TREATMENT MODALITIES FOR PATIENTS WITH VARUS MEDIAL KNEE OSTEOARTHRITIS

TIJS DUIVENVOORDEN

Treatment Modalities for Patients with Varus Medial Knee Osteoarthritis

Tijs Duivenvoorden

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Treatment Modalities for Patients with Varus Medial Knee Osteoarthritis

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Copromotoren:	dr. M. Reijman dr. R.W. Brouwer
Overige leden:	Prof.dr. R.G.H.H. Nelissen Prof.dr. P. Patka Prof.dr. J.M.W. Hazes

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Chapter 1

General introduction

GENERAL INTRODUCTION

Preface

Knee osteoarthritis (OA) is one of the most common joint disorders and causes considerable pain and immobility. (1) In the Netherlands more than 310,000 of the almost 17 million inhabitants have symptomatic clinical knee OA. (2) The prevalence of symptomatic knee OA has increased substantially over the last 20 years. Aging and obesity do account for this trend. (3)

The knee joint has three different compartments. The medial and lateral tibiofemoral compartment and the patellofemoral compartment could be affected separately or in combination by OA.

Malalignment of the knee increases the risk for progression of OA. (4, 5) In case of varus malalignment the medial compartment of the knee is most commonly affected due to an increased mechanical load. (4-6)

This thesis will focus on the range of treatment modalities for patients with varus medial knee OA. Most of these treatments are based on altering the knee biomechanics, to reduce the medial compartment load. (4, 5) The initial treatment is non-operative, and consists of patient education, weight reduction, physical therapy, use of orthoses, intra-articular steroid injections and if needed pain medication. (7-9)

When non-operative treatment fails surgical treatment will mostly be considered. The surgical treatment consists of valgus high tibial osteotomy (HTO), unilateral knee arthroplasty (UKA) or a total knee arthroplasty (TKA). Patients with knee OA are also being treated arthroscopically (both lavage and debridement), however this option has generated much controversy. (10)

Non-operative treatment

The first steps of the non-operative treatment of varus medial knee OA include patient education, weight reduction, pain medication and physical therapy. (7, 11) Physical therapy is based on gait retraining, builds up muscle strength and endurance and is considered as the most effective intervention in the management of OA. (8, 12)

After these first steps an orthosis is often prescribed to reduce symptoms of medial knee OA. There is a large variety of orthoses. The laterally wedged insole and valgus knee brace are most commonly used. (9) Patients wearing a laterally wedged insole or valgus knee brace report improved Patient Reported Outcomes (PROs). (13, 14)

Although insole and brace therapy may be effective treatment modalities in terms of improved PROs, the working mechanism is still not fully clarified. It is assumed that these orthoses as well as physical therapy alter the knee biomechanics and unload the diseased compartment. (8) However this needs to be evaluated in longitudinal studies,

for the reason that the durability of this dynamic effect has never been shown. When non-operative treatment fails, surgeon and patient will often consider surgical treatment.

Surgical treatment

To treat medial knee OA several surgical options are available. An HTO is a suitable treatment option to postpone the need for a TKA in active patients with early stage knee OA. (15, 16) The goal of an HTO is to unload the diseased medial compartment by bringing the weight bearing axis from the medial compartment to the tibial spines or healthy lateral compartment of the knee. (17)

To perform an HTO different techniques are available. The lateral closing-wedge and the medial opening-wedge technique are most commonly performed.(16, 18) The principle of the closing-wedge technique is to remove a bony wedge from the proximal tibia. When the opening-wedge technique is performed, one osteotomy cut is made, which will be opened to achieve valgus correction.

The closing-wedge HTO is the traditional method. However since the introduction of the angular stable plate fixation opening-wedge HTO is gaining popularity. (19) Before introduction of these fixation plates, loss of correction of the opening wedge HTO was very often seen. The development of this new plate fixation technique has led to a renewed interest in the HTO, especially in Europe.

Little is known about the long-term results of the opening-wedge osteotomy compared to the closing-wedge osteotomy. For the opening-wedge osteotomy, retrospective studies show survival rates ranging from 51% to 97.6 % at ten years' follow-up. However, there is a lack of radiological and clinical long-term results from well-designed prospective studies. These data are important for choosing the right surgical technique for the right patient.

A UKA is frequently chosen as surgical alternative to treat mild varus medial knee OA. Especially non-obese patients who are 55 to 65 years old with moderate unicompartmental OA, mild varus malalignment, no joint instability and a good range of motion are ideal candidates for an HTO as well as a UKA. (15)

The third available surgical option in the treatment of medial knee OA is the Kinespring. (20) This novel and very experimental surgical placed spring aims to unload the medial compartment, however until now very limited evidence and only sponsored trials are available.

When the medial as well as the lateral compartment of the knee suffers from OA or an HTO or UKA fails, a TKA is often performed as a next step. Revision of HTO and UKA are considered to be both technically more challenging than primary TKA. A TKA after HTO is more challenging in terms of surgical exposure and tibial component positioning and after UKA in terms of bone stock loss and the need for bone grafting.

An HTO does not seem to affect the results of a subsequent TKA. (21-24) However, revision of UKA to TKA apparently performs worse than primary TKA. (21-24) Patients undergoing conversion of a failed HTO to TKA report higher PROs in terms of pain and functional outcome than patients with a failed UKA. (15, 21)

Not only a UKA prior to TKA seems to influence the results of a TKA, also other non-surgical related factors could contribute to less optimal results. These non-surgical related factors include patient characteristics, psychological symptoms and preoperative expectancies.(25) However the extent of the influence of these factors remains unclear.

Effect of interventions

The goal of an intervention in the treatment of medial knee OA is reducing symptoms and slowing disease progression. Evaluation of the effect of interventions in orthopaedic research was traditionally based on technical and surgical aspects assessed by the treating surgeon. A lot of studies have focused on the survival- and complication rates of procedures. Recently, the patient's perspective became more topic of interest. The reduction of symptoms is increasingly reported with Patient Reported Outcome Measures (PROMs), such as pain relief, joint function, health-related quality of life, and patient satisfaction after knee surgery.

To monitor disease progression of OA, a prospective long term follow up study is the gold standard. These studies are rare, for the reason that they are expensive and take much time. The need for long term follow up studies is caused by the slow progression of knee OA.

A third method to evaluate the effectiveness of an intervention is to focus on the potential working mechanism. The biomechanical effect of interventions on patients with varus medial knee OA can be evaluated with gait analysis or whole leg radiographs. These instruments could monitor a change in walking pattern or leg alignment.

In this thesis we will analyze the effect of different non-operative and surgical interventions for varus medial knee OA. We will analyze the therapeutic effect using PROMs, imaging and biomechanical instruments.

Research questions

This thesis aims to answer the following research questions

1. Do patients treated with a laterally wedged insole or valgus brace benefit from their intervention?
2. Do laterally wedged insoles or valgus braces have an influence on the walking pattern?
3. Closing-wedge or opening-wedge HTO, which technique has the best long term results?
4. Do preoperative expectations have an influence on patient satisfaction after TKA?
5. Do anxiety and depressive symptoms influence PROs and patient satisfaction after TKA?

Aims and outline of this thesis

The present thesis is a clinical approach to evaluate the effect of different treatment modalities for patients with varus medial knee OA. We were interested in the existing evidence for the therapeutic effect of two conservative treatment options, namely the valgus knee brace and laterally wedged insole (chapter 2). Therefore, we performed an update of the Cochrane review "Braces and orthoses for osteoarthritis of the knee".

Effects of conservative treatment of knee OA are mainly based on epidemiological studies with clinical outcome measures as primary outcome. The biomechanical evaluation of orthoses shows potentially beneficial biomechanical changes to joint loading, but this needs to be evaluated in relation to clinical outcome measures in longitudinal studies. In chapter 3 we performed gait analysis of patients wearing a valgus knee brace or laterally wedged insole to determine these biomechanical changes. We hypothesized that a dynamical alteration could clarify the clinical benefits of patients.

After failure of non-operative treatment of medial knee OA, there are several surgical options. One of these treatment options is the High Tibial Oosteotomy (HTO). We were interested in the long term results of this treatment. In chapter 4 we present the six year results of a Randomized Controlled Trial comparing closing-wedge and opening-wedge HTO.

Closing-wedge and opening-wedge HTO are well-established surgical techniques. Both techniques have certain risks for adverse events. In chapter 5 we present the adverse event- and survival-rate of 466 consecutive opening- and closing-wedge high tibial osteotomies performed in our clinic.

When conservative treatment or HTO fails to alleviate pain and limitations in patients with knee OA, a TKA is mostly the next step. Patient satisfaction is the ultimate goal of the procedure. Although the majority of patients are satisfied after TKA, a subset is not. The explanation of these unsatisfactory results is not always completely physical, like adverse events, comorbidities, variation in surgery itself or residual pain. The persistence of complaints also seem to be related to not directly surgical related factors, such as unrealistic expectations of patients. We performed a systematic review in chapter 6 to summarize the literature about the relationship between preoperative expectations or fulfillment of expectations and patient satisfaction after TKA.

Anxiety and depressive symptoms are possibly other non-surgical related risk factors for disappointing results of TKA. To determine the influence of preoperative anxiety and depressive symptoms on PROs and patient satisfaction after TKA, we performed a prospective multicentre study in chapter 7. Finally in chapter 8, the most important results of these studies, as well as their limitations and implications are discussed.

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Chapter 2

Braces and orthoses for osteoarthritis of the knee

T. Duivenvoorden, R.W. Brouwer, T.M. van Raaij, A.P. Verhagen, J.A.N. Verhaar, S.M.A. Bierma-Zeinstra

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ABSTRACT

Background. Individuals with osteoarthritis (OA) of the knee can be treated with a knee brace or a foot/ankle orthosis. The main purpose of these aids is to reduce pain, improve physical function and, possibly, slow disease progression. This is the second update of the original review published in Issue 1, 2005, and first updated in 2007.
Objectives. To assess the benefits and harms of braces and foot/ankle orthoses in the treatment of patients with OA of the knee.
Search methods. We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE (current contents, HealthSTAR) up to March 2014. We screened reference lists of identified trials and clinical trial registers for ongoing studies.
Selection criteria. Randomised and controlled clinical trials investigating all types of braces and foot/ankle orthoses for OA of the knee compared with an active control or no treatment.
Data collection and analysis. Two review authors independently selected trials and extracted data. We assessed risk of bias using the 'Risk of bias' tool of The Cochrane Collaboration. We analysed the quality of the results by performing an overall grading of evidence by outcome using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach. As a result of heterogeneity of studies, pooling of outcome data was possible for only three insole studies.
Main results. We included 13 studies (n = 1356): four studies in the first version, three studies in the first update and six additional studies (n = 529 participants) in the second update. We included studies that reported results when study participants with early to severe knee OA (Kellgren & Lawrence grade I-IV) were treated with a knee brace (valgus knee brace, neutral brace or neoprene sleeve) or an orthosis (laterally or medially wedged insole, neutral insole, variable or constant stiffness shoe) or were given no treatment. The main comparisons included (1) brace versus no treatment; (2) foot/ankle orthosis versus no treatment or other treatment; and (3) brace versus foot/ankle orthosis. Seven studies had low risk, two studies had high risk and four studies had unclear risk of selection bias. Five studies had low risk, three studies had high risk and five studies had unclear risk of detection bias. Ten studies had high risk and three studies had low risk of performance bias. Nine studies had low risk and four studies had high risk of reporting bias.

Four studies compared brace versus no treatment, but only one provided useful data for meta-analysis at 12-month follow-up. One study (n = 117, low-quality evidence) showed lack of evidence of an effect on visual analogue scale (VAS) pain scores (absolute percent change 0%, mean difference (MD) 0.0, 95% confidence interval (CI) -0.84 to 0.84), function scores (absolute percent change 1%, MD 1.0, 95% CI -2.98 to 4.98) and health-related quality of life scores (absolute percent change 4%, MD -0.04, 95% CI -0.12 to 0.04) after 12 months. Many participants stopped their initial treatment because of lack of effect (24 of 60 participants in the brace group and 14 of 57 participants in the no treatment group; absolute percent change 15%, risk ratio (RR) 1.63, 95% CI 0.94 to 2.82). The other studies reported some improvement in pain, function and health-related quality of life (P value ≤ 0.001). Stiffness and treatment failure (need for surgery) were not reported in the included studies.

For the comparison of laterally wedged insole versus no insole, one study (n = 40, low-quality evidence) showed a lower VAS pain score in the laterally wedged insole group (absolute percent change 16%, MD -1.60, 95% CI -2.31 to -0.89) after nine months. Function, stiffness, health-related quality of life, treatment failure and adverse events were not reported in the included study.

For the comparison of laterally wedged versus neutral insole after pooling of three studies (n = 358, moderate-quality evidence), little evidence was found of an effect on numerical rating scale (NRS) pain scores (absolute percent change 1.0%, MD 0.1, 95% CI -0.45 to 0.65), Western Ontario-McMaster Osteoarthritis Scale (WOMAC) stiffness scores (absolute percent change 0.1%, MD 0.07, 95% CI -4.96 to 5.1) and WOMAC function scores (absolute percent change 0.9%, MD 0.94, 95% CI - 2.98 to 4.87) after 12 months. Evidence of an effect on health-related quality of life scores (absolute percent change 1.0%, MD 0.01, 95% CI -0.05 to 0.03) was lacking in one study (n = 179, moderate-quality evidence). Treatment failure and adverse events were not studied for this comparison in the included studies.

Data for the comparison of laterally wedged insole versus valgus knee brace could not be pooled. After six months' follow-up, no statistically significant difference was noted in VAS pain scores (absolute percent change -2.0%, MD -0.2, 95% CI -1.15 to 0.75) and WOMAC function scores (absolute percent change 0.1%, MD 0.1, 95% CI -7.26 to 0.75) in one study (n = 91, low-quality evidence); however both groups showed improvement. Stiffness, health-related quality of life, treatment failure and adverse events were not reported in the included studies for this comparison.

Authors' conclusions. Evidence was inconclusive for the benefits of bracing for pain, stiffness, function and quality of life in the treatment of patients with medial compartment knee OA. On the basis of one laterally wedged insole versus no treatment study, we conclude that evidence of an effect on pain in patients with varus knee OA is lacking. Moderate-quality evidence shows lack of an effect on improvement in pain, stiffness

and function between patients treated with a laterally wedged insole and those treated with a neutral insole. Low-quality evidence shows lack of an effect on improvement in pain, stiffness and function between patients treated with a valgus knee brace and those treated with a laterally wedged insole. The optimal choice for an orthosis remains unclear, and long-term implications are lacking.

PLAIN LANGUAGE SUMMARY

Research question

This summary of a Cochrane review presents what we know from research about the effects of braces and foot/ankle orthoses in the treatment of patients with osteoarthritis of the knee. We searched for evidence up to March 2014. We found 13 studies (n = 1356) and included in this update six additional studies (n = 529 participants).

Study characteristics

We included studies reporting results in patients with early to severe knee OA (Kellgren & Lawrence grade I-IV) treated with a knee brace (valgus knee brace, neutral brace, neoprene sleeve) or an orthosis (laterally or medially wedged insole, neutral insole, variable or constant stiffness shoe) or given no treatment.

Background: What is osteoarthritis and what are braces and orthoses?

Osteoarthritis is the most common form of arthritis that can affect the hands, hips, shoulders and knees. In osteoarthritis, the cartilage that protects the ends of bones breaks down, causing pain and swelling. Osteoarthritis can occur in different areas of the knee or can affect the whole knee. Depending on the area, osteoarthritis can change the alignment of joints.

Braces and orthoses are devices that you wear to support your knee joint. Orthoses are insoles that fit comfortably inside your shoes. Braces are made of combinations of metal, foam, plastic, elastic material and straps. A knee brace can be fitted specially for the person wearing it.

Key results

This review shows the following in people with osteoarthritis of the knee.

Wearing a knee brace compared with no brace:

- may result in little or no difference in reducing pain and improving knee function and quality of life after 12 months (low-quality evidence); and

- causes many patients to stop their initial treatment because of lack of effect in both groups.
  Stiffness and treatment failure (need for surgery) were not reported.

Wearing a laterally wedged insole compared with no insole:

- may result in little or no difference in reducing pain (low-quality evidence).
  Function, stiffness, health-related quality of life, treatment failure and side effects were not reported.

Wearing a laterally wedged insole compared with wearing a neutral insole:

- probably results in little or no difference in reducing pain and improving function, stiffness and quality of life after 12 months (moderate-quality evidence).
  Treatment failure and side effects were not reported.

Wearing a laterally wedged insole compared with a valgus knee brace:

- may result in little or no difference in reducing pain and improving function after sx months (low-quality evidence).
  Stiffness, health-related quality of life, treatment failure and side effects were not reported
  We often do not have precise information about side effects and complications. Side effects may include pain in the back of the knee, low back pain, foot sole pain or skin irritation.

Quality of the evidence

- Low-quality evidence suggests that people with OA who use a knee brace may have little or no reduction in pain, improved knee function and improved quality of life.
- Moderate-quality evidence suggests that people with OA of the knee who wear laterally wedged insoles or neutral insoles probably have little or no improvement in pain, function and stiffness

BACKGROUND

Description of the condition

Osteoarthritis (OA) of the knee is a common medical condition that is often seen in general practice and causes considerable pain and immobility. In the United States, approximately 9% of individuals aged 60 years and older suffer from knee OA (Losina 2013). The prevalence of symptomatic knee OA has increased substantially over the past 20 years. Aging, obesity and increased awareness of knee pain have accounted

for this trend (Nguyen 2011). Risks for a poor functional outcome in individuals with knee OA involve collateral and cruciate ligament laxity, age, body mass index (BMI) and degree of pain (Sharma 2003). In addition to consequences for the patient, OA presents a considerable burden for society because of its chronic course, high costs of interventions and related productivity costs (Healy 2002; Hermans 2012).

Osteoarthritis of the entire knee is distinguished from OA of one compartment (Grelsamer 1995), which generally is caused by a mechanical problem (Brouwer GM 2007; Tetsworth 1994). Individuals with OA of the medial compartment often have a varus alignment, and the mechanical axis and load bearing pass through the medial compartment. Those with OA of the lateral compartment generally have a valgus alignment, and the mechanical axis and load bearing pass through the lateral compartment. Malalignment increases risk and progression of knee OA and predicts decline in physical function (Brouwer GM 2007; Sharma 2001; Tanamas 2009).

Initial treatment for patients with OA of the knee is conservative, consisting of restricted activity, decreased body mass index (BMI), patient education and physical therapy (Foley 2003; Fransen 2001; Fransen 2008; Garner 2005; Goorman 2000; Hoffmann 2001;Huang 2000; Hurley 1998; Zhang 2010). Pharmacological treatments tend to only modify symptoms (e.g. analgesics, anti-inflammatory drugs); however some are intended to be curative (hyaluronic acids, chondroitin sulphate) (Bellamy 2006; Cepeda 2006;Gibofsky 2003; Karlsson 2002; Leopold 2003; Nuesch 2009; Towheed 2006; Uebelhart 2004; Whittle 2011).

Electro-acupuncture, transcutaneous electrical nerve stimulation (TENS), braces, foot/ankle orthoses and leech therapy are not standard treatments (Rutjes 2009) but can be effective in symptom reduction (Deshaies 2002; Michalsen 2003; Ng 2003). If symptoms persist, surgical therapy such as high tibial osteotomy or knee arthroplasty can be considered (Brouwer RW 2007; Fletcher 2006;Stukenborg 2001) .

Description of the intervention

A knee brace or a foot/ankle orthosis is defined as "any medical device added to a person's body to support, align, position, immobilize, prevent or correct deformity, assist weak muscles, or improve function" (Deshaies 2002). The general purpose of braces and orthoses is to decrease pain, improve physical function and possibly slow disease progression. Proprioception/stability is a hypothesised but unproven underlying explanatory factor. Lateral wedge insoles and special valgus braces are designed to reduce load in the medial compartment (Hewett 1998; Katsuragawa 1999; Kirkley 1999; Komistek 1999; Lindenfeld 1997; Maillefert 2001;Reeves 2011).

Several types of orthoses are available to treat patients with medial knee OA non-operatively. This review includes studies comparing the laterally wedged insole, the valgus knee brace, the neutral knee brace, the neoprene sleeve and variable shoe stiff-

ness versus each other or versus no treatment. The valgus knee brace and the laterally wedged insole are used most commonly in the non-operative treatment of varus medial knee OA.

How the intervention might work

The goal of the interventions is to improve function, reduce symptoms and possibly slow disease progression. The valgus knee brace and the laterally wedged insole are used with the goal of unloading the diseased medial compartment by creating a valgus effect on the knee. Neutral braces and neoprene sleeves are thought to immobilise and stabilise the knee. Neutral insoles, shoes of variable stiffness and lateral wedged insoles could have a cushioning effect (Reeves 2011).

Why it is important to do this review

The literature suggests that patients with varus medial knee OA may benefit from braces and foot/ankle orthoses. However many different types of braces and foot/ankle orthoses are available. It remains unclear which brace or foot/ankle orthosis will provide the greatest benefit or harm to patients treated for varus medial knee OA (Parkes 2013; Reeves 2011; Zhang 2010).

Objectives

To assess the benefits and harms of braces and foot/ankle orthoses in the treatment of patients with OA of the knee.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and controlled clinical trials investigating all types of braces and foot/ankle orthoses for OA of the knee compared with no treatment or other treatment such as restricted activity, patient education, physiotherapy, pharmacological treatment and orthoses or surgical treatment.

Types of participants

Adult patients (> 18 years) with OA of the knee confirmed by radiological investigation (Kellgren & Lawrence (K&L) grade I-IV).

Types of interventions

All types of braces (rigid knee braces intended to reduce load, knee sleeves/supporters) and foot/ankle orthoses (laterally or medially wedged insoles with or without an ankle support or variable stiffness shoes) for individuals with OA of the knee. The main comparisons were (1) brace versus no treatment; (2) foot/ankle orthosis versus no treatment or other treatment; and (3) brace versus foot/ankle orthosis.

Types of outcome measures

Major outcomes

We considered major outcomes such as pain, function, stiffness, quality of life, treatment failure (need to undergo surgery), serious adverse events and total number of adverse events.

Minor outcomes

We also considered other outcomes such as radiographic scores, compliance and walking distance.

We considered all major outcomes and presented them in the 'Summary of findings' table.

Search methods for identification of studies

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE (current contents, HealthSTAR) until October 2002 in the original review, until May 2007 in the first update and until March 2014 in the second update to identify clinical trials investigating braces and foot/ankle orthoses for OA of the knee. We performed MEDLINE searches for clinical trials using the strategy of The Cochrane Collaboration (Appendix 1, completed March 2014). We applied no language restriction. Moreover we checked the reference lists of included studies and clinical trial registers for ongoing studies.

DATA COLLECTION AND ANALYSIS

Selection of studies

Two review authors initially selected trials on the basis of title and abstract. We assessed title, keywords and abstract to establish whether the study met the inclusion criteria regarding diagnosis, design and intervention. For each selected study, we retrieved the full article for final assessment. Next, two review authors independently performed

a final selection of trials to be included in the review, using a pretested standardised form. We resolved disagreements on inclusion by discussion.

Data extraction and management

Three review authors independently extracted data on the intervention, types of outcome measures, follow-up, loss to follow-up and outcomes using a standardised form. We have presented the various outcome measures separately. We resolved disagreements or discrepancies on data extraction by discussion.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias of included studies. We resolved disagreements in a consensus meeting and when necessary consulted an independent third person. The Cochrane Collaboration recommends a specific tool for assessing risk of bias in each included study. This comprises a description and a judgement for each entry in a 'Risk of bias' table, wherein each entry addresses a specific feature of the study. The judgement for each entry involves providing a response of 'low risk of bias', 'high risk of bias' or 'unclear risk of bias', indicating lack of information or uncertainty about the potential for bias.

Entries used to assess risk of bias include the following (see also 'Risk of bias' table).

- Random sequence generation (selection bias).
  - Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.
- Allocation concealment (selection bias).
  - Selection bias (biased allocation to interventions) due to inadequate concealment of allocations before assignment.
- Blinding (performance bias and detection bias).
  - Performance bias or detection bias due to knowledge of allocated interventions after assignment.
- Blinding of participants and personnel (performance bias).
  - Performance bias due to knowledge of allocated interventions by participants and personnel during the study.
- Blinding of outcome assessment (detection bias).
  - Detection bias due to knowledge of allocated interventions by outcome assessors.
- Incomplete outcome data (attrition bias).
  - Attrition bias due to quantity, nature or handling of incomplete outcome data.
- Selective reporting (reporting bias).
  - Selection of a subset of original variables recorded on the basis of results.

Measures of treatment effect

For dichotomous outcomes, we calculated risk ratios (RRs) with corresponding 95 per cent confidence intervals (95% CIs). For continuous outcomes, we calculated mean differences (MDs) with 95% CIs.

Unit of analysis issues

Not applicable.

Dealing with missing data

It is unclear to us whether we missed outcome data. Many studies have not published a research protocol. Therefore, we analysed only available data.

Data synthesis

We used RevMan 5 software to analyse the data and have presented the various outcomes in analysis graphs. We used both fixed-effect and random-effects models. In cases of substantial between-trial heterogeneity, we used random-effects analysis instead of a fixed-effect approach. Pooling of outcomes was possible only for the comparison of lateral wedged insole versus neutral insole. We considered the rest of the trials to be clinically heterogeneous in terms of study population and intervention.

'Summary of findings' table

We created a 'Summary of findings' table for the major outcomes of pain, function, stiffness, health-related quality of life, treatment failure, serious adverse events and total adverse events.

We analysed the quality of the presenting results by performing an overall grading of evidence by outcome using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach (Guyatt 2008a; Guyatt 2008b; Schünemann 2008). We assigned the highest quality rating to randomised trial evidence.

The GRADE approach specifies the following levels of quality.

- High quality: Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low quality: We are very uncertain about the estimate.

Trial evidence can be downgraded to moderate, low or very low quality depending on the presence of the following factors.

- Limitations in design and implementation of available studies suggesting high likelihood of bias.
- Indirectness of evidence (indirect population, intervention, control, outcomes).
- Unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses).
- Imprecision of results (wide confidence intervals).
- High probability of publication bias.

Quality will fall by one level for each factor, up to a maximum of three levels for all factors. If very severe problems are noted for any one factor (e.g. when assessing limitations in design and implementation, all studies were unconcealed and unblinded and lost more than 50% of participants to follow-up), the quality of randomised trial evidence may fall by two levels on the basis of that factor alone.

If pooling of study results is not possible, then a single study is included and by definition low-quality evidence, which can be downgraded according to risk of bias items.

RESULTS

Description of studies

Results of the search

The search strategy (Appendix 1, completed May 2014) yielded a total of 217 records from the following databases: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE (current contents, HealthSTAR). The search resulted in identification of the citations of 25 reports of potentially eligible studies, for which (where possible) full reports were obtained. We included a total of 13 studies in the review. We needed the opinion of a third review author once (Shakoor 2008) before we could come to a final decision.

Overall, this review consists of 13 included studies, 12 excluded studies, no ongoing studies and no studies awaiting classification (Figure 1). We checked the reference lists of the included studies but identified no further studies.

Included studies

We included 13 studies described in 17 publications involving 1356 participants; we included four studies in the first version, added three studies in the first update and added six more studies in this second update. We have described these studies in detail in the Characteristics of included studies table.

One group (Maillefert 2001) published separately six-month and two-year results, another group presented separately six-month and one-year results (Erhart-Hledik

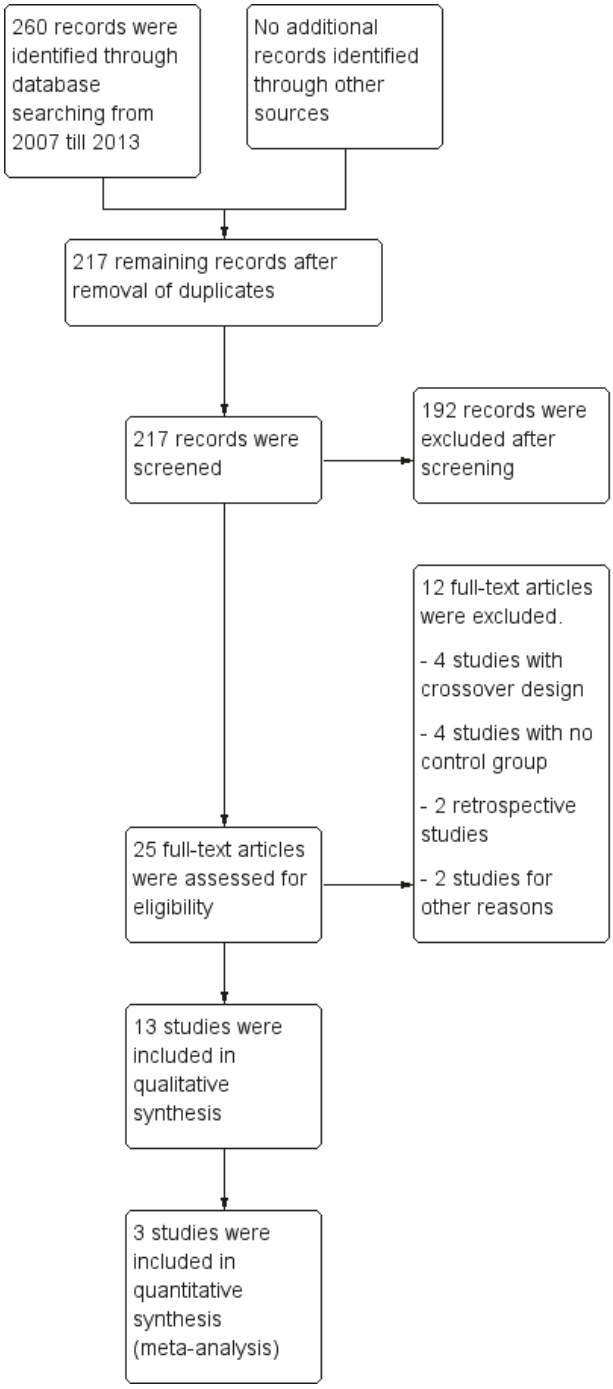

Fig. 1 Flow diagram of the study according to the PRISMA statement.

2012) and another group (Toda 2001) published separately eight-week, six-month and two-year results. We have described the 13 selected studies in detail in the Characteristics of included studies table. Four studies (Brouwer 2006; Kirkley 1999; Müller-Rath 2011; Sattari 2011) investigated knee braces, and eight studies (Barrios 2009; Bennell 2011; Erhart-Hledik 2012; Maillefert 2001; Sattari 2011; Toda 2001; Toda 2002; Toda 2008) examined foot/ankle orthoses for medial compartment OA of the knee. Two studies (Raaij van 2010; Sattari 2011) compared a knee brace with a foot orthosis. Only two studies (Brouwer 2006; Rodriques 2008) also assessed the benefits of a brace or a foot/ankle orthosis for treating lateral compartment osteoarthritis. No studies assessed the benefits of a brace or an insole for general OA of the knee. In 12 studies the degree of OA was scored according to Kellgren & Lawrence (K&L) (Kellgren 1957), and in one study (Brouwer 2006) according to Ahlback (Ahlback 1968). In two studies osteoarthritic changes were also checked on magnetic resonance imaging (MRI) (Bennell 2011; Erhart-Hledik 2012). The mean number of participants in the 13 studies was 103 (range 30-207). Mean participant age was 62 years (range 48-65 years). In two trials, all participants were females (Toda 2001; Toda 2002). (See also Characteristics of included studies.)

Barrios 2009 published an RCT of 66 participants with symptomatic medial knee OA (K&L grade II-IV). In this RCT, a treatment group - a full-length (9.1 degrees (standard deviation (SD) 3.9 degrees)) laterally wedged insole into the shoe (n = 35) - had been compared with a control group - a non-custom neutral insole into the shoe (n = 31). Block randomisation was performed based on OA grade, gender and age (older or younger than 55 years). Allocation was done by an administrative assistant who was unaware of the methods used. The study included 29 males and 37 females with medial tibiofemoral OA (scored according to K&L), mean age of 62.4 years and mean BMI of 33.0 kg/m^2. Baseline characteristics (gender, BMI, OA grade) did not differ between groups. A total of 20/35 (57%) participants remained in the treatment group and 25/31 (81%) in the control group at final one-year follow-up. The primary outcome measure was mean Western Ontario-McMaster Osteoarthritis Scale (WOMAC) subscore (100-0); secondary outcomes included a six-minute walking test and a stair negotiation test. Mean and P values were presented, but SD values were missing.

Bennell 2011 reported a double-blinded RCT of 200 participants with mild to moderately severe medial knee OA and radiological evidence of osteophytes in the medial compartment or medial joint space narrowing on an x-ray film. In this RCT, a treatment group - a full-length five-degree laterally wedged insole (n = 103) - was compared with a control group - a flat insole (n = 97). The randomisation procedure consisted of a computer-generated block method using sealed envelopes. Participants included 82

men and 118 women; mean age was 64 years. Mean BMI was 29.2. The degree of radiological OA was scored according to K&L on posteroanterior radiographs and on MRI. Mean varus alignment was 181 degrees. Follow-up was 12 months. Eleven participants in the intervention group and ten in the control group were lost to follow-up.

Brouwer 2006 published a multi-centre RCT of 117 participants with symptomatic unicompartmental knee OA (Ahlback > 0). In this RCT, investigators studied the additive effect of a brace intended to reduce load in the conservative treatment of unicompartmental (medial or lateral) knee OA. A total of 60 participants were included in the intervention group (brace and standard conservative treatment) and 57 in the control group (standard conservative treatment alone). The brace is available for right and left knees in four sizes. The brace consists of a thigh shell and a calf shell (both of carbon fibre) connected by titanium hinges on the medial and lateral sides. The adjustable side bar on the medial side of the brace provides valgus (1-12.5 degrees) with medial unloading, or varus (1-10 degrees) with lateral unloading. The randomisation procedure consisted of a computer-generated block method using sealed envelopes. Participants included 59 men and 58 women. Mean age was 59 years. Mean BMI was 29. The degree of OA was scored according to Ahlback. Patients with an Ahlback score of I or II were included. Mean varus alignment was nine degrees. Mean valgus alignment was six degrees (hip-knee-ankle (HKA) angle). Follow-up was 12 months. Four participants in the control group were lost to follow-up.

Erhart-Hledik 2012 reported an RCT of 79 participants with symptomatic medial knee OA and osteoarthritic changes on MRI. In this study a treatment group - variable-stiffness shoe (n = 40) - was compared with a control group - constant stiffness shoe (n = 39). The randomisation procedure was not described. Participants included 42 men and 37 women. Mean age was 60 years. Mean BMI was 27.7. The degree of radiological OA was scored on MRI at baseline. Follow-up was 12 months. Eight participants in the intervention group and 13 in the control group were lost to follow-up.

Kirkley 1999 reported an RCT comparing (1) a valgus brace with medical treatment (n = 41); (2) a neoprene sleeve with medical treatment (n = 36); and (3) a control (i.e. medical treatment only) (n = 33). Individuals with OA of the knee and pain localised to the medial compartment were included in this trial. The valgus brace was custom made and consisted of a polyethylene thigh shell connected to a polyethylene calf shell through a polyaxial hinge on the medial side, which allowed application of four degrees valgus. The randomisation procedure consisted of a computer-generated block method using sealed envelopes. Follow-up was six months. Nine participants were lost to follow-up (neoprene sleeve - two/control - seven). Participants included 79 men and

31 women. Mean age was 59 years. Mean varus alignment was nine degrees. Degree of OA of the knee was described only in the unloader brace group. Outcome data were presented as means and P values but without standard deviations; this made pooling impossible. Additional information was obtained from The Kirkley Research Group, but this information was not sufficient for analysis.

Maillefert 2001 presented an RCT of 156 participants with symptomatic medial knee OA (K&L > I). Laterally wedged insoles (n = 82) were compared with neutral insoles (n = 74). Both insoles were made of Ledos material, which consists of pure rubber with cork powder. The laterally elevated insoles were individually modelled, with elevation depending on static pedometer evaluation. The randomisation procedure was not described. Participants included 41 men and 108 women. Mean age was 65 years. Mean BMI was 29. Degree of varus alignment was not measured. After six months' follow-up, nine participants (four from the wedged insole group) were lost to follow-up. Two-year follow-up results were provided in 2004 (Pham 2004). A total of 106 participants completed the two-year follow-up: neutrally wedged insole (n = 51) versus laterally wedged insole (n = 55).

Müller-Rath 2011 reported a non-blinded RCT of 33 participants with symptomatic medial knee OA with a minimum of grade II according to the radiographic classification of K&L. Two treatment groups were included: a valgus knee brace (n = 13) and an elastic knee bandage (n = 10). The control group consisted of untreated individuals (n = 10). The randomisation procedure was not described. Participants included 24 men and nine women; mean age was 53.2 years. Mean BMI was 27.2. Mean alignment was 189 degrees of varus femoro-tibial angle (FTA). The number of participants lost to follow-up was not reported.

