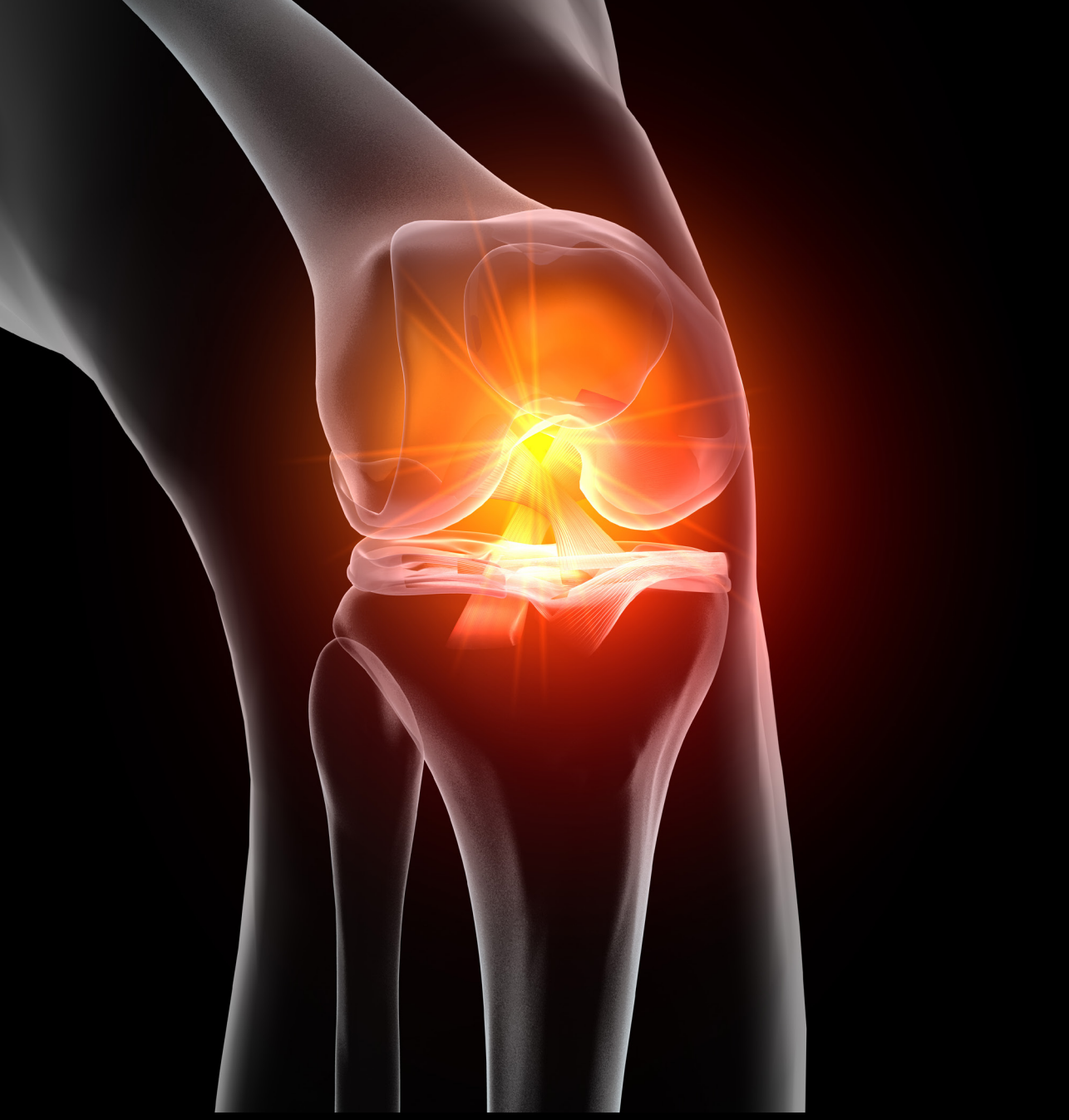

Optimal treatment for patients after anterior cruciate ligament rupture

Vincent Eggerding

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Optimal treatment for patients after anterior cruciate ligament rupture

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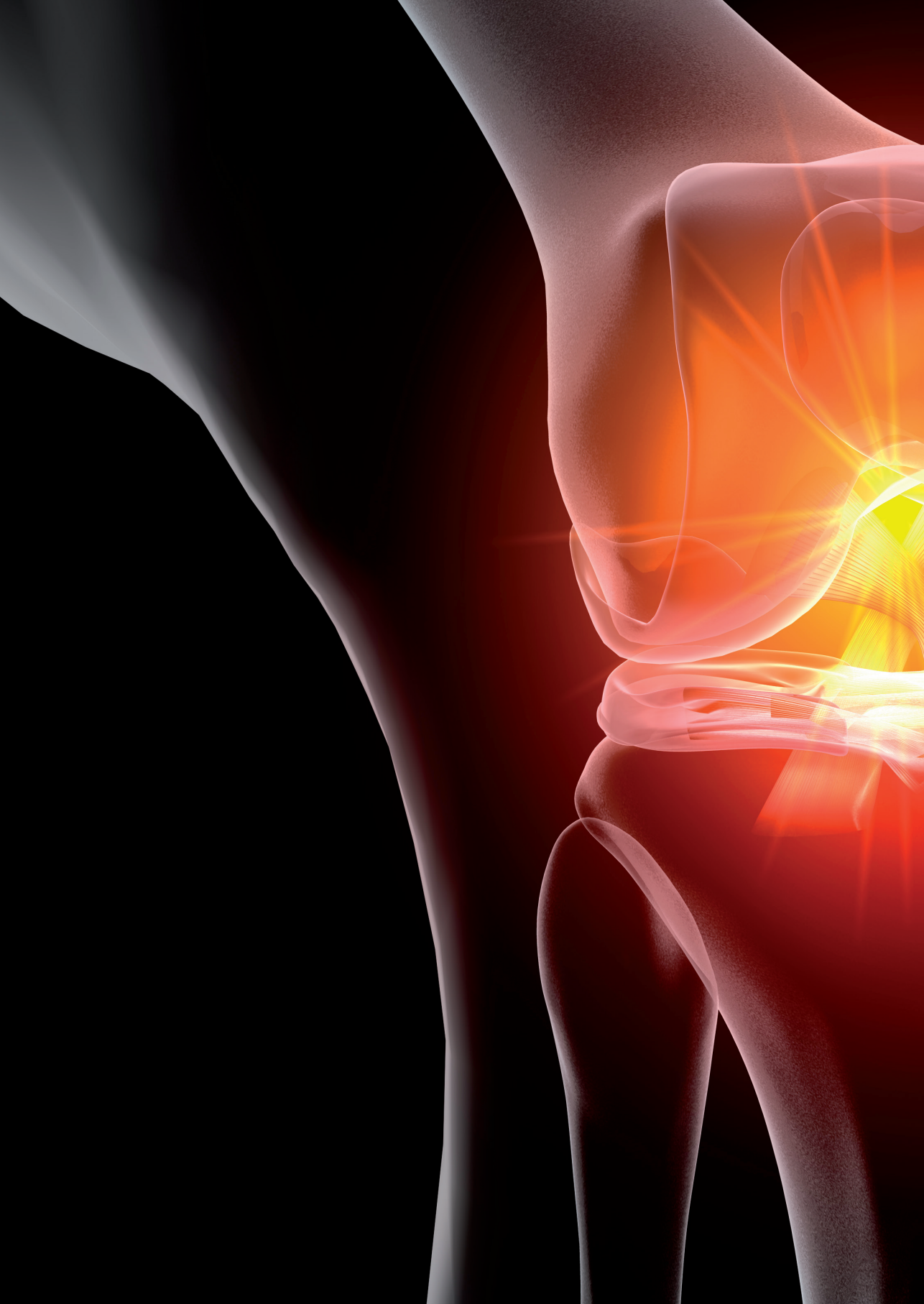

