Few evidence was found in the indexed literature on the value of physical examination for diagnosing an acute lateral ankle sprain.
- The guideline with moderate risk of bias from the Dutch association for sport medicine (VSG) is the only one to mention swelling in the assessment of patients with ankle trauma.[15] The authors did not found any predictive value of swelling after ankle trauma: they do not recommend to consider swelling in the assessment of the severity of the lesions.
- None of the most recent guidelines with moderate risk of bias[3, 15] found evidence in the literature that palpation on its own could help in differentiating between a partial and a complete rupture of the ligament or for excluding a bone lesion. However both guidelines mention the importance of palpation in the context of Ottawa ankle rules (see 4.3). Palpation is also a part of the delayed clinical examination advised by the Royal Dutch Society for Physical Therapy (KNGF).[3] Only the guideline from the Dutch association for sport medicine (VSG) recommended pain palpation in the lateral ligaments area. This recommendation was based on experts' opinion.[15]
- The stakeholders and experts involved in this KCE guideline underlined the importance of grading the ankle sprain during the initial assessment of the lesion (based on symptoms and physical examination) since the therapy could differ according to the severity of the sprain (expert consensus).

Key message regarding inspection and palpation

- **No evidence was found of the predictive value of clinical signs on their own in the assessment of the severity of the ankle sprain.**
- **Inspection and palpation may contribute to the assessment of acute lateral ankle sprain according to guidelines (expert consensus).**
- **The experts and stakeholders involved in this guideline insisted on the importance of grading the severity of ankle sprain during the initial assessment for chosing the most accurate therapy (expert consensus).**

4.2.2 Functional tests

Several manual tests exist to examine an ankle. This guideline focuses on tests that aim at specifying the diagnosis and severity of ankle sprain. The "anterior drawer test" and the "talar tilt test" are two manual tests used to assess the ankle stability and the likelihood of ligament rupture:

The anterior drawer test

- The anterior drawer test is a functional clinical test routinely used in ankle sprain with the aim of testing the integrity of the anterior talofibular ligament. During this test the examiner provides an anterior glide of the calcaneus and talus on the stabilized tibia. The test should be comparatively done on the healthy ankle and is considered to be positive when there is excessive translation of one side in comparison to the opposite extremity.
- The validity of this test has been poorly studied.[24] An inter-individual variability between clinicians was noted by authors[2] and the usefulness of the test appears to be limited by some factors such as a history of previous ankle sprain or inability of the patient to relax.[25]

- To minimize the inter-individual testing variation of the anterior drawer test, one study with moderate risk of bias[26] presented an instrument named “the ankle meter” consisting of two plastic scales (heel scale and tibia scale). It was used to quantify the measure of the anterior drawer test within 48 hours after an ankle sprain in 45 patients. However, even if a significant correlation was found between clinical and stress radiography measures (R=0.91, p<0.05), this study did not provide information about the validity of both tests (anterior drawer test with ankle meter and stress radiography) for the diagnosis of ligament rupture.
- The Royal Dutch Society for Physical Therapy (KNGF)[3] recommends to use the anterior drawer test as a part of the delayed clinical examination, 4-7 days after trauma. They based this recommendation on one study with moderate risk of bias (see chapter 4.2.3). The guideline from the Dutch association for sport medicine (VSG) stresses the importance of the pratical experience (training and skill) of the clinician who performs the anterior drawer test.[15]

The talar tilt test

- The talar tilt test (inversion stress test or varus stress test) aims to assess the integrity of the calcaneofibular and the anterior talofibular ligaments.[24] During this test the ankle is stressed with a varus force. The test is positive if there is an absolute angulation greater than 23° or a difference >10° between the 2 ankles. The test has to be comparative.
- The validity of this test is poorly studied and has been questioned.[2, 24] No recent RCTs were found on this topic.

Key message regarding the functional tests

- **The validity of the anterior drawer and the talar tilt tests is not demonstrated in the assessment of the severity of the ankle sprain (no evidence).**

4.2.3 Timing of clinical examinations

Clinical examinations performed in the immediate phase (a few hours) after an ankle sprain can be difficult because of the pain and the diffuse swelling which hamper palpation.[25]

- One guideline from the Netherlands[3] recommends to perform an examination 4 to 7 days after trauma to detect a possible rupture of the ligament. This recommendation is based on one study from Van Dijk et al.[27] In this study with moderate risk of bias the clinical examination (hematoma, localisation of pain at palpation and anterior drawer test) after 5 days was compared to the clinical examination performed in the 48 hours after the trauma in 135 patients. The definitive diagnostic was provided by intraoperative findings in operated patients and by clinical diagnosis at follow-up for non-operated patients. The results showed that clinical examination 5 days after trauma has a higher sensitivity (96% if experienced investigator and 89% if inexperienced) than immediate clinical examination (71%). A higher specificity was also found for an examination 5 days after the trauma (84% if experienced investigator and 70% if inexperienced) versus immediate examination (33%).
- Experts and stakeholders involved in this study underlined the importance of a clinical re-evaluation about 4 days after the trauma if severe symptoms persist. They did not advocate for the use of anterior drawer test (expert consensus).

Key message regarding the clinical examination

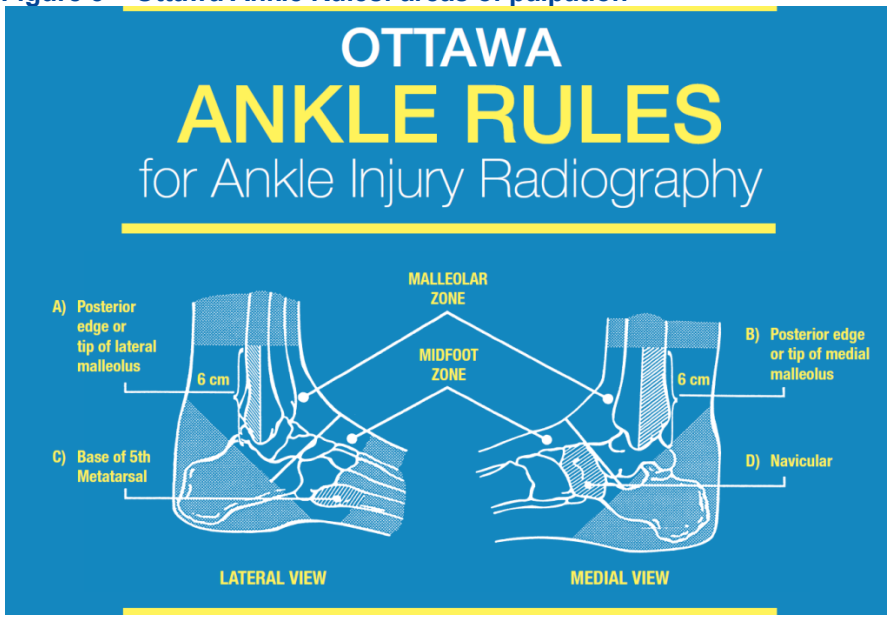
- **When severe symptoms persist, a clinical examination about 4 days after ankle trauma gives a high chance to diagnose a rupture of the ligament or a fracture (expert consensus).**

4.3 Physical examination: Ottawa ankle rules (and derived)

4.3.1 Description of the Ottawa ankle rules

The Ottawa Ankle Rules (OAR) were developed by Stiell et al.[22] in 1992 to assess adult patients presenting with acute ankle and foot injuries. They consist of a set of decision rules to determine whether a clinically significant fracture can be diagnosed on the basis of clinical examination only, without X-rays.

Figure 5 – Ottawa Ankle Rules: areas of palpation



Source: Ottawa Hospital Research Institute (http://www.ohri.ca/)
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Figure 6 – Ottawa Ankle Rules: criteria for X-ray series requiring

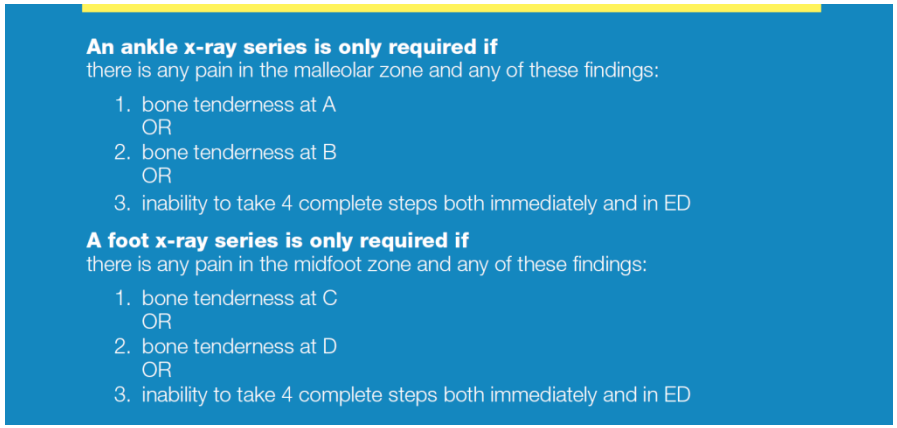


Figure 7 – Ottawa Ankle Rules: Recommendations for the use

Because of a large number of false-positive results in the OAR (see below, chapter 4.3.2), sports medicine physicians at the University of Buffalo determined a modified set of ankle rules, called the "Buffalo malleolar rule".[28] They kept most of the original rules but changed the original area of palpation from the posterior borders of the malleoli to over the midcrests of the malleoli, away from the ligament attachments.[28, 29] This rule was used in predominantly younger, sport-injured patients.[28]

As the difference between Buffalo malleolar rule and OAR is minor, both tests are treated as one. Moreover, one prospective cohort study with moderate risk of bias comparing the modified OAR (Buffalo malleolar rule) with the OAR in 193 patients did not find any significant difference in specificity between both rules(P>0.05).[28]

4.3.2 Validity of the Ottawa Ankle Rules

Since their development in 1992, many trials evaluated the validity of the OAR for excluding fractures of the ankle in patients with ankle sprain.

- One meta-analysis with moderate risk of bias summarized the accuracy of the OAR from 1990 to 2002.[7] The authors selected 27 studies describing 15 581 patients. Among these 27 studies, 12 assessed the ankle, 8 the mid-foot, 10 combined the ankle and the mid-foot in adults and 6 combined the ankle and the mid-foot in children. Several studies considered the application of the OAR within the 48 hours after the injury instead of within one week. The results showed:
  - That pooled sensitivities for the assessement of the ankle equaled 98% (95CI%: 96-99).
  - According to a sub-group analysis, the highest pooled sensitivities (99.6%; 95%CI: 98-100) were found in studies assessing the application of the rule within 48 hours, and the lowest in studies of combined ankle and mid-foot assesment (96.4%; 95%CI: 94-99).
  - The specificities (not pooled) for the assessment of the ankle equaled 40% (95%CI: 28-48).
  - According to a sub-group analysis, the highest sensitivities (48%; interquartile range 42-77) were found in studies with a low prevalence of fracture (<25th centile of all studies) and the lowest (26%; interquartile range 19-34) in studies of combined assesment (96.4%).
- Eight more recent studies assessing the validity of the Ottawa ankle rules (in patients within 10 days after an ankle injury) were found.[28-35] Most of them were prospective studies, with low to moderate risk of bias. Many studies used X-ray as reference but some selected usual care.[28,30,33] Clinical heterogeneity was noted between the studies in terms of setting (not only on ED), patients characteristics (sometimes children were included), timing of OAR application (within 10 days or 48 hours), kind of providers (not only physicians). The results presented in Table 9 show:
  - Sensitivities of OAR ranging from 92 to 100%.
  - Specificities ranging from 16 to 51%.

Table 9 – Diagnostic indicators performance of the OAR in identifying fracture

Setting	n	n missed fractures	Sensitivity % (95%CI)	Specificity % (95%CI)	Positive predictive value % (95%CI)	Negative predictive value % (95%CI)	Risk of bias
Australian, ED (urban teaching hospital), junior or senior physicians trained to use OAR[31]	265	0	100 (92-100)	16 (11-21)	19 (14-24)	100 (90-100)	Low
Swiss, ED (district hospital), surgeons or physicians in training to become general practitioners or medical students, all informed about OAR[32]	251	0	100 (89-100)	21 (16-27)	-	-	Moderate
• **Surgeons**			100 (77-100)	32 (20-46)			
• **Non-surgeons**			100 (82-100)	17 (11-23)			
The Netherlands, ED (urban university teaching), specialized emergency nurses (SEN) trained in ankle injuries and junior emergency physicians[34]	106[a]						Low
• **SEN**			93 (64-100)	49 (38-60)	22 (13-35)	98 (87-100)	
• **Junior physicians**			93 (64-100)	39 (29-50)	19 (11-31)	97 (84-100)	
US, ED (suburban teaching), emergency nurses and emergency physicians, both trained in OAR[35]	103						Moderate
• **Emergency nurses**			92	36	32	90	
• **Emergency physicians**			92	47	38	94	
Danish, ED (rural hospital), junior or senior doctors with OAR training provided to new junior doctors[33]	1014[b]	2	99	51	-	-	High
New York, sports medicine center, primary care sports medicine physician or nurse practitioners, all instructed about OAR[28]	193[b,c]	0	100 (78-100)	45 (43-46)	-	-	Moderate
New Yorks, orthopaedic walk-in clinic, physical therapists and orthopaedic surgeons[29]	157[c,d]						Moderate
• **Physical therapists**		0	100 (93-100)	40 (32-48)	6 (2-10)	100 (93-100)	
• **Orthopaedic surgeons**		0	100 (93-100)	46 (38-54)	7 (3-11)	100 (93-100)	
New Zealand, primary care setting(after-hours medical center), OAR analysed retrospectively [30]	196	0	100 (75-100)	47 (41-55)	12 (7-19)	-	High

ED=Emergency department; [a]within 48hours after the injury; [b]children included; [c]OAR modified (Buffalo rules); [d]military cadets 18 to 25 years old

Key message regarding the validity of the Ottawa ankle rules

- **The Ottawa Ankle Rules are effective at ruling out ankle fractures after sprain injury: when the test is negative, a fracture can be excluded (moderate level of evidence).**
- **The Ottawa Ankle Rules do not allow confirming a more serious lesion: a positive test does not systematically means a fracture (moderate level of evidence).**
- **The validity of the modified OAR (Buffalo rule) is not higher than the validity of the OAR (low level of evidence).**

4.3.3 Validity of other decision tools: tuning fork test, Bernese ankle rules, Leiden ankle rules and Utrecht ankle rules

Several rules and diagnostic processes have been developed to improve the specificity of the OAR and to assist clinicians in the decisions on whether or not to perform an X-ray. Five studies were identified in the recent literature on this topic.

4.3.3.1 Tuning fork test

The use of vibrations to diagnose a fracture is an old process based on the theory that if the bone is broken, the crack may vibrate causing a painful sensation.

- In one prospective study with low risk of bias, the authors investigated the suitability of a tuning fork testing for increasing the specificity of detecting a fracture of the lateral malleolus in patients with positive OAR test.[36] In 50 patients with a positive OAR test, the tuning fork (128 Hz) was positioned on the lateral malleolus and then on the distal fibula shaft (5-10 cm proximal to the point of maximal tenderness). The test was considered abnormal if there was any sensation of discomfort or pain for any of the test positions. X-rays were used as a reference. When applying the tuning fork testing on the tip of the lateral malleolus, the sensitivity was calculated as 100% (95%CI: 46-100) and the specificity as 61% (95%CI: 46-75). When applying the test on the distal fibula shaft, the sensitivity was still 100% (95%CI: 46-100) while the specificity reached 95% (95%CI: 83-99). This results suggest that additional tuning fork test in "Ottawa positive" patients may lead to a marked reduction in ankle radiographies.
- However, the experts and stakeholders involved in this guideline underlined the lack of evidence, several limitations of the test (operator-dependency, subjectivity) and its uncommon use in practice.

4.3.3.2 Bernese ankle rule

The Bernese ankle rules consist of three consecutive steps avoiding palpation on the injured region: indirect fibular stress (10 cm proximally to the fibular tip), direct medial malleolar stress, and compression stress of the mid- and hind foot (talus+calcaneus). Indirect forces are applied to the injured region by the flat of the hand or the whole area of the thumb (medial malleolus) instead of the fingertip.

- One study with low risk of bias[37] applied the Bernese Ankle rules in 354 patients with an ankle injury. All subjects were tested by X-ray as well. The Bernese ankle test produced a sensitivity of 100% and a specificity of 91%.

4.3.3.3 Leiden Ankle Rules and Utrecht Ankle Rules

The Leiden ankle rule uses a score derived from 13 weighted variables ordered in 7 rows. It was developed on the basis of published likelihood ratios and personal experience of the investigators. The Utrecht ankle rules consist of 16 variables derived from the Leiden ankle rules and subsequently modified on the basis of the personal preferences of the researchers.

- One prospective study with low risk of bias compared the Leiden and the Utrecht ankle rules with the OAR in 647 patients presented in ED within 5 days after an ankle injury.[38] The reference standard (X-ray) diagnosed 74 fractures, from which 41 only were clinically significant and thus taken into account. An analysis of the performance of the OAR was also provided for the ankle and the foot rules separately but the comparaison with the Leiden and the Utrecht rules was based on the overal OAR (Table 10). The 2 locally developped rules offered a larger potential reduction in the number of radiographies required when compared to the OAR but they missed more fractures.

- The same prospective study with low risk of bias presented a comparaison of the Leiden ankle rules, the physicians' judgement supported by structured data collection and, the OAR.[39] The reference standard was also X-ray but all 74 fractures, clinically significant or not, were considered for the analysis and no distinction was done between ankle and foot rules. The results are showed in Table 10. The OAR had the highest sensitivity but the lowest specifity. The physicians' judgement missed 13 fractures but only 1 clinically significant and was associated with a great reduction in the use of radiographies.
- An older prospective study with high risk of bias assessed the Leiden rule in 514 patients within 10 days after an ankle trauma.[40] X-ray was performed if the score of the rule was ≥8 points. Follow-up (telephone interview) 6 weeks after the injury was used to verify the absence of missed fractures. The rules led to a reduction of X-rays but missed several diagnoses of fracture.

Table 10 – Diagnostic indicators performance of the OAR and other decision rules in identifying fracture

Setting	n	True Positive	True Negative	False Positive	False Negative	Sensitivity % (95%CI)	Specificity % (95%CI)	Risk of bias
The Netherlands, ED (urban teaching hospital), junior surgical and orthopaedic residents[38]	647							Low
• **OAR (foot & ankle)**					1	98 (87-100)	26 (22-29)	
• **Leiden ankle rules**					5	88 (74-96)	57 (53-61)	
• **Utrecht ankle rules**					17	59 (42-74)	84 (81-87)	
The Netherlands, ED (urban teaching hospital), junior surgical and orthopaedic residents[39]	647							Low
• **OAR**					8	89 (80-95)	26 (23-30)	
• **Leiden ankle rules**					15	80 (69-88)	59 (55-63)	
• **Physicians' judgement**					13	82 (72-90)	68 (64-71)	
The Netherlands, ED (university hospital)[40]	514	24	428	57	5	83 (69-94)	88 (85-91)	High
• **Leiden ankle rules (score ≥8)**								

Key message regarding the validity of other ankle rules

- **The use of a tuning fork test, in addition to the OAR, could increase the specificity of the OAR according to one small prospective study with a low risk of bias (low level of evidence). However the experts and stakeholders involved in this guideline underlined the limitations and limited use of this test in daily practice (expert consensus).**
- **The clinical use of the Bernese ankle rules reduces the false positive findings by the OAR according to one prospective study with low risk of bias (low level of evidence).**
- **Specificities but also the risk of missing fracture are higher with the Leiden ankle rules and the Utrecht ankle rules than with the OAR (low level of evidence).**

4.3.4 Implementation of the Ottawa ankle rules

The Ottawa ankle rules were developed to avoid unnecessary X-rays but estimates on the reduction of radiographies varied broadly, ranging from 13% to more than 40%.[29-31] Several factors were proposed to explain the variability of the specificities of the OAR and should be taken into account in the application of the OAR.

4.3.4.1 Target population

Some medical conditions hamper the applicability of the OAR: neurologic deficits, psychiatric disorders, polytrauma, bone disease, pregnancy.[38, 39, 41]

The cultural dimension in the patient's expression of pain is another factor that can modify the performance of the OAR. This factor was quoted by Bachmann in his systematic review: a vivid expression of pain could result in higher false positive rates whilst stoical individuals could lead to higher false negative rates.[7]

A high threshold for seeking assistance can also lead to a higher incidence of severe lesion in the medical setting.[39] However no recent study analyzed this assumption and it is difficult to define the threshold of pain in Belgium.

4.3.4.2 Setting

The emergency department is the most studied setting in the validity assessment of the OAR. The applicability of the same decision rules in primary care could be questioned.

- The Dutch guidelines for physiotherapists stress the risk of a higher false positive rate in primary care since the incidence of ligament ruptures is lower in this practice population.[3] They strongly recommend the use of the OAR in the ED for excluding a fracture after a acute lateral ankle sprain and they recommend the application of the OAR in primary care as a part of the clinical decision-making for excluding a fracture after a acute lateral ankle sprain.
- In their systematic review, Bachmann et al. stressed that the usefulness of the OAR as a decision tool in primary care had not been assessed.[7]
- One study with moderate risk of bias in a sport medicine institute showed that OAR (Buffalo ankle rule) functioned also in a setting where the yearly ankle rate (2.4-8.5%) was different from that found usually in ED (16-22%).[28]
- Another study with moderate risk of bias was performed in a military academy where the incidence of clinically significant fracture equalled 5.8%. The sensitivity of the OAR (Buffalo ankle rule) equalled 100% and the specificity ranged between 40-46%, which was consistent with several other studies (Table 9).[29]
- One study with high risk of bias valided the OAR in primary care with a sensitivity of the OAR equalling 100% (95%CI: 75-100) and a specificity of 47% (95%CI: 40-54).[30] As the sensitivity of the general practitioners' (GP) judgement was also 100% (95%CI: 75-100) and the specificity was 37% (95%CI: 30-44), the authors suggested that clinically experienced practitioners may be able to apply the important elements of the guidelines without being aware of it.

4.3.4.3 *Experience of staff*

In their systematic review, Bachmann et al.[7] suggested that differences in clinical skills and experience of staff performing the test could influence the accuracy of the OAR but they also outlined the lack of studies reporting the characteristics of the staff performing the test as, for intance, the numbers of years of work at an ED. More recent sudies have considered this item in their analysis and found:

- No difference between junior and senior physicians
  - In one study with low risk of bias, no difference was showed between junior and senior physicians in the validity of the OAR: the sensitivity was 100% and the specificity was low (15%) for both.[31]
  - A non statistical difference was found between surgeons and non-surgeons (physicians in training to become GP and medical student working at the ED) in a study with moderate risk of bias: the sensitivity was equal to 100% for both assessors and the specificity equalled 32% (95%CI: 20-46) for surgeons compared to 17% for the non-surgeons (95%CI: 11-23).[32]
- No difference between health care profesionnals with different backgrounds
  - One study of moderate risk of bias assessed whether triage nurses could appropriately interpret the Ottawa Ankle Rules in an emergency department.[35] Each of the 103 included patient received a blinded clinical assessment including the OAR by both one **nurse** and one **emergency physician** (EP). Sensitivity of the nurse's and the EP's interpretation of OAR for fracture was both 92% (Table 9) and there was a slight difference concerning the specificity (26% versus 47%) which did not reach statistical significance. The high fracture rate (26%) of the cohort was particular.
  - In one study with low risk of bias,[34] each injury was blindly assessed by both a trained **emergency nurse** and an **junior emergency physician** by means of the OAR in 108 patients. The sensitivity for both assessors for detecting fractures was 93% (95%CI: 64-100). The specificity of the nurses was 49% (CI95 38-60) compared with 39% (95%CI: 29-50) for doctors, a non statistical difference between groups (Table 9).
  - In a following randomized controlled trial with low risk of bias,[42] the same authors compared the diagnostic accuracy of **specialized emergency nurses** (SENs) with **junior emergency physicians** for 512 patients with ankle injury. The results confirmed that SENs were at least as accurate as junior emergency physicians in the assessment and the management of ankle injuries. Moreover the care provided by SENs was found to be significantly better than the care provided by the emergency physicians and the median waiting time at the ED was significantly reduced with the SEN (21 minutes for SENs vs 32 minutes for EPs).
  - One study with moderate risk of bias compared the accuracy of the modified OAR between **physical therapists** and **orthopaedic surgeons** in cadets.[29] No difference was showed between physical therapists and orthopaedic surgeons. The sensitivity was 100% and the specificity was low (around 40%) for both. Inter-observer agreement between the orthopaedic surgeons and physical therapists regarding the overall decision to obtain radiographies was high. Based on the results of this study, it can be concluded that trained physical therapists can appropriately apply the modified OAR.
- Difference between trained and non trained professionnel regarding the OAR
  - In several studies, the provider received information or training on the application of the OAR.[29, 31-34] The importance of training for the correct application and interpretation of the OAR is outlined by some authors.[29, 31, 33]

    This education can take different forms:
    - a 30-minute introduction to the OAR and a reminder at a 5 minute meeting after 4 weeks for physicians in ED,[33]
    - 1-hour lecture, pocket cards and posters in the ED,[43]
    - 1-day or 2-day course for nurses on anatomy and biomechanics (trauma mechanisms) of the ankle and the foot, and how to treat specific injurie.[34, 42]
  - Only one study with moderate risk of bias questioned the utility of educational campaigns for GPs in New Zealand in the light of the spontaneous good clinical judgement of these practitioners.[30]

- No evidence to promote the patients' own clinical examination with the use of the OAR
  - One study with moderate risk of bias assessed if patients could apply the OAR to themselves within 48 hours after an ankle injury.[44] A poor inter-observer relationship was found between the 50 patients which used the OAR to themselves and the clinicians. The authors suggest that Ottawa ankle rules should not be used by non-paramedic public.

4.3.4.4 *Timing of OAR*

Most studies considered the application of the OAR within the week or the 10 days after the ankle injury. Thus it is difficult to specify a timing for the OAR in the management of the acute ankle sprain. The meta-analysis of Bachman et al. showed higher sensitivities in studies where the OAR were applied within 48 hours after injury[7] but no recent study confirms this result.

Key message regarding the implementation of the Ottawa ankle rules

- **Patients' conditions may hamper the applicability of the OAR (very low level of evidence).**
- **The OAR are valid in settings where the incidence of fracture is lower than in ED (low level of evidence).**
- **The OAR can be performed by different health care disciplines (moderate level of evidence) although a good initial standardized education program remains an important prerequisite (low level of evidence).**
- **The OAR should not be used by the patients themselves (very low level of evidence).**
- **It's difficult to define the best timing for the OAR application (no evidence).**

4.4 Imaging

This chapter focuses on the utility of imaging for excluding a fracture and for specifying the severity of the ligament tear in the first phase of the diagnosis. The diagnosis process needed in the presence of persistent symptoms several days after ankle injury is not considered.

4.4.1 *X-ray*

The gold standard to exclude a fracture in case of ankle injury with positive OAR is the X-ray. Radiographies may identify malleolar fractures, talar dome fractures or disruption of the ankle syndesmosis.[14] Anterio-posterior, lateral and mortise views are usual.[14] The mortise projection is an antero-posterior view with the leg internally rotated 15 to 20 degrees to allow the X-ray beam to be nearly perpendicular to the intermalleolar line.[14]

No recent studies assessed the sensitivity, specificity, positive predictive value or negative predictive value of the X-ray in the diagnosis of ankle sprain. Moreover, the experts and stakeholders involved in this study underlined the bad quality of the imaging in some cases and the lack of antero-posterior view of the lower leg.

Stress radiographies of the ankle were often performed in the past. They consisted of an application of an anterior load (for the anterior drawer test) or inversion (for the talar tilt test) during X-ray exposure. The stress could be manually performed or with the help of a device to assist positioning.[2] The procedure was painful and required at least local anaesthesia. No recent studies were found on stress radiographies in the acute phase of ankle sprain. Moreover, some authors and experts concluded that stress X-rays do not longer have clinical relevance in the acute phase because of their inaccurate assessment of mechanical laxity.[2]

Key message regarding radiography

- **X-rays have been used as the gold standard in studies on OAR.**
- **There is no recent study on the value of X-rays for the diagnosis of a fracture in case of ankle sprain.**

4.4.2 *Ultrasonography*

Ultrasound is sometimes used as a tool for emergency musculoskeletal assessment to visualize soft tissue and bony structures while avoiding radiation.

- The Dutch guideline for physiotherapists referred to the results of two studies to question the added value of ultrasonography above physical examination for specifying the **severity of the ligament tear**.[3]
  - One study with high risk of bias assessed whether talocrural joint effusion in ultrasonography could indicate a ligament tear in 110 patients within 48 hours of moderate and severe ankle sprain.[45] In 40 of the 110 patients in whom ultrasonography showed talocrural effusion, a 1.5 T magnetic resonance imaging (MRI) was performed within 8 days. Joint effusion was confirmed by MRI in all 40 patients. In 39 of these 40 patients, MRI visualized damage to the anterior talofibular ligament, accompanied in 5 cases by damage to the calcaneofibular ligament. In 14 cases, MRI showed cartilage damage or bony contusions. The authors concluded that talocrural effusion on ultrasonography may identify patients with severe ankle sprain and can be easily learned and perfomed in the ED. However, studies with larger sample sizes, using homogeneous MRI criteria, are needed and the possibility that ligament tears may occur in the absence of talocrural effusion persists.
  - The second study quoted in this Dutch guideline is the study of Van Dijk et al.[27] that stated that with a sensitivity of 92% and a specificity of 64%, ultrasonography was inferior to physicial examination on day 5 after trauma (n=135) (see chapter 4.2.3).
- One more recent study with low risk of bias assessed whether the use of ultrasonography could detect foot and ankle **fractures** in 110 patients with positive OAR.[46] An ultrasound scan (US) was performed blind to findings from radiographies. The US operators previously attended a 2-day course on musculoskeletal US. The sensitivity and specificity of the ultrasound were 91% respectively (95%CI: 66-98 for sensitivity and 95%CI: 88-92 for specificity). The positive predictive value was 53% (95%CI: 38-100) and the negative predictive value was 99% (95%CI: 96-100). Following the first missing fracture, the US protocol was changed to scan the posterior edge and 10 cm above each malleoli (as opposed to the 6 cm in the OAR). The results indicate that if ultrasonography was employed ahead of X-ray in OAR positive patients, the number of radiographies would decrease by approximately 80% and the risk of missign a fracture would be low.

Key message regarding ultrasonography

- **A talocrural effusion at ultrasonography was associated to ligament damage in one study with high risk of bias (very low level of evidence).**
- **In positive OAR patients, one study with low risk of bias showed that ultrasonography can exclude fractures and reduce the need for radiographies (low level of evidence).**

4.4.3 Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) is a technique which uses a powerful magnetic field to visualize detailed internal structures. MRI does not use radiation but it is an expensive technique with limited availability in hospitals.

- The Dutch guideline for physiotherapists[3] considers that MRI offers little additional value in the diagnosis of acute lateral ankle sprain. The authors referred to the results of two studies:
  - A prospective study assessed the accuracy of the MRI for diagnosing the severity of lateral ankle ligament tears.[47] In this, 60 athletically active patients were examined by 0.5 T MRI and lateral stress radiography measuring talar tilt within 7 days after a first inversion trauma. In 15 patients (talart tilt ≥15°), the findings at the MRI were compared with those at surgery. MRI sensitivity was estimated at 74% and specificity at 100%. MRI was also compared to bilateral stress radiography with poor agreement between the two techniques to detect complete tears (kappa=0.030; 95%CI: -0.12, 0.178). Authors concluded that young, athletically active patients should undergo MRI to detect severe lateral collateral ligament injuries.
  - One RCT with moderate risk of bias[48] assessed the predictive value of a short[a] 0.2 T MRI examination in 197 patients with acute ankle trauma. The included subjects were randomized to either undergoing X-ray only or X-ray combined with the short MRI. The aim was to identify patients who did not require additional treatment and could thus, be discharged without further follow-up. The results showed 5 fractures missed by MRI but visible on the X-ray.

[a] 15 min instead of the standard 30-45 min

Additional treatment was necessary in 109 patients. In the multivariate analysis, positive or uncertain MRI results show a predictive value of subsequent treatment (OR:2.61, 95%CI:1.28-5.30) but not negative MRI results (OR:0.66, 95%CI: 0.27-1.61). The authors concluded that a limited MRI examination has an additional predictive value in identifying patients needing treatment but not in identifying patients who can be discharged without further follow-up. Therefore, the authors conclude that short MRI cannot replace radiographies in the prediction of need for additional treatment.

Key message regarding magnetic resonance imaging

- **One study with high risk of bias showed that MRI could be useful in patients with severe effusion to diagnose ligament rupture (very low level of evidence)**
- **A short MRI cannot replace a X-ray for the prediction of need for additional treatment according to one study with moderate risk of bias (very low level of evidence).**

4.4.4 Computer assisted tomography

- No studies published since 2000 were identified in the literature on this topic.

Key message regarding computer assisted tomography

- **No recent evidence was found on the utility of computer assisted tomography in the acute phase of acute lateral ankle sprain diagnosis.**

4.5 Discussion: diagnosis of ankle sprain

Poor evidence

The paragraphs above highlighted the importance but the lack of evidence for history taking and specific clinical signs. However Ottawa Ankle Rules are of utmost importance for selecting patients eligible for X-ray, thereby decreasing the risks, waiting time and costs linked to that procedure. The available evidence does not support the use of other imaging procedures.

The Royal Dutch Society for Physical Therapy outline in a recent publication the findings in relation to diagnosis as displayed above:[49]

- The authors do not find any evidence on the value of clinical examination. They suggest a possible interest of combination of signs (haematoma, local pressure pain at palpation or positive anterior drawer test) to detect a possible (partial) lateral ligament rupture. They mention, as in their previous guideline version, the study of van Dijk et al.[27] from 1996 to support the interest of a physical examination performed 5 days after the trauma;
- They base their recommendation to use the Ottawa Ankle Rules on "four review studies of importance";[7, 50-52]
- They confirm the lack of evidence to support the use of ultrasound and MRI in acute lateral ankle sprain.