Raaij van 2010 reported a non-blinded RCT of 91 participants with symptomatic medial knee OA (K&L ≥ I). Participants were block-randomised to treatment with a 10-mm laterally full-length wedged insole (index group, n = 45) or a valgus brace (control group, n = 46). Baseline characteristics were similar regarding mean age (55 years), mean BMI (29 kg/m^2), medial and lateral OA grades, analgesic use, mean VAS pain score (5.6 (0-10 scale)) and mean WOMAC function (47 (0-100 scale)). Gender differed statistically significantly (index group 65% female vs control group 35% female). At six months, a non-blinded investigator assessed VAS and WOMAC scores as well as varus alignment correction in the frontal plane using the HKA angle on standardised whole leg films.

Rodriques 2008 randomly assigned 30 consecutive women with bilateral valgus deformity knee OA to two groups: medial insole (insoles with 8-mm medial elevation at the rearfoot (n = 16)) and neutral insoles (similar insoles without elevation (n = 14)). Both groups also wore ankle supports. The demographic features of both groups were similar regarding mean age (62 years), mean BMI (30 kg/m^2), mean disease duration (five years), radiographic osteoarthritis severity (K&L), race distribution and sedentary habits. A blinded examiner assessed VAS, Lequesne and WOMAC scores, along with femorotibial, talocalcaneal and talar tilt angles at baseline and after eight weeks.

Sattari 2011 reported an RCT of 60 participants with knee pain, genu varum and moderate to severe medial knee OA (K&L grade III or IV). Investigators included two treatment groups: a custom-molded valgus stress knee support (n = 20) and a 1/4-inch laterally wedged insole (n = 20). The control group (n = 20) received only general management that was universally applied to all three groups, consisting of activity modification, heating agents, straight leg raising, isometric quadriceps home exercises and analgesic use, when needed. The randomisation procedure was computer-generated. Participants included 22 men and 38 women. Mean age was 48 years. Mean VAS pain score was 6.9. The degree of radiological OA was scored according to K&L. Follow-up was nine months. Five participants were lost to follow-up.

Toda 2001 published a prospective trial comparing an elastic subtalar strapped insole (n = 46) versus a traditional lateral wedge insole (n = 44). This study included individuals with symptomatic medial knee OA (K&L II-IV). The wedge of the strapped insole was made from urethane with elevation of 6.35 mm strapped to an ankle sprain supporter. The traditional insole was a lateral rubber heel wedge with elevation of 6.35 mm. Quasi-randomisation was performed according to birth date. All participants were female. Mean age was 65 and mean BMI was 25. Follow-up was eight weeks, and no participant was lost to follow-up. Standing radiographs of participants with and without their respective insoles were taken before entry into the eight-week study. Degree of varus was 181 degrees FTA. Six-month results were published in 2004. A total of 61 participants completed the six-month follow-up: subtalar strapped insole (n = 29) versus traditional laterally wedged insole (n = 32). Two-year results were published in 2006. Only 42 participants completed the two-year follow-up: subtalar strapped insole (n = 21) versus traditional laterally wedged insole (n = 21). Analysis was performed without an intention-to-treat approach. All results were presented in the original articles as pre/post analysis, not as between-group differences (Toda 2001). However, for both the original review and the updated review, the study author was contacted for more information; he sent the missing information on between-group analysis of FTA, VAS and Lequesne index scores.

Toda 2002 published a second trial comparing a subtalar strapped insole (n = 42) with a sock-type ankle supporter (n = 46). Individuals with symptomatic medial knee OA were included in this trial (K&L II-IV). The wedge of the strapped insole was made from urethane with elevation of 6.35 mm strapped to an ankle sprain supporter. The sock-type ankle support extended from malleoli to metatarsals and consisted of a lateral wedged heel insole with elevation of 6.35 mm. The trial took place in the same year (2000) as the first study. The quasi-randomisation procedure was performed according to birth date. All participants were female. Mean age was 65 and mean BMI was 25. Degree of varus was 181 degrees (FTA). Follow-up was eight weeks, and no participant was lost to follow-up. Results were presented as pre/post analysis, not as between-group differences. Second, the Lequesne index was presented graphically and no exact numbers were given. However, the study author was contacted for more information again, and he provided the missing information on between-group analysis of the Lequesne index.

Toda 2008 published a third RCT of 227 participants with symptomatic medial knee OA (K&L I-IV). In this study a placebo - a neutral wedged insole into shoes (n = 45) - was compared with four interventions - a wedged insole with shoes (n = 45), a sock-type ankle supporter with a wedged insole without shoes (n = 46), a subtalar strapped insole with shoes (n = 45) and a subtalar strapped insole without shoes (n = 46). The randomisation procedure consisted of a computer-generated block method using sealed envelopes. Baseline characteristics and outcomes were presented only for the 207 participants who completed the 12-week follow-up. A total of 20 of 227 participants did not complete the study, which included 24 men and 183 women. Mean age was 65 years. Mean BMI was 25. Degree of OA was scored according to K&L. Degree of varus was 181 degrees (FTA). Most results were presented as pre/post analysis, and only intake of non-steroidal anti-inflammatory drugs (NSAIDs) was compared between placebo and different interventions.

Outcome measures included function scores, VAS scores (pain), analgesic/NSAID intake, walking distance, WOMAC scores (pain, function and stiffness), Hospital for Special Surgery knee scores (HSS; function), McMaster Toronto Arthritis score (MACTAR; function), Lequesne index (pain and function), degree of OA (Ahlback and K&L), global patient assessment, quality of life (EQ-5D; a measure of health status), leg alignment (HKA angle; FTA), compliance and side effects.

Excluded studies

After retrieving the full text for final assessment, the review authors excluded 12 studies (Baker 2007; Birmingham 2001; Horlick 1993;Hunter 2012; Katsuragawa 1999; Kuroyanagi 2007; Matsuno 1997; Rooser 1988; Sasaki 1987; Shakoor 2008; Toda

2002b; Tohyama 1991): two studies (Sasaki 1987; Tohyama 1991) because of a retrospective design, four studies because of a cross-over design (Baker 2007; Hunter 2012; Kuroyanagi 2007; Shakoor 2008), four studies because of lack of a control group (Birmingham 2001;Horlick 1993; Katsuragawa 1999; Matsuno 1997) and two studies (Rooser 1988; Toda 2002b) because investigators did not report the targeted outcome measure.

Risk of bias in included studies

Further details on risk of bias of each study are available in Figure 2, Figure 3 and the 'Risk of bias' tables (Characteristics of included studies).

Allocation (selection bias)

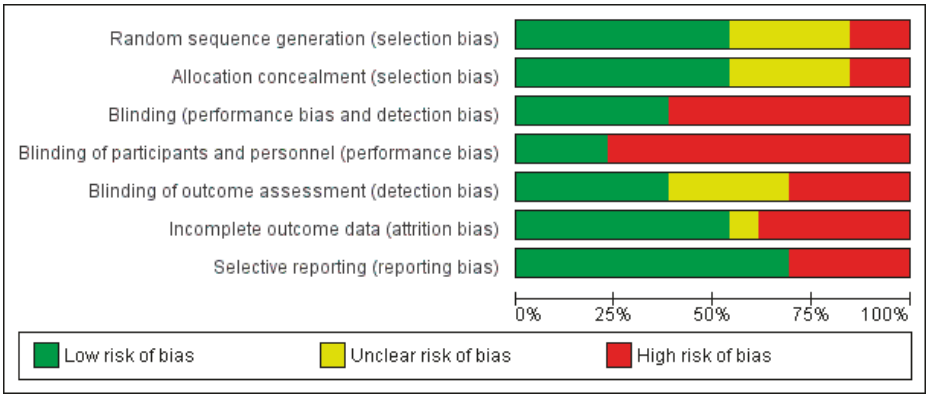

Fig. 2 Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Randomisation was performed in all studies. However in four studies, the procedure was not clearly described (Maillefert 2001; Müller-Rath 2011; Rodriques 2008; Sattari 2011). In the other nine studies, the randomised sequence was adequately generated and clearly described (Barrios 2009; Bennell 2011; Brouwer 2006; Erhart-Hledik 2012; Kirkley 1999; Raaij van 2010; Toda 2001; Toda 2002; Toda 2008). In seven studies, randomisation and concealment of allocations before assignment were adequately generated (Barrios 2009;Bennell 2011; Brouwer 2006; Erhart-Hledik 2012; Kirkley 1999; Raaij van 2010; Toda 2008).

Blinding (performance bias and detection bias)

In many studies, blinding procedures for treatment providers, participants and outcome assessors were insufficient. In most trials, blinding procedures for outcome assessors, treatment providers and participants were scored as 'high risk'. In five studies at least one

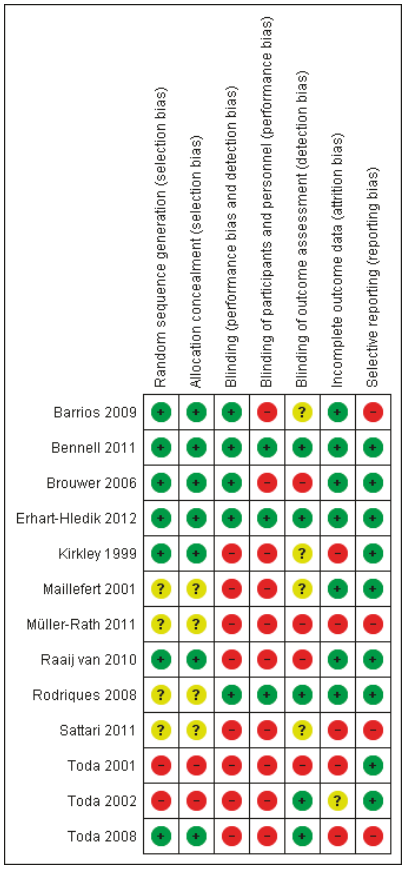

Fig. 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

of the outcome assessors was blinded (Bennell 2011; Erhart-Hledik 2012; Rodriques 2008; Toda 2002; Toda 2008), and in only three of these studies, care providers and participants were also blinded (Bennell 2011; Erhart-Hledik 2012; Rodriques 2008).

Incomplete outcome data (attrition bias)

In six studies, incomplete outcome data were not adequately addressed. These studies with drop-outs did not include an intention-to-treat analysis (Kirkley 1999; Müller-Rath 2011; Sattari 2011; Toda 2001; Toda 2002; Toda 2008).

Selective reporting (reporting bias)

In most studies, the selective outcome reporting item was unclear because no study protocol was provided (Kirkley 1999; Müller-Rath 2011; Sattari 2011; Toda 2001; Toda 2002; Toda 2008).

Effects of interventions

We have described comparisons of three main groups, namely, knee brace, foot/ankle orthosis and knee brace versus laterally wedged insole. Below we present the effects of interventions for the main comparisons, and we present the quality of evidence scored by the GRADE approach for each outcome. A 'Summary of findings' table was created using GRADEpro (http://ims.cochrane.org/revman/gradepro) for the three main comparisons, namely, valgus knee brace versus no brace (see Summary of findings table 1; Summary of findings table 2), laterally wedged insole versus neutral insole (see Summary of findings table 1;Summary of findings table 3) and valgus knee brace versus laterally wedged insole (see Summary of findings table 4). We have included in our 'Summary of findings' tables the outcomes of pain, stiffness, physical functioning, health-related quality of life, treatment failure, serious adverse events and total adverse events. Pooling of outcomes was possible only for the comparison of laterally wedged insole versus neutral insole. Data on other comparisons could not be pooled. Almost all studies used different interventions and comparison treatments with a wide variety of outcome measures, often with different follow-up times.

Valgus knee brace versus no treatment

Four studies described the results of knee braces versus no treatment in OA of the knee (Brouwer 2006; Kirkley 1999; Müller-Rath 2011; Sattari 2011).

Pain scores

We found four studies that reported pain scores. Brouwer 2006 reported improved VAS pain score after 12 months' follow-up; however no statistically significant difference was found with no treatment (MD 0, 95% CI -0.8 to 0.8). Kirkley 1999 reported significantly better WOMAC pain scores in the brace group compared with the no brace group (P value < 0.001) after six months. Müller-Rath 2011reported statistically significantly improved VAS score in a valgus knee brace group after 16 weeks but no improvement in the control group (no treatment). Müller-Rath 2011 provided no between-group comparison. In Sattari 2011 the severity of pain decreased statistically significantly more in the knee brace group compared with the no treatment group (MD -2.8, 95% CI -3.6 to -2.0) after nine months (see also Analysis 1.1).

Function

We found three studies that reported function scores. Brouwer 2006 reported statistically non-significant results or lack of evidence of effect of HSS knee function for patients with a valgus knee brace and no brace after 12 months of follow-up (MD 1.0, 95% CI -3.0 to 5.0). Kirkley 1999 found after six months' follow-up better WOMAC physical function scores in the brace group than in the no brace group (P value ≤ 0.001). Müller-

Rath 2011 reported improved Tegner, Insal, Lequesne and WOMAC scores in a valgus knee brace group but no improvement in the control group (no treatment). Müller-Rath 2011 provided no between-group comparisons (see alsoAnalysis 1.2).

Stiffness

Stiffness was not reported in the included studies.

Health-related quality of life

We found two studies that reported health-related quality of life. Brouwer 2006 found no statistically significant differences in EuroQol score after 12 months between participants with and without a knee brace (MD -0.04, 95% CI -0.12 to 0.04). Kirkley 1999 found after six months' follow-up statistically significant improvement in disease-specific quality of life (P value 0.001) in favour of the brace group (see also Analysis 1.4).

Treatment failure

Treatment failure was not reported in the included studies.

Serious adverse events

Serious adverse events were not reported in the included studies.

Total adverse events

In total, 24 of 60 participants in the brace group and 14 of 57 participants in the control group in Brouwer 2006 stopped their initial treatment, most often because of lack of effect (RR 1.63, 95% CI 0.94 to 2.82) (see also Analysis 1.5). Other reasons for stopping were skin irritation (n = 2) and poor fit (n= 2). Sattari 2011 and Müller-Rath 2011 reported no side effects in either group.

Radiographic scores

Radiographic scores were not reported in the included studies.

Compliance

Compliance was not reported in the included studies.

Walking distance

We found two studies that reported walking distance. Brouwer 2006 reported no statistically significant difference in walking distance after 12 months in a brace group compared with a no brace group (MD 0.4, 95% CI -0.9 to 1.7). Sattari 2011 reported statistically significantly increased walking distance in the brace group after nine

months in contrast to the control group, which received no treatment (MD 1.2, 95% CI 1.0 to 1.5) (see also Analysis 1.3).

According to the GRADE approach

Low-quality inconclusive evidence suggests that patients with varus medial knee OA benefit more from brace treatment than from no treatment for the outcomes of pain, function and health-related quality of life (Guyatt 2008a; Guyatt 2008b; Schünemann 2008).

Foot/Ankle orthosis

Four studies (Barrios 2009; Bennell 2011; Maillefert 2001; Sattari 2011) described the results of a foot/ankle orthosis for medial compartment OA of the knee (foot/ankle orthosis vs no treatment or a neutral insole) (see also Summary of findings table 3).

Laterally wedged insole versus no treatment

One study (Sattari 2011) described the effects of a laterally wedged insole versus no treatment.

Pain scores

In Sattari 2011, a statistically significantly decreased pain score is described in the insole group compared with the no treatment group (MD -1.6, 95% CI -2.3 to -0.9) (see also Analysis 3.1).

Function

Function was not reported in the included study.

Stiffness

Stiffness was not reported in the included study.

Health-related quality of life

Health-related quality of life was not reported in the included study.

Treatment failure

Treatment failure was not reported in the included study.

Serious adverse events

Serious adverse events were not reported in the included study.

Total adverse events

Adverse events were not reported in the included study.

Radiographic scores

Radiographic scores were not reported in the included study.

Compliance

Compliance was not reported in the included study.

Walking distance

Sattari 2011 described no statistically significant differences in walking distance after nine months between laterally wedged insole versus no treatment (MD 0.7, 95% CI 0.5 to 0.9) (see also Analysis 3.2).

Laterally wedged insole versus neutral insole

Three studies (Barrios 2009; Bennell 2011; Maillefert 2001) described the effects of a laterally wedged insole versus a neutral insole.

Pain scores

In Barrios 2009, the WOMAC pain subscale improved statistically significantly in both study groups (neutral insole and laterally wedged insole) compared with baseline at one-year follow-up. Between-group comparisons showed no statistically significant differences (MD -2.5, 95% CI -13.5 to 8.5). Bennell 2011 showed small mean reductions in pain scores over time in a neutral insole group and in a laterally wedged insole group; however these reductions were smaller than the minimal clinically important difference. Between-group comparisons did not show a statistically significant difference (MD 1.0, 95% CI -3.8 to 5.8). At six months' follow-up,Maillefert 2001 described a statistically significantly increased WOMAC pain score in a neutral group compared with a laterally wedged insole group (MD 6.4, 95% CI 0.0 to 12.9) (see also Analysis 4.1 and Analysis 4.2).

Function

We found three studies that reported function. In Barrios 2009, the WOMAC function subscale score improved statistically significantly in both study groups (neutral insole and laterally wedged insole) compared with baseline at one-year follow-up. Between-group comparisons showed no statistically significant differences (MD 1.4, 95% CI -9.2 to 12.0). Bennell 2011 showed in both neutral insole and laterally wedged insole groups small mean reductions in WOMAC function scores over time; however these reductions were smaller than the minimal clinically important difference. Between-group

comparisons did not show a statistically significant difference (MD 1.0, 95% CI -4.1 to 6.1). Maillefert 2001 described a non-statistically significant difference in WOMAC function score after six months in a laterally wedged insole group compared with a neutral insole group (MD 0.6, 95% CI -6.9 to 8.1) (see also Analysis 4.4).

Stiffness

We found three studies that reported stiffness. In Barrios 2009, the WOMAC stiffness subscale score improved statistically significantly in both study groups (neutral insole and laterally wedged insole) compared with baseline at one-year follow-up. Between-group comparisons showed no statistically significant differences (MD 4.1, 95% CI -10.1 to 18.3). Bennell 2011 showed in both neutral insole and laterally wedged insole groups small mean reductions in WOMAC stiffness scores over time; however these reductions were smaller than the minimal clinically important difference. Between-group comparisons did not show a statistically significant difference (MD 0.0, 95% CI -7.3 to 7.3). Maillefert 2001 found at six months' follow-up no statistically significant difference in WOMAC stiffness in a neutral compared with a wedged insole group (MD -1.1, 95% CI -9.0 to 6.8) (see also Analysis 4.3).

Health-related quality of life

Health-related quality of life was not reported in the included studies.

Treatment failure

During 12-month follow-up, 43% of participants in the lateral wedge group versus 19% of those in the neutral insole group changed their initial treatment in Barrios 2009. Mean duration of insole use in Bennell 2011 was statistically significantly less in the laterally wedged insole group than in the neutral insole group.

Serious adverse events

Serious adverse events were not reported in the included studies.

Total adverse events

Adverse events were not reported in the included studies.

Radiographic scores

Radiographic scores were not reported in the included studies.

Compliance

Maillefert 2001 found statistically significantly better compliance with the laterally wedged insole (87.8%) than with the neutral insole (74.3%).

Walking distance

Walking distance was not reported in the included studies.

According to the GRADE approach

Evidence is lacking to suggest that a laterally wedged insole is more effective than no treatment. Moderate evidence suggests that a laterally wedged insole is as effective as a neutral insole for the outcomes of pain, function and stiffness (Guyatt 2008a; Guyatt 2008b;Schünemann 2008).

Knee brace versus laterally wedged insole

Two studies (Raaij van 2010; Sattari 2011) described the results when a valgus knee brace versus a laterally wedged insole was used for medial compartment OA of the knee (see also Summary of findings table 4).

Pain scores

We found two studies that reported pain scores. In Raaij van 2010 after six months' follow-up, VAS pain scores statistically significantly improved in both the insole group and the brace group compared with baseline measurements, but no statistically significant differences were observed between the two study groups for this outcome (MD 0.2, 95% CI -1.15 to 0.75). In Sattari 2011, severity of pain decreased statistically significantly in the knee brace group and in the laterally wedged insole group. Investigators reported less pain in the brace group (MD -2.8, 95% CI -3.6 to -2.0) after nine months (see also Analysis 2.3).

Function

We found one study that reported function scores. Raaij van 2010 reported statistically significantly improved WOMAC function scores in both the insole group and the brace group compared with baseline measurements but noted no statistically significant differences between the two study groups for this outcome (MD 0.1, 95% CI -7.26 to 0.75) (see also Analysis 2.2).

Stiffness

None of the studies reported a specific stiffness score.

Health-related quality of life

Health-related quality of life was not reported in the included studies.

Treatment failure

Treatment failure was not reported in the included studies.

Serious adverse events

Serious adverse events were not reported in the included studies.

Total adverse events

Adverse events were not reported in the included studies.

Radiographic scores

Radiographic scores were not reported in the included studies.

Compliance

Compliance was not reported in the included studies.

Walking distance

We found one study that reported walking distance. Sattari 2011 reported an MD of 0.5 km (95% CI 0.23 to 0.77) in favour of the brace group (see also Analysis 2.1).

According to the GRADE approach

Low-quality evidence suggests no statistically significant differences in clinical effect between the laterally wedged insole group and the valgus knee brace group for the outcomes of pain and function (Guyatt 2008a; Guyatt 2008b; Schünemann 2008).

DISCUSSION

Summary of main results

We conducted this review to assess the benefits and harms of braces and orthoses for treatment of patients with osteoarthritis (OA) of the knee. We included a total of 13 studies (n = 1356). These studies have reported results for patients with early to severe knee OA (Kellgren & Lawrence (K&L) I-IV) treated with a valgus knee brace, a laterally wedged insole, a neutral insole or a variable or constant stiffness shoe, or given no treatment.

We found inconclusive evidence for the benefits of a valgus knee brace: Only four controlled trials were published. Kirkley 1999 concluded that in patients with varus knee OA, a brace provides additional beneficial effects in terms of pain and function compared with medical treatment alone. However, baseline characteristics were different between study groups, and the quality of the study was low. Brouwer 2006 concluded that a brace offers little or no additional effect compared with conservative treatment alone in patients with unicompartmental OA. However, many patients do not adhere in the long run to this kind of treatment because the positive effects are too small

or because the side effects are too large. Müller-Rath 2011 reported improved Tegner, Insal, Lequesne, Western Ontario-McMaster Osteoarthritis Scale (WOMAC) and visual analogue scale (VAS) scores in the knee brace group after 16 weeks of treatment. They reported no improvement in the control group (no treatment) and described no side effects of treatment; however this study was sponsored, and study authors were not able to provide their data because of a server breakdown. Sattari 2011 reported a statistically significantly decreased pain score in the knee brace group compared with the no treatment group after nine months. Walking distance was increased statistically significantly in the brace group in contrast to the no treatment group after nine months. Investigators described no side effects of the brace. All four studies showed some clinical effect; however the methodological quality of these studies was low.

Moderate-quality evidence shows the benefits of a laterally wedged insole (vs no treatment or a neutral insole) for medial compartment OA: We included seven controlled trials in this review with conflicting evidence. Barrios 2009, Maillefert 2001, Sattari 2011, Toda 2002and Toda 2008 reported statistically significantly improved patient-reported outcomes after a laterally wedged insole was worn; however Bennell 2011 and Toda 2001 reported reductions smaller than the minimal clinically important difference.

Conflicting evidence was found for preference of a neutral or a laterally wedged insole. Results reported by Barrios 2009 favoured the laterally wedged insole, Maillefert 2001 favoured the neutral insole and Bennell 2011 reported no statistically significant differences between the two insoles. Pooling of results of three studies comparing laterally wedged and neutral insoles resulted in lack of evidence of an effect on WOMAC pain scores, WOMAC stiffness scores and WOMAC function scores at one month and at 12 months (see alsoSummary of findings table 3).

Data for the comparison of laterally wedged insole versus valgus knee brace could not be pooled. After six months' follow-up, VAS pain scores and WOMAC function scores were improved and did not differ statistically significantly in the two groups (see alsoSummary of findings table 4).

Overall completeness and applicability of evidence

Four trials investigated a knee brace and eight studies examined foot/ankle orthoses for medial compartment OA of the knee. It is important to note that the findings of these studies may lack generalisability: In the studies of Toda and Rodriques (Toda 2001; Toda 2002; Rodriques 2008), all participants were female, and in Kirkley 1999 and Sattari 2011, most participants were male. In all studies the age of participants was relatively high (mean 63 years). In the Kirkley 1999 trial, baseline characteristics differed between participants. It is important to present full data: Kirkley 1999 presented change scores without baseline scores and without a standard deviation. Toda 2001 and Toda

2002 presented pre-analysis and post-analysis results but did not report between-group differences.Müller-Rath 2011 presented their scores only graphically and could not provide their data because of a server breakdown.

Particularly, researchers studied the effects of braces and orthoses for medial compartment OA. Compared with lateral compartment OA of the knee, medial compartment OA has a much higher prevalence because lateral compartment OA is associated with trauma and is less clinically frequent. This is probably why only one randomised controlled trial (RCT) (Brouwer 2006) examined the effect of a brace or an orthosis for lateral compartment or general OA of the knee. Furthermore, varus bracing for lateral OA is probably less effective; the adduction moment at the knee during the stance phase of walking causes mainly medial loading (Johnson 1980). In general OA of the knee, there is no compartment to unload, and perhaps a sleeve or a neutral brace will benefit. No studies compared a brace or an orthosis with operative treatment such as high tibial osteotomy or unicompartmental knee arthroplasty.

Quality of the evidence

Two studies in this review had low risk of any type of bias, six studies had moderate risk and five studies had high risk. The randomisation procedure frequently was not described or was insufficient. Except for the trials of Bennell 2011, Brouwer 2006, Kirkley 1999, Raaij van 2010 and Toda 2008, the randomisation procedure was not described or was inadequate. In most studies, blinding procedures were insufficient, although we realise that when braces are used, blinding is not always possible; for footwear inserts, it is generally less difficult. Results were based on small studies, leading to imprecision.

Potential biases in the review process

One study did not report the number of participants lost to follow-up. This study was funded by Medi, provider of orthoses. Outcomes were presented only graphically in this publication. Study authors were not able to provide their data on request because of a "server breakdown" (Müller-Rath 2011).

Agreements and disagreements with other studies or reviews

Other meta-analyses or systematic reviews were not available for comparison of our results.

AUTHORS' CONCLUSIONS

We conclude that in cases of varus medial compartment knee OA, low-quality inconclusive evidence shows benefits of bracing for pain, stiffness, function and quality of life

in the treatment of medial compartment knee OA. Moderate-quality evidence suggests that a laterally wedged insole is as effective as a neutral insole. Evidence is lacking to suggest that a laterally wedged insole is more effective than no treatment. Also evidence of low quality suggests no statistically significant difference in clinical effect between the laterally wedged insole and the valgus knee brace.

The optimal choice for an orthosis remains unclear, and long-term implications are lacking.

Implications for research

The methodological quality of studies investigating the benefits of braces and orthoses has to be improved, particularly the randomisation procedure and blinding measures. Moreover to improve the generalisability of results, studies should not be limited to female participants.

Short-term benefit must be established first to justify the considerable resources required by and the ethical implications involved in a lengthy study. Subsequently, a follow-up period of at least five years is needed because OA is a chronic disease. One general knee score would allow pooling of results. We recommend using the WOMAC because this has been shown to be a valid instrument for measurement of OA (Bellamy 1997). Between-groups analysis is necessary to show relevant differences. Future studies should provide complete data on outcome measures, including means and standard deviations or 95% confidence intervals.

It is important to score side effects because they influence the patient's compliance with the intervention. This especially concerns braces, which can be obtrusive in many cases. For insoles, bigger and less stylish shoes are needed. New trials should investigate the long-term benefits of braces and orthoses compared with standard conservative care. More studies are needed to identify predictive factors for the success of brace and insole treatment. If feasible, braces should be compared with ankle/foot orthoses. If braces and orthoses are effective, they should be compared with operative treatment such as high tibial osteotomy or knee arthroplasty for medial compartment OA. It will be interesting to learn for how long surgery can be delayed by this kind of conservative treatment (Gossec 2007).

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CONTRIBUTIONS OF AUTHORS

Reinoud Brouwer (RB) proposed the review. RB, Sita Bierma-Zeinstra (SB) and Arianne Verhagen (AV) wrote the protocol. RB, Tom van Raaij (TR) and Tijs Duivenvoorden (TD) selected the studies following review of the abstracts. RB, TD and TR made the final selection after reading the full articles. RB, TD, SB and Jan Verhaar (JV) assessed methodological quality. RB, TD and AV performed data extraction. With contributions from all co-authors, RB wrote the review.

DECLARATIONS OF INTEREST

Conflict of interest is possible because two included studies (Brouwer 2006; Raaij van 2010) were conducted by four of the authors (RB, TR, SB, JV) of this systematic review.

Differences between protocol and review

No major differences exist between the protocol and the review.

Published notes

This is an update of the original review, which was published in Issue 1, 2005. We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE for controlled clinical trials until May 2007. As a result of the search, we have included six new studies in this updated review. The conclusions of this update are consistent with those provided in the original review.

CHARACTERISTICT OF INCLUDED STUDIES

Barrios 2009		
Methods	RCT; block randomisation	
Participants	Medial tibiofemoral OA: n = 66 Male/female: 29/37 Mean age (years): 62 Mean BMI (kg/m^2): 33 Grade of OA according to Kellgren & Lawrence: II = 27, III = 24, IV = 15	
Interventions	I = full-length (9°) wedged insole into shoe (n = 35) vs C = non-custom neutral insole into shoe (n = 31) Follow-up: 12 months	
Outcomes	WOMAC, 6-minute walking test, stair negotiation test	
Notes	Mean and P values are presented, but SD values are missing	
Risk of bias table		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "a block-randomization was performed based on OA grade, gender, and age (greater or less than 55 years)"
Allocation concealment (selection bias)	Low risk	Quote: "the allocation was done by an administrative assistant unaware of the methodologies used"
Blinding (performance bias and detection bias)	Low risk	Quote: "the subjects were blinded from group assignment"
Blinding of participants and personnel (performance bias)	High risk	Participants assigned to the treatment group were tested to determine the amount of wedging Quote: "subjects who had no pain relieve (after wedging) were excluded from the study"
Blinding of outcome assessment (detection bias)	Unclear risk	Blinding of assessors was not mentioned
Incomplete outcome data (attrition bias)	Low risk	Intention-to-treat
Selective reporting (reporting bias)	High risk	Quote: "subjects who had no pain relieve (after wedging) were excluded from the study"

Bennell 2011		
Methods	RCT; computer-generated block randomisation	
Participants	Painful medial knee osteoarthritis: n = 200 Male/ female: 82/118 Mean age (years): 64 Mean BMI (kg/m^2): 29.2 Mean varus (degrees): 181 Grade of medial OA according to Kellgren & Lawrence: II = 95, III = 105	
Interventions	I = full-length (5º) wedged insole into shoe (n = 103) vs C = neutral insole into shoe (n = 97) Follow-up: 12 months	
Outcomes	NRS scale (pain), WOMAC scale, physical activity scale for the elderly, average number of steps taken per day	
Notes	No competing interests	
Risk of bias table		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Participants were stratified by disease severity (Kellgren and Lawrence grades 2 and 3) and sex and randomly allocated in permuted blocks of 6 to 12"
Allocation concealment (selection bias)	Low risk	Quote: "An independent investigator used a computer program to generate the randomisation sequence a priori. Allocation was sealed in opaque and consecutively numbered envelopes held centrally. Envelopes were opened sequentially by an independent person"
Blinding (performance bias and detection bias)	Low risk	Quote: "a double blind randomised controlled trial"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Participants were informed that two types of insoles were being compared but the insoles and study hypotheses were not described"
Blinding of outcome assessment (detection bias)	Low risk	Quote: "A blinded examiner assessed the participants at baseline and 12 months" according to patient-reported outcome measures; participants were blinded as well
Incomplete outcome data (attrition bias)	Low risk	Intention-to-treat
Selective reporting (reporting bias)	Low risk	Complete data were reported

Brouwer 2006		
Methods	RCT; computer-generated block randomisation	
Participants	Unicompartmental knee OA: n = 117 Male/ female: 69/48 Mean age (years): 59 Mean BMI (kg/m^2): 28.5 Varus: n = 95/valgus: n = 22 Mean varus (degrees) = 188 Mean valgus (degrees) = 173	
Interventions	I = Brace intended to reduce load (n = 60) vs C = standard conservative treatment (n = 57) Follow-up: 12 months	
Outcomes	VAS, HSS knee score, walking distance, EuroQol	
Notes	No competing interests	
Risk of bias table		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomised according to a computer-generated procedure in blocks of 24"
Allocation concealment (selection bias)	Low risk	Quote: "the allocation of treatment was concealed until after the patient was included and baseline measurements were executed; sealed envelopes contained the group assignment"
Blinding (performance bias and detection bias)	Low risk	Outcome assessor of the HSS knee was blinded for allocation
Blinding of participants and personnel (performance bias)	High risk	Participants were not blinded; outcome assessor of the HSS knee was blinded
Blinding of outcome assessment (detection bias)	High risk	Study used patient-reported outcome measures; participants were not blinded. Functional outcome (HSS knee score) was measured blinded
Incomplete outcome data (attrition bias)	Low risk	Intention-to-treat
Selective reporting (reporting bias)	Low risk	Complete data were reported

Erhart-Hledik 2012		
Methods	RCT; randomisation procedure not described; outcome assessment partially blinded	
Participants	Medial compartment knee OA: n = 79 Male/female: 42/37 Mean age (years): 60 Mean BMI (kg/m^2): 27.7	
Interventions	I = Variable-stifness shoe (n = 40) vs C = constant stiffness shoe (n = 39) Follow-up = 6 and 12 months	
Outcomes	WOMAC	
Notes	6-Month results were presented earlier. Patients were included on the basis of MRI. Anteroposterior radiograph was used during follow-up	
Risk of bias table		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "using a random number generator"
Allocation concealment (selection bias)	Low risk	Quote: "The randomization code was revealed to the study coordinator in charge of subject recruitment and in contact with the subjects regarding WOMAC scores, once recruitment, data collection, and analyses were completed"
Blinding (performance bias and detection bias)	Low risk	Quote: "Subjects were blinded to their shoe type"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Subjects were blinded to their shoe type (The researcher performing the gait analysis was not blinded to the shoe type)"
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Subjects were blinded to their shoe type"
Incomplete outcome data (attrition bias)	Low risk	Intention-to-treat
Selective reporting (reporting bias)	Low risk	Complete data were reported; study author provided additional data for this review

Kirkley 1999		
Methods	RCT; computer-generated blocked randomisation scheme with use of sealed envelopes; blinding of outcome assessment not described	
Participants	Varus arthrosis: n = 119 Male/female: 79/31 Mean age (years): 59 Mean varus (degrees): 189	
Interventions	I = unloader brace (n = 41) vs C1 = neoprene brace (n = 36) vs C2 = medical treatment only (n = 33) Follow-up: 6 months	
Outcomes	WOMAC and MACTAR scores Function assessed with use of the 6-minute walking and the 30-second stair climbing test	
Notes	No competing interests	
Risk of bias table		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "a computer-generated blocked randomisation scheme"
Allocation concealment (selection bias)	Low risk	Quote: "with use of sealed envelopes"
Blinding (performance bias and detection bias)	High risk	Participants were not blinded to the intervention
Blinding of participants and personnel (performance bias)	High risk	Participants were not blinded
Blinding of outcome assessment (detection bias)	Unclear risk	Study used patient-reported outcomes. Outcome assessor of patient-reported outcome measures was not blinded
Incomplete outcome data (attrition bias)	High risk	No intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	Complete data were reported

Maillefert 2001		
Methods	RCT; randomisation procedure not described; outcome assessment partially blinded	
Participants	Painful medial knee osteoarthritis: n = 156 Male/female: 41/108 Mean age (years): 65 Mean BMI (kg/m^2): 29 Grade of OA according to Kellgren & Lawrence: II = 69, III = 60, IV = 18	
Interventions	I = laterally wedged insole (n = 78) vs C = neutrally wedged insole (n = 69); follow-up: 1, 3, 6 months	
Outcomes	WOMAC, concomitant treatment, compliance	
Notes	No competing interests	
Risk of bias table		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation sequence generation procedure was not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment procedure was not described
Blinding (performance bias and detection bias)	High risk	Participants were blinded to randomisation
Blinding of participants and personnel (performance bias)	High risk	Quote: "The practitioner nor the patient was blinded to the randomization"; however the research nurse was blinded to allocation
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "Any missing data were collected by a research nurse, unaware of the randomisation by telephone"
Incomplete outcome data (attrition bias)	Low risk	Quote: "Analysis was made using an intention-to-treat approach"
Selective reporting (reporting bias)	Low risk	Complete data were reported