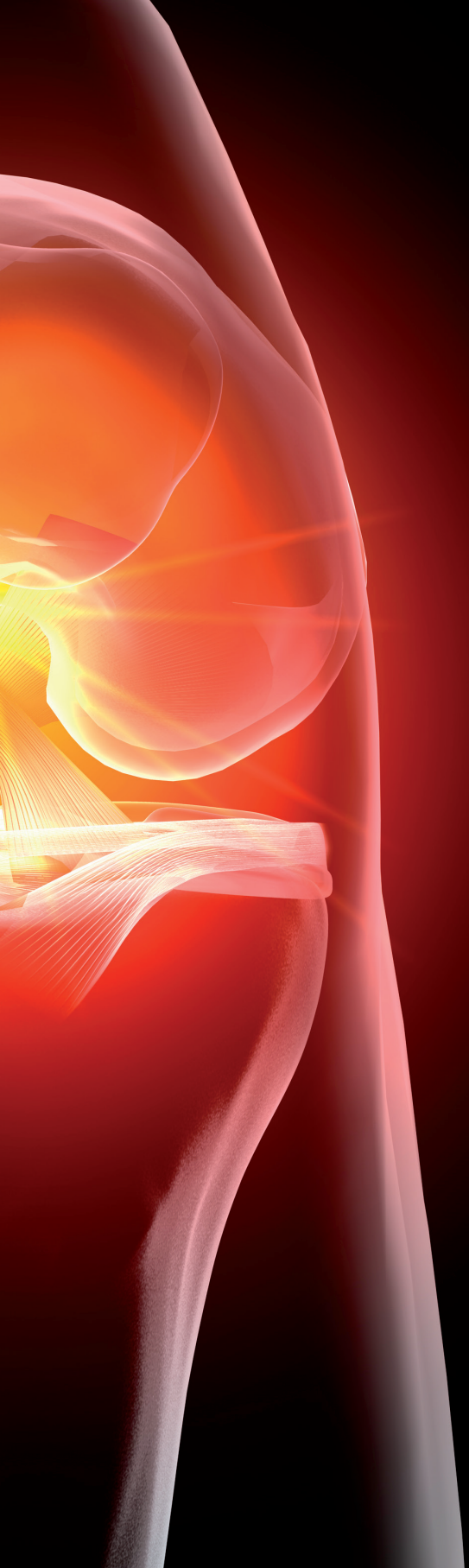

Chapter 1

General introduction and outline of thesis

The anterior cruciate ligament (ACL) is one of the ligaments which connects the femur with the tibia; It's originated at the intercondylar notch at the medial side of the lateral femoral condyle and inserts at the tibial eminence (see figure 1). The ACL is the primary constraint to anterior translation of the tibia. The ACL also contributes to internal rotation and varus/valgus instability with the knee in extension. The ACL consists of two bundles, which are configured in a manner that ensures functional stability throughout range of motion. (1)

ACL rupture is a commonly seen injury of the knee, which usually affects the young and active population. Short-term consequences are disability with swelling, pain and reduced knee function. For these young and active patients the injury has a great impact on functioning in daily living and sports participation. This could be partly explained by the fact that that a major part of these patients experience symptoms consistent with posttraumatic stress disorder such as avoidance and hyperarousal. (2)

Knee-related quality of life of patients following an ACL rupture is reduced for more than 20 years compared to population norms, but even more when compared to peers. (3) For the first few years this could be explained by a significant portion of patients not returning to previous activity level. For instance after ACL reconstruction 17 % of patients active on elite level and 45 % active on competitive level don't return to pre-trauma activity level. (4, 5) In the long run there is a four to six fold increase in osteoarthritis of the knee compared to the non-injured knee. (6) Overall can be said that an ACL rupture has huge consequences on the short and long term.

With amongst others the growth of youth sports and an increase awareness of the importance to remain physically active, we see an increase in the incidence of ACL ruptures and an even higher increase in number of reconstructions of the ACL. (7)

The highest increase in incidence of registered ACL rupture is seen in girls in their teen years with 143 % from 1997 to 2014. (8) The true population incidence may be even higher, because some patients with an ACL rupture will not be identified. (9) This could be due to the fact that some patients will only experience mild symptoms, have a beneficial recovery, and never see a physician.

In the United States, the incidence of ACL reconstruction increased from 61.4 reconstructions per 100.000 person years in 2002 to 71.8 reconstructions per 100.000 person years in 2014. (10)

In the Netherlands patients after a knee trauma will be seen initially by a general practitioner, a physical therapist or at the emergency department. The initial treatment is rest and decrease of swelling. In case of recurrent instability or suspicion for intra-articular injury patients are referred to an orthopedic surgeon. (11)

According to the Dutch guideline the first treatment of a diagnosed ACL rupture consists of rehabilitation and activity modification. Rehabilitation initially consists of reduction of swelling and optimization of the range of motion. Consequently, the goal is optimization of knee function, upper leg strength and proprioception. After this initial rehab, the patient can increase the activity up to the desired activity level. In case of recurrent instability or

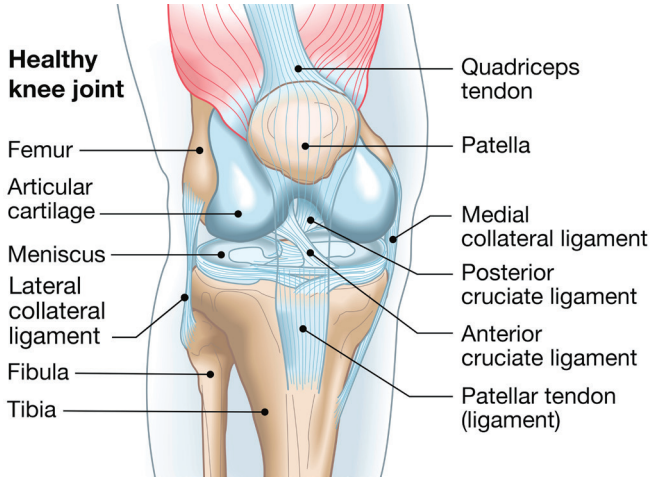

Figure 1: Illustration of the anatomy of the knee, with the anterior cruciate ligament central in the knee.

an inability to reach the desired activity level an ACL reconstruction can be considered. (12)

However, in clinical practice patients are treated more often with an early ACL reconstruction. (13) One of the main reasons for this is the assumed increased risk of associated injury to the cartilage, meniscus and other ligaments of the knee. (14)

Reconstruction of the ACL is one of the most commonly performed orthopedic procedures. Besides the increase of ACL reconstructions, we also see an increase in immediate costs per ACL reconstruction. (15) Next to the direct costs for diagnostics, surgery and rehabilitation, also costs for loss of productivity will be made. This leads to an increase in health care costs and burden for society. For example, for the Dutch society with above 8400 ACL reconstructions in 2018 this amounts to more than 55 million euro in direct costs per year. (16)

For some perspective on treatment for ACL rupture, a brief summary of history, present and future is described below.

A BRIEF HISTORY

The ACL was probably first described in the famous Smith Papyrus around 3000 BC. The function and consequences of injury was described by Claudius Galen of Pergamon (131-201 BC), a Greek physician in the Roman empire. (17) Almost 2000 years later the Weber brothers described that the ACL consisted of two different bundles, their individual function and consequences of transection of this ligament.(18) It was up to 1900 that William Battle was the first to publish a direct repair of the ACL with the use of silk sutures. (19) Since then a true evolution of the operation technique took place from direct repair to reconstruction,

from open to arthroscopic treatment, the use of extra-articular tenodesis to anatomical repair. With the advancements in reconstructive surgery the belief rose that everyone with an ACL rupture should be reconstructed.

In the second part of the twentieth century also a more sceptical view on the reconstruction of the ACL was noticed. It was recognised that a significant part of patients after ACL injury could have a good knee function with non-operative treatment and that sometimes operatively treated patients could have a worse knee function as recognised in the cliché 'no knee is so bad, that it can't be made worse by surgery'. In 1984 Noyes et al. described a rule of thirds; patients can become a coper, adapter or a non-coper after ACL rupture. (20) It was observed that a portion of patients after ACL rupture can perform as optimal as previously, some could manage by adjusting their activity level and a third of patients were unable to function with an ACL deficient knee.

Since then thousands of studies have been published on optimisation of the operation (e.g. type of graft, graft position, anterolateral reconstruction), but only a few on the identification of the right treatment for the individual patient after ACL rupture. In 2010 Frobell et al. published their randomized controlled trial in the New England Journal of Medicine comparing operative versus non-operative treatment for patients after ACL rupture. (21) They concluded that a strategy of early ACL reconstruction was not superior to rehabilitation and an optional reconstruction in case of recurrent instability. They showed that in their study after 2 years, 61% of patients after ACL rupture treated with rehabilitation were eventually not treated with an ACL reconstruction.

PRESENT

With the conclusion of the KANON trial of Frobell et al., that early reconstruction was not superior to rehabilitation plus an optional reconstruction and the high percentage of patients who remained without reconstruction after rehabilitation, one would expect that the number of reconstructions would decrease and guidelines would be adjusted. (21)

However, since the KANON trial treatment protocols did not change globally. For example, the guideline for American orthopaedic surgeons (AAOS) advises surgical reconstruction of the ACL after rupture, especially in the young (age 18-35 years) and active individual. Conflicting with this recommendation is, amongst others, the fact that especially the young and active patient is at high risk for re-rupture and concomitant damage to the meniscus, cartilage and collateral ligaments. The Dutch guideline recommends ACL reconstruction if symptomatic instability of the knee, as a result of an ACL injury, is not reduced after physiotherapy or after adjustment of activity. Furthermore the guideline states that actual age is not a factor of importance for the decision to perform an ACL reconstruction and that activity level is probably the most important predictor for the necessity. (12)

Long-term studies do not show a difference in incidence of osteoarthritis between patients treated with a rehabilitation alone versus a reconstruction. (22) This might indicate that a large amount of the damage to the joint is inflicted in the primary trauma; in other words the arthritis cascade is started at the time of the primary injury. Another explanation for this lack of long-term improvement with a reconstruction of the ACL is that surgery might be a second strike for the knee joint with articular damage, debris and postoperative synovitis. Also, patients after an operation and additional rehabilitation might not be willing to reduce their activity level and use the reconstruction as a so-called 'license to abuse' their knee.