Implementation of the OAR

Discussions with the stakeholders added some food for thought on the overuse of X-rays in ankle trauma: the following points could hamper the implementation of the OAR in Belgian practice:

- Patient's demand;
- Insurances' request of X-rays in case of school, work or sport accidents;
- Fear for missed fractures and the potential legal consequences that this could bring;
- Lack of training of emergency physicians to perform OAR;
- Workload and organization of emergency departments: in some hospitals all patients with ankle trauma are systematically sent to X-ray before physical examination for fluxing the patients' inflow;
- The referral by a GP with X-ray request.

For improving the implementation of OAR, the stakeholders offered some suggestions:

- Specific actions that target the patients i.e. leaflets and campaigns on unnecessary use of radiographies after a well-performed examination.
- Advice to systematically well-document the results of the physical examination and mainly the OAR in the patient medical record.
- Proposal of a second delayed examination for patients whose pain and walking ability have not improved after several days; this proposal should be part of the first consultation.
- A triage based on OAR by trained health professionals in emergency departments although the medico-legal liability would need to be well defined.

Use of ultrasound

The stakeholders involved in this guideline underlined several organizational aspects that limit seriously the use of ultrasound for the immediate assessment of the ankle sprain:

- Lack of radiologists specialized in bone and joint ultrasonography;
- Very few of them available during out-of-hours;
- Increase of the risk of overbooked imaging unit and waiting time for patient (with delayed diagnosis).

In this context, the stakeholders called for considering radiography as the first line diagnostic technique.

4.6 Recommendations concerning the diagnosis of ankle sprain

The Recommendations and the Best practices below are based on a discussion with experts and stakeholders after having balanced the quality of the evidence against the consequences for the patients (pain, discomfort) and organizational aspects.

History taking

Best practice (expert consensus)
History taking is recommended in the initial assessment of an acute ankle sprain. It should contain at least a description of the injury mechanism, the first symptoms and their evolution, the early management of the injury, the history of previous ankle sprain and a general medical history.

Physical examination

Best practice (expert consensus)
Inspection and palpation should be a part of the initial assessment of an acute ankle sprain.
An attempt to grade the severity of the ankle sprain during the initial assessment of the sprain should be done, based on symptoms and physical examination.
A clinical re-evaluation 3 to 4 days after ankle trauma should be performed to ascertain the severity of the ankle sprain.

Ottawa Ankle Rules

Recommendation	**Strength of Recommendation**	**Level of Evidence**
The use of Ottawa Ankle Rules (OAR) is recommended to exclude a fracture after acute ankle sprain.	Strong	Moderate
Training of health care providers on OAR application is recommended.	Strong	Low

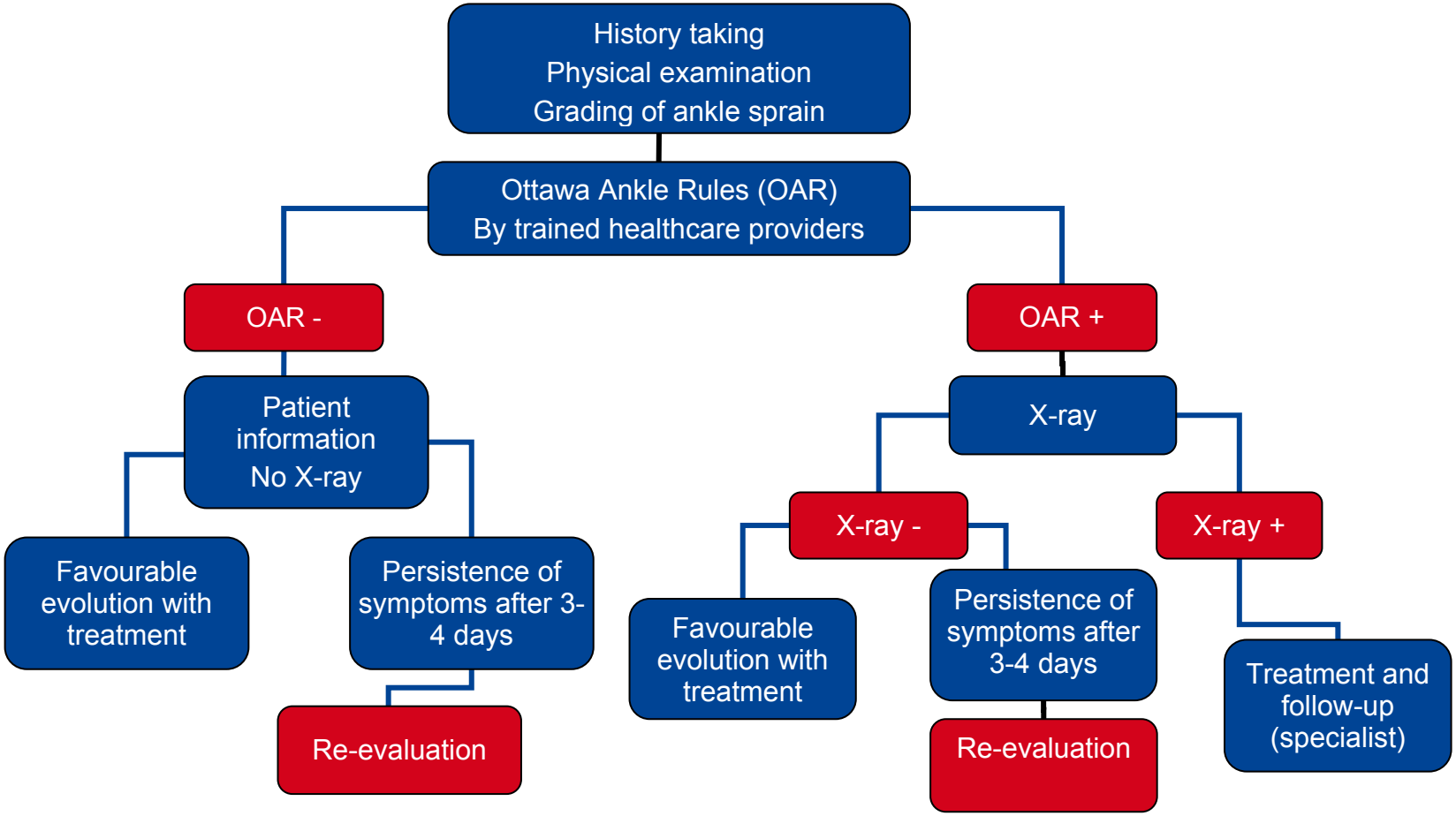
Best practice (expert consensus)
The results of the OAR should be systematically recorded in each medical record. Other clinical tests (e.g. drawer test, talar tilt test, tuning fork test) and clinical rules (as the Bernese, the Utrecht or the Leiden rules) should not be used in the assessment of acute ankle sprain.

Imaging

Recommendation	Strength of Recommendation	Level of Evidence
If the OAR give **positive results**, a radiography of good quality (3 views) is the recommended diagnostic technique for excluding a fracture in acute ankle sprain.	Strong	Moderate
If the OAR give **positive results**, ultrasonography performed by a physician specially trained in joint and bone ultrasonography could be considered for excluding fractures while reducing the need for radiographies. However, the experts underline the fact that the organisational constraints (e.g. waiting times, unavailability of trained radiologist) call for considering radiography as the first line diagnostic technique.	Weak	Very low
If the OAR give **negative results**, radiographies should not be performed in the initial assessment of an acute ankle sprain.	Strong	Moderate
Magnetic Resonance Imaging (MRI) should not be part of the initial assessment of an acute ankle sprain.	Strong	Very low
No recommendation can be formulated in relation to the use of CT scan in case of an acute ankle sprain (no evidence available).		

Best practice (expert consensus)
Patients should be systematically informed about the uselessness of X-ray after negative OAR results.

5 ALGORITHM FOR DIAGNOSIS



6 RESULTS FOR THERAPY

6.1 Drug therapy

6.1.1 Analgesic and anti-inflammatory oral medication

Several oral medications can be used for analgesic and/or anti-inflammatory effect in the management of acute ankle sprain:

- Paracetamol (or acetaminophen): the most commonly used analgesic drug (non-opioid analgesic). It is the active metabolite of the phenacetin, responsible for the analgesic effect.
- Nonsteroidal anti-inflammatory drugs (NSAIDs): aimed at reducing pain and inflammation by inhibiting cyclo-oxygenase (COX) which plays a role in the formation of prostaglandins. The COX exists in two distinct isoforms:
  - The COX-1 isoform, present in many tissues and necessary for physiological (homeostatic) functions, such as gastric mucosal protection and normal platelet aggregation;
  - The COX-2 isoform, mainly expressed locally in inflamed tissues.

  Non-selective NSAIDs, such as diclofenac, piroxicam, naproxen, nimesulide and ibuprofen, inhibit both COX-1 and COX-2. Selective COX-2 inhibitors, as celecoxib and valdecoxib, only inhibit COX-2.[53]
- Opioïds:
  - Tramadol is a synthetic, centrally-acting analgesic agent with a dual mechanism of action, binding to the opioid receptor and blocking the reuptake of the monoamines serotonin and norepinephrine
  - Hydrocodone is a semi-synthetic, analgesic acting as an opiate agonist (not available in Belgium).

Many studies have compared clinical outcomes in the treatment of acute ankle sprain between different drug types and between different formulations of NSAIDs. We present the results below according to the kind of drug and the comparator.

6.1.1.1 Efficacy of paracetamol

No study was found (after 2000) which assessed the efficacy or tolerability of paracetamol versus placebo in the treatment of acute ankle sprain.

Three studies compared paracetamol with a non-selective NSAID.

- A multi-center RCT with low risk of bias[54] compared paracetamol extended release 3 900 mg/day (1 300 mg 3 times daily every 8 hours[b]) and ibuprofen 1 200 mg/day (400 mg 3 times daily every 8 hours) for the management of pain associated with grade I or II lateral ankle sprain. The oral drugs were given from the early 24 hours over a period of 9 days. In this study all patients (n=260) were instructed to make use of rest, ice, compression, and elevation. Investigators provided crutches, compression bandages, and exercises at their discretion.
  - Paracetamol and ibuprofen had comparable analgesic action as measured by pain on walking (visual analog scale (VAS)) on day 4 and day 9.
  - No differences were found for any other outcomes: ability to walk, swelling, ankle hematoma, ankle range of motion (ROM), anterior drawer test, overall satisfaction and time to resume to normal activity (as early as 4 days after injury for both).
  - Both treatments were well tolerated. Overall, 11.5% of patients reported adverse events, with no significant difference between treatment groups. The most common adverse events, reported by 6.5% of patients were gastrointestinal symptoms (mainly nausea and upper abdominal pain) with no significant difference between treatment groups.
- A study with low risk of bias[55] compared the use of paracetamol 1 500 mg/day in 3 doses with diclofenac 150 mg/day (Voltaren®) in 2 doses in patients with acute Grade II lateral ankle sprain (n=90). Treatment was given in the early 24 hours after the trauma over a period of 10 days. Patients were instructed not to use any other drugs during the treatment phase. Additionally, all patients were treated with the RICE protocol. An ankle bandage was applied and non weight-bearing was proposed for 10 days to all patients, as well as elevation of the foot for

[b] In Belgium, the maximum dosis of paracetamol tablet is 1000 mg

the first 3 days. On the third day the bandage was removed for measurements. Patients were encouraged to start walking after 10 days.

- Diclofenac and paracetamol had the same effect on pain reduction (VAS) of ankle sprain both at the third and the tenth day after injury.
- More acute ankle oedema was present in patients who were treated with diclofenac than in patients who were treated with paracetamol on the third day after injury (10.3 mm with the figure 8 method and 4.3 ml with the volumetric method with p=0.03). But no statistical difference was found 10 days after trauma.

- Another study[56] with moderate risk of bias, compared paracetamol 1 500 mg/day in 3 doses with diclofenac sodium 150 mg/day in 2 doses for a period of 5 days both in the 48 hours after trauma (n=100). Range of motion and stretching exercises were instructed to patients for the rehabilitation program. Patients were allowed to apply non-pharmacological treatments including RICE and crutches. Ankle sprains with Grade III were excluded.
  - The paracetamol group showed more pain decrease on weight-bearing (VAS) on day 2 and 10 than the diclofenac sodium group (VAS $MD_{day\ 2}$ -8.8 ; 95%CI: -14.0 to -3.5; p=0.0013; VAS $MD_{day\ 10}$ -3.7 ; 95%CI: -6.8 to -0.5; p=0.02) but no difference at 6 weeks.
  - There were no significant differences for any other outcome measure for both treatment groups: swelling, ankle range of motion, time to return to recreational activities (about 10 days) and physician global assessment.
  - The incidence of adverse effects on the diclofenac sodium group (30%) was higher than in the paracetamol group (18%), although there was no significant difference. These adverse effects mostly concerned the gastrointestinal system.

For the Dutch association for sport medicine (VSG), the general guidelines on pain have to be followed after acute ankle sprain involving paracetamol as the first choice and NSAID as second choice.[15]

Key message regarding treatment with paracetamol versus non-selective NSAIDS

- **No superior analgesic effect was found for diclofenac or ibuprofen compared with paracetamol at therapeutic doses for the early treatment of ankle sprain (moderate level of evidence, 3 RCTs). One RCT with moderate risk of bias showed more pain decrease with paracetamol compared to diclofenac sodium 2 and 10 days after the injury.**
- **One RCT with low risk of bias showed a better impact of paracetamol on oedema after 3 days versus diclofenac (very low level of evidence, 1 RCT). No difference was found for this outcome in the 2 other RCTs.**
- **No difference was found between paracetamol and diclofenac or ibuprofen for others outcomes as hematoma, ankle range of motion, overall satisfaction, time to resume to normal or recreational activities and physician global assessment (very low level of evidence, 2 RCTs).**
- **Two RCTs included adverse effects in the outcomes and were unable to find statistical differences between paracetamol and diclofenac or ibuprofen.**

6.1.1.2 Efficacy of COX-2 selective NSAIDs

One study comparing valdecoxib and diclofenac[57] was excluded due to the fact that valdecoxib was removed from the market. Four RCTs were identified on celecoxib, all sponsored by the pharmaceutical industry. Patients with a history of serious gastrointestinal, renal, or hepatic disease, and patients with other rheumatic diseases or a history of drug or alcohol abuse were excluded from the sample in the 4 studies.

- Celecoxib versus placebo

One multi-center RCT with low risk of bias tested the use of celecoxib 400 mg/day in 2 doses (n=148) versus placebo (n=142) during 10 days <48 h after acute ankle sprain.[58] RICE or other standard therapeutically modalities were allowed. Other analgesic medications (e.g. paracetamol), hospitalization, bed rest, surgery and non rigid removable cast were excluded.

- Celecoxib was more effective than placebo in providing pain relief on weight-bearing at day 4 and 8 ($VAS_{day\ 4}$ 35.3 vs 42.4; p<0.05; $VAS_{day\ 8}$ 23.3 vs 31.2 ; p<0.05).
- The celecoxib group recovered and returned earlier to function (after 5 days) than did the placebo group (8 days) (p=0.01).
- The authors report that incidence of adverse effects was similar among all treatment groups.

- Celecoxib versus non-selective NSAIDs

Four studies compared celecoxib with a non-selective NSAID as ibuprofen, naproxen or diclofenac. All concern Grade I and II lateral ankle sprain.

- The study described above also compared celecoxib 400 mg/day in 2 doses (n=148) with ibuprofen 2 400 mg/day in 3 doses (n=155) during 10 days <48h after an acute ankle sprain.[58]
  - Celecoxib was as effective as the maximum recommended dose of ibuprofen in providing pain relief on weight-bearing at day 4 and 8.
  - No statistical difference was noted for the recovery and return to function between the celecoxib group and the ibuprofen group (5 versus 6 days).
  - Incidence of adverse effects was similar in all treatment groups.
- A second multi-center RCT with low risk of bias compared celecoxib 400 mg/day in 2 doses (n=198) with naproxen 1 000 mg/day in 2 doses (n=198) during a 7 days period <48h after ankle sprain.[59] In addition to these drugs, physicians could prescribe standard non-pharmacological treatments including RICE and the use of crutches, a cane, an ankle brace, and so forth. Patients were not permitted to use any additional drug, either analgesics or antiulcer medications.
  - A similar reduction in pain was found with naproxen and celecoxib at day 4 and day 8 based on a VAS.
  - The median time to normal function/activity was obtained by day 5 for both celecoxib and naproxen.
  - The achieved clinically significant improvement, defined as normal walking/activity with no pain or normal walking/activity with pain, at the final visit was no different for the patients on celecoxib (77%) and the patients on naproxen (78%).
  - The adverse effect profiles were similar between the 2 drugs, although there was a greater number of gastrointestinal side effects with naproxen (with a significant difference between celecoxib (2%) and naproxen (6%) for dyspepsie p=0.032).
- A multi-center RCT with low risk of bias was conducted in different Asian countries. It compared celecoxib (400 mg loading dose followed by 400 mg/day in 2 doses) (n=189) and diclofenac Slow Release (75 mg loading dose following by 150 mg/day in 2 doses) (n=181) for 8 days <48h after ankle sprain.[60] During the treatment period, no other analgesic medications were permitted. Other medications prohibited during the trial were diuretics, anticoagulants, lithium, digoxin, and anti-ulcer drugs. The use of non-pharmacological therapies (massage, canes, crutches, RICE, taping/bracing) were allowed.
  - Celecoxib was as effective as diclofenac Slow Release based on the patient's assessment of ankle pain VAS on day 4.
  - There was no difference between the celecoxib and the diclofenac groups in the proportion of patients who returned to normal activity at day 4 (17% versus 14%) and at day 9 (51% versus 46%).
  - No serious adverse events occurred during the study. Incidence of upper gastrointestinal adverse events was low in both treatment groups.
- A multi-center RCT with high risk of bias was conducted in populations from Middle East and Latin America.[53] This study compared celecoxib (400 mg loading dose followed by 400 mg in 2 doses) (n=141) and a standard dose of non-selective NSAIDs (n=137) over 7 days <48h after ankle sprain. Paracetamol up to a dose of 2 g/day could be taken as add-on analgesia during the trial. No other analgesic medications, including opioids and tramadol, were permitted. Non-pharmacological treatments were allowed if considered to be standard care by the investigator. The authors concluded that
  - Celecoxib was as efficacious as non-selective NSAIDs in treating acute pain due to ankle sprain (VAS weight-bearing at day 3).
  - No differences were found between the 2 groups in the patient's assessment of normal function/activity.

- The authors reported 13.5% adverse events in the celecoxib versus 17% in the NSAIDs group. They attributed gastrointestinal adverse events linked to the treatment happened in 4 patients from the celecoxib group and in 16 patients from the non-selective NSAID group.

Key message regarding treatment with celecoxib versus placebo and non-selective NSAIDs

- **All four RCTs focusing on celecoxib were explicitely supported by Pfizer. None of them compared celecoxib with paracetamol, i.e. the standard analgesic treatment.**
- **One RCT concludes that celecoxib 400mg/day during 7 days is more effective than placebo for treating acute pain due to ankle sprain with earlier return to function (very low level of evidence, 1 RCT).**
- **Celecoxib 400mg/day during 7 days is as effective as non-selective NSAID's in standard dosage for treating acute pain due to ankle sprain (very low level of evidence, 4 RCTs).**
- **Celecoxib 400mg/day during 7 days appears as effective as non-selective NSAID's for return to normal activities after ankle sprain (very low level of evidence, 4 RCTs).**
- **Very few treatment-related adverse events was found in the Celecoxib and in the non-selective NSAID groups but patients with a history of serious gastrointestinal, renal, or hepatic disease, and patients with other rheumatic diseases or a history of drug or alcohol abuse were excluded from the studies.**

6.1.1.3 Efficacy of tramadol

- Tramadol-paracetamol versus hydrocodone-paracetamol or placebo

In a multi-center RCT with low risk of bias,[61] a low dose of tramadol (75 mg) was combined with paracetamol (650 mg) in a single tablet and hydrocodone was also combined with paracetamol (7.5 mg/650 mg) in another. A comparison was done between patients with a Grade I or II ankle sprain who received tramadol-paracetamol (n=192), patients who received hydrocodone-paracetamol (n=204) and a control group with placebo (n=207). Subjects were instructed to take the treatment from 48h after the injury up to 4 times daily as needed for pain for up to 5 days. Standard care related to ankle sprain was added (i.e. RICE). Subjects were encouraged (but not required) to wait at least 1 hour after the initial dose of study medication before taking supplemental analgesic medication.

- Tramadol/paracetamol and hydrocodone/paracetamol provided a greater total pain relief than placebo during the first 4 hours: they decreased pain intensity during the first 4 hours and increased average pain relief on days 1 to 5.
- No significant difference was found between the tramadol/paracetamol and hydrocodone/paracetamol groups in terms of pain intensity and pain relief.
- Common adverse events included somnolence, nausea, dizziness, and vomiting. At least one adverse event was reported by approximetely 40% of subjects in the tramadol/paracetamol and the hydrocodone/paracetamol groups and by approximately 19% of subjects in the placebo group. No serious adverse events or deaths were reported in this study.

- Valdecoxib versus tramadol and placebo

A multicenter RCT with low risk of bias[62] compared a 7 day treatment in patients with Grade I or II ankle sprain. Four groups were created: valdecoxib 40 mg loading followed by 40 mg/d in 2 doses (n=223); valdecoxib 40 mg loading followed by 20 mg/d in 1dose (n=235); tramadol 200 mg/day in 4 doses (n=238); or placebo (n=123). Patients could add paracetamol if needed (up to 4 g/d) but not within the 6 hours prior to any scheduled study visit. In addition, patients could add other non-pharmacological interventions including RICE, crutches, cane, contrast baths, ankle taping/bracing, rigid double-upright ankle brace, strengthening and proprioceptive exercises, transcutaneous electrical nerve stimulation (TENS), diathermy, massage therapy, ultrasound, and acupuncture.

- The comparison between tramadol and placebo (valdecoxib has been excluded from this analysis) concludes that tramadol failed to distinguish itself from placebo in most efficacy analyses (pain at day 4, normal walking on days 4 and 7).
- The authors report adverse events among 58% in the tramadol group versus 43% in the placebo group. The incidence of severe

AE was 7.6% and 3.3% in patients receiving tramadol or placebo, respectively.

Key message regarding treatment with tramadol

- **One study with low risk of bias showed that tramadol/paracetamol (75 mg/650 mg 4x/day) and hydrocodone/paracetamol (7.5 mg/650 mg 4x/day) had a comparable clinical utility and were more effective than placebo in the management of acute musculoskeletal pain caused by ankle sprain with partial ligament tears (1 RCT, low level of evidence).**
- **One study with low risk of bias failed to demonstrate a higher efficacity of tramadol 200 mg/day than placebo (1 RCT, very low level of evidence).**
- **The adverse effects were significantly more frequent in the tramadol group than in the placebo group.**

6.1.2 Venotonic drugs

Venotonic drugs have been sometimes prescribed for the treatment of ankle sprain. The underlying assumption being that these drugs could decrease swelling by an action on veins as well as on lymphatic vessels and capillaries (better venous tone, lymph drainage and microcirculation function).

In a recent prospective, single-blind RCT, with high risk of bias, Fotiadis et al.[63] studied the effectiveness of venotonic drugs (Daflon®) in 81 adults presenting to the emergency department with type II and III acute (<24 hours) lateral ankle sprain. One group of patients (n=43) received standard treatment with analgesic (paracetamol 500 mg 2 times daily for 3 days), immobilisation, lace-up bracing (air cast), elevation for at least 3 days and toe touch weight-bearing for 7 days. The second group (n=43) was additionally treated with micronized purified flavonoid fraction (Daflon 1 000 mg 3 times daily) for 20 days. The authors did not find any significant difference between groups for any of the outcomes under study (pain and swelling at baseline, day 7 and day 20).

Key message regarding treatment with venotonic drugs

- **One study with high risk of bias failed to find a positive effect from the addition of Daflon 1 000 mg 3 times daily during 20 days to the treatment of pain or swelling related to acute Grade II or III ankle sprain (1 RCT, very low level of evidence).**

6.1.3 Topical non-steroidal anti-inflammatory drugs (NSAIDs)

Topical NSAIDs are frequently used in sprain, strains and muscle or tendon soreness, and may be combined with other common treatments for ankle injuries such paracetamol or RICE. Topical NSAIDs are formulated to be directly applied to the pain site, acting locally and avoiding any adverse events that could be related to the systemic absorption of such drugs. Available formulations vary and can include creams, gels, sprays but also plasters containing the active ingredient. Contraindications include use on broken skin or wounds.

A recent high quality systematic review (SR)[64] included RCTs on the efficacy and tolerability of topically applied NSAIDs in acute pain, mainly from sprains and strains. The authors of this review evaluated studies comparing topical NSAIDs with placebo as well as topical NSAIDs versus an active comparator (oral or topical NSAIDs). The primary outcome was “clinical success” defined as a 50% reduction in pain or equivalent measure (e.g. “very good” or “excellent” global assessment of treatment, or “none” or “slight” pain on rest or movement), measured by means of a categorical scale. Adverse events (AE) were a secondary outcome.

6.1.3.1 Topical NSAIDs versus placebo

Thirty one studies were identified by the authors of the SR (see the systematic review[64] for full references) comparing topical NSAIDs with placebo (n=3455). These studies were rated as having low or unclear risk of bias. The results showed a higher efficacy of topical NSAIDS versus placebo:

- The proportion of patients “successfully” treated with topical NSAIDs was 65% (range 31%-100%) versus 43% (8%-83%) of those treated with placebo.
- The relative clinical success of topical NSAID treatment versus placebo was 1.5 (95%CI: 1.4-1.6),

- The number needed to treat (NNT) for successful treatment was 4.5 (95%CI: 3.9-5.3).
- No significant differences were found in terms of adverse events between those treated with topical NSAIDs versus those treated with placebo.

The SR also presented the results according to each active NSAID. Below we summarize these results as well as those from additional, more recent, RCTs, published after the SR of reference.

- Topical diclofenac versus placebo

Three studies[65-67] were considered in the systematic review: two had low risk of bias and one had unclear risk of bias (n=626).

- The proportion of patients "successfully" treated with topical diclofenac was 52% (range 39%-92%) versus 25% (8%-36%) in the placebo group.
- The relative benefit of diclofenac treatment versus placebo was 2.1 (95%CI:1.7-2.6).
- The number needed to treat (NNT) for successful treatment was 3.8 (95%CI: 2.9-5.1).

Three additional studies comparing topical diclofenac to a placebo were published after the systematic review.

- In 2011, a multi-center placebo controlled trial with a low risk of bias[68] evaluated the efficacy and tolerability of daily applications of the diclofenac epolamine 1.3% topical patch compared to a placebo patch over a 7-day period (n=134).
  - There was a significantly greater decrease in VAS scores in the DETP group at day 7 (decrease from 66.9mm at baseline to 10.5mm in the treatment group versus 70.0mm at baseline to 18.4mm in the placebo group, p=0.0008);
  - There were significant differences in favor of the treatment also reported for other outcomes: VAS scores captured 4 hours after the first application of the patch, and reduction of at least 30% in pain VAS scores from baseline until day 2.
  - There was no difference in tolerance between the two groups at days 3 or 7.
- A novel plaster (Flectoparin Tissugel®) was developed based on the hypothesis that a compound with haemorheological and anti-exudative properties such as heparin sodium could enhance the anti-inflammatory analgesic and anti-exudative properties of diclofenac epolamine (DHEP). The efficacy and tolerability of this product was evaluated in a randomized, placebo-controlled multi-centered trial, with a low risk of bias,[69] in 233 adults with an acute (<48 hours) ankle sprain.
  - The reduction in pain during mobilisation and oedema was significantly higher in the DHEP heparin group than in the placebo group (p<0.01) throughout the entire study period (7 days).
  - No differences were found in terms of pain at rest, pain on passive stretch or the possibility of single foot leaning.
  - Only mild to moderate AEs were observed, which resolved without treatment.
- A further randomised, double-blind, placebo controlled multi-center trial, with low risk of bias[70] compared daily applications of DHEP (diclofenac epolamine) plaster (n=146), DHEP/heparin plaster (n=142) and placebo plaster (n=142) over a 7-day period in acute (<48 hours) ankle sprain.
  - Both active treatments were significantly superior to placebo for reducing pain on movement at day 3 (VAS), for reducing daily spontaneous pain and pain intensity scores while leaning on the injured limb. No significant differences were noted in extension of oedema.
- Topical ibuprofen versus placebo

Five studies (n=436) were included in the systematic review:[71-75] four of them had an unclear risk of bias and one with low risk.

- The proportion of patients "successfully" treated with topical ibuprofen was 55% versus 33% of those treated with placebo.
- The relative benefit of ibuprofen treatment versus placebo was 1.6 (95%CI:1.3-2.0).
- The number needed to treat (NNT) for successful treatment was 4.6 (95%CI: 3.3-8.0)

- Topical ketoprofen versus placebo

Seven studies (n=683) were included in the systematic review:[76-82] three of them had an unclear risk of bias and four had a low risk of bias.

  - The proportion of patients "successfully" treated with topical ketoprofen was 73%, versus 47% of those treated with placebo.
  - The relative benefit of ketoprofen treatment versus placebo was 1.6 (95%CI: 1.4-1.8).
  - The number needed to treat (NNT) for successful treatment was 3.9 (95%CI: 3.0-5.3).

- Topical piroxicam versus placebo

Three studies[83-85] with a low risk of bias involved 504 patients.

  - The proportion of patients "successfully" treated with topical piroxicam was 70% versus 47% of those treated with placebo.
  - The relative benefit of piroxicam treatment versus placebo was 1.5 (95%CI: 1.3-1.7).
  - The number needed to treat (NNT) for successful treatment was 4.4 (95%CI: 3.2-6.9).

- Topical indomethacin versus placebo

Two studies[83,84] with a low risk of bias involved 341 patients.

  - The proportion of patients "successfully" treated with topical indomethathin was 58% versus 46% of those treated with placebo.
  - The relative benefit of indomethacin treatment versus placebo was 1.3 (95%CI: 1.03-1.6).
  - The number needed to treat (NNT) for successful treatment was 8.3 (95%CI: 4.4-65).

6.1.3.2 Topical NSAIDs versus oral NSAIDs

Three studies (n=405) were included in the systematic review:[86-88] two with low risk of bias and one with moderate risk of bias. There was insufficient data to draw clear conclusions about the efficacy of topical NSAIDs in comparison with the same NSAIDs on an oral formulation. The limited available evidence did not show any difference in adverse events between topical and oral NSAIDs.

6.1.3.3 Topical NSAIDs versus different formulations of the same topical NSAID:

Four studies were included (n=280)[89-92]: three had unclear risk of bias and one had low risk of bias. There was insufficient data to draw clear conclusions about the efficacy of different formulations of the same topical NSAID.

6.1.3.4 Diclofenac epolamine (DHEP) plaster versus plaster of DHEP combined with heparin

One trial, with a low risk of bias by Constantino et al.[70] previously quoted included a comparison of daily applications of DHEP plaster (n=146) with a DHEP/heparin plaster (n= 142) and placebo (n=142). The authors conclude that significant differences in terms of reduction of pain on movement after 3 days and reduction of pain while leaning on the injured limb (based on VAS score) exist in favour of the DHEP + heparin plaster. Other outcomes were similar between the two groups (see 6.1.3.1).

6.1.3.5 Topical NSAIDs versus other topical NSAIDs

Eight studies, with various risks of bias[83,84,93-98] compared the effectiveness of various topical NSAIDs. The authors of the systematic review conclude to a slight superiority of topical piroxicam versus indomethacin, with less adverse events. No other comparison was possible due to small sample sizes.

Although not reflected in the evidence analyzed, an increased risk of adverse events with ketoprofen has been noticed in clinical practice and mentioned by the expert group. This appears to be primarily linked to photosensitivity and allergies and has been recognized by the Belgian center for drug information (CBIP-BCFI)[c], the British National Formulary[d] and the Medicines and Healthcare Regulatory Agency[e].

Thus, these increased risks were kept in mind in the drafting of the recommendations.

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[c] www.cbip.be for French-speaking or www.bcfi.be for Dutch-speaking

[d] www.bnf.org

[e] www.mhra.gov.uk

Key message regarding treatment with topical NSAIDs

- **A high quality systematic review including 31 RCTs (and 3 additional recent RCTs with low risk of bias) concludes that topical NSAIDs appear to be effective for reducing pain (34 RCTs, moderate level of evidence).**
- **Few differences were noted between topical agents: the number to treat (versus placebo) is close to 4 patients for all the analysed topical NSAIDs with the exception of indomethacin (8.3 patients) (34 RCTs, moderate level of evidence).**
- **Few differences were found between a plaster (adhesive dressing) that combines diclofenac and heparin and a diclofenac epolamine plaster (1 RCT, low level of evidence).**
- **No significant differences were found in the literature between topical NSAIDs and placebo in terms of adverse events. An increased risk of adverse events with ketoprofen was mentioned by the expert group.**

6.1.4 Alternative topical therapies: Comfrey (Symphytum officinale) root extract ointment ("consoude")

Comfrey ("consoude") is a herbal medicine remedy consisting of a root extract ointment that aims to decrease inflammation after trauma. Our literature review identified three studies looking at the efficacy and tolerability of comfrey root extract ointment in the treatment of ankle sprain.

- The first study is a single-blind, multi-center RCT, with moderate risk of bias (n=164). This study compared the application of 6 cm long ointment layer, four times a day of comfrey root extract ointment ("gel de consoude") or diclofenac gel (Voltaren®).[99] Comparable reductions on pain at rest and in motion from baseline to days 4 and 7 (VAS) were found in both treatment groups. No significant differences were found between groups regarding reductions in swelling incidence or adverse events.
- A second multicentre, double-blind RCT,[100] with moderate risk of bias, compared comfrey extract ointment versus placebo in 142 adults with unilateral, acute (<6 hours) ankle distorsion. Statistically significant differences were found for pain under pressure and swellling at days 4 and 7. Other outcomes, including adverse events, did not differ between the study groups.
- Kucera et a.l[101] compared ointments containing comfrey product with different strengths: one had a composition corresponding to 25g of fresh herb per every 100g of ointment while the comparator had a composition corresponding to 2.5 g of fresh herb per 100g of cream. This RCT, with a low risk of bias, involved 203 patients with acute (<24 hours) ankle sprain. At day seven, the standardised mean differences in pain and swelling between both groups were in favor of the high concentration ointment group ($p<0.05$).