Müller-Rath 2011		
Methods	RCT; randomisation procedure and blinding of outcome assessment not described	
Participants	Symptomatic varus knee OA: n = 33 Male/female: 24/9 Mean age (years): 53 Mean BMI (kg/m^2): 27.2	
Interventions	I = valgus knee brace or elastic knee bandage vs C = no treatment Follow-up: 16 weeks	
Outcomes	Tegner, Insall, Lequesne, WOMAC, HSS, VAS	
Notes	Number of participants lost to follow-up is not reported. Study is funded by Medi, provider of orthoses. Study authors could not provide their data because of a "server breakdown"	
Risk of bias table		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias)	High risk	Not blinded
Blinding of participants and personnel (performance bias)	High risk	Not blinded
Blinding of outcome assessment (detection bias)	High risk	Not blinded
Incomplete outcome data (attrition bias)	High risk	No lost participants were reported; study authors could not provide their data because of a "server breakdown"
Selective reporting (reporting bias)	High risk	No intention-to-treat

Raaij van 2010		
Methods	RCT; computer-generated blocked randomisation	
Participants	Medial knee OA: n = 91 Male/female: 46/45 Mean age (years): 55 Mean BMI (kg/m^2): 29 Mean varus (degrees) = 187 Degree of medial OA according to Kellgren & Lawrence (n): I = 37, II = 17, III = 35, IV = 2 Degree of lateral OA according to Kellgren & Lawrence (n): 0 = 67, I = 22, II = 2	
Interventions	I = 10-mm laterally full-length wedged insole (n = 45) vs C = valgus brace (n = 46)	
Outcomes	VAS (pain), WOMAC, degree of varus (hip-knee-ankle angle)	
Notes		
Risk of bias table		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "participants were randomised according to a computer-generated procedure (block randomisation, with variable sizes of the blocks)"
Allocation concealment (selection bias)	Low risk	Quote: "the randomizations codes were held by an independent observer to ensure masked blocking"
Blinding (performance bias and detection bias)	High risk	Unblinded trial
Blinding of participants and personnel (performance bias)	High risk	Quote: "completely unblinded"
Blinding of outcome assessment (detection bias)	High risk	Quote: "one non-blinded investigator, a trained orthopedic surgeon, assessed the follow-up measurements"
Incomplete outcome data (attrition bias)	Low risk	Quote: "by intention-to-treat"
Selective reporting (reporting bias)	Low risk	Complete data were reported

Rodriques 2008		
Methods	RCT; randomisation procedure not described; outcome assessment blinded	
Participants	Bilateral valgus deformity knee OA: N = 30 All female Mean age (years): 62 Mean BMI (kg/m^2): 30 Degree of OA lateral compartment according to Kellgren & Lawrence: II = 16, III = 8, IV = 6	
Interventions	I = medially wedged insole (n = 16) vs C = neutral insole (n = 14) Follow-up: 2 months	
Outcomes	VAS pain (night, rest, movement), Lequesne index score, WOMAC	
Notes		
Risk of bias table		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation sequence procedure is not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment procedure is not described
Blinding (performance bias and detection bias)	Low risk	Double-blind trial
Blinding of participants and personnel (performance bias)	Low risk	Quote: "patients of both groups received the same new shoe and were blind to insole use"
Blinding of outcome assessment (detection bias)	Low risk	Quote: "outcomes were administered at baseline and after 8 weeks by a blinded examiner"
Incomplete outcome data (attrition bias)	Low risk	Complete data were reported
Selective reporting (reporting bias)	Low risk	Complete data were reported

Sattari 2011		
Methods	RCT; computer-generated randomisation	
Participants	Varus knee OA: n = 60 Male/female: 22/38 Mean age (years): 48 Mean BMI (kg/m^2): not reported Degree of OA medial compartment according to Kellgren & Lawrence: III = 39, IV = 21	
Interventions	I = custom-molded valgus stress knee support (n = 20) or 1/4-inch lateral wedged insole (n = 20) vs C = no intervention Follow-up: 9 months	
Outcomes	VAS (pain), Lequesne index (walking distance)	
Notes	Conflicts of interest are not described	
Risk of bias table		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation sequence procedure is not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment procedure is not described
Blinding (performance bias and detection bias)	High risk	Participants were not blinded; outcome assessors were blinded; study used patient-reported outcome measures
Blinding of participants and personnel (performance bias)	High risk	Participants were not blinded
Blinding of outcome assessment (detection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	High risk	Quote: "5 patients were removed from the study because of absence from follow-up. They were substituted with new patients, to maintain 20 patients in each group"
Selective reporting (reporting bias)	High risk	No intention-to-treat

Toda 2001	
Methods	RCT; randomisation performed by date of birth. Blinded assessments of level of pain according to VAS, Lequesne index, radiographic outcome
Participants	American College of Rheumatology criteria for knee osteoarthritis (n = 90) All female Mean age (years): 65 Mean varus (FTA; degrees): 181 Degree of OA according to Kellgren & Lawrence: II = 55, III = 27, IV = 8
Interventions	I = strapped insole (n = 46) vs C = lateral wedge insole (n = 44) Follow-up: 8 weeks, 6 months and 2 years
Outcomes	VAS, Lequesne (pain) index score, radiographic changes
Notes	In Table 3 of the first publication, median value of final VAS score in strapped insole group is incorrect No between-groups analysis was performed

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "Randomisation was performed by date of birth"
Allocation concealment (selection bias)	High risk	Quote: "Randomisation was performed by date of birth"
Blinding (performance bias and detection bias)	High risk	Participants were not blinded; outcome assessors were blinded; study used patient-reported outcome measures; radiographic changes were measured blinded
Blinding of participants and personnel (performance bias)	High risk	Participants were not blinded to the intervention. Research nurse was blinded to objectives of the study
Blinding of outcome assessment (detection bias)	High risk	Study used patient-reported outcome measures (PROMs). Outcome assessor of PROMS, namely, the participant, was not blinded in this study. However participant and research nurse were blinded to objectives of the study
Incomplete outcome data (attrition bias)	High risk	No intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	Complete data were reported

Toda 2002		
Methods	RCT; randomisation performed by date of birth	
Participants	American College of Rheumatology criteria for knee OA: n = 88 All female Mean age (years): 65 Mean BMI (kg/m^2): 25 Degree of varus (FTA; degrees): 181	
Interventions	I = subtalar strapped support (n = 44) vs C = sock-type support (n = 46) Follow-up: 8 weeks	
Outcomes	Lequesne (pain) index, radiographic changes	
Notes	Scores were shown in figures; no exact numbers were given No between-groups analysis was performed	
Risk of bias table		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Quote: "Randomisation was performed by date of birth"
Allocation concealment (selection bias)	High risk	Quote: "Randomisation was performed by date of birth"
Blinding (performance bias and detection bias)	High risk	Participants were not blinded; outcome assessment was blinded; study used patient-reported outcome measures. Radiographic changes were measured blinded
Blinding of participants and personnel (performance bias)	High risk	Quote: "in this study, participants were not blinded to the treatment. However, participants were not told whether the method of fixation at ankle joint, belt or sock-type, was thought to be important"
Blinding of outcome assessment (detection bias)	Low risk	Quote: "All other items were assessed by physical therapists who were uninformed of the objective of the study when patients presented the OOC" "The radiographic assessment was completed by 3 orthopedic surgeons prior to being informed of the category of the patients"
Incomplete outcome data (attrition bias)	Unclear risk	Scores were shown in figures; no exact numbers were given
Selective reporting (reporting bias)	Low risk	Complete data were reported

Toda 2008		
Methods	RCT; computer-generated blocked randomisation	
Participants	Patients with medial compartment OA of the knee according to American College of Rheumatology criteria and a criterion stipulating standing femorotibial angle greater than 176 degrees: n = 207 Male/female: 24/183 Mean age (years): 65 Mean BMI (kg/m^2): 25 Grade of OA according to Kellgren & Lawrence: I = 17, II = 133, III = 35, IV = 22 Varus: 181 degrees (FTA)	
Interventions	I = wedged insole with shoes (n = 45), sock-type ankle supporter with wedged insole without shoes (n = 46), subtalar strapped insole with shoes (n = 45) and subtalar strapped insole without shoes (n = 46) vs C = neutral wedged insole into shoes (n = 45)	
Outcomes	Lequesne index VAS pain NSAID intake	
Notes	Baseline characteristics and outcomes (differences compared with baseline) were presented only for the 207 participants who completed 12-week follow-up Most results were presented as pre/post analysis, and only NSAID intake was compared between placebo and the different interventions	
Risk of bias table		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The randomisation procedure for the allocation was a computer-generated block method using sealed envelopes"
Allocation concealment (selection bias)	Low risk	Quote: "In the initial visit, clinicians were given randomly generated treatment allocations with sealed opaque envelopes in a series of blocks of 10"
Blinding (performance bias and detection bias)	High risk	Participants were not blinded to the intervention; study used patient-reported outcome measures
Blinding of participants and personnel (performance bias)	High risk	Participants were not blinded to the intervention; research nurse was blinded to objectives of the study
Blinding of outcome assessment (detection bias)	Low risk	Quote: "a research nurse who was blind to the objectives of the study asked the participants to assess the Lequesne index and the VAS for subjective knee pain at baseline and 12-weeks assessments"; however participants were not blinded to the intervention, and patient-reported outcome measures were used
Incomplete outcome data (attrition bias)	High risk	Intention-to-treat analysis
Selective reporting (reporting bias)	High risk	Baseline characteristics and outcomes (differences compared with baseline) were presented for only the 207 participants who completed 12-week follow-up

CHARACTERISTICS OF EXCLUDED STUDIES

Baker 2007	
Reason for exclusion	Cross-over design
Birmingham 2001	
Reason for exclusion	No control group
Horlick 1993	
Reason for exclusion	Participants are their own controls
Hunter 2012	
Reason for exclusion	Cross-over design
Katsuragawa 1999	
Reason for exclusion	No control group
Kuroyanagi 2007	
Reason for exclusion	Cross-over design
Matsuno 1997	
Reason for exclusion	No control group
Rooser 1988	
Reason for exclusion	Rheumatoid arthritis after total knee arthroplasty Healthy controls
Sasaki 1987	
Reason for exclusion	Retrospective trial
Shakoor 2008	
Reason for exclusion	Cross-over design
Toda 2002b	
Reason for exclusion	Correlation study
Tohyama 1991	
Reason for exclusion	Retrospective study

SUMMARY OF FINDING TABLES

1 Braces and orthoses for varus medial osteoarthritis of the knee

Valgus knee braces and orthoses for varus medial osteoarthritis of the knee						
Patient or population: patients with varus medial osteoarthritis of the knee **Settings:** general hospital **Intervention:** valgus knee brace or lateral wedge insole **Comparison:** no brace or neutral insole						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**Number of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Control	**Intervention**				
Valgus knee brace compared with no brace						
Pain on walking (VAS) Scale from 0 to 10 Follow-up: 12 months *(Higher score is worse)*	Mean pain score in control groups was **5.2**	Mean pain in intervention groups was **equal** (0.84 lower to 0.84 higher)		115 (1 study)	⊕⊕⊖⊖ **Low** [a,b]	MD = 0.00 (95% CI -0.84 to 0.84) Absolute percent change = 0% (95% CI -8.4 to 8.4) Relative percent change = 0% (95% CI -1.6 to 1.6) NNTB = not statistically significant
Knee function (HSS) Scale from 0 to 100 Follow-up: 12 months *(Higher score is better)*	Mean function score in control groups was **69**	Mean function in intervention groups was **1.00 higher** (2.98 lower to 4.98 higher)		110 (1 study)	⊕⊕⊖⊖ **Low** [a,b]	MD = 1.00 (95% CI -2.98 to 4.98) Absolute percent change = 1.0% (95% CI 3.0 to 5.0) Relative percent change = 0.01% (95% CI 0.05 to 0.07) NNTB = not statistically significant
Quality of life (EQ-5D) Scale from 0 to 100 Follow-up: 12 months *(Higher score is better)*	Mean health-related quality of life score in control groups was **0.6**	Mean health-related quality of life score in intervention groups was **0.04 lower** (0.12 lower to 0.04 higher)		117 (1 study)	⊕⊕⊖⊖ **Low** [a,b]	MD = 0.04 (95% CI -0.12 to 0.04) Absolute percent change = 0.04% (95% CI -0.12 to 0.04) Relative percent change = 0.07% (95% CI -0.2 to 0.07) NNTB = not statistically significant

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Intervention				
Total number of adverse events (withdrawals due to lack of effect) [c] Follow-up: 12 months	**Low-risk population**		**RR 1.63** (0.94 to 2.82)	117 (1 study)	⊕⊕⊖⊖ **Low** [a,b]	Absolute percent change = 15% (95% CI -1% to 32%) Relative percent change = 63% (95% CI -6% to 182%) NNTB = not statistically significant
	246 per 1000	**400 per 1000** (239 to 694)				
Lateral-wedge insole compared with neutral insole						
Pain on walking (NRS) Scale from 0 to 10 Follow-up: mean 12 months *(Higher score is worse)*	Mean pain on walking score in control groups was **2.6**	Mean pain on walking in intervention groups was **0.1 higher** (0.45 higher to 0.65 lower)		224 (2 studies)	⊕⊕⊕⊖ **Moderate**[a]	MD = 0.10 (95% CI -0.45 to 0.65) Absolute percent change = 1.0% (95% CI 4.5 to -6.5) Relative percent change = 3.8% (95% CI 1.7 to -25.0) NNTB = not statistically significant
Physical function (WOMAC) - 12 months Scale from 0 to 100 Follow-up: mean 12 months *(Higher score is better)*	Mean function score in control groups was **36.6**	Mean function in intervention groups was **0.94 higher** (2.98 lower to 4.87 higher)		358 (3 studies)	⊕⊕⊕⊖ **Moderate**[a]	MD = 0.94 (95% CI -2.98 to 4.87) Absolute percent change = 0.9% (95% CI -3.0 to 4.9) Relative percent change = 2.6% (95% CI -8.1 to 13.3) NNTB = not statistically significant
Health-related quality of life (HRQoL) Scale from 0 to 1.0 Follow-up: 12 months *(Higher score is better)*	Mean health-related quality of life score in control groups was **0.7**	Mean health-related quality of life score in intervention groups was **0.01 lower** (0.05 lower to 0.03 higher)		179 (1 study)	⊕⊕⊕⊖ **Moderate**[a]	MD = 0.00 (95% CI -0.06 to 0.06) Absolute percent change = 1.0% (95% CI -5.0 to 3.0) Relative percent change = 1.4% (95% CI -7.1 to 4.3) NNTB = not statistically significant

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk**(and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
[a]Limitations in design and implementation of available studies suggest high likelihood of bias.
[b]Imprecision: Results are based on only one study with 117 people.
[c]Many participants stopped their initial treatment because of lack of effect.

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Abbreviations; **CI:** Confidence interval; **EQ-5D:** EuroQol-5D; **HSS:** Hospital for Special Surgery knee score; **NNTB:** number needed to treat for an additional beneficial outcome; **NRS:** numerical rating scale; **RR:** Risk ratio; **VAS:** Visual analogue scale; **WOMAC:** Western Ontario-McMaster Osteoarthritis Scale.

2 Valgus knee brace compared with no brace for varus medial osteoarthritis of the knee

Valgus knee brace compared with no brace for varus medial osteoarthritis of the knee					
Patient or population: patients with varus medial osteoarthritis of the knee **Settings:** general hospital **Intervention:** valgus knee brace **Comparison:** no brace					
Outcomes	**Illustrative comparative risks* (95% CI)**		**Number of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**			
	No brace	**Valgus knee brace**			
Pain VAS: scale from 0 to 10 Follow-up: 12 months *(Higher score is worse)*	Mean pain score in control groups was **5.2**	Mean pain on walking in intervention groups was **equal** (0.84 lower to 0.84 higher)	115 (1 study)	⊕⊕⊖⊖ **Low** [a,b]	MD = 0.00 (95% CI -0.84 to 0.84) Absolute percent change = 0% (95% CI -8.4 to 8.4) Relative percent change = 0% (95% CI -1.6 to 1.6) NNTB = not statistically significant
Stiffness	See comment	See comment	Not estimable[c]	See comment	Outcome not reported in included studies
Function HSS: scale from 0 to 100 Follow-up: 12 months *(Higher score is better)*	Mean function score in control groups was **69**	Mean function in intervention groups was **1.00 higher** (2.98 lower to 4.98 higher)	110 (1 study)	⊕⊕⊖⊖ **Low** [a,b]	MD = 1.00 (95% CI -2.98 to 4.98) Absolute percent change = 1.0% (95% CI 3.0 to 5.0) Relative percent change = 0.01% (95% CI 0.05 to 0.07) NNTB = not statistically significant

Outcomes	Illustrative comparative risks* (95% CI)		Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk			
	No brace	Valgus knee brace			
Health-related quality of life EQ-5S: scale from 0 to 100 Follow-up: 12 months *(Higher score is better)*	Mean health-related quality of life score in control groups was **0.6**	Mean health-related quality of life score in intervention groups was **0.04 lower** (0.12 lower to 0.04 higher)	117 (1 study)	⊕⊕⊖⊖ **Low** [a,b]	MD = 0.04 (95% CI -0.12 to 0.04) Absolute percent change = 0.04% (95% CI -0.12 to 0.04) Relative percent change = 0.07% (95% CI -0.2 to 0.07) NNTB = not statistically significant
Treatment failure	See comment	See comment	Not estimable[c]	See comment	Outcome not reported in included studies
Serious adverse events	See comment	See comment	Not estimable[c]	See comment	Outcome not reported in included studies
Total number of adverse events (withdrawals due to lack of effect)[d]	**Study population**		117 (1 study)	⊕⊕⊖⊖ **Low** [a,b]	RR = 1.63 (95% CI 0.94 to 2.82) Absolute percent change = 15% (95% CI -1% to 32%) Relative percent change = 63% (95% CI -6% to 182%) NNTB = not statistically significant
	400 per 1000	246 per 1000			

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk**(and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a]Limitations in design and implementation of available studies suggest high likelihood of bias.
[b]Imprecision: Results are based on only one study with 117 participants.
[c]No useful data were available.
[d]Many participants stopped their initial treatment because of lack of effect.

Abbreviations; **CI:** Confidence interval; **NNTB:** Number needed to treat for an additional beneficial outcome; **RR:** Risk ratio.

3 Lateral wedge insole compared with neutral insole for varus medial osteoarthritis of the knee

Lateral wedge insole compared with neutral insole for varus medial osteoarthritis of the knee					
Patient or population: patients with varus medial osteoarthritis of the knee **Settings:** general hospital **Intervention:** lateral wedge insole **Comparison:** neutral insole					
Outcomes	**Illustrative comparative risks* (95% CI)**		**Number of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**			
	Neutral insole	**Lateral wedge insole**			
Pain NRS: scale from 0 to 10 Follow-up: mean 12 months *(Higher score is worse)*	Mean pain on walking score in control groups was **2.6**	Mean pain on walking in intervention groups was **0.1 higher** (0.45 higher to 0.65 lower)	224 (2 studies)	⊕⊕⊕⊖ **Moderate** [a]	MD = 0.10 (95% CI -0.45 to 0.65) Absolute percent change = 1.0% (95% CI 4.5 to -6.5) Relative percent change = 3.8% (95% CI 1.7 to -25.0) NNTB = not statistically significant
Stiffness WOMAC: scale from 0 to 100 Follow-up: mean 12 months *(Higher score is better)*	Mean stiffness score in control groups was **41.6**	Mean stiffness in intervention groups was **0.07 higher** (4.96 lower to 5.1 higher)	358 (3 studies)	⊕⊕⊕⊖ **Moderate** [a]	MD = 0.07 (95% CI -4.96 to 5.10) Absolute percent change = 0.1% (95% CI -5.0 to 5.1) Relative percent change = 0.2% (95% CI -11.9 to 12.3) NNTB = not statistically significant
Function WOMAC: scale from 0 to 100 Follow-up: mean 12 months *(Higher score is better)*	Mean function score in control groups was **36.6**	Mean function in intervention groups was **0.94 higher** (2.98 lower to 4.87 higher)	358 (3 studies)	⊕⊕⊕⊖ **Moderate** [a]	MD = 0.94 (95% CI -2.98 to 4.87) Absolute percent change = 0.9% (95% CI -3.0 to 4.9) Relative percent change = 2.6% (95% CI -8.1 to 13.3) NNTB = not statistically significant

Outcomes	Illustrative comparative risks* (95% CI)		Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk			
	Neutral insole	Lateral wedge insole			
Health-related quality of life HRQoL: scale from 0 to 1.0 Follow-up: 12 months *(Higher score is better)*	Mean health-related quality of life score in control groups was **0.7**	Mean health-related quality of life score in intervention groups was **0.01 lower** (0.05 lower to 0.03 higher)	179 (1 study)	⊕⊕⊕⊖ **Moderate** [b]	MD = 0.00 (95% CI -0.06 to 0.06) Absolute percent change = 1.0% (95% CI -5.0 to 3.0) Relative percent change = 1.4% (95% CI -7.1 to 4.3) NNTB = not statistically significant
Treatment failure	See comment	See comment	Not estimable[c]	See comment	Outcome not reported in included studies
Serious adverse events	See comment	See comment	Not estimable[c]	See comment	Outcome not reported in included studies
Total number of adverse events	See comment	See comment	Not estimable[c]	See comment	Outcome not reported in included studies

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk**(and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a]Downgraded for limitations in design and implementation of available studies suggesting high likelihood of bias.
[b]Downgraded for imprecision: Results were based on only one study with 179 participants.
[c]No useful data were available.

Abbreviations; **CI:** Confidence interval; **NNTB:** Number needed to treat for an additional beneficial outcome.

4 Valgus knee brace compared with lateral wedge insole for varus medial osteoarthritis of the knee

Valgus knee brace compared with lateral wedge insole for varus medial osteoarthritis of the knee					
Patient or population: patients with varus medial osteoarthritis of the knee **Settings:** general hospital **Intervention:** valgus knee brace **Comparison:** lateral wedge insole					
Outcomes	**Illustrative comparative risks* (95% CI)**		**Number of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**			
	Lateral wedge insole	**Valgus knee brace**			
Pain VAS: scale from 0 to 10 Follow-up: 6 months *(Higher score is worse)*	Mean pain score in control groups was **4.8**	Mean pain score in intervention groups was **0.2 lower** (1.15 lower to 0.75 higher)	91 (1 study)	⊕⊕⊖⊖ **Low** [a,b]	MD = -0.20 (95% CI -1.15 to 0.75) Absolute percent change = -2.0% (95% CI -11.5 to 7.5) Relative percent change = -4.2% (95% CI -24.0 to 15.6) NNTB = not statistically significant
Stiffness	See comment	See comment	Not estimable	See comment	Outcome not reported in included studies
Function WOMAC: scale from 0 to 100 Follow-up: 6 months *(Higher score is better)*	Mean function score in control groups was **50.7**	Mean function score in intervention groups was **0.1 higher** (7.26 lower to 0.75 higher)	91 (1 study)	⊕⊕⊖⊖ **Low** [a,b]	MD = 0.10 (95% CI -7.26 to 7.46) Absolute percent change = 0.1% (95% CI -7.26 to 0.75) Relative percent change = 0.2% (95% CI -14.3 to 1.5) NNTB = not statistically significant

Outcomes	Illustrative comparative risks* (95% CI)		Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk			
	Lateral wedge insole	Valgus knee brace			
Health-related quality of life	See comment	See comment	Not estimable[c]	See comment	Outcome not reported in included studies
Treatment failure	See comment	See comment	Not estimable[c]	See comment	Outcome not reported in included studies
Serious adverse events	See comment	See comment	Not estimable[c]	See comment	Outcome not reported in included studies
Total number of adverse events	See comment	See comment	Not estimable[c]	See comment	Outcome not reported in included studies

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk**(and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a]Downgraded for imprecision: Results were based on only one study with 91 participants.
[b]Downgraded for limitations in design and implementation of available studies suggesting high likelihood of bias.
[c]No useful data were available.

Abbreviations; **CI:** Confidence interval; **NNTB:** number needed to treat for an additional beneficial outcome; **RR:** Risk ratio.

DATA AND ANALYSES

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1 Brace versus no treatment				
1.1 Pain (VAS)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1.1 6 months	1	115	Mean Difference (IV, Random, 95% CI)	-0.10[-0.91, 0.71]
1.1.2 9 months	1	40	Mean Difference (IV, Random, 95% CI)	-2.80[-3.58, -2.02]
1.1.3 12 months	1	115	Mean Difference (IV, Random, 95% CI)	0.00[-0.84, 0.84]
1.2 Knee function (HSS)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.2.1 6 months	1	110	Mean Difference (IV, Random, 95% CI)	1.40[-2.36, 5.16]
1.2.2 12 months	1	110	Mean Difference (IV, Random, 95% CI)	1.00[-2.98, 4.98]
1.3 Walking distance (km)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.3.1 6 months	1	116	Mean Difference (IV, Random, 95% CI)	-0.10[-1.32, 1.12]
1.3.2 9 months	1	40	Mean Difference (IV, Random, 95% CI)	1.20[0.95, 1.45]
1.3.3 12 months	1	117	Mean Difference (IV, Random, 95% CI)	0.40[-0.87, 1.67]
1.4 Quality of life (EQ-5D)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.4.1 6 months	1	117	Mean Difference (IV, Random, 95% CI)	-0.05[-0.14, 0.04]
1.4.2 12 months	1	117	Mean Difference (IV, Random, 95% CI)	-0.04[-0.12, 0.04]
1.5 Total adverse events	1	117	Risk Ratio (M-H, Random, 95% CI)	1.63[0.94, 2.82]
2 Brace versus lateral wedge insole				
2.1 Walking distance	1	40	Mean Difference (IV, Random, 95% CI)	0.50[0.23, 0.77]
2.1.1 9 months	1	40	Mean Difference (IV, Random, 95% CI)	0.50[0.23, 0.77]
2.2 WOMAC 6 months	1	91	Mean Difference (IV, Random, 95% CI)	0.10[-7.26, 7.46]
2.3 Pain (VAS)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.3.1 6 months	1	91	Mean Difference (IV, Random, 95% CI)	-0.20[-1.15, 0.75]

DATA AND ANALYSES (continued)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
2.3.2 9 months	1	40	Mean Difference (IV, Random, 95% CI)	-2.80[-3.58, -2.02]
3 Lateral wedge insole versus no insole				
3.1 Pain (VAS)	1	40	Mean Difference (IV, Random, 95% CI)	-1.60[-2.31, -0.89]
3.2 Walking distance (km)	1	40	Mean Difference (IV, Random, 95% CI)	0.70[0.52, 0.88]
4 Lateral wedge insole versus neutral insole				
4.1 Pain (NRS)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1.1 Pain on walking 1 month	1	59	Mean Difference (IV, Random, 95% CI)	-0.10[-0.97, 0.77]
4.1.2 Maximum pain change with stairs 1 month	1	59	Mean Difference (IV, Random, 95% CI)	Not estimable
4.1.3 Average pain at rest 12 months	1	179	Mean Difference (IV, Random, 95% CI)	-0.40[-1.06, 0.26]
4.1.4 Pain on walking 12 months	2	224	Mean Difference (IV, Random, 95% CI)	0.10[-0.45, 0.65]
4.1.5 Maximum pain change with stairs 12 months	1	45	Mean Difference (IV, Random, 95% CI)	0.00[-0.58, 0.58]
4.2 Pain (WOMAC)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.2.1 1 month	2	206	Mean Difference (IV, Random, 95% CI)	1.17[-7.69, 10.03]
4.2.2 3 months	1	147	Mean Difference (IV, Random, 95% CI)	5.50[-1.95, 12.95]
4.2.3 6 months	1	147	Mean Difference (IV, Random, 95% CI)	6.40[-0.07, 12.87]
4.2.4 12 months	3	358	Mean Difference (IV, Random, 95% CI)	0.89[-2.89, 4.67]
4.2.5 24 months	1	106	Mean Difference (IV, Random, 95% CI)	2.80[-6.12, 11.72]
4.3 Stiffness (WOMAC)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.3.1 1 month	2	206	Mean Difference (IV, Random, 95% CI)	5.74[-0.49, 11.97]
4.3.2 3 months	1	147	Mean Difference (IV, Random, 95% CI)	4.20[-2.61, 11.01]
4.3.3 6 months	1	147	Mean Difference (IV, Random, 95% CI)	6.00[-0.48, 12.48]

DATA AND ANALYSES (continued)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
4.3.4 12 months	3	358	Mean Difference (IV, Random, 95% CI)	0.07[-4.96, 5.10]
4.3.5 24 months	1	106	Mean Difference (IV, Random, 95% CI)	1.80[-7.22, 10.82]
4.4 Physical function (WOMAC)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.4.1 1 month	2	206	Mean Difference (IV, Random, 95% CI)	2.47[-2.49, 7.44]
4.4.2 3 months	1	147	Mean Difference (IV, Random, 95% CI)	5.20[-0.94, 11.34]
4.4.3 6 months	1	147	Mean Difference (IV, Random, 95% CI)	6.00[-0.48, 12.48]
4.4.4 12 months	3	358	Mean Difference (IV, Random, 95% CI)	0.94[-2.98, 4.87]
4.4.5 24 months	1	106	Mean Difference (IV, Random, 95% CI)	-0.40[-9.47, 8.67]
4.5 Health-related quality of life	1	179	Mean Difference (IV, Random, 95% CI)	0.00[-0.06, 0.06]
4.6 Physical activity scale for the elderly	1	179	Mean Difference (IV, Random, 95% CI)	15.00[-8.45, 38.45]
4.7 Number of steps taken per day	1	179	Mean Difference (IV, Random, 95% CI)	1371.00[38.53, 2703.47]
4.8 Global patient assessment at 24 months	1	106	Mean Difference (IV, Random, 95% CI)	1.60[-7.41, 10.61]
4.9 Compliance at 6 months	1	156	Risk Ratio (M-H, Random, 95% CI)	1.18[1.01, 1.38]
4.10 Time for negotiation of stairs	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.10.1 1 month	1	59	Mean Difference (IV, Random, 95% CI)	1.10[-1.18, 3.38]
4.10.2 12 months	1	45	Mean Difference (IV, Random, 95% CI)	-0.30[-3.06, 2.46]
4.11 6-Minute walk distance	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.11.1 1 month	1	59	Mean Difference (IV, Random, 95% CI)	23.00[-18.61, 64.61]
4.11.2 12 months	1	45	Mean Difference (IV, Random, 95% CI)	-25.20[-77.37, 26.97]
5 Subtalar strapped insole versus inserted lateral wedge insole				
5.1 Pain (VAS)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only

DATA AND ANALYSES (continued)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
5.1.1 8 weeks	1	90	Mean Difference (IV, Random, 95% CI)	-9.20[-18.28, -0.12]
5.1.2 6 months	1	61	Mean Difference (IV, Random, 95% CI)	-11.80[-22.04, -1.56]
5.1.3 24 months	1	42	Mean Difference (IV, Random, 95% CI)	-2.00[-13.34, 9.34]
5.2 Lequesne index	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.2.1 8 weeks	1	90	Mean Difference (IV, Random, 95% CI)	-0.60[-2.81, 1.61]
5.2.2 6 months	1	61	Mean Difference (IV, Random, 95% CI)	-1.50[-4.23, 1.23]
5.2.3 24 months	1	42	Mean Difference (IV, Random, 95% CI)	-2.30[-5.45, 0.85]
5.3 FTA - angle	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.3.1 8 weeks	1	90	Mean Difference (IV, Random, 95% CI)	-1.30[-3.45, 0.85]
5.3.2 6 months	1	61	Mean Difference (IV, Random, 95% CI)	-3.00[-5.84, -0.16]
5.3.3 24 months	1	42	Mean Difference (IV, Random, 95% CI)	-2.70[-5.13, -0.27]
5.4 Side effects at 8 weeks	1	90	Risk Ratio (M-H, Fixed, 95% CI)	5.74[0.72, 45.77]
6 Subtalar strapped insole versus sock-type insole				
6.1 FTA angle	1	88	Mean Difference (IV, Random, 95% CI)	-0.90[-2.89, 1.09]
6.2 Aggregate score	1	88	Mean Difference (IV, Random, 95% CI)	-1.40[-3.57, 0.77]
7 Medial wedge insole versus neutral insole				
7.1 VAS rest	1	30	Mean Difference (IV, Random, 95% CI)	-0.40[-2.16, 1.36]
7.2 VAS movement	1	30	Mean Difference (IV, Fixed, 95% CI)	-2.20[-4.04, -0.36]
7.3 VAS night	1	30	Mean Difference (IV, Fixed, 95% CI)	-1.50[-3.12, 0.12]
7.4 WOMAC	1	30	Mean Difference (IV, Fixed, 95% CI)	-6.70[-17.09, 3.69]
7.5 Lequesne	1	30	Mean Difference (IV, Fixed, 95% CI)	-2.40[-5.28, 0.48]

DATA AND ANALYSES (continued)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
8 Variable stiffness shoe versus constant stiffness shoe				
8.1 Pain (WOMAC)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
8.1.1 6 months	1	60	Mean Difference (IV, Random, 95% CI)	-3.70[-8.57, 1.17]
8.1.2 12 months	1	55	Mean Difference (IV, Random, 95% CI)	-1.10[-6.43, 4.23]
8.2 Stiffness (WOMAC)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
8.2.1 6 months	1	60	Mean Difference (IV, Random, 95% CI)	-1.90[-4.34, 0.54]
8.2.2 12 months	1	44	Mean Difference (IV, Random, 95% CI)	-1.40[-4.52, 1.72]
8.3 Physical function (WOMAC)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
8.3.1 6 months	1	60	Mean Difference (IV, Random, 95% CI)	-6.90[-24.14, 10.34]
8.3.2 12 months	1	55	Mean Difference (IV, Random, 95% CI)	-4.90[-24.54, 14.74]

Database and coverage	Search date	Number of references retrieved	Number of references after de-duplication
MEDLINE Ovid SP 2007-2013	March 1, 2014	82	56
EMBASE 2007-2013	March 1, 2014	167	161
The Cochrane Library	March 1, 2014	23	11
	Totals	**272**	**228**

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DATA AND ANALYSES

Sources of support

Internal sources

- No sources of support provided

External sources

- No sources of support provided

APPENDICES

1 Search strategy and summary of results

Database: MEDLINE Ovid SP
Search strategy:

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("osteoarthritis, knee"/ OR ((osteoarthritis/ OR (osteoarthritis OR osteoarthrosis OR "degenerative joint disease" OR "osteo arthritis" OR "osteo arthrosis" OR "degenerative arthritis").ab,ti.) AND ("knee joint"/ OR (knee*).ab,ti.))) AND (exp "Orthotic Devices"/ OR (brace* OR bracing OR orthotic* OR orthoses OR orthosis).ab,ti.)
Database: EMBASE
Search strategy:

———————————————————————————————————————

('knee osteoarthritis'/de OR ((osteoarthritis/de OR (osteoarthritis OR osteoarthrosis OR 'degenerative joint disease' OR 'osteo arthritis' OR 'osteo arthrosis' OR 'degenerative arthritis'):ab,ti) AND (knee/de OR (knee*):ab,ti))) AND (orthosis/de OR (brace* OR bracing OR orthotic* OR orthoses OR orthosis):ab,ti) AND [01-05-2007]/sd
Database: The Cochrane Library
Search strategy

———————————————————————————————————————

((((osteoarthritis OR osteoarthrosis OR 'degenerative joint disease' OR 'osteo arthritis' OR 'osteo arthrosis' OR 'degenerative arthritis'):ab,ti) AND ((knee*):ab,ti))) AND ((brace* OR bracing OR orthotic* OR orthoses OR orthosis):ab,ti)

Chapter 3

Do laterally wedged insoles or valgus braces unload the medial compartment of the knee in patients with osteoarthritis?

T. Duivenvoorden, T.M. van Raaij, H.L.D. Horemans, R.W. Brouwer, P.K. Bos, S.M.A. Bierma-Zeinstra, J.A.N. Verhaar, M. Reijman

Clin Orthop Relat Res. 2015 Jan; 473(1):265-74

ABSTRACT

Background. The results of conservative treatment of knee osteoarthritis (OA) are generally evaluated in epidemiological studies with clinical outcome measures as primary outcomes. Biomechanical evaluation of orthoses shows that there are potentially beneficial biomechanical changes to joint loading; however, evaluation in relation to clinical outcome measures in longitudinal studies is needed.

Questions/ Purposes. We asked (1) is there an immediate effect on gait in patients using a laterally wedged insole or valgus brace; (2) is there a late (6 weeks) effect; and (3) is there a difference between subgroups within each group with respect to patient compliance, body mass index, and OA status?

