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# STUDY PLAN

## SURGICAL OR CONSERVATIVE TREATMENT FOR ANKLE FRACTURES IN ADULTS?

### *A systematic review and meta-analysis of the benefits and harms*

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## INTRODUCTION

Fractures of the ankle are common and constitutes about 10% of all bone injuries.<sup>1</sup> A recent study on the epidemiology of 9,767 patients with ankle fractures reported the overall incidence to be 168.7/100,000/year.<sup>2</sup> Increasing incidence of ankle fractures have been reported during the past decades.<sup>1,3,4</sup> This is primarily thought to be caused by an increase in the number of people participating in sports and a shift in demographics towards an elderly population.<sup>1,3,4</sup>

The mean age of patients with ankle fractures is reported between 41-49 years with a bimodal distribution with peaks in younger males and older females.<sup>1,2,4</sup> Unimalleolar fractures represent about 70% of all fractures, bimalleolar fractures 20% and trimalleolar fractures about 10%.<sup>1,4,5</sup>

The primary goal when treating ankle fractures is to restore the anatomical function of the ankle joint. Surgical or conservative (non-surgical) treatment interventions can be used.<sup>6,7</sup> Surgical intervention involves reposition and surgical fixation of the fracture with screws, plates, or pins. The aim is to provide anatomical restoration and stability of the fractured bone/bones and facilitate early mobilization. Conservative treatment intervention involves immobilization in a below-knee cast for several weeks. Depending on the fracture comminution, stability of the ankle joint following reposition, general soft tissue status, soft tissue injuries, patients' history of co-morbidity, age and local traditions/individual surgeons' choice, conservative or surgical treatment methods are favored.

However, both surgical and conservative treatment options are associated with risk of complications.<sup>7</sup> Conservative treatment involves immobilization for several weeks and may lead to muscle atrophy, stiffness and swelling of the ankle joint and cartilage degeneration.<sup>7</sup> Moreover, increased risk of malalignment, nonunion and prolonged immobilization are all complications reported in connection with conservative treatment.<sup>7,8</sup> Surgical interventions are associated with the risk of: infection, deep vein thrombosis, reoperation, failure of hardware, amputation and mortality.<sup>7,9</sup>

Despite fractures of the ankle being very common, consensus regarding treatment with surgery or by conservative means, lacks evidence. Several studies have indicated that surgical treatment of ankle fractures may be superior to conservative treatment.<sup>10-13</sup> In contrast other authors have

reported that closed ankle fractures may have comparable or better outcome when conservative treatment methods are used.<sup>8,14,15</sup> A recent systematic review by Donken et al.<sup>7</sup> (2012) reported insufficient evidence to conclude whether surgical or conservative treatment are superior in long-term outcomes following ankle fractures in adults. However, the study by Donken et al.<sup>7</sup> only included four trials, and several randomized trials have been published recently.<sup>8,15</sup>(all new available studies from the literature search will be added) The literature lacks a recent systematic review including all relevant large-scale randomized studies evaluating the long-term effect of surgically and conservative treatment interventions respectively.

The primary objective of the present study is, based on available (published) studies, to investigate the effect, benefits as well as harms, of surgical versus conservative treatment of ankle fractures in adults.

## **METHODS**

The protocol for this systematic review will be developed using the PRISMA-P statement and the review will be reported using the PRISMA statement.<sup>16</sup> Prospectively the study protocol will be published online on the web-site of Aalborg University Hospital<sup>17</sup> and the review will be registered in PROSPERO.<sup>18</sup>

The review will be performed based on a systematic search in the following bibliographic databases: Medline via Pubmed, Embase, Web of Science and Cochrane Central Register of Controlled Trials. The search strategy will be by inspiration from previous research and be conducted by a research librarian to ensure a complete and transparent search.<sup>7</sup> All available randomized until the 16. of February 2017 will be included. A hand-search of reference lists of relevant articles will also be conducted for other potential relevant references. Only trials written in English will be included.

### **Study selection**

To estimate the long-term effect of treatment interventions following ankle fractures in adults this study will include randomized or cluster randomized trials comparing surgical and conservative treatment of ankle fractures in adults. All included studies must fulfil the following criteria: (1) Full-text English papers published in peer-reviewed journal available; (2) Contain original data

from a randomized or a cluster randomized trial; (3) Comparing surgical and conservative treatment interventions following an ankle fracture; (4) Investigate patient-reported outcomes and/or functional outcomes and/or radiological outcomes.

Moreover, the systematic literature review will include adverse events following surgical and conservative treatment respectively. All original studies and reports available from a literature search will be included. This in order to include possible adverse events related to the surgical and conservative treatment modalities. Possible adverse events will be reported as a secondary outcome in this systematic review.

All possible relevant studies from the search identified by titles and abstracts are downloaded into Mendeley and duplicates removed. Two authors (PL and RE) will independently perform the selection of studies based on the full references given by the bibliographic databases. This will be followed by full text evaluation of the selected studies. Disagreement between the two reviewers will be solved by consensus or by the inclusion of a third reviewer (MSR).