Key message regarding treatment with comfrey root extract ointment

- **There is limited evidence showing that Comfrey root extract ointment ("pommade/gel de consoude") is as effective as topical diclofenac for pain during the first week after ankle sprain (1 RCT, very low level of evidence).**

6.2 Rest, Ice, Compression and Elevation

Rest, ice, compression and elevation (RICE) is an easily applicable and popular treatment of acute lateral ankle sprain in adults. The assumptions that underline this practice are the following ones:

- Rest is used to reduce the metabolic demands of the tissue that has been injured and consequently minimize blood flow. It is also applied with the aim to decrease the stress during the fine fibrin bond repair process.
- Ice (cryotherapy) is used to reduce temperature, consequently reduce metabolic demand, induce vasoconstriction and limit bleeding in the injured area. It would also have an effect at the nerve level in promoting analgesia.
- Compression is applied to limit the amount of oedema caused by exudation of fluid from damaged capillaries in the tissue: it would reduce hemorrhage and swelling.
- Elevation of the injured ankle is applied to lower pressure on the blood vessels and to increase drainage of the inflammatory exsudates through the lymphatic system.

- One very recent high quality systematic review analyses the evidence for this fourfold intervention. The authors analysed trials concerning at least 1 of the 4 treatments included in RICE therapy begun within 72 hours after the ankle sprain trauma.[102] The authors assessed studies comparing rest with mobilization, ice with no ice, compression with no compression and elevation with no elevation. The systematic review included 11 studies involving 868 patients.

6.2.1 Rest versus mobilisation

The authors of the systematic review selected 5 studies of various quality: they conclude that there is moderate evidence for some type of immediate posttraumatic ankle joint mobilization. The majority of the studies examined interventions without weight-bearing.

- The highest quality study of the five studies included 101 patients with an acute grade I or II ankle sprain.[103] Patients were randomised to early therapeutic exercise or to a standard protection, rest, ice, compression, and elevation intervention. The authors reported an overall treatment effect in favour of the exercise group at week 1 and 2 for the primary outcome i.e. subjective ankle function. Activity level (e.g. time spent walking) was also significantly higher in the exercise group. The groups did not differ at any other time point for pain at rest, pain on activity, or swelling. The reinjury rate at 16 weeks was 4% (two in each group).
- The four other studies had a higher risk of bias. The first one reports a shorter sick leave and faster return to sport participation after early functional treatment than after conventional treatment.[104] Two studies compared RICE alone with RICE combined with a manipulative intervention: the authors conclude that the addition of antero-posterior mobilisation or osteopathic manipulative treatment to RICE would provide a significant improvement in ROM.[105, 106] The last study had very poor data reporting.[107]

No additional RCTs were identified.

The guideline from the Dutch association for sport medicine (VSG), on the basis of expert consensus, recommended that the patients move their ankle within the pain limit in the first days after the trauma and discouraged absolute rest.[15]

6.2.2 Ice versus no ice

The authors of the systematic review[102] conclude that the evidence from RCTs to support the use of ice in the treatment of acute ankle sprain is limited. They base their conclusions on five RCTs of variable quality:

- Two studies that compared ice with heat therapy had positive results:
  - One study with moderate risk of bias[108] showed that ice bath in combination with exercise for 20 minutes 1x daily for 3 days (initiated third day post injury) significantly decreased swelling compared with heat application;
  - One study with a high risk of bias[109] concludes that cryotherapy for 12 – 20 minutes, 1-3 times per day for 3 days is more effective than heat therapy for recovery in terms of pain and return to activities (p-values < 0.05)
- Three other studies produced non significant results:
  - One study with a high risk of bias[110] that compared the combination of cryotherapy and bandaging with bandaging alone;
  - A second study with moderate risk of bias[111] that analysed the effect of a single application of ice and compression for 20 minutes within the first two days;
  - The third study with a low risk of bias[112] found no difference in outcome measures (pain, swelling, ROM and ability to bear weight) after a single application of cold, elevation and compression.

Additionally one RCT (moderate risk of bias) comparing two interventions with ice was identified.[113] The efficacy of an intermittent cryotherapy treatment protocol was compared with a standard cryotherapy treatment protocol during the first 72 hours. Significant results were noted for the outcome “pain on activity”. The other outcomes (function, swelling, pain at rest) did not differ between groups.

For the Dutch association for sport medicine (VSG), after expert discussion, ice should be considered to reduce the local pain after acute ankle sprain, as far as this is done in a responsible manner (0-7°C; 15 minutes; 4-6 times/day; no cold packs).[15]

6.2.3 Compression versus compression: intermittent pneumatic compression versus elastic bandage

The systematic review identified one small study (44 patients) with moderate risk of bias.[114] The RCT's authors found a significant effect of IPC on oedema (p<0.001), ROM (p<0.001), pain (p<0.001) and ankle function.

The authors of the systematic review[102] conclude that the evidence to support the use of compression on ankle sprain is limited.

No additional RCTs were identified.

For the Dutch association for sport medicine (VSG), applying a compression directly after acute ankle sprain should be considered, by an elastic bandage in the first 24 hours and then a soft brace. This recommendation is based on expert consensus.[15]

6.2.4 Elevation versus no elevation

The systematic review mentioned above as well as the authors of this guideline did not identify any relevant RCT.[102]

For the Dutch association for sport medicine (VSG), the leg elevation should be considered in the first days after the acute lateral ankle sprain in order to ensure a reduction in the swelling. This recommendation is based on expert consensus.[15]

6.2.5 RICE versus no RICE

The Royal Dutch Society for Physical Therapy (KNGF) and the Dutch association for sport medicine (VSG) mentioned both that the use of ice and compression, in combination with rest and elevation (RICE), is useful in the acute phase of lateral ankle sprain for the well-being of the patient. This recommendation is based on expert consensus.[3, 15]

The expert and stakeholders involved in this guideline did not support the use of RICE in acute lateral ankle sprain but underlined the usefulness of rest in the immediate phase of the treatment to decrease pain and risk of complications.

Key message regarding the RICE intervention

There is limited evidence to support the use of RICE after ankle sprain.

- **There is low evidence on the short-term effect of some type of posttraumatic mobilization versus rest in the acute phase of an ankle sprain (ROM/ankle function, return to activities: 3 RCTs, low level of evidence; pain: 2 RCTs, very low level of evidence)**
- **Evidence is conflicting concerning the use of ice for pain (4 RCTs), oedema (4 RCTs) and return to activities (3 RCTs) after ankle sprain (very low level of evidence): the 2 RCTs that concluded to a positive effect of ice compared its application with heat therapy.**
- **Evidence regarding the use of compression to treat pain, oedema and functional impairment after ankle sprain is too limited to draw conclusions (1 RCT, very low level of evidence)**
- **There is no current and available evidence to support or reject the use of elevation.**

6.3 Electrophysical therapy

6.3.1 Ultrasound

Ultrasound is used in the treatment of a wide variety of musculoskeletal disorders including acute ankle sprain. The underlying assumption is that the increase in temperature would help soft tissue healing.

Two systematic reviews were identified in the literature search. However, one of these reviews[115] only included one relevant study that was also included in the second, more recent review. Consequently, only the findings from the high quality Cochrane review by van den Bekerom (2011)[116] are included in this guideline. No RCT published after the systematic review was identified.

Van den Bekerom et al.[116] included randomised and quasi-randomized controlled clinical trials including people with pain, swelling and/or functional disability caused by acute ankle ligament injuries. Trials comparing active ultrasound treatment with placebo intervention, with no treatment or with other types of interventions including exercise therapy,

immobilisation, laser therapy or medication were considered. In total six trials involving 606 participants were included.

6.3.1.1 *Ultrasound therapy versus placebo (sham ultrasound)*

None of the five included studies[117,118,119,120,121] were able to demonstrate statistically significant differences between the two treatment groups for any of the outcome measures including general improvement, pain, swelling, functional disability and range of motion (ROM). The studies varied with respect to the type of ultrasound (pulsed or continuous).

6.3.1.2 *Ultrasound therapy versus other treatment modalities*

Only one study reported significant effects of ultrasound therapy compared with elastoplast tape on recovery after 7 days. This study had some data discrepancies possibly attributable to undeclared loss to follow-up.[122]

Two other studies did not find any significant difference between ultrasound and the comparator treatment[117, 120] (respectively felbinac gel and electrotherapy).

For the Dutch association for sport medicine (VSG), physical techniques (US, laser) should not be applied after acute lateral ankle sprain.[15] The use of physical therapy has no added value in the treatment of ankle sprain according to the Royal Dutch Society for Physical Therapy (KNGF).[3]

Key messages regarding the treatment with ultrasound

Ultrasound does not appear to be effective for outcomes including general improvement (3 RCTs), pain (2 RCTs) and swelling (2 RCTs) (low level of evidence).

6.3.2 *Laser therapy*

Laser therapy is believed to influence the consequences of an impairment or disorder by changing the energy state of a cell, consequently alerting the electromagnetic communication between cells in a favourable way. Photochemical theory offers an alternative explanation/belief: the absorption of laser light that takes place may activate cellular or extracellular substances, responsible for the postulated bioeffects.

One systematic review by Bleakley[115] included two papers on laser therapy: one with low risk of bias and one with moderate risk.[123, 124]

- The first study concludes that the combination of low-level laser treatment with RICE therapy is more effective to reduce swelling than than RICE only or RICE combined with placebo laser.[124]
- De Bie et al.[123] on the contrary found that participants receiving placebo laser had significantly better ankle function than the patients receiving laser therapy. Additionally, this study showed that neither high nor low-level laser was more effective than placebo in reducing pain or oedema.
- No additional RCTs were identified.

Key messages on laser therapy

There is limited and conflicting evidence on the efficacy of laser therapy in the acute treatment of ankle sprain (2 RCTs, very low level of evidence).

6.4 Ankle Support

Ankle sprain is commonly treated in one of two ways;

- with a rigid devices (below-knee cast) placed around the ankle so the joint is unable to move, a treatment form often referred to as immobilisation.
- with non-rigid ankle supports including elastic bandages, tape, lace-up ankle support or semi-rigid (brace) ankle support. These supports allow some joint movements. Non-rigid and semi-rigid supports are often referred to as 'functional treatment'.

6.4.1 Immobilisation devices

One systematic review and two additional RCTs compared immobilisation devices with less rigid supports.

- A high quality systematic review of 21 trials (n=2184)[125] showed that a treatment with supports allowing partial mobilisation is superior to immobilisation for the treatment of ankle sprain. Statistically significant differences in favor of treatment with these supports when compared with immobilisation were found for seven outcome measures:
  - More patients had returned to work at short term follow-up (RR 5.75, 95%CI: 1.01 - 32.71);
  - The time taken to return to work was shorter (Weighted mean difference (WM) 8.23 days, 95%CI: 6.31 - 10.16);
  - Patients treated functionally were more satisfied with their treatment (Relative risk (RR) 1.83, 95%CI: 1.09 to 3.07);
  - Fewer patients suffered from persistent swelling at short term follow-up (RR 1.74, 95%CI: 1.17 - 2.59);
  - Fewer patients suffered from objective instability as tested by stress X-ray (WMD 2.60, 95%CI: 1.24 - 3.96);
  - More patients returned to sport in the long term (RR) 1.86, 95%CI: 1.22 - 2.86);
  - The time taken to return to sport was shorter (WMD 4.88 (days), 95%CI: 1.50 - 8.25).

  No significant benefits were seen with immobilisation. The methodological quality of the studies included in the review varied greatly and therefore conclusions should be interpreted with some caution.

An update of this systematic review concluded there continued to be a lack of high-quality evidence to support clinical decisions about which treatment is best in the management of severe ankle sprain which provided the basis for the RCT by Lamb et al. described below.

- One additional RCT[126] (n=121) with a moderate risk of bias compared the therapeutic efficacy of cast immobilisation (3 weeks) and non-rigid support (with strapping). The study population presented grade III ruptures of the lateral ankle ligaments. In both groups, patients were walking with full weight-bearing within 2 days of starting treatment. The functional group showed significantly better results for return to physical activity , pain, swelling, stifness, and subjective instability at 3 months; for pain and swelling after 6 months. No intergroup difference was observed for any symptom at 12 months, including for the rate of re-injury.
- Finally, one large RCT[127] (n=584), with a low risk of bias, assessed patients with severe ankle sprain, defined as patients being unable to bear weight at least three days after injury. Patients were randomised into four groups in order to compare the effectiveness of three types of mechanical support. Tubular compression bandage was selected as reference treatment (cheapest, most commonly used and allows movement in any plane). Results found that tubular compression bandage and Bledsoe boot were the least effective treatment. At 3 months clinically important benefits were found for below-knee cast and to a lesser extent for Aircast brace (quality of ankle function, pain, symptoms and activities). The groups randomised to Aircast and Bledsoe had better mental health-related quality of life. There were no differences in outcomes between the 4 groups at 9 months.

The Royal Dutch Society for Physical Therapy (KNGF) mentioned that functional treatment in the treatment of acute lateral ankle sprain is preferable to immobilisation during 4 weeks. The Working Group considered that a short period of plaster immobilisation (0-5 days) or similar rigid support facilitating a smooth decrease of pain and swelling, may have a place in the treatment of acute lateral ankle sprain.[3]

6.4.2 Support allowing partial mobilisation

Two systematic reviews with low risk of bias compared different types of non or semi-rigid ankle support for the treatment of acute ankle sprain. No additional RCTs have been found.

- The most recent one by Kelmer et al.[128] presented a narrower scope focusing purely on brace versus any other functional treatment;
- The SR by Kerkhoffs[125] covered comparisons between four different types of functional treatments (i. e. tape, elastic bandage, semi-rigid (brace) ankle support and lace-up ankle support).

Despite some inevitable duplication, the results of both SR are described below.

No new, relevant RCTs were identified.

The review of Kemler et al.[128] attempted to evaluate the effectiveness of ankle braces compared with other types of ankle supports (e.g. ankle tape, TubigripTM). This systematic review is based on 7 studies with low risk and 1 with high risk of bias. The authors found only a significant effect on functional outcomes when using a brace versus other ankle supports. There was no evidence of effect on any other outcome (pain, swelling, instability, and return to sports, daily activities and work).

The review of Kerkhoffs et al.[125] assessed the effectiveness of various functional treatments for acute ruptures of the lateral ankle ligament. They evaluated 4 methods: elastic bandage/stocking, tape, lace-up ankle support and semi-rigid ankle support. They made 6 types of comparisons:

- Elastic bandage versus tape

Four trials, one with low risk of bias and 3 with unclear risk of bias, compared elastic bandage versus tape. Only outcomes on complications could be pooled from two trials:[129, 130] treatment with tape resulted in more complications (mostly skin problems) than treatment with elastic bandage (RR 0.11; 95%CI: 0.01-0.86). All other outcomes were reported in single trials and no statistically significant differences were found.

- Elastic bandage versus semi-rigid ankle support

Four trials, two with low risk of bias and two with unclear risk of bias, were considered for this comparison. Results pooled for two trials[104, 131] showed that the use of a semi-rigid ankle support offered a significant reduction in time to return to work compared to elastic bandage: Weighted mean difference (WMD) in days 4.24 (95%CI: 2.42-6.06). The study by Karlsson et al.[104] showed also a benefit for the semi-rigid ankle support in terms of time to return to sports, with a WMD in days of 9.60 (95%CI: 6.34-12.86). No differences were found in the single trials in terms of pain, swelling or injury recurrence.

- Elastic bandage versus lace-up ankle support

One study with unclear risk of bias from Zeegers et al.[131] only showed significant short term positive results for lace-up ankle support when compared to elastic bandage in terms of swelling. No differences were found in time to return to work or pain.

- Tape versus lace-up ankle support

The same study[131] had similar results for lace-up ankle support when compared to tape: the authors only found significant short term positive results for lace-up ankle support on swelling. No other significant differences were reported.

- Tape versus semi-rigid ankle support

Two trials with unclear risk of bias[131, 132] found no statistical significant differences on any of the studied outcomes (e.g. return to work, pain or swelling).

- Semi-rigid ankle support versus lace-up ankle support

Only Zeegers et al.[131] compared semi-rigid ankle support with lace-up ankle support. The results of this study showed a significant difference in favour of lace-up ankle support in swelling in the short term. No significant differences were found for return to work or pain.

For the Dutch association for sport medicine (VSG), only semi-rigid protection can take place in the treatment of acute lateral ankle sprain and can control, in the acute phase, the active mobilization and weight-bearing.[15]

The Royal Dutch Society for Physical Therapy (KNGF) considered that in the acute phase (0-7 days) the treatment of acute lateral sprain should be aimed at the reduction of pain and swelling. The Working Group is of the opinion that in the phase after the diagnosis a lace-up or a semi-rigid brace is preferable. In the (top) sport population there is in this phase certainly place for tape treatment.[3]

Key message regarding treatment with ankle support

Immobilisation devices versus non-rigid or semi-rigid supports

- **Based on the studies selected, non-rigid or semi-rigid supports of mild or moderate acute lateral ankle sprain appeared to be more effective than cast immobilisation for patients' symptom (very low level of evidence), return to normal activities and re-injury (low level of evidence).**
- **In case of severe ankle sprain, there is conflicting evidence on the effect of immobilisation versus other ankle supports for pain (very low level of evidence) although immobilisation appears to offer some advantages for quality of ankle function compared to non-rigid or semi-rigid supports at 3 months (very low level of evidence).**

Types of non-rigid or semi-rigid supports

- **Elastic bandages are preferred over tape because they result in less complications (low level of evidence).**
- **Semi-rigid supports (braces) appears to offer benefits in term of faster return to work or sport when compared to elastic bandages (low level of evidence).**
- **Braces offer better functional outcomes and no disadvantages over other support alternatives (low level of evidence).**
- **The limited available evidence does not allow for a clear choice between the different types of non-rigid and semi-rigid supports.**

6.5 Manual therapy

Manual therapy is a physical treatment primarily used by physiotherapists, massage therapists, chiropractors, and osteopaths to treat musculoskeletal injuries. Manual therapy commonly includes mobilization and manipulation of muscles and joints.

Two different systematic reviews[115, 133] with a low risk of bias, selected the same two studies on the effect of manual therapy (i.e. mobilization) in the treatment of acute ankle sprain.[106, 134]

Both studies (respectively with low and unclear risk of bias) conclude that manipulation in addition with standard therapy (RICE and analgesics) have an effect on the range of movement a few days after injury. However this effect did not last at later stages of rehabilitation.

In conclusion, there is some limited evidence on the effect of manual therapy on the range of motion in short term (2 RCTs, very low level of evidence). There is a lack of evidence for any other relevant outcomes.

The Royal Dutch Society for Physical Therapy (KNGF) considered that there is no place for manual mobilizations of the ankle in patients with acute lateral ankle sprain.[3]

Key message regarding manual therapy

- **Two studies on manual therapy did not provide evidence for its use in ankle sprain (2 RCTs, very low level of evidence)**

6.6 Exercise therapy

Protection, rest, ice, compression and elevation, synonymous with management of acute soft tissue injury, suggest a passive approach to treatment. Many ED's subsequently favour a non-weight bearing approach to treatment e.g. by using crutches, with others favouring rest and immobilisation with a cast.

On the other hand animal models describe a range of biomechanical and physiological mechanisms that support the use of early active mobilization after soft tissue injury. The purpose of rehabilitation exercise is to improve muscle strength, range of movement, and sensorimotor control, elements which are commonly impaired after an ankle sprain.

Two systematic reviews assessed the evidence on the effect of exercise therapy in the treatment of ankle sprain:

- A systematic review with low risk of bias, by van der Wees et al.[133] assessed the effectiveness of exercise therapy and manual mobilization in acute ankle sprain and functional ankle instability in all settings (home-based unsupervised and clinical supervised settings). This review included exercise therapy (proprioceptive training, coordination training, strength training or functional exercise) compared with placebo, no treatment or another intervention. The pooled effect size (based on two RCTs with moderate and high risk of bias, n=140) showed a statistical significant risk reduction (RR=0.37 - 95%CI: 0.18-0.74) of recurrent ankle sprains in favor of exercise

therapy in the long term (8-12 months). No consistent effect were found for the other outcomes under study.

- The systematic review of Van Rijn et al.[135] with low risk of bias examined the effectiveness of adding supervised exercise to conventional treatment compared with conventional treatment alone for the rehabilitation of acute ankle sprain. All exercise interventions in this review included proprioceptive training components. Immobilisation, non-supervised treatment including exercise instructions or the use of external support were all considered to be conventional treatment modalities. Pain, instability, recurrent sprain, recovery, function, return to work and return to sport were the outcomes under study.

  This systematic review showed limited evidence for adding supervised exercises (proprioceptive and other exercises) to conventional treatment compared with conventional treatment alone for two outcomes: recovery (measured by a VAS scale or by calculating the mean period in days to recovery) and return to sport at short term (= up to two weeks). There was no evidence for effectiveness of additional supervised exercises for any of the other outcome measures. Contrary to the results of the previous systematic review, van Rijn et al. showed that supervised exercise i.e. walking, running and balance/proprioceptive exercises in addition to usual care does neither reduce the rate of recurrent sprain nor improve recovery time.

Two additional RCTs were identified:

- Bleakley et al.[103] compared in an RCT with a moderate risk of bias (n=101) an accelerated intervention incorporating early therapeutic neuromuscular exercise during the first week after acute ankle sprain with a standard RICE intervention. This early exercise protocol during the first week after ankle sprain improved only subjective ankle function but had no effect on pain at rest, pain with activity or swelling.
- A large RCT with a moderate risk of bias by Hupperets et al.[136] in 522 athletes found a reduction in the rate of recurrent ankle sprain when adding home-based proprioceptive training (balance exercises) to usual care (RR=0.63, 95%CI: 0.45-0.88).

No recommendation can be drawn for exercises after acute lateral ankle sprain according to the Dutch association for sport medicine (VSG)[15]. The Royal Dutch Society for Physical Therapy (KNGF) recommended exercise therapy in severe acute lateral ankle sprain. It is recommended to implement the exercise therapy at home as much as possible.[3]

Key message regarding exercise therapy

- **The use of supervised proprioceptive exercise therapy for recovery (2 RCTs) and return to sport (3 RCTs) is supported by a very low level of evidence (5 RCTs, very low level of evidence)**
- **The use of home-based, unsupervised proprioceptive/balance exercise therapy for preventing recurrent ankle sprain is supported by a very low level of evidence (1 RCT, very low level of evidence)**
- **The effect of exercise therapy, whether performed at home, unsupervised or in a clinical setting, on other outcomes is not supported by the evidence**

6.7 Other conservative treatments

Our literature search found 3 additional conservative treatments, each assessed within a single RCT. These treatments are all considered uncommon for ankle sprain under current Belgian practice and therefore, have not been taken into account in the elaboration of recommendations.

6.7.1 Hyperbaric oxygen

A RCT with low risk of bias[137] compared the effectiveness of hyperbaric oxygen at 2 atmospheres absolute pressure against versus air at 1.1 atmosphere absolute pressure in a hyperbaric chamber. This treatment was provided in patients with acute (<72 hours) ankle sprain grade II and III in addition to conventional treatment with (n=32). The only differences found concerned an increase in joint function and the overall change from initial to final evaluation in favour to the hyperbaric oxygen treatment.

6.7.2 Proteolytic enzyme

Proteolytic enzyme therapy is an alternative treatment containing three active components: hydrolase trypsin, endopeptidase bromelain, and flavonoid rutoside. One multi-center RCT, with low risk of bias[138], compared Phlogenzym (combination of 100 mg of rutoside, 90mg of bromelain and 48 mg of trypsin) to each of the single substances included in the product at the doses mentioned above; double combinations of

those same substances (i.e. trypsin plus bromelain, trypsin plus rutoside and bromelain plus rutoside) at the same doses mentioned above and placebo (n=721). Phlogenzyme was not found to be more effective in reducing pain, diminishing ankle volume or increasing range of motion in patients suffering from an acute ankle sprain (treated with a brace) than the single substances, double combinations or placebo.

6.7.3 Hyaluronic acid intra-articular injections

Hyaluronic acid (HA) is a naturally occurring biological substance, representing an unbranched, high–molecular weight polysaccharide as a major component of ligamentous, cartilaginous, and synovial ultrastructure. A multi-center RCT, with low risk of bias,[139] evaluated the efficacy and safety of periarticular hyaluronic acid injections in acute (<48 hours) grade I or II lateral ankle sprain over a 90-day study period. One hundred and fifty-eight competitive athletes were randomized to receive HA (0.7-1.2mL) or normal saline (0.7-1.2mL) in addition to standard care (RICE, oral or topical medication, and assistive devices but no physiotherapy). Hyaluronic acid injections appear to be effective at controlling pain, offering a significantly greater patient satisfaction and resulting in more rapid return to pain-free sport activities when compared to placebo injections, with few adverse effects (1 RCT, very low level of evidence).

6.8 Surgical treatment

Surgical treatment for ankle sprain is not common. In general, surgery is reserved for injuries that fail to respond to other treatment forms.

Consequently, this guideline included conservative treatment only. For the reader interested in surgical treatment the authors of this guideline identified a systematic review on surgical versus conservative treatment[140] and an article where the authors performed a meta-analysis on operative and functional treatment versus functional treatment alone.[141]

6.9 Discussion: therapy for acute lateral ankle sprain

Limitations of the literature

The review of literature on the treatment of ankle sprain provided evidence for the effectiveness of some treatments. In particular topical NSAIDs and paracetamol are effective for the pain alleviation with rare and minor adverse events. The effectiveness of oral NSAIDs is counterbalanced by possible secondary effects. Ankle supports allowing partial mobilisation appeared to be more effective than immobilisation in non-severe ankle sprain.

The strengths of this systematic review are its comprehensiveness (inclusion of most usual conservative treatments) and the quality appraisal of all studies identified for each intervention.

However, the interpretation of the results needs to take into account the following points:

- The **quality of the included studies** in this guideline presents a large variety in the risk of bias. Many studies had a high risk of bias:
  - Only a limited number of trials described an adequate method of **allocation concealment**
  - In behavioral interventions, including exercise, it is not possible to perform double-blinding. Yet the option of **blinding the assessment** by objective outcome measures commonly lacked in the study designs.
  - A number of studies failed to analyze data on an **intention-to treat principle**: the result is a possible overestimation of the efficacy of interventions.
- Most studies included **populations that differ from the general population** e.g. patients with a better general health status than those treated in general practice or in emergency departments. For oral medication by instance, patients with gastrointestinal, renal, or hepatic disease, and patients with other rheumatic diseases or a history of drug or alcohol abuse were excluded from the studies. These numerous exclusions are important to bear in mind for the generalisability of results in the usual clinical practice.
- The **populations are heterogeneous** in terms of severity of injury: most studies concerned grade I and II ankle sprain but some focused on grade II, other on grade II and III. An additional problem is that the

severity of diagnosis is not always clearly defined in the studies. One counterexample is the RCT of Lamb[127] that compared the efficacy of different ankle supports in a population of patients with severe ankle sprain that answered to specific criteria.

- The **patients' characteristics** (e.g. age, type of activity) were often not considered despite their potential impact on the choice of the treatment.
- The **modalities of interventions**, even for the same treatment, **greatly differ:** one illustration is the exercise treatment whose modalities vary between studies (intensity, type, frequency, supervision, duration).
- There is a **lack of gold standard** (or at least a standard intervention considered as the standard treatment) in the studies: the best example is the lack of trials that consider paracetamol as the best comparator for oral analgesic medication.
- The **comparisons** themselves are **heterogeneous**: an example is the variety of ankle supports under study as illustrated by the systematic review of Kerkhoffs et al.[125] The multiplicity of interventions together with the paucity of studies for a given treatment resulted in pairwise comparisons without the possiblity to identify any gold standard.
- The **outcome measurement varies** between studies: pain is usually the main outcome studied but the type of pain measure differs from one study to the other: pain at rest, pain in weight bearing. Return to activities is another outcome relevant for the patient but less frequently considered. Many studies adopted functional outcomes as criteria for success: their measure greatly vary between studies and their possible significance for the patient can raise questions in comparison with the patient's outcomes previously mentioned (pain, return to activities). In addition for a given outcome the time for measurement largely varies between studies (e.g. pain at day 3, 7 or 10).
- The **incidence** of **adverse outcomes** cannot be defined as the studies were underpowered for detecting them: this is the reason why information on oral medications have been completed by another EBM Belgian source i.e. the Belgian Centre for therapeutic information (CBIP/BCFI).
- The **combination of interventions** within a design complicates the comparison between studies: for example the permission (or not) to add oral medication to the treatment studied can influence the pain alleviation.
- The **start of the intervention** is mainly in the acute phase of the ankle sprain (<48h) but the information did not allow to analyse the importance of a very early (<6h) intervention.

The result is that conclusions can be drawn on the efficacy of types of interventions but it remains difficult to define a hierarchy within specific treatment categories. Yet further aspects should be considered when the evidence does not allow for choosing for a specific treatment modality: the patient's preferences, the costs and possible side effects are important factors to bear in mind in individual clinical decisions. Patient's information is important in this context to allow them to share clinical decisions and to guarantee a correct follow-up of the lesion.

Stakeholders' perspectives

The stakeholders involved in this guideline underlined the need for research that considers the severity of the ankle sprain. The reviewed literature is rarely clear on the grading of ankle sprain (not available or not clearly defined); this was particularly important for the moderately severe ankle sprain.

6.10 Recommendations concerning the therapy of ankle sprain

The Recommendations and the Best practices below are based on a discussion with experts and stakeholders after having balanced the quality of the evidence against the consequences for the patients (acceptability, adverse events) and organizational aspects.

Medication

Recommendation	Strength of Recommendation	Level of Evidence
Topical non-steroidal anti-inflammatory drugs (diclofenac, ibuprofen, and piroxicam) are recommended for pain alleviation in acute ankle sprain.	Strong	Moderate
There is no sound clinical evidence to recommend the use of a plaster (adhesive dressing) that combines diclofenac and heparin in the treatment of acute ankle sprain.	Weak	Low
There is no sound clinical evidence to recommend the use of a comfrey root extract ointment in the treatment of acute ankle sprain.	Weak	Very low
Paracetamol at therapeutic doses (4 x 500 mg to 4 x 1 g/day) is recommended as an additional analgesic treatment in acute ankle sprain.	Strong	Low
Oral non-steroidal anti-inflammatory drugs (NSAIDs) can be considered instead of topical NSAIDs when topical NSAIDs combined with paracetamol are not effective for pain alleviation in acute ankle sprain.	Weak	Low
Treatment with COX-II inhibitors might be considered in patients with gastrointestinal, renal or hepatic disease.	Weak	Low
Diosmin combined with hesperidin cannot be recommended in the treatment of the swelling in acute ankle sprain.	Weak	Very low

RICE

Recommendation	Strength of Recommendation	Level of Evidence
There is no sound clinical evidence to recommend the use of rest in acute ankle sprain.	Weak	Very low
There is no sound clinical evidence to recommend the use of ice in acute ankle sprain.		
There is no sound clinical evidence to recommend the use of compression in acute ankle sprain.		
The lack of good quality studies does not allow to assess the effectiveness and to recommend elevation in acute ankle sprain.		
The lack of good quality studies does not allow to assess the effectiveness and to recommend RICE (combination of Rest, Ice, Compression and Elevation) in acute ankle sprain.		

Best practice (expert consensus)
Rest without weight-bearing within the 3 first days after acute ankle sprain is advised to avoid early overload and decrease pain.

Electrophysical therapy

Recommendation	Strength of Recommendation	Level of Evidence
Therapeutic ultrasound is not recommended in the treatment of acute ankle sprain.	Strong	Low
Laser therapy is not recommended in the treatment of acute ankle sprain.	Strong	Very low

Ankle support

Recommendation	Strength of Recommendation	Level of Evidence
Treatment with non-rigid (e.g. elastic bandages, tapes) or semi-rigid ankle support (e.g. braces) is preferred to immobilisation with below-knee cast for the immediate treatment of a non severe acute ankle sprain.	Strong	Low
In severe cases, i.e. where the patient is unable to bear weight after 3 days, a short period (up to 10 days) of immobilisation with a below-knee cast can be considered on a case by case basis.	Strong	Low

Best practice (expert consensus)
The use of simple non adhesive elastic bandages is not advised in the treatment of acute ankle sprain.