Methods. This was a secondary analysis of data from a previous randomized controlled trial of patients with early medial knee OA. A total of 91 patients were enrolled in that trial, and 73 (80%) completed it after 6 months. Of the enrolled patients, 80 (88%) met prespecified inclusion criteria for analysis in the present study. The patients were randomized to an insole or brace. Gait was analyzed with and without wearing the orthosis (insole or brace) at baseline and after 6 weeks. Measurements were taken of the knee adduction moment, ground reaction force, moment arm, walking speed, and toe-out angle. Data were analyzed with regression analyses based on an intention-to-treat principle.

Results. A mean reduction of 4% (±10) (95% confidence interval [CI], -0.147 to -0.03, p=0.003) of the peak knee adduction moment and 4% (±13) (95% CI, -0.009 to -0.001, p=0.01) of the moment arm at baseline was observed in the insole group when walking with an insole was compared with walking without an insole. A mean reduction of 1% (±10) (95% CI, -0.002 to -0.001, p=0.001) of the peak knee adduction moment and no reduction of the moment arm were measured after 6 weeks. No reduction of knee adduction moment, moment arm, or ground reaction force was seen in the brace group at baseline and after 6 weeks. Subgroup analysis showed no differences in biomechanical effect for obesity, stage of OA, and whether patients showed a clinical response to the treatment.

Conclusions. Laterally wedged insoles unload the medial compartment only at baseline in patients with varus alignment and by an amount that might not be clinically important. No biomechanical alteration was seen after 6 weeks of wearing the insole. Valgus brace therapy did not result in any biomechanical alteration. Taken together, this study does not show a clinically relevant biomechanical effect of insole and brace therapy in patients with varus medial knee OA.

Level of evidence. Level I, therapeutic study. See Instructions for Authors for a complete description of levels of evidence.

INTRODUCTION

The conservative treatment of patients with varus medial knee osteoarthritis (OA) is aimed at altering the biomechanics of the knee to reduce the medial load, reduce symptoms, and slow progression of medial knee OA in cases of malalignment [4, 18, 24]. In knee OA of the medial compartment, symptom reduction and functional improvement have been reported in patients fitted with a valgus unloader knee brace [11] or a laterally wedged insole [2, 14, 25]. Recently, a placebo-controlled trial found a valgus knee brace to be more effective than a neutral brace [11]. Other studies concluded that a laterally wedged insole may be no more effective than the neutral equivalent [2, 20] and that a neutral insole can reduce the load of the medial compartment [9, 14]. However, a Cochrane review rated the evidence as "low quality" that both the valgus knee brace and laterally wedged insole have benefits in the treatment of symptomatic medial knee OA [7]. These clinical effects are attributed to the mechanical unloading of the diseased compartment. However, the exact working mechanism is not fully understood and remains a subject of discussion.

Recently, we published the results of our randomized clinical trial (RCT) (ISRCTN92527149) investigating the clinical effects and static correction of malalignment in the frontal plane of a laterally wedged insole compared with a valgus brace [26]. Correction of malalignment was evaluated with a standardized standing whole-leg radiograph. Although both groups (valgus brace and wedged insole) had improved patient-reported outcomes, no significant change in alignment was seen on this static evaluation [26], so whether a brace or insole corrects malalignment in the frontal plane remains controversial [8, 15, 21, 23, 26].

Another possible explanation for the observed clinical improvement could be a dynamic alteration. If a laterally wedged insole or valgus brace unloads the medial compartment of the knee, and thus has a dynamic effect during walking, this could explain the clinical improvements seen in earlier studies. For this reason, we also performed a gait analysis in this RCT [28] in which patients with varus medial knee OA wearing a laterally wedged insole or valgus knee brace were included.

The aim of the present study is to present the results of our gait analysis of patients with medial knee OA treated with a laterally wedged insole or valgus knee brace. We asked (1) is there an immediate effect on gait in patients using a laterally wedged insole or valgus knee brace; (2) is there a late (6 weeks) effect; and (3) is there a difference between subgroups within each group with respect to patient compliance, body mass index (BMI), and OA status?

MATERIALS AND METHODS

We used gait analysis data obtained from an RCT (ISRCTN92527149) [26] in which patients with medial knee OA were treated with a laterally wedged insole or valgus brace. Patients with symptomatic medial knee OA who visited the outpatient clinic between January 2006 and September 2007 were eligible for inclusion.

The criteria for inclusion were pain and tenderness over the medial joint space in combination with radiographic osteoarthritic signs according to the Kellgren-Lawrence system of Grade I or higher and varus malalignment [13]. The criteria for exclusion were age younger than 35 years, symptoms not related to medial compartment OA, or an insufficient command of the Dutch language. This study was conducted according to the Declaration of Helsinki. Moreover, the protocol was approved by the local ethics committee and all patients gave their written informed consent.

All patients were enrolled by one investigator (TMvR). A total of 91 patients were enrolled in the study [28], and 73 (80%) completed it. One patient with medial knee pain and clinical varus malalignment was excluded because no varus alignment was assessed by whole-leg radiograph, resulting in a total sample of 91 patients. These 91 patients were randomized to a laterally wedged insole (45 patients) or a valgus brace (46 patients). Patients were randomized according to a computer-generated procedure (block randomization with variable sizes of blocks); the randomization codes were held by an independent observer (SMAB-Z) to ensure masked blocking (Fig. 1). Three patients in the insole group and eight patients in the brace group refused to participate in the gait analysis after 6 weeks, which resulted in 80 patients (88%). Of these patients, three in the insole group and six in the brace group changed their initial treatment during followup to other nonoperative or surgical treatments. The primary reason was no effect of treatment (three of three patients in the insole group and three of six patients in the brace group), but other reasons included bad fit of the brace, reduction of symptoms, and increased crepitus at the knee. Two patients were lost to followup for unknown reasons (Fig. 1).

The outcome assessor was not blinded to allocation. The grade of OA was scored according to Kellgren and Lawrence [13], measured on a standing short posteroanterior radiograph. Nineteen patients (42%) in the insole group and 12 patients (26%) in the bracing group had a Kellgren and Lawrence score ≥ III (Table I).

Mechanical alignment was assessed using the hip-knee-ankle angle (on a standing whole-leg radiograph). We used lateral fluoroscopic control by superimposing the dorsal aspect of the femoral condyles to ensure a perfect AP full-length exposure. The hip-knee-ankle angle is the angle measured between the following two lines: the mechanical axis of the femur (from the center of the femoral head to the central point between the tibial spines) and the mechanical axis of the tibia (from the center of the

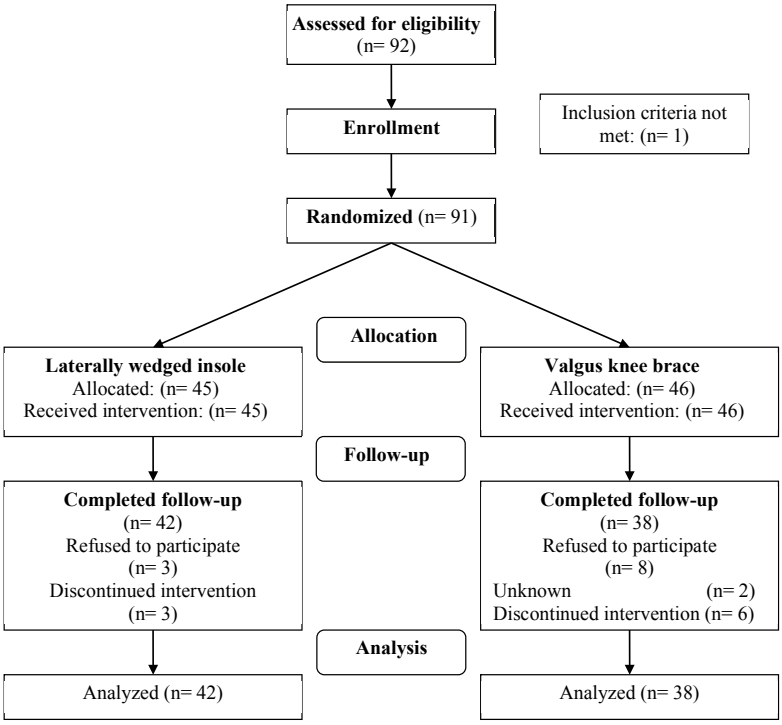

Fig. 1 Flowchart shows the study course.

tibial spines to the center of the ankle). Earlier, we reported high intraobserver correlation coefficient (ICC = 0.98; 95% confidence interval [CI], 0.94-0.99) and interobserver (ICC = 0.97; 95% CI, 0.94-0.99) agreements for measurement of the hip-knee-ankle angle using this technique [6]. Before followup, among the insole and brace groups, three and eight patients refused to participate in the followup gait assessment, respectively. The patients who did not participate in the gait analysis at 6 weeks had a higher hip-knee-ankle angle compared with participants ($p < 0.05$).

Treatment groups

All patients had been treated initially according to the guidelines of the Dutch College of General Practitioners, including patient education, physical therapy, and prescription of analgesic use. Patients were assigned either to the intervention group, receiving a shoe-inserted leather sole with a lateral-wedge cork elevation of 10 mm (6° wedge) along the entire length of the foot (Fig. 2), or to the control group receiving a knee brace (Fig. 3). The shoe-inserted sole was custom-made and fit by a specialized orthopaedic shoe technician.

Table I. Baseline characteristics of the study population and for the two intervention groups

Baseline characteristics	Study population (n = 80)	Insole group (n = 42)	Brace group (n = 38)	Drop-out (n = 11)
Women, number (%)	41 (51)	28 (67)	13 (34)	4 (36)
Age (years)	54 (7)	54 (7)	54 (7)	56 (7)
BMI (kg/m^2)	30 (5)	30 (5)	31 (5)	30 (4)
VAS (0-10)	6 (3)	6 (3)	6 (2)	6 (4)
WOMAC (0-100)	47 (18)	47 (19)	47 (16)	40 (20)
Walking distance, number (%)				
Unimpaired	36 (45)	16 (38)	20 (53)	6 (55)
> 1 km	29 (36)	17 (40)	12 (31)	4 (36)
500 m to 1 km	10 (13)	5 (12)	5 (13)	1 (9)
< 500 m	5 (6)	4 (10)	1 (3)	0 (0)
Analgesic use, number (%)				
None	36 (45)	18 (43)	18 (47)	8 (73)
When needed	19 (24)	10 (24)	9 (24)	1 (9)
Daily	25 (31)	14 (33)	11 (29)	2 (18)
Osteoarthritis medial K&L				
grade, number (%)	35 (41)	15 (36)	20 (53)	4 (36)
1	14 (18)	8 (19)	6 (16)	2 (18)
2	30 (38)	18 (43)	12 (32)	5 (46)
3	1 (1)	1 (2)	0 (0)	0 (0)
4				
Osteoarthritis lateral K&L				
grade, number (%)	57 (71)	29 (69)	28 (74)	9 (82)
0	19 (24)	10 (24)	9 (24)	2 (18)
1	2 (3)	1 (2)	1 (2)	0 (0)
2				
HKA angle (°)*	7 (4)	7 (4)	7 (4)	10 (4)†
Peak KAM (Nm)		51 (18)	55 (18)	NA
Mean KAM (Nm)		31 (14)	33 (12)	NA
Angular impulse (Nm/sec)		23 (10)	26 (10)	NA

All values are presented as mean (± SD) unless indicated otherwise; *positive angle represents varus alignment, negative angle represents valgus alignment; †significant difference between study population and lost to followup;

Abbreviations: BMI = body mass index; VAS = visual analogue scale; K&L = Kellgren & Lawrence; HKA = hip-knee-ankle angle; KAM = knee adduction moment; NA = not available.

The valgus knee brace was commercially available for the right/left leg in four sizes (MOS Genu®; Bauerfeind AG, Kempen, Germany) and consisted of a thigh shell and a calf shell connected by coated aluminum hinges on the medial and lateral sides (Fig. 3). A specialized orthopaedic technician applied the brace. The degree of valgization depended on the degree of malalignment and the acceptance of the patient. Patients were

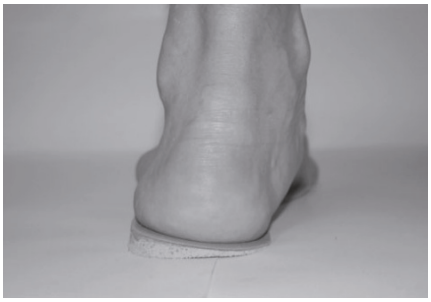

Fig. 2. An image of a left foot showing leather sole and a laterally wedged cork elevation of 10 mm (6° wedge)

Fig. 3. Lateral view of the right knee showing MOS Genu® knee brace with fixated markers.

instructed to wear the insole or brace as much as tolerated, and they were asked to register the number of hours per week they wore the orthosis.

Gait Analysis

When either the insole or valgus brace was first provided, we collected the baseline data directly. We analyzed the patients' gait at baseline and after 6 weeks with and without the orthosis. Kinematic data (100 Hz) were collected unilaterally using three infrared cameras (Qualisys Proreflex, Gothenburg, Sweden). Passive retroreflective markers were placed at the following anatomic sites for the purpose of calibration: greater tro-

chanter, medial and lateral femoral epicondyle, head of the fibula, tibial tuberosity, and medial and lateral malleoli. Markers located at the base of the first and at the tuberosity of the fifth metatarsal bone and at the lateral tuberosity of the calcaneus were glued to the shoe (Fig. 3). Patients were asked to wear the same comfortable shoes during the measurements and control pictures were taken to check the marker placement.

In addition, eight markers were put on two rigid frames that were attached by tape and Velcro straps to the middle part of the upper and lower leg. After a static calibration measure, all markers were removed except those on the frames and on the shoe. Kinetic data (200 Hz) were collected using an AMTI OR 6-7 force plate (AMTI, Watertown, MA, USA).

Each patient completed five walking trials of 20 m with an average speed of 1 m/s with and without orthoses. Walking speed was self-determined. Patients wore their own shoes and were instructed to use the same footwear during followup. Postprocessing calculation of the kinematic and kinetic data was conducted using custom-made Matlab algorithms (MathWorks, Natick, MA, USA) blinded for the type of orthosis. The positions of anatomic landmarks were derived from the positions of the markers on the frames. Anatomic landmarks for the upper leg were the greater trochanter and femoral epicondyles. Anatomic landmarks for the lower leg were the tibial tuberosity and malleoli. From these landmarks, right-handed segment coordinate systems were defined. Joint kinematics were calculated using an X-Y-Z Euler rotation sequence equivalent to the joint coordinate system. Joint kinetics were calculated using three-dimensional inverse dynamics, and the external joint moment data were normalized to body mass (Nm/kg).

The biomechanical kinematic parameters of interest were the knee adduction moment, knee angular adduction impulse [22], ROM of the knee, toe-out angle of the foot, and walking speed. Knee adduction moment (Nm/kg) is widely regarded as a surrogate measure of the difference between medial and lateral knee loading.

Throughout the entire stance phase of walking, the external adduction moment acts around the knee. The magnitude of knee adduction moment is influenced by the magnitude of the ground reaction force, the moment arm, and the mass and acceleration of lower limb segments (Fig. 4) [12, 22]. Peak knee adduction moment represents the maximum load differential between the medial and lateral compartment during one gait cycle. Mean knee adduction moment represents the mean load during the entire stance phase. The angular adduction impulse represents the total load on the medial compartment during one gait cycle. Walking with the foot externally rotated or a toe-out gait can reduce knee adduction moment in patients with medial knee OA [22] (Fig. 5). We determined the toe-out angle from the line of progression drawn through the midpoint between the malleoli and the midpoint between the markers on the forefoot.

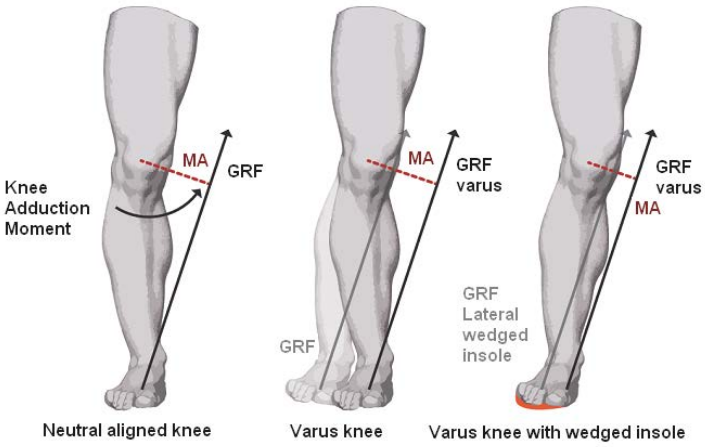

Fig. 4. KAM during walking for a neutral aligned knee, a varus knee and a varus knee with wedged insole is shown. The magnitude and direction of GRF are shown by the length and direction of the straight black or gray arrows. The length of the MA of the GRF acting about the knee is indicated by a dotted line. **(1) Neutral-aligned knee:** KAM increases if the GRF increases or the length of MA increases. **(2)** For a **varus knee deformity** (superimposed over a neutrally aligned knee[light-shaded leg]), the MA (dotted line) is increased. **(3)** For the **varus knee with a wedged insole**, our hypothesis is that both the laterally wedged insole and valgus knee brace shift the center of pressure, causing the GRF to pass closer to the center of the knee. This effect decreases MA and reduces KAM compared to the situation without a lateral wedge.
Abbreviations: KAM = knee adduction moment; GRF = ground reaction force; MA = moment arm.

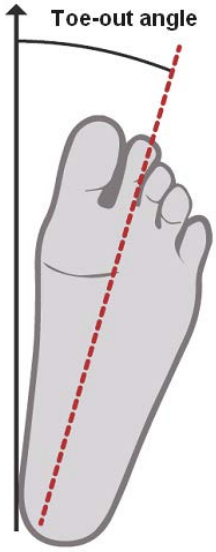

Fig. 5. Schematic diagram illustrating the "toe-out" angle. The toe-out angle is defined as the degree of external rotation of the foot

Sample Size

The sample size calculation in the initial RCT [26] was based on visual analog scale (VAS) pain score, which was the primary outcome of our RCT. Brouwer et al [5] included patients according to similar criteria and reported a baseline mean VAS pain score of 6.0 (± 2.2). We hypothesized that a 1-point difference in VAS between the two groups would represent a clinically relevant difference, being 15% of the baseline score. To detect such a difference with two-sided testing ($\alpha = 0.05$ and a power of 80%), we needed 40 patients in each group. With the assumption of a 15% rate of loss to followup, we included 91 patients. We did not recalculate statistical power or sample size for the present secondary analysis of knee biomechanics.

Statistical Analysis

To evaluate the presence of a possible selective dropout during followup, we compared the baseline characteristics of the 80 patients seen at 6 weeks and the 11 patients lost to followup by using the Kruskal-Wallis test. We analyzed the immediate effect at baseline and the late effects after 6 weeks of wearing the orthoses. To evaluate the difference in improvement between both intervention groups at 6 weeks followup, linear regression analyses were performed with adjustment for the baseline values of the outcome measures. Knee adduction moment, ground reaction force, and moment arm were considered dependent variables. Allocated intervention, toe-out angle, walking speed, hip-knee-ankle angle, and BMI were considered independent variables.

Additionally, we performed explorative subgroup analyses in which we investigated the relationships between compliance, obesity, and radiographic severity of OA and our outcome measures. We divided patients into two groups based on brace use: those who used the brace more than 42 hours per week (7 days times 6 hours, or 75% of the working day) and those who did not.

The SPSS program, Version 20 (SPSS Inc, Chicago, IL, USA) was used for statistical analysis, and a p value of 0.05 was considered to be statistically significant.

RESULTS

Immediate Effect: Difference Between Wearing and Not Wearing the Orthosis

At baseline, both interventions showed an immediate effect of wearing the orthosis. Peak knee adduction moment decreased by 4% (± 10) in the insole group and increased by 5% (± 16) in the brace group ($p = 0.003$). Mean knee adduction moment decreased by 1% (± 0) in the insole group and did not change in the brace group by 0% (± 0) ($p = 0.001$). The angular impulse decreased with 1% (± 17) in the insole group and

increased with 8% (± 25) in the brace group (p = 0.196). The moment arm decreased by 4% (± 13) in the insole group and increased by 6% (± 18) in the brace group (p = 0.01). The ground reaction force was not reduced in either group (Table II).

Table II. Immediate effect, reported as percentage change in knee adduction moment measures, ground reaction force, and moment arm at baseline, when wearing the orthosis (wedged insole or brace) compared with no orthosis

Outcome	Insole group (n = 38)	Brace group (n = 42)	Beta[#]	95% confidence interval	p value[†]
Knee adduction moment					
Peak (%)	-4 (10)[*]	5 (16)[*]	-0.089	-0.147 to -0.03	**0.003**
Mean (%)	-1 (0)[*]	0 (0)[*]	-0.001	-0.002 to -0.001	**0.001**
Angular impulse (%)	-1 (17)[*]	8 (25)[*]	-1.578	-3.989 to 0.833	0.196
Ground reaction force (%)	0 (10)	1 (7)	-8.604	-41.371 to 24.162	0.602
Moment arm (%)	-4 (13)	6 (18)	-0.005	-0.009 to -0.001	**0.01**

All values are presented as mean (± SD) unless indicated otherwise; p values of significantly reduced outcome are presented in bold; [*]positive value represents increased knee adduction moment, negative value represents decreased knee adduction moment; [†]corrected for toe-out angle and walking speed; [#]beta represents the regression coefficient of the linear regression analysis.

Late Effect (6 weeks): Difference Between Wearing and Not Wearing the Orthosis

After 6 weeks of wearing the orthosis, no difference in change of peak knee adduction moment, ground reaction force, or moment arm was found between the insole and brace groups. The change of peak knee adduction moment in the insole group (-1% [± 10]) did not differ with the change in the brace group (1 [± 12], p = 0.328). The change in ground reaction force did also not differ in the insole-group (0% [± 6]) compared with the brace group (2% [± 16], p = 0.969). The change of moment arm in the insole group was 0% (± 14) and in the brace group was 1% (± 11) (p = 0.188). The mean knee adduction moment decreased 4% (± 18) in the insole group and increased 4% (± 10) in the brace group (p = 0.035). The angular impulse decreased 2% (± 16) in the insole group and increased 6% (± 22) in the brace group (p = 0.036) (Table III).

Subgroup Analysis: Differences Between Wearing and Not Wearing the Orthosis

Within each of the brace and insole groups, no difference in knee adduction moment, angular impulse, ground reaction force, or moment arm between patients who did and did not use the brace at least 42 hours per week was found. Moreover, between obese and non-obese patients, and patients with doubtful (Kellgren and Lawrence ≤ II) versus definite or moderate radiographic OA (Kellgren and Lawrence ≥ III), no differences were seen in knee adduction moment, angular impulse, ground reaction force, or moment arm (Table IV).

Table III. Late Effects, Reported As Patient-reported Outcomes And Percentage Changes In Knee Adduction Moment Measures, Ground Reaction Force, And Moment Arm, Between Walking With And Without An Orthosis (Wedged Insole Or Brace) After 6 Weeks Of Wearing The Orthosis

Outcome	Insole group (n = 38)*	Brace group (n = 42)*	Beta¶	95% confidence interval	p value
Compliance, number (%)*	29 (76)	19 (45)	-	-	0.213
Improved walking distance, number (%)‖	11 (29)	7 (17)	-	-	0.375
Knee adduction moment					
Peak (%)†	-1 (10)	1 (12)	-0.024	-0.073 to 0.025	0.328§
Mean (%)†	-4 (18)	4 (10)	-0.073	-0.141 to -0.005	**0.035**§
Angular impulse (%)	-2 (16)	6 (22)	-2.448	-4.730 to -0.165	**0.036**§
Ground reaction force (%)	0 (6)	2 (16)	-0.001	-0.059 to 0.057	0.969§
Moment arm (%)	0 (14)	1 (11)	-0.019	-0.046 to 0.009	0.188§

All values are presented as mean (± SD) unless indicated otherwise; p values of significantly reduced outcomes are presented in bold; *compliant, if the orthosis was worn > 42 hours/week; †positive value represents an increased knee adduction moment, negative value represents a decreased knee adduction moment; ‡corrected for sex and use of pain medication at baseline and followup; §corrected for toe-out angle and walking speed; ‖38% in the insole and 53% in the brace group had an unimpaired walking distance at baseline; ¶beta represents the regression coefficient of the linear regression analysis.

Table IV. Difference between with and without an orthosis (wedged insole or brace) for compliant and noncompliant patients after 6 weeks of wearing the orthosis

	Insoles		Brace	
Outcome	Compliant (n = 29)*	Noncompliant (n = 13)*	Compliant (n = 19)*	Noncompliant (n = 19)*
Improved walking distance, number (%)‡	8 (28)	3 (23)	1 (5)	6 (32)
Knee adduction moment‖				
Peak, % (SD)†	-2 (7)	0 (17)	-1 (11)	4 (13)
Mean, % (SD)†	-9 (38)	-3 (8)	3 (10)	5 (9)
Angular impulse, % (SD)†	-3 (15)	3 (21)	7 (20)	4 (26)
Ground reaction force, % (SD)†	0 (6)	-2 (7)	2 (6)	1 (7)
Moment arm, % (SD)†	-1 (13)	4 (17)	1 (13)	1 (7)

All values are presented as mean (± SD) unless indicated otherwise; *compliant, if the orthosis was worn > 42 hours/week; †negative value represents a reduction; ‡41% of compliant and 31% of noncompliant patients had an unimpaired walking distance at baseline in the insole group; in the brace group, the values were 58% of compliant and 47% of noncompliant patients; §significant difference between the compliant and noncompliant groups; ‖corrected for body mass index, hip-knee-ankle angle, baseline values, toe-out angle, walking speed, and compliance.

DISCUSSION

Many patients with varus medial knee OA report improved clinical outcomes after treatment with a laterally wedged insole or valgus knee brace [7, 26]. These clinical effects are attributed to the mechanical unloading of the diseased compartment. However, the exact working mechanism is not fully understood and remains a subject of discussion. The aim of this study was to evaluate the biomechanical alterations in patients with medial knee OA randomized for laterally wedged insole or valgus knee brace treatment in a longitudinal study.

Some limitations of our study need to be addressed. First, the study was conducted in a tertiary referral university medical center, which could affect the generalizability of its results. However, the eligibility criteria were not highly selective and we therefore believe that the included patients are representative of patients with medial knee OA. Second, we did not analyze the contralateral leg and did not measure the lateral trunk lean; however, our patients were instructed to walk maintaining the trunk in a tall, upright position. Footwear was not standardized to quantify the joint moments. Patients were instructed to wear their same comfortable, flexible shoes during followups, and we therefore assumed that shoes did not affect the results of our study. Third, we included patients with a radiographic grade of OA ranging from I to IV on the Kellgren and Lawrence scale. Half of the patients had radiographic evidence of moderate knee OA. A study by Shimada and colleagues [25] reported that insoles have the greatest effect on knee adduction moment in early to mild OA (Kellgren and Lawrence Grade I-II). Our subgroup analysis showed no difference in effect sizes between the mild and moderate OA groups. However, our subgroup analysis might be underpowered and, therefore, the results may be an underestimation of the actual effect size.

In addition, patients who were compliant were defined a priori as patients using the insole or brace more than 42 hours per week (7 days times 6 hours, which represents 75% of the working day). The optimal time to wear an insole or brace during the day has not been determined, and compliance remains arbitrary. Therefore, this arbitrarily chosen threshold could affect the conclusions of our subgroup analysis. Lastly, the degree of valgus moment provided by the braces depended on the degree of malalignment and the acceptance of the patient. Patients were instructed to wear the brace as long as tolerated. Both malalignment and acceptance vary between patients and, therefore, so will the degree of correction. No other reasonable option was available. As a result, less tolerant patients could benefit less from the therapy.

This study showed an immediate reduction in the mean peak knee adduction moment of 4% (± 10) as a result of a reduction in mean moment arm of 4% (± 13) in the insole group. No reduction of knee adduction moment was seen in the brace group. An immediate reduction of 4% in peak knee adduction moment in the insole group

is similar to that reported in other studies. A recent review of the literature reported reductions ranging from 4% to 12% for the laterally wedged insole with an inclination of 5° [22]. It was not possible to compare our results of the valgus brace with the literature. Only a few small studies, which investigated different types of braces, are available and the effect sizes vary [7]. Reductions of the medial load found in our and other studies are small and, although statistically significant, it is doubtful whether these small differences are clinically meaningful. Multiple authors have suggested that even small increases or decreases in knee adduction moment could have substantial effects on the progression of OA [3, 26]. However, to the best of our knowledge, no study with a followup longer than 12 months has been performed so far. For this reason, in our opinion, it is still unknown whether these small reductions in peak or mean medial load actually have disease-modifying effects on the progression of OA. A long-term followup study is necessary to establish such an effect.

After 6 weeks of wearing insoles, no reduction of peak knee adduction moment and no reduction of moment arm were seen. No reduction of knee adduction moment, ground reaction force, or moment arm was seen in the brace group at baseline and after 6 weeks. So, laterally wedged insoles were shown to reduce the knee adduction moment at baseline; however, the effect could no longer be found after 6 weeks. Nonetheless, the clinical improvements, as measured by VAS knee pain and WOMAC scores, were still present at 6 weeks [26]. This temporary biomechanical effect has not been described previously. Most previous studies analyzed gait only once, at baseline [8, 10, 16].

Our subgroup analysis did not indicate a different biomechanical effect related to obesity, stage of OA, or and whether patients showed a clinical response to the insole or knee brace treatment at baseline or after 6 weeks. Our subgroup analysis might be underpowered; however, big between-group differences would not be expected. Theoretically, insoles could reduce the ground reaction force by a so-called "cushioning effect." Although we used soft wedged insoles along the entire length of the foot, we did not observe a reduction of ground reaction force in our study. A frequently used treatment modality for reducing ground reaction force is weight loss. Persons who are overweight with varus alignment will benefit greater owing to the interaction between alignment and body mass on dynamic knee joint loading with the association between alignment and load highest in patients with the highest mass [17, 19]. One study reported that a reduction in body weight of 1 kg (10 N) was associated with a 1% reduction (0.496 Nm) in knee adduction moment [17]. In comparison with our results, in which we observed a reduction of 4% of peak knee adduction moment in the insole group, weight reduction should be highly effective.

To reduce knee adduction moment in patients with medial knee OA, either moment arm or ground reaction force should be reduced. Insoles and braces are supposed options for reducing moment arm, to decrease the medial compartment load. Laterally

wedged insoles reduce knee adduction moment temporarily, but the reduction of moment arm, and thus the valgus effect, is doubtful. Two small studies that compared the knee adduction moment data of neutral versus laterally wedged insoles show conflicting effects of the lateral wedge, but the differences were small in both studies [1, 2].

We conclude that only laterally wedged insoles result in a reduced mechanical load of the medial compartment, albeit temporarily. After 6 weeks of wearing, no reduced mechanical load was seen. The valgus knee brace did not result in a reduced mechanical load of the medial compartment at baseline and after 6 weeks. Thus, in this study we found no biomechanical argument to support the use of laterally wedged insoles or a valgus knee brace.

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Chapter

4

Comparison of closing-wedge and opening-wedge High Tibial Osteotomy for medial compartment osteoarthritis of the knee: a Randomized Controlled Trial with a six-year follow-up.

T. Duivenvoorden, R.W. Brouwer, A. Baan, P.K. Bos, M. Reijman, S.M.A. Bierma-Zeinstra, J.A.N. Verhaar

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ABSTRACT

Background. Varus deformity increases the risk of progression of medial compartment knee osteoarthritis. The aim of this study was to investigate the clinical and radiographic mid-term results of closing-wedge and opening-wedge high tibial osteotomy when used to treat this condition.

Methods. From January 2001 to April 2004, ninety-two patients were randomized to either a closing-wedge or opening-wedge high tibial osteotomy. The clinical outcome and radiographic results were examined preoperatively; at one year; and, for the present study, at six years postoperatively. The outcomes that wer reviewed included maintenance of the achieved correction, progression of osteoarthritis based on (Kellgren and Lawrence classification), severity of pain (as assessed on a visual analogue scale [VAS]), knee function (as measured with the Hospital for Special Surgery [HSS] score and Knee Injury and Osteoarthritis Outcome Score [KOOS]), walking distance, complications and survival with conversion to a total knee arthroplasty as the end point. The results were analyzed on basis of the intention-to-treat principle.

Results. Six years postoperatively, the hip-knee-ankle (HKA) angle (and standard deviation) was 3.2° ± 4.1° of valgus after a closing-wedge high tibial osteotomy and 1.3° ± 5.0° of valgus after an opening-wedge high tibial osteotomy (p= 0.343). In both groups the six-year post-operative HKA-angles did not differ from the respective one-year post-operative angles. No difference in severity of pain or knee function was found between the two groups. Four complications (9%) occurred in the closing-wedge group and 17 (39%), in the opening-wedge group. Ten (22%) of the patients in the closing-wedge and three (8%) in the opening-wedge group needed conversion to a total knee arthroplasty within the six-year period (p = 0.05). The difference in the percentage of cases with conversion to total knee arthroplasty was 14% (95% confidence interval [CI]= 21.7 to 0.2).

Conclusions. In the group patients without conversion to a total knee arthroplasty, there was no difference between the closing-wedge and opening-wedge high tibial osteotomies in terms of clinical outcomes or radiographic alignment six years post-operatively. Opening-wedge osteotomy was associated with more complications, but closing-wedge osteotomy was associated with more early conversions to total knee arthroplasty.

Level of Evidence. Therapeutic Level I. See Instructions for Authors for a complete description of levels of evidence.

INTRODUCTION

Knee osteoarthritis is one of the most common joint disorders, and it causes considerable pain and immobility. Malalignment increases the risk of progression of osteoarthritis of the knee.(1, 2) For patients with osteoarthritis of the medial compartment of the knee, a valgus high tibial osteotomy is a treatment option. Various techniques are available, such as closing-wedge, opening-wedge and dome osteotomy.(3-6) Each technique has its advantages and disadvantages.(4,7-10)

It is clear from previous retrospective studies that a succesfull outcome requires an appropriate selection of patients as well as achievement and maintenance of sufficient correction of alignment. (3,5,11) Loss of correction correlates with the type of fixation of the osteotomy site, grade of correction, and time to osseous union.(12,13)

Little is known about the long-term results of opening-wedge osteotomy as compared with those of closing-wedge osteotomy.(14) Retrospective studies of opening-wedge osteotomy have shown survival rates (rates of procedures not converted to total knee arthroplasty) ranging from 51% to 97.6 % after ten years' follow-up. (14-16) However, there is a lack of radiographi and clinical long-term results from well-designed prospective studies. Therefore, the aim of the present study was to determine the radiographic and clinical mid-term results as well as the survival rate (rate of procedures not converted to total knee arthroplasty) in participants of our randomized controlled trial comparing opening-wedge and closing-wedge osteotomy.

PATIENTS AND METHODS

All patients who attended the outpatient clinic of the Department of Orthopedics of our institution because of medial joint pain of the knee from January 2001 to April 2004 were potentially eligible for inclusion.

The criteria for inclusion in the study were radiographic evidence of medial compartment knee osteoarthritis with an Ahlbäck-score (17) of less than grade III, medial joint pain and varus malalignment of 1° to 14°.

The criteria for exclusion were symptomatic osteoarthritis of the lateral compartment, rheumatoid arthritis, knee motion <100°, grade-3 (18) collateral ligament laxity, a previous fracture or open operation in the lower limb, and a flexion contracture >10°. Patients with a contralateral high tibial osteotomy were excluded if the first knee had been included in this trial; thus, if both knees were symptomatic, only the first knee was included. No limits were placed on the degree of patellofemoral osteoarthritis, age, or body mass index (BMI).

The protocol was approved by the local Ethics Committee (MEC 196.813/2000/232) and all patients gave written informed consent.