Nowadays we see an increase in early ACL reconstruction in clinical practice. This might be due to the fact that ACL reconstruction is a well-developed procedure, with limited complications and a standardized rehabilitation program. (23) In case a patient starts with rehabilitation, there is a certain risk that this could be unsuccessful. As a consequence of this, recovery time will be prolonged, because of delayed ACL reconstruction and a second rehabilitation.

On the other hand, ACL reconstruction has the risk of multiple complications as stiffness (1-4%), septic arthritis (0.1-1.7%), deep venous thrombosis (0.53 to 14.9 %) and re-rupture of the graft (3.2-11.1%). (24, 25)

In current clinical practice the treatment choice is made by shared decision making. The treatment preference of the patient is influence by many factors, such as opinion of the physical therapist, social media, treatment of elite athletes, employer, sport coaches, social circumstances and treatment of peers. The treatment preference of the physician varies between early ACL reconstructions for all, versus ACL reconstruction only in case of recurrent instability. With this thesis we attempted to elucidate the treatment for patients with an acute ACL rupture and supply clinicians and patients handles to help guide them on their treatment.

In this thesis we describe the outcomes of the COMPARE study; a multicentre randomized controlled trial for patients after acute ACL rupture. Patients were randomized to either an early reconstruction within 6 weeks after randomization or a rehabilitation of 3 months followed by an optional reconstruction in case of recurrent instability. Patients were evaluated at baseline, 3, 6, 9, 12 and 24 months.

A LOOK INTO THE FUTURE

One of the challenges in clinical practice of treatment for patients after ACL rupture is the absence of clear indicators for the need of a reconstruction of the ACL. This is illustrated by the ambiguous statement in guidelines that actual age is not an indicator for reconstruction of the ACL, but younger patients are more entitled to an reconstruction because of higher

activity level. (12, 26) In this thesis we report a systematic review of prognostic factors for patients for the need of reconstruction after ACL rupture.

To improve treatment for patients after ACL rupture and to prevent unnecessary surgical procedures it is important to identify objective indicators for non-operative treatment and for ACL reconstruction and predictors of clinical outcome after different treatments regimens.(26)

Stability of the knee following ACL rupture is dependent of multiple factors as ligament laxity, quadriceps strength, lower extremity alignment, propriocepsis, postural patterns, hormones and anatomy of which the bony morphology of the femur and tibia is one factor. (27, 28) Anatomy of the tibia and femur that have been suggested to influence stability are posterior tibial slope, size of the intercondylar notch, tibial eminence size, lateral and medial tibial slope. (29-31)

In this thesis we have attempted to identify certain aspects of shape that differ between patients who tear their ACL and who have an intact ACL after a knee distortion. Furthermore we assessed whether there certain shape aspects were correlated with clinical outcome after ACL rupture.

Another possible future use of these anatomical variability's as risk factors for ACL rupture is to identify subgroups of athletes at high risk of ACL rupture. These 'high-risk athletes' could be subjected to ACL injury prevention programmes (IPP). IPP have been developed and shown to reduce the risk of ACL rupture by 53%. (32, 33) These programmes consist of strength exercises, plyometrics, agility, balance and flexibility and they can be incorporated in a warming up session. (33)

Another improvement in the future might be the incorporation of computer-assisted surgery to optimize surgery. This is already in use for amongst others total knee arthroplasty, spine operations and osteotomies. In the operating room is the computer connected with a camera and certain anatomical points and instruments of the surgeon are marked with reference markers. The computer is able to combine these markers with imaging studies (x-ray and CT-scan) and advise the surgeon on best localisation of technical aspects of the operation (for instance cutting surface, screw position, amount of correction). In ACL surgery this could be used amongst others for optimal tunnel placement. In this thesis we present a review of the use of computer assisted surgery for knee ligament reconstruction.

OUTLINE OF THIS THESIS

In chapter 2 we present the clinical outcomes of the Compare study. We randomized 167 patients with an acute ACL rupture for either an early ACL reconstruction or a rehabilitation programme for 3 months followed by an optional reconstruction. Follow up was for a period of 2 years and outcomes are presented for the randomisation groups and for the eventual treatment received by the participating patients.

Nowadays, next to clinical outcomes, also the cost-aspect is important to make treatment guidelines. In chapter 3 we report the comparison of the cost-effectiveness of the two treatment strategies used after acute ACL tear with the use of data from the Compare study: early ACL reconstruction versus rehabilitation plus an optional reconstruction.

In chapter 4 we systematically summarized the available literature on prognostic factors identifying which patient require surgical reconstruction after ACL rupture.

In chapter 5 and 6 the results of 2 studies are reported in which we used statistic shape modelling (SSM) to identify certain aspects of shape and relate them to the risk of an ACL rupture (Chapter 5) and clinical outcome after ACL rupture (chapter 6). SSM is a software programme that without a hypothesis separates aspects of shape and is able to summarize the distribution of these aspects in a population.

Chapter 5 evaluates differences in shape features of the knee on x-rays between patients with an intact and a ruptured ACL. We present a matched case-control study of 336 patients after knee distortion with the half of these patients with an ACL rupture and half with an intact ACL. Our aim was to evaluate the relationship between shape variations and the presence of an ACL rupture.

In chapter 6 we assessed if shape features of the knee on the x-rays can predict clinical outcomes after ACL rupture. We analysed lateral and Rosenberg view radiographs of 182 prospectively followed patients after ACL rupture, whether certain shape aspects were associated with the IKDC score.

Finally, we present an update of the Cochrane review in chapter 7 on the use of computer assisted surgery for ligament reconstruction. Systematically we searched and appraised literature for the use of computer-assisted surgery for ligament reconstruction.

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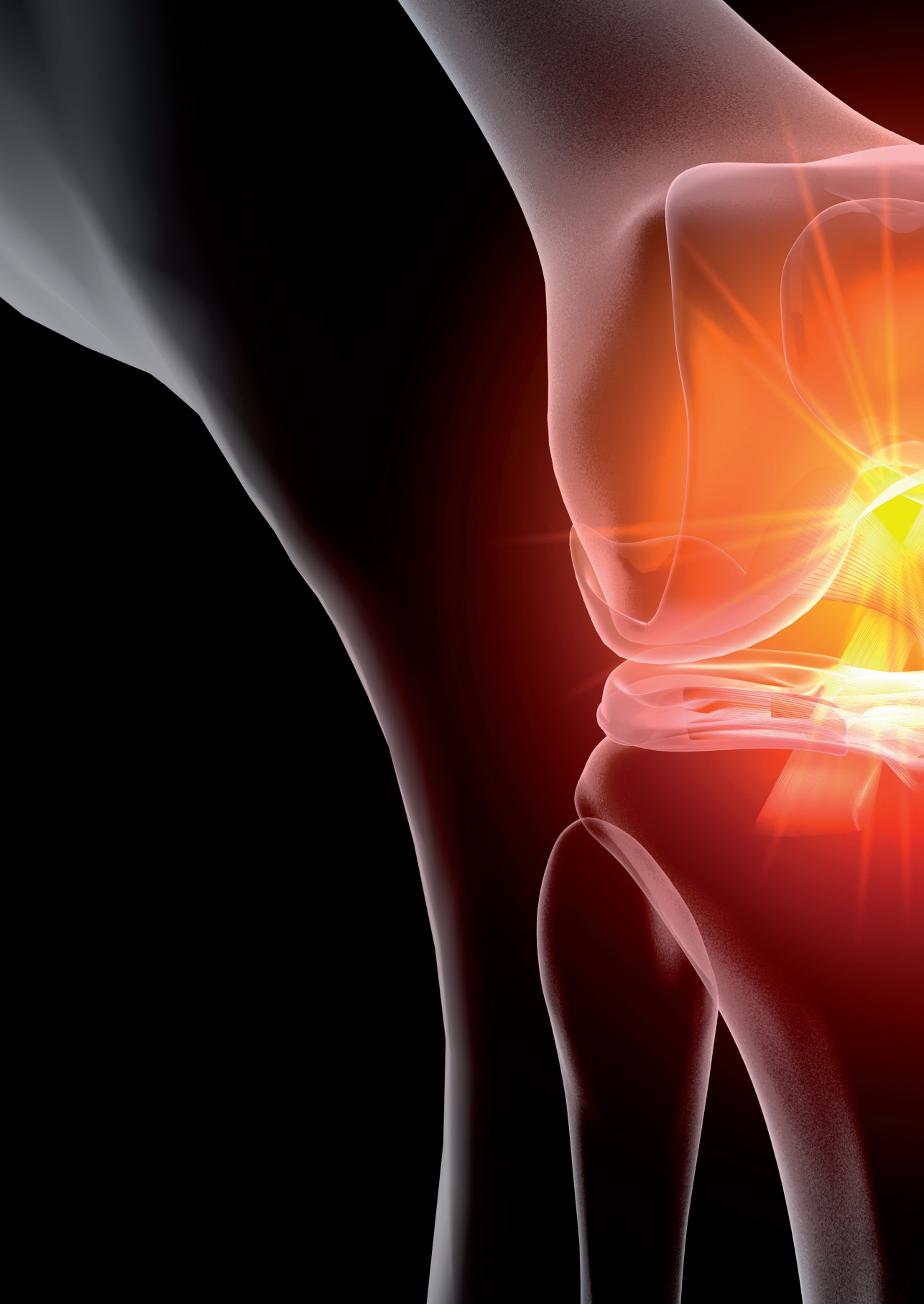