Exercise therapy

Recommendation	Strength of Recommendation	Level of Evidence
Early exercise therapy including proprioceptive/balance training components is recommended in the treatment of acute ankle sprain (as soon as possible). There is no sound clinical evidence to differentiate between different types of exercise intervention or to recommend a specific setting (home-based unsupervised or supervised in a clinical setting) to undergo these interventions.	Strong	Low

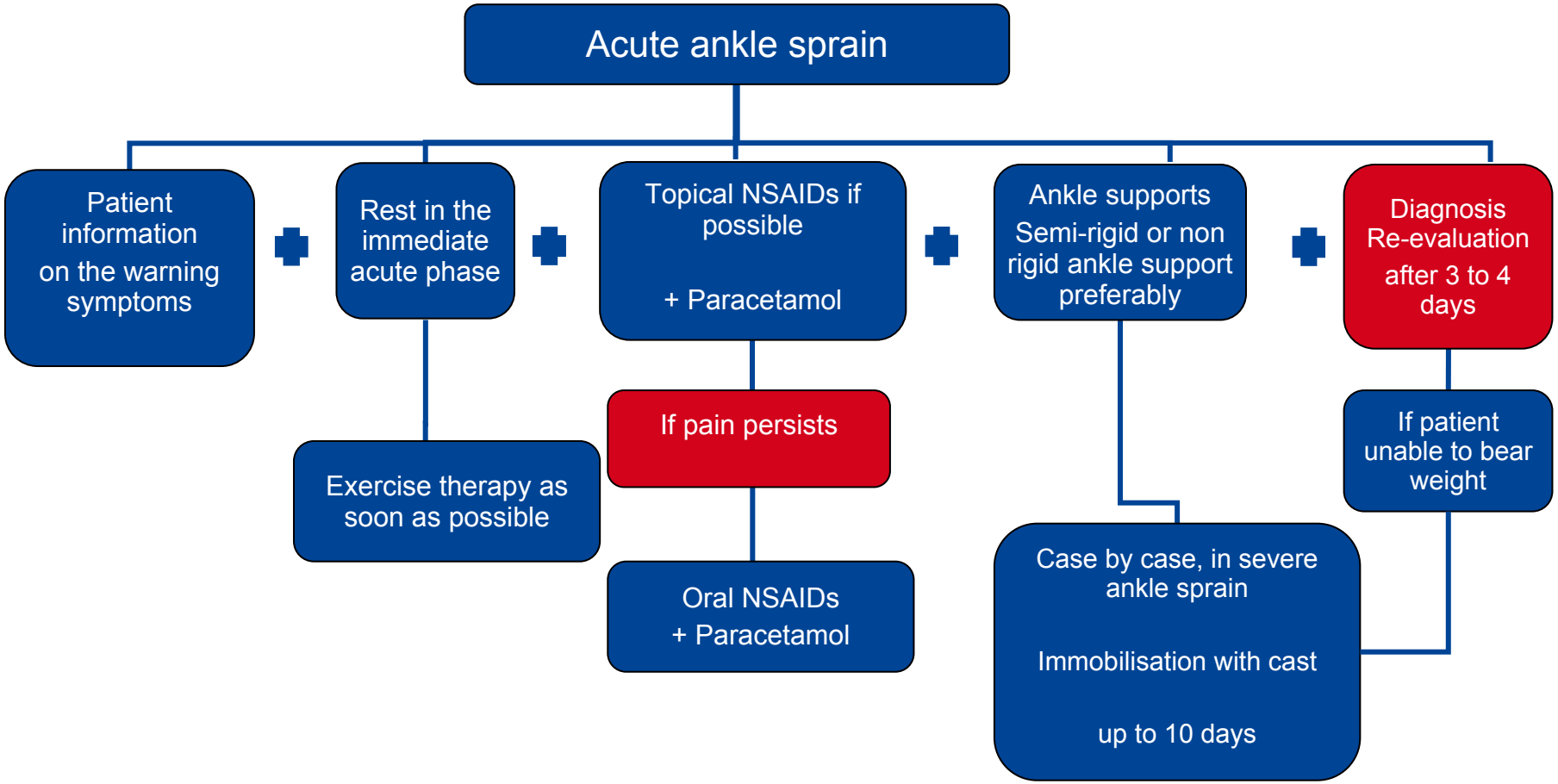
Manual therapy

Recommendation	Strength of Recommendation	Level of Evidence
Manual therapy cannot be recommended in the treatment of acute ankle sprain.	Weak	Very low

Patients' information

Best practice (expert consensus)
Patients should be systematically informed about the benefits and risks of each treatment and the warning symptoms in case of unfavourable evolution of an acute ankle sprain.

7 ALGORITHM FOR THERAPY



8 IMPLEMENTATION OF THE GUIDELINE

8.1 At practice level: adaptation to individual situations

- Guidelines are not meant to be inflexible or dogmatic: they will be adapted to the individual patient's situation according to the physician's judgment. The organization of the primary care practice or of the emergency department, the cost of the different therapeutic options, the patient's preferences will influence the applicability of the guidelines. The involvement of health professional stakeholders in the draft of this guideline allowed to consider its applicability in daily practice. Some barriers were clearly mentioned either by some study authors or by the stakeholders involved in this guideline. Several of them were analysed as the potential reluctance to avoid X-rays use in negative OAR or the organisational difficulties to use ultrasound for excluding a fracture in positive OAR (see chapter 4.5).

8.2 Implementation by professional societies

- The second objective of the involvement of health professional stakeholders was to facilitate the dissemination and implementation through scientific societies. These stakeholders represented the associations of physiotherapists, emergency nurses, emergency physicians, general pratitioners, orthopedic surgeons, radiologists and podiatrists. The implementation process was discussed with them: they agreed to consider this guideline as a topic for their future scientific congress (e.g. BeSEDIM) as well as for the training of students (e.g. in emergency care). The researchers further contacted scientific societies to keep up with the future events susceptible to include this guideline.

8.3 Monitoring the guideline dissemination

The KCE will record the implementation of the report with the use of the following ways:

- Monitoring of publications in indexed and non-indexed reviews;
- Record of presentations at conferences or congresses;
- Identification of citations of the report in the general and medical press.

8.4 Monitoring the guideline implementation

The development of indicators for the implementation of this guideline in practice should be developed by the clinicians either at the level of the practice (e.g. emergency department) or preferably at a higher level (for example by professional organizations). Illustrations of clinical domains for indicators are:

- For the diagnosis:
  - Record of OAR results in the medical record
  - X-ray performed in case of positive OAR
  - X-ray performed in case of negative OAR
  - Use of other imaging techniques than X-ray
  - Combination of different imaging techniques
- For the treatment
  - Prescription of oral analgesics (type and dosage)
  - Prescription of topical NSAIDs for low and moderate grade ankle sprain
  - Type of support used in non-severe and severe cases respectively
  - Follow-up: health services use, imaging techniques, recurrence, referral to specialist

Further refinement and corresponding criteria should be defined by the clinicians. The resources needed for a data registry should be also discussed with policy makers.

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APPENDICES

APPENDIX 1. SEARCH STRATEGY FOR DIAGNOSIS

Appendix 1.1. Medline

Date	29-11-2011
Database (name + access ; e.g.: Medline OVID)	Medline
Search Strategy (attention, for PubMed, check « Details »)	((Diagnosis/Broad[filter])) AND ("ankle injuries"[MeSH Terms] OR ("ankle"[All Fields] AND "injuries"[All Fields]) OR "ankle injuries"[All Fields] OR ("ankle"[All Fields] AND "injury"[All Fields]) OR "ankle injury"[All Fields]) Limits: English, French, German, Dutch Publication Date from 2000/1/1 to 2011/11/29
Note	The diagnosis filter broad is used in order not to miss some articles about the Ottawa rules.

Appendix 1.2. Embase

Date	1-12-2011
Database (name + access ; e.g.: Medline OVID)	Embase
Search Strategy (attention, for PubMed, check « Details »)	#5 = #4 AND ([dutch]/lim OR [english]/lim OR [french]/lim OR [german]/lim) AND [embase]/lim AND [2000-2011]/py **n =769** #4 = #1 AND #2 AND #3 **n = 790** #3 #3.21 = #3.6 OR #3.20 **n = 4,494,917** #3.20 = #3.7 OR #3.8 OR #3.9 OR #3.10 OR #3.11 OR #3.12 OR #3.13 OR #3.14 OR #3.15 OR #3.16 OR #3.17 OR #3.18 OR #3.19 #3.19 'functional assessment'/exp AND [embase]/lim AND [2000-2011]/py #3.18 'physical examination'/exp AND [embase]/lim AND [2000-2011]/py #3.17 'anamnesis'/exp AND [embase]/lim AND [2000-2011]/py #3.16 'diagnostic reasoning'/exp AND [embase]/lim AND [2000-2011]/py #3.15 'quantitative diagnosis'/exp AND [embase]/lim AND [2000-2011]/py #3.14 'qualitative diagnosis'/exp AND [embase]/lim AND [2000-2011]/py

#3.13 'diagnosis'/exp AND [embase]/lim AND [2000-2011]/py
#3.12 'non invasive measurement'/exp AND [embase]/lim AND [2000-2011]/py
#3.11 'musculoskeletal diagnosis'/exp AND [embase]/lim AND [2000-2011]/py
#3.10 'diagnosis, measurement and analysis'/exp AND [embase]/lim AND [2000-2011]/py
#3.9 'differential diagnosis'/exp AND [embase]/lim AND [2000-2011]/py
#3.8 'diagnostic accuracy'/exp AND [embase]/lim AND [2000-2011]/py
#3.7 'clinical assessment tool'/exp AND [embase]/lim AND [2000-2011]/py
#3.6 #3.1 OR #3.2 OR #3.3 OR #3.4 OR #3.5
#3.5 'nuclear magnetic resonance imaging'/exp AND [embase]/lim AND [2000-2011]/py
#3.4 'x ray analysis'/exp AND [embase]/lim AND [2000-2011]/py
#3.3 'ankle radiography'/exp AND [embase]/lim AND [2000-2011]/py
#3.2 'radiodiagnosis'/exp AND [embase]/lim AND [2000-2011]/py
#3.1 'echography'/exp AND [embase]/lim AND [2000-2011]/py

#2
#2.5 = #2.1 OR #2.2 OR #2.3 OR #2.4 **n = 4,289**
#2.4 'ankle lateral ligament'/exp AND [embase]/lim AND [2000-2011]/py
#2.3 'ankle instability'/exp AND [embase]/lim AND [2000-2011]/py
#2.2 'ankle injury'/exp AND [embase]/lim AND [2000-2011]/py
#2.1 'ankle sprain'/exp AND [embase]/lim AND [2000-2011]/py

#1
#1.7 = #1.1 OR #1.2 OR #1.3 OR #1.4 OR #1.5 OR #1.6 **n = 1,110,349**
#1.6 'practice guideline'/exp AND [embase]/lim AND [2000-2011]/py
#1.5 'meta analysis'/exp AND [embase]/lim AND [2000-2011]/py
#1.4 'randomized controlled trial'/exp AND [embase]/lim AND [2000-2011]/py
#1.3 'controlled clinical trial'/exp AND [embase]/lim AND [2000-2011]/py
#1.2 'review'/exp AND [embase]/lim AND [2000-2011]/py
#1.1 'systematic review'/exp AND [embase]/lim AND [2000-2011]/py

Appendix 1.3. Pedro

Date	**12-12-2011**
Database (name + access ; e.g.: Medline OVID)	Pedro
Search Strategy (attention, for PubMed, check « Details »)	Ankle sprain **n = 91** Ankle sprain AND systematic review since 2000 **n = 27** Ankle sprain AND practice guideline since 2000 **n = 2** Ankle sprain AND clinical trial since 2000 **n = 63** Lateral ankle injur* since 2000 **n = 34** Lateral ankle trauma since 2000 **n = 6** Lateral ligament complex since 2000 **n = 4**
Note	The last three search strategies delivered a few extra articles other than with the 'ankle sprain' search.
Date	27-08-2012
Database (name + access ; e.g.: Medline OVID)	Embase
Search Strategy (attention, for PubMed, check « Details »)	#ct26augfull-1 (#2) **'computer assisted tomography'**/mj AND **'ankle injury'**/expReviews: **n = 74**

Appendix 1.4. CINAHL

Date	**29-11-2011**
Database (name + access ; e.g.: Medline OVID)	CINAHL
Search Strategy (attention, for PubMed, check « Details »)	TX ankle sprain OR TX ankle trauma OR TX ankle injury - Limiters - Published Date from: 20000101-20111131; Publication Type: Meta Analysis, Practice Guidelines, Randomized Controlled Trial, Review, Systematic Review; Language: Dutch, English, French, German Search modes - Boolean/Phrase n = 131

Appendix 1.5. Medion

Date	29-11-2011
Database (name + access ; e.g.: Medline OVID)	Medion
Search Strategy (attention, for PubMed, check « Details »)	Ankle **n = 5** Ankle sprain **n = 0** Ankle trauma **n = 0** Ankle injury **n = 0**

Appendix 1.6. Cochrane

Date	31-10-2011
Database (name + access ; e.g.: Medline OVID)	Cochrane
Search Strategy (attention, for PubMed, check « Details »)	"**ankle injury** in **Title, Abstract or Keywords** or **ankle sprain** in **Title, Abstract or Keywords** or **ankle trauma** in **Title, Abstract or Keywords** and **diagnosis** in **Title, Abstract or Keywords**, from 2000 to 2011 in **Cochrane Central Register of Controlled Trials**" Reviews: **n = 14** Clinical trials: **n = 339** "**ankle injury** in **Title, Abstract or Keywords** or **ankle sprain** in **Title, Abstract or Keywords** or **ankle trauma** in **Title, Abstract or Keywords** and **therapy** in **Title, Abstract or Keywords**, from 2000 to 2011 in **Cochrane Central Register of Controlled Trials**" Reviews: **n =15** Clinical trials: **n = 340**

Appendix 1.7. Guidelines

Date	31-10-2011		
Search engine	Search term	number	PICO
GIN guideline resource	Ankle sprain OR ankle trauma OR ankle injury	1	
National Guideline Clearinghouse	Ankle sprain	5	
New Zealand Guidelines	Ankle sprain OR ankle trauma OR ankle injury	0	
NICE guidelines	Ankle sprain OR ankle trauma OR ankle injury	0	
SIGN guidelines	Ankle sprain OR ankle trauma OR ankle injury	0	

APPENDIX 2. SEARCH STRATEGY FOR THERAPY

Appendix 2.1. Medline

Date	6-12-2011
Database (name + access ; e.g.: Medline OVID)	Medline
Search Strategy (attention, for PubMed, check « Details »)	#1 "ankle injuries"[MeSH Terms] OR ("ankle"[All Fields] AND "injuries"[All Fields]) OR "ankle injuries"[All Fields] OR ("ankle"[All Fields] AND "injury"[All Fields]) OR "ankle injury"[All Fields] **n = 11,406** AND #2 “randomized controlled trial”[pt]) OR “controlled clinical trial”[pt] OR randomized[All Fields] OR randomly[All Fields] OR trial[All Fields] OR groups[All Fields] **n = 2,037,482** AND #3 (“Ankle Injuries/therapy”[Mesh] NOT Ankle Injuries/surgery[Mesh]) OR treatment [tw]) OR (Physical Therapy Modalities[Mesh] OR “Physiotherapy”[tw] OR exercise therapy [Mesh] OR “exercise therapy” [tw] OR coordination[tw] OR mobilisation [tw] OR mobilization [tw] OR strengthening [tw] OR stabilisation [tw] OR stabilization [tw] OR proprioception [tw] OR rehabilitation [tw] OR balance [tw] OR cryotherapy[MeSH] OR cryotherapy[tw]) OR (Braces[Mesh] OR "ankle brace"[tw] OR orthotic devices [Mesh] OR “orthotic devices” [tw] OR insole*[tw] OR Casts, Surgical[Mesh] OR "surgical cast"[tw] OR Compression Bandages[Mesh] OR “compression bandage"[tw]) OR “pharmaceutical preparations”[Mesh] OR (“wound healing” [Mesh] OR “wound healing "[tw]) OR (“Directly observed therapy”[Mesh] OR “Directly observed therapy”[tw])

	OR (“secondary prevention” [MeSH] OR "secondary prevention"[tw]) **n = 3,722,004** #1 AND #2 AND #3 **n = 1,063** Limits: English, French, German, Dutch Publication Date from 2000/1/1 to 2011/12/06 **n = 668**

Appendix 2.2. Embase

Date	**21-11-2011**
Database (name + access ; e.g.: Medline OVID)	Embase
Search Strategy (attention, for PubMed, check « Details »)	#10 = #9 AND ([dutch]/lim OR [english]/lim OR [french]/lim OR [german]/lim) AND [embase]/lim AND [2000-2011]/py **n = 485** #9 = #1 AND #2 AND #8 **n = 499** #8 = #3 OR #4 OR #5 OR #6 OR #7 **n = 1,990,447** #7 physical AND 'medicine'/exp AND [embase]/lim AND [2000-2011]/py **n = 168,794** #6 balance AND impairment AND [embase]/lim AND [2000-2011]/py **n = 15,048** #5 motor AND 'coordination'/exp AND [embase]/lim AND [2000-2011]/py **n = 709** #4 secondary AND 'prevention'/exp AND [embase]/lim AND [2000-2011]/py **n = 21,684** #3 #3.22 = #3.1 OR #3.2 OR #3.3 OR #3.4 OR #3.5 OR #3.6 OR #3.7 OR #3.8 OR #3.9 OR #3.10 OR #3.11 OR #3.12 OR #3.13 OR #3.14 OR #3.15 OR #3.16 OR #3.17 OR #3.18 OR #3.19 OR #3.20 OR #3.21 **n = 1,840,187** #3.21 'wound healing'/exp AND [embase]/lim AND [2000-2011]/py #3.20 'movement therapy'/exp AND [embase]/lim AND [2000-2011]/py #3.19 'electrostimulation therapy'/exp AND [embase]/lim AND [2000-2011]/py #3.18 'drug therapy'/exp AND [embase]/lim AND [2000-2011]/py #3.17 'manipulative medicine'/exp AND [embase]/lim AND [2000-2011]/py #3.16 'rehabilitation'/exp AND [embase]/lim AND [2000-2011]/py #3.15 'rehabilitation research'/exp AND [embase]/lim AND [2000-2011]/py #3.14 'proprioception'/exp AND [embase]/lim AND [2000-2011]/py #3.13 'muscle training'/exp AND [embase]/lim AND [2000-2011]/py #3.12 'joint mobilization'/exp AND [embase]/lim AND [2000-2011]/py #3.11 'mobilization'/exp AND [embase]/lim AND [2000-2011]/py #3.10 'walking aid'/exp AND [embase]/lim AND [2000-2011]/py #3.9 'plaster cast'/exp AND [embase]/lim AND [2000-2011]/py

#3.8 'brace'/exp AND [embase]/lim AND [2000-2011]/py
#3.7 'convalescence'/exp AND [embase]/lim AND [2000-2011]/py
#3.6 'directly observed therapy'/exp AND [embase]/lim AND [2000-2011]/py
#3.5 'kinesiotherapy'/exp AND [embase]/lim AND [2000-2011]/py
#3.4 'orthotics'/exp AND [embase]/lim AND [2000-2011]/py
#3.3 'drug'/exp AND [embase]/lim AND [2000-2011]/py
#3.2 'compression bandage'/exp AND [embase]/lim AND [2000-2011]/py
#3.1 'physiotherapy'/exp AND [embase]/lim AND [2000-2011]/py

#2
#2.5 = #2.1 OR #2.2 OR #2.3 OR #2.4 **n = 4,276**
#2.4 'ankle lateral ligament'/exp AND [embase]/lim AND [2000-2011]/py
#2.3 'ankle instability'/exp AND [embase]/lim AND [2000-2011]/py
#2.2 'ankle injury'/exp AND [embase]/lim AND [2000-2011]/py
#2.1 'ankle sprain'/exp AND [embase]/lim AND [2000-2011]/py

#1
#1.7 = #1.1 OR #1.2 OR #1.3 OR #1.4 OR #1.5 OR #1.6 **n = 1,106,421**
#1.6 'practice guideline'/exp AND [embase]/lim AND [2000-2011]/py
#1.5 'meta analysis'/exp AND [embase]/lim AND [2000-2011]/py
#1.4 'randomized controlled trial'/exp AND [embase]/lim AND [2000-2011]/py
#1.3 'controlled clinical trial'/exp AND [embase]/lim AND [2000-2011]/py
#1.2 'review'/exp AND [embase]/lim AND [2000-2011]/py
#1.1 'systematic review'/exp AND [embase]/lim AND [2000-2011]/py

Appendix 2.3. Pedro

Date	12-12-2011
Database (name + access ; e.g.: Medline OVID)	Pedro
Search Strategy (attention, for PubMed, check « Details »)	Ankle sprain **n = 91** Ankle sprain AND systematic review since 2000 **n = 27** Ankle sprain AND practice guideline since 2000 **n = 2** Ankle sprain AND clinical trial since 2000 **n = 63** Lateral ankle injur* since 2000 **n = 34** Lateral ankle trauma since 2000 **n = 6** Lateral ligament complex since 2000 **n = 4**
Note	The last three search strategies delivered a few extra articles other than with the 'ankle sprain' search.

Appendix 2.4. CINAHL

Date	29-11-2011
Database (name + access ; e.g.: Medline OVID)	CINAHL
Search Strategy (attention, for PubMed, check « Details »)	TX ankle sprain OR TX ankle trauma OR TX ankle injury - Limiters - Published Date from: 20000101-20111131; Publication Type: Meta Analysis, Practice Guidelines, Randomized Controlled Trial, Review, Systematic Review; Language: Dutch, English, French, German Search modes - Boolean/Phrase **n = 131**

Appendix 2.5. Medion

Date	29-11-2011
Database (name + access ; e.g.: Medline OVID)	Medion
Search Strategy (attention, for PubMed, check « Details »)	Ankle **n = 5** Ankle sprain **n = 0** Ankle trauma **n = 0** Ankle injury **n = 0**

Appendix 2.6. Cochrane

Date	31-10-2011
Database (name + access ; e.g.: Medline OVID)	Cochrane
Search Strategy (attention, for PubMed, check « Details »)	"**ankle injury** in **Title, Abstract or Keywords** or **ankle sprain** in **Title, Abstract or Keywords** or **ankle trauma** in **Title, Abstract or Keywords** and **diagnosis** in **Title, Abstract or Keywords**, from 2000 to 2011 in **Cochrane Central Register of Controlled Trials**" Reviews: **n = 14** Clinical trials: **n = 339** "**ankle injury** in **Title, Abstract or Keywords** or **ankle sprain** in **Title, Abstract or Keywords** or **ankle trauma** in **Title, Abstract or Keywords** and **therapy** in **Title, Abstract or Keywords**, from 2000 to 2011 in **Cochrane Central Register of Controlled Trials**" Reviews: **n =15** Clinical trials: **n = 340**

Appendix 2.7. Guidelines

Date	31-10-2011		
Search engine	Search term	number	PICO
GIN guideline resource	Ankle sprain OR ankle trauma OR ankle injury	1	
National Guideline Clearinghouse	Ankle sprain	5	
New Zealand Guidelines	Ankle sprain OR ankle trauma OR ankle injury	0	
NICE guidelines	Ankle sprain OR ankle trauma OR ankle injury	0	
SIGN guidelines	Ankle sprain OR ankle trauma OR ankle injury	0	

APPENDIX 3. AMOUNT OF ARTICLES BY DATABASE

Appendix 3.1. Diagnosis

769 (embase) + 1565 (medline)= 2169 articles + 165 duplicates

2169 + 91 (Pedro ankle sprain)= 2260 (no duplicates)

2260 + 34 (Pedro ankle lateral injur*)= 2286 + 8 duplicates (26 new articles)

2286 + 6 (Pedro lateral ankle trauma)= 2288 + 4 duplicates (2 new articles)

2288 + 4 (Pedro lateral ligament complex) = 2288 + 4 duplicates (no new articles)

2288 + 131 (CINAHL) = 2364 + 55 duplicates (76 new articles)

2364 + 353 (Cochrane) = 2716 + 1 duplicate (352 new articles)

In this database, still 269 duplicates were identified and therefore excluded , bringing the total amount of articles to **2535**.

Appendix 3.2. Therapy

485 (embase) + 668 (medline)= 1090 + 63 duplicates

+ 91 (Pedro ankle sprain)= 1181 (no duplicates)

+ 34 (Pedro ankle lateral injur*)= 1196 + 19 duplicates (15 new articles)

+ 6 (Pedro lateral ankle trauma)= 1197 + 5 duplicates (1 new article)

+ 4 (Pedro lateral ligament complex) = 1197 + 4 duplicates (no new articles)

+ 131 (CINAHL) = 1285 + 43 duplicates (88 new articles)

+ 355 (Cochrane) = 1639 + 1 duplicate (354 new articles)

In this database, still 399 duplicates were identified and therefore excluded, bringing the total amount of articles to **1240**.

In addition 4 guidelines were found.

APPENDIX 4. QUALITY APPRAISAL FOR DIAGNOSIS

Appendix 4.1. Quality appraisal of systematic reviews

Author, year	Questions (AMSTAR)											
	1	2	3	4	5	6	7	8	9	10	11	
Bachmann, 2003	Y	Y	Y	Y	Y	Y	N	N	Y	N	Y	Moderate
Hubbard, 2008	Y	Can't answer	Y	Y	N	Y	Y	N	Not applicable	N	N	High
Seah, 2010	Y	N	N	Y	N	Y	N	N	Not applicable	N	N	High
Simpson, 2010	N	Can't answer	Y	Y	N	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	N	High
Smith, 2003	N	N	Y	N	N	N	N	N	Not applicable	N	N	High

1. Was an ''a priori'' design provided? The research question and inclusion criteria should be established before the conduct of the review.
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated, and where feasible, the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.
4. Was the status of publication (i.e., grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided.
6. Were the characteristics of the included studies provided? In an aggregated form, such as a table, data from the original studies should be provided on the participants, interventions, and outcomes. The ranges of characteristics in all the studies analyzed, e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.
7. Was the scientific quality of the included studies assessed and documented? ''A priori'' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo-controlled studies, or allocation concealment as inclusion criteria); for other types of studies, alternative items will be relevant.
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e., Chi-squared test for homogeneity, I2). If heterogeneity exists, a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e., is it sensible to combine?).
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).
11. Was the conflict of interest included? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.

Appendix 4.2. Quality appraisal of RCT's and other prospective studies for diagnosis

Author, year	Questions (QUADAS)															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Risk of bias	Comments
Blackham, 2008	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Mod	Voluntary Patients
Breitenseher, 1997	N	Y	unclear	Y	N	N	Y	Y	Y	Y	Y	Y	Y	unclear	High	Athletic patients, surgery in 15 patients
Broomhead, 2003	Y	Y	Y	Y	Y	Y	Y	Y	unclear	Y	Y	Y	Y	Y	Low	
Can, 2008	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low	Lack of test in several patients
Canagasabey, 2011	Y	Y	Y	Y	Y	Y	Y	Y	unclear	Y	N	Y	Y	Y	Low	Period after injury lacking
Derksen, 2007	Y	Y	Y	Y	Y	Y	Y	Y	unclear	Y	unclear	Y	Y	Y	Low	
Derksen, 2005	Y	Y	Y	Y	Y	Y	Y	Y	unclear	Y	unclear	Y	Y	Y	Low	
Dissmann, 2006	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low	12-16 year old included
Eggli, 2005	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	unclear	Y	Y	Y	Low	Period after injury lacking
Fiesseler, 2004	N	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Mod	
Glas, 2002	Y	Y	Y	Y	Y	Y	Y	Y	unclear	Y	Y	Y	N	Y	Low	
Guillodo, 2007	Y	Y	Y	N	N	N	Y	Y	Y	Y	unclear	Y	Y	Y	Mod	
Knudsen, 2010	Y	N	Y	Y	N	N	Y	Y	unclear	Y	unclear	Y	Y	Y	High	Children, No patient excluded

Leddy, 2002	Y	Y	Y	Y	N	N	Y	Y	unclear	Y	Y	Y	Y	Y	Mod	Children
Nikken, 2005	unclear	N	Y	Y	Y	Y	N	Y	Y	unclear	unclear	N	Y	Y	High	
Pijnenburg, 2002	Y	Y	Y	Y	Y	Y	Y	Y	unclear	Y	Y	Y	Y	Y	Low	
Spahn, 2004	N	N	Y	Y	Y	Y	Y	Y	Y	Y	unclear	Y	unclear	unclear	Mod	No fracture
Springer, 2000	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Mod	Military
Van Dijk, 1996	N	Y	Y	Y	Y	N	Y	N	Y	Y	unclear	Y	unclear	Y	Mod	No patient excluded
Van Riet, 2000	Y	Y	Y	N	N	N	Y	Y	N	Y	unclear	Y	Y	Y	High	
Wynn-Thomas, 2002	Y	Y	Y	Y	N	N	Y	Y	unclear	Y	N	Y	Y	Y	High	

1. Was the spectrum of patients representative of the patients who will receive the test in practice?
2. Were selection criteria clearly described?
3. Is the reference standard likely to correctly classify the target condition?
4. Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?
5. Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?
6. Did patients receive the same reference standard regardless of the index test result?
7. Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?
8. Was the execution of the index test described in sufficient detail to permit replication of the test?
9. Was the execution of the reference standard described in sufficient detail to permit its replication?
10. Were the index test results interpreted without knowledge of the results of the reference standard?
11. Were the reference standard results interpreted without knowledge of the results of the index test?
12. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?
13. Were uninterpretable/ intermediate test results reported?
14. Were withdrawals from the study explained?

Appendix 4.3. Quality appraisal of guidelines

AGREE II instrument for guidelines	WVVH			KNGF			VSG			Bussières		
	Appraiser 1	Appraiser 2	Total	Appraiser 1	Appraiser 2	Total	Appraiser 1	Appraiser 2	Total	Appraiser 1	Appraiser 2	Total
1. The overall objective(s) of the guideline is (are) specifically described.	2	1	3	7	7	14	7	7	14	7	7	14
2. The clinical question(s) covered by the guideline is (are) specifically described.	1	1	2	7	7	14	7	7	14	3	2	5
3. The patients to whom the guideline is meant to apply are specifically described.	2	3	5	5	6	11	7	7	14	5	6	11
4. The guideline development group includes individuals from all the relevant professional groups.	2	3	5	5	6	11	6	6	12	4	3	7
5. The patients' views and preferences have been sought.	1	1	2	1	1	2	2	2	4	3	2	5
6. The target users of the guideline are clearly defined.	3	3	6	7	7	14	7	7	14	6	7	13
7. The guideline has been piloted among target users.	3	2	5	6	7	13	6	6	12	5	5	10
8. Systematic methods were used to search for evidence.	1	2	3	2	2	4	7	7	14	2	2	4
9. The criteria for selecting the evidence are clearly described.	1	2	3	6	5	11	6	6	12	1	2	3
10. The methods used for formulating the recommendations are clearly described.	1	2	3	4	5	9	4	4	8	6	6	12
11. The health benefits, side effects and risks have been considered in formulating the recommendations.	3	4	7	5	5	10	6	6	12	5	5	10
12. There is an explicit link between the recommendations and the supporting evidence.	2	3	5	7	6	13	7	6	13	7	6	13
13. The guideline has been externally reviewed by experts prior to its publication.	2	3	5	5	6	11	3	2	5	6	7	13
14. A procedure for updating the guideline is provided.	1	1	2	7	6	13	7	7	14	5	5	10
15. The recommendations are specific and unambiguous.	5	5	10	7	6	13	7	7	14	6	7	13
16. The different options for management of the condition	5	5	10	6	6	12	6	6	12	5	6	11

are clearly presented.												
17. Key recommendations are easily identifiable.	5	5	10	7	7	14	6	7	13	5	6	11
18. The guideline is supported with tools for application.	5	4	9						0			0
19. The potential organisational barriers in applying the recommendations have been discussed.	2	2	4	7	6	13	5	6	11	7	6	13
20. The potential cost implications of applying the recommendations have been considered.	6	5	11									
21. The guideline presents key review criteria for monitoring and/or audit purposes.	1	1	2	6	5	11	1	1	2	1	1	2
22. The guideline is editorially independent from the funding body.	7	6	13	1	1	2	7	7	14	2	2	4
23. Conflicts of interest of guideline development members have been recorded.	3	1	4	7	7	14	7	7	14	7	7	14
Overall assessment	3	3	6	5	6	11	6	6	12	5	5	10
Strongly agree 7 - 6 - 5 - 4 - 3 - 2 - 1 - Strongly disagree												

AGREE score (%)	WVVH	KNGF	VSG	Bussières
Scope and Purpose	11.11	91.67	100.00	66.67
Stakeholder involvement	19.44	58.33	66.67	52.78
Methodology	17.71	70.83	77.08	61.46
Clarity and presentation	66.67	91.67	91.67	80.56
Applicability	37.50	83.33	37.50	45.83
Editorial independence	54.17	50.00	100.00	58.33

Strongly recommend		X	X	
Recommend (with provisos or alterations)	X			X
Would not recommend				

APPENDIX 5. QUALITY APPRAISAL FOR THERAPY

Appendix 5.1. Quality appraisal of systematic reviews

Systematic reviews	Questions (AMSTAR)											Risk of bias
Author, year	1	2	3	4	5	6	7	8	9	10	11	
Kemler 2011	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Low
Kerckhoffs 2002	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low
Kerckhoffs 2002	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low
Massey 2010	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low
Seah 2011	Y	N	N	Y	N	Y	N	N	NA	N	N	Moderate
Van den Bekerom 2011	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low
Van den Bekerom 2012	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low
Van Der Wees 2006	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Low
Van Rijn 2010	Y	N	Y	Y	N	Y	Y	Y	Y	N	Y	Moderate

1. Was an 'a priori' design provided?
2. Was there duplicate study selection and data extraction?
3. Was a comprehensive literature search performed?
4. Was the status of publication (i.e. grey literature) used as an inclusion criteria?
5. Was a list of studies (included and excluded) provided?
6. Were the characteristics of the included studies provided?
7. Was the scientific quality of the included studies assessed and documented?
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?
9. Were the methods used to combine the findings of studies appropriate?
10. Was the likelihood of publication bias assessed?
11. Was the conflict of interest included?

Appendix 5.2. Quality appraisal of RCTs

RCT	Questions (Dutch Cochrane Instrument)													Risk of bias
Author, year	1	2	3	4	5	6	6a	6b	7	7a	7b	8	9	
Ardevol 2002	Y	Y	N	N	U	Y			N			Y	Y	Moderate
Bleakley 2010	Y	Y	N	N	Y	Y			N		N	Y	Y	Moderate
Borromeo 1997	Y	U	Y	N	Y	Y			Y			Y	Y	Low
Cardenas-Estrada 2009	Y	Y	N	N	N	Y			Y			Y	Y	High
Costantino 2011	Y	Y	Y	Y	Y	Y			Y			Y	Y	Low
Coudreuse 2010	Y	Y	Y	Y	Y	N	Y		Y			Y	Y	Low
D'Anchise	Y	U	Y	N	Y	Y			Y			Y	Y	Moderate
Dalton 2006	Y	Y	Y	Y	U	N			Y			Y	Y	Low
Ekman 2002	Y	Y	Y	Y	Y	Y			Y			Y	Y	Low
Ekman 2006	Y	Y	Y	Y	Y	Y			Y			Y	Y	Low
Fotiadis 2011	Y	Y	N	N	Y	Y			Y			Y	Y	High
Hewitt 2007	Y	Y	Y	Y	Y	U			Y			Y	Y	Low
Hupperets 2009	Y	Y	N	N	Y	Y			N			Y	Y	Moderate
Kayali 2007	Y	U	Y	Y	U	Y			U			U	U	Moderate
Kerkhoffs 2004	Y	U	Y	U	U	N			Y			Y	Y	Low

Koll 2004	Y	U	Y	U	U	N		Y		Y	Y	Low
Kucera 2004	Y	U	Y	Y	U	N		Y		Y	Y	Low
Lamb 2009	Y	Y	Y	N	Y	Y		Y		Y	Y	Low
Lionberger 2011	Y	Y	Y	Y	U	N		Y		Y	Y	Low
Lyrtzis 2011	Y	U	Y	Y	Y	Y		Y		Y	Y	Low
Nadarajah 2006	Y	Y	Y	Y	Y	Y		Y		Y	Y	Low
Petrella 2007	Y	U	Y	U	U	Y		Y		Y	U	Low
Petrella 2004	Y	Y	Y	Y	Y	Y		Y		Y	Y	Low

1. Was de toewijzing van de interventie aan de patiënten gerandomiseerd?
2. Degene die patiënten in het onderzoek insluit hoort niet op de hoogte te zijn van de randomisatievolgorde. Was dit hier het geval?
3. Waren de patiënten geblindeerd voor de behandeling?
4. Waren de behandelaars geblindeerd voor de behandeling?
5. Waren de effectbeoordelaars geblindeerd voor de behandeling?
6. Waren de groepen aan het begin van de trial vergelijkbaar?