Ninety-two patients were enrolled and were randomized, by a computer-generated procedure in blocks of sixteen to one of the two procedures. Patients were randomized to one of four orthopedic surgeons who performed the operations. All surgeons were experienced with both techniques. Details of the study design and the one-year results were published earlier and the trial was registered in ClinicalTrials.gov (NCT01977261). (9)

After a mean follow-up time of seven years (range 6.1 – 10.5 years) postoperatively, we invited all participating patients for outpatient evaluation. Some patients were not

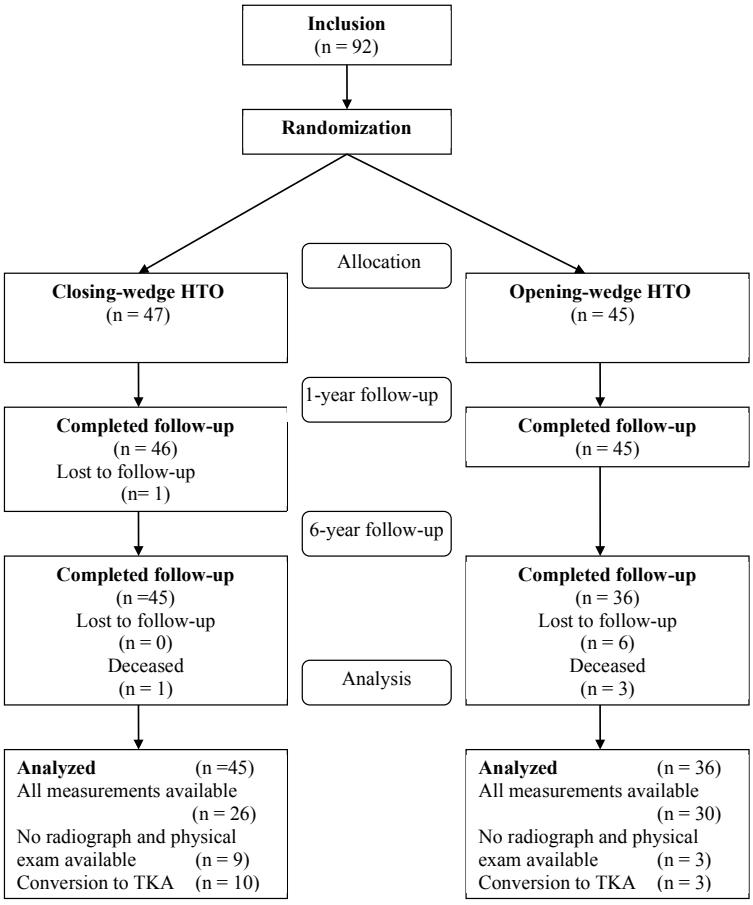

Fig. 1 Flow chart of the study
Abbreviations: HTO, high tibial osteotomy; TKA, total knee arthroplasty

able to visit in person, because of a long travel distance, problems with travel logistics, or other reasons, but they they completed questionnaires.

All non-responders were sent a reminder by mail and were contacted by telephone. Additionally, municipal records were searched to find the correct addresses and telephone numbers of the non-responders. Eleven patients were lost to follow-up (Fig. 1).

The grade of osteoarthritis was scored according to the classification of Kellgren and Lawrence (19), on the basis of measurements on a standing short posteroanterior radiograph. The mechanical alignment was assessed using the hip-knee-ankle angle (HKA) angle, which was obtained from a standardized standing whole-lower-extremity radiograph.(20) We used lateral fluoroscopic control by superimposing the dorsal aspect of the femoral condyles to ensure a perfect anteroposterior full-length exposure. The HKA angle was determined by measuring the angle between the mechanical axis of the femur (from the center of the femoral head, determined with use of Mose circles (21), to the central point between the tibial spines), and the mechanical axis of the tibia (from the center of the tibial spines to the center of the ankle).

Treatment groups

Patients were randomized to receive either (1) closing-wedge high tibial osteotomy fixed with two stepped vitallium staples (Stryker: Schönkirchen, Germany) or (2) opening-wedge high tibial osteotomy fixed with a Puddu plate (Arthrex; Naples, Florida).

For the closing-wedge technique, the Allopro calibrated osteotomy guide (Zimmer; Winterthur, Switzerland) was used to obtain accurate resection of bone. The common peroneal nerve was exposed and retracted. Subsequently, the anterior aspect of

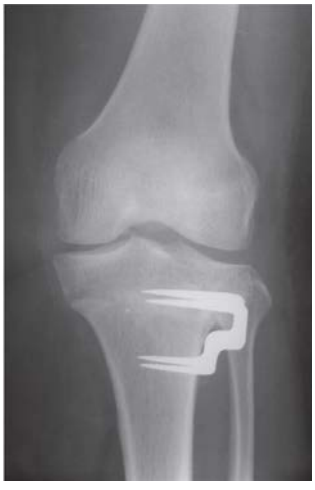

Fig. 2 Closing-wedge high tibial osteotomy stabilized by two staples.

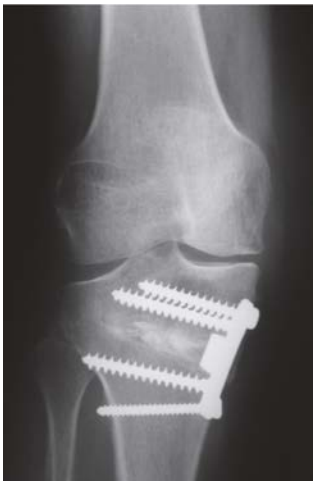

Fig. 3 Opening-wedge high tibial osteotomy stabilized by a Puddu plate

the proximal part of the fibular head, representing the anterior part of the proximal tibiofibular syndesmosis, was resected. The osteotomy site was fixed with two staples (Fig. 2). At the end of the procedure, a fasciotomy of the anterior compartment was performed to prevent compartment syndrome.

For the opening-wedge technique, the extent of the wedge depended on the length of the osteotomy and the diameter of the proximal tibia and was calculated preoperatively (Fig 3.). The Arthrex instruction manual provides a goniometric formula table, which gives the extent of the opening wedge for a specific correction. Additionally, the degree of correction performed during the procedure was controlled with fluoroscopic perioperatively. If the opening wedge was >7.5 mm, the open gap was filled with bone harvested from the ipsilateral iliac crest.

The goal of both techniques was to achieve a correction of 4° physiological valgus. Both groups received the same rehabilitation program. Patients were mobilized on the first postoperative day and partial weight-bearing was begun therafter.

Preoperative evaluation

Age, sex, BMI, severity of medial and lateral osteoarthritis (Ahlbäck score on a scale ranging from 0 to 6, and Kellgren and Lawrence score on a scale ranging from 0 to 4) (17, 19), varus malalignment (HKA angle) (20), severity of pain measured by a visual analogue scale (VAS) (22), knee function using the Hospital for Special Surgery Score (HSS-score) (18), and walking distance were scored preoperatively.

Outcome assessment at six years

All follow-up measurements were performed by one non-blinded physician. The difference between the maintained valgus correction and the objective of 4° of overcorrection was determined. In addition, the HKA angle was dichotomized into (1) correctly aligned (between 2° and 6° of valgus alignment) or (2) not correctly aligned alignment outside this range).

The severity of pain (as assessed with the VAS), walking distance and knee function score were evaluated.

The knee function score was measured with the HSS and the Knee injury and Osteoarthritis Outcome Score (KOOS).(23, 24) BMI, early and late complications, and additional surgery such as removal of implants or conversion to total knee prosthesis were noted.

Sample size

The sample size of the initial trial was calculated on the basis of the primary outcome namely, the alignment measured on the standing whole-lower-extremity radiograph one year postoperatively.

The hypothesis was that the success rate of the opening-wedge procedure would be higher than of the closing-wedge procedure. We hypothesized that the success rate would be for the opening-wedge procedure 85% and 60% for the closing-wedge procedure. A successful operative result was defined as achievement of approximately 4° of valgus alignment. To detect such a difference with one-sided testing ($\alpha = 0.05$ and a power of 80%), forty-six patients were required in each group.

Statistical analysis

The radiographics were evaluated by two observers, independently of each other, to measure the severity of the osteoarthritis and the HKA angle. One observer repeated the measurements after two weeks. To determine the intraobserver and interobserver reproducibility, we calculated the intraclass correlation coefficient (ICC) for the HKA angle and the kappa statistic for the severity of radiographic osteoarthritis measured with the Kellgren and Lawrence score.

To evaluate the possibility of selective dropout during follow-up, we used the Kruskal-Wallis or Chi-square test to compare the baseline characteristics of the patients seen at six years postoperatively with those of the patients lost to follow-up.

To test the difference between the two intervention groups during mid-term follow-up, a linear regression model with repeated measures was used with the baseline value and the different measurements in the model. If there was doubt about violation of assumptions regarding residuals' distributions, then we carried out a Mann-Whitney test comparing the two groups with respect to the average of the measurements. HKA angle, VAS knee pain score, HSS knee score and walking distance were used as the dependent variables in the model. The type of high tibial osteotomy was used as the independent variable. Sex, age, BMI and follow-up time were considered as possible confounders and were included in the regression models if they changed the relationship between the dependent variable and the type of high tibial osteotomy by at least 10%.

A Kaplan-Meier survival analysis, with conversion to a total knee arthroplasty as the end point, was carried out. We repeated the analysis with assumption of a worst-case scenario- i.e., that cases lost to follow-up were converted to a total knee arthroplasty, with the date of the last available radiograph considered as the date of failure of the high tibial osteotomy. A p-value of 0.05 was considered to be significant.

Source of Funding

No external funds were received in support of this study.

RESULTS

From January 2001 to April 2004, 122 patients underwent a high tibial osteotomy, and ninety-two of them were recruited for this trial. Of the excluded patients, thirteen had a previous fracture or open operation in the lower limb, three were scheduled to have a combined procedure, one patient had osteoarthritis of the lateral compartment, and one had rheumatoid arthritis. Seven patients refused to participate for various reasons.

Of the ninety-two included patients, forty-seven were randomized to receive a closing-wedge osteotomy and forty-five, an opening-wedge. The mean follow-up time was 7.3 years (range, 6.1 – 10.5 years) for both groups combined, and the two groups did not differ significantly with regard to follow-up time.

Two patients of the closing-wedge group and nine patients of the opening-wedge group were lost to follow-up. Of these eleven patients, one patient in the closing-wedge and three in the opening-wedge group died as result of non-osteotomy-related factors. Characteristics of the eleven patients lost to follow-up were similar to those of the patients completing the study (Table I).

Table I. Baseline characteristics of the total study population, separately for opening-wedge and closing-wedge osteotomy and the patients lost to follow-up.

	Total group (n = 81)	Closing-wedge osteotomy (n = 45)	Opening-wedge osteotomy (n = 36)	Lost to follow-up (n = 11)
Women, n (%)	30 (37)	13 (29)	12 (33)	1 (9)
Age (yrs)	49.8 (8.5)	49.5 (9.2)	49.9 (7.9)	53.8 (7.9)
BMI (kg/m^2)	28.2 (4.9)	28.2 (4.0)	27.3 (5.4)	27.2 (5.0)
VAS (0-10)	6.1 (1.8)	6.3 (1.6)	6.0 (2.0)	6.6 (1.4)
HSS-score (0-100)	71.6 (9.6)	71.5 (9.9)	72.3 (9.5)	68.0 (10.8)
Walking distance (km)	3.0 (2.8)	3.1 (2.9)	3.4 (2.9)	2.8 (3.0)
HKA-angle (°), median (IQR)*	6 (4-8)	6 (4.5-9) †	5 (4-8) †	6 (6-9)
Medial compartment OA K&L grade III, n (%)	12 (15)	5 (11)	7 (19)	0 (0)

All values are presented as mean (± SD) unless stated otherwise.

* positive angle represents varus alignment, negative angle represents valgus alignment

† $p<0.05$ for difference between the two groups

Abbreviations; BMI, body mass index; VAS, Visual Analogue Scale knee pain; HSS, Hospital for Special Surgery; HKA-angle, Hip-Knee-Ankle-angle; OA, osteoarthritis; IQR, Inter Quartile Range; K&L, Kellgren & Lawrence

We analysed eighty-one patients in the current study, and a whole-lower-extremity radiograph was available for sixty-five of them. Twelve patients were not able to visit the outpatient clinic in person because of long travel distance, problems with travel logistics or other reasons, but they completed questionnaires. Ten (22%) of the patients in the closing-wedge group and three (8%) in the opening-wedge group underwent a total knee arthroplasty (Fig. 1).

The results of the intraobserver and interobserver reproducibility tests of the Kellgren & Lawrence scores were $\kappa = 0.82$ (95% confidence interval [CI] 0.67 to 0.97) and $\kappa = 0.77$ (95% CI 0.56 to 0.98), respectively. The results of the intraobserver and interobserver reproducibility tests of the HKA angle were ICC= 0.97 (95% CI 0.96 to 0.98) and ICC= 0.94 (95% CI 0.92 to 0.96), respectively.

Outcomes six year postoperatively (Table II)

At 6 years postoperatively, the mean HKA angle (and standard deviation) was 3.2° ± 4.1° SD of valgus in the closing-wedge group and 1.3° ± 5.0° of valgus in the opening-wedge group.

Valgus alignment within the range 2° and 6° was not found in sixteen (44%) of the patients in the closing-wedge group and in sixteen (48%) of the patients in the opening-wedge group with available radiographs. Five patients (15%) of the opening-wedge group had a recurrent varus alignment six years postoperatively; none of these patients had a valgus alignment seen on the one-year whole-lower-extremity radiograph.

The only significant difference that we found was in the rate of conversion to a total knee arthroplasty during follow-up period: ten (22%) patients in the closing-wedge group and three (8%) in the opening-wedge group underwent a total knee arthroplasty ($p = 0.05$). The difference in rates of conversion to total knee arthroplasty was 14% (95% CI= 21.7 to 0.2).

Differences between one-year and six-year postoperative follow-up results in closing-wedge and opening-wedge groups

No significant difference was found between the one-year and six-year follow-up clinical results in either group. (Table III). The severity of osteoarthritis measured on radiographs was increased in both compartments of the knee in both the closing-wedge and the opening-wedge group.

Early and late complications during follow-up period (Table IV)

Early complications (within the first postoperative year)

In the opening-wedge group, thirty-three of the forty-five patients required bone grafting. Nonunion developed in two patients of the opening-wedge group, one with

Table II. Outcome for closing-wedge osteotomy *versus* opening-wedge osteotomy at six-year follow-up.

	Closing-wedge osteotomy (n = 45)	Opening-wedge osteotomy (n = 36)	p-value
TKA during follow-up, n (%)	10 (29)	3 (9)	p = 0.05
HKA-angle (°) *	-3.2 (4.1)#	-1.3 (5.0)	NS†
n (%) outside range of [2°-6°] valgus	16 (43)	16 (50)	NS
Progression of medial compartment OA, rate (%)#	28/ 36 (78)	21/ 33 (63)	NS
Progression of lateral compartment OA, rate (%)#	33/ 36 (92)	32/ 33 (97)	NS
VAS (0-10)	4.0 (3.2)	3.4 (3.2)	NS†
HSS (0-100)	81.8 (13.0)	80.8 (13.8)	NS†
KOOS (0-100)			
Pain	67.3 (26.2)	67.7 (24.7)	NS†
Symptoms	68.7 (21.0)	70.0 (22.8)	NS†
ADL	68.2 (27.2)	67.7 (26.8)	NS†
Sports	40.4 (30.7)	36.2 (32.1)	NS†
Quality of life	47.2 (27.9)	44.6 (25.8)	NS†
Walking distance (km)	6.7 (4.2)	8.2 (4.7)	NS†

All values are presented as mean (± SD) unless stated otherwise. All outcomes were assessed on the patients without a TKA during follow-up. Of the patients with a TKA during follow-up, the last pre-TKA x-ray was analyzed.

* Positive angle represents varus alignment, negative value represents valgus alignment

† Corrected for baseline HKA-angle, gender, age, body mass index, and follow-up time

Measured according to Kellgren & Lawrence. 9 x-rays missing in the closing-wedge group, 3 X-rays missing in the opening-wedge group

Abbreviations; TKA, Total Knee Arthroplasty; HKA-angle, Hip-Knee-Ankle-angle; VAS, Visual Analogue Scale knee pain; HSS, Hospital for Special Surgery; KOOS, Knee Injury and Osteoarthritis Outcome Scale; NS, not significant, ADL, activities of daily living.

a wedge of 12.5 mm with bone graft and the other with a wedge of 7.5 mm without bone graft. Persistent pain at the iliac crest was reported by nine patients. One of them had additional surgery because of a symptomatic exostosis at the donor site. Another sustained an injury to the lateral femoral cutaneous nerve.

One patient in the closing-wedge group required a corrective varus osteotomy because of overcorrection of the initial osteotomy. Three patients in the opening-wedge group had a further valgus osteotomy because of recurrent varus alignment.

Late complications (More than one year postoperatively)

Because of pain, the staples or the plate were removed from nineteen patients (40%) in the closing-wedge group and from twenty-seven patients (60 %) in the opening-wedge group.

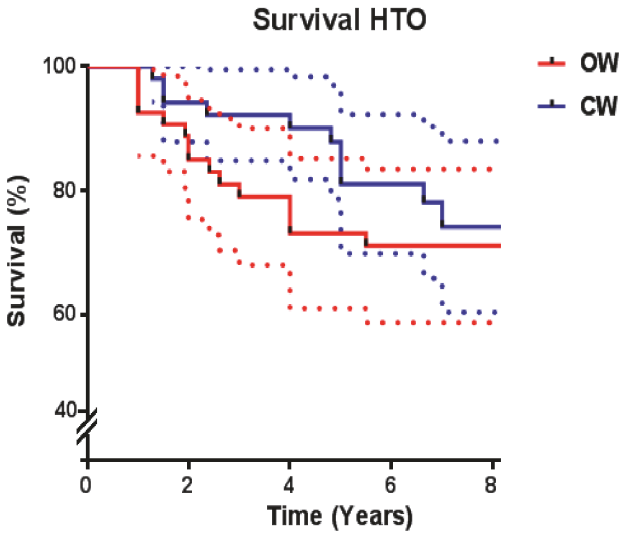

Fig. 4 Survival curve (with 95% CI) for the opening-wedge *versus* closing-wedge osteotomy, with TKA as the endpoint
Abbreviations; OW, opening-wedge; CW, closing-wedge; HTO, High Tibial Osteotomy

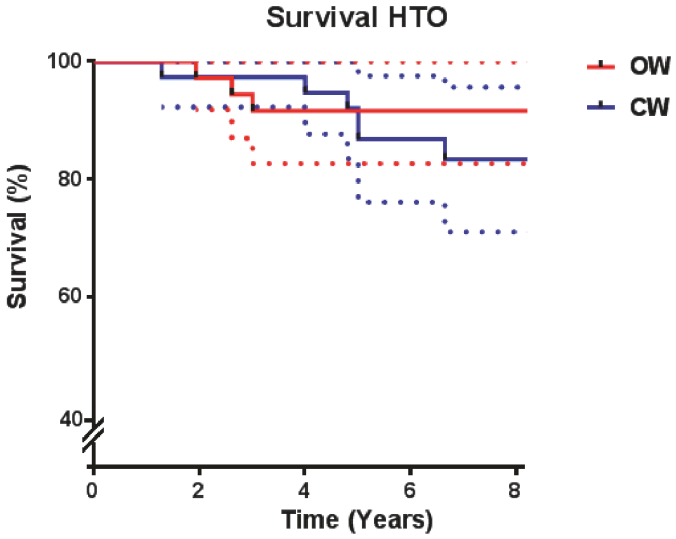

Fig. 5 Survival curve (with 95% CI) of the worst-case scenario of opening-wedge *versus* closing-wedge osteotomy, with TKA as the endpoint.
Abbreviations; OW, opening-wedge; CW, closing-wedge; HTO, High Tibial Osteotomy

Table III. Outcome for closing-wedge and opening-wedge osteotomy at baseline, one and six years postoperatively.

	Closing-wedge osteotomy			Opening-wedge osteotomy			p-value†
	baseline	1 year	6 year	baseline	1 year	6 year	
HKA-angle (°) *	5.7 (2.7)	-3.4 (3.6)	-3.2 (4.1)	6.6 (2.4)	-1.3 (4.6)	-1.3 (5.0)	NS
VAS (0-10)	6.3 (1.6)	3.6 (2.2)	4.0 (3.2)	6.0 (2.0)	3.6 (2.9)	3.4 (3.2)	NS
HSS (0-100)	71.5 (9.9)	79.4 (12.0)	81.8 (13.0)	72.3 (9.5)	80.9 (13.5)	80.8 (13.8)	NS
Walking distance (km)	3.1 (2.9)	4.6 (3.6)	6.7 (4.2)	3.4 (2.9)	5.3 (4.4)	8.2 (4.7)	NS

All values are presented as mean (± SD) unless stated otherwise.
* Positive angle represents varus alignment, negative value represents valgus alignment
† Differences between closing-wedge and opening-wedge were analyzed during follow-up with repeated measures linear regression analysis. Gender, age, body mass index and follow-up time were considered as possible confounders.
Abbreviations; HKA-angle, Hip Knee Ankle-angle, VAS, Visual Analogue Scale knee pain; HSS, Hospital for Special Surgery

Table IV. Early and late complications after closing-wedge and opening-wedge osteotomy

	Closing-wedge osteotomy (n = 47)	Opening-osteotomy (n = 45)
Early complications		
Wound infection	0	1
Nonunion	0	2
Palsy of the common peroneal nerve	1	0
Pain in proximal tibiofibular joint	1	0
Iliac crest morbidity	0	9
Fracture of the tibial plateau	1	2
Re-operation (further valgus correction)	0	3
Re-operation (reduction of valgus correction)	1	0
Late complications		
Revision to joint arthroplasty	10	3
Removal of osteosynthesis material	19	27

Early complications, < 1 year; late complications, > 1 year

Failure

Failure was defined as conversion to a total knee arthroplasty; 16% of the patients underwent a total knee arthroplasty within six years after the high tibial osteotomy. Ten patients (22%) in the closing-wedge group and three patients (8%) in the opening-wedge group underwent total knee arthroplasty because of progression of symptoms during the follow-up period this difference between groups was significant ($p = 0.05$) (Fig. 3).

When we assumed a worst-case scenario, in which cases lost to follow-up were considered to have been converted to a total knee arthroplasty, we found no significant difference between the closing-wedge and opening-wedge osteotomy groups at six years postoperatively (Fig. 4).

DISCUSSION

The aim of this randomized controlle trial was to compare the radiographic and clinical mid-term results and the survival rates between closing-wedge and opening-wedge osteotomies used to treat varus knee deformity. Ten patients (22%) in the closing-wedge group and three (8%) in the opening-wedge group needed a conversion to a total knee arthroplasty within six years. We found no relationship between conversion to total knee arthroplasty and preoperative varus deformity, preoperative radiographic grade of osteoarthritis or achieved correction.

In the group of the patients without conversion to a total knee arthroplasty, there was no difference between closing-wedge and opening-wedge high tibial osteotomies in terms of clinical outcomes or radiographic alignment at six years postoperatively. The staples were removed from nineteen (40%) of the patients in the closing-wedge group, and the fixation plate was removed from twenty-seven (60%) in the opening-wedge group. Complications developed in seventeen patients (38%) in the opening-wedge group and four (9%) in the closing-wedge group. The primary complication in the opening-wedge group was morbidity at the iliac crest bone graft donor site (nine of the seventeen complications in that group).

Our finding that 84% of the patients did not require a total knee arthroplasty after high tibial osteotomy within a mean follow-up period of six years, compares well with the results of other studies. Conversion rates ranging from 51% to 98% at ten years after closing-wedge osteotomy have been reported.(14) The rates for the opening-wedge osteotomy, which has been less extensively studied, have ranged from 74% to 92%.(15,16) When we extrapolate the survival rates in our study, we expect that the percentages will fall within these ranges. Thus, both closing-wedge and opening-wedge osteotomies have good survival rates.

Opening-wedge osteotomy was associated with a higher complication rate. Morbidity, caused by harvesting cancellous bone at the iliac crest to perform the bone-grafting, accounted for nearly half of the early complications. In a recent randomized controlled trial, Zorzi and colleagues concluded that autologous bone graft is unnecessary in wedges <12.5mm.(25) It is clear that avoidance of cancellous bone graft will decrease

the complication rate of the opening-wedge procedure. Therefore, we recommend to leave autologous iliac bone graft for patients in whom the opening-wedge is <12.5mm.

Five patients in the opening-wedge group had recurrent varus alignment six years postoperatively. None of these patients had 4° of valgus alignment on the whole-lower-extremity radiograph at one year postoperatively. This malalignment was probably caused by early loss of correction due to suboptimal stabilization of the Puddu plate used (9), with increasing malalignment of the mechanical axis in subsequent years. Other authors have reported that the Puddu-plate is not strong enough to sustain peri-operative correction.(26) The authors of another study concluded that the use of a rigid locking plate for both opening-wedge and closing-wedge osteotomies provides better stability.(27) We recommend fixation with a rigid locking plate instead of a Puddu plate.

Because of pain, the staple or plate was removed from nineteen patients (40%) in the closing-wedge group and from twenty-seven patients (60%) in the opening-wedge group. These high removal rates are comparable with those in the literature. Hoell et al. reported an implant removal rate of 50% in patients treated with an opening-wedge osteotomy and reported significantly more implant removals in those patients than in patients treated with closing-wedge osteotomy ($p<0.05$). (28)

High tibial osteotomy implants are fixed laterally when a closing-wedge procedure is used and medially when an opening-wedge procedure is used. Most people have less soft tissue at the medial site of the lower limb; therefore, the explanation for this difference in implant removal rates between opening and closing-wedge osteotomies could be anatomic.

There are some limitations of our study. First, despite intensive efforts to reach all of our patients, eleven patients were lost to follow-up. Because there were no significant differences in baseline characteristics between these patients and those who were followed, we assume that there was no selective dropout. The dropout of patients did reduce the power of the study, but the power of the survival analysis was reasonable (79%). Moreover, the survival analysis was repeated with the lost patients considered to have had a failure. We assume that the lost patients did not significantly influence our six-year results.

Second, four orthopedic surgeons performed these procedures. Although all had experience with both techniques, a single surgeon would have been preferable to reduce possible operator-dependent variability. However, a higher number of surgeons improves the generalizability of the results.

Finally, the outcome assessor at six years postoperatively was not blinded to the group allocation, and the radiographs could not be blinded with regard to group allocation. The HKA angle could have been influenced by a preference for one of the two procedures. However, the HKA angle was measured by two independent observers, and showed a high reproducibility of 0.94.

Physical examination was also not blinded. However, because the study hypothesis was that the closing-wedge osteotomy would produce a better one-year post-operative results; bias due to a non-blinded assessor would be in favor of the closing-wedge osteotomy and result in a better HSS score in the closing-wedge group. No difference was seen between the results of the closing-wedge and opening-wedge groups. We assume that observer bias did not influence our results because the patients' self-assessed outcomes, such as pain and walking distance, did not show any differences between groups.

Achievement and maintainance of an adequate operative correction are required for a successful outcome. (3,5,11) Opening-wedge osteotomy is thought to allow a more accurate correction than closing-wedge osteotomy. In our study, the achieved and maintained correction following opening-wedge osteotomy was influenced by loss of correction due to suboptimal plate design. We are aware of only one randomize controlled trial comparing the accuracy of closing-wedge osteotomy with that of opening-wedge osteotomy performed with use of a rigid locking plate, but that study lacked power (n=50) (11).

In conclusion, at six years postoperatively, no clinical or radiographic difference between closing-wedge and opening-wedge osteotomy was found. The disadvantage of the closing-wedge osteotomy was the lower survival rate (more conversions to total knee arthroplasty) and the disadvantage of opening-wedge osteotomy was the higher number of complications. On the basis of the results of our study and the recent literature, we advise using an opening-wedge high tibial osteotomy with rigid plate fixation and without autologous bone graft for patients with medial osteoarthritis of the knee and varus malalignment <12° to minimize the risk of complications and maximize the survival.

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Chapter 5

Adverse events and survival after closing- and opening-wedge High Tibial Osteotomy: a comparative study of 412 patients

T. Duivenvoorden, P. van Diggele, M. Reijman, P.K. Bos, J. van Egmond, S.M.A. Bierma-Zeinstra, J.A.N. Verhaar

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ABSTRACT

Purpose. Varus medial knee osteoarthritis (OA) can be treated with a closing-wedge (CW) or opening-wedge (OW) high tibial osteotomy (HTO). Little is known about the adverse event (AE)-rate of these techniques. The purpose of this study was to examine the AE- and survivalrate of a consecutive series of 412 patients undergoing CW- or OW-HTO.

Methods. Medical records were retrospectively screened and all patients who underwent HTO from 1993-2012 at the Erasmus University Medical Centre were assessed with a self-administered questionnaire. Patients filled in the Intermittent and Constant Osteoarthritis Pain Score, Knee injury and Osteoarthritis Outcome Score, and a general questionnaire focusing on AE.

Results. Medical records of 412 patients (354 CW- and 112 OW-HTO's) were screened. Of the 358 eligible patients 291 (81%) returned their questionnaire. A total number of 80 AE (17%) were found in 466 osteotomies. In the CW-group 47 (13%) serious adverse events (SAE) and 2 (0.6%) AE were found. In the OW-group 17 (15%) SAE and 14 (13%) AE were found. The most common AE was in 14 (4%) patients of the CW-group sensory palsy of the common peroneal nerve. In the OW-group was in 11 (9.8%) patients the most common AE persistent pain at the iliac crest. Hardware was removed in 48% of the CW-osteotomies and 71% of the OW-osteotomies ($p< 0.05$). The probability of survival was 75% after 10 years in the CW-group versus 90% in the OW-group ($p<0.05$). In both groups an equal number of patients were "in need for prosthesis" according to OARSI-criteria.

Conclusions. OW-HTO was associated with more AE than CW-HTO. OW-HTO resulted in better survival than CW-HTO. However in both groups an equal number of patients were in need for prosthesis.

Level of evidence. Level III retrospective comparative study

INTRODUCTION

Knee osteoarthritis (OA) is one of the most common joint disorders, and causes considerable pain and immobility. In case of varus alignment the medial compartment is mostly affected [1, 19]. Varus medial knee OA in young and active patients can be treated with a valgus high tibial osteotomy (HTO). Various techniques are available from which closing-wedge (CW) and opening-wedge (OW) HTO are performed most frequently. Both have advantages and disadvantages, and overall good short and mid-term outcomes have been reported [2, 4, 7, 13, 15, 17].

Although types of adverse events after HTO are well described, little is known about their actual incidence [3, 4, 16, 20, 21]. In a prospective study of 40 patients Van Bekerom et al. found significant more adverse events in an OW-group, whereas in a randomized controlled trial of 50 patients Gaasbeek et al. found a higher adverse event rate in a CW-group. Song et al. found no difference in adverse events rate in his retrospective study of 194 patients [8, 20, 21]. Thus, only a few relatively small studies have compared the adverse event rate of CW- and OW-HTO and the results of these studies are contradictory.

The success of a HTO is expressed in the number of years until conversion to a joint prosthesis is performed. Several studies have studied the survival of the HTO and factors influencing the survival [5, 13, 17]. They all defined failure as redo procedure of the HTO or conversion to unicompartmental knee arthroplasty (UKA) or total knee arthroplasty (TKA). However, this endpoint may introduce a decision bias and thus lead to an overestimation of the survival, because he decision to convert an HTO is affected by the opinion of patient as well as surgeon. Patients who do not undergo further surgery do not necessarily have a good result and might have high pain scores and a low functional outcome. Therefore, the Osteoarthritis Research Society International (OARSI) defined criteria for a surrogate measure of the "need for joint replacement surgery" [9]. With these criteria it is possible to define a non-survivor based on the pain score and functional outcome. Adjustment of the original survival rate with this Patient Reported Outcome based measure would result in a more accurate estimate of the real survival.

The hypothesis of this retrospective study was to find a higher adverse event rate and lower survival rate in patients undergoing OW- in comparison with CW-HTO.

MATERIALS AND METHODS

The medical records of all patients who underwent CW- or OW-HTO at the Erasmus University Medical Centre (a university teaching hospital) between 1993 and 2012 were screened. This period was chosen for the reason that medical records are preserved for at least 20 years in our hospital and we would achieve a minimal follow up of 1 year.

All 412 patients were asked to fill in a written questionnaire in 2013. When patients did not respond within three weeks, they were contacted by telephone. When these patients did not answer their telephone, a reminder was sent by mail after checking their address in the municipal administration.

Measurements

Patient characteristics as gender, preoperative age, body mass index (BMI) and Hip-Knee-Ankle- angle (HKA-angle) were collected for all 412 patients. Medical records were screened to identify the osteotomy technique, operating time, type of fixation material and adverse events. Pain, functional status and adverse events, were measured with Patient Reported Outcome Measures (PROMs). Pain and functional status were measured to define a survivor according to the OARSI criteria [9].

Pain was measured with the Intermittent and Constant Osteoarthritis Pain score (ICOAP) (0-100) [11]. The functional status was measured with the Knee injury and Osteoarthritis Outcome Score - Physical Function Short Form (KOOS-PS) [3, 10, 18]. The KOOS-PS is intended to elicit people's opinions about the difficulties they experience with activity due to problems with their knee. Standardized response options are given (5-point Likert Scale) and each question was scored from 0 to 4. Then, a normalized score from 0-100 is calculated. The criteria defined by the OARSI to determine patients in need for joint replacement surgery were used. They concluded that the sum-score [pain (measured with the ICOAP (0-100)) + physical function (measured with the KOOS-PS (0-100)) >80] is a discriminatory cut-off point to define an indication for joint replacement [9].

Adverse events

Adverse events were initially assessed from medical records. Moreover, to avert under-registration, adverse events were also assessed with a self-administered questionnaire at follow-up. Patients were specifically asked in this questionnaire for wound infection, thrombo embolism, bleeding, paresthesia, dropping foot, reflex sympathetic dystrophy syndrome, persistent pain or pain at the iliac crest, non-union. When patients scored positive for an adverse event, the adverse event was checked by a telephonic examination. In this study the adverse events of all 412 patients are presented, of whom the medical records were screened."

Adverse events were classified into adverse events (AE) and serious adverse events (SAE). Adverse events were defined as serious, when, patients have an undesirable experience associated with a medical intervention leading to death, a life-threatening situation, initial or prolonged hospitalization, disability or permanent damage, or a needed intervention to prevent permanent impairment or damage according to the definition of the FDA.

Surgical techniques

Closing-wedge group. CW-HTO was performed with a lateral approach. The common peroneal nerve (CPN) was exposed and retracted. The proximal tibiofibular joint was opened and one cm of the proximal tibiofibular bone was resected. The proximal osteotomy site and the slope of the osteotomy were marked using two Kirschner (K)-wires. Under C-arm guidance, the first osteotomy was performed with an oscillating saw and completed with an osteotome. The second osteotomy was performed with help of an aiming device (Arthrex; Naples, Florida). Fixation was achieved using two staples or a Tomofix plate. Different types of fixation material were used over years; staples (Stryker; Schönkirchen, Germany), Tomofix- (Synthes GmbH; Oberdorf, Switzerland) and Puddu-plate (Arthrex; Naples, Florida). Before closing the wound, a fasciotomy of the anterior compartment was performed.

Opening-wedge group. OW-HTO was performed with an anteromedial incision. The pes anserinus tendons and medial collateral ligament were dorsally retracted. Under C-arm guidance, 2 K-wires were placed in an oblique fashion from medial to lateral to serve as a cutting guide for the osteotomy. An osteotomy was performed using an oscillating saw. Care was taken to avoid violation of the lateral cortex. The distracting osteotomes were placed ventrally and dorsally and gradually distracted to achieve the right alignment. OW-osteotomies were fixated using either a Puddu plate without plate

Table I. Patient characteristics of the total study population, separately for opening-wedge versus closing-wedge HTO and responders versus non-responders

	Total group of osteotomies (n= 466)	Closing-wedge osteotomy (n= 354)	Opening-wedge osteotomy (n= 112)	Responders (n= 291)	Non-responders (n= 121)‡
Follow-up time (yrs)	9.8 (4.9)	10.6 (5.1)†	7.4 (3.2)†	NA	NA
Women, n (%)	190 (40.8)	151 (42.7)	39 (34.8)	134 (46)	36 (30)
age (yrs)*	49.2 (9.3)	49.4 (9.0)	48.7 (10.1)	49.7 (8.7)	47.9 (10.6)
BMI (kg/m^2)*	29.1 (5.4)	29.5 (5.8)	28.5 (4.5)	29.0 (5.4)	29.3 (5.3)
HKA-angle (deg)*#	6.6 (2.6)	6.3 (2.2)†	7.4 (3.5)†	6.6 (2.6)	6.6 (2.7)
Surgery time (min)	116.9 (30.3)	112.7 (28.8)†	130.3 (31.4)†	118.8 (30.7)	112.2 (29.1)
Duration of hospitalization (days)	5.5 (2.9)	5.5 (2.3)	5.5 (4.2)	5.2 (2.4)	6.1 (3.6)

All values are presented as mean (± SD) unless stated otherwise.

‡ 77% of the lost patients underwent closing-wedge HTO.

† p<0,05 for difference between the two groups.

*The preoperative values are presented.

#A positive value means varus malalignment

Abbreviations: BMI; Body Mass Index, deg; degree, HTO; High Tibial Osteotomy, HKA-angle; Hip-Knee-Ankle angle, min; minutes, NA; Not Applicable, yrs; years

locking screws (until 2006) or Tomofix plate (from 2006 until now). In 56 patients with large wedges of the OW-group a spongiosaplasty was performed using autologous bone harvested at the iliac crest. The Ethics Committee of the Erasmus Medical Centre approved the protocol (MEC-2013-140).

Statistical analysis

Statistical analysis was performed using PASW Statistics (SPSS science Inc., Chicago, USA version 20) and a p-value< 0.05 was considered as statistically significant. Data of CW- and OW-HTO patients are presented separately. Between group differences were tested with the independent t-test (Student T-test) or Chi-square test.