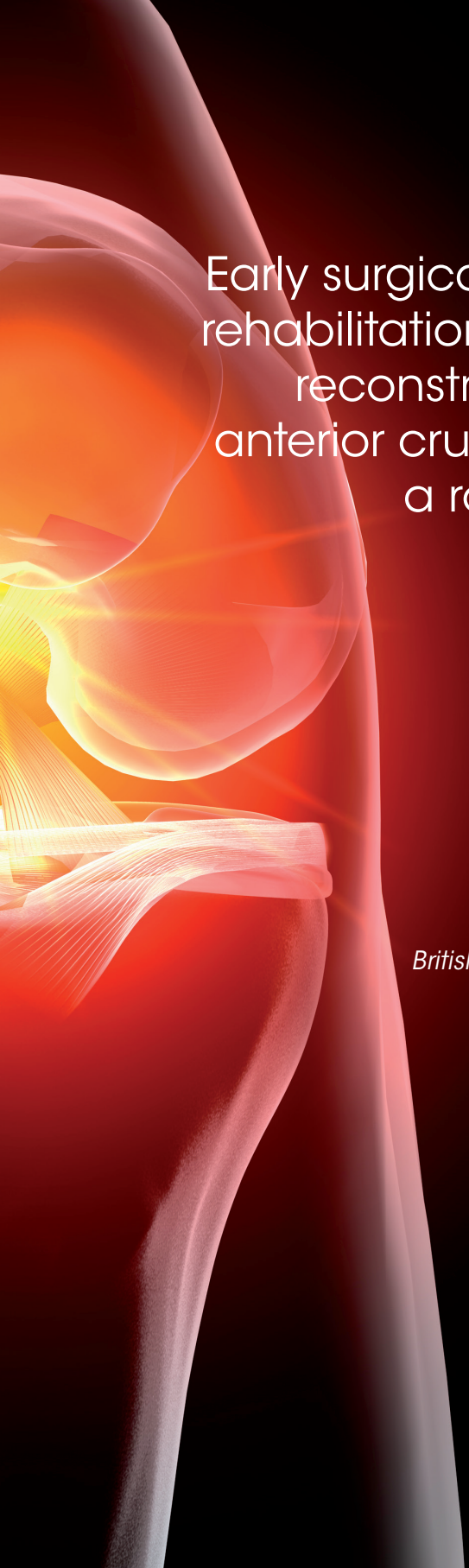

Chapter 2

Early surgical reconstruction versus rehabilitation plus elective delayed reconstruction for patients with anterior cruciate ligament rupture: a randomized clinical trial

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ABSTRACT

Objective To assess whether there is a clinically relevant difference in patients' perception of symptoms, knee function and ability to participate in sports over a period of two years after ACL rupture between two commonly used treatment regimens.

Design, setting and participants Open-labelled, multicentre, parallel randomized controlled trial. Patients were evaluated at 3, 6, 9, 12 and 33 24 months. Patients were recruited at 6 hospitals in the Netherlands, namely Albert Schweitzer Hospital, Erasmus MC University Medical Centre, Haaglanden Medical Centre, Elisabeth Tweesteden Hospital, Reinier de Graaf Gasthuis, and St. Antonius Hospital. Patients 18 to 65 years of age with an acute ACL rupture were included. Intervention(s) Eighty-five patients were randomized to early ACL reconstruction, and 82 to rehabilitation plus optional delayed ACL reconstruction after a three months period (primary non-operative treatment).

Main outcome The main outcome was patients' perception of symptoms, knee function and ability to participate in sports activities assessed with the International Knee Documentation Committee Score (IKDC) (optimal score, 43 100) at each time point during 24 months.

Results Between May 2011 and April 2016 a total of 167 patients were enrolled and randomized. Among 167 patients who were randomized (mean age 31.3 years; 67 (40.%) women) 163 (98%) completed the trial. Forty-one (50%) patients of the rehabilitation plus optional delayed ACL reconstruction group were eventually reconstructed during the two years of follow-up. The mean baseline IKDC score for the early ACL reconstruction, and rehabilitation plus optional delayed ACL reconstruction group were 45.9 and 46.2 respectively. We found a significant difference in IKDC score over 2 year follow-up period. After 24 months of the early ACL reconstruction group had a statistically significant better but not clinically relevant IKDC score of 84.7 versus 79.4 (between-group difference of 5.3 with 95% CI 0.6 to 9.9). After three months follow-up the IKDC score was significantly better for rehabilitation plus optional delayed ACL reconstruction group (between group difference of -9.3 with 95% CI -14.6 to -4.0). After nine months follow-up this difference in IKDC score changed in favour of the early ACL reconstruction group which became smaller thereafter. In the early ACL reconstruction group four re-ruptures and three ruptures of the contralateral ACL occurred during follow-up. In the rehabilitation plus optional delayed ACL reconstruction group these numbers were two re-ruptures and one rupture of the contralateral ACL.

Conclusions In this trial of patients with acute ACL rupture, early surgical reconstruction, compared with rehabilitation followed by elective surgical reconstruction, resulted in improved patients' perception of symptoms, knee function and ability to participate in sports at 2 year follow-up that was statistically significant but of uncertain clinical importance. Study interpretation should consider that 50% of the patients randomized to the rehabilitation group did not need surgical reconstruction.

INTRODUCTION

Anterior cruciate ligament (ACL) rupture is a common injury with an acute trauma. It leads to a painful, swollen knee, with secondary instability complaints, meniscal and chondral damage and at long term a tenfold increased risk of osteoarthritis. (1-5) The incidence is 49 to 75 per 100,000 persons years, with an individual as well as socioeconomic burden. (6-8) A seminal trial (KANON) provided evidence that non operative treatment of an ACL rupture with exercise treatment was successful in at least half of these patients. (9, 10) A strategy of early ACL reconstruction had similar functional outcome after two years of follow-up compared to a strategy of rehabilitation plus optional delayed ACL reconstruction. Ten years have passed since this seminal publication, yet this does not seem to have changed clinical practice. On the contrary, instead of ACL reconstructions decreasing they are still increasing. (6-8) It is vital that this disorder is treated appropriately, soon after its traumatic onset either by operative treatment or by exercise therapy. So, it is important to come to an optimal evidence based treatment strategy for patients with an ACL rupture. Compared to the previous KANON study we used another primary outcome measure, namely the International Knee Documentation Committee Score. As reported earlier by our group, this had better measurement properties and is therefore more useful than the KOOS questionnaire to evaluate these patients. (11) The aim of the trial was to assess whether there was a clinically relevant difference in patients' perception of symptoms, knee function and ability to participate in sports activities, as measured with the International Knee Documentation Committee (IKDC) Score over a period of two years after ACL rupture between two commonly used treatment regimens; an early reconstruction versus rehabilitation plus optional delayed ACL reconstruction.

METHODS

Study design

The COMPARE (Conservative versus Operative Methods for Patients with ACL Rupture Evaluation) trial was an open-labelled, multicentre, parallel randomized controlled trial and evaluated the effectiveness of two treatment strategies of acute ACL rupture. Patients were recruited between May 2011 and April 2016 at 6 hospitals (one university hospital and five non university hospitals) in the Netherlands. The Erasmus University Medical Centre ethics committee approved the research protocol, and all patients gave written informed consent.

Patient involvement

Patients were involved in the design and conduct of this research. During the preparation of the study, priority of the research question, choice of outcome measures, and methods of recruitment were discussed with patients. We plan to disseminate the study results to study participants.

Patients

Patients were recruited from the outpatient clinic of Albert Schweitzer Hospital, Erasmus MC University Medical Centre, Haaglanden Medical Centre, Elisabeth Tweesteden Hospital, Reinier de Graaf Gasthuis, and St. Antonius Hospital. Patients aged 18 – 65 years with an acute (within two months after the initial trauma) complete primary ACL rupture (confirmed by MRI and clinical examination) and willing to be randomized were eligible for the trial. Exclusion criteria were history of ACL injury of the contralateral knee, presence of another disorder that affects the activity level of the lower limb, dislocated bucket handle lesion of the meniscus with an extension deficit, or insufficient command of the Dutch language. Eligible patients received oral and written standardized information about the trial.

Randomization and masking

After the patient signed the informed consent form, and the baseline measurements had been carried out, the patient was randomized into one of the two groups. One independent person (central randomization) had access to the computer generated randomization lists (block randomization, with variable size of the blocks (range 2-6); stratified for orthopedic surgeon and per age group (< 30 and ≥ 30 years)).

Interventions

Patients were randomized to one of the two treatments for ACL rupture: early ACL reconstruction or rehabilitation plus optional delayed ACL reconstruction. After randomization, the patient was informed about the treatment assignment; the surgeon responsible for the treatment was also informed.