6a. Nee, maar in de analyse is hiervoor wel gecorrigeerd

6b. Nee, en in de analyse is hiervoor niet gecorrigeerd

7. Is van een voldoende proportie van alle ingesloten patiënten een volledige follow-up beschikbaar?

7a. Nee, een selectieve loss-to-follow-up is voldoende uitgesloten

7b. Nee, een selectieve loss-to-follow-up is niet voldoende uitgesloten

8. Zijn alle ingesloten patiënten geanalyseerd in de groep waarin ze waren gerandomiseerd?
9. Zijn de groepen, afgezien van de interventie, gelijk behandeld?

APPENDIX 6. EVIDENCE TABLES FOR DIAGNOSTIC STUDIES

Appendix 6.1. Evidence table for systematic review (excluding SR not used in this guideline because high risk of bias)

Reference	Publication date	Objective	Included studies	Last search	Patient	Intervention	Compare	Outcome	Data-extraction/ results	Authors conclusion	Risk of bias
Bachmann, 2003	2003	Systematic review with an aim to summarise the evidence on accuracy of the OAR.	27 RCTs (pooled for analysis): 1. Aginaga 1999 2. Auleley 1998 3. Kerr 1994 4. Lucchesi 1995. 5. Mann 1998 6. Papacostas 2001 7. Perry 1999 8. Singh-Ranger and Marathias 1999 9. Stiell1992 10. Stiell 1993 11. Stiell 1994 12. Yuen 2001 13. Chandra and Schafmayer 2001 14. Garces 2001 15. Glas 2002 16. Keogh 1998 17. Leddy 1998 18. Mc Bride 1997 19. Pigman 1994 20. Salt and Clancy 1997 21. Tay 1999 22. Verma 1996 23. Boutis 2001 24. Chande 1995 25. Karpas 2002 26. Libetta 1999 27. Plint 1999	2002	Adults and children (separated into 2 groups) and included if within 1 week after an acute ankle sprain	Ottawa Ankle Rules 3 subgroups: - assessment of the ankle - assessment of the mid-foot - assessment of the ankle and the mid-foot combined.	Radiography is treated as the reference standard but not all included studies used radiography.	Test sensitivities, specificities, likelihood ratios and /or standard errors.	High sensitivities of the OAR reported. Among all subgroup analysis the subgroup that received the highest specificity was the Group where OAR was applied within 48h of injury In this group sensitivity reached 99.6% (95%CI: 98.2-100) In studies of combined assessment sensitivity reached 96.4% (95%CI: 93.8-98.6) Low specificity of the OAR was reported. In studies with a prevalence of fractures below the 25th centile of all studies, specificities reached 47.9% (Interquartile range 42.3%-77.1%) In studies of combined assessment specificity reached 26.3% (Interquartile range 19.4-34.3)	Evidence supports the use of OAR as an accurate instrument for excluding fractures in ankle and mid-foot. The sensisitivity of the OAR is almost 100% and the specificity is modest. The use of the OAR should reduce the number of unnecessary radiographs by 30-40%	Moderate Quality assessment of the primary studies was not included Publication bias was not assessed

Appendix 6.2. Evidence table for primary studies

Reference	Publication date, study type	Objective	Patient	Intervention	Compare	Outcome	Data-extraction	Authors conclusion	Guideline authors conclusion
Blackham, J. E. J., Claridge, T., & Benger, J. R. (2008). Can patients apply the Ottawa ankle rules to themselves? Emergency Medicine Journal, 25(11): 750-751.	2008, case-control study	To determine whether patients with an ankle injury obtained the same results as clinicians when applying the Ottawa ankle rules to themselves.	Patients (> 15 years) presenting to the Emergency Department. N = 50	Participants were asked to examine their own ankle and to enter the results on the questionnaire before formal clinical assessment.	The patient was then seen by an emergency department clinician who was blind to the patient's assessment of his or her own injury.	The Kappa statistic was used to determine the level of agreement	All patients felt they needed a radiograph compared with 90% of clinicians. The Kappa scores for walking immediately was -0.32, for the malleolus lateralis 0.56 and for the malleolus medialis 0.45.	Poor interobserver agreement was found between patients and clinicians.	Not all patients received an X-ray as golden standard. Low risk of Bias
Breitenseher, M.J., Trattnig, S.,Kukla, C. et al. (1997). MRI versus lateral stress radiography in acute lateral ankle ligament injuries. Journal of Computer Assisted Tomography, 21(2): 280-285	1997 Prospective randomized study	To detect the extent of recent lateral ankle ligament inversion injuries	Athletically active patients (18-45 years old) N=60	MRI	Lateral stress radiography (talar tilt test) And Lesion saw during surgery repair in 15 patients	Complete lateral ankle ligament tears checked by surgery	MRI vs stess X-ray = poor agreement (kappa = 0.030, 95%CI:-0.120-0.178) MRI vs surgery: sensitivity = 74% and specificity = 100 %	Stress radiography tends to over- and underestimate the severity of lateral ligament trauma	Specific population, Intraoperative findings in a subgroup of 15 patients High risk of bias
Broomhead, A., & Stuart, P. (2003). Validation of the Ottawa Ankle Rules in Australia. Emerg Med (Fremantle), 15(2): 126-132.	2003, prospective cohort study	To validate the Ottawa rules following appropriate education in the use of the rules.	N = 366 (> 18 years)	Junior and senior physicians assessed the OAR.	All patients were X-rayed, irrespective of whether the OAR were positive or negative and were reported blinded from the OAR.	Sensitivity specificity, + and - predictive value.	Sensitivity 100% and specificity 15.8%. The positive predictive value was 18,7. The negative predictive value was 100.	The OAR had a sensitivity of 100% for ankle and midfoot fractures when used by both junior and senior physicians.	The ankle and foot injuries occurred in the previous 10 days. Good initial education program as standardization for the clinical assessment. Low risk of bias.
Can, U., Ruckert,	2008,	To examine the	Patients (> 18	A group of	All patients	Sensitivity and	All cases with a	This study	The researchers

Reference	Publication date, study type	Objective	Patient	Intervention	Compare	Outcome	Data-extraction	Authors conclusion	Guideline authors conclusion
R., Held, U., Buchmann, P., Platz, A., Bachmann, L. M. (2008). **Safety and efficiency of the Ottawa ankle rule in a Swiss population with ankle sprains. Swiss Medical Weekly, 138(19-20): 29**	prospective cohort study	accuracy and differences of accuracy between surgeons and non-surgeons of the Ottawa Ankle Rule (OAR).	years) presenting with an acute ankle sprain N = 359	surgeons and non-surgeons assessed the OAR.	underwent blinded radiographic assessment.	specificity.	fracture had a positive OAR result (sensitivity 100%) and of 218 patients without a fracture, the OAR was negative in 45 cases (specificity 21%). In the subgroup of patients assessed by surgeons, sensitivity was 100% and specificity was 32%. In the non-surgical group, sensitivity was also 100% but specificity was lower (17%).	produced similar results than those published previously in various other settings. The OAR is more difficult to judge properly by well-instructed non-surgical assessors.	failed to register the result of the OAR in 42 cases which might have caused selection bias, despite the fact that their results are quite similar from those from the literature. Moderate risk of bias
Canagasabey, M. D., Callaghan, M. J., Carley, S. (2011). **The sonographic Ottawa Foot and Ankle Rules study (the SOFAR study). Emerg Med J, 28(10): 838-840.**	2011, case-control study	To determine whether ultrasound can detect a bony injury of the foot and ankle in a typical adult population presenting to an emergency department.	Patients (> 16 year) presenting with a foot or ankle injury to an Emergency Department with positive OAR N = 110	An ultrasound scan (USS) was performed by an emergency department member on patients with positive Foot and Ankle Rules.	Radiographic reporting was conducted blind to USS findings.	The sensitivity, specificity, predictive value and likelihood.	The sensitivity of USS is 90.9%, and the specificity is 90.9%. The positive predictive value is 0.526. The negative predictive value is 0.989. The positive likelihood ratio is 10.00, and the negative likelihood ratio is 0.100.	These results indicate that diagnostic USS shows great potential for the assessment of foot and ankle fractures and that if ultrasonography was employed ahead of radiography in Ottawa Foot and Ankle Rules-positive patients, there would be a potential reduction in radiograph requests of approximately 80%.	The one single missed fracture with USS, was due to a limited scan protocol rather than to the impossibility to visualize the fracture. Rather small number of patients. Moderate risk of bias.

Reference	Publication date, study type	Objective	Patient	Intervention	Compare	Outcome	Data-extraction	Authors conclusion	Guideline authors conclusion
Derksen, R. J., Bakker, F. C., Geervliet, P. C., de Lange-de Klerk, E. S., Heilbron, E. A., Veenings, B., Haarman, H. J. (2005). **Diagnostic accuracy and reproducibility in the interpretation of Ottawa ankle and foot rules by specialized emergency nurses, American Journal of Emergency Medicine, 23: 725-729**	2005, prospective cohort study	To evaluate the diagnostic accuracy and reproducibility of specialized emergency nurses in assessing ankle sprains by applying the Ottawa Ankle Rules (OAR) and Ottawa Foot Rules (OFR).	N = 106	Each injury was randomized and blinded assessed by both a trained emergency nurse and an HO by means of the OAR and OFR.	Furthermore in all patients, radiography was performed. Finally, treatment was initiated by the HO on the basis of his/her own findings and the accompanying X-ray	The diagnostic accuracy for the application of OAR and OFR was calculated for both groups and was compared using z statistics. Furthermore, from the paired results, reproducibility was calculated using Kappa (k)statistics.	The sensitivity for the SEN group was 0.93 compared with 0.93 for the HO group (no significance [ns]). The specificity of the nurses was 0.49 compared with 0.39 for the doctors (ns). The positive predictive value for the SEN group was 0.22 compared with 0.19 for the HO group (ns). The negative predictive value for the nurses was 0.98 compared with 0.97 for the doctors (ns). The interobserver agreement for the OAR and OFR subsets was j = 0.38 for the lateral malleolus; j = 0.30, medial malleolus; j = 0.50, navicular; j = 0.45, metatarsal V base; and j = 0.43, weight-bearing. The overall interobserver agreement for the OAR was j = 0.41 and j = 0.77 for the OFR.	Specialized emergency nurses are able to assess ankle and foot injuries in an accurate manner with regard to the detection of acute fractures after a short, inexpensive course.	The possibility exists that, without the standard radiography and when having to suffer the clinical consequences of their decision, nurses (and also house officers) could act somewhat more cautiously. Low risk of bias.
Derksen, R. J., Bakker, F. C., de	2007, a randomized	To compare the accuracy of	242 patients (18 - 65 years) were	SENs and HOs performed the	After one week radiographs	Sensitivity, specificity,	The sensitivity of SENs was 0.94	Specialized emergency	Patients received an X-

Reference	Publication date, study type	Objective	Patient	Intervention	Compare	Outcome	Data-extraction	Authors conclusion	Guideline authors conclusion
Lange-de Klerk, E. S. M., Spaans, I. M., Heilbron, E. A., Veenings, B., & Haarman, H. J. T. M. (2007). Specialized emergency nurses treating ankle and foot injuries: a randomized controlled trial, American Journal of Emergency Medicine, 25: 144-151.	controlled trial	specialized emergency nurses to the standard care provided by house officers in assessing and treating ankle and foot injuries.	assessed by the SEN and 233 (18-65 years) by the HO.	same assessment and treatment algorithm.	were made of all injuries that were not radiographed earlier, as part of the gold standard.	positive and negative predictive values.	compared with 0.78 of HOs. Specificity was 0.94 for SENs compared with 0.95 for HOs. The delivered care by SENs was found to be significantly better and the median waiting time at the ED was significantly reduced (21 minutes for SENs vs 32 minutes for HOs).	nurses are capable of assessing and treating ankle/foot injuries accurately with excellent patient satisfaction and with a reduction of waiting times.	ray one week after the examination in the emergency department. Low risk of bias.
Dissmann, P. D., & Han, K. H. (2006). The tuning fork test - A useful tool for improving specificity in "Ottawa positive" patients after ankle inversion injury. Emergency Medicine Journal, 23(10): 788-790.	2006, prospective cohort study	To determine the suitability of tuning fork testing in combination with existing Ottawa guidance for increasing the specificity in detecting fractures of the lateral malleolus.	Patients (> 12 years) presenting to the Emergency Department. N = 50	A single trained investigator examined all patients with already ''Ottawa positive'' findings for possible lateral malleolus injury by applying a tuning fork (C° 128 Hz).	The tuning fork test findings were compared with formal reports of plain ankle radiographs using simple cross-table analysis.	The sensitivity, specificity and likelihood of the tuning fork test.	Sensitivity and specificity were 100% and 61% for tuning fork testing on the TLM, and 100% and 95% for testing on the DFS. Diagnostic accuracy was recorded as 65% and 96%, respectively. The associated positive likelihood ratios were 2.59 for the TLM and for the DFS, with negative likelihood ratios of 0 and 0, respectively 95% CIs for the negative likelihood ratios could not be calculated from the study data.	This study suggests that additional tuning fork testing of ''Ottawa positive'' patients may lead to a marked reduction in ankle radiographs.	One single trained investigator - Already Ottawa positive findings. Low risk of bias.
Eggli, S., Sclabas, G. M.,	2005, prospective	To determine whether a new	Consecutive patients were	All patients were clinically	Afterward, standardized	The sensitivity	The Bernese ankle test	Compared with the original	The clinical examination was

Reference	Publication date, study type	Objective	Patient	Intervention	Compare	Outcome	Data-extraction	Authors conclusion	Guideline authors conclusion
Zimmermann, H., & Exadaktylos, A. K. (2005). The Bernese ankle rules: a fast, reliable test after low-energy, supination-type malleolar and midfoot trauma. J Trauma, 59(5), 1268-127	cohort study	indirect stress technique could increase the specificity of the Ottawa Rules.	evaluated in a prospective manner N=354	investigated by the same five permanent senior medical residents	anteroposterior and lateral radiographs of the ankle and an anteroposterior and oblique radiograph of the midfoot were obtained.	and specificity.	produced a sensitivity of 100% and a specificity of 91%.	Ottawa ankle rules, the number of false-positive findings could be significantly reduced, resulting in a reduction of 84% in radiographs after low-energy, supination- type trauma ankle and midfoot trauma.	based on three consecutive steps: indirect fibular stress, direct medial malleolar stress, and compression stress of the mid- and hindfoot. Low risk of bias.
Fiesseler, F., Szucs, P., Kec, R., & Richman, P. B. (2004). Can nurses appropriately interpret the Ottawa Ankle Rule? Am J Emerg Med, 22(3): 145-148.	2004, prospective cohort study	To determine if emergency department triage nurses could appropriately interpret the Ottawa Ankle Rules (OAR).	Patients (> 17 years) presenting to an emergency department. N = 103	Each patient received a physical examination of the ankle, including the OAR. Subsequently, nurses ordered ankle radiographs at their discretion by applying the OAR.	Physicians could add a radiograph request based on his or her interpretation of the OAR, if not previously ordered by a nurse.	Sensitivity, specificity, negative predictive value, and positive predictive value were calculated as appropriate. Kappa (k) values were calculated to assess interobserver agreement (IOA).	IOA between nurses and physicians was moderate for overall interpretation of OAR (kappa 0.44). IOA (kappa) for each criterion varied from (1) moderate for fifth metatarsal pain (0.56), posterior malleolar pain (0.44), medial malleolar pain (0.40), and weight bearing with foot pain (0.48); to (2) fair for weight bearing with ankle pain (0.32) and navicular pain (0.21). Sensitivity of the nurse's interpretation of OAR for fracture was 92%, specificity 36%, negative	Nurses showed only a moderate ability to interpret the overall OAR for ordering of X-rays. Nurses' understanding of the individual criterion were variable. Sensitivity between nurses and physicians was similar. Triage nurses should only use these rules to determine the need for radiographs with the appropriate physician supervision/ backup.	Those who did not have a radiographic study answered a structural telephone interview 1 to 2 weeks after their ED visit. Moderate risk of bias.

Reference	Publication date, study type	Objective	Patient	Intervention	Compare	Outcome	Data-extraction	Authors conclusion	Guideline authors conclusion
							predictive value 90%, and positive predictive value 32%. Sensitivity of the EP's utilization of the OAR for fracture was 92%, specificity 47% with a negative predictive value 94%, and a positive predictive value 38%.		
Glas, A. S., Pijnenburg, B. A., Lijmer, J. G., Bogaard, K., de, R. M., Keeman, J. N., Bossuyt, P. M. (2002). Comparison of diagnostic decision rules and structured data collection in assessment of acute ankle injury. CMAJ, 166(6):727-33.	2002, prospective cohort study	To compare the diagnostic performance in ruling out fractures by 2 decision rules (OAR and Leiden ankle rules) and physician's judgment based using structured data collection	Patients (>18 years) presenting at the ED with acute ankle injury N=647	For each case: - history taking and physical examination - OAR -Leiden ankle rules - Radiography	The decisions to perform a radiography based on the OAR, Leiden ankle rules and clinical judgment based on the physical examination were compared to each other and compared to the fractures detected by RX.	Accuracy of each intervention in detecting fractures in terms of specificity, sensitivity and AUC and significant fractures missed	Sensitivity was -89% for OAR -80% for Leiden ankle rules -82% for physician's judgment Specificity was -26% for OAR -59% for Leiden ankle rules -68% for physician's judgment AUC was -69% for OAR -77% for Leiden ankle rules -80% for physician's judgment Significant fractures missed were -1 for OAR -5 for Leiden ankle rules -1 for physician's	Physician's judgment, aided by structured data collection, was similar to existing international and local decision rules in terms of sensitivity in identifying cases requiring radiography examinations for patients with ankle trauma	Well-designed study with some minor limitations as bias because the physicians knew in advantage that radiographs would be obtained regardless of their clinical judgment. Low risk of bias.

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							judgment		
Guillodo, Y., Riban, P., Guennoc, X., Dubrana, F., Saraux, A. (2007). Usefulness of ultrasonographic detection of talocrural effusion in ankle sprains. J Ultrasound Med, 26(6): 831-836.	2007, prospective cohort study	To evaluate the prevalence of ultrasonographic talocrural joint effusion in moderate and severe ankle sprains and to determine the cause of effusion by magnetic resonance	Patients (>18 years) with moderate to severe ankle (grade 2 and 3) sprains who presented at the ED of 3 hospitals in France N=110	Ultrasonography to detect talocrural joint effusion	No comparison when no effusion, MRI (when ultrasound test was positive) to detect ligamentous injury	Prevalence of joint effusion (by ultrasound) and cause of the effusion (by MRI)	-talocrural effusion in 40patients (36%) by ultrasound (effusion confirmed by MRI in all patients) -39 patients had damage to the anterior talofibular ligament of which 5 also had damage to the calcaneofibular ligament and 14 had cartilage damage or a bone contusion -1 patient had a subluxation of the peroneus brevis tendon and a contusion of the talus	Talocrural effusion on ultrasonography may identify patients with severe ankle sprains. Magnetic resonance imaging should be performed in patients with talocrural effusion. Further work is needed to evaluate the usefulness of MRI in acute ankle sprains without talocrural effusion.	A limitation of this study was the lack of a comparison with a golden standard. Patients only received an MRI when effusion was detected by ultrasonography. So, no conclusions can be drawn if there is damage to structures when there is no effusion. The range of days between the ultrasound and the MRI was 8 days which also seems a bit much. Moderate risk of bias.
Knudsen, R., Vijdea, R., & Damborg, F. (2010). **Validation of the Ottawa ankle rules in a Danish emergency department. Dan Med Bull, 57(5): A4142.**	2010, prospective cohort study	To provide evidence about the use of the OAR as a method for prediction of significant fractures in a Danish clinical setting	Patients (all ages) admitted to the ED with an acute blunt ankle or midfoot injury N= 882 patients control group N=1014 intervention group	OAR in the intervention group	clinical evaluation without OAR in the control group	Accuracy of the OAR compared to the accuracy of the clinical evaluation without OAR	- Less radiographs with OAR (57%) compared with clinical evaluation (62%) - Higher sensitivity with OAR (99%) compared with clinical evaluation (97%) - Higher specificity with OAR (51%) compared to clinical evaluation	The OAR may reduce the number of X-rays and possibly also save costs and time if implemented in Denmark.	Some limitations were seen in the design of the trial, since the intervention group and the control group were two different populations and no standard reference was conducted in the groups. Selection criteria

Reference	Publication date, study type	Objective	Patient	Intervention	Compare	Outcome	Data-extraction	Authors conclusion	Guideline authors conclusion
							(44%)		of the patients were also not described clearly. High risk of bias.
Leddy, J. J., Kesari, A., & Smolinski, R. J. (2002). Implementation of the Ottawa ankle rule in a university sports medicine center. Med Sci Sports Exerc, 34(1): 57-62	2002, prospective cohort study	To implement the OAR with a modification to improve specificity for identifying malleolar fractures (Buffalo rule)	Patients (all ages) presenting to a university sports medicine walk-in clinic with acute ankle/midfoot injury N=217	The modified OAR	regular OAR, a radiography was only taken when the OAR was positive, a telephone follow-up was performed in the patients without radiography	Accuracy of the modified OAR in terms of specificity and sensitivity	100% sensitivity, 45% specificity for malleolar fracture, 35% for midfoot fracture No significant improvement of the modified OAR compared to the regular OAR	The OAR reduced radiography in acute ankle/midfoot injury and saved money in relatively younger patients in the outpatient sports urgent care setting without missing any clinically significant fractures. The specificity of the modified OAR was not a significant improvement over the OAR malleolar rule.	A limitation of this study was the lack of a comparison of the diagnosis with a golden standard (radiography) since in this study the modified OAR were compared with the regular OAR and only those with a positive OAR were send for radiography. Next to this, 11% of the patients were children (≤17 years). Moderate risk of bias.
Nikken, J. (2005). Acute ankle trauma: value of a short dedicated extremity MR imaging examination in prediction of need for treatment. Radiology,	2005, prospective randomized controlled study	To assess the predictive value of a short MR imaging examination to identify need for further treatment	Patients (all ages) referred by traumatologist, orthopedic surgeon, or emergency physician, with a recent ankle injury (within 7 days of trauma) N=107	Radiography, MR imaging examination	Group with radiography, and group with radiography and MR	Univariable and multivariable regression analysis, with four models for prediction of treatment	Age (OR=1.02), radiographic (OR=7.92) and MR imaging results (OR=2.42) were predictive of treatment. In the multivariable analysis, positive or uncertain MR imaging results (OR=2.61)	Limited MR imaging examination has additional predictive value for identification of who needs treatment , but does not help in the identification of those who can be discharged	It was unclear how the patient population was defined. They state that they only included patients who needed radiography but no criteria were given. Furthermore the

Reference	Publication date, study type	Objective	Patient	Intervention	Compare	Outcome	Data-extraction	Authors conclusion	Guideline authors conclusion
234(1):134-142							contributed significantly to prediction of treatment. Negative MR imaging results did not contribute significantly (OR=0.66)	without follow-up	reference test was not independent of the index test and there is the possible problem of availability of MR. Results show limited evidence for the use of MR in the evaluation of an ankle sprain. High risk of bias.
Pijnenburg, A. (2001). Radiography in acute ankle injuries: the Ottawa ankle rules versus local diagnostic decision rules. Annals of Emergency Medicine, 39(6):599-604	2001, prospective cohort study	To evaluate the validation and accuracy of the OAR and to compare the OAR to local decision rules.	Patients (>18) presenting to ED with acute ankle injury N=647	OAR, Leiden Ankle Rules and Utrecht Ankle Rules	Radiography	Sensitivity, specificity, reduction of radiographs, ROC curves and area under ROC curves	OAR, Leiden Ankle Rules and Utrecht Ankle Rules had a sensitivity of respectively 98%, 88% and 59%. Potential savings in radiographs was respectively 24%, 54% and 82%. Higher score for the area under ROC curve for Leiden (AUC 0.84) and Utrecht (AUC 0.83) than OAR (AUC 0.76).	The higher sensitivity of the OAR makes these more suitable for implementation in the Netherlands	The local ankle rules have a higher reduction of radiographs, but they potentially miss significant ankle fractures. Therefore, the OAR are more suitable. Low risk of bias.
Spahn, G. (2004). The ankle meter: an instrument for evaluation of anterior talar drawer in ankle sprain. Knee Surg Sports Traumatol Arthrose. 12(4):338-342	2004, case-control study	To produce an instrument for measurement of the anterior drawer (ATD) of the ankle in order to determine joint instability	- Patients (all ages) presenting at a clinic with an acute lateral ankle sprain N= 45 -Healthy control group N=38	Assessment of anterior drawer test using the ankle meter	Stress radiography	1. Results of ATD measurement in the control group 2. Validity of the ADT measurement 3.Correlation between ATD	1. No significant differences in left or right ankles, significantly higher for female subjects 2. No significant difference between control group and uninjured ankle of	It is possible to measure the ATD using a simple tool and without high cost, which allows an assessment of the severity of the ankle sprain and a	Test is performed within 48 hours after ankle sprains which raises the question of applicability in the acute stadium, although this study states no

Reference	Publication date, study type	Objective	Patient	Intervention	Compare	Outcome	Data-extraction	Authors conclusion	Guideline authors conclusion
						measuring and stress radiography 4.Influence of pain on the results of the ATD test	patients. Significant difference in the ankles after sprain 3. Significant correlation between ATD clinical measurement and ATD stress radiography. (R=0.91, p<0.05) 4. No correlation with the results of ATD in clinical (R=0.12) or radiological (R=0.15)	classification	influence of pain. Moderate risk of bias.
Springer, B. (2000). A prospective study of modified Ottawa ankle rules in a military population. The American Journal of Sports Medicine), 28(6):864-868	2000, prospective cohort study	To determine the potential reduction of the need for radiographs using modified OAR and interobserver agreement between physical therapists and orthopedic surgeons	Military Academy cadets (18-25y) presenting at walk-in clinic with an acute ankle or midfoot injury (within previous 10 days- N=156	Modified OAR (''Buffalo'' rule)	Radiography, blinded to modified OAR results	Sensitivity, specificity, predictive values	-Therapists: for ankle and foot respectively 100% and 100% sensitivity, 40% and 79% specificity , pos predictive value 0.062 and 0.086, negative predictive value 1.0and 1.0 -Orthopedic Surgeon: for ankle and foot respectively 100% and 100% sensitivity, 46% and 79% specificity , pos predictive value 0.069 and 0.086, negative predictive value 1.0 and 1.0	High accuracy of modified OAR results and Physical therapists are able, with extra training, to perform the modified OAR	Results based on a specific population which makes it difficult to extrapolate. Moderate risk of bias.

Reference	Publication date, study type	Objective	Patient	Intervention	Compare	Outcome	Data-extraction	Authors conclusion	Guideline authors conclusion
							- Interobserver agreement was high (kappa = 0.82)		
Van Dijk, N., Mol, B.W., Lim, L.S et al. Diagnosis of ligament rupture of the ankle joint. Acta Orthop Scand, 67(6):566-570.	1996, Prospective cohort study	To enhance the reliability of physical diagnosis.	Patients 18-40 years old presented in ED within 2 days after acute inversion injury. N=160	- Physical examination within 48h after trauma; - Arthrogram within 48h after trauma - Delayed examination 5 days later; - Stress radiography 5 days after trauma - US for 74 consecutive patients	Intraoperative findings for 135 patients Clinical diagnosis at follow up at 6 month for the non-operatively treated group (25 patients).	Specificity and sensitivity	Delayed physical examination at 5 days after the injury has the best result and provides a sensitivity = 96% and a specificity = 84% for the detection of a ligament rupture	Delayed physical examination at 5 days after the injury led to the highest overall sensitivity and specificity for the detection of ligament rupture. Additional diagnostic procedures, at a considerable cost, yielded little additional information.	The results concern examination performed by experienced investigator Moderate risk of bias
van Riet, Y. E., van der Schouw, Y. T., van der Werken, C. (2000). **Fewer X-rays while maintaining quality of clinical care using clinical protocols for physical diagnostics in ankle injuries. Ned Tijdschr Geneesk, 144(5):224-28**	2000, prospective cohort study	To determine whether it is possible to decrease the number of X-rays in acute ankle injury while keeping the health care constant, using a scoring system	Patient with an acute ankle injury who presented in the ED in an academic hospital in the Netherlands N=514	-Leiden ankle scoring system -Radiography in case Leiden score ≥8 (N=81)	No comparison, but telephone follow-up at six weeks	Specificity and sensitivity and reduction in the amount of radiographies	-83% sensitivity -88% specificity -60% reductions in amount of radiographies	Radiological examination in patients with acute ankle complaints was reduced while health care remained almost constant. The decision to perform radiography when the score was ≥8 was kept to be used in the future.	A limitation of this study was the lack of a comparison with a golden standard (radiography). Only those with a score ≥8 were send for radiography. Next to this, in this prospective study a telephone follow-up was performed after 6 weeks. The authors tried to compare their Leiden scoring system with the OAR, but did not

Reference	Publication date, study type	Objective	Patient	Intervention	Compare	Outcome	Data-extraction	Authors conclusion	Guideline authors conclusion
									take all items of the OAR into consideration and their comparison with the OAR was therefore not valid in our opinion. High risk of bias.
Wynn-Thomas, S. (2002). **The Ottawa ankle rules for the use of diagnostic X-ray in after hours medical centres in New Zealand, New Zealand Medical Journal, 115(1162):U184**	2002, prospective cohort study	To measure baseline use of OAR, validate the OAR and explore the impact on X-rays in a primary care, after hours medical centre setting	Patients (>18years) presenting to an after hours medical centre with acute ankle/midfoot injury N= 216	OAR	Radiography, Phone call follow-up	Survey, sensitivity , specificity, predictive value and reduction of X-rays	- 100% sensitivity, - 47% specificity, - 12% positive predictive value - reduction X-ray utilization by 16%	OAR are valid in a New Zealand primary care setting with a slight reduction of X-ray (less than in previous studies). The authors emphasize that the definition of clinically insignificant fractures is a grey area that deserves consideration	A limitation for this study is that not every patient received the reference test (X-ray), but some were monitored by phone call follow-up. Furthermore the research team was not blinded the OAR result High risk of bias.