To evaluate the presence of a possible selective dropout during follow-up, baseline characteristics of the responders (those who filled in the questionnaire) were compared with the non-responders with the Kruskal-Wallis or Chi-square test.

Differences between CW- and OW-HTO patients were analyzed using the independent t-test (Student T-test) or Chi-square test.

Multiple survival analyses according to Kaplan and Meier were carried out. In the first survival analysis conversion to a UKA or TKA was considered as end-point. In the second survival analysis "being in need for a UKA or TKA" according to the OARSI-criteria was considered as end-point [14]. Patients with a conversion to a UKA or TKA

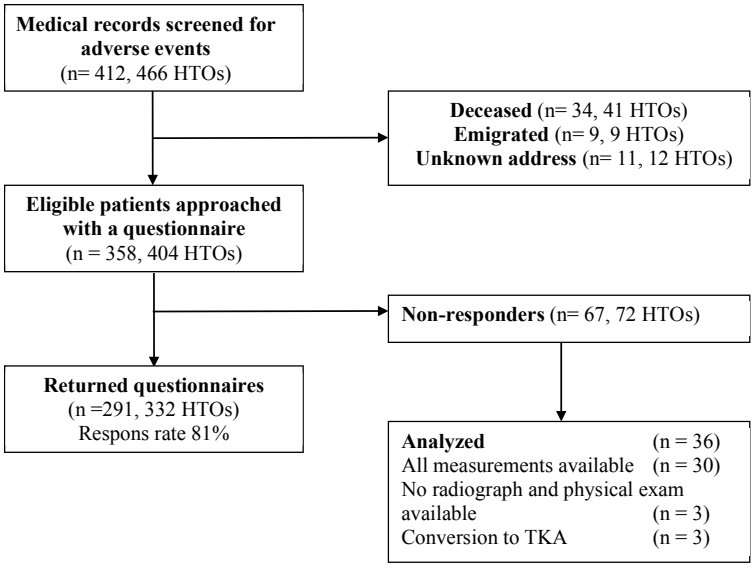

Fig. 1. Flowchart of the study.
Abbreviations; HTO, high tibial osteotomy TKA, Total Knee Arthroplasty.

were also considered as "being in need for a UKA or TKA". Differences in survival between CW- and OW-HTO were calculated with the log rank test.

We have found in this study with 49/354 AE in the CW-group and 31/112 AE in the OW-group a RR of 2.0. The power of this study with 354 patients in the CW-group and 112 patients in the OW-group was 0.94 to find a RR of 2.0.Concerning the survival after HTO we found in this study, with 73/354 non-survivors in the CW-group and 8/112 in the OW-group a RR of 3.0. The power of this study to find a RR of 3.0 with 354 patients in the CW-group and 112 patients in the OW-group was 0.99 to find a RR of 3.0.

RESULTS

Adverse events

A total number of 80 AE (17%) were found in 466 osteotomies. In the CW-group 47 (13%) SAE and 2 (0.6%) AE were found. In the OW-group 17 (15%) SAE and 14 (13%) AE were found. The most common AE was in 14 (4%) patients of the CW-group temporary sensory palsy of the CPN. In the OW-group was in 11 (19.7%) patients the most common AE persistent pain at the iliac crest of those who had cancellous bone grafting from the iliac crest in OW-HTO. Moreover a non-union occurred in 12 patients (8 (2.3%) in the CW-group and 4 (3.6%) in the OW-group). Hardware was removed in 48% of the CW-osteotomies and 71% of the OW-osteotomies ($p< 0.05$). All adverse events are outlined in table II.

Survival

During the follow-up period 81 osteotomies (17.4%) have been revised to UKA or TKA: 73 in the CW-group and eight in the OW-group (Figure 3). When conversion to UKA or TKA was considered as end-point the OW-group had a better survival than the CW-group ($p< 0.05$) (Figure 2). When the OARSI criteria for "being in need for a UKA or TKA" was considered as end-point and this was added to conversion to a prosthesis, no difference in survival between CW- and the OW-group was found.

DISCUSSION

The aim of this study was to present the adverse event- and survival rate of 466 HTOs performed in our university teaching hospital. The most important finding of this study was the overall adverse event rate of 28% in the OW-group and 14% in the CW-group. This AE-rate is lower than reported in several studies. Other studies show adverse event rates ranging from 24% to 63% [2, 14, 20, 21]. However, Gaasbeek et al. reported an

Table II. Adverse events for the closing- and opening wedge group.*

	Closing-wedge osteotomy (n= 354)	Opening-wedge osteotomy (n= 112)
Serious adverse events	*number of events, n (%)*	
Sensory palsy of the CPN	14 (4.0)	0
Motoric palsy of the CPN	1 (0.3)	0
Pseudoarthrosis	8 (2.3)	4 (3.6)
Wound infection treated with antibiotics	6 (1.7)	5 (4.5)
Fracture of the tibial plateau	2 (0.6)	2 (1.9)
Re-HTO[†]	7 (2.0)	3 (2.7)
Delayed union	1 (0.3)	0
Lesion of the ATA	1 (0.3)	0
Malposition of hardware	1 (0.3)	0
Deep venous thrombosis	2 (0.6)	0
Pulmonary embolus	0	1 (0.9)
Infection of the urinary tract	2 (0.6)	1 (0.9)
Post-surgery diffuse lung emphysema	1 (0.3)	0
Compartment syndrome	1 (0.3)	1 (0.9)
Hardware removal[+]	169 (47.7)	79 (70.5)
Adverse events		
Iliac crest pain[#]	0	11 (19.7)[‡]
Wound infection without antibiotic treatment	1 (0.3)	2 (1.9)
CRPS	1 (0.3)	1 (0.9)

Regional Pain Syndrome

*120 patients did not return their questionnaire for several reasons, their adverse events were only assessed by medical record screening.

[†] Re-HTO was performed because of over- or undercorrection or loss of correction.

[+] Ten hardware removals in the closing-wedge group and two in the opening-wedge group were performed prior to total knee arthroplasty.

[‡] 56 patients (50%) of the opening-wedge group underwent spongiosaplasty with autologous bone harvested at the iliac crest. Off these patients 11 patients reported pain at the iliac crest for more than six weeks.

Abbreviations: CPN, Common Peroneal Nerve; ATA, Anterior Tibial Artery; CRPS, Complex

adverse event rate of 12% [8]. The higher adverse event rate in the OW-group is in agreement with Van Bekerom et al. who reported 55% adverse events in the OW-group (n= 20) and 20% in the CW-group (n= 20). However, Song et al. found more adverse events in the CW-group (28%, n= 104) than in the OW-group (20%, n= 90). Miller et al. and Floerkemeier et al. studied only adverse events after OW-osteotomy. They reported adverse event rates of 37% (n= 46) and 6% (n= 533) respectively [7, 16]. Results of the different studies seem to be contradictory. In the majority of the studies

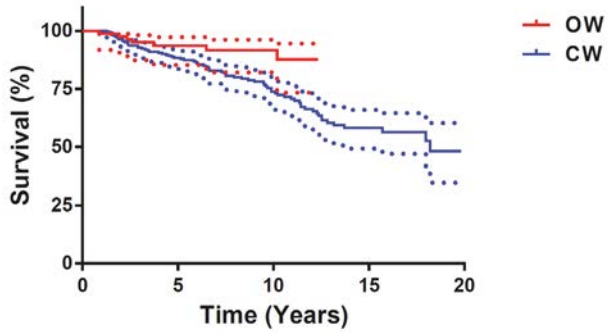

Fig. 2. Survival curve of closing- and opening-wedge osteotomy. Survival considered with conversion to UKA or TKA as end-point.
Abbreviations; OW, opening-wedge; CW, closing-wedge; HTO, High Tibial Osteotomy; UKA, unicompartmental knee arthroplasty; TKA, total knee arthroplasty

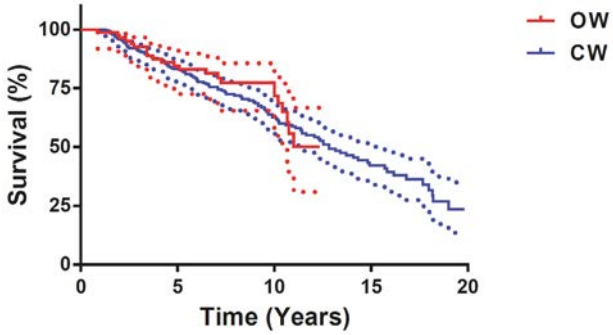

Fig. 3. Survival curve of closing- and opening-wedge osteotomy. Survival considered with "being in need for a UKA of TKA" according to the OARSI-criteria in addition to "being conversed to UKA or TKA" as end-point.
Abbreviations; OW, opening-wedge; CW, closing-wedge; HTO, High Tibial Osteotomy; UKA, unicompartmental knee arthroplasty; TKA, total knee arthroplasty

only medical records were screened to identify adverse events. This could have led to an underestimation. The strength of this study is the additional information assessed with a self-administered questionnaire after screening of the medical records in a relatively large number of patients. Consequently we assume that our results are a more accurate estimate of the real adverse event rate.

Different types of fixation material were used over years: however no difference was found in removal-rate between staples and plates. The hardware removal rates are similar to the literature. Multiple studies report a hardware removal rate of >50% of the patients in an OW-group and significantly more hardware removals in the OW-group

in comparison with the CW-group [4, 6, 12]. The more superficial medial position of hardware with less coverage of soft tissue might be a possible explanation for the higher hardware removal rate in the OW-group.

Another major adverse event was pain at the iliac crest, caused by harvesting the cancellous bone for gap filling in an OW-HTO. In a recent randomized controlled trial, Zorzi and colleagues concluded that a cancellous bone graft in wedges less than 12.5mm is not necessary [22]. It is clear that the complication rate will decrease in the OW-group when bone grafting can be avoided.

During the follow-up period 17.4% of the osteotomies have been revised to UKA or TKA. When conversion to a prosthesis was taken as endpoint, the OW-group had a significantly better survival than the CW-group. For CW-osteotomy the probability of survival was 75% after ten years and 50% after twenty years. For OW-osteotomy the probability of survival was 90% after ten years. Hui et al. found in their retrospective study of 455 CW-osteotomies a probability of survival of 79% after ten years and 56% at fifteen years, which is comparable with our results [15].

When "being in need for a UKA or TKA" according to the OARSI-criteria in addition to joint replacement [9] was considered as end-point, no difference in survival between the CW- and the OW-group was found. So it seems that patients with a CW-HTO were converted earlier than patients with an OW-HTO. There is no existing literature to compare this result with.

Some limitations of our study need to be addressed. Adverse events were measured retrospectively with medical record screening. This could lead to an underestimation of the adverse event rate, due to known under-reporting in medical records. For this reason we have also assessed the adverse events with a self-administered questionnaire. We identified with this additional information more cases of wound infection, deep venous thrombosis, iliac crest pain and sensory palsy of the CPN. The response rate of the questionnaire was 81%, which is high for a study with patient with a follow-up until 20 years. So the results of this study could still be an underestimation of the real adverse event rate, particularly the number of wound infections, deep venous thrombosis, iliac crest pain and cases of sensory palsy of the CPN could be underestimated. Because of recall bias all minor adverse events may be underrepresented. However, to our best knowledge this is the first study in a large group of patients with this approach.

Secondly, the HTO procedures were performed and supervised by different surgeons over the study period in a university teaching hospital. Moreover, during the study period the OW-technique was introduced. Although all surgeons were experienced, a single surgeon with experience with both techniques would have been preferable to reduce possible operator-dependent variability. Introduction of a new operation technique could lead to an increased risk for adverse events. However, this situation reflects common orthopaedic practice and improves the generalizability of the results.

CONCLUSION

OW-HTO was associated with more adverse events than CW-HTO. Hardware was removed more often in patients with CW- than OW-HTO. OW-HTO resulted in a better survival than CW-HTO, however an equal proportion of patients were in need for prosthesis in both groups.

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CONFLICT OF INTEREST

The authors report no conflict of interest.

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Chapter 6

Do preoperative expectations affect patient satisfaction after total knee arthroplasty? A systematic review.

T. Duivenvoorden, H. Verburg, S.M.A. Bierma-Zeinstra,
J.A.N. Verhaar, M. Reijman

Submitted

ABSTRACT

Background. A subset of patients has suboptimal results and is disappointed about their total knee arthroplasty (TKA). Numerous studies suggest that unrealistic expectations contribute to suboptimal results of TKA; however, a systematic overview is missing.

Objectives. To summarize the literature on the relationship between preoperative expectations and patient satisfaction after primary TKA. Our two hypotheses were that high expectations or unfulfilled ones lead to more dissatisfaction.

Methods. Eligible articles were obtained from PubMed publisher, MEDLINE, EMBASE, Cochrane, PsycINFO, CINAHL, and Web-of-Science and Google scholar from inception to March 2015. Search terms included TKA, expectations and satisfaction. Two reviewers independently selected the studies. Studies with a prospective or retrospective design with a minimum follow-up of six months were included. Two reviewers independently conducted the quality assessment and one reviewer extracted the data. Finally, we decided to perform a best evidence synthesis.

Results. Eight of 6802 studies met the inclusion criteria and were included in this systematic review. Limited evidence was found that there is no significant relation between expectations and satisfaction regarding limitations in recreation, walking distance, use of a walking aid and expected time to full recovery. Conflicting evidence was found that expectations regarding general improvement, pain reduction and limitations in activities of daily living lead to more dissatisfaction. Moderate evidence was found that patients with fulfilled expectations were more often satisfied than patients with unfulfilled expectations.

Conclusions. Limited or conflicting evidence was found that high expectations do not lead to more dissatisfaction. Moderate evidence was found that unfulfilled expectations lead to more dissatisfaction.

Level of evidence. Level III, systematic review of level II and level III studies

INTRODUCTION

When conservative treatment fails to alleviate pain and limitations in patients with end-stage osteoarthritis (OA) of the knee, total knee arthroplasty (TKA) is a cost-effective surgical option.[1] Surgical techniques and prostheses have improved in recent years, and outcomes after TKA are generally good. Patient satisfaction is the ultimate goal of the procedure. Although most patients are satisfied, a subset is not. The explanation of these disappointing results is not always completely physical, like adverse events, comorbidities, variation in surgery itself or residual pain, but seem to be related to other not directly surgical related factors, such as anxiety and depressive symptoms or unrealistic expectations of patients.[2,3]

Most patients probably have high expectations of TKA outcome.[4] But in addition to patients' expectations, it has been reported that orthopedic surgeons also tend to overestimate the expected functional improvement of their patients.[5] Due to the increased prevalence of obesity and OA, patients undergoing TKA in the coming decades will be younger and therefore typically more active.[6] Thus, the preoperative expectations of these young and active patients could even be higher than the expectations prevailing among today's older cohort of TKA patients.

Studies evaluating preoperative patient expectations have shown that patients with the greatest expectations of surgery demonstrate the best outcomes when undergoing heart surgery, abdominal hysterectomy, and lumbar spine surgery. Other authors, however, have stressed that patients should have realistic or even low expectations of surgery, because fulfilment of these tempered expectations may lead to greater satisfaction.[6] It remains to be seen which relationship between preoperative expectations and patient satisfaction exists in patients undergoing TKA.

In an earlier systematic review authors evaluated the influence of psychological factors on postoperative pain, functional outcome and patient satisfaction in patients undergoing TKA. They concluded that limited evidence exists that preoperative expectations have no influence on patient satisfaction for patients undergoing total hip arthroplasty (THA) or TKA.[8] In another systematic review of the literature on the influence of patient expectations on different Patient Reported Outcomes (PROs) in general, the authors reported that no relationship could be found between expectations and satisfaction.[9] However, the influence of expectations on patient satisfaction was not the primary objective of these systematic reviews and, consequently, the search strategy was not specifically designed to address such questions. Therefore they may have missed some essential publications and only analyzed the relationship between preoperative expectations and patient satisfaction in general.

Patient satisfaction consists of multiple domains, including satisfaction regarding general improvement, pain reduction, improvement in ADL and so on. To design an

effective counselling program for managing preoperative expectations, it is important to analyze this relationship for every single domain.

Our first hypothesis was that high expectations regarding general outcome, pain reduction and improvement of mobility lead to more dissatisfaction with these specific domains. Our second hypothesis was that also unfulfilled expectations of these specific domains lead to more dissatisfaction. There is some evidence that patient education can modify preoperative expectations.[10] So, preoperative expectations could be an important modifiable risk factor for dissatisfaction.

The purpose of this study was to summarize the literature about the relationship between preoperative expectations or fulfillment of expectations and patient satisfaction after TKA. This knowledge could be important for managing preoperative expectations in the future.

METHODS

Data Sources and Searches

We performed a search for relevant studies in EMBASE, PubMed publisher, MEDLINE, Cochrane, PsycINFO, CINAHL, and Web-of-Science and Google scholar since their inception up to March 2015. Search terms included total knee arthroplasty, preoperative expectations and patient satisfaction. The full electronic search strategy for the EMBASE database is presented in Table I.

Additionally, citation tracking was performed by manually screening the reference lists of eligible studies.

Study selection

Two reviewers (TD, HV) assessed the studies on whether they met the following inclusion criteria:

- The study must have a prospective or retrospective design
- The study must have a minimum follow-up of 6 months
- The study must describe a population of at least 20 patients
- Patients had to have a primary TKA for osteoarthritis
- The study must have measured preoperative expectations or fulfillment of expectations and patient satisfaction
- The study must describe the relationship between preoperative expectations and patient satisfaction
- The original data had to be available (no (systematic) review or meta-analysis)

Disagreement on inclusion was resolved by discussion, and a final decision of a third reviewer (JV) was not necessary.

Table I Search strategy in EMBASE

((arthroplasty/exp OR 'joint prosthesis'/exp OR 'orthopedic surgery'/de OR 'joint surgery'/de OR 'knee surgery'/exp OR 'knee injury'/exp/dm_su OR (arthroplast* OR ((knee* OR joint* OR orthop*) NEAR/3 (replac* OR prosthe* OR endoprosthe* OR arthroprosthe* OR megaprosthe* OR implant* OR reconstruct* OR hemiarthroplast* OR surger* OR operat* OR repair*)) OR TKR OR TKA):ab,ti)
AND
('preoperative period'/de OR 'preoperative care'/de OR 'preoperative education'/de OR 'preoperative evaluation'/de OR 'predictor variable'/de OR prediction/de OR 'prediction and forecasting'/de OR 'predictive value'/de OR 'risk factor'/exp OR (predict* OR preoperat* OR presurg* OR prearthroplas* OR (pre NEXT/1 (operat* OR surg* OR arthroplast*)) OR (before NEAR/6 (operat* OR surg* OR arthroplast* OR TKR OR TKA)) OR (risk NEAR/3 factor*)):ab,ti)
AND
('emotion'/exp OR 'psychological aspect'/exp OR stress/exp OR 'mental health'/exp OR 'mood disorder'/exp OR 'psychologic assessment'/exp OR wellbeing/exp OR 'anxiety disorder'/exp OR 'patient attitude'/de OR 'patient compliance'/exp OR 'patient participation'/exp OR 'patient preference'/exp OR 'refusal to participate'/exp OR 'treatment refusal'/exp OR 'psychologic test'/exp OR (((patient* OR client* OR personal* OR preoperat* OR presurg*) NEAR/6 (expect* OR concern OR concerns OR concerned OR question OR questions OR prefer* OR refus* OR participation* OR complian* OR noncomplian* OR adhere* OR nonadher*)) OR perception OR percieved OR injustice* OR emotion* OR anxi* OR psycho* OR expectation* OR (stress* NEAR/3 patient*) OR distress* OR mental* OR 'well being' OR wellbeing OR mood OR depress* OR attitude* OR catastroph* OR happy OR happiness OR unhappy OR unhappiness OR fear):ab,ti)
AND
[english]/lim NOT ([animals]/lim NOT [humans]/lim) NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim)

Quality assessment

The methodological quality of observational studies can vary, which may influence the results and conclusions of these studies, and subsequently, the results and conclusions of a systematic review. We scored the internal and external validity of the selected studies using eight questions from existing quality assessment tools.[11,12,13] The questions used to score the internal and external validity were:

1. Inclusion of consecutive patients?
2. Description of in- and exclusion criteria?
3. Did the authors report the participation rate and did patients give informed consent?
4. Unbiased assessment of outcome and determinant?
5. Was the follow-up period appropriate?
6. Did they report a loss to follow-up of less than 20%?
7. Is there any information about the sample size calculation?
8. Were the statistical tests appropriate and did they adjust for confounders?

Two reviewers (TD, MR) assessed the quality independently. Disagreements were solved by discussion, and a final decision of a third reviewer (SB) was not necessary.

Studies were classified as high quality when they scored ≥5 points and when minimally questions 1, 4 and 8 were scored as "yes".

Data extraction

One reviewer (TD) extracted the study characteristics, follow-up times, outcome and determinants, and the relationship between outcome and determinant.

Best evidence synthesis

Because the studies were considered heterogeneous with regard to outcome measure, determinant and methodological quality, we decided not to pool the data but instead to perform a "best evidence synthesis".[14,15]

The following ranking of levels of evidence was formulated: 1. strong evidence is provided by 2 or more studies with high quality and generally consistent findings in all studies (≥75% of the studies reported consistent findings); 2. moderate evidence is provided by 1 high-quality study and 2 or more low-quality studies and generally consistent findings in all studies (≥ 75%); 3. limited evidence is provided by 2 or more low-quality studies or 1 high-quality study and generally consistent findings (≥75%); 4. conflicting evidence is provided by conflicting findings (<75% of the studies reported consistent findings); 5. no evidence is provided when no studies could be found.

RESULTS

Identification and selection of literature

The search resulted in 6802 articles, whose abstracts were reviewed. Through screening of the abstracts, 45 were identified as possibly relevant, for which full articles were studied. After review of the full text, 5 prospective and 3 retrospective articles met all inclusion criteria. The reasons for excluding articles were: did not measure the aimed outcome or determinant (n = 32), no relationship was described between outcome measure and determinant (n = 2), and no separate data for TKA were available, even after contact with the author (n = 3) (Fig. 1).

Description of included studies

Table II presents the characteristics of the 8 included studies. Date of publication of the studies ranges from 2006 – 2012. The number of patients ranges from 46 to 598 in the prospective studies and from 253 to 1703 in the retrospective studies. In two prospective studies preoperative expectations were measured on a Likert scale. Three other prospective studies used modified questionnaires. The preoperative expectations

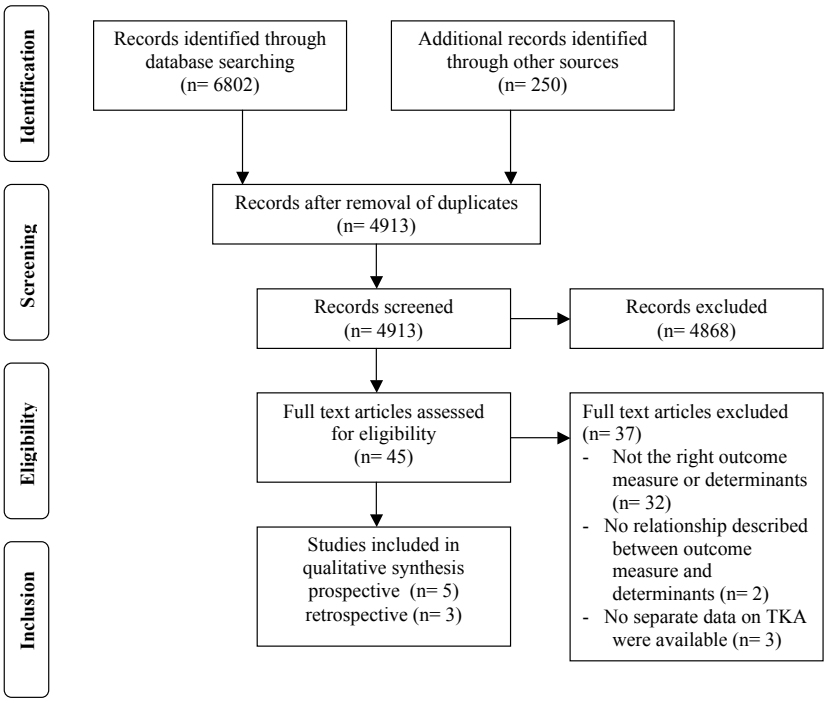

Fig. 1. Flowchart of the study selection according to the PRISMA-statement.

in all retrospective studies were determined by questioning whether the postoperative results had met the patients' expectations.

Quality assessment

The results of the quality assessment are presented in Table III. The scores on the 8 questions ranged from 2 to 6. Three studies scored ≥5 points, did include consecutive patients, made unbiased assessments of the outcome and determinant, and used appropriate statistical tests and adjusted for confounders; therefore, these three were classified as "high quality".

Preoperative expectations

Preoperative expectations were measured by using expectations questionnaires incorporating either VAS or Likert scales. The questions asked about patient expectations were very heterogeneous. Questions were asked about patient expectations regarding overall success[16,17,18,19,20,21], severity of pain[16,,22,23], limitations in ADL[16,23] or recreation[22], walking distance[21], use of a walking aid[22] or expected time to full recovery[23].

Table II Characteristics of the included studies

	Number of patients	Gender, % female	Age, yr*	BMI, kg/m^{2*}	Follow-up, months	Used satisfaction measure	Dichotomised scores to "satisfied"	Subject of expectation
Prospective								
Lingard 2006 (21)	598	58	69 (range 38 to 89)	29.3 ± 5.8	12	4-point Likert	NR	Pain, limitations in recreation, walking distance, walking aid
Mannion 2009 (22)	112	70	67 ± 9	-	24	4-point Likert	Very satisfied and somewhat satisfied	Pain, limitations in ADL
Scott 2012 (17)	323	61	70.6 (range 33 to 91)	-	12	4-point Likert	Very satisfied and satisfied	General
Suda 2010 (18)	46	70	67.4 ± 8.7	28.5 ± 5.3	36	VAS/ Likert	NR	General
Vissers 2010 (15)	44	55	median 63.5 (range 42 to 78)	median 30.8 (range 24.2 to 44.9)	6	5-point Likert	Very satisfied	General, pain, limitations in ADL
Retrospective								
Bourne 2009 (20)	1703	60	69 ± 9	32 ± 6	12	5-point Likert	Very satisfied and satisfied	General
Noble 2006 (19)	253	59	68.1 (range, 23 to 90)	-	12	5-point Likert	Very satisfied and satisfied	General
Scott 2010 (16)	1141	61	70.1 (range 35 to 92)	-	12	4-point Likert	Very satisfied and satisfied	General

* Values are presented as mean ± SD, or reported otherwise.

Abbreviations; ADL; activities of daily living; BMI, body mass index; Likert; Likert scale, -; not reported, VAS; visual analogue scale

Table III Quality assessment

	Internal and external validity								
	1	2	3	4	5	6	7	8	Total
High Quality									
Lingard 2006 (21)	√	√	√	√	√	X	X	√	6
Mannion 2009 (22)	√	√	√	√	√	X	X	√	6
Scott 2012 (17)	√	X	X	√	√	√	X	√	5
Low Quality									
Bourne 2009 (20)	X	√	X	X	√	√	X	√	4
Scott 2010 (16)	√	X	X	X	√	√	X	√	4
Vissers 2010 (15)	X	√	X	√	X	√	X	√	4
Noble 2006 (19)	X	X	X	X	√	√	X	√	3
Suda 2010 (18)	X	X	X	√	√	X	X	X	2

1. Inclusion of consecutive patients?
2. Description of in- and exclusion criteria?
3. Did the authors report the participation rate and did patients give informed consent?
4. Unbiased assessment of outcome and determinant?
5. Was the follow-up period appropriate?
6. Did they report a loss to follow-up less than 20%?
7. Is there any information about the sample size calculation?
8. Were the statistical tests appropriate and did they adjust for confounders?

Patient satisfaction

Patient satisfaction was measured with either a VAS or Likert scale. These questions were also very heterogeneous, but corresponded always with the expectation questions. Questions were asked about patient satisfaction regarding overall success[16,17,18,19,20,21], severity of pain[16,22,23], limitations in ADL[16,23] or recreation[22], walking distance[22], use of a walking aid[22] or expected time to full recovery[23].

Influence of preoperative expectations on patient satisfaction

Relationships between expectations and satisfaction regarding general improvement were presented in two different ways. Two studies presented a correlation coefficient or p-value. In these studies, conflicting evidence was found for the relationship between expectations and satisfaction. One low-quality study reported no significant relationship and one low-quality study reported a positive relationship, which means that higher expectations are related to more dissatisfaction (Table IV).

Table IV Relationship between preoperative expectations and patient satisfaction

	Quality	General	Pain	Limitations in ADL	Limitations in recreation	Walking distance	Use of a walking aid	Expected time to full recovery
Lingard 2006 (21)	High	-	NS	-	NS	NS	NS	-
Mannion 2009 (22)	High	-	**0.274**	**0.262**	-	-	-	NS
Scott 2010 (16)	Low	**0.773**	-	-	-	-	-	-
Vissers 2010 (15)	Low	NS	NS	NS	-	-	-	-
BES		Conflicting	Conflicting	Conflicting	Limited	Limited	Limited	Limited

Significant values are presented in bold

Abbreviations: -, not reported; ADL, activities of daily living; BES, best evidence synthesis; NS, no significant relationship

Four studies presented the percentage of satisfied or dissatisfied patients with fulfilled expectations. In these studies, moderate evidence was found that patients with fulfilled expectations were more often satisfied than patients with unfulfilled expectations. Patients with unfulfilled expectations were more often dissatisfied than patients with fulfilled expectations (Table V).

Regarding pain, conflicting evidence was found for the relationship between expectations and satisfaction. One high-quality and one low-quality study reported no signifi-

Table V Relationship between fulfilled expectations and patient satisfaction[a]

	Quality	Dissatisfied/ neutral	Satisfied	p-value
Scott 2012 (17)	High	15%	66%	**<0.001**
Bourne 2009 (20)	Low	49.4%	78.5 %	**< 0.0001**
Noble 2006 (19)	Low	50 %	86 %	**< 0.0001**
Suda 2010 (18)	Low	-	61%	-
BES				Moderate

[a]Percentage of patients with fulfilled expectations
Abbreviations: -, not reported; BES, best evidence synthesis

cant relationship and one high-quality study a positive relationship, which means that higher expectations are related to more dissatisfaction.

Regarding limitations in ADL, conflicting evidence was found for the relationship between expectations and satisfaction. One high-quality study reported no significant relationship and one high-quality study reported a positive relationship, which means that higher expectations are related to more dissatisfaction.

Regarding limitations in recreation, walking distance, use of a walking aid and expected time to full recovery, limited evidence was found that there is no significant relationship between expectations and satisfaction (Table IV).

DISCUSSION

In this systematic review we summarized the available literature concerning the influence of preoperative expectations on patient satisfaction after TKA. Our first hypothesis was that unrealistically high expectations lead to more dissatisfaction. Our second hypothesis was that unfulfilled expectations also lead to more dissatisfaction.

Regarding limitations in recreation, walking distance, use of a walking aid and expected time to full recovery, limited evidence was found for there being no significant relationship between expectations and satisfaction. Moderate evidence was found that patients with fulfilled expectations were more often satisfied than patients with unfulfilled expectations. Conflicting evidence was found that high expectations regarding general improvement, pain reduction and limitations in ADL lead to more dissatisfaction.

Besides these findings, the most important finding of this systematic review is the small number of publications describing the relationship between expectations and satisfaction. Moreover, the evidence for this frequently assumed relationship is limited. Therefore, it is important to be cautious in making conclusions based on the existing

literature. For the future, research needs to be done to determine this expected relationship and to develop a standardized method for managing patient expectations.

Another systematic review summarized the literature regarding the influence of patient expectations on PROs in general and also analyzed the relationship between expectations and satisfaction.[9] Unfortunately, that review missed some essential studies, and the authors merged data for both THA and TKA in reaching their conclusion. Many other studies reported that patients undergoing THA are less satisfied with their implant than patients undergoing TKA.[25,26] Furthermore, hip patients are generally more active than knee patients,[27] and the two may also have different preoperative expectations.

Moreover, in a study of a specific population of patients undergoing both TKA and THA, the authors reported that these patients were more satisfied about their hip than knee prosthesis in terms of both range of motion and quality of life.[28] So, the relationship between preoperative expectations and patient satisfaction might not be similar for these two groups of patients.

Some limitations of our systematic review need to be addressed. Firstly, we included three retrospective studies in our systematic review. Expectations reported after a procedure has been performed are subject to recall bias and the response may depend on the outcome of the procedure. To avoid this, measurement of expectations before surgery is essential. Despite this limitation, we decided to include retrospective studies because of the limited number of prospective studies we found. The strength of the included retrospective studies was the large sample size. Therefore, inclusion of these retrospective studies allowed us to present a complete systematic overview of all available literature.

Secondly, none of the studies reported a sample size calculation. Particularly in small studies, it is uncertain that no relationship between two determinants exists or that there might have been a lack of power to determine a relationship. Consequently, with no information regarding a sample size calculation, it is better to be cautious when concluding that no relationship exists.

Thirdly, the heterogeneity of the studied determinants and outcome measures could limit the level of certainty of our conclusion. Because the studies were considered heterogeneous with regard to outcome measures, determinants, questionnaires, and methodological quality, we refrained from statistically pooling the data and instead performed a best evidence synthesis. The wide variability in outcome measures and determinants makes it difficult to compare the results of different studies. Therefore, more standardization is needed when evaluating the influence of preoperative expectations on patient satisfaction after TKA.

In conclusion, limited evidence was found that high expectations regarding limitations in recreation, walking distance, use of a walking aid and expected time to full

recovery do not lead to more dissatisfaction about these domains. Conflicting evidence was found that high expectations regarding general improvement, pain reduction and limitations in activities of daily living lead to more dissatisfaction. Moderate evidence was found that unfulfilled expectations lead to more dissatisfaction. More research needs to be done to develop standardized methods to determine and better manage patient expectations.

Author contributions

T. Duivenvoorden performed the systematic search, study selection, quality assessment and data extraction and wrote the manuscript, H. Verburg performed the study selection and critically reviewed the manuscript, S.M.A. Bierma-Zeinstra shared her expertise on the field of osteoarthritis and critically reviewed the manuscript, J.A.N. Verhaar shared his expertise on the field of knee prosthesiology and critically reviewed the manuscript, M. Reijman performed the quality assessment and critically reviewed the manuscript.

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Conflict of interest

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Chapter 7

Anxiety and depressive symptoms before and after total hip and knee arthroplasty: a prospective multicentre study

T. Duivenvoorden, M.M. Vissers, J.A.N. Verhaar, J.J.V. Busschbach, T. Gosens, R.M. Bloem, S.M.A. Bierma-Zeinstra, M. Reijman

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ABSTRACT

Background. A subset of patients with total hip (THA) or total knee arthroplasty (TKA) has suboptimal postoperative results in terms of Patient-Reported Outcomes (PROs), and psychological factors could contribute to these suboptimal results.
Objectives. To examine the prevalence of anxiety and depressive symptoms in patients undergoing primary THA or TKA preoperatively and postoperatively, and the relationship between preoperative anxiety and depressive symptoms on PROs of THA and TKA.
Design. In this prospective study patients were measured preoperatively, and 3 and 12 months postoperatively. Patients filled in the Hospital Anxiety and Depression Scale, Knee injury and Osteoarthritis Outcome Score (KOOS) or Hip disability and Osteoarthritis Outcome Score (HOOS) and a satisfaction questionnaire.
Results. Data were obtained from 149 hip and 133 knee patients. The prevalence of anxiety symptoms decreased significantly from 27.9% to 10.8% 12 months postoperatively in hip patients, and from 20.3% to 14.8% in knee patients. Depressive symptoms decreased significantly from 33.6% to 12.1% 12 months postoperatively in hip patients, and from 22.7% to 11.7% in knee patients. In hip and knee patients, preoperative depressive symptoms predicted smaller changes in different HOOS or KOOS subscales and patients were less satisfied 12 months postoperatively.
Conclusions. Preoperatively, the prevalence of anxiety and depressive symptoms was high. At 3 and 12 months postoperatively, the prevalence of anxiety and depressive symptoms was decreased in both hip and knee patients. However, patients with preoperative anxiety and depressive symptoms had worse PROs 3 and 12 months after THA and TKA and were less satisfied than patients without anxiety or depressive symptoms.

INTRODUCTION

Osteoarthritis (OA) of the hip or knee is one of the most frequently occurring disorders of the locomotor system, and the leading cause of pain and disability in the older population. When conservative treatment fails, total hip arthroplasty (THA) and total knee arthroplasty (TKA) are cost-effective surgical options for patients with end-stage OA (1).