Early ACL reconstruction

Arthroscopic ACL reconstruction was scheduled within 6 weeks after randomization. Surgeons had the option to choose their technique and graft of preference for the individual patient and to perform additional intra-articular surgery if deemed necessary. All six participating hospitals had two or less orthopaedic surgeons performing ACL reconstructions; all participating surgeons had a minimum of ten years' experience. After surgery, patients were referred for physical therapy until good functional control was achieved. (1)

Rehabilitation plus optional delayed ACL reconstruction

For non-operative treatment, patients were referred to a physical therapist for a supervised physical therapy program for a minimum of three months. This was according to the recommendation of the Dutch ACL guideline. (1) After a minimum of three months rehabilitation, patients could opt for ACL reconstruction in case of persistent instability, or an inability to reach the desired activity level.

Outcomes

The primary outcome was the patients' perception of symptoms, knee function and ability to participate in sports activities as measured by the International Knee Documentation Committee score (IKDC) assessed over a period of 24 months follow-up. A higher IKDC score reflects more favourable patients ratings of symptoms, knee function, and ability to participate in sports activities (optimal score is 100). The IKDC is a valid and responsive (ability to detect changes in time) tool for patients with an ACL rupture. (11-13)

Secondary outcomes were the knee specific outcome scores Knee Injury and Osteoarthritis Outcome Score (KOOS exist of sum scores of each 5 subscales (range 0-100; optimal score is 100), Lysholm (range 0-100; optimal score is 100)), return to pre-injury sport level (yes, no), occurrence of giving way (yes, no), sporting activity level (Tegner score, range 0-10 (highest activity score is 10)), knee pain (numeric rating scale 0-10, (optimal score is 0)) and satisfaction with treatment (5 point Likert scale, with satisfied defined as moderate and very satisfied). Also, serious adverse events (meniscal lesions, complications, and re-interventions) were secondary outcomes.

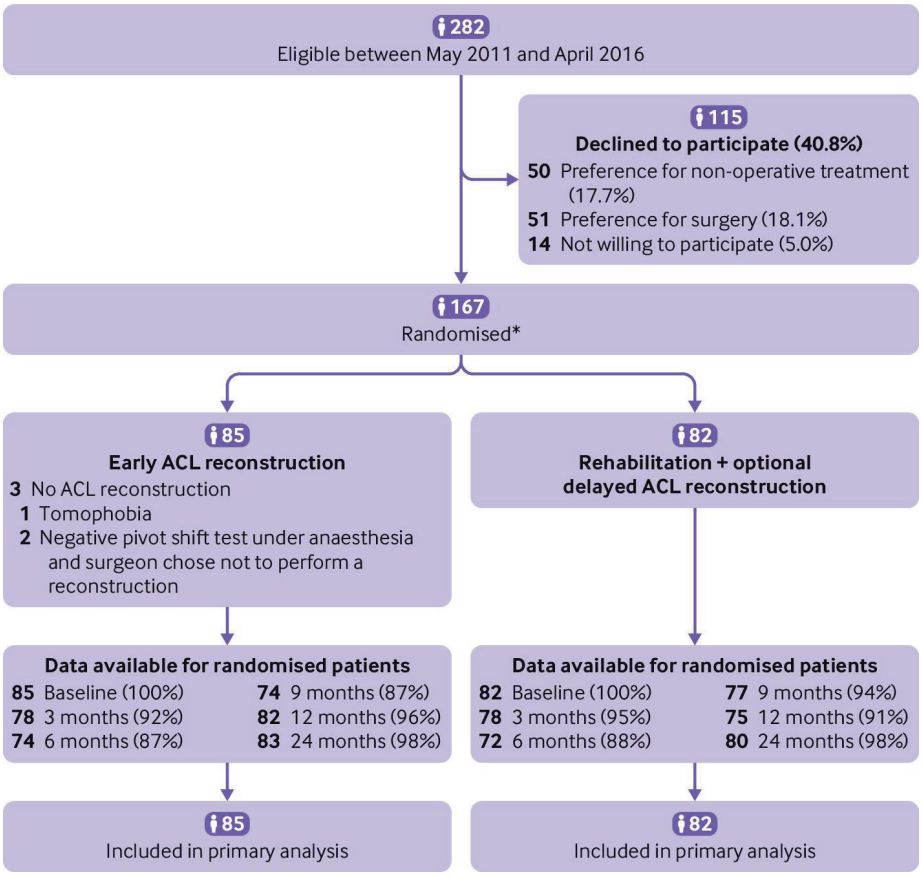
Patients were seen at the outpatient clinic at baseline, 12 and 24 months, and filled out the questionnaires additionally at 3, 6 and 9 months after randomization. All questionnaires were completed digitally and the 9 patient study data were coded, using data management software (Gemstracker version 1.6.3, Erasmus 150 MC, Rotterdam, the Netherlands).

For the sample size calculation we used the results of a study of Siebold et al. (14) Patients with an ACL rupture waiting to undergo an ACL reconstruction, had a mean pre-operative International Knee Documentation Committee Score of 56 (within-group standard deviation of 13) and 19 months postoperative a mean score of 90 (± SD of 10). We powered the study to detect a seven points difference between both groups in International Knee Documentation Committee Score (based on an effect size of minimally 0.5). Using a power of 90% and a type I error rate of 5%, we calculated that we needed 75 patients per group, resulting in 150 patients in total. Taking into account a potential loss to follow up of 25% in 2 years, the target sample was set to 188 patients. However, based on a much lower loss to follow-up of less than 10%, seen during interim report to the grant provider, we refined this estimation to 166 patients.

Statistical Analysis

In our primary analysis patients were analysed according to their randomization group. To answer our primary research question, we used mixed models to evaluate the between group difference in the course in IKDC score over the total follow-up period, as indicated by the interaction between time point and randomized allocation. The IKDC score (at baseline and after 3, 6, 9, 12 and 24 months of follow-up) was used as a dependent variable. The repeated measures and covariance structure was modelled as unstructured. The model was estimated using the Restricted Maximum Likelihood (REML). The randomized allocation was used as an independent variable. Follow-up period and the interaction between

Figure 1: Flowchart study



follow-up and randomized allocation were entered into the model as fixed factors. We adjusted the analysis for potential confounders, namely sex, BMI, and age. Both strata's used in the randomization procedure, namely orthopedic surgeon and age group (< 30 and ≥ 30 years), were added as random factor into the model. The following model assumptions were checked: linearity, homoscedasticity and normality of residuals. We did not find any violation of the model assumptions. Secondary analysis included analysis of the between group difference in of KOOS, Lysholm, and pain severity (NRS, in rest and during activity), by using mixed models (see method as reported above) at the different time points. Return to pre-injury sport level, satisfaction with treatment, and adverse events were reported as comparative frequencies. Because of the potential for type 1 error due to multiple comparisons, findings for analyses of secondary endpoints should be interpreted as exploratory. Additionally, we described (post-hoc) the following groups regarding the primary outcome: early surgical reconstruction of the ACL, non-operative treatment, and delayed surgical reconstruction after unsuccessful rehabilitation.

Statistical significance was set at the 2-sided .05 level.

Table 1: Baseline characteristics of the study population

	Early ACLR (n=85)	Rehabilitation plus optional delayed ACLR (n=82)
Age at inclusion, years	31.2 (10.3)	31.4 (10.7)
Female sex, n (%)	36 (42.4)	31 (37.8)
Male sex, n (%)	49 (57.6)	51 (62.2)
BMI, kg/m²	24.3 (3.7)	25.0 (4.1)
College education, n (%)	30 (35.3)	36 (43.9)
Paid work, n (%)	71 (83.5)	64 (78.0)
Tegner pre-injury	7.0 (2.3)	7.1 (2.0)
ACL injured during sport, n (%)	76 (89.4)	71 (86.6)
Time between injury and inclusion, days (median & IQR)	39.0 (25.5; 53.0)	40.5 (29.8; 52.5)
MRI findings, n (%)		
- meniscal tear	38 (44.7)	37 (45.1)
- MCL injury	30 (35.3)	31 (37.8)
- LCL injury	8 (9.4)	0 (12.2)
- cartilage defect	23 (27.1)	16 (19.5)

Data are presented as mean and standard deviation between parentheses, or reported otherwise
ACL = anterior cruciate ligament / BMI = body mass index / MRI = magnetic resonance imaging / ACLR = anterior cruciate ligament reconstruction / MCL = medial collateral ligament / LCL = lateral collateral ligament / n = number / IQR = inter quartile range. Tegner score evaluates sporting activity level (range 0-10 (highest activity score is 10))

RESULTS

Patients

Between May 2011 and April 2016 a total of 167 patients were enrolled of the 282 patients who were 188 eligible. The end of the participant follow-up was April 2018. Eighty-five patients were randomized to the early ACL reconstruction group and eighty-two to the rehabilitation plus optional delayed ACL reconstruction group (see Figure 1 and Table 1). Three patients (3.5%) of the early ACL reconstruction group were not reconstructed; one because of tomophobia and two because the surgeon decided not to perform an ACL reconstruction because of a negative pivot shift test during surgery. Forty-one (50%) patients of the rehabilitation plus optional delayed ACLR group were eventually reconstructed during the two years of follow-up, with an average of 10.6 months after randomization. All of these 41 patients met the criteria for ACL reconstruction (that is, occurrence of giving way and rotational instability by means of a positive pivot shift test)) as recommended by the Dutch guideline. (15) Two-year follow-up was completed for 98% of all included patients.