### **Data extraction and risk of bias**

Two independent reviewers (PL and RE) will extract data using a specifically designed standardized data extracting form and compare the extracted data afterwards for consistency. All inconsistencies between the two forms will be resolved by discussion between the two data extractors. Any disagreement between the data extractors after the initial discussion will be solved by involving a third person (MSR).

General study information, participants and intervention characteristics, compliance, adverse events, withdrawals and outcome measures will be extracted. If data is not available from tables or the result section, the authors of the study in question will be contacted. Whenever possible, results from the intention-to-treat population will be used.

Included randomized and cluster-randomized studies will be assessed for risk of bias by two independent reviewers (PL and RE) using the Cochrane Collaboration's tool for assessing risk of bias in randomised trials.<sup>19</sup> Each trial will be evaluated across seven domains of bias, including one or more items that are appraised in two parts. Firstly, the relevant trials' characteristics related to the item will be summarized. Secondly, each bias domain is judged as high or low risk of bias, according to their possible effect on the results of the trial. When the possible effect is unknown or

insufficient detail is reported, the item is judged as unclear. All the above concerning risk of bias will follow the description in the Cochrane Handbook for Systematic Review of Interventions, version 5.1 (Part 2: 8.5.1).<sup>19</sup> When we assess risk of bias in cluster-randomized trials, particular types of bias are included in the “other bias” domain, according to how to assess risk of bias in cluster-randomized trials recommended in Cochrane Handbook for Systematic Review of Interventions, version 5.1 (Part 3: 16.3.2).<sup>19</sup> Any disagreements between reviewers will be resolved by discussion. Consultation with a third part (MSR) will be used if disagreements still appear after discussion. Assessment of the methodological quality will not be performed, as no evidence for such appraisals and judgements exists and therefore can be misleading when interpreting the results. The use of quality scales and summary scores is considered problematic due to considerable variations between items and dimensions covered in these scales, with little evidence relating to the internal validity of these assessments.

The risk of bias assessment includes the following seven domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and researchers (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other bias (including specific bias for cluster-designed studies). High risk of bias is expected from the domains concerning blinding of participants and researchers (performance bias), and blinding of outcome assessment (detection bias), due to the different nature of the two interventions in question.

### **Primary outcome**

The primary outcome measurements are ankle specific function scores reported with a minimum of six month follow-up and a maximum of three years, defined as short term functional outcome. Endpoints shorter than six months and longer than 10 years will also be collected and reported but the short-term functional outcome are considered primary.

Functional outcome scores may include (but are not limited to) Olerud-Molander score, FAOS and Lower Extremity Functional Scale, prioritized in this order.

### **Secondary Outcome**

Secondary outcomes include general health questionnaires and include (but are not limited to): instruments such as SF-36, SF-12 and EQ5D, prioritized in this order. Other secondary outcomes include pain scores, major adverse events, health care cost of treatment, radiological outcomes including development of osteoarthritis and joint congruency. Secondary outcomes include both short-term outcomes defined as between six months and 3 years follow-up and long-term outcomes defined as 3 to 10 years follow-up.

## **DATA SYNTHESIS AND ANALYSES**

### **Primary analysis**

The primary analysis will compare the functional outcomes between surgical and conservative treatment of ankle fractures in adults. The outcomes are expected to be continuous and the difference between groups will be expressed as the standardized mean difference (SMD). The SMD will be estimated individually for all included trials. The SMD will be estimated as the mean difference between surgical intervention and conservative treatment divided by the pooled SD. If the SD is not available it will be estimated from the standard error (SE) or confidence interval (CI) or other methods recommended by the Cochrane Handbook for Systematic review.<sup>19</sup> Data from the trials will be pooled as appropriate using a random-effects model.

If a meta-analysis is not possible because of different outcomes we will summarize the study results in a table and discuss them narratively.

### **Secondary analyses**

The secondary analyses will include a comparison between surgical and conservative treatment of ankle fractures on general health questionnaire, pain, adverse events, health care costs and radiological outcomes. All continuous variables will be expressed as SMD between surgical and conservative interventions. Binary outcomes (for example adverse events defined as yes/no) for each trial will be expressed as odds ratios and 95% confidence intervals. If possible, data from the trials will be pooled as appropriate using a random-effects model.

To investigate whether the results were dependent on follow-up time, we also did meta-analysis on all available follow-up time points with at least two studies available.

### **Predefined subgroup analyses**

We will perform a subgroup analyses to explore the effect of age and gender on the outcome after surgical and conservative treatment. This analysis will only be done on our primary outcome.

Moreover, we will perform a subgroup analyses to explore the risk of major adverse events after surgical and conservative treatment.

In all subgroup analyses we will explore if the SMD between surgical and conservative treatment is different in those above or equal to 60 years and below the age of 60 years. If data is not available from tables or the result section of the included studies, the authors in question will be contacted.

The funnel plot and the Egger test will be used to examine publication bias.

All analyses will be performed using Stata, version 14 (Stata Corp., College Station, Texas) or RevMan, version 4.2 (Wintertree Software Inc., Oxford, United Kingdom) software.



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