APPENDIX 7. EVIDENCE TABLES FOR THERAPY STUDIES

Appendix 7.1. Evidence tables for systematic reviews

Reference	Publication date	Objective	Included studies	Last search	Patient	Intervention	Compare	Outcome	Data-extraction/ results	Authors conclusion	Risk of bias
Kemler, E., Ingrid, Backx, F., & Niek. (2011). A systematic review on the treatment of acute ankle sprain: brace versus other functional treatment types. Sports Medicine, 41(3), 185-197.	2011	Systematic review to evaluate the effectiveness of ankle braces as treatment for acute ankle sprains compared with other types of functional treatments	RCTs: 1. Beynnon, 2006 2. Boyce, 2005 3. Dettori, 1994 4. Karlsson, 1996 5. Lamb, 2009 6. Leanderson and Wredmark, 1995 7. Neumann, 1994 8. Twellaar, 1993	April 2009	Individuals (sports participation as well as non-sports participation) with an acute ankle sprain (grade I to III) (age from 9 to 61 years)	Use of an ankle brace as primary treatment	Control interventions including any type of functional treatment as elastic wrap, tape, …	Re-injury, symptoms (pain, swelling, instability), functional outcomes and/or time to resumption of sports, daily activities and/or work	- Recurrent sprains: no evidence - Residual complaints (pain, swelling, instability): no evidence - Functional outcome: strong evidence in favor of treatment with brace - Time to resumption to sports, daily activities and work: no evidence to support the use of braces	This systematic review based on 7 high quality studies and 1 low quality study found evidence for a better functional outcome when using a brace and treatment with ankle braces did not show any unfavorable effects. Compared with other functional treatments, ankle braces are not less effective in the treatment of acute ankle sprains.	Low
Kerkhoffs Gino, M. M. J., Rowe Brian, H., Assendelft Willem, J. J., Kelly Karen, D., Struijs Peter, A. A., & van Dijk, C. N. (2002). Immobilisation and functional treatment for	2002	Systematic review to assess the effectiveness methods of immobilization for acute lateral ligament injury and to compare the immobilisation with functional treatment strategies	RCTs: 1. Avci 1998 2. Brakenbury 1983 3. Brooks 1981 4. Brostrom 1966 5. Caro 1964 6. Cetti 1984 7. Dettori 1994 8. Eiff 1994 9. Freeman	2000	Skeletally mature individuals with an acute injury to the lateral ligament complex of the ankle (or population with children if amount children was small (<10%))	Immobilisation either by plaster cast or special boots	a) physiotherapy b) functional interventions (including elastic bandage, softcast, tape or orthosis with associated	Return to sports and work, pain, swelling, subjective and objective instability, recurrent injury, ankle mobility/range of motion (ROM) and patient satisfaction.	<u>Immobilisation versus functional treatment</u> - Return to sports and work: period was significantly shorter for functional treatment - Pain: no difference between functional treatment and immobilization - Swelling: short term: significantly in	Good review which shows that no outcome measures favours immobilisation as a treatment of choice. Functional treatment seems a more appropriate treatment and should be encouraged.	Low

Reference	Publication date	Objective	Included studies	Last search	Patient	Intervention	Compare	Outcome	Data-extraction/ results	Authors conclusion	Risk of bias
acute lateral ankle ligament injuries in adults. Cochrane Database of Systematic Reviews, (3).			1965 10. Gronmark 1980 11. Hedges 1980 12. Klein 1991 13. Konradsen 1991 14. Korkala 1987 15. Lind 1984 16. Milford 1990 17. Moller-Larsen 1988 18. Munk 1995 19. Regis 1995 20. Roycroft 1983 21. Sommer 1993				coordination training) c) non-intervention	Grouped in short-term (within 6 weeks of randomization), intermediate-term (6 weeks – 1 year), long-term (more than 1 year, not reported since not addressed in this guideline)	favor of functional treatment Intermediate: no differences - Subjective instability or giving way: no differences - Objective instability: no differences - Recurrent sprain: no differences - ROM: in favor of functional treatment - Satisfaction: in favor of functional treatment <u>Immobilisation versus physiotherapy</u>: no evidence <u>Different types of immobilization</u>: In favor of semi-rigid compared to rigid cast in terms of return to work <u>Immobilisation versus no treatment</u>: No evidence		
Kerkhoffs Gino, M. M. J., Struijs Peter, A. A., Marti Rene, K., Assendelft Willem, J. J., Blankevoort, L., & van Dijk, C. N. (2002).	2002	Systematic review to assess different functional treatment strategies for acute lateral ankle ligament injuries in adults	RCTs: 1. Allen 1985 2. Dettori 1994 3. Jongen 1992 4. Karlsson 1997 5. Leanderson 1995 6. Pasila 1975	2002	Young to middle aged adults who had an acute injury to the lateral ligament complex of the ankle	• elastic bandage/ stocking, • adhesive and elastic athletic tape, • lace-up ankle support, • semi-rigid ankle support	Comparing one treatment with another.	1. Return to sports, 2. Return to work, 3. Pain, 4. Swelling, 5. Subjective instability, 6. Objective instability,	1. Lace-up ankle support had significantly better results for persistent swelling at short-term follow up when compared with semi-rigid ankle support, elastic bandage and to tape.	Definitive conclusions are hampered by the variety of treatments used, and the inconsistency of reported follow-up times. The most effective treatment, both clinically and in	Low

Reference	Publication date	Objective	Included studies	Last search	Patient	Intervention	Compare	Outcome	Data-extraction/ results	Authors conclusion	Risk of bias
Different functional treatment strategies for acute lateral ankle ligament injuries in adults. Cochrane Database of Systematic Reviews, (3).			7. Sommer 1993 8. Twellaar 1993 9. Zeegers 1995					7. Recurrent injury, 8. Ankle mobility / range of motion, 9. Complications, 10. Patient satisfaction	2. Use of a semi-rigid ankle support resulted in a significantly shorter time to return to work when compared with an elastic bandage, 3. Tape treatment resulted in significantly more complications, the majority being skin irritations, when compared with treatment with an elastic bandage.	costs, is unclear from currently available randomised trials	
Massey, T. Derry, S. Moore, RA. McQuay, HJ. (2012) Topical NSAIDs for acute pain in adults (Review) Cochrane Database of Systematic Reviews, (3).	2010	To review the evidence from double-blind RCTs on the efficacy and safety of topical NSAIDs in acute pain resulting from strains, sprains or sports or over-use type injuries.	RCTs: 1.Airaksinen 1993 2.Akermark 1990 3.Aoki 1984 4.Auclair 1989 5.Billigmann 1996 6.Campbell 1994 7.Chatterjee 1997 8.Curioni 1985 9.Diebshlag 1990 10.Dreiser 1988 11.Dreiser 1989 12.Dreiser 1990 13.Dreiser 1994 14. Fioravanti 1990	Dec 2009	Adult patients with acute (<48 hrs) pain of at least moderate intensity from sprains and strains or sports injuries	Topical NSAIDs	Placebo or active treatments such as oral NSAIDs or other formulations of the same topical NSAID)	Primary outcomes: "Clinical success": 50% reduction in pain or equivalent measure Secondary outcome: Adverse events	For all topical NSAIs (pooled data) versus placebo the NNT to obtain clinical success was 4,5 (3,9-5,3) during 6-14 days. Adverse events were generally limited to mild skin reactions. The available data was not enough to compare individual topical NSAIDs with each other or oral formulations of the same NSAIDs	Topical NSAIDs are effective at reducing acute pain from sprains and strains and offer a better tolerability profile than oral NSAIDs	Low

Reference	Publication date	Objective	Included studies	Last search	Patient	Intervention	Compare	Outcome	Data-extraction/ results	Authors conclusion	Risk of bias
			15.Fijimaki 1985 16.Gallacchi 1990 17.Governali 1995 18.Gualdi 1987 19.Haig 1986 20.Hofman 2000 21.Hosie 1993 22.Jenoure 1997 23.Joussellin 2003 24.julien 1989 25.Kockelbergh 1985 26.Linde 1985 27.Machen 2002 28.Mahler 2003 29.Mazieres 2005 (a) 30.Mazieres (b) 31. McLatchie 1989 32.Morris 1991 33.Noret 1987 34.Parrini 1992 35.Picchio 1981 36.Predel 2004 37.Ramesh 1983 38.Rowbotham 2003 39.Russell								

Reference	Publication date	Objective	Included studies	Last search	Patient	Intervention	Compare	Outcome	Data-extraction/ results	Authors conclusion	Risk of bias
			1991 40 Sanguinetti 1989 41.Sinneger 1981 42.Spacca 2005 43.Sugioka 1984 44.Thorling 1990 45.Tonutti 1994 46.Vecchiet 1989 47.Whitefield 2002								
Seah, R., & Mani-Babu, S. (2011). Managing ankle sprains in primary care: what is best practice? A systematic review of the last 10 years of evidence. British Medical Bulletin; 97,105-135.	2011	Best available evidence for managing ankle injuries in the community	Guidelines, systematic reviews or meta-analysis, RCTs, cohort studies, case control studies, cross-sectional studies: 20 selected articles	Dec 2009	Patients ≥ 18years with acute and/or chronic (>6weeks) ankle sprains occurring within the primary care/ community/ general practice or urgent/emergency care setting	- Conservative treatment -Interventional treatment -recurrence prevention	Comparisons with other treatments	Patient oriented evidence: Length of stay, recurrence and time of return to work or sport	-For interventional treatment: surgery leads to increased joint stability -For recurrence prevention: beneficial effect of ankle support in form of semi-rigid orthosis or Aircast brace	Although some minor limitations in the literature search and the critical appraisal, several high level articles were reviewed and conclusions are drawn on a well documented base.	Moderate
van den Bekerom Mp Fau - Struijs, P. A. A., L. Struijs Pa Fau - Blankevoort, et al. (2012). "What is the	2012	To analyze the effectiveness of applying rest, ice, compression, and elevation (RICE) therapy begun within 72	11 RCTs 1.Green 2001 2. Karlsson 1996 3. Brooks 1981 4. Eisenhart 2003 5. Bleakley	July-Aug 2010	Adults with acute ankle sprains and symptoms of swelling and pain after an inversion trauma	Rest, Ice, Compression and elevation (RICE therapy) Items were assessed separately	Rest versus mobilisation Ice versus no ice Compression versus no	Pain, ROM, Return to work, return to sport, complications, side-effects and patient satisfaction	Rest vs mobilisation: Some type of immidiate posttraumatic mobilisation is benefecial for acute ankle sprains Ice vs no ice: The evidence to	Insufficient evidence is available from randomized controlled trials to determine the relative effectiveness of RICE therapy for	Low

Reference	Publication date	Objective	Included studies	Last search	Patient	Intervention	Compare	Outcome	Data-extraction/ results	Authors conclusion	Risk of bias
evidence for rest, ice, compression, and elevation therapy in the treatment of ankle sprains in adults?" 47**(4): 435-43. doi 10.4085/1062-6050-47.4.14.**		hours after trauma for patients in the initial period after ankle sprain.	2010 6. Airaksinen 1990 7. Sloan 1989 8. Laba 1989 9. Cote 1988 10. Hocutt 1982 11. Basur 197				compression Elevation versus no elevation		support the use of ice is limited Compression vs no compression: The evidence on use, sort and duration of compression is limited Elevation versus no elevation: No relevant evidence was identified on elevation	acute ankle sprains in adults	
van den Bekerom Michel, P. J., van der Windt Daniëlle, A. W. M., ter Riet, G., van der Heijden Geert, J., & Bouter Lex, M. (2011). Therapeutic ultrasound for acute ankle sprains. Cochrane Database of Systematic Reviews, (6).	2011	Systematic review to assess the effects of ultrasound therapy in the treatment of acute ankle sprains	RCTs: 1. Makuloluwe 1977 2. Nyanzi 1999 3. Oakland 1993 4. Van Lelieveld 1979 5. Williamson 1986 6. Zammit 2005	Sept 2010	Patients with pain, swelling and/or functional disability caused by acute ligament injuries	Ultrasound therapy	Placebo, no treatment of other types of interventions as exercise therapy, immobilisation, laser therapy, of medication	General improvement, adverse events, pain, swelling, functional disability, range of motion	Ultrasound versus placebo: No difference between the groups for general improvement, pain, swelling, functional disability, ROM Ultrasound versus other treatment modalities: - faster recovery with ultrasound compared to immobilization with Elastoplast - no differences between ultrasound and Felbinac gel in general improvement -no differences in recovery between ultrasound and electrophysiotherapy	This high quality systematic review shows that there is little evidence for beneficial effects of ultrasound therapy for acute ankle sprains. Although that only one of the included studies was of adequate quality, we do not encourage the usage of ultrasound in the treatment of acute ankle sprains.	Low
van der Wees, P. J.,	2006	Systematic review to	RCTs: 1. Bernier 1998	March 2005	Patients with acute ankle	At least one of the	Placebo, no	Recurrent sprains,	Exercise therapy versus usual care:	This systematic review of good	Low

Reference	Publication date	Objective	Included studies	Last search	Patient	Intervention	Compare	Outcome	Data-extraction/ results	Authors conclusion	Risk of bias
Lenssen, A. F., Hendriks, E. J. M., Stomp, D. J., Dekker, J., & de Bie, R. A. (2006). Effectiveness of exercise therapy and manual mobilisation in acute ankle and functional instability: A systematic review. Australian Journal of Physiotherapy, 52(1), 27-37.		assess the effectiveness of exercise therapy and manual mobilization in acute ankle sprains and functional instability	2. Brooks 1981 3. Collins 2004 4. Eils 2001 5. Eisenhart 2003 6. Green 2001 7. Hess 2001 8. Hoiness 2003 9. Holme 1999 10. Nilsson 1983 11. Oostendorp 1987 12. Pellow 2001 13. Powers 2004 14. Stasinopoulos 2004 15. Tropp 1985 16. Verhagen 2004 17. Wester 1996		sprain or with functional instability (the latter is not addressed since not of importance for this guideline)	interventions in the trial had to be an intervention aimed at exercise therapy or at manual mobilization of the ankle joint	treatment or other interventions	functional disability, gait pattern, subjective instability, postural control, ankle joint ROM, pain	- significant less recurrent injuries in the exercise therapy group - no effect on postural sway. Exercise therapy versus external support: - no evidence Exercise therapy versus immobilisation: No evidence Manual mobilisation: - significant positive effect on the ankle dorsiflexion ROM	quality shows that exercise therapy is effective in the prevention of recurrent ankle sprains and that mobilization has an effect on ankle dorsiflexion ROM. The effect of exercise therapy on other treatments is unclear. However, it need to be addressed that only 6 of the included RCTs were of high quality so the results must be viewed in perspective of the poor methodological quality of the other studies.	
Van Rijn, R. M., Van Ochten, J., Luijsterburg, P. A. J., Van Middelkoop, M., Koes, B. W., & Bierma-Zeinstra, S. M. A. (2010). Effectiveness of additional supervised	2010	Systematic review to examine the effectiveness of conventional treatment (non-surgical) combined with supervised exercises compared with conventional treatment alone for the	RCT or controlled clinical trial 1. Basset 2007 2. Brooks 1981 3. Holme 1999 4. Hultman 2010 5. Karlsson 1996 6. Nilsson 1983 7. Oostendorp 1987	July 2010	Adolescent and adult patients with an acute lateral ankle sprain	Conventional treatment (either immobilisation or non-supervised treatment or use of external support) combined with supervised exercises	Conventional treatment alone	Pain, instability, re-sprain, return to sport and work, recovery, and functional scores for short term (within 2 weeks of randomization),	Pain: conflicting evidence of effectiveness Instability: moderate evidence of no effectiveness of supervised exercises at intermediate follow-up, conflicting evidence of effectiveness at long-term follow-up Re-sprain: moderate	This systematic review with a good methodological quality showed that there is only moderate or limited evidence in favour of adding supervised exercises to conventional treatment compared to	Moderate

Reference	Publication date	Objective	Included studies	Last search	Patient	Intervention	Compare	Outcome	Data-extraction/ results	Authors conclusion	Risk of bias
exercises compared with conventional treatment alone in patients with acute lateral ankle sprains: Systematic review. BMJ, 341(7780), 980.		rehabilitation of acute ankle sprains	8. Reinhardt 1999 9. Roycroft 1983 10. van Rijn 2007 11. Wester 1996					intermediate term (2 weeks – 3 months) and long term (more than 3 months) follow-up	evidence of no effectiveness of supervised exercises for the intermediate follow-up, conflicting evidence for effectiveness at long term follow-up Recovery: limited evidence for effectiveness of supervised exercises at short term follow-up and limited evidence for no effectiveness at intermediate and long term follow-up Function: conflicting evidence at short term follow-up and limited evidence for no effectiveness at long term follow-up Return to work: conflicting evidence for effectiveness of supervised exercises at short term follow-up in reducing time to return to work and limited evidence of no effectiveness at intermediate and long term follow-up Return to sport: limited evidence for the effectiveness of additional supervised exercises at short term follow-up in	conventional treatment alone according to the outcome measures of recovery and return to sport at short term. There was no strong evidence for effectiveness of additional supervised exercises for any of the outcome measures. It need to be addressed that the results are pooled from only 11 studies of which 10 being assessed as having high risk of bias. Next to this, the level of evidence for each outcome parameters was based on a maximum of 5 studies.	

Reference	Publication date	Objective	Included studies	Last search	Patient	Intervention	Compare	Outcome	Data-extraction/ results	Authors conclusion	Risk of bias
									reducing the time to return to sport, conflicting evidence for effectiveness at intermediate follow-up and limited evidence for no effectiveness at long term follow-up		

Appendix 7.2. Evidence tables for primary studies

Reference	Publication date, study type	Objective	Patient	Intervention	Compare	Outcome	Data-extraction	Authors conclusion	Guideline authors conclusion
Ardèvol, J., Bolíbar, I., Belda, V., & Argilaga, S. (2002). Treatment of complete rupture of the lateral ligaments of the ankle: a randomized clinical trial comparing cast immobilization with functional treatment. Knee Surg Sports Traumatol Arthrosc, (6), 371-377. Retrieved from http://www.mrw.interscience.wiley.com/cochrane/clcentral/articles/596/CN-00411596/frame.html	2002, randomized controlled study	To compare the therapeutic efficacy between cast immobilization and functional treatment of grade III ruptures of the lateral ankle ligaments. n = 140	Men or women, aged under 35 years, treated consecutively at the Emergency Department in the first phase of a grade III tear of the ATFL or ATFL plus CFL.	Functional treatment with cryotherapy for 40 min every 12 h and strapping for the first 2 days, and weight bearing and strapping until the 17th day. Thereafter they followed proprioceptive rehabilitation.	Immobilization with a below-knee plaster cast, elevation of the foot, and 50 mg diclofenac every 8 h for 2 days. Then weight bearing was allowed. The plaster was taken off after 21 days. Thereafter they followed proprioceptive rehabilitation.	- reduction in objective laxity - late symptoms of the injury (instability, swelling, pain, stiffness) - reinjury - sporting level on return to activity - time before returning to sport -> 3, 6, and 12 months after sprain	The functional group showed significantly earlier and better return to physical activity, fewer symptoms at 3 and 6 months but no intergroup difference at 12 months. Functional treatment also showed better decrease in joint laxity. No intergroup differences were found in the reinjury rate.	Functional treatment is safe, associated with a more rapid recovery, and particularly suitable in athletic populations.	Moderate risk of bias Competitive or recreational sportmen population (>4H /week). 15% loss to follow up Patients and treating doctors were not blinded. It was unclear if the data managers were blinded.
Bleakley et al, (2010), Effect of accelerated rehabilitation on function after ankle sprain: randomised controlled trial., BMJ 2010;340:c1964	2010, randomized controlled trial	To compare an accelerated intervention incorporating early therapeutic exercise after acute ankle sprains with a standard protection, rest, ice, compression, and elevation intervention.	101 patients of age 16-65 years with an acute (<7 days) grade 1 or 2 ankle sprain.	Early therapeutic exercise + Ice, Compression (baseline to week 1) Standardised treatment (week 1-4): ankle rehabilitation exercices	Ice, compression (baseline to week 1) Standardised treatment (week 1-4): ankle rehabilitation exercices	The primary outcome was subjective ankle function (lower extremity functional scale). Secondary outcomes were pain at rest and on activity, swelling, and physical	An overall treatment effect was in favour of the exercise group (P=0.0077); this was significant at both week 1 (baseline adjusted difference in treatment 5.28, 98.75% confidence interval 0.31 to 10.26; P=0.008) and week 2 (4.92, 0.27 to 9.57; P=0.0083).	An accelerated exercise protocol during the first week after ankle sprain improved ankle function. The group receiving this intervention was more active during that week than the group receiving standard care.	Moderate risk of bias. Insufficient power to show a difference in the secondary outcomes 15% loss to follow up - drop out was higher in the

Reference	Publication date, study type	Objective	Patient	Intervention	Compare	Outcome	Data-extraction	Authors conclusion	Guideline authors conclusion
						activity at baseline and at one, two, three, and four weeks after injury. Ankle function and rate of reinjury were assessed at 16 weeks. Linear mixed model analysis was used. The level of significance was set at a Bonferroni corrected level of 0.0125 (0.05/4).		Both groups had good ankle function at the 16 week follow-up, with just four reinjuries.	exercise group
Borromeo, CN., Ryan, JL., Marchetto, PA., Peterson, R., Bove, AA. (1997). Hyperbaric oxygen therapy for acute ankle sprains. Am. J. Sports Med. 25(5):619-25	1997 Double blind RCT	To compare treatment with hyperbaric oxygen with a sham (treatment with air) in patients suffering from an acute ankle sprain	Individuals 15-55 years of age suffering from acute (<72 hrs) ankle sprains, grades I,II and III.	Three sessions (210 min over 1 week) with hyperbaric oxygen at 2 atmospheres absolute pressure. In a hyperbaric chamber. Other standard treatments for ankle sprains allowed (e.g. NSAIDs, strapping, etc) (n-16)	Three sessions (210 min over 1 week) with air at 1,1 atmospheres absolute pressure in a hyperbaric chamber. Other standard treatments for ankle sprains allowed (e.g. NSAIDs, strapping, etc) (n=16)	Joint function (7-point scale) Ankle oedema/swelling (volumeter) Subjective pain (VAS) Time to recovery	Change from initial to final evaluation on joint function significantly greater in the hyperbaric oxygen group (SMD 0,12 (95%CI -5,3-0,77). No significant differences noted between the two groups in terms of subjective pain. Time to recovery was the same in both groups.	No significant outcome found between the two treatment groups.	Low risk of bias Well balanced baseline characteristics Very small sample size - imprecision Only study assessing Hyperbaric oxygen in ankle sprains Generalisability, likely to be a challenge

Reference	Publication date, study type	Objective	Patient	Intervention	Compare	Outcome	Data-extraction	Authors conclusion	Guideline authors conclusion
Cardenas-Estrada et al, (2009), Efficacy and Safety of Celecoxib in the Treatment of Acute Pain due to Ankle Sprain in a Latin American and Middle Eastern Population., The Journal of International Medical Research 2009; 37: 1937 – 1951	2009, open-label, multicentre, randomized, comparative study	To compare the efficacy and safety of celecoxib with NSAIDs in treating acute ankle sprain with moderate-to severe ankle pain.	278 patients of age 18-74 years presenting with pain (≥ 45 mm on VAS) due to 1st or 2d degree ankle sprain (involving the anterior talofibular ligament and/or the calcaneofibular ligament)	Celecoxib (400 mg loading dose followed by 200 mg twice daily).	Standard doses of non-selective NSAIDs.	A change in the patient's assessment of ankle pain on a visual analogue scale at day 3 compared with baseline. An analysis of covariance (ANCOVA) model with effects for treatment, country and the baseline ankle pain VAS score was used. (p < 0,05)	From a baseline of 73 mm, mean VAS pain scores decreased to 29 and 32 mm in the celecoxib and non-selective NSAID groups, respectively.	Using an initial loading dose, celecoxib was at least as efficacious as non-selective NSAIDs in treating acute pain due to ankle sprain.	High risk of bias. Trial sponsored by Pfizer Less adverse effects in celecoxib
Costantino, C., Kwarecki, J., Samokhin, A. V., Mautone, G., & Rovati, S. (2011). Diclofenac epolamine plus heparin plaster versus diclofenac epolamine plaster in mild to moderate ankle sprain: A randomized, double-blind, parallel-group, placebo-controlled, multicentre,	2011, randomized double blind parallel group placebo study Controlled multicentre phase III study.	To compare the efficacy and tolerability of a newly developed fixed-dose diclofenac epolamine/heparin plaster with that of a diclofenac epolamine plaster or a placebo plaster in the treatment of mild to moderate ankle sprains in adults.	Outpatients aged 18 to 65 years with a grade 1 or 2 ankle sprain within the previous 48 hours and with perimalleolar oedema. n = 430	DHEP/Heparin 1,3%/5600IU plaster applied once daily for 7 days. (n = 142)	DHEP plaster 1,3% applied once daily for 7 days. (n = 146) Placebo plaster applied once daily for 7 days. (n = 144)	Primary outcome: mean change from baseline in pain on movement on day 3 as measured by a VAS. Secondary outcome: - pain while leaning in the injured limb - spontaneous pain - oedema extension	DHEP/Heparin plaster had a sign greater mean reduction in pain on movement after 3 days than DHEP, providing greater pain relief than placebo. DHEP/Heparin plaster resulted in significant less daily pain while leaning on the injured limb than DHEP. Oedema reduced sign with DHEP/Heparin than with placebo on day 7.	A fixed dose DHEP/Heparin plaster is effective and has advantages over the DHEP plaster in relieving pain and possible also swelling associated with mild to moderate acute ankle sprains with oedema in adults.	Low risk of bias. Multicentre study (n = 13) Sponsored by IBSA Institut Biochémique SA. Data quality monitoring by extern. (Contract Research Organisation Medical and Pharmaceutical Products sprl

Reference	Publication date, study type	Objective	Patient	Intervention	Compare	Outcome	Data-extraction	Authors conclusion	Guideline authors conclusion
phase III trial. Clinical Drug Investigation, 31(1), 15-26.						- rescue medication consumption - overall treatment efficacy.	Local adverse effects were very infrequent, of mild severity and occurred no more frequently with active treatments than with placebo.		100% treatment compliance.
Coudreuse, J.-M., de Vathaire, F. (2010). Effect of a plaster containing DHEP and heparin in acute ankle sprains with oedema: a randomized, double-blind, placebo-controlled, clinical study. Current Medical Research & Opinion, 26(9):2221-2228	2010, randomized, double-blind, placebo-controlled study	To evaluate the efficacy and safety of the DHEP heparin plaster in patients with acute painful and edematous benign ankle sprain	Patients (18-65y) with a painful lateral ankle sprain with edema (<48h) Swelling >20mm vs uninjured ankle VAS > 50mm n=233	Group-I: DHEP heparin plaster for 7 days	Group-II: Placebo plaster for 7 days	- Efficacy: Primary outcome: swelling Secondary outcome: pain (VAS) in active mobilization, at rest, on passive stretch; pain on pressure, functional disability, possibility of single foot leaning, global rating of efficacy - Safety: Global rating of tolerability	-Efficacy: Primary measures: significantly greater reduction in edema in DHEP heparin treated group Secondary measures: Significantly greater pain reduction in DHEP heparin treated group for pain on mobilization, pain on pressure; no difference for pain at rest, pain on passive stretch and possibility of single foot leaning; global assessment of efficacy in favor of DHEP heparin group ($p<0.05$) - Safety: Good-to-excellent	The combination of DHEP with heparin, which has proven positive effects on local microcirculation, was able to improve edema reabsorption and accelerate pain relief when compared with placebo	Low risk of bias. Trial which indicates a superior effect of a plaster with DHEP heparin than a standard plaster on reduction of pain and swelling Multicentre study: 32 12% loss to follow up Sponsored study by IBSA Institut Biochimique
Dalton, J., Schweinle, J. (2006). Randomized controlled noninferiority trial to compare extended release acetaminophen and ibuprofen	2006, multicenter, randomized, double-blind, parallel-group study	To compare acetaminophen extended release 3,900mg daily to ibuprofen 1,200mg daily for treatment of grade I or II lateral ankle	Patients (>18y) with grade I or II lateral ankle sprain (<24h) VAS ≥ 40mm n=260	Group-I: acetaminophen extended release 1,300mg, 3/ d n=132	Group-II: ibuprofen 400mg, 3/d n=128	- Efficacy: Primary outcome: pain on walking (VAS) on day 4 Secondary outcome: Pain on	-Efficacy: Primary measure: acetaminophen extended release was non-inferior to ibuprofen, with no difference between groups. Secondary measure:	Acetaminophen extended release 3,900mg daily was comparable to ibuprofen 1,200mg daily for treatment of grade I or II lateral ankle	Low risk of bias. Trial which indicates that acetaminophen extended release is a good alternative for ibuprofen Multicentre study 42

Reference	Publication date, study type	Objective	Patient	Intervention	Compare	Outcome	Data-extraction	Authors conclusion	Guideline authors conclusion
for the treatment of ankle sprains. Ann Emerg Med, 48(5):615-623		sprains				walking (day 9), change in ability to walk, swelling, ankle bruising, ankle range of motion, overall satisfaction, anterior drawer test and time to resume to normal activity - safety: Adverse events	Comparable to primary measure - safety: No safety issues were identified	sprains. Both treatments were well tolerated.	No placebo group. Crutches, bandages and exercises were allowed if necessary. Sponsored by McNeil Consumer & Speciality Pharmaceuticals
D'Anchise, R., Bulitta, M., & Giannetti, B. (2007). Comfrey extract ointment in comparison to diclofenac gel in the treatment of acute unilateral ankle sprains (distortions). Arzneimittel-Forschung/Drug Research, 57(11), 712-716.	2007, multicenter, randomized, single blind, controlled, parallel-group, clinical study	To show the difference of an ointment of Comfrey extract in comparison to diclofenac gel in the treatment of acute unilateral ankle sprain and to compare the safety of both study drugs	Patients with acute unilateral ankle sprains n=164	Group-I: Kytta-Salbe® n = 82	Group-II: Diclofenac gel containing 1.16g of diclofenac diethylamine salt n = 82	- Efficacy: Primary outcome: AUC of the tenderness Secondary outcome: pain (VAS) at rest and on movement, swelling, ankle movement, rescue medication, global assessment of efficacy by investigator and patient - Safety: Global assessment of tolerability by investigator and patient	- Efficacy: Primary measures: statistical superiority of the comfrey extract vs diclofenac for AUC; ratio of tenderness values of the injured/contralateral side were significantly different at visit 2, but not at visit 3 (final) Secondary measures: No significant difference for pain and swelling; investigators rated the Comfrey extract superior to the diclofenac preparation - safety: No serious adverse effects and no significant differences between groups	It is very encouraging and impressive to realize that comfrey extract, a natural product, seems to be an effective and safe alternative to the standard topical treatment with NSAIDs	Moderate risk of bias. Trial suggesting comfrey extract as a good alternative for diclofenac Observer blind study. Sponsored by Merck Selbstmedikation GmbH Multicentre sudy Age range of patients was not clear Patient

Reference	Publication date, study type	Objective	Patient	Intervention	Compare	Outcome	Data-extraction	Authors conclusion	Guideline authors conclusion
							regarding number of AEs		population Is not well defined
Ekman, E. F., Fiechtner, J. J., Levy, S., & Fort, J. G. (2002). Efficacy of celecoxib versus ibuprofen in the treatment of acute pain: a multicenter, double-blind, randomized controlled trial in acute ankle sprain. Am J Orthop (Belle Mead NJ), (8), 445-451	2002, multicenter, randomized, double-blind, parallel-group study	To determine the efficacy and tolerability of celecoxib with those of a conventional NSAID and placebo in the treatment of ankle sprain	Patients (>18) with acute grade I or II lateral ankle sprain (involving the anterior talofibular ligament and/or the calcaneofibular ligament) (<48h) VAS ≥ 45mm > 2 on patient's global assessment and patient's assessment of normal function/activity n=455	Group-I: Celecoxib 200mg, 2/day n = 134 Group-II: Ibuprofen 800mg, 3/day n = 138	Group-III: placebo n = 133	- Efficacy: Primary outcome: pain (VAS) and global assessments responses on day 4 Secondary outcome: pain (VAS) and global assessment responses on day 8 and 11, physician's global assessment of ankle injury grades, patient and physician satisfaction assessment respons, withdrawal because of treatment failure - Safety: Adverse events	- Efficacy: Celecoxib was non-inferior to ibuprofen at all time points, primary and secondary efficacy results show that celecoxib was more effective than placebo and as effective as ibuprofen - Safety: No serious adverse events were reported	Celecoxib (400mg/day) was more effective than placebo and as effective as the maximum recommended dose of ibuprofen (2400mg/day) in providing pain relief and accelerating recovery	Low risk of bias. The first and second author are employed by Pfizer Inc
Ekman, E. F., Ruoff, G., Kuehl, K., Ralph, L., Hormbrey, P., Fiechtner, J., & Berger, M. F. (2006). The COX-2 specific inhibitor Valdecoxib versus tramadol	2006, multicenter, randomized, double-blind, parallel-group study	To determine the efficacy, safety and tolerability of valdecoxib, its inferiority to tramadol, and its superiority to placebo in relieving the signs and	Patients (16-65y) with grade I or II lateral ankle sprain (involving the anterior talofibular ligament and/or the calcaneofibular ligament) (<48h)	Group-I: Valdecoxib, 20mg, 2/d, 7 days n = 208 Group II; Valdecoxib, 20mg, 1/d, 7	Group IV: Placebo n = 111	- Efficacy: Primary outcome: pain (VAS) on weight bearing on day 4 Secondary outcome: pain (VAS) on weight bearing	- Efficacy: Primary measure: Valdecoxib is non-inferior to tramadol; improvement of VAS score was significantly higher in tramadol and valdecoxib group vs control group, but not	Valdecoxib was comparable with tramadol and was significantly better than placebo in treating acute ankle sprain, and it enabled more patients to resume normal	Low risk of bias. Trial indicating that valdecoxib is at least as effective as tramadol, with less adverse events Multicentre study:

Reference	Publication date, study type	Objective	Patient	Intervention	Compare	Outcome	Data-extraction	Authors conclusion	Guideline authors conclusion
in acute ankle sprain: a multicenter randomized, controlled trial. Am J Sports Med, (6), 945-955		symptoms of a grade I and II ankle sprain	VAS ≥ 60mm > 2 on patient's global assessment and patient's assessment of normal function/activity n=829	days n = 209 Group-III: Tramadol, 50mg 4/d, 7 days n = 191		on day 7, patient's and physician's global assessment of ankle injury, patient's assessment of normal function/activity, APS questionnaire score, patient willingness to use the same medication, patient's overall satisfaction with study medication - Safety: Adverse events	between tramadol and valdecoxib Secondary outcomes: Non-inferiority between valdecoxib and tramadol by treatment differences on both day 4 and 7; Analysis of other secondary efficacy end points further supported these findings, showing that valdecoxib was at least as effective as tramadol and superior to placebo; - Safety: Tramadol resulted in a 4-fold higher rate of withdrawals due to adverse events compared with valdecoxib treatment (p<0.001); the rates of withdrawal between the valdecoxib group and placebo group were similar	walking on days 4 and 7. Both valdecoxib and Tramadol were well tolerated.	87 Sponsored by Pfizer global Pharmaceuticals and Pharmacia Corporation
Fotiadis, E., Kenanidis, E., Samoladas, E., Chytas, A., Lyrtzis, C., Koimtzis, M., Chalidis, B. (2011). Are venotonic drugs effective for	2011, prospective, randomized study	To evaluate the effect of venotonic drugs in clinical outcomes of patients with ankle sprain	Patients (>18y) with type II and type III acute lateral ankle sprain (<24h) n=81	Group-I: standard treatment with painkillers, immobilization, lace-up bracing and toe touch weight bearing +	Group-II: Standard treatment with painkillers, immobilization, lace-up bracing and toe touch weight bearing.	Swelling, pain (VAS)	No significant differences between treatment groups in pain levels (0,64 and 0,32 at week 20 for the Daflon and the standard therapy groups (p=0,908)) or ankle perimeter	Venotonic drugs seem not to decrease the posttraumatic oedema or pain in patients who suffer from moderate or severe ankle sprain	High risk of bias. Patients were not blinded for treatment allocation Per-protocol analysis