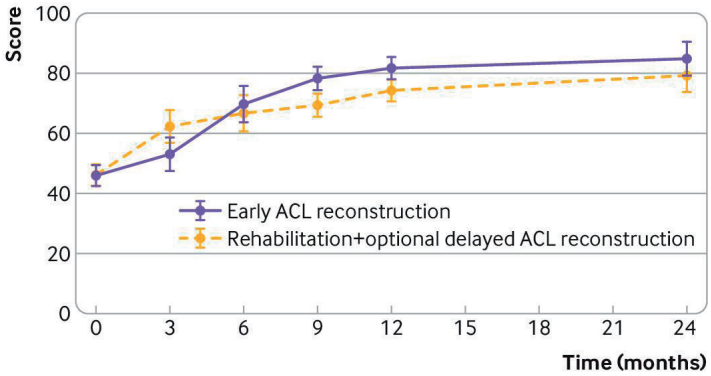
Primary outcome

Both treatment groups improved in IKDC score during the follow-up period of two year (see Figure 2 and Table 2). We found a significant difference in course in IKDC score over

Table 2: Primary outcome (estimated International Knee Documentation Committee score) for the as randomised analyses for each measurement period*

		Follow-up (months)				
Primary outcome	**Baseline**	**3**	**6**	**9**	**12**	**24**
IKDC score						
Early ACL reconstruction	45.9 (42.4 to 49.4)	53.0 (47.5 to 58.6)	69.6 (63.5 to 75.6)	78.2 (74.3 to 82.2)	81.6 (77.9 to 85.2)	84.7 (78.8 to 90.5)
Rehabilitation+optional ACL reconstruction	46.2 (42.6 to 49.8)	62.3 (56.8 to 67.9)	66.8 (60.9 to 72.8)	69.3 (65.4 to 73.3)	74.4 (70.6 to 78.2)	79.4 (73.6 to 85.2)
Difference between groups	−0.3 (−5.3 to 4.8)	−9.3 (−14.6 to −4.0)	2.8 (−2.9 to 8.5)	8.9 (3.3 to 14.5)	7.1 (1.9 to 12.4)	5.3 (0.6 to 9.9)

Data are mean (95% confidence interval).
ACL=anterior cruciate ligament; IKDC=International Knee Documentation Committee.
Significant difference was found in the course of the IKDC score over the two year follow-up period (P<0.001 for interaction between follow-up and randomised allocation).
A higher International Knee Documentation Committee score indicates more favourable patient ratings for symptoms, knee function, and ability to participate in sporting activities (optimum score 100).
* Adjusted for sex, body mass index, age, and surgeon.



Values represents mean and 95% confidence intervals Data is adjusted for sex, BMI, age, and surgeon significant difference in course in IKDC score over 2 year follow-up period (p-value < 0.001 for interaction between follow-up and randomized allocation) A higher International Knee Documentation Committee score reflects more favorable patients ratings of symptoms knee function and ability to participate in sports activities (optimal score is 100

Figure 2: International Knee Documentation Committee Score over a follow-up period of 24 months

the 2-year follow-up period (p-value < 0.001 for interaction between follow-up point and randomized allocation). A significant difference in IKDC score at 24 months was found in favour of early ACL reconstruction group (between group difference of 5.3 with 95% CI of 0.6 to 9.9). After three months a significant difference was found in favour of the rehabilitation plus optional delayed ACL reconstruction group (between group difference of -9.3 with 95% CI of -14.6 to -4.0). After nine months follow-up this difference in IKDC score changed in favour of the early ACL reconstruction group (between group difference of 8.9 with 95% CI of 3.3 to 14.5). At 12 months follow-up the difference between groups became smaller (between group difference of 7.1 with 95% CI of 1.9 to 12.4).

Secondary outcomes

The early ACL reconstruction group had a statistically significant better KOOS-sport score (80.8 with 95% CI of 75.5: 86.0 versus 72.8 with 95% CI of 67.4; 78.2; between group difference in change score of -7.9 (95% CI of -15.4; -0.4)) and better quality of life (76.6 with 95% CI of 71.8; 81.4 versus 65.8 with 95% CI 214 of 60.8; 70.7; between group difference in change score of -10.9 (95% CI of -17.2; -4.0)) score at two year follow-up, compared to the rehabilitation plus optional delayed ACLR group (see supplement 2 eTable 2). The KOOS scores of the other subscales were not significant different between both groups. For the Lysholm score we found a statistically significant higher score at three months follow-up for the rehabilitation plus optional delayed ACL reconstruction group (eTable 1 in supplement 2). Pain severity during rest, and during activity, were not significant different between the groups at any time point.

Table 3: Secondary outcomes at the two year follow-up

	Early ACL reconstruction (n=83)		Rehabilitation+optional delayed ACL reconstruction (n=80)		Difference between groups in change scores
Secondary outcome	**Baseline**	**Two year follow-up**	**Baseline**	**Two year follow-up**	
KOOS					
Pain	59.8 (52.8 to 66.8)	90.5 (83.5 to 97.5)	60.5 (53.5 to 67.5)	87.1 (80.2 to 94.0)	3.4 (−0.7 to 7.5)
Symptoms	55.8 (49.3 to 62.4)	86.8 (80.4 to 93.2)	49.9 (43.3 to 56.5)	82.5 (76.2 to 88.8)	4.3 (−0.5 to 9.1)
Activities of daily living	65.2 (57.4 to 72.9)	93.6 (85.8 to 101.5)	66.6 (58.8 to 74.3)	92.0 (84.2 to 99.8)	1.6 (−1.3 to 4.6)
Sport	27.5 (22.1 to 33.0)	80.8 (75.5 to 86.0)*	29.2 (23.6 to 34.8)	72.8 (67.4 to 78.2)*	−7.9 (−15.4 to −0.4)†
Quality of life	30.4 (26.5 to 34.2)	76.6 (71.8 to 81.4)*	30.9 (27.0 to 34.9)	65.8 (60.8 to 70.7)*	−10.9 (−17.2; −4.0)†
No (%) with occurrence of giving way	—	2/81 (2.5)*	—	12/80 (15.0)*	—
No (%) with return to sporting level before injury	—	35/81 (43.2)	—	25/80 (31.3)	—
No (%) satisfied with treatment	—	75/81 (92.6)	—	73/80 (91.3)	—

Data are mean (95% confidence interval) unless otherwise stated.

Other treatments

In the early ACL reconstruction group 24 arthroscopic meniscus procedures (18 meniscectomies, 4 repairs and 2 both) were performed during ACL reconstruction compared to 17 in the rehabilitation plus optional delayed ACL reconstruction (11 meniscectomies, 5 repairs and 1 both). One meniscectomy procedure in the early ACL reconstruction group was performed before the ACL reconstruction session.

Serious adverse events

The number of serious adverse events for both treatment groups are presented in Table 3. In the early ACL reconstruction group three ruptures of the contralateral ACL occurred compared to one in the rehabilitation plus optional delayed ACL reconstruction group. Four re-ruptures occurred in the early ACL reconstruction group and two in the rehabilitation plus optional delayed ACL reconstruction group.

Post-hoc analysis

The post-hoc as-treated evaluation of the recovery of IKDC Score of the three groups of patients are 232 reported in eFigure 1 and eTable 3 in supplement 2. Giving way complaints were significantly more present in the rehabilitation plus optional delayed ACL reconstruction group after two years of follow-up (15.0% versus 2.5% respectively).

DISCUSSION

In this multicentre, randomized controlled trial for acute ACL injury treatment, we found that early surgical reconstruction, compared with rehabilitation plus optional surgical reconstruction, resulted in improved patients' perception of symptoms, knee function and ability to participate in sports after 2 year follow-up that was statistically significant but of uncertain clinical importance. Study interpretation should consider that 50% of the patients randomized to the rehabilitation group did not need surgical reconstruction.

The abovementioned also implies that half of the patients did not well with non-operative treatment. The previous KANON trial showed after two years of follow-up that 39% of the patients had an ACL reconstruction, which increased to 51% after five years of follow-up. (9, 10) The study population of the KANON trial was however, younger (approximately 5 years) and had a higher pre-injury sport level (9 compared to 7). The publication of the KANON trial apparently did not affect the operative treatment decision making, as the number of ACL reconstructions is still increasing worldwide. However, the results of both the KANON trial and our trial show that reconstruction is unnecessary in at least half of the patients. In daily practice another reason to choose a surgical reconstruction is that recurrent giving-way episodes may lead to secondary injuries of meniscus and cartilage. We found more surgical interventions for a meniscal tear in the early ACL reconstruction group. Also after

Table 4: econdary outcomes for the as randomised analyses for each measurement period