Surgical techniques and design of the prostheses have been improved, and the results after THA and TKA are generally good. However, a subset of patients has suboptimal postoperative results with respect to pain, physical functioning and quality of life (QOL), and may not be satisfied with the results of their THA or TKA (2, 3). These outcomes are described as Patient Reported Outcomes (PROs), which the FDA defines as "… a report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else" (4).

The suboptimal results of THA and TKA in terms of PROs (5) in subgroups of patients cannot be entirely explained by patients' physical characteristics, adverse events, physical co-morbidities or surgery itself, but seem to be related to other characteristics, including psychological symptoms (6). PROs reflecting the patient perspective on interventions, are increasingly important in effectiveness evaluation. For instance, since 1 April 2009 all providers of care funded by the National Health Service (NHS) in England have been required to provide Patient Reported Outcome Measures (PROMs) in four elective surgical procedures: hip replacement, knee replacement, varicose vein surgery and hernia surgery (7).

Psychological symptoms were found to be associated with lower scores on PROs like QOL and increased pain and symptom sensitivity (8). In addition, psychological symptoms negatively influence patients' motivation, energy, coping with illness and adherence of patients. Therefore, psychological symptoms may have an important influence on the treatment results and recovery in terms of PROs following THA or TKA. Such an effect may be common as psychological symptoms are highly prevalent in the elderly, especially in those with chronic medical illnesses (9). The question then arises whether patients with end-stage hip or knee OA, who have suffered chronic pain and disability for many years, have indeed an increased prevalence of psychological symptoms. Previous studies have reported a high prevalence of psychological symptoms in patients with end-stage knee OA.(10-15) It is also reported that patients with psychological symptoms report lower PROs.(8, 16-17 However, the impact of THA and TKA on these psychological symptoms is still unclear. Will these psychological symptoms decrease when the source of chronic pain and disability has been removed after total joint arthroplasty (TJA)?We hypothesized that, the prevalence of psychologi-

cal symptoms will be high in end-stage hip as well as knee OA patients, and that these symptoms would likely improve along with pain and disability after arthroplasty.

Finally, it becomes relevant to examine whether we can relate preoperative psychological symptoms to the outcomes of THA or TKA. If such is the case, interventions aiming at a reduction of these psychological symptoms in these subgroups, either before or after THA or TKA, might increase the effectiveness of THA and TKA in terms of PRO. We showed earlier that patients with a lower mental health before THA and TKA had worse PROs post-surgery (16, 17). However, it was unclear whether anxiety and depressive symptoms had an influence on the outcome after THA and TKA. This is relevant as both mental symptoms can relatively easily be treated, for instance by using short term cognitive behavioural therapy (18, 19).

In summary: the primary aim of this study was to examine the prevalence of anxiety and depressive symptoms in patients prior to THA and TKA, and 3 and 12 months post-surgery to determine the impact of THA and TKA on these psychological symptoms. The second aim was to evaluate the influence of preoperative anxiety and depressive symptoms on the outcome 12 months after THA and TKA.

METHODS

This study was based on a prospective design with three assessment points. Patients were measured preoperatively while on the waiting list, 3 and 12 months after THA or TKA. Patients filled in three questionnaires at these three assessment points.

Patients

All patients on the waiting list for primary THA or TKA at the department of Orthopaedics of Erasmus University Medical Center in Rotterdam, Reinier de Graaf Hospital in Delft, and St. Elisabeth Hospital in Tilburg in the period March 2009 and August 2010 were eligible. This study was approved by the local Medical Ethics Committee.

Measurements

Patients on the waiting list (baseline measurement) were measured without a fixed time point. Patients received the questionnaires by mail. In case of non-response a reminder was sent by mail after 3 weeks. If patients did not respond to the reminder, they were contacted by telephone 3 weeks later.

The main determinants were anxiety and depressive symptoms. These two symptoms were measured with the HADS, a validated questionnaire to screen anxiety and depressive symptoms. The HADS consists of 14 items, each rated from 0 to 3 according to the severity of distress experienced (0 indicates no distress and 3 indicates maximum

distress). The HADS is divided into an Anxiety subscale and a Depression subscale, each with seven questions; each subscale score ranges from 0 to 21. Both subscales were used as independent variables to evaluate the influence of preoperative anxiety or depressive symptoms on the PROs after THA or TKA .

There are two methods to analyze the HADS data. First, raw scores can be summed for each subscale separately. Second, raw scores of the subscales can be used to classify patients into those with and without anxiety or depressive symptoms. The optimal cut-off score for the presence of both anxiety and depressive symptoms is ≥ 8; the sensitivity and specificity for this cut-off is about 0.80(20-22).

The present study includes patients using antidepressants, or patients being treated by a psychologist or psychiatrist because of anxiety or depressive symptoms. Depression was defined using a cut-off of 8 or more on the HADS, or use of antidepressants or treatment by a mental health provider for anxiety or depression. The Hip disability and Osteoarthritis Outcome Score (HOOS) (23,24) and the Knee injury and Osteoarthritis Outcome Score (KOOS) (25,26) were used to evaluate hip and knee specific outcomes. The HOOS and KOOS questionnaires include five subscales: pain, symptoms, functioning in activities of daily living (ADL), functioning in sport and recreation, and hip or knee-related QOL. Standardized response options are given (5-point Likert scale), and each question is scored from 0 to 4. Then, a normalized score from 0 to 100 is calculated for each subscale (100 indicating no symptoms, and 0 indicating extreme symptoms) (23-26).

Finally, patients filled in a general questionnaire about patient characteristics, use of pain medication, use of antidepressants, treatment by a psychologist or psychiatrist because of anxiety or depressive symptoms and patient satisfaction. Patient satisfaction was measured on a 5-point Likert scale 12 months postoperatively and included questions about the overall result, pain reduction, improvement in ADL and QOL. We dichotomized our satisfaction results as satisfied or unsatisfied on the basis of the Likert scale. The two responses 'very satisfied' and 'satisfied' were dichotomized to satisfied and 'neutral', 'unsatisfied' and 'very unsatisfied' were dichotomized to unsatisfied.

Statistical analysis

Statistical analysis was performed using PASW Statistics (SPSS science Inc., Chicago, USA). Data of the hip and knee patients are presented separately.

Differences between hip and knee patients, and differences between the study population and patients lost to follow-up, were analyzed using independent t-tests (Student's t-test). Differences between the preoperative, 3 and 12 months postoperative data were analyzed with dependent t-tests. Effect sizes were calculated to examine the effect of THA or TKA on anxiety or depressive symptoms 3 and 12 months postoperatively. Effect sizes were calculated as mean of the 3 or 12 months results minus the mean of

the baseline (preoperative) data divided by the standard deviation (SD) of the baseline results.

To evaluate the influence of preoperative anxiety or depressive symptoms on the PROs after THA or TKA multivariable linear regression analysis was used. Dependent variables were the change scores of the HOOS or KOOS subscales between 12 months postoperative and preoperative scores. The independent variables were preoperative anxiety and depressive HADS score (dichotomized as < 8 and ≥ 8). This relationship was adjusted for age, gender, time spent on waiting list preoperative score on HOOS and KOOS subscale and unbalanced characteristics between study population and patients lost to follow-up. To check for linearity we plot the standardized residuals of the used variables against the standardized predicted values.

To evaluate the influence of preoperative anxiety or depressive symptoms on patient satisfaction multivariable logistic regression analysis was used. Dependent variable was patient satisfaction. Independent variables were preoperative anxiety and depressive HADS score (dichotomized as < 8 and ≥ 8). This relationship was adjusted for age, gender, time spent on waiting list and unbalanced characteristics between study population and patients lost to follow-up.

RESULTS

Between March 2009 and August 2010, 451 patients were eligible to participate in the study and received questionnaires by mail. Of these eligible patients, baseline results of 384 patients were available (response rate 85%). Of 268 patients (response rate 70%) both baseline, 3 and 12 months postoperative data were available. These results were used in the present analysis (Fig. 1). To evaluate whether lost patients introduced selection bias we compared baseline characteristics of the study population with the patients lost to follow-up.

Table I presents the baseline characteristics of the study population and of patients lost to follow-up. There were no significant differences between the study population and patients lost to follow-up with respect to the primary outcome measures 'prevalence of anxiety and depressive symptoms' (Table I). For hip patients, the presence of familial depression, time on the waiting list and the outcome of the subscale symptoms on the HOOS-score were unbalanced characteristic between the study population and the patients lost to follow-up. For knee patients, gender was an unbalanced characteristic. Consequently, we adjusted the regression analyses for these variables.

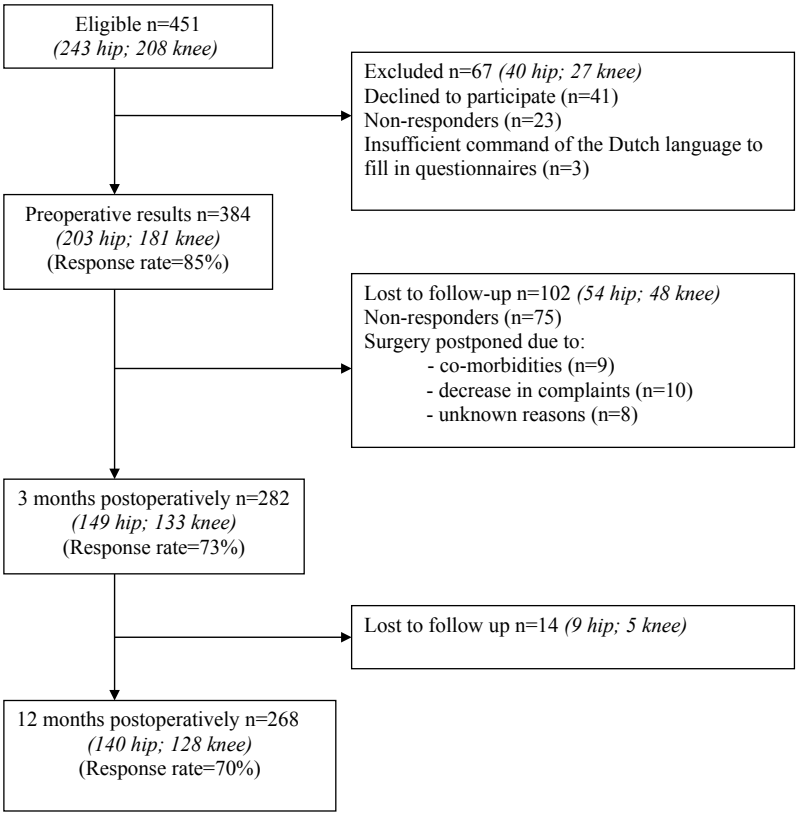

Fig. 1. Flow chart of the study population.

Prevalence

Table II presents the preoperative, 3 and 12 months postoperative HADS-score for hip and knee patients. The preoperative prevalence of depressive symptoms was significantly higher in hip than in knee patients (33.6% vs 22.7%; p-value = 0.047). For hip patients the mean HADS anxiety and depression score showed a significant decrease 3 and 12 months postoperatively compared to baseline ($p<0.0001$). In this group less patients had anxiety or depressive symptoms 3 and 12 months postoperatively ($p<0.0001$).

For knee patients the mean HADS anxiety and depression score showed almost a similar pattern, except that the number of patients with anxiety symptoms 12 months postoperatively was not significant lower than preoperative. Between 3 and 12 months postoperatively the HADS anxiety and depression scores (mean and prevalence) did not change significant for both hip and knee patients (Table II). The effect size of THA and TKA on anxiety symptoms was 0.31 and 0.28.The effect size of THA and TKA on depressive symptoms was 0.48 and 0.32.

Table I Baseline characteristics of the study patients and of patients lost to follow-up

	Hip		Knee	
	Study population n = 140	LTFU n = 63	Study population n = 128	LTFU n = 53
Age, years	67.9 ± 9.6	66.5 ± 13.6	66.2 ± 9.7	66.2 ± 9.5
Gender, women n, (%)	89 (63.6)	33 (52.4)	72 (56.3)	40 (75.5)[a]
Education				
- Less than high school, n (%)	40 (28.8)	16 (25.8)	35 (27.6)	19 (35.8)
Time on waiting list at baseline measurement, weeks	9.1 ± 12.6	13.6 ± 17.5[a]	14.6 ± 16.6	18.6 ± 18.3
Total time spent on waiting list, weeks	22.7 ± 20.6	29.6 ± 23.5[a]	31.0 ± 22.9	34.1 ± 27.3
HOOS/KOOS, score 0-100; 100 best score				
- Pain	32.7 ± 17.7	36.0 ± 20.6	35.9 ± 17.2	35.8 ± 21.0
- Symptoms	50.5 ± 10.8	47.2 ± 11.8[a]	43.3 ± 20.5	41.1 ± 20.5
- ADL	29.9 ± 17.8	33.4 ± 21.9	37.8 ± 19.7	35.7 ± 21.4
- Sport	14.3 ± 17.8	19.4 ± 27.0	8.8 ± 17.5	13.4 ± 24.0
- QOL	21.4 ± 16.7	20.0 ± 19.2	17.7 ± 14.9	20.9 ± 17.2
History of depressive disorders, n (%)	26 (18.6)	12 (21.1)	24 (18.8)	6 (13.6)
Familial depression, n (%)	32 (22.9)	3 (5.3)[a]	14 (10.9)	4 (9.1)
HADS depressive symptoms				
- ≥ 8, n (%)	37 (26.4)	23 (36.5)	26 (20.3)	13 (24.5)
- use of antidepressants, n (%)	15 (10.8)	3 (5.4)	7 (5.5)	4 (8.5)
- treatment, n (%)[b]	2 (1.5)	1 (1.9)	2 (1.7)	0
- Total, n (%)[c]	47 (33.6)	23 (36.5)	29 (22.7)	14 (26.4)
HADS anxiety symptoms				
- ≥ 8, n (%)	31 (22.1)	11 (17.5)	23 (18.0)	9 (17.0)
- use of antidepressants, n (%)	15 (10.8)	3 (5.4)	7 (5.5)	4 (8.5)
- treatment, n (%)[b]	2 (1.5)	1 (1.9)	2 (1.7)	0
- Total, n (%)[c]	39 (27.9)	12 (19.0)	26 (20.3)	10 (18.9)

Values are presented as mean ± standard deviation, unless otherwise indicated.

[a] $p<0.05$, variables were inserted in the multivariable model to test for unbalanced characteristics

[b] Patients under treatment of a psychologist or psychiatrist

[c] HADS score ≥ 8 or use of antidepressants or treatment by a psychologist or psychiatrist

Abbreviations: LTFU, lost to follow-up; ADL, activities of daily living; QOL, quality of life; HOOS, Hip disability and Osteoarthritis Outcome Score; KOOS, Knee injury and Osteoarthritis Outcome Score; HADS, Hospital Anxiety and Depression Scale.

Influence on PROs

In hip patients, preoperative anxiety and depressive symptoms both predicted lower change scores on the HOOS subscales pain, ADL, and QOL. Anxiety symptoms predicted also a lower change score on the HOOS subscale sport. These relationships were

Table II Preoperative and 3- and 12-month postoperative prevalence of anxiety and depressive symptoms of the patients who completed all measurements for hip and knee

	Hip (n = 140)			Knee (n = 128)		
	Preoperative	3 months postoperative	12 months postoperative	Preoperative	3 months postoperative	12 months postoperative
HADS anxiety symptoms						
Score, mean ± SD	4.6 ± 4.2	**3.1 ± 3.5**[b]	**3.3 ± 3.3**[b]	4.2 ± 3.6	**3.1 ± 3.5**[b]	**3.2 ± 3.6**[a]
- ≥ 8, n (%)	31 (22.1)	**14 (10.9)**[b]	**13 (9.4)**[a]	23 (18.0)	**14 (10.9)**[a]	17 (13.3)
- antidepressants, n (%)	15 (10.8)	6 (4.7)	**3 (2.1)**[b]	7 (5.5)	6 (4.7)	2 (1.6)
- treatment[c], n(%)	2 (1.5)	2 (1.6)	1 (0.7)	2 (1.7)	2 (1.6)	0
Total, n (%)	39 (27.9)	**18 (14.1)**[b]	**15 (10.8)**[b]	26 (20.3)	**18 (14.1)**[a]	19 (14.8)
HADS depressive symptoms						
Score, mean ± SD	5.1 ± 4.0	**3.3 ± 3.3**[b]	**3.2 ± 3.3**[b]	4.3 ± 3.8	**3.4 ± 3.4**[b]	**3.1 ± 3.4**[b]
- ≥ 8, n (%)	37 (26.4)	**11 (7.1)**[b]	**14 (10.0)**[b]	26 (20.3)	**18 (14.1)**[a]	**14 (10.9)**[a]
- antidepressants, n (%)	15 (10.8)	10 (7.1)	**3 (2.1)**[b]	7 (5.5)	6 (4.7)	2 (1.6)
- treatment[c], n (%)	2 (1.5)	3 (2.1)	1 (0.7)	2 (1.7)	2 (1.6)	0
Total, n (%)	47 (33.6)	**18 (12.9)**[b]	**17 (12.1)**[b]	29 (22.7)	**21 (16.4)**[a]	**15 (11.7)**[a]

Values are presented as mean ± standard deviation, unless otherwise indicated. Significant p-values are presented in bold.

[a]Significant difference with preoperative score $p<0.05$

[b]Significant difference with preoperative score $p<0.0001$

[c]Patients under treatment of a psychologist or psychiatrist or using antidepressants

Abbreviations: SD, standard deviation. HADS, Hospital Anxiety and Depression Scale.

independent of age, gender, preoperative score on the HOOS subscale, and the unbalanced characteristics time on waiting list and familial depression (Table III). Tested in the same way, in knee patients preoperative anxiety symptoms predicted lower changes scores of the ADL, sport and QOL subscales of the KOOS questionnaire at 12 months postoperative. Depressive symptoms predicted a lower change score on the KOOS subscales pain, ADL and QOL. These relationships were independent for age, gender and the preoperative score on the KOOS subscale (Table IV).

Influence on patient satisfaction

Hip patients with preoperative anxiety symptoms were less satisfied 12 months postoperatively, compared to patients without anxiety symptoms, about pain reduction, overall result, improvement of ADL and QOL. Hip patients with depressive symptoms were less satisfied about improvement of QOL.

Knee patients with preoperative depressive or anxiety symptoms were both less satisfied about the improvement in QOL (Table V).

Table III Relationship between baseline anxiety or depressive symptoms and changes in HOOS for hip OA patients

	Anxiety symptoms							Depressive symptoms						
	HADS		HADS		Adjusted relationship[a]			HADS		HADS		Adjusted relationship[a]		
Hip	< 8 n = 115	≥ 8 n = 38	< 8 n = 115	≥ 8 n = 38				< 8 n = 103	≥ 8 n = 50	< 8 n = 103	≥ 8 n = 50			
HOOS	12 months postoperative score		Change in score at 12 months vs preoperative			Beta	95% CI	12 months postoperative score		Change in score at 12 months vs preoperative			Beta	95% CI
Pain	84.5 ± 18.9	74.9 ± 25.7	50.5 ± 22.8	44.8 ± 28.4	+	-7.6	(-13.1;-2.1)	85.5 ± 18.3	75.3 ± 24.8	50.3 ± 22.3	46.6 ± 28.2	+	-9.1	(-14.1; 4.0)
Symptoms	57.1 ± 11.5	55.4 ± 12.6	6.6 ± 14.9	8.3 ± 15.1	-	-4.5	(-9.8;0.7)	57.1 ± 11.7	55.7 ± 12.0	5.5 ± 14.7	10.1 ± 15.0	+	-6.2	(-10.9;-1.4)
ADL	77.7 ± 20.2	67.0 ± 25.0	46.6 ± 22.8	37.8 ± 27.9	+	-9.5	(-15.1;-4.0)	78.7 ± 19.9	67.7 ± 24.1	46.4 ± 23.0	40.4 ± 26.7	+	-10.2	(-15.3;-5.1)
Sport	59.7 ± 28.8	51.2 ± 27.3	43.8 ± 29.1	37.3 ± 28.6	+	-9.1	(-17.7;-0.4)	60.7 ± 28.0	51.4 ± 29.0	43.8 ± 28.1	39.1 ± 30.9	-	-4.7	(-12.5;3.2)
QOL	70.0 ± 23.8	56.6 ± 25.7	48.2 ± 26.3	37.0 ± 25.8	+	-11.2	(-18.1;-4.3)	70.4 ± 23.7	58.8 ± 25.8	46.8 ± 26.1	42.5 ± 27.3	+	-9.0	(-15.4;-2.6)

Values are presented as mean ± standard deviation

\+ Significant independent relationship between baseline anxiety or depressive symptoms and change in outcome

\- No significant independent relationship

[a]Relationship between preoperative anxiety or depressive symptoms and change in scores of the HOOS subscales, adjusted for age, gender and preoperative score of the HOOS subscale and unbalanced characteristics (waiting time, HOOS symptoms score and familial depression) between study population and patients lost to follow-up.

Abbreviations: HADS, Hospital Anxiety and Depression Scale; HOOS, Hip disability and Osteoarthritis Outcome Score; ADL, activities of daily living; QOL, quality of life.

Table IV Relationship between baseline anxiety and depressive symptoms and changes in KOOS for knee OA patients

	Anxiety symptoms							Depressive symptoms						
	HADS		HADS		Adjusted relationship[a]			HADS		HADS		Adjusted relationship[a]		
Knee	< 8 n = 114	≥ 8 n = 27	< 8 n = 114	≥ 8 n = 27				< 8 n = 109	≥ 8 n = 32	< 8 n = 109	≥ 8 n = 32			
KOOS	12 months postoperative score		Change in score at 12 months vs preoperative			Beta	95% CI	12 months postoperative score		Change in score at 12 months vs preoperative			Beta	95% CI
Pain	84.2 ± 17.5	75.0 ± 20.3	47.7 ± 21.5	47.4 ± 23.4	-	-6.8	(-14.4;0.8)	85.0 ± 16.1	73.4 ± 22.7	48.3 ± 20.2	45.5 ± 26.8	+	-10.0	(-17.1;-3.0)
Symptoms	79.2 ± 17.0	72.0 ± 18.9	35.2 ± 21.8	38.0 ± 19.4	-	-4.6	(-11.5;2.4)	79.9 ± 16.3	71.1 ± 20.1	35.7 ± 21.7	35.6 ± 20.1	-	-6.4	(-12.9;0.1)
ADL	81.0 ± 18.6	71.4 ± 16.2	42.8 ± 23.6	40.0 ± 20.2	+	-8.3	(-16.0;-0.6)	81.8 ± 17.0	70.6 ± 20.7	42.9 ± 23.0	40.1 ± 23.0	+	-9.7	(-16.8;-2.6)
Sport	45.8 ± 31.1	32.6 ± 27.4	37.6 ± 34.2	22.2 ± 28.3	+	-14.1	(-27.6;-0.6)	44.1 ± 30.8	41.1 ± 31.2	36.0 ± 34.2	30.6 ± 31.8	-	-3.5	(-16.1;9.1)
QOL	69.2 ± 23.5	57.2 ± 25.0	50.1 ± 27.1	47.0 ± 24.7	+	-11.2	(-21.5;-0.8)	69.4 ± 23.3	58.4 ± 25.4	50.4 ± 27.1	46.7 ± 25.0	+	-10.1	(-19.8;-0.4)

Values are presented as mean ± standard deviation

\+ Significant independent relationship between baseline anxiety or depressive symptoms and change in outcome

\- No significant independent relationship

[a]Relationship between preoperative anxiety or depressive symptoms and change in scores of the KOOS subscales, adjusted for age, gender and preoperative score of the KOOS subscale and unbalanced characteristics (gender) between study population and patients lost to follow-up.

Abbreviations: HADS, Hospital Anxiety and Depression Scale; KOOS, Knee injury and Osteoarthritis Outcome Score; ADL, activities of daily living; QOL, quality of life.

Table V Relationship between baseline anxiety and depressive symptoms and patient satisfaction 12 months postoperative

	Hip					Knee				
	<8 (n=117)	≥ 8 (n=41)	Adjusted relationship[a]			<8 (n=115)	≥ 8 (n=26)	Adjusted relationship[a]		
HADS-anxiety				Adjusted OR	95% CI				Adjusted OR	95% CI
Satisfied[b]										
Overall, n (%)	101 (86)	27 (66)	+	0.24	(0.10;0.62)	96 (83)	20 (77)	-	0.64	(0.23;1.83)
Pain reduction, n (%)	105 (90)	29 (71)	+	0.30	(0.11;0.81)	101 (88)	20 (77)	-	0.46	(0.15;1.37)
Improvement in ADL, n (%)	96 (82)	24 (59)	+	0.32	(0.13;0.76)	98 (85)	19 (73)	-	0.47	(0.96;1.06)
Improvement in QOL, n (%)	103 (88)	28 (68)	+	0.22	(0.08;0.59)	103 (90)	17 (65)	+	0.20	(0.07;0.57)
	<8 (n=104)	≥ 8 (n=54)	Adjusted relationship[a]			<8 (n=115)	≥ 8 (n=26)	Adjusted relationship[a]		
HADS-depression				Adjusted OR	95% CI				Adjusted OR	95% CI
Satisfied[b]										
Overall, n (%)	89 (86)	39 (72)	-	0.44	(0.18;1.05)	92 (80)	24 (92)	-	0.65	(0.24;1.76)
Pain reduction, n (%)	93 (89)	41 (76)	-	0.38	(0.14;1.01)	96 (83)	25 (96)	-	0.56	(0.90;1.00)
Improvement in ADL, n (%)	84 (81)	36 (67)	-	0.58	(0.26;1.31)	94 (79)	23 (88)	-	0.50	(0.19;1.34)
Improvement in QOL, n (%)	91 (88)	40 (74)	+	0.37	(0.14;0.96)	97 (84)	23 (88)	+	0.35	(0.13;0.98)

+ Significant independent relationship between baseline anxiety or depressive symptoms and change in outcome

- No significant independent relationship

(All patients who completed baseline and the 12-month measurement were included in this analysis)

[a]Relationship between preoperative anxiety or depressive symptoms and patient satisfaction, adjusted for age, gender, and unbalanced characteristics (waiting time, HOOS symptoms score and familial depression) between the study population and patients lost to follow-up.

[b]Satisfaction was scored on a 5-point Likert scale. Values were dichotomised: very unsatisfied, unsatisfied and moderately satisfied were classified as unsatisfied; and satisfied and very satisfied were classified as satisfied.

Abbreviations: HADS; Hospital Anxiety and Depression Scale. ADL, activities of daily living; QOL, quality of life.

DISCUSSION

We found in this study a high prevalence of anxiety and depressive symptoms in a population with end stage hip and knee OA. After surgery a significant decrease of the prevalence of anxiety and depressive symptoms for both hip and knee patients was seen. In hip as well as knee patients, preoperative depressive symptoms predicted a lower PRO after surgery. Hip and knee patients with preoperative anxiety or depressive symptoms were less satisfied postoperatively.

We hypothesized that, because of the close relationship between psychological symptoms and pain and disability, the prevalence of psychological symptoms would be high in end-stage hip and knee OA patients. Preoperatively, we found a higher prevalence of depressive symptoms in hip than in knee OA patients. This might be a result of the difference in ability to perform their ADL preoperatively. But to confirm this hypothesis, more research needs to be done.

Compared to other chronic diseases the prevalence of depressive symptoms in hip OA patients was relatively high (33.6% compared to 16-24% in patients with coronary heart disease, diabetes or breast cancer) (27-29). The prevalence of anxiety symptoms was relatively low in our population compared to other chronic diseases (27-29). However, it should be mentioned that prevalence of depressive and anxiety symptoms is dependent of age, gender, and disability.

The HADS has been used in previous studies screening OA populations, but these studies screened heterogeneous populations existing of patients with hip, knee, ankle or CMC-1 OA. (30-31) This is the first study screening homogeneous hip and knee OA populations separately. That means our data are unique, and therefore it was not possible to compare our results to a completely similar population. In a general Dutch population of similar age mean HADS anxiety and depression scores of 3.9 ± 3.6 and 4.6 ± 3.6, respectively, were reported (22).

So, it appears that the prevalence of depressive symptoms is relatively high in our population and the prevalence of anxiety symptoms is somewhat lower.

The results of the study also confirm our second hypothesis that, when pain and disability decreases after THA or TKA, the prevalence of psychological symptoms also decreases. The decrease was larger in hip than in knee patients. At 12 months postoperative no further decrease was seen in the prevalence of anxiety and depressive symptoms compared to 3 months postoperative. So it seems that there is a significant improvement in these factors that is maintained until at least 12 months. In a systematic review we evaluated the influence of psychological symptoms on the outcome of THA or TKA. We found that global preoperative mental health and pain catastrophizing do influence the outcome after THA or TKA (17). Less convincing evidence was found for the influence of anxiety or depressive symptoms on outcome. Our systematic review

did not elucidate whether the influence of psychological symptoms differed between knee and hip patients. However, results of the present study suggest that the influence of anxiety or depressive symptoms on PRO does differ after THA and TKA. For hip patients, preoperative anxiety symptoms have more influence on these outcomes, whereas for knee patients preoperative depressive symptoms have more influence on outcome 12 months post-surgery.

The identification of individuals at risk for poor post-surgical outcome may be important for optimizing the results after THA and TKA. Treating patients with anxiety disorders or depression with psychotherapy before surgery may possibly lead to better results after THA or TKA. Additional studies are required to explore these hypotheses.

Some limitations of this study need to be addressed. First, the percentage patients lost to follow-up was relatively high (30%). The hip patients differed on the time spent on the waiting list (shorter) and the prevalence of familial depression (higher) of those lost to follow-up. The knee OA patients were less often female. However, the prevalence of anxiety and depressive symptoms was similar of the study patients and those lost to follow-up. So we assume that selection bias did not affect our results and conclusions.

Second, we did not assess the number of needed patients before the start of our study. When we started our study no data of adequate studies were available to base our calculation on, and consequently our sample size calculation would be based on assumptions. After data collection we performed a power calculation. We have used the pain, ADL and QOL subscales of the HOOS and KOOS score after 12 months to assess the power of the different comparisons. The range of the power to determine a significant difference was 0.80 – 0.98 for the different subscales.

Third, preoperative measurements were not taken at a fixed time point. The length of time patients were on the waiting list for surgery varied. The present study does not allow to conclude whether the prevalence of anxiety or depressive symptoms changes during the waiting period. Furthermore, we did not adjust our analysis for co-morbidities. As shown in a recent study of Hawker et al. is co-morbidity an important predictor for TJA outcome (32). The current design of the study was approved by the local Medical Ethics Committee. Because the data was collected by questionnaires signed informed consent was not required. Consequently we had no permission to use data of medical records of the patients. Hence we had no data of co-morbidity of patients. This could have influenced our results.

Finally, having anxiety or depressive symptoms is not the same as having an anxiety disorder or depression. The HADS questionnaire is a tool for screening on anxiety or depressive symptoms. Having an anxiety disorder or depression has to be diagnosed by a specialist. Therefore, we assume that the prevalence of anxiety or depressive symptoms is an overestimation of the actual prevalence of anxiety disorders or depression.

In conclusion, the results of the present study show a high prevalence of depressive symptoms in patients with end-stage hip and knee OA compared to other chronic diseases. The prevalence of depressive symptoms was higher in hip than in knee patients and the influence of anxiety or depressive symptoms on the postoperative outcome differed after THA and TKA. At twelve months post-surgery, the prevalence of anxiety or depressive symptoms was significantly decreased in both hip and knee patients. However, patients with preoperative anxiety or depressive symptoms had worse outcomes twelve months after THA and TKA than patients without these symptoms. The findings of our study should be confirmed in other populations with end stage knee or hip OA indicated for a total joint replacement.

Author contributions

T. Duivenvoorden designed the study, acquired data, performed data-analysis and critically revised the manuscript, M.M. Vissers designed the study, acquired data, performed data-analysis and wrote the manuscript., J.J.V. Busschbach shared his expertise on the field of PROs and critically reviewed the manuscript, J.A.N. Verhaar designed the study and critically reviewed the manuscript, T. Gosens and R.M. Bloem coordinated the study in their centre and critically reviewed the manuscript, S.M.A. Bierma-Zeinstra shared her expertise on the field of OA and critically reviewed the manuscript, M. Reijman designed the study and critically revised the manuscript.

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Conflict of interest

The authors report no conflict of interest

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Chapter 8

General discussion

GENERAL DISCUSSION

This thesis focuses on the effects of non-operative and surgical treatment of patients with varus medial knee osteoarthritis (OA). The main findings and limitations of the different studies have been discussed in the previous chapters. In this chapter the results of this thesis are discussed in a broader perspective and suggestions for future research are made.

Patient selection

To get satisfactory results of the treatment in patients with varus medial knee OA, patient selection and proper indication are the most important and challenging steps. The treatment of varus medial knee OA differs considerably between hospitals in the Netherlands and the 7-years-old Dutch guideline, which is somewhat ambiguous. (1) For this reason this chapter discusses a new treatment algoritm for patients with varus medial knee OA based on the most recent literature.

Traditionally, the first step in the treatment of varus medial knee OA is a non-operative approach, advising patients to change their demanding activities, reduce weight, start with physical therapy (excersises) or take pain killers. If needed an orthoses may be prescribed. When the pain progresses or is not sufficiently controlled with a non-operative treatment anymore, surgical treatment should be considered.

Based on recent literature, severity of pain, limitation of activity level and radiological severity of OA are useful parameters to select patients who might benefit from conservative treatment and those who will benefit more from surgical treatment. (2, 3, 4) In general patients with mild - moderate pain and mild degenerative changes on the radiographs are suitable for starting with a conservative treatment. For patients with more severe pain and/or more advanced signs of OA on the radiograph, surgical treatment is more appropriate (Fig. 1).

The two most important options for surgical treatment of OA are re-alignment procedures which change the mechanical axis of the leg and implantation of a joint prosthesis, either total knee replacement or unicompartimental joint implants. In the surgical treatment of varus medial knee OA a joint prosthesis is currently more often chosen than a re-alignment procedure as the high tibial osteotomy (HTO). There may be many reasons for this preference. Suggested as main reasons are decreased experience with the realignment technique, faster recovery after joint prosthesis and a higher risk for complications in osteotomies. However, results after unilateral (UKA) or total knee arthoplasty (TKA) in patients with mild to moderate knee OA seems to be inferior to re-alignment procedures in young patients. (3,4)

Recent studies have shown that patients with mild varus medial knee OA have better and more longstanding results, than patients operated in a later stage of the disease

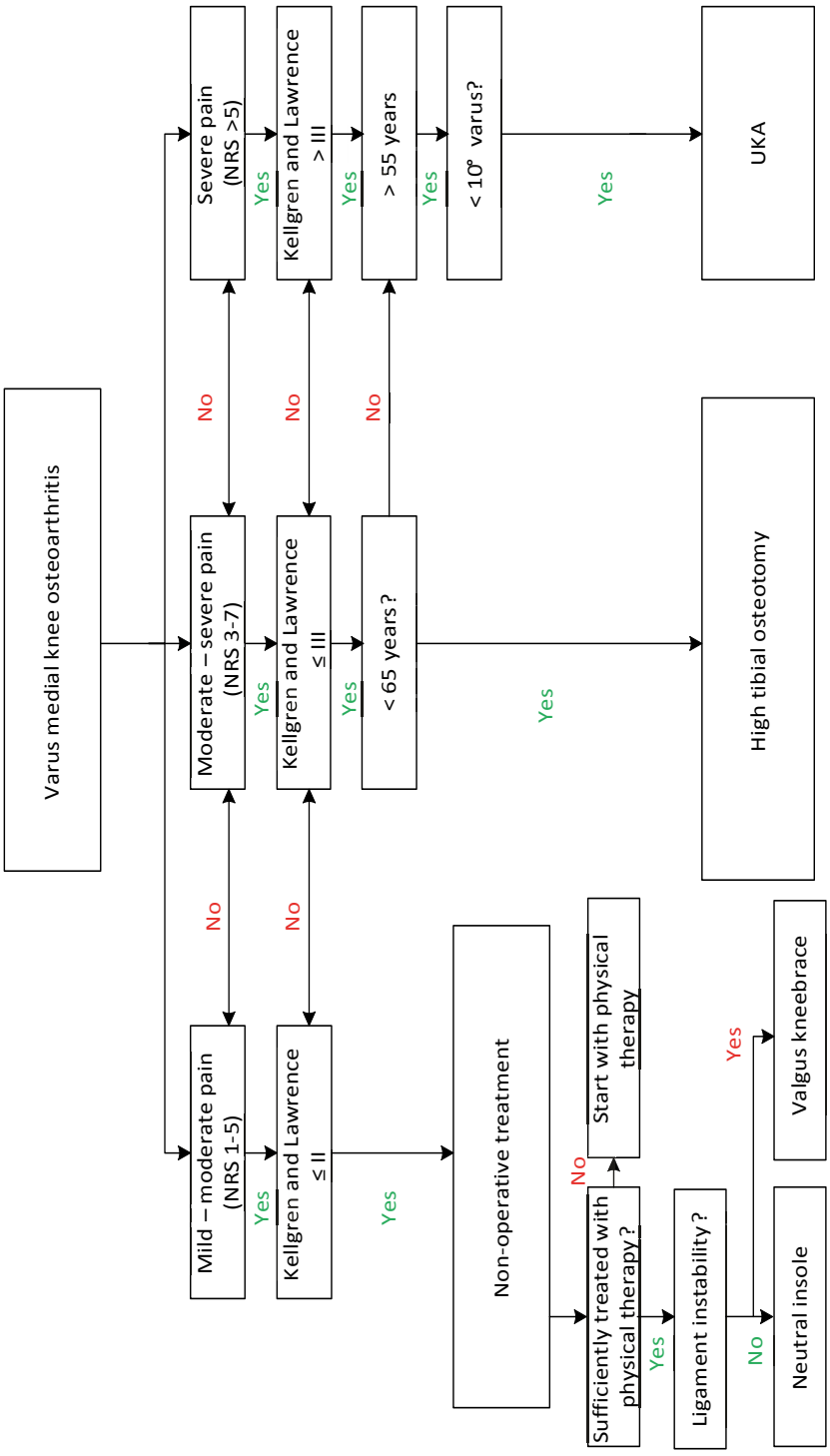

Fig. 1. Treatment algorithm for patients with varus medial knee osteoarthritis.
Abbreviations: VAS, Visual Analogue Scale; UKA, unicompartmental knee arthroplasty.

after an HTO. (5,6) Hence the question arises whether it would be better to perform an HTO in an early stage of the osteoarthritic process and favourably changing the progression of the osteoarthritis. However, currently there is no literature to support this hypothesis. A randomized controlled trial will be necessary to answer this question.