Reference	Publication date, study type	Objective	Patient	Intervention	Compare	Outcome	Data-extraction	Authors conclusion	Guideline authors conclusion
decreasing acute posttraumatic oedema following ankle sprain? A prospective randomized trial. Arch Orthop Trauma Surg, 131:389-392				Micronized purified flavonoid fraction (Daflon, 1.000mg x 3/day, 20 days					
Hewitt, D., Knox, T., Xiang, J., Jordan, D., Rosenthal, N. (2007). Tramadol/ Acetaminophen or Hydrocodone/ Acetaminophen for the treatment of ankle sprain: a randomized, placebo-controlled trial. Annals of Emergency Medicine, 49 (4):468-480	2007, multicenter, randomized, placebo-controlled, blinded study	To evaluate the effect of Tramadol/ Acetaminophen (T/A) or Hydrocodone/ Acetaminophe (H/A) on pain relief	Patients (18-75y) with an acute ankle sprain with clinical diagnosis of partial ligament tear (<48h) VAS ≥ 50mm n=603	Group-I: 2 capsules of 37.5mg tramadol/ 325mg acetaminophen Group-II: 1 capsule of 7.5mg hydrocodone/ 650mg acetaminophen group + 1 placebo capsule	Group-III: 2 placebo capsules	- Efficacy: VAS, pain intensity numeric rating scale and pain relief numeric rating scale, activity impairment, overall assessment of study medication - Safety: adverse effects	- Efficacy: During first 4h post dose all outcome variables were significantly better in T/A group and H/A group in comparison with placebo, no significant difference between T/A and H/A group. At final visit mean pain relief scores were greatest in H/A group, intermediate in T/A group, and lowest in control group with significant difference between A/H and placebo. Pain intensity numeric rating scale scores were not different - Safety: No serious adverse effects were reported	T/A and H/A were well tolerated, had comparable clinical utility, and were more effective than placebo in the management of acute musculoskeletal pain caused by ankle sprain	Low risk of bias. It was not clear if study groups were comparable at baseline for all outcome variables. Drop out of 13%, primarily due to lack of efficacy and adverse event Sponsored by pharmaceutical industry
Hupperets et al. (2009) Effect of unsupervised home based proprioceptive training on recurrences of ankle sprain:	2009, randomised controlled trial	To evaluate the effectiveness of an unsupervised proprioceptive training programme on recurrences of ankle sprain	522 athletes who had sustained a lateral ankle sprain up to two months before inclusion N= 256 in intervention	Usual care + Eight week home based proprioceptive training programme	Usual care	Self reported recurrence of ankle sprain	Effect was found for self-reported recurrent ankle sprains RR= 0.63, 95%CI= 0.45-0.88	The use of a proprioceptive training programme is effective for the prevention of self reported recurrences	Moderate risk of bias -No blinding + allocation concealment

Reference	Publication date, study type	Objective	Patient	Intervention	Compare	Outcome	Data-extraction	Authors conclusion	Guideline authors conclusion
randomised controlled trial		after usual care	group, N= 266 in control group						+ ITT analysis
Kayali, C., Agus, H., Surer, L., Turgut, A. (2007). The efficacy of paracetamol in the treatment of ankle sprains in comparison with diclofenac sodium. Saudi Medical Journal, (12), 1836-1839	2007, prospective, double-blind, parallel group study	To evaluate effectiveness of paracetamol in comparison with diclofenac sodium in acute ankle sprains	Patients (>18y) with a first- or second degree lateral ankle sprain (<48h) VAS ≥ 45mm n=100	Group-I: Diclofenac sodium 150mg/d, 5 days Patients received rehabilitation after 5 days.	Group-II: Paracetamol 1500mg/d, 5 days. Patients received rehabilitation after 5 days.	- Efficacy: Ankle pain (VAS) on weight bearing, time to return to recreational activities, physicians global assessment, swelling, ankle ROM - Safety: Adverse effects	No significant differences for all outcome measures for both treatment groups	Diclofenac sodium and paracetamol are effective and well tolerated as a short term treatment alternatives for acute ankle sprains	Moderate risk of bias. Unclear if treating personnel and/or investigator were blinded for group allocation No mentioning of drop out Unclear if treatment groups were equally treated besides the treatment protocol
Kerckhoffs, G., Struijs, P., de Wit, C., Rahlfs, V., Zwipp, H., van Dijk, C. (2004). A double blind, randomised, parallel group study on the efficacy and safety of treating acute lateral ankle sprain with oral hydrolytic enzymes. Br J Sports Med, 38(4):431-435.	2004, multinational, mulitcentre, double blind, randomized, parallel group design	To compare the effectiveness and safety of the triple combination Phlogenzym (rutoside, bromelain, and trypsin) with double combinations, the single substances and placebo	Patients (16-53y) with acute lateral ankle sprain (<18h) VAS > 30mm n=721	Group-I: Phlogenzym Group-II: trypsin plus bromelain Group-III: Trypsin plus rutoside Group-IV: Bromelain plus rutoside Group-V: Trypsin (48mg) Group-VI: Bromelain (90mg) Group-VII:	Group-VIII: Placebo. Patients received a brace after 4 days.	-Efficacy: Primary outcome: pain step test, ankle volume, ROM Secondary outcome: global judgment of efficacy (investigator) - safety: Adverse events and global judgment of tolerability	- Efficacy: Combined efficacy criteria: 1. Phlogenzym vs placebo: no significant differences, but the Phlogenzym group showed some inferiority (odds ratio 0,4-0,7), p=0,996 2. Phlogenzym vs two-drug combinations: no significant differences, (p=0,922) but Phlogenzym is indicated to be slightly inferior in efficacy 3. Phlogenzym and	- Phlogenzym was not shown to be superior to the three two-drug combinations, the three single substances, or placebo - tolerabilty of Phlogenzym rated as very good	Low risk of bias. Unclear if treating physician and/or investigator were blinded for group allocation Study groups differed from some baseline measurements

Reference	Publication date, study type	Objective	Patient	Intervention	Compare	Outcome	Data-extraction	Authors conclusion	Guideline authors conclusion
				Rutoside (100mg) For all: 2 tablets, 3 times daily, 10 days. Patients received a brace after 4 days.			two-drug groups vs placebo: no significant differences, but Phlogenzym and the two-drug groups are indicated to be slightly inferior in efficacy Secondary measures: Phlogenzym was found to be slightly superior to placebo (p=0.049) - Safety: No differences between study groups		
Koll, R., Buhr, M., Dieter, R., Predel, H.G., Petrowicz, O., Giannetti, B., Klingenburg, S., Staiger,C., (2004). Efficacy and tolerance of a comfrey root extract (Extr. Rad. Symphyti) in the treatment of ankle distorsions: results of a multicenter, randomized, placebo-controlled, souble-blind study. Phytomedicine 11:470-477	2004 Multicenter, randomized ouble blind, placebo-controlled trial	To evaluate the efficacy and safety of a medicinal plant (Comfrey) in the treatment of acute ankle sprains	Adults (18-60 years of age) with uncomplicated, acute (<6 hrs) ankle sprains.	Comfrey extract (Kytta-Salbe® f) Four treatments/day for 8 days with 2 gr of ointment (6cm strand of ointment) (n=80)	Placebo (same appearance and consistence as comfrey). Treatment amounts and frequency as well as overall duration was the same as in the Comfrey group (n=62)	Primary outcome: pain under pressure Secondary variables: swelling, pain scaling, range of movement, consumption of rescue medicine (ie paracetamol) and final evaluation of efficacy by both patients' and physicians	Primary outcome: Significant difference in pain relief in favor of Comfrey compared to placebo over the study period Secondary outcomes: Significantly superior reduction in ankle swelling with Comfrey compared to placebo (p<0,01) Joint mobility increased with Comfrey when compared to placebo. Global efficacy evaluation was better for Comfrey versus placebo for both patients and physicians (p<0,001)	The results from the study confirm the analgesic, anti-inflammatory and anti-exudative properties of Comfrey, as well as its good tolerability profile.	Low risk of bias Small sample size Baseline characteristics of the patients not always well balanced (concomitant diseases)
Kucera, M., Barna, M., Horácek, O.,	2004 Randomised controlled,	To study the efficacy and safety of a	Adults (18-50 years) with acute (<24 hrs)	Comfrey ointment (Traumaplant	Traumaplant ointment – low strength comfrey	Pain (VAS) Functional impairment	Comfrey ointment significantly reduced pain and functional	Traumaplant appears to be effective in the	Low risk of bias No detailed

Reference	Publication date, study type	Objective	Patient	Intervention	Compare	Outcome	Data-extraction	Authors conclusion	Guideline authors conclusion
Kováriková, J., Kucera, A., Efficacy and safety of topically applied Symphytum herb extract cream in teh treatment of ankle distorsion: results of a randomized controlled clinical double blind study., (2004). Wien Med Wochenschr 154(21-22):498-507	double blind, trial	topical Comfrey product (Traumaplant) in acute ankle sprains.	ankle sprains	10% Symphytum herb, corresponding to 25gr of fresh herb/100gr of ointment). 2-3 gr of ointment applied 3 times/day (n=104)	product (1% Symphytum herb,corresponding to 2,5gr of fresh herb/100 gr ointment). 2-3 gr of ointment applied 3 times/day (n=99)	(10-point scale) Ankle swelling (figure of eight) Overall judgment on efficacy (5-point scale) Tolerability	impairment at day 3-4 and 7; (p<0,001) . Reductions in swelling were also significantly larger in the Comfrey group at days 3-4 (p<0,01) but not at day 7 when no significant differences were found. The tolerability profile of Comfrey was excellent	treatment of ankle sprains, while presenting a good tolerability profile.	explanation on concealed allocation. Baseline characteristics not always balanced
Lamb, S. E., J. L. Marsh, et al. (2009). "Mechanical supports for acute, severe ankle sprain: a pragmatic, multicentre, randomised controlled trial." Lancet 373(9663): 575-81.	2009, Randomised Controlled trial	Assess three different types of mechanical support	Patients with severe ankle sprains	Aircast brace, Bledsoe boot or 10-day below-knee-cast	Tubular compression	Primary outcome was ankle function at 3 months measured by the Foot and Ankle Score	Patients who received the below-knee cast had a more rapid recovery than those given the tubular compression bandage. Clinically important benefits at 3 months in quality of ankle function with the cast compared with tubular compression bandage (mean diff erence 9%; 95% CI 2·4–15·0), as well as in pain, symptoms, and activity. Mean diff erence in quality of ankle function between Aircast brace and tubular compression bandage was 8%; 95% CI 1·8–14·2, but there were little diff erences	Authors Authors recomms below-knee cast because they showed the widest range of benefits	Low risk of bias A short period of immobilisation might be helpful in severe ankle sprain cases

Reference	Publication date, study type	Objective	Patient	Intervention	Compare	Outcome	Data-extraction	Authors conclusion	Guideline authors conclusion
							for pain, symptoms, and activity. Bledsoe boots off ered no benefit over tubular compression bandage,		
Lionberger, D., Joussellin, E., Lanzarotti, A., Yanchick,J., Magelli, M. (2011). Diclofenac epolamine topical patch relieves pain associated with anke sprain. Journal of Pain Research, 4:47-53	2011, multicenter, randomized, placebo-controlled , double-blind clinical study.	To demonstrate the efficacy and tolerability of diclofenac epolamine topical patches (DEPT) in the treatment of minor acute ankle sprains	Patients (18-65y) who sustained an ankle sprain (<48h) VAS ≥ 50mm n=134	Group-I: Diclofenac epolamine topical patch (1/day, 7days)	Group-II: Placebo patch (1/day, 7 days)	- Efficacy: Primary outcome: spontaneous pain (VAS, diary). Secondary outcome: analgesic effect, anti-inflammatory effect, patient assessment of treatment efficacy, swelling - Safety: assessment of tolerability, adverse events	- Efficacy: Primary measures: Significantly higher decrease in pain in the DEPT group, significantly higher success rate at most of measuring moments Secondary measures: no statistically different effect on edema, other variables were statistically different in favor of the DEPT group - Safety: No significant differences with adverse effect of mild to moderate severity	This study assessed the superior analgesic efficacy of the DETP compared with placebo in minor sports injuries with a four-hour onset, while maintaining superior pain relief for the treatment duration. The DETP affords localized NSAID treatment, thereby minimizing systemic drug exposure. Therefore, the DEPT has an important role as an alternative to traditional oral NSAID's, without the adverse event profile of the oral agents	Low risk of bias. Study is sponsorized by Alpharma Pharmaceuticalsa nd King Pharmaceuticals ®, Inc.,
Lyrtzis, C., Konstantinos, N., Papadopoulos, C., Noussios, G., Papathanasiou, E. (2011).	2011, Prospective, double-blind, randomized study	To evaluate the effect of diclofenac and paracetamol in the reduction of acute edema and pain	Patients (18-60y) with acute grade II sprains of the lateral collateral ligaments (<24h)	Group-I: diclofenac (75mg orally, 2/day) in addition to RICE protocol, ankle brace, non	Group-II: paracetamol (500mg, 3/day) in addition to RICE protocol, ankle brace, non weight bearing for 10	Ankle joint edema ("figure-of-eight" and volumetric method) and pain (VAS)	Significant decreases in edema were found compared to baseline for both groups. There was no statistical differences between the 2 groups	Paracetamol should be used in grade II ankle sprains because it has the same analgesic action as diclofenc with	Low risk of bias. Investigators were not blinded.

Reference	Publication date, study type	Objective	Patient	Intervention	Compare	Outcome	Data-extraction	Authors conclusion	Guideline authors conclusion
Efficacy of paracetamol versus diclofenac for grade II ankle sprains. Foot & Ankle International, 32 (6):571-575		following ankle sprains	n=90	weight bearing for 10 days and 3 days of elevation.	days and 3 days of elevation.		except for edema at the third post-traumatic day which was lower in the paracetamol group. After 10 days there was no difference anymore for edema.	fewer side effects and less expense. Results refer to the early post-traumatic period and cannot be generalized to for post-traumatic edema at the late post-traumatic period.	
Nadarajah, A., Abrahan, L., Lau, F., Hwang, L., Fakir-Bolte, C. (2006). Efficacy and tolerability of celecoxib compared with diclofenc slow release in the treatment of actue anke sprain in an Asian population. Singapore Med J, 47(6):534-542	2006, multicenter, double-blind, randomized, parallel-group trial	To evaluate the efficacy and tolerability of celecoxib compared with diclofenac slow release in the treatment of first- or second-degree ankle sprain in an Asian population	Patients (>18y) with first- or second-degree ankle sprain (<48h) VAS ≥ 45mm n=370	Group-I: 200mg celecoxib capsule + placebo tablet 2/day, 7days	Group-II: Placebo capsule + 75mg diclofenac slow release (SR) tablet, 2/day, 7 days	- Efficacy: Primary outcome: Pain on full weight bearing (VAS) Secondary outcome: pain at last visit,patient's global assessment of ankle injury, patient assessment of normal function/activity, physician's global assessment of ankle injury - Safety: Adverse events, tolerability	-Efficacy: Primary measures: no significant difference between groups, supporting non-inferiority of celecoxib Secondary measures: pain at last visit, patient assessment of ankle injury was significantly different and in favor for celecoxib group; patient assessment of normal function/activity, physician's global assessment of ankle injury was not different - safety: No difference	Celecoxib is as effective as diclofenac SR in treating ankle sprains. With its platelet-sparing properties, celecoxib may offer an advantage over diclofenac SR in managing musculoskeletal injuries	Low risk of bias. Asian population One of the authors was employee of Pfizer Global Pharmaceuticals
Petrella, R., Petrella, M., Cogliano, A. (2007). Periarticular hyaluronic acid in acute ankle sprain. Clin J	2007, randomized controlled study	To assess the efficacy and tolerability of periarticular HA vs placebo in treatment of acute ankle sprain	Patients (>18y) with a first- or second degree ankle sprain (<48h) VAS ≥ 45mm n=158	Group-I: Hyaluronic acid (HA) treatment with a single injection (0.7-1.2mL)	Group-II: placebo injection (normal saline 0.7-1.2mL)	- Efficacy: Primary outcome was VAS of pain on weight bearing. The secondary	- Efficacy: All efficacy parameters improved in both groups at all follow-ups. Intergroup comparisons after 4 days showed a	HA treatment of acute ankle sprain was highly satisfactory in the short term and the long term vs placebo.	Low risk of bias. Patients were blinded for their treatment, however, it was unclear if treating

Reference	Publication date, study type	Objective	Patient	Intervention	Compare	Outcome	Data-extraction	Authors conclusion	Guideline authors conclusion
sport Med, 17(4):251-257						outcome was VAS of pain on walking (20m), patient's assessment of return to normal function/activity in sport, patient's satisfaction assessments at 4, 8, 30 and 90 days post-treatment - Safety: assessments of adverse events	statistically significant difference in favor of HA on most efficacy parameters. If parameters were not significant between the HA group and the placebo group, improvement was more marked in the treatment group. - Safety: no difference in adverse effects	This was associated with reduced pain and more rapid return to sport, with few associated adverse events	doctor and investigator were blinded for group allocation Additional treatment (after 8 days) was not documented
Petrella, R., Ekman, E., Schuller, R, Fort, J. (2004). Efficacy of celecoxib, a COX-2-specific inhibitor, and naproxen in the management of acute ankle sprain. Clin J Sport Med,14(4):225-231	2004, multicenter double-blind, parallel group, randomized controlled study	To compare the efficacy and safety of celecoxib with non-selective NSAID naproxen	Patients (>18y) with a first- or second degree lateral ankle sprain (<48h) VAS ≥ 45mm n=397	Group-I: Celecoxib 200mg BID for 7 days	Group-II: Naproxen 500mg BID for 7 days	- Primary outcome: pain (VAS) and patient's global assessment. - Secondary outcomes: physician's global assessment, patients and physician's satisfaction assessment, patient's assessment of normal function/activity	- Primary measures: no significant difference for VAS and Patient's Global Assessment, non-inferiority of celecobix compared to naproxen - Secondary measures: no significant differences except for adverse effects: more dyspepsia in patients on naproxen	COX-2-specific inhibitors appear to be as effective as NSAIDs as anti-inflammatory therapy. COX-2-specific inhibitors provide safety advantages that should be considered	Low risk of bias. Sponsored study by pharmaceutical industry

APPENDIX 8. GRADE EVIDENCE PROFILE TABLES

GRADE Evidence profile: paracetamol versus NSAIDs in acute treatment of Grade I or II ankle sprains

Outcome	No of studies (design)	Risk of bias (a)	Inconsistency (b)	Indirectness (c)	Imprecision (d)	Publication bias (e)	No patients	Reasons for downgrading	Level of evidence
Pain	3 RCT (Dalton 2006, Lyrtzis 2011, Kayali 2007)	-1	0	0	-1	0	450	a. unclear allocation concealment for 1 RCT; no or unclear blinding of evaluator in 1 RCT; d. no reporting of CI in 1 RCT and CI very large in another	Low
Ankle swelling	3 RCT (Dalton 2006, Lyrtzis 2011, Kayali 2007)	-1	-1	0	-1	0	450	a. unclear allocation concealment for 1 RCT; no or unclear blinding of evaluator in 1 RCT; d. no reporting of CI in 1 RCT and CI very large in another	Very low
Ankle ROM	2 RCT (Dalton 2006, Kayali 2007)	-1	0	0	-2	0	360	a. unclear allocation concealment for 1 RCT; d. <400 patients for a continuous variable; no reporting CI in 1 RCT and CI very large in another	Very low
Return to normal activities	2 RCT (Dalton 2006, Kayali 2007)	-1	0	0	-2	0	360	a. unclear allocation concealment for 1 RCT; d. <400 patients for a continuous variable; no reporting CI in 1 RCT and CI very large in another	Very low
Adverse events	2 RCT (Dalton 2006, Kayali 2007)	-1	0	0	-1	0	360	a. unclear allocation concealment for 1 RCT; d. not sufficient power to detect side effect	Low

GRADE Evidence profile: Celecoxib versus placebo in acute treatment of Grade I or II ankle sprains

Outcome	No of	Risk of	Inconsistency	Indirectness	Imprecision	Publication	No	Reasons for	Level of

	studies (design)	bias (a)	(b)	(c)	(d)	bias (e)	patients	downgrading	evidence
Pain	1 RCT (Ekman 2002)	0	-1	0*	-1	-1	290	b. 1 trial only: consistency of results cannot be judged. No proof that results are reproducible; d. sample size <400 patients for a continuous variable; e. pharmaceutical sponsoring	Very low
Return to normal activities	1 RCT (Ekman 2002)	0	-1	0*	-1	-1	290	b. 1 trial only: consistency of results cannot be judged. No proof that results are reproducible; d no reporting CI; e. pharmaceutical sponsoring	Very low
Adverse events	1 RCT (Ekman 2002)	0	-1	0*	-1	-1	290	b. 1 trial only: consistency of results cannot be judged. No proof that results are reproducible; d no reporting CI; e. pharmaceutical sponsoring	Very low

* *patients without gastro-intestinal, renal, hepatic… diseases*

GRADE Evidence profile: Celecoxib versus NSAIDs in acute treatment of Grade I or II ankle sprains

Outcome	No of studies (design)	Risk of bias (a)	Inconsistency (b)	Indirectness (c)	Imprecision (d)	Publication bias (e)	No patients	Reasons for downgrading	Level of evidence
Pain	4 RCT (Ekman 2002, Petrella 2004, Nadarajah 2006, Cardenas 2009)	-1	0	0*	-1	-1	1347	a. 1 RCT without blinding; d No reporting CI in all RCT; e. same pharmaceutical sponsoring in 4 RCT	Very low
Return to normal activities	4 RCT (Ekman 2002, Petrella 2004, Nadarajah 2006, Cardenas 2009))	0	0	0*	-1	-1	1347	a. 1 RCT without blinding; d No reporting CI in all RCT; e. same pharmaceutical sponsoring in 4 RCT	Very low
Adverse events	4 RCT (Ekman 2002, Petrella 2004, Nadarajah 2006, Cardenas 2009)	-1	0	0*	-1	-1	1347	a. 1 RCT without blinding; d. No reporting CI in all RCT; e. same pharmaceutical sponsoring in 4 RCT	Very low

* *patients without gastro-intestinal, renal, hepatic… diseases*

GRADE Evidence profile: Tramadol/paracetamol versus placebo in acute treatment of Grade I or II ankle sprains

Outcome	No of studies (design)	Risk of bias (a)	Inconsistency (b)	Indirectness (c)	Imprecision (d)	Publication bias (e)	No patients	Reasons for downgrading	Level of evidence
Pain	1 RCT (Hewitt 2007)	0	-1	0	0	-1	399	b. 1 trial only: consistency of results cannot be judged. No proof that results are reproducible; d sample size <400 patients for a continuous variable; e. pharmaceutical sponsoring	Low
Adverse events	1 RCT (Hewitt 2007)	0	-1	0	0	-1	399	b. 1 trial only: consistency of results cannot be judged. No proof that results are reproducible; e. pharmaceutical sponsoring	Low

GRADE Evidence profile: Tramadol versus placebo in acute treatment of Grade I or II ankle sprains

Outcome	No of studies (design)	Risk of bias (a)	Inconsistency (b)	Indirectness (c)	Imprecision (d)	Publication bias (e)	No patients	Reasons for downgrading	Level of evidence
Pain	1 RCT (Ekman 2006)	0	-1	0	-1	-1	361	b. 1 trial only: consistency of results cannot be judged. No proof that results are reproducible; d no reporting CI; e. pharmaceutical sponsoring	Very low
Adverse events	1 RCT (Ekman 2006)	0	-1	0	-1	-1	361	b. 1 trial only: consistency of results cannot be judged. No proof that results are reproducible; d no reporting CI; e. pharmaceutical sponsoring	Very low

GRADE Evidence profile: Venotonic drugs (Daflon 1000mg) versus standard care in acute treatment of Grade II or III ankle sprains

Outcome	No of studies (design)	Risk of bias (a)	Inconsistency (b)	Indirectness (c)	Imprecision (d)	Publication bias (e)	No patients	Reasons for downgrading	Level of evidence
Pain	1 RCT (Fotiadis 2011)	-2	-1	0	-2	0	81	a. patients not blinded No ITT analysis b. 1 trial only: consistency of results cannot be judged. No proof that results are reproducible d. <400 patients for a continuous variable	Very low
Ankle swelling	1 RCT (Fotiadis 2011)	-1	0	0	-2	0	81	a. No ITT analysis b. 1 trial only: consistency of results cannot be judged. No proof that results are reproducible d. <400 patients for a continuous variable	Very low
Return to normal activities	1 RCT (Fotiadis 2011)	-2	0	0	-2	0	81	a. patients not blinded No ITT analysis b. 1 trial only: consistency of results cannot be judged. No proof that results are reproducible d. <400 patients for a	Very low

									continuous variable

GRADE Evidence profile (based on SR by Massey et al. 2012): Topical NSAIDs versus placebo

Outcome	No of studies (design)	Risk of bias (a)	Inconsistency (b)	Indirectness (c)	Imprecision (d)	Publication bias (e)	No patients	Reasons for downgrading	Level of evidence
Pain	31 RCT (see SR for references)	-1	0	0	0	0	3455	a. studies often lacking an explanation on randomization, treatment allocation or blinding methods	Moderate
Adverse events	30 RCT (see SR for references)	-1	0	0	0	0	3786	a. studies often lacking an explanation on randomization, treatment allocation or blinding methods	Moderate

GRADE Evidence profile (based on SR by Massey et al. 2012): Topical NSAIDs versus different formulations of the same topical NSAID

Outcome	No of studies (design)	Risk of bias (a)	Inconsistency (b)	Indirectness (c)	Imprecision (d)	Publication bias (e)	No patients	Reasons for downgrading	Level of evidence
Pain	4 RCT (Gallacchi 1990, Governali 1995, Fioravanti 1999, Mahler 2003)	-1	-1	0	-1	0	280	a. most studies lacking an explanation on randomization, treatment allocation or blinding methods b.unclear, inconsistent results d. For 3 studies CI include effects and no effects	Very low

GRADE Evidence profile (based on SR by Massey et al. 2012): Topical versus oral NSAIDs

Outcome	No of studies (design)	Risk of bias (a)	Inconsistency (b)	Indirectness (c)	Imprecision (d)	Publication bias (e)	No patients	Reasons for downgrading	Level of evidence
Pain	3 RCT (Akermark 1990, Hosie 1993, Whitefield 2002)	-1	-2	0	0	0	405	a. two studies lack an explanation on randomization and treatment allocation methods b. contradicting results	Very low
Adverse events	2 RCT (Akermark 1990, Hosie 1993)	-1	0	0	-2	0	305	a. one study (the largest) lack an explanation on randomization and treatment allocation methods d. small sample size. Low number of events not enough to evaluate any potential differences	Very low

GRADE Evidence profile: DEPT (diclofenac epolamine) patch versus placebo patch

Outcome	No of studies (design)	Risk of bias (a)	Inconsistency (b)	Indirectness (c)	Imprecision (d)	Publication bias (e)	No patients	Reasons for downgrading	Level of evidence
Pain	1 RCT (Lionberger 2011)	0	-1	0	-1	+1	134	b. 1 trial only: consistency of results cannot be judged. No proof that results are reproducible d. sample size<400 for a continuous variable e. results coming from one small, positive industry-sponsored trial only	Very low
Ankle swelling	1 RCT (Lionberger 2011)	0	-1	0	-1	+1	134	b. 1 trial only: consistency of results cannot be judged. No proof that results are reproducible d. sample size<400 for a continuous variable e. results coming from one small, positive industry-sponsored trial only	Very low
Adverse events	1 RCT (Lionberger 2011)	0	-1	0	-1	+1		b. 1 trial only: consistency of results cannot be judged. No proof that results are reproducible	Very low

								d. small sample size e. results coming from one small, positive industry-sponsored trial only	

GRADE Evidence profile: Flectoparin Tissugel® (diclofenac epolamine + heparin) versus placebo

Outcome	No of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	No patients	Reasons for downgrading	Level of evidence
Pain	2 RCT (Coudreuse 2010, Costantino 2011)	0	0	0	-1	0	663	d. Only two studies; one gave no details on CIs for difference between groups	Moderate
Ankle swelling	2 RCT RCT (Coudreuse 2010, Costantino 2011)	0	0	0	-1	0	663	d. Only two studies; one gave no details on CIs for difference between groups	Moderate
Adverse events	2 RCT RCT (Coudreuse 2010, Costantino 2011)	0	0	0	-1	0	663	d. Only two studies; one gave no details on CIs for difference between groups	Moderate

GRADE Evidence profile: Flectoparin Tissugel® (diclofenac epolamine + heparin) versus DHEP 1,3% (diclofenac epolamine) plaster

Outcome	No of studies (design)	Risk of bias (a)	Inconsistency (b)	Indirectness (c)	Imprecision (d)	Publication bias (e)	No patients	Reasons for downgrading	Level of evidence
Pain	1 RCT (Costantino 2011)	0	-1	0	0	+1	430	b. 1 trial only: consistency of results cannot be judged. No proof that results are reproducible e. results coming from one small, positive industry-sponsored trial only	Low
Ankle swelling	1 RCT (Costantino 2011)	0	-1	0	0	+1	430	b. 1 trial only: consistency of results cannot be judged. No proof that results are reproducible e. results coming from one small, positive industry-sponsored trial only	Low
Adverse events	1 RCT (Costantino 2011)	0	-1	0	0	+1	430	b. 1 trial only: consistency of results cannot be judged. No proof that results are	Low

								reproducible e. results coming from one small, positive industry-sponsored trial only	

GRADE Evidence profile: comfrey ointment versus diclofenac gel

Outcome	No of studies (design)	Risk of bias (a)	Inconsistency (b)	Indirectness (c)	Imprecision (d)	Publication bias (e)	No patients	Reasons for downgrading	Level of evidence
Pain	1 RCT (D'Anchise 2007)	-1	-1	0	-1	0	164	a. patients not blinded No explanation on allocation/randomization b. 1 trial only: consistency of results cannot be judged. No proof that results are reproducible d. sample size <400 for a continuous variable	Very low
Ankle swelling	1 RCT (D'Anchise 2007)	-1	-1	0	-1	0	164	a. patients not blinded No explanation on allocation/randomization b. 1 trial only: consistency of results cannot be judged. No proof that results are reproducible d. sample size <400 for a continuous variable	Very low
Adverse events	1 RCT (D'Anchise 2007)	-2	-1	0	-1	0	164	a patients not blinded No explanation on allocation/randomization b. 1 trial only: consistency of results cannot be judged. No proof that results are reproducible d. small sample size variable	Very low

GRADE Evidence profile: comfrey ointment versus placebo ointment

Outcome	No of studies (design)	Risk of bias (a)	Inconsistency (b)	Indirectness (c)	Imprecision (d)	Publication bias (e)	No patients	Reasons for downgrading	Level of evidence
Pain	1 RCT (Koll 2004)	-1	-1	0	-1	0	142	a allocation not well explained and baseline characteristics not well balanced b. 1 trial only: consistency of results cannot be judged. No proof that results are reproducible d.sample size<400 for a continuous variable	Very low
Ankle swelling	1 RCT (Koll 2004)	-1	-1	0	-1	0	142	a. allocation not well explained and baseline characteristics not well balanced b. 1 trial only: consistency of results cannot be judged. No proof that results are reproducible d.sample size<400 for a continuous variable	Very low
Adverse events	1 RCT (Koll 2004)	-1	-1	0	-1	0	142	a. allocation not well explained and baseline characteristics not well balanced b. 1 trial only: consistency of results cannot be judged. No proof that results are reproducible d. small sample size	Very low

GRADE Evidence profile: high strength comfrey ointment versus low strength comfrey ointment

Outcome	No of studies (design)	Risk of bias (a)	Inconsistency (b)	Indirectness (c)	Imprecision (d)	Publication bias (e)	No patients	Reasons for downgrading	Level of evidence
Pain	1 RCT (Kucera 2004)	-1	-1	0	-1	0	203	a. allocation not well explained and baseline characteristics not well balanced b. 1 trial only: consistency of results cannot be judged. No proof that results are reproducible d.sample size<400 for a continuous variable	Very low
Ankle swelling	1 RCT (Kucera 2004)	-1	-1	0	-1	0	203	a. allocation not well explained and baseline characteristics not well balanced b. 1 trial only: consistency of results cannot be judged. No proof that results are reproducible d.sample size<400 for a continuous variable	Very low
Functional impairement	1 RCT	-1	-1	0	-1	0	203	a. allocation not well explained and baseline characteristics not well balanced b. 1 trial only: consistency of results cannot be judged. No proof that results are reproducible d.sample size<400 for a continuous variable	Very low
Adverse events	1 RCT (Kucera 2004)	-1	-1	0	-1	0	203	a. allocation not well explained and baseline characteristics not well balanced b. 1 trial only: consistency of results cannot be judged. No proof that results are reproducible d. small sample size	Very low

GRADE Evidence Profile: Rest versus mobilisation (results from SR by van den Bekerom, 2012)

Outcome	No of studies (design)	Risk of bias (a)	Inconsistency (b)	Indirectness (c)	Imprecision (d)	Publication bias (e)	No of patients	Reasons for downgrading	Level of evidence
Improvement in ROM/ankle function	3 RCTs (Green, Eisenhart, Bleakley)	0	0	-1	-1	Not detected	197	a. allocation not well explained and baseline characteristics not well balanced b. 1 trial only: consistency of results cannot be judged. No proof that results are reproducible d.sample size<400 for a continuous variable	Low
Return to activities (sport, work)	3 RCTs (Karlsson, Brooks, Bleakley)	-1	0	-1	0	Not detected	428	a. allocation not well explained and baseline characteristics not well balanced b. 1 trial only: consistency of results cannot be judged. No proof that results are reproducible d.sample size<400 for a continuous variable	Low
Pain	2 RCTs (Brooks, Eisenhart,)*	-1	-1	0	-1	Not detected	296	a. allocation not well explained and baseline characteristics not well balanced b. 1 trial only: consistency of results cannot be judged. No proof that results are reproducible d.sample size<400 for a continuous variable	Very Low
								a. allocation not well explained and baseline characteristics not well balanced b. 1 trial only: consistency of results cannot be judged. No proof that results are reproducible d. small sample size	

**The Green et al. study on pain-free dorsal flexion is reported under improvement in ROM/Ankle Function*

GRADE Evidence profile: Ice versus no ice (results from SR by van den Bekerom, 2012)

Outcome	No of studies (design)	Risk of bias (a)	Inconsistency (b)	Indirectness (c)	Imprecision (d)	Publication bias (e)	No of patients	Reasons for downgrading	Level of evidence
Pain	4 RCTs (Sloan, Laba, Hocutt, Basur)	-2	-2	0	-1	Not detected	270	a. Majority of studies were of lower quality. b. Difference in whether or not a significant effect was reported d. total sample size for continuous variable is less than 400	Very low
Ankle swelling	4 RCTs (Sloan, Laba, Cote, Basur)	-1	-2	0	-1	Not detected	263	a. 2 RCTs of reasonable quality, two RCTs of lower quality. b. The studies provided inconsistent results d. Total sample size for continuous variable is less than 400	Very low
Return to activities	3 RCTs (Laba, Hocutt, Basur)	-1	-2	0	-1	Not detected	127	a. 3 RCTs of various quality. b. The studies provided very inconsistent results d. Total sample size for continous variable is less than 400	Very low