		Follow-up (months)				
Secondary outcome	**Baseline**	**3**	**6**	**9**	**12**	**24**
Lysholm score						
Early ACL reconstruction	64.5 (60.5 to 68.6)	77.3 (71.8 to 82.8)	86.6 (79.7 to 93.5)	88.8 (84.9 to 92.8)	90.3 (87.8 to 92.9)	90.6 (85.4 to 95.9)
Rehabilitation+optional ACL reconstruction	64.7 (60.6 to 68.9)	79.6 (74.1 to 85.1)	81.4 (78.9 to 85.9)	84.6 (80.7 to 88.5)	86.2 (83.5 to 88.9)	87.1 (81.9 to 92.3)
Difference between groups	−0.2 (−6.0 to 5.6)	−2.3 (−6.8 to 2.2)	5.2 (0.9 to 9.5)	4.2 (0.2 to 8.2)	4.1 (0.4 to 7.8)	3.5 (0.2 to 6.9)
NRS at rest						
Early ACL reconstruction	2.5 (1.7 to 3.3)	1.4 (0.8 to 2.0)	0.9 (0.4 to 1.4)	0.9 (0.4 to 1.4)	1.0 (0.5 to 1.4)	0.5 (0.1 to 1.0)
Rehabilitation+optional ACL reconstruction	2.3 (1.5 to 3.1)	1.4 (0.7 to 2.0)	1.2 (0.7 to 1.7)	1.4 (0.9 to 1.9)	1.3 (0.8 to 1.7)	0.9 (0.4 to 1.3)
Difference between groups	0.2 (−0.5 to 0.9)	0 (−0.6 to 0.7)	−0.3 (−0.8 to 0.2)	−0.4 (−1.0 to 0.1)	−0.3 (−0.9 to 0.3)	−0.3 (−0.8 to 0.1)
NRS during activity						
Early ACL reconstruction	5.0 (4.4 to 5.6)	3.6 (2.6 to 4.6)	2.7 (2.0 to 3.4)	2.4 (1.8 to 3.1)	1.8 (1.2 to 2.4)	1.6 (1.0 to 2.3)
Rehabilitation+optional ACL reconstruction	5.1 (4.5 to 5.7)	3.9 (3.0 to 4.9)	3.0 (2.3 to 3.7)	2.9 (2.2 to 3.5)	2.7 (2.0 to 3.3)	2.2 (1.6 to 2.9)
Difference between groups	−0.2 (−1.0 to 0.7)	−0.3 (−1.1 to 0.4)	−0.3 (−1.1 to 0.4)	−0.4 (−1.1 to 0.3)	−0.9 (−1.6 to −0.2)	−0.6 (−1.2 to 0)

Data are mean (95% confidence interval).
ACL=anterior cruciate ligament; NRS=numeric rating scale for knee pain (0-10, optimum score 0).
Lysholm score (range 0-100; optimum score 100).

Table 5: Serious adverse events

Adverse event	**Early ACL reconstruction (n=85)**	**Rehabilitation+optional delayed ACL reconstruction (n=82)**
Re-rupture of ACL reconstruction (No)	4	2
Rupture of contralateral ACL (No)	3	1
Removal of tibial screw (No)	1	2
Arthroscopic intervention for meniscal tear after ACL reconstruction or new knee trauma (No)	4	3
Arthroscopic debridement for extension deficit (No)	2	4

ACL=anterior cruciate ligament.

the ACL reconstruction, meniscus procedures were performed, because of a new trauma. This suggests that a surgical reconstruction will not decrease this risk.

Patients with an ACL rupture have a high increased risk of knee OA. (16) It is still unclear which treatment option is the best for preventing OA development. The evidence of this is conflicting, as reported by our group in 2015 and recently by the group of Oiestad. (16, 17) Longer follow-up of our study is warranted to evaluate the long term risk of knee OA.

A difference of 7 points between both groups in IKDC score, was used to assess the needed number of patients in our study. This was based on an effect size of 0.5 which is described as a medium effect. During the preparation of our study there were no publications about the Minimal Clinically Important Difference (MCID) of the IKDC. Since than several papers reported MCID ranging between 11.5 and 20.5 in those who have undergone various surgical procedures for various knee pathologies. (18, 19) In our study the between group differences at any time point did not surpass the lowest reported MCID, and especially the fact that after two years of follow-up the between group differences did neither surpass the lowest reported MCID or our predefined difference makes the clinical relevance of this difference doubtful.

The fact that 50% of the patients in the rehabilitation group opted for a delayed reconstruction means that these patients were unsatisfied with the results of conservative treatment. The next urgent question is whether these patients would have been better off with an early reconstruction. Therefore, future research should be directed towards a timely and correct identification of exactly these patients in the acute stage, and prospectively comparing this group of early reconstruction with rehabilitation with an optional delayed reconstruction. Such research will be challenging because of certain dogmas in the treatment of patients with ACL rupture as e.g. the conviction that high activity level patients always require reconstruction. (20)

Strengths

Our study has several strengths; first, the inclusion of a large number of patients willing to participate in a study in which they were randomized for an operative or a non-operative treatment. As reported earlier, patients' willingness to participate in an RCT, especially in which a surgical intervention is compared with a non-operative intervention, is a challenging and limiting factor for recruitment. (21) Because of the difficulty of including patients for this kind of studies, we believe that our study will not be replicated in the near future. Secondly, compared to the previous KANON study we used another primary outcome measure. As reported earlier by our group, had better measurement properties and is therefore more useful than the KOOS questionnaire to evaluate these patients. (11) Thirdly, the high follow-up rate and few protocol violations strengthen the validity of our outcomes. Fourthly, the multicentre design of our study enables the generalizability of our study results.

Limitations

Our study has certain limitations; first, the potential presence of recruitment-bias. Of the patients, who were eligible, 101 declined to participate because of a strong preference for one of both treatment options. Because these preferences were equally divided, it is doubtful whether the results of our study would have been different if all potential patients had participated. The group that had delayed surgery is a selected subgroup, and a comparison to the group that had early surgery, or to the group that did not opt for the delayed surgery is probably heavily biased and was consequently not formally tested.

Conclusions

Among patients with acute ACL rupture, surgical reconstruction alone, compared with rehabilitation plus optional surgical reconstruction, resulted in improved patients' perception of symptoms, knee function and ability to participate in sports at 2 year follow-up that was statistically significant but of uncertain clinical importance. Study interpretation should consider that 50% of the patients randomized to the rehabilitation group did not need surgical reconstruction.

Acknowledgement

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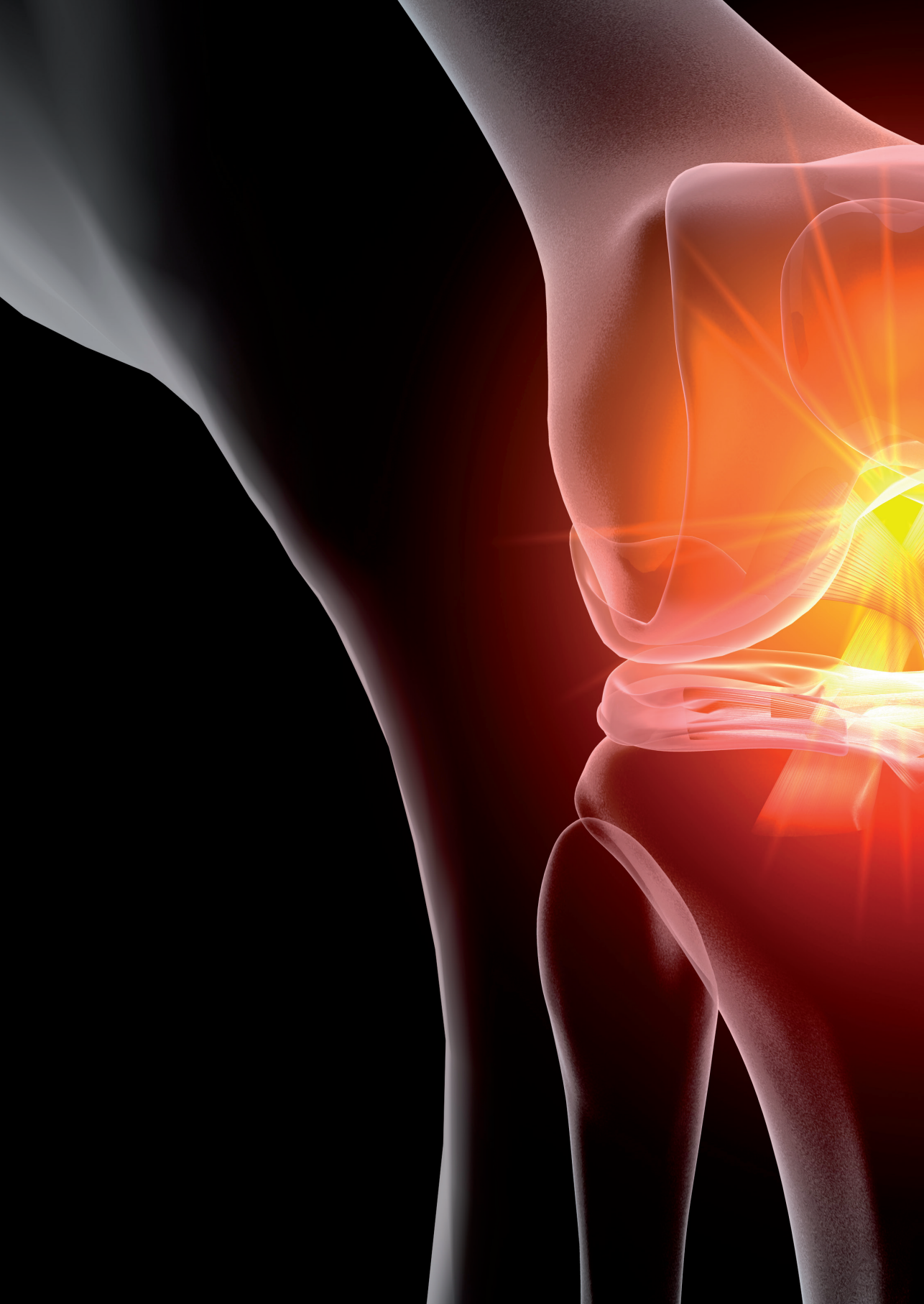