The non-operative treatment of varus medial knee OA

In the non-operative treatment of patients with varus medial knee OA, who do not have instability of the knee a neutral insole should be preferred. There is strong evidence that patients can be better treated with a neutral insole than with a laterally wedge insole. (7-8) Although the working mechanism of insoles is still not fully understood, results of a Cochrane meta-analysis, a placebo-controlled trial and gait analysis studies do not show any benefits of the lateral wedge. However literature shows that it's better to treat patients with a laterally wedged insole than without treatment. (7-10)

A valgus knee brace is the most appropriate treatment for patients with complaints of mediolateral-instability of the knee. A Cochrane review shows slightly better overall results of a valgus knee brace in comparison with a neutral knee brace. However patients wearing a neutral knee brace report more reduction of instability of the knee. Knee braces often give side effects such as skin irritation and a low adherence. (11) Valgus knee bracing is related to more brace positioning problems and slipping. (7)

The surgical treatment of varus medial knee OA

In the 1980s HTO was estimated to constitute about 30% of the primary knee reconstruction surgery. Incidence of osteotomies, however, has decreased significantly because of the high clinical success of the joint implants. Nowadays, in 94.5% of the patients with varus medial knee OA going for surgery, a UKA was performed in the USA. An HTO is more frequently performed in Europe. However also in Europe the number of HTOs has decreased by one third in the last decade. The introduction of the opening-wedge technique together with new fixation techniques have led to a renewed interest, especially in Europe. (12,13)

One of the most challenging steps in the surgical treatment of varus medial knee OA is selecting an appropriate treatment. Besides pain, activity level and radiographical severity of OA, age of the patient is an important patient characteristic for this selection. Patients can be treated conservatively at any age. However, concerning the surgical treatment the ideal candidate for an HTO is a relatively young patient. UKA is mostly performed in patients older than 55 years. Younger patients are in general more active and have a higher life expectancy and therefore have a higher risk on revision surgery. (14) When HTO or UKA fails, patients are mostly converted to a TKA. It seems that HTO does not influence the clinical results after TKA very much, however there are a

limited number of publications about this topic. (15,16) Previous UKA influence the clinical results after TKA negatively. Studies show that patients undergoing revision surgery after UKA, have a reduced ROM, lower PROMs and are less satisfied compared to patients undergoing primary TKA. (17) A Swedish Implantation Register based study of 1276 patients concludes that the survival of a TKA after previous reconstructive surgery is compromised by HTO as well as UKA, however no difference between HTO and UKA was found. (18)

So, because of the risk on revision surgery and the negative influence of UKA on the results of a TKA, for young patients an HTO seems to be more appropriate than a UKA.

There is only limited literature about the most appropriate treatment for obese patients. No relation has been found between BMI and survival or clinical outcome of UKA, except for extreme obesity. (19,20) The influence of BMI on the outcome of HTO has not been studied yet. (21)

There is a lot of debate about the preferred HTO-technique. The actual trend moves from the traditional closing-wedge technique to the opening-wedge technique. There is no literature that supports this trend. A meta-analysis concluded that there is no difference in outcome between closing- and opening-wedge technique in the first postoperative years. (22) Moreover an RCT did not found a difference in PROMs or radiographic alignment between both techniques after 6 years. However, in this study opening-wedge HTO was associated with more complications, but closing-wedge HTO was associated with more early conversions to total knee arthroplasty. (23) Increasing surgeons' experience with the procedure and standardisation of the technique might lead to a reduction of complications.

Psychological factors related to satisfaction after treatment

Another important factor, discussed in this thesis, for getting satisfactory results are psychological factors. Psychological factors that contribute to patient satisfaction after knee arthroplasty are preoperative anxiety and depressive symptoms, and fulfilled expectations. Chapters 6 and 7 focus on the relationship between these psychological factors and the outcome of knee arthroplasty. The prevalence of psychological symptoms is high in patients with end-stage OA of the knee. The prevalence of these symptoms in knee OA patients is comparable with other chronic diseases such as coronary heart disease, diabetes or breast cancer.

After surgery a significant decrease of the prevalence of these symptoms is seen. The effect of a surgical procedure on these psychological symptoms persists for at least 1 year. However, patients with preoperative anxiety and depressive symptoms are less often satisfied than patients without these symptoms 1 year after surgery. This relationship was seen even in those whose depressive and anxiety symptoms decreased. The influence of anxiety or depressive symptoms on satisfaction does differ between total hip arthroplasty (THA) and TKA. For hip patients, preoperative anxiety symptoms have more influence on satisfaction, whereas for knee patients preoperative depressive symptoms have more influence on outcome 12 months post-surgery. A clear explanation for this difference is still not found. The question arises whether it's better to first treat the psychological symptoms or the knee OA. But to find an answer to this question more research is needed. (24,25)

Another psychological factor related to the outcome of surgical treatment of varus medial knee OA are preoperative expectations. In this thesis we described that unfulfilled expectations lead to more dissatisfaction. It remains unclear whether high expectations lead to dissatisfaction. In our systematic review for these frequently assumed relationships we only found limited and conflicting evidence of low to moderate quality. Other studies suggest that greater fulfillment of expectations led to higher postoperative satisfaction in patients undergoing total hip replacement, rotator cuff tear repair, lumbar- or cervical spine surgery. (26, 27, 28) However in patients under going carpal tunnel release preoperative expectations might not correlate with patient satisfaction. (29)

Previous studies have shown that many patients overestimate their postoperative improvement. (30-32) We also know that it is possible to modify patient expectations with preoperative education. (33) Before we conclude that satisfaction rates can be raised with extra preoperative information much more research is needed.

Limitations of this thesis

There are some limitations to this thesis, which need to be addressed. For the non-operative treatment of varus medial knee OA, there is a lack of studies with a long term follow up. Long-term follow-up studies are important when studying a chronic condition as varus medial knee OA, which slowly progresses. So in our Cochrane review presented in this thesis about the non-operative treatment of varus medial knee OA, we could only draw conclusions about the short-term effects of the different interventions.

In our second systematic review about the influence of preoperative expectations on satisfaction after TKA a very limited amount of low quality evidence was found. Therefore, we have to be very careful in drawing conclusions. However, there is an increasing number of publications and in the near future we expect more scientific attention for this important topic.

The results of the survival analyses of the HTO studies in this thesis may be biased by a "decision-bias as we have used conversion to a joint prosthesis as endpoint in the survival analyses of our prospective follow-up study. The decision to convert a patient with an HTO to a joint implant depends on the opinion of patient and surgeon. It would have been better to use a more unbiased outcome, such as the OARSI-research definition for patients in need for joint replacement surgery. (34) This definition is based on PROMs and radiological signs of OA. In our own prospective study we did not use this definition because it was published before. (23)

We have used this OARSI-research definition in our cross-sectional follow-up study, however this study had a retrospective design and was therefore liable to selection bias. Because of a lack of baseline data we could not adjust for between group differences at baseline properly. So this study is less suitable for comparing both HTO-techniques. However, this study measures accurately the survival of all HTO procedures in our clinic.

To perform a more accurate estimate of the survival and to compare both HTO-techniques in a large group of patients, a register-based study should be performed. (16, 17) However there is not such a register in the Netherlands yet.

Recommendations for future research

In this thesis we evaluated the effects of different treatment modalities for varus medial knee OA. Many studies evaluating treatment results focus on the short-term effects, often within one year. The progression of OA, however, is mostly slow and for that reason long term follow-up studies are more important. There is a lack of follow-up studies to determine the long term treatment effect of non-operative interventions. To determine the effect of non-operative treatment on the progression of OA, more research needs to be done. The introduction of improved cartilage imaging technique might result in new evidence.

The survival analyses in long term follow up studies are also frequently biased. To compare the survival rate of different HTO-techniques adequately, a prospective long term follow-up study analyzing the survival with the OARSI-criteria should be performed. (34)

We found that preoperative anxiety and depressive symptoms, and unfulfilled expectations were related to patient satisfaction. Moreover preoperative anxiety and depressive symptoms were related to lower PROs postoperatively. Treating patients with anxiety disorders or depression before surgery may possibly lead to better results after TKA. However, additional studies are required to support these hypotheses.

To help patients to acquire more realistic expectations, they need more detailed preoperative education about the outcome after TKA. Shared decision making may be a valuable technique. Today's patients have high expectations regarding the outcome after TKA and in general they overestimate their postoperative possibilities. (30, 31, 32) Moreover, it should be noticed that surgeons also overestimate the functional improvement of their patients. (31) Extra and more detailed preoperative education could manage these high expectations. However, further investigations need to be done first to determine the effectiveness of education on expectations and the postoperative satisfaction in patients undergoing TKA.

It remains unclear, whether these relationships between psychological variables and outcome after TKA can be extrapolated to patients undergoing other types of knee surgery.

Clinical implications

The results of this thesis can be used to optimize the outcome of the non-operative and surgical treatment of varus medial knee OA.

According to the non-operative treatment valgus knee brace- and insole therapy are both effective in terms of improved PROs. A neutral insole is as effective as a laterally wedged insole. Patients without instability of the knee might benefit more from insole therapy because of the higher compliance. Although patients experience beneficial effects of brace and insole therapy, no clear biomechanical effect has been shown. No difference in improved PROs between laterally wedged insoles and neutral insoles have been found in literature. (8, 10) In conclusion, the most suitable treatment options for patients with varus medial knee OA are a valgus knee brace in patients with complaints of knee instability and neutral insoles in patients without such complaints.

According to the surgical treatment of varus medial knee OA closing-wedge and opening-wedge HTO both has good mid-term results. After these procedures there is no need for a TKA in 85% of the patients during the first six years. Moreover, the survival rate of the current HTO might already have been improved as result of the development of improved fixation techniques.

In addition, physicians should be aware that preoperative psychological factors may lead to worse outcomes after surgery.

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Chapter 9

Summary

SUMMARY

Osteoarthritis (OA) is one of the most common joint disorders in the Western population, which causes pain, stiffness, loss of function and disability. In patients with OA the cartilage, located at the ends of long bones, is damaged. OA is most prevalent in the knee joint. In case of varus malalignment the medial compartment of the knee is most commonly affected. The initial treatment of varus medial knee OA is non-operative, and consists of patient education, weight reduction, physical therapy, use of orthoses, intra-articular steroid injections and if needed pain medication.

Orthoses are intended to unload the medial compartment of the knee. Not all patients experience benefit of orthoses and therapeutic effect vary between studies. Therefore the first aim of this thesis was to evaluate the therapeutic effect of orthoses in the treatment of varus medial knee OA.

When non-operative treatment fails surgical treatment will mostly be considered. The surgical treatment consists of valgus high tibial osteotomy (HTO), unilateral knee arthroplasty (UKA) or a total knee arthroplasty (TKA). In case of isolated medial knee OA, a HTO or UKA is mostly the preferred intervention.

OA is a chronic disease which could progress over years. One of the goals of a HTO is to slow down disease progression and to postpone the need for a TKA as long as possible, by unloading the diseased compartment. Multiple studies comparing different HTO techniques are published with a 1 or 2 year follow-up, however there is a lack of prospective long term results, especially for the relatively new opening-wedge technique. Therefore the second aim of this thesis was to study the long term results of both closing- and opening-wedge HTO.

In general, results after TKA and HTO are good. However, a subset of patients has suboptimal improvement in pain, physical functioning, and quality of life and are not satisfied with their postoperative result. The explanation of these suboptimal results is not always completely physical. Psychological factors, such as anxiety and depressive symptoms or preoperative expectations, could be related to these suboptimal results. The ultimate goal of all orthopaedic procedures is patient satisfaction. Identification of modifiable risk factors for dissatisfaction could contribute to optimization of this important outcome. Therefore the final question addressed in this thesis is whether the different psychological factors are related to patient satisfaction after TKA.

In Chapter 2 we summarized the literature about the therapeutic effect of orthoses in the treatment of knee OA. In this Cochrane review 13 studies including 1356 patients were included. Overall, quality of evidence found in these studies was moderate or low. The follow-up time varied from 1 – 24 months. No long term follow-up study determining the influence on progression of OA has been performed. We concluded that a valgus knee brace and a laterally wedged insole both have small beneficial effects

in terms of improvement of pain, symptoms and functional outcome in patients with varus medial knee OA. No certain difference between both interventions was seen in this Cochrane review. The long term adherence was low for both intervention, especially the knee brace group. Moreover, there might be no difference in therapeutic effect between a laterally wedged insole and a neutral insole.

In Chapter 3 we present the results of our biomechanical evaluation of the valgus knee brace and laterally wedged insole. In this study we performed gait analysis of patients with varus medial knee OA treated with one of these two interventions for six months. Gait analysis was performed at baseline and after six weeks of wearing the intervention. In this study we found that wedged insoles only unload the medial compartment at baseline. At baseline a reduction of the peak Knee Adduction Moment (surrogate measure of the medial load) of 3.6% was seen. No biomechanical alteration was seen after 6 weeks of wearing the insole. Valgus brace therapy did not result in any biomechanical alteration at baseline and after 6 weeks. So in this study we could not confirm that the beneficial effects of orthoses can be explained by a certain dynamical alteration, in other words a changed gait pattern.

In Chapter 4 the six year results of our RCT comparing closing and opening-wedge HTO are presented. After six year opening-wedge HTO was associated with more complications (37% vs 9%), however closing-wedge HTO was associated with more early conversions to TKA (25% vs 8%). Of the patients who had no conversions to a TKA, no difference in clinical outcome and radiological alignment was seen.

We present in Chapter 5 the results of a retrospective assessment of all patients who underwent a HTO in our clinic. We found in this study of 412 patients more adverse events in a closing-wedge group than in an opening-wedge group (28% versus 14%). Hardware was removed in 48% of the closing-wedge HTO's and 71% of the opening-wedge HTO's. Another major adverse event was iliac crest pain, caused by harvesting the bone for spongiosaplasty (19,7% of the patients in the opening-wedge group). The survival of the opening-wedge group was significantly better than the closing-wedge group, when conversion to a prosthesis was taken as endpoint, however an equal number of patients were in need for a UKA or TKA in both groups.

We summarized the literature about the influence of preoperative expectations on patient satisfaction after TKA in Chapter 6. In this systematic review 3 high and 5 low quality studies were included. Although it is a frequently assumed relation, we conclude in this review that there is only limited or conflicting evidence that high expectations lead to more dissatisfaction. However, moderate evidence was found that unfulfilled expectations lead to more dissatisfaction.

In Chapter 7 we present the results of our multicenter study, in which we examined the prevalence of two important psychogical symptoms, namely depressive and anxiety symptoms in patients with end-stage OA of the knee. These psychological symptoms

were measured with the Hospital Anxiety and Depression Scale, a widely used validated questionnaire. Besides, we determined the influence of these symptoms on the outcome of TKA. We found in this study a high prevalence of anxiety (20.3%) and depressive symptoms (22.7%) in a population with end stage knee OA. After surgery a significant decrease of the prevalence of these symptoms was seen. The prevalence of anxiety symptoms decreased to 14.8% and of depressive symptoms to 11.7%. Preoperative depressive symptoms predicted lower patient reported outcomes after surgery. Patients with preoperative anxiety or depressive symptoms were less satisfied postoperatively.

The main topics of this thesis are placed in a broader perspective in Chapter 8. The limitations of this thesis and some recommendations for future research are discussed in this chapter.

Appendices

Nederlandse samenvatting

NEDERLANDSE SAMENVATTING

Artrose is één van de meest voorkomende aandoeningen van de gewrichten in de Westerse populatie en veroorzaakt pijn, stijfheid, verlies van beweeglijkheid en invaliditeit. Bij patiënten met artrose is het kraakbeen beschadigd, wat zich op de uiteinden van de botten bevindt. Van alle gewrichten komt artrose het vaakst in de knie voor. Knie artrose wordt ook wel gonartrose genoemd. In het geval van een varus beenas is het mediale compartiment van de knie het vaakst aangedaan. De initiële therapie van variserende mediale gonartrose is conservatief en bestaat uit voorlichting, gewichtsreductie, fysiotherapie, gebruikt van ortheses, intra-articulaire steroïd injecties en wanneer nodig pijnstillers. Ortheses zijn bedoeld om het mediale compartiment van de knie te ontlasten. Niet iedere patiënt ervaart voordelen van ortheses en het therapeutische effect varieert tussen de verschillende studies. Daarom is het eerste doel van dit proefschrift om de therapeutische effecten van ortheses te evalueren in de behandeling van variserende mediale gonartrose.

Chirurgische therapie wordt meestal overwogen, wanneer conservatieve therapie faalt. De chirurgische therapie bestaat uit een valgiserende hoge tibiakop osteotomie (HTO), unilaterale knieprothese (UKP) of totale knieprothese (TKP). In het geval van geïsoleerde mediale gonartrose is een HTO of UKP de interventie van voorkeur.

Artrose is een chronische ziekte welke progressief is over jaren. Het doel van een HTO is om de progressie van deze ziekte te remmen en een TKP zolang mogelijk uit te stellen door het aangedane compartiment te ontlasten. Er zijn meerdere studies gepubliceerd die verschillende HTO technieken vergelijken met een follow-up van 1 tot 2 jaar. Er is echter een gebrek aan prospectieve lange termijn resultaten, met name voor de relatief nieuwe open wig techniek. Daarom was het tweede doel van dit proefschrift om de lange termijn resultaten van zowel de gesloten als open wig HTO te bestuderen.

Over het algemeen zijn de resultaten na een TKP en HTO goed. Een gedeelte van de patiënten geeft echter aan een suboptimale verbetering van de pijn, het functioneren en de kwaliteit van leven te ervaren en zijn niet tevreden met het postoperatieve resultaat. De verklaring voor deze suboptimale resultaten is niet altijd volledig fysiologisch. Psychologische factoren, zoals angst en depressieve klachten of de preoperatieve verwachtingen die patiënten hebben, kunnen gerelateerd zijn aan deze suboptimale resultaten. Een belangrijk doel van alle orthopaedische procedures is patiënttevredenheid. Het identificeren van modificeerbare risicofactoren voor ontevredenheid kan bijdragen aan optimalisatie van deze belangrijke uitkomstmaat. Daarom was de laatste onderzoeksvraag in dit proefschrift of de eerdergenoemde verschillende psychologische factoren gerelateerd zijn aan patiënttevredenheid na een TKP.

In hoofdstuk 2 hebben we de literatuur over het therapeutisch effect van ortheses in de behandeling van gonartrose samengevat. In dit Cochrane review zijn 13 studies met

in totaal 1356 patiënten geïncludeerd. Over het algemeen was de kwaliteit van de studies gemiddeld of laag. De follow-up tijd varieerde tussen de 1 en 24 maanden. Er is tot op heden nog geen studie verricht met een lange termijn follow-up. De conclusie van dit review was dat een valgiserende kniebrace en een inlegzool met laterale wig beide een klein klinisch effect hebben bij patiënten met variserende mediale gonartrose. Er werd geen duidelijk verschil tussen beide interventies gezien. De therapietrouw was laag voor beide interventies en vooral in de kniebrace groep. Verder lijkt er geen verschil in therapeutisch effect tussen een inlegzool met laterale wig en een neutrale inlegzool te zijn.

In hoofdstuk 3 presenteren we de resultaten van ons biomechanisch onderzoek. In dit onderzoek vergeleken wij middels ganganalyse het biomechanische effect van een valgiserende kniebrace en een inlegzool voorzien van laterale wig, bij patiënten met variserende mediale gonartrose. Ganganalyse werd verricht bij start van de studie en na 6 weken dragen van de interventie. In dit onderzoek ontdekten wij dat in het geval van de inlegzool het mediale compartiment alleen op baseline ontlast werd. Op baseline vonden wij een afname van de peak Knee Adduction Moment (surrogaat maat voor belasting van het mediale compartiment) van 3.6%. Na 6 weken werd er geen biomechanische verandering meer gezien bij deze patiënten. Het dragen van een valgiserende kniebrace resulteerde helemaal niet in enige biomechanische verandering op baseline en na 6 weken. In dit onderzoek kunnen wij de positieve effecten van deze 2 ortheses dus niet bevestigen met een duidelijke dynamische verandering, oftewel een ander looppatroon.

In hoofdstuk 4 hebben we de 6 jaar resultaten van onze RCT gepresenteerd, waarin gesloten- met open wig HTO werd vergeleken. Na 6 jaar was de open wig HTO geassocieerd met meer complicaties (37% vs 9%), echter de gesloten wig HTO was geassocieerd met meer vroege conversies naar een TKP (25% vs 8%). In de groep patiënten die geen TKP heeft gehad werd geen verschil in klinische uitkomstmaten en radiologische alignement gezien.

We presenteren in hoofdstuk 5 de resultaten van het retrospectieve onderzoek, waarin we alle patiënten hebben geanalyseerd die ooit een HTO hebben gehad in het Erasmus MC. In dit onderzoek van 412 patiënten werden meer adverse events in de gesloten wig groep gevonden, dan in de open wig groep (28% vs 14%). Het osteosynthesemateriaal werd bij 48% van de patiënten met een gesloten wig HTO verwijderd en bij 71% van de open wig groep. Een ander veel voorkomend adverse event was pijn t.h.v. de crista iliaca, veroorzaakt door de spongiosaplastiek (19,7% van de patiënten in de open wig groep). De overleving was significant beter in de open wig groep wanneer conversie naar een prothese als afkappunt werd genomen. Het aantal patiënten met een indicatie voor een prothese wat in beide groepen echter gelijk.

We hebben in hoofdstuk 6 de invloed van preoperatieve verwachtingen op de patiënttevredenheid na een TKP geëvalueerd. Ondanks dat het bestaan van deze relatie vaak aangenomen wordt, concluderen wij in dit systematic review dat er slechts een beperkte hoeveelheid en tegenstrijdig bewijs is voor de bewering dat hoge verwachtingen tot meer ontevredenheid leidt. Er werd wel bewijs van een gemiddelde kwaliteit gevonden voor de bewering dat niet een vervulde verwachting tot meer ontevredenheid leidt.

In hoofdstuk 7 presenteren wij de resultaten van ons multicenter onderzoek, waarbinnen wij de prevalentie van 2 belangrijke psychische klachten, namelijk angst en depressieve klachten, bij patiënten met eind stadium gonartrose onderzochten. Deze psychische klachten werden gemeten met de Hospital Anxiety and Depression Scale, een veelgebruikte en gevalideerde vragenlijst. Daarnaast onderzochten we de invloed van deze symptomen op de uitkomst na een TKP. We vonden in dit onderzoek een hoge prevalentie van angst (20,3%) en depressieve klachten (22,7%) in een populatie met patiënten met eind stadium gonartrose. Na de operatie werd er een grote afname van de prevalentie van deze klachten gezien. De prevalentie van angstklachten daalde naar 14.8% en van depressieve klachten naar 11,7%. Preoperatieve depressieve klachten gingen gepaard met lagere patiënt gerapporteerde uitkomstmaten na de operatie. Patiënten met preoperatieve angst- of depressieve klachten waren na de operatie minder vaak tevreden.

De belangrijkste onderwerpen uit dit proefschrift worden in hoofdstuk 8 in een breder perspectief geplaatst. De beperkingen van dit proefschrift en een aantal aanbevelingen voor toekomstig onderzoek worden verder nog besproken in dit hoofdstuk.

Appendices

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Daarnaast heeft iedere voetballer natuurlijk een zaakwaarnemer (paranimf) nodig. Hoewel er tegenwoordig steeds meer verhalen de ronde gaan over malafide zaakwaarnemers, die vooral op eigen geldelijk gewin uit zijn, kan ik dat over mijn zaakwaarnemers zeker niet zeggen.

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De logistiek in een Academisch Ziekenhuis is niet altijd even eenvoudig en daarom is het fijn om terug te kunnen vallen op secretaresses die wèl weten hoe de zaken georganiseerd zijn. Beste Simone, ik heb door de jaren heen geen logistieke vraag weten te bedenken, die jij met al jouw ervaring niet kon beantwoorden. Hartelijk dank voor alle hulp die je me hebt geboden bij het regelen van afspraken en velerlei andere administratieve zaken. Natuurlijk ook veel dank aan Suzanne en Esther. Esther, je bent alweer even weg uit het ziekenhuis, maar door alles wat je gedaan hebt mag jouw naam hier zeker ook niet ontbreken.

Graag wil ik ook alle stafleden van de afdeling Orthopaedie uit het Erasmus MC bedanken. Hartelijk dank aan alle stafleden die mij van raad en daad voorzien hebben tijdens mijn onderzoekstijd. Daarnaast hartelijk dank aan alle studie-operateurs voor hun deelname aan de HTO-trial.

De vergelijking doortrekken naar een vroegere amateurclub is misschien wat lastig in een dankwoord. Niemand wil de twijfelachtige eer van een amateurclub toebedeeld krijgen.

Toch wil ik graag een groep mensen bedanken waar het allemaal begonnen is; de vakgroep Orthopaedie uit het Reinier de Graaf Gasthuis. Bij jullie heb ik kennisgemaakt met de Orthopaedie en mijn eerste ervaring binnen de Orthopaedie op mogen doen. Daarnaast wil ik jullie danken voor jullie participatie in het "depressie-onderzoek" (hoofdstuk 7).
Uit het Reinier de Graaf Gasthuis wil ik ook graag de arts-assistenten en stafleden van de afdeling Chirurgie bedanken. Tijdens mijn vooropleiding gaven jullie mij de tijd en ruimte om dit proefschrift af te ronden. Daarnaast heb ik een ontzettend mooie en leerzame tijd met jullie gehad.

De boog kan natuurlijk niet altijd gespannen staan. Daarom is het fijn om een groep vrienden en familie om je heen te hebben, waarmee je je vrije tijd in kunt vullen. Een speciaal woord van dank richting mijn jeugdvrienden van de [KIJKDOOS]. Wij kennen elkaar al sinds de brugklas. En ook al kiest iedereen zijn eigen weg, het is ontzettend leuk dat wij elkaar nog steeds met enige regelmaat zien. Daarnaast wil ik ook de heren van Heerendispuut Scaevola en mijn voetbalmaatjes; Elmo, Jord, Steev en Arjan bedanken voor alle gezelligheid. Het is iedere keer weer een feest om met jullie naar Feyenoord te gaan.

Pap, mam, jullie hebben de afgelopen jaren heel vaak voor mij klaar gestaan. Helpen met verhuizen, klussen, altijd kon ik op jullie rekenen. Dit geldt natuurlijk ook voor mijn broer Bram, "kleine" zusjes Marjolein en Lysanne, Cintha, Frank en Jeroen. Heel veel dank voor alles wat jullie voor mij gedaan hebben en ook voor de getoonde interesse in mijn onderzoeken. Ik weet dat ik er door drukte de afgelopen jaren wat minder vaak bij ben geweest, maar beloof dat ik dit na mijn promotie dubbel en dwars in zal halen.

En als allerlaatste, maar natuurlijk als allerbelangrijkste, mijn voetbalvrouw Marlies. Lieve Marlies, jij had vooral een belangrijk aandeel in de broodnodige afleiding van dit proefschrift. Jij remt me af en houdt me af en toe met beide benen op de grond, maar tegelijkertijd geef je mij de ruimte om mijn dromen en ambities waar te maken. Dit is iets waar ik je ontzettend dankbaar voor ben. Ik kijk uit naar alle mooie dingen, die wij samen nog mogen beleven. Ik ben ontzettend gek op je!

Appendices

Curriculum vitae

CURRICULUM VITAE

Tijs Duivenvoorden was born on April 24th 1986 in Wageningen, the Netherlands. In 2004 he graduated from the ISW Gasthuislaan (Gymnasium) in 's-Gravenzande, and went on to study Medicine at the Erasmus University Rotterdam. After a medical internship in India and South-Africa, he completed his university education in 2011 becoming a doctor of medicine.

He started his carreer as an unaccredited orthopedic resident in the Reinier de Graaf hospital in Delft. After six months of residency in the Reinier de Graaf hospital he started his PhD-project at the department of Orthopaedic Surgery of the Erasmus University Medical Centre Rotterdam, headed by professor J.A.N. Verhaar. In 2014 he was awarded with the "Young researcher award" of the European Society of Sports Traumatology Knee Surgery and Arthroscopy.

In 2013 he got accepted for the orthopaedic training program in the ROGO Rotterdam. In January 2014, he started his training program in the Reinier de Graaf Hospital at the department of General Surgery. In July 2015 he continued his training program at the department of Orthopaedic Surgery of the Erasmus Medical Centre. Tijs Duivenvoorden is expected to finish his orthopaedic training program at the end of 2019.

Appendices

List of publications

LIST OF PUBLICATIONS

1. T. Duivenvoorden, M. M. Vissers, J.A.N. Verhaar, J.J.V. Bussbach, T. Gosens, R.M. Bloem, S.M.A. Bierma-Zeinstra, M. Reijman Anxiety and depressive symptoms before and after total hip and knee arthroplasty: a prospective multicentre study. Osteoarthritis Cartilage 2013 Dec;21(12):1834-40

2. T. Duivenvoorden, R.W. Brouwer, A. Baan, P.K. Bos, M. Reijman, S.M.A. Bierma-Zeinstra, J.A.N. Verhaar Comparison of closing-wedge and opening-wedge High Tibial Osteotomy for medial compartment osteoarthritis of the knee: a Randomized Controlled Trial with a six-year follow-up.
   J Bone Joint Surg Am, 2014 Sep 03;96(17):1425-1432.

3. T. Duivenvoorden, T.M. van Raaij, H.L.D. Horemans, R.W. Brouwer, P.K. Bos, S.M.A. Bierma-Zeinstra, J.A.N. Verhaar, M. Reijman Do laterally wedged insoles or valgus braces unload the medial compartment of the knee in patients with osteoarthritis?
   Clin Orthop Relat Res 2015 Jan;473(1):265-74

4. T. Duivenvoorden, R.W. Brouwer, T.M. van Raaij, A.P. Verhagen, J.A.N. Verhaar, S.M.A. Bierma–Zeinstra Braces and orthoses for osteoarthritis of the knee
   Cochrane Database Syst Rev. 2015 Mar 16;3:CD004020.

5. R.W. Brouwer, M.R. Huizinga, T. Duivenvoorden, T.M. van Raaij, , A.P. Verhagen, S.M.A. Bierma-Zeinstra, J.A.N. Verhaar Osteotomy for treating knee osteoarthritis
   Cochrane Database Syst Rev 2014 Dec 13;12:CD004019

6. T. Duivenvoorden, P. van Diggele, M. Reijman, P.K. Bos, J. van Egmond, S.M.A. Bierma-Zeinstra, J.A.N. Verhaar Adverse events after closing- and opening-wedge high tibial osteotomy: a comparative study of 412 patients
   Knee Surg Sports Traumatol Arthrosc 2014 May 31 [Epub ahead of print]

7. I. Zengerink, T. Duivenvoorden, D. Niesten, H. Verburg, N. Mathijssen. Obesity does not influence the outcome after unicompartmental knee arthroplasty Acta Orthopaedica Belgica vol. 81 Winter 2015 (in publish)

8. T. Duivenvoorden, H. Verburg, S.M.A. Bierma-Zeinstra, J.A.N. Verhaar, M. Reijman Do preoperative expectations affect patient satisfaction after total knee arthroplasty? a systematic review.
   (Submitted)

Appendices

PhD Portfolio Summary

PHD PORTFOLIO

Summary of PhD training and teaching

Erasmus MC
Universitair Medisch Centrum Rotterdam

Name PhD student: T. Duivenvoorden, MD
Erasmus MC Department: Orthopaedic Surgery
Research School: -

PhD period: 2012 - 2015
Promotor(s): J.A.N. Verhaar, MD, PhD
Supervisor: M. Reijman, PhD

1. PhD training

	Year	Workload (Hours/ECTS)
General courses		
- Biomedical English Writing and Communication	2012	4.0
- Statistical course: Introduction to data analysis	2012	1.9
- Regression Analysis for clinicians, NIHES	2013	1.9
- BROK ('Basiscursus Regelgeving Klinisch Onderzoek')	2013	1.0
Specific courses (e.g. Research school, Medical Training)		
- Resident Orthopaedic Surgery (not in training)	Jan 2012 – Jun 2012	
- PhD-student, department of Orthopaedic Surgery, Erasmus University Medical Center, Rotterdam, The Netherlands	Jul 2012 – Dec 2013	
- Resident Orthopaedic Surgery (in training)	Jan 2014 - present	
Seminars and workshops		
-		
Presentations		
- Oral Lecture: Do laterally wedged insoles or valgus braces really unload the medial compartment of the knee? Results of a RCT. *NOV annual meeting*, RAI Amsterdam **Nominated for best clinical research and oral presentation, Biomet award**	Feb 2013	1.0
- Oral Lecture: Better survival of opening wedge high tibial osteotomy: results of 6 year follow-up of an opening versus closing wedge RCT. *NOV annual meeting*, RAI Amsterdam	Feb 2013	1.0
- Poster presentation: Do laterally wedged insoles and valgus knee braces really unload the medial compartment of the knee? results of a RCT – OARSI 2014, Parijs	April 2014	1.0
- Poster presentation: Better survival of valgus opening-wedge High Tibial Osteotomy: 10-year results of a RCT comparing closing wedge and opening wedge technique – OARSI 2014, Parijs	April 2014	1.0

	Year	Workload (Hours/ECTS)
- Oral lecture: Do laterally wedged insoles or valgus braces really unload the medial compartment of the knee? Results of a RCT- ESSKA Meeting 2014, RAI Amsterdam **Awarded with the Young Researcher Award**	May 2014	1.0
- Oral lecture: 10-year follow-up of closing- versus opening-wedge high tibial osteotomy: results of a RCT - ESSKA Meeting 2014, RAI Amsterdam	May 2014	1.0
- Oral lecture: Meer complicaties na open- dan na gesloten-wig Hoge Tibiakop Osteotomie - *NOV Spring meeting*, Jaarbeurs Utrecht	May 2014	1.0
- Oral lecture: 10 jaar follow-up van gesloten versus open wig Hoge Tibiakop Osteotomie: een RCT - NOV Spring meeting, Jaarbeurs Utrecht	May 2014	1.0
(Inter)national conferences		
- NOV autumn meeting 2012	2012	
- NOV annual meeting 2013	2013	
- 2nd Luxembourg Osteotomy Congress	Apr 2013	
- ESSKA Amsterdam	May 2014	
Other		
-		
2. Teaching		
Lecturing		
- Oral lecture: Depression and anxiety disorders before and after total hip and total knee arthroplasty. *Opleidingsdag ROGO Rotterdam*, sociëteit het meisjeshuis Delft	2011	0.6
- Oral lecture: Do laterally wedged insoles or valgus braces really unload the medial compartment of the knee? Results of a RCT. *Wetenschapsdag*, Erasmus MC Rotterdam	2013	0.6
Supervising practicals and excursions, Tutoring		
- Teaching minor-students basic orthopaedic knowledge	2012	1.5
	2013	2.0
- Teaching master students basic research skills	2013	0.4
Supervising Master's theses		
- Supervising Jeroen van Egmond; biomarkers in conservatively treated patients with varus medial knee OA	2013	3.0
- Supervising Peter van Diggele; Adverse events after closing-wedge or opening-wedge High Tibial Osteotomy	2013	3.0
Other		
- Reviewer international journals under supervision of M. Reijman PhD	2013	1.5