GRADE Evidence profile: Compression vs no compression (results from SR by van den Bekerom, 2012)

Outcome	No of studies (design)	Risk of bias (a)	Inconsistency (b)	Indirectness (c)	Imprecision (d)	Publication bias (e)	No of patients	Reasons for downgrading	Level of evidence
Pain (4 weeks f/u)	1 RCT (Airaksinen)	-1	-1	0	-2	Not detected	44	a. One RCT of moderate quality b. only one small RCT so not clear if reproducible d. sample size (n=44)	Very low
Ankle swelling (4 weeks f/u)	1 RCT (Airaksinen)	-1	-1	0	-2	Not detected	44	a. One RCT of moderate quality b. only one small RCT so not clear if reproducible) d. sample size (n=44)	
ROM (4 weeks f/u)	1 RCT (Airaksinen)	-1	-1	0	-2	Not detected	44	a. One RCT of moderate quality b. only one small RCT so not clear if reproducible) d. sample size (n=44)	Very low

GRADE Evidence profile: Ultrasound vs placebo (results from SR by van den Bekerom, 2011)

Outcome	No of studies (design)	Risk of bias (a)	Inconsistency (b)	Indirectness (c)	Imprecision (d)	Publication bias (e)	No of patients	Reasons for downgrading	Level of evidence
General improvement	3 RCTs	-1	0	0	-1	Not detected	341	a. Two large RCTs and one small, moderate quality d. CI Includes both benefits and harm	Low
Pain	2 RCTs (Oakland, Nyanzi)	-1	0	0	-1	Not detected	198	a. RCTs were of various quality d. CI Includes both benefits and harm	Low
Swelling	2 RCTs (Nyanzi, Van Lelieveld)	-1	0	0	-1	Not detected	91	a. RCTs were of various quality d. CI Includes both benefits and harm, total sample size is less than 100	Low

GRADE Evidence profile: Laser vs placebo

Outcome	No of studies (design)	Risk of bias (a)	Inconsistency (b)	Indirectness (c)	Imprecision (d)	Publication bias (e)	No of patients	Reasons for downgrading	Level of evidence
Pain (short and intermediate term)	1 RCT (de Bie, 1998)	0	-1	0	-2	Not detected	145	b. One RCT so not clear if reproducible d. CI includes effect and no effect, sample size is low	Very Low
Ankle function (short and intermediate term)	1 RCT (de Bie, 1998)	0	-1	0	-2	Not detected	145	b. One RCT so not clear if reproducible d. CI includes effect and no effect, sample size is low	Very Low

GRADE Evidence profile: Functional treatment vs immobilisation (results from SR by Kerkhoffs, 2002)

Outcome	No of studies (design)	Risk of bias (a)	Inconsistency (b)	Indirectness (c)	Imprecision (d)	Publication bias (e)	No of patients	Reasons for downgrading	Level of evidence
Pain short-term	3 RCTs	-1	- 1	0	-1	Not detected	213	a. Two of tree RCTs had unclear allocation concealment b.Studies reported inconsistent results d. CI included both benefits and harms	Very low
Pain intermediate term	5 RCTs	-1	-1	0	-1	Not detected	308	a. 4 of the 5 RCTs had no or unclear allocation concealment b. Studies reported inconsistent results d. CI included both benefits and harms	Very low
Pain long-term	5 RCTs	-1	-1	0	-1	Not detected	283	a. 3 of the 5 RCTs had no or unclear allocation concealment b. Studies reported inconsistent results d. CI included both benefits and harms	Very Low
Swelling short term	3 RCTs	-1	-1	0	-1	Not detected	260	a. 2 of the 3 RCTs had no or unclear allocation concealment b. Studies reported inconsistent results d. CI included both benefits and	Very Low

								harms	
Swelling intermediate term	1 RCT	0	-1	0	-2	Not detected	77	b. Only one RCT available not clear if reproducible d. downgraded for low sample size (n=77)	Very Low
Swelling long term	4 RCTs	-1	-1	0	-1	Not detected	280	a. Two of the RCTs had unclear allocation concealment b. Studies reported inconsistent results d. CI included both benefits and harms	Very Low
Return to pre-injury level work short term	2 RCTs	-1	0	0	-1	Not detected	150	a.; One RCT had unclear allocation concealment d. CI included both benefits and harms	Low
Return to pre-injury level work intermediate term	3 RCTs	-1	-1	0	-1	Not detected	214	a. Two RCTs had unclear allocation concealment b; Studies reported inconsistent results d. CI included both benefits and harms	Very Low
Return to pre-injury level sport short term	3 RCTs	0	-1	0	-1	Not detected	180	b. Studies provide inconsistent results d. population size is less than 400 (small effect)	Low
Return to pre-injury level sport intermediate term	4 RCTs	-1	-1	0	-1	0	294	a. Majority of studies had unclear allocation concealment b. Studies reported inconsistent results d. CI included both benefits and harms	Very Low
Return to pre-injury level sport long term	5 RCTs	0	-1	0	0	-1	360	b. Studies reported slightly inconsistent results d. CI effect size > 0.5	Low
Recurrent injury short term	1 RCT	0	-1	0	-2	0	77	b. Only one RCT available not clear if reproducible d. CI included both benefits and harms	Very Low
Recurrent injury intermediate	6 RCTs	-1	-1	0	-1	0	456	a. The majority of RCTs had unclear allocation concealment	Very low

term								b. RCTs provided inconsistent results d. CI included both benefits and harms	
Recurrent injury long term	6 RCTs	-1	0	0	-1	0	487	D. CI included both benefits and harms	Low

GRADE Evidence Profile: Functional treatment vs immobilisation severe and complete rupture

Outcome	No of studies (design)	Risk of bias (a)	Inconsistency (b)	Indirectness (c)	Imprecision (d)	Publication bias (e)	No of patients	Reasons for downgrading	Level of evidence
Quality of ankle function (FAOS) 3 months f/u	1 RCT (Lamb, 2009)	-1	-1	0	-1	Not detected	584(all groups)	a. RCT had moderate risk of bias b. Only one RCT that was not multi-centered was available d.Effect size is small (0.36) and the upper or lower confidence limit crosses an effect size of 0.5 in either direction).	Very Low
Pain 3 months f/u	2 RCTs (Ardevol 2001, Lamb 2009)	0	-2	0	-1	Not detected	705	b. The RCTs contradict each other on results for pain. d. The effects size on the large well conducted RCT is very small (0.27)	Very Low
Reinjury	1 RCT (Lamb, 2009)	-1	-1	0	-1	Not detected	121	a. RCT had moderate risk of bias b. Only one RCT that was not multi-centered was available d. total sample size was low	Very Low

GRADE Evidence profile for functional treatment (based on SR by Kerkhoffs et al. 2002): Elastic bandage versus tape

Outcome	No of studies (design)	Risk of bias (a)	Inconsistency (b)	Indirectness (c)	Imprecision (d)	Publication bias (e)	No patients	Reasons for downgrading	Level of evidence
Pain (short term)	2 RCT (Allen 1985, Zeegers 1995)	-1	0	0	-1	0	148	a. studies with unclear allocation concealment and no blinding d. CI includes both benefits and harms	Low
Pain (long term)	1 RCT (zeegers 1995)	-1	-1	0	-1	0	121	a. study with unclear allocation concealment and no blinding b.1 trial only: consistency of results cannot be judged. No proof that results are reproducible d. CI includes both benefits and harms	Very low
Swelling (short and long-term)	1 RCT (Zeegers 1995)	-1	-1	0	-1	0	121	a. study with unclear allocation concealment and no blinding b.1 trial only: consistency of results cannot be judged. No proof that results are reproducible d. CI includes both benefits and harms	Very low
ROM (short and long term)	1 RCT (Zeegers 1995)	-1	-1	0	-1	0	122	a. study with unclear allocation concealment and no blinding b.1 trial only: consistency of results cannot be judged. No proof that results are reproducible d. CI includes both benefits and harms	Very low
Return to work	2 RCTs (Jongen 1992, Zeegers 1995)	-1	-1	0	-1	0	199	a. studies with unclear allocation concealment and no blinding b.unclear results d. CI includes both benefits and harms	Very low
Adverse events	2 RCT (jongen	-1	0	0	-1	0	208	a. one study with unclear allocation concealment and	Low

	1992, Pasila 1975)							no blinding d. broad CI	

GRADE Evidence profile for functional treatment (based on SR by Kerkhoffs et al. 2002): Elastic bandage versus semi-rigid (brace) ankle support

Outcome	No of studies (design)	Risk of bias (a)	Inconsistency (b)	Indirectness (c)	Imprecision (d)	Publication bias (e)	No patients	Reasons for downgrading	Level of evidence
Pain (short term)	2 RCTs (Karlsson 1996, zeegers 1995)	-1	0	0	-1	0	208	a. No blinding. one study with unclear allocation concealment d. CI includes effect and no effect	Low
Pain (long term)	1 RCT (zeegers 1995)	-1	-1	0	-1	0	124	a.unclear allocation concealment and no blinding b.1 trial only: consistency of results cannot be judged. No proof that results are reproducible d. CI includes benefits and harms	Very low
Swelling (short-term)	1 RCTs (zeegers 1995)	-1	-1	0	-1	0	124	a.One study with unclear allocation concealment and no blinding b.1 trial only: consistency of results cannot be judged. No proof that results are reproducible d. CI includes benefits and harms	Very low
Swelling (long-term)	2 RCTs (Karlsson 1996, zeegers 1995)	-1	0	0	-1	0	208	a.One study with unclear allocation concealment and no blinding d. CI includes benefits and harms	Low
ROM (short and long term)	1 RCTs (zeegers 1995)	-1	-1	0	-1	0	124	a. unclear allocation concealment and no blinding b.1 trial only: consistency of results cannot be judged. No proof that results are reproducible d. CI includes benefits and	Very low

								harms	
Return to work/sports or sports	2 RCTs (Karlsson 1996, Leanderson 1995)	-1	0	0	-1	0	157	a. no blinding d. Large CI, sample size <400 for a continuous variable	Low
Recurrent injury	1 RCT (Dettori 1994)	-1	-1	0	-2	0	46	a.unclear allocation concealment and randomization methods b.1 trial only: consistency of results cannot be judged. No proof that results are reproducible d. CI includes benefits and harms; very low sample size	Very low

GRADE Evidence profile for functional treatment (based on SR by Kerkhoffs et al. 2002): Elastic bandage versus lace-up ankle support

Outcome	No of studies (design)	Risk of bias (a)	Inconsistency (b)	Indirectness (c)	Imprecision (d)	Publication bias (e)	No patients	Reasons for downgrading	Level of evidence
Pain (short and long-term)	1 RCT (zegeers 1995)	-1	-1	0	-1	0	122	a. unclear allocation concealment and no blinding b.1 trial only: consistency of results cannot be judged. No proof that results are reproducible d. CI includes benefits and harms	Very low
Swelling (short-term)	1 RCT (zegeers 1995)	-1	-1	0	-1	0	122	a. unclear allocation concealment and no blinding b.1 trial only: consistency of results cannot be judged. No proof that results are reproducible d. Large CI, sample size <400 for a continuous variable	Very low
Swelling (long-term)	1 RCT (zegeers 1995)	-1	-1	0	-1	0	122	a. unclear allocation concealment and no blinding b.1 trial only: consistency	Very low

								of results cannot be judged. No proof that results are reproducible d. CI includes benefits and harms	
ROM (short and long term)	1 RCT (zegeers 1995)	-1	-1	0	-1	0	122	a. unclear allocation concealment and no blinding b.1 trial only: consistency of results cannot be judged. No proof that results are reproducible d. CI includes benefits and harms	Very low
Return to work	1 RCT (zegeers 1995)	-1	-1	0	-1	0	122	a. unclear allocation concealment and no blinding b.1 trial only: consistency of results cannot be judged. No proof that results are reproducible d. CI includes benefits and harms	Very low

GRADE Evidence profile for functional treatment (based on SR by Kerkhoffs et al. 2002): Tape versus semi-rigid (brace) ankle support

Outcome	No of studies (design)	Risk of bias (a)	Inconsistency (b)	Indirectness (c)	Imprecision (d)	Publication bias (e)	No patients	Reasons for downgrading	Level of evidence
Pain (short and long-term)	1 RCT (zegeers 1995)	-1	-1	0	-1	0	121	a. unclear allocation concealment and no blinding b.1 trial only: consistency of results cannot be judged. No proof that results are reproducible d. CI includes benefits and harms	Very low
Swelling (short and long-term)	1 RCT (zegeers 1995)	-1	-1	0	-1	0	121	a. unclear allocation concealment and no blinding b.1 trial only: consistency of results cannot be judged. No proof that results are reproducible d. CI includes benefits and harms	Very low
ROM (short-term)	1 RCT (zegeers 1995)	-1	-1	0	-1	0	122	a. unclear allocation concealment and no blinding b.1 trial only: consistency of results cannot be judged. No proof that results are reproducible d. CI includes benefits and harms	Very low
ROM (long-term)	1 RCT (zegeers 1995)	-1	-1	0	-2	0	99	a. unclear allocation concealment and no blinding b.1 trial only: consistency of results cannot be judged. No proof that results are reproducible d. CI includes benefits and harms; very low sample size	Very low
Recurrent injury (intermediate	1 RCT (Sommer	-1	-1	0	-2	0	66	a. unclear allocation concealment and randomization methods	Very low

term)	1993)							and no blinding b.1 trial only: consistency of results cannot be judged. No proof that results are reproducible d. CI includes benefits and harms; very low sample size	
Return to work	1 RCT (zegeers 1995)	-1	-1	0	-1	0	121	a. unclear allocation concealment and no blinding b.1 trial only: consistency of results cannot be judged. No proof that results are reproducible d. CI includes benefits and harms	Very low

GRADE Evidence profile for functional treatment (based on SR by Kerkhoffs et al. 2002): Tape versus lace-up ankle support

Outcome	No of studies (design)	Risk of bias (a)	Inconsistency (b)	Indirectness (c)	Imprecision (d)	Publication bias (e)	No patients	Reasons for downgrading	Level of evidence
Pain (short - term)	1 RCTs (zegeers 1995)	-1	-1	0	-1	0	119	a. unclear allocation concealment and no blinding b.1 trial only: consistency of results cannot be judged. No proof that results are reproducible d. CI includes benefits and harms	Very low
Pain (long-term)	2 RCTs (zegeers 1995, Twellaar 1993)	-1	-1	0	-1	0	231	a. unclear allocation concealment and no blinding b.unclear results d. CI includes benefits and harms	Very low
Swelling (short-term)	1 RCT (zeegers 1995)	-1	-1	0	-1	0	119	a. unclear allocation concealment and no blinding b.1 trial only: consistency of results cannot be judged. No proof that results are reproducible	Very low

								d. Large CI; sample size <400 for a continuous variable	
Swelling (long-term)	2 RCTs (zegeers 1995, Twellaar 1993)	-1	0	0	-1	0	231	a. unclear allocation concealment and no blinding d. CI includes benefits and harms	Low
ROM (short and long term)	1 RCT (zeegers 1995)	-1	-1	0	-1	0	119	a. unclear allocation concealment and no blinding b.1 trial only: consistency of results cannot be judged. No proof that results are reproducible d. CI includes benefits and harms	Very low
Return to work	1 RCT (zegeers 1995)	-1	-1	0	-1	0	119	a. unclear allocation concealment and no blinding b.1 trial only: consistency of results cannot be judged. No proof that results are reproducible d. CI includes benefits and harms	Very low

GRADE Evidence profile for functional treatment (based on SR by Kerkhoffs et al. 2002): Semi-rigid (brace) versus lace-up ankle support

Outcome	No of studies (design)	Risk of bias (a)	Inconsistency (b)	Indirectness (c)	Imprecision (d)	Publication bias (e)	No patients	Reasons for downgrading	Level of evidence
Pain (short-term)	1 RCTs (zegeers 1995)	-1	-1	0	-1	0	124	a. unclear allocation concealment and no blinding b.1 trial only: consistency of results cannot be judged. No proof that results are reproducible d. CI includes benefits and harms	Very low
Pain (long-term)	1 RCTs (zegeers 1995)	-1	-1	0	-1	0	122	a. unclear allocation concealment and no blinding b.1 trial only: consistency of results cannot be judged. No proof that results are reproducible d. CI includes benefits and harms	Very low
Swelling (short-term)	1 RCT (zeegers 1995)	-1	-1	0	0	0	122	a. unclear allocation concealment and no blinding b.1 trial only: consistency of results cannot be judged. No proof that results are reproducible d. large CI	Very low
Swelling (long-term)	1 RCT (zeegers 1995)	-1	-1	0	-1	0	122	a. unclear allocation concealment and no blinding b.1 trial only: consistency of results cannot be judged. No proof that results are reproducible d. CI includes benefits and harms	Very low
ROM (short and long term)	1 RCT (zeegers 1995)	-1	-1	0	-1	0	122	a. unclear allocation concealment and no blinding b.1 trial only: consistency of results cannot be judged. No proof that	Very low

								results are reproducible d. CI includes benefits and harms	
Return to work	1 RCT (zegeers 1995)	-1	-1	0	-1	0	122	a. unclear allocation concealment and no blinding b.1 trial only: consistency of results cannot be judged. No proof that results are reproducible d. CI includes benefits and harms	Very low

GRADE Evidence profile for functional treatment (based on SR by Kemler et al. 2011): Brace versus other functional therapies

Outcome	No of studies (design)	Risk of bias (a)	Inconsistency (b)	Indirectness (c)	Imprecision (d)	Publication bias (e)	No patients	Reasons for downgrading	Level of evidence
Pain	4 RCTs (Twellaar, Boyce, Beynnon, Dettori)	-1	-2	0	-1	0	392	a. Blinding of assessors or clinicians not clear. Baseline characteristics not well balanced in two of the 4 studies b. unclear results d. <400 patients for a continuous variable	Very low
Swelling	4 RCTs (Boyce, Twellaar, Neumann, Dettori)	-1	0	0	-1	0	310	a. Blinding of assessors or clinicians not clear. Baseline characteristics not always well balanced. d. <400 patients for a continuous variable	Low
Functional outcome	5 RCTs (Lamb, Boyce, Beynnon, Karlsson, Leanderson,)	-1	-1	0	0	0	1005	a. Blinding of assessors or clinicians not clear. b. the largest study and a further one found a benefit but two smaller ones found no difference in outcomes	Low
Recurrent injuries	4 RCTs (Beynnon, Neumann, Dettori, Twellaar)	-1	0	0	0	0	472	a. Blinding of assessors or clinicians not clear. Baseline characteristics not well balanced. In ¾ studies	Moderate
Return to sports	3 RCTs	-1	-1	0	-1	0	378	a. Blinding of assessors or	Very low

	(Karlsson, Beynnon, Neumann)							clinicians not clear. b. unclear results d. < 400 patients for a continuous variable	
Return to work	6 RCTs (Leanderson, Karlsson, Twellaar, Neumann, Beynnon, Dettori)	-1	-1	0	-1	0	631	a. No blinding of patients in 3/6 studies. Blinding of assessors or clinicians not clear. b. unclear results (only 2 small studies showed a significant benefit) b. significant results from only two small studies of less than 100 patients each	Very low

GRADE Evidence profile (based on SR by Bleakley, 2008): RICE + Manual therapy vs RICE

Outcome	No of studies (design)	Risk of bias (a)	Inconsistency (b)	Indirectness (c)	Imprecision (d)	Publication bias (e)	No of patients	Reasons for downgrading	Level of evidence
ROM (ankle dorsal flexion in degrees)	2 RCTs	-1	0	0	-2	Not detected	96	a. One of the RCTs had unclear risk of bias d. Confidence interval includes both benefits and harms, one RCT does not provide a significant effect	Very Low
Pain	1 RCT	-1	-1	0	-1	Not detected	55	a. RCT with unclear risk of bias b. Only one non-multi centered RCT, consistency cannot be determined d. Sample size for continuous variable was low	Very Low

GRADE Evidence profile: Supervised Exercise vs conventional treatment (based on SR by Van Rijn, 2010)

Outcome	No of studies (design)	Risk of bias (a)	Inconsistency (b)	Indirectness (c)	Imprecision (d)	Publication bias (e)	No of patients	Reasons for downgrading	Level of evidence
Pain, short-term	2 RCTs, (Nilsson 1983, Wester 1996)	-2	0	0	-1	Not detected	166	a. Two of the RCTs had high risk of bias d. The confidence intervals provided are very large suggesting large uncertainty	Very Low
Pain, long-term	3 RCTs (Van Rijn 2007, Oostendorp 1987, Nilsson 1983)	-1	0	0	-1	Not detected	345	a. Two of the RCTs had high risk of bias d. The confidence intervals provided are very large suggesting large uncertainty	Low
Ankle function, short term	2 RCTs (Basset 2007 , Hultman 2010)	-1	-1	0	-1	Not detected	112	a. the RCTs had a high risk of bias including unsure allocation concealment b. There is variety in results reported across studies and the scales deployed are not consistent d. low sample size for continuous variable	Very Low
Ankle Function, long term	1 RCTs (Karlsson 1996)	-1	-1	-1	-1	Not detected	84	a. RCT had high risk of bias with unsure allocation concealment b. Only one trial, not multi-centered c. study were in athletes only d. Insufficient sample size for continuous variable	Very Low
Re-injury	5 RCTs (Van Rijn 2007, Holme 1999, Nilsson 1983, Reinhardt 1999, Wester 1996)	-1	-1	-1	-1	Not detected	525	a. Various risk of bias across studies b. Studies reported either significant difference in favor of exercise or no difference c. Some studies were on athletes and recruits or professional soldiers d. Study by Van Rijn show large variance in results	Very Low

Return to work	6 RCTs (Karlsson 1996, Brooks 1981, Nilsson 1983, Oostendorp 1987, Reinhardt 1999, Hultman 2010)	-2	-1	-1	-1	Not detected	465	a. All studies had a high risk of bias b. Studies reported inconsistent results c. Some studies were on very specific study populations d. In several studies effect size could not be calculated	Very Low
Return to sport	3 RCTs (Karlsson 1996, Reinhardt 1999, Oostendorp 1987)	-2	0	-1	-1	Not detected	180	a. All studies had a high risk of bias c. Only studies in specific sub populations d. Not possible to calculate effect sizes in D; Low sample size for continuous variable	Very low

GRADE Evidence profile: Unsupervised Exercise vs conventional treatment

Outcome	No of studies (design)	Risk of bias (a)	Inconsistency (b)	Indirectness (c)	Imprecision (d)	Publication bias (e)	No of patients	Reasons for downgrading	Level of evidence
Re-injury	1 RCT (Hupperet 2009)	0	-1	-1	0	Not detected	522	b. Only one trial not multi-centered c. study is on athletes	Low

GRADE Evidence Profile: Accelerated rehabilitation vs rehabilitation

Outcome	No of studies (design)	Risk of bias (a)	Inconsistency (b)	Indirectness (c)	Imprecision (d)	Publication bias (e)	No of patients	Reasons for downgrading	Level of evidence
Ankle function	1 RCT (Bleakley 2010)	-1	-1	0	-2	Not detected	101	a. RCT had an unclear risk of bias b. Only one trial and uncertain whether results are reproducible d. Sample size for continuous variable is low and results have very large confidence intervals suggesting uncertainties	Very low

APPENDIX 9. SUMMARY OF RECOMMENDATIONS SCORES

Appendix 9.1. Recommendations scores for diagnosis

Item	Recommendation	GoR	LoE	1	2	3	4	5	6	7	8	9	10	11	12	13	Comments	Min	Max	Mean	Median	%4 or 5
History taking	History taking should contain at least a description of the injury mechanism, the first symptoms and their evolution, the first management of the injury and a global medical history	Strong	Very low	5	4	5	4	5	5	5	5	5	5	5	4	5	And previous history of ankle sprain	4	5	5	5	100%
Physical examination	Inspection and palpation are recommended in the initial assessment of acute ankle sprain	Strong	Very Low	5	4	5	5	5	5	5	5	5	5	5	4	5		4	5	5	5	100%
	Anterior drawer test and talar tilt tests should not be performed in the acute phase (48 hours after injury)	Weak	Low	5	2	5	4	5	4	2	4	5	5	5	5	2	Drawer test is also clinically achievable/ OK if experimented physicians/ ATD easier immediately than after some days	2	5	4	5	77%
	A clinical reevaluation after 4 to 7 days after ankle trauma is recommended. The presence of hematoma, local pain at palpation and a positive anterior drawer test result during this re-evaluation give a better chance to diagnose a rupture of the ligament than the same examination within 48h	Strong	Low	4	5	5	4	5	3	4	5	5	5	5	4	2	ATD easier immediately than after some days/ risk of disruption of the healing process	2	5	4	5	85%
Ottawa ankle rules	The use of OAR is recommended to exclude a fracture after acute ankle sprain	Strong	Moderate	5	4	5	4	5	2	5	5	5	5	4	4	5		2	5	4	5	92%

Item	Recommendation	GoR	LoE	1	2	3	4	5	6	7	8	9	10	11	12	13	Comments	Min	Max	Mean	Median	%4 or 5
	A training of the health care professionals about the OAR application is recommended	Strong	Low	5	5	5	3	5	4	5	5	5	5	4	5	5		3	5	5	5	92%
	It is recommended to systematically document the result of the OAR in the patients medical record	Strong	Very low	5	5	5	4	5	4	5	5	4	5	4	4	5		4	5	5	5	100%
	In positive OAR patients, the tuning fork test on the distal fibula shaft could be considered for excluding fractures and further reducing the need for radiographies	Weak	Very low	NA	3	4	4	NA	2	3	3	3	3	5	3	3	Risk of false (-), subjective intrepretation	2	5	3	3	27%
	The use of other decision rules is not recommended to exclude a fracture after acute ankle sprain	Strong	Low	NA	4	5	4	NA	4	4	5	5	4	5	4	5		4	5	4	4	100%
Imaging	A radiography (3 views) is recommended in front of a positive OAR	Strong	Moderate	5	4	5	4	5	5	5	5	5	5	5	5	4	Use of Rx is required **only** if the OAR is positive/Quality of the X-rays is more important than the number of views	4	5	5	5	100%
	In positive OAR patients, ultrasonography could be considered for excluding fractures and further reducing the need for radiographies	Weak	Very low	NA	2	3	3	5	1	2	3	3	2	5	3	1	operator-dependent, time-consuming/ need of specialised echographist, risk of long waiting time since echo unit are overbooked, no change in the treatment, increase of patients concern if no explication provided by the	1	5	3	3	17%

Item	Recommendation	GoR	LoE	1	2	3	4	5	6	7	8	9	10	11	12	13	Comments	Min	Max	Mean	Median	%4 or 5
																	echographist					
	The use of MRI should not be performed in the initial assessement of acute ankle sprain	Strong	Very low	5	5	5	4	5	4	5	5	5	5	5	5	5		4	5	5	5	100%

Appendix 9.2. Recommendations scores for therapy

Item	Recommendation	GoR	LoE	1	2	3	4	5	6	7	8	9	10	11	12	13	Comments	Min	Max	Mean	Median	%4 or 5
Medication	Topical NSAIDs (diclofenac, ibuprofen, ketoprofen and piroxicam) are recommended for pain alleviation in acute ankle sprain.	Strong	Moderate	5	5	NA	4			1	3	4		5		2	Money for nothing,,,/ Problem with adverses effects such photo-sensibilisation / Je trouve la recommandation pas assez claire. Plutôt que de la présenter par produit, je la présenterait par palier de douleur car c'est cela qui intéresse le clinicien et le patient 1° paracétamol + topical NSAIDs 2° paracétamol + oral NSAIDs	1	5	4	4	63%
	Paracetamol is recommended as the additional analgesic treatment	Strong	Low	5	5	NA	4			1	5	5		5		2	Surely a good placebo	1	5	4	5	75%
	If topical NSAIDs combined with paracetamol are not effective for pain alleviation, oral NSAIDs could be considered, with a preference for celecoxib	Weak	Low	5	4	NA	3			2	3	4		2		2	Ice and immobilization are most usually very effective in pain alleviation. Moreover, Inflammation is process that is required at the beginning of the tear healing; be sure not to use topical and oral in combination, if oral is needed than topical must be stopped;/ Voor mij is dit een verkeerde interpretatie van de evidence, ik denk dat een betere formulering voor minder verwarring zorgt ttz Volgens de evidence (gebaseerd op 4 RCT's) bestaat er geen verschil tussen celecoxib en een niet-selectieve NSAID, ze zijn beiden even effectief. Dus ik begrijp niet waarom ik eerder celecoxib moet voorschrijven wetende dat deze COX-II inhibitoren veel duurder zijn. Ik zou in de	2	5	3	3	38%

Item	Recommendation	GoR	LoE	1	2	3	4	5	6	7	8	9	10	11	12	13	Comments	Min	Max	Mean	Median	%4 or 5
																	aanbeveling vermelden dat COX-II inhibitoren aangewezen zijn bij patiënten met gastrointestinale, renale...klachten/ no evidence and risk of many bias; so why do we recommend one kind of NSAIDs?					
	Daflon® is not recommended in the treatment of acute ankle sprain	Strong	Very low	5	5	NA	5			5	5	5		5		5		5	5	5	5	100%
	There is a lack of studies to recommend a plaster that combines diclofenac and heparin versus topical diclofenac alone in the treatment of acute ankle sprain	Weak	Low	5	5	NA	4			3	4	3		4		5	Hardly applicable: either the sprain is light, then a plaster is a non sense, or it is a severe one, then topical diclofenac is a non sense (I believe it is totally useless in ankle sprain in general)/ no experience enough to appreciate	3	5	4	4	75%
	There is a lack of studies to recommend a comfrey root extract ointment (“pommade/gel de consoude”) versus topical diclofenac in the treatement of acute ankle sprain	Weak	Very low	5	5	NA	4			5	5	2		5		5	In de praktijk wordt vaak Traumeel voorgeschreven is dit nagegaan in deze studie?	2	5	5	5	88%
RICE	Based on the current available evidence, the use of RICE (Rest-Ice-Compression-Elevation) cannot be routinely recommended as a treatment for acute ankle sprain	Strong	Very Low	NA	5	NA	4			4	5	3		4		1	Except Rest and Ice in the acute phase; no evidence of positive effect but no adverse effect with this therapy!! /Ce n’est pas parce que nous n’avons pas de preuve scientifique publiée de l’efficacité du traitement par RICE qu’il faut le balayer d’un trait. Je ne suis pas un fervent de	1	5	4	4	71%

Item	Recommendation	GoR	LoE	1	2	3	4	5	6	7	8	9	10	11	12	13	Comments	Min	Max	Mean	Median	%4 or 5
																	la glace et je suis opposé à la compression pour la douleur qu'elle provoque, mais l'observation clinique quotidienne me fait penser que le drainage postural et le repos relatif après entorse font partie du traitement initial. Ce n'est pas parce qu'on n'a pas prouvé leur rôle qu'il faut écrire que cela ne sert à rien.					
Physical Therapy	Ultrasound is not recommended in the treatment of acute ankle sprain (strong recommendation, low level of evidence).	Strong	Low	NA	4	NA	5			5	5	5		5		5		4	5	5	5	100%
	Laser therapy cannot be recommended in the treatment of acute ankle sprain due to conflicting evidence	Strong	Very low	NA	4	NA	4			5	5	5		5		5		4	5	5	5	100%
Immobilisation/functional therapy	Functional treatment is preferred to immobilisation for the immediate treatment of non severe ankle sprain (strong recommendation, low level of evidence). The available evidence does not allow to draw any recommendation about the kind of ankle support (elastic versus semi-rigid)	Strong	Low	5	4	NA	4			4	3	5		5		2	I would replace the term "functional treatment" with "ankle support" / Je trouve le message global confus et mal stadifié. La première cause en est l'absence de définition de la gravité d'une entorse de cheville comme dit ci-dessus. Je trouve anormal de laisser entendre que le traitement par simple bandage élastique est aussi valable que celui par chevillère semi-rigide(pex. Aircast) notamment dans les entorses de gravité modérée à sévère. Certes, la	2	5	4	4	75%

Item	Recommendation	GoR	LoE	1	2	3	4	5	6	7	8	9	10	11	12	13	Comments	Min	Max	Mean	Median	%4 or 5
																	littérature ne permet pas actuellement d'être formel dans les conclusions. Néanmoins, le traitement par bandage élastique est trop souvent associé à une médiocrité du diagnostic initial. Il conduit fréquemment à une sous estimation de l'entorse par le patient et à une insuffisance de prise en charge thérapeutique qui sont sources de chronicité et de complication. La contention plus ou moins stricte est un élément essentiel du traitement de l'entorse, il faut donc que les recommandations soient aussi développées et complètes que possible pour le patient et le praticien.					
	In very severe cases where the patient is unable to bear weight after 3 days, a short period of immobilisation with a below knee cast or Aircast® can be considered on a case by case basis	Strong	Low			NA	4			5	3	5		5		5		3	5	5	5	83%
Exercice therapy	Exercise therapy whether supervised or unsupervised can be recommended in the treatment of ankle sprain in order to reduce the risk of recurrent sprain. The available evidence does not allow to draw	Strong	Low	NA	4	NA	4			4	4	5		5		4	Proprioception seems logical, even though EBM couldn't make the difference (but EBM is here scarcely applicable)/ J'approuve cette recommandation mais je regrette qu'elle ne soit pas un peu plus détaillée, notamment en terme de timing de la rééducation proprioceptive en fonction de	4	5	4	4	100%

Item	Recommendation	GoR	LoE	1	2	3	4	5	6	7	8	9	10	11	12	13	Comments	Min	Max	Mean	Median	%4 or 5
	any recommendation in favour of a particular exercice intervention.																la gravité initiale de l'entorse.					
Manual therapy	Manual therapy cannot be routinely recommended	Weak	Very low	NA	4	NA	5			5	4	4		5		5		4	5	5	5	100%
Patients' information	Patients' information on the benefit-risk of each treatment and on the warning clues of a bad evolution of ankle sprain is recommended.	Strong	Very low	5	5	NA	4			5	5	5		5		5		4	5	5	5	100%