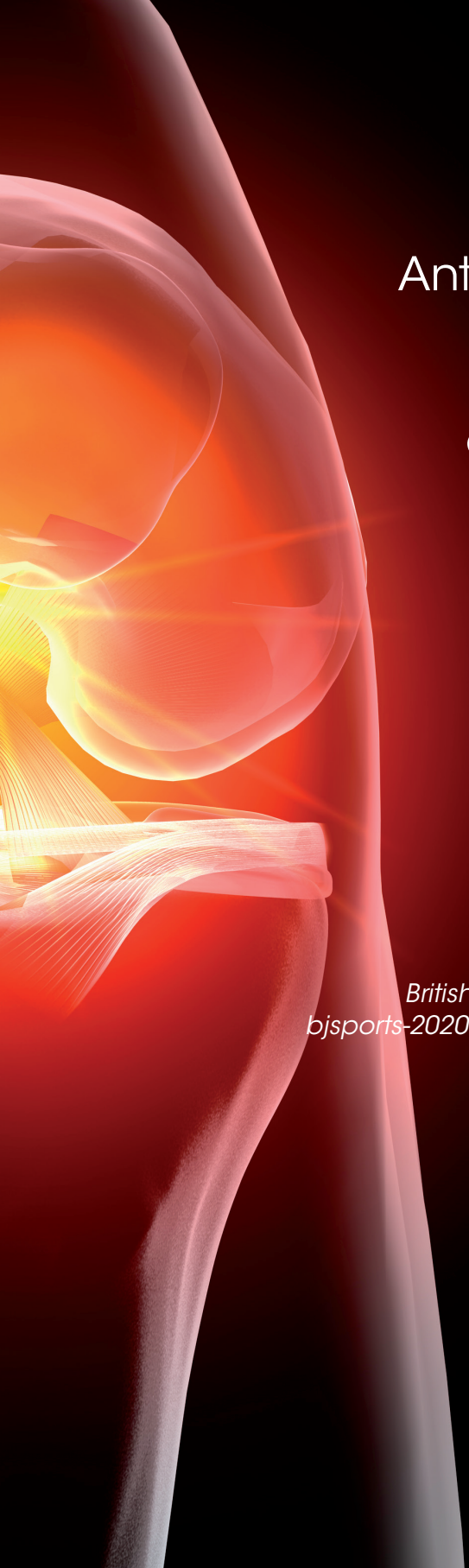

Chapter 3

Anterior cruciate ligament reconstruction for all is not cost-effective after acute anterior cruciate ligament rupture

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ABSTRACT

Objectives To evaluate cost-effectiveness for two commonly used treatment strategies for patients after anterior cruciate ligament (ACL) rupture; early ACL reconstruction (index) versus rehabilitation plus an optional reconstruction in case of persistent instability (comparator).

Methods Patients aged between 18 to 65 years of age with a recent ACL rupture (< 2 months) were randomized between either an early ACL reconstruction (index) or a rehabilitation plus an optional reconstruction in case of persistent instability (comparator) after 3 months of rehabilitation. A cost-utility analysis was performed to compare both treatments during follow up of 2 years. Cost-effectiveness was calculated as incremental costs per Quality-adjusted life year (QALY) gained, using two perspectives: the health care and societal perspective. The uncertainty for costs and health effects was assessed by means of non-parametric bootstrapping.

Results A total of 167 patients were included in the study, of which 85 were randomized to the early ACL reconstruction (index) group and 82 to the rehabilitation and optional reconstruction group (comparator). From the health care and societal perspective it takes 48460 € and 78179 €, respectively, to gain a QALY when performing early surgery compared to rehabilitation plus an optional reconstruction. This is unlikely to be cost-effective.

Conclusion Routine early ACL reconstruction (index) is not considered cost-effective as compared to rehabilitation plus optional reconstruction for a standard ACL population (comparator) given the maximum willingness to pay of 20,000 €/QALY. Early recognition of the patients that have better outcome of early ACL reconstruction might make rehabilitation and optional reconstruction even more cost-effective.

INTRODUCTION

Anterior cruciate ligament (ACL) rupture is one of the most common injuries in the young athlete. For patients after ACL rupture knee-related quality of life is impaired for more than 20 years compared to population norms, and even more when compared to peers. (1, 2) Not only for the individual, but also from a societal perspective ACL rupture has a huge impact. The number of ACL ruptures and reconstructions are increasing. In the past 15 years the number of ACL reconstructions in the Netherlands increased with over 130 % from around 3600 reconstructions in 2003 to over 8400 in 2018. (3, 4) This increase in number of reconstructions leads to an increased socioeconomic burden.

Treatment options after ACL rupture are an early ACL reconstruction, or a rehabilitation and optional reconstruction in case of persistent instability. Both treatments can lead to comparable clinical results and do not show a difference in the occurrence of post-traumatic osteoarthritis. (5-7)

On one hand, rehabilitation and optional reconstruction after this rehabilitation period is more uncertain for patient and surgeon with the risk of recurrent instability and delayed reconstruction versus an early ACL reconstruction. On the other hand in case of early ACL reconstruction, such surgery has the risk of complications as amongst others stiffness (1-4%), septic arthritis (0.1-1.7%), deep venous thrombosis (0.53 to 14.9 %) and re-rupture of the graft (3.2-11.1%) (8, 9), while a part of the patients would not have needed this surgery when they had tried rehabilitation first.

With the increasing health care costs and comparable clinical outcome of different medical treatments, value calculations are becoming increasingly important.(10) They provide essential information for patients, physicians and policy makers in health care to support their decisions.

Several studies have been published on the costs of ACL reconstruction with different grafts and with a decision tree analysis for competitive athletes, but so far not with the use of real patient-data of a randomized controlled trial. (11-13)

The aim of this study was to evaluate the cost-effectiveness of early ACL reconstruction (index) versus rehabilitation plus an optional reconstruction after acute ACL rupture (comparator) with the use of data of a randomized controlled trial.

METHODS

This cost-effectiveness study was performed with the data of the COMPARE study (Conservative vs Operative Methods for Patients with ACL Rupture Evaluation), an open label randomized controlled trial for patients after an acute ACL rupture. Patients were randomized to an early ACL reconstruction(index), or rehabilitation plus an optional reconstruction in case of recurrent instability after a rehabilitation period of three months

(comparator). For a full description of the study and results we refer to the clinical outcome study. (14)

Briefly, data on quality of life (QoL), medical costs and productivity costs were collected through patient questionnaires performed at baseline, and 3, 6, 9, 12 and 24 months follow-up. (15-17)

The COMPARE study was approved by the medical ethics committee of the Erasmus MC (MEC-2010-291) and registered in the Dutch trial registry NTR 2618. All patients signed informed consent.

Cost-effectiveness was calculated as incremental costs per Quality-adjusted life year (QALY) gained of early ACL reconstruction(index) compared to rehabilitation plus optional reconstruction (comparator), using two perspectives: the medical perspective and the societal perspective.(18)

We used the 3-Level EuroQol questionnaire (EQ-5D-3L) to assess QoL.(19) The 3-Level Euroqol covers five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems and extreme problems. The outcome score is between 1 (best quality of life) and 0 (very poor comparable to death), and a normative value for persons aged 30-39 is 0.901. Some health states can be considered as even worse than death and therefore even negative values are possible (20).

Over the period of 2 years the difference in area under the curve of the QoL between-groups was calculated to determine the QoL gain per year in QALY.

From the medical perspective, medical costs related to knee problems were included: cost of hospital care (including incremental imaging, surgery and outpatient clinics visits), non-hospital care (such as physical therapy, general practitioners care) and medication use with the use of the iMTA Medical Consumption Questionnaire (iMCQ).

From the societal perspective both medical and non-medical costs related to knee problems were included. Non-medical costs refer to productivity costs related to paid work (due to absence from work because of knee related problems, using the friction cost method and/or reduced productivity at work) and costs related to a lower ability to perform unpaid activities because of knee related problems (such as household tasks) with the use of the iMTA Productivity Cost Questionnaire (iPCQ.)(15) Other non-medical costs refer to travel costs to and from hospitals and suppliers of community care. Non-medical costs were calculated using the most recent Dutch guidelines for economic evaluation studies in health care. (17)

Analysis

Patients were analyzed according the intention-to-treat principle. Missing values for costs and/or quality of life were imputed, based on linear interpolation in case the amount of missing values was less than 20%. Adjustments for baseline values would have used if there

Table 1: Baseline characteristics

	Early reconstruction (n=85)	Rehabilitation plus an optional reconstruction (n=82)
Age, years	31.2 (± 10.3)	31.4 (± 10.7)
Female, no (%)	36 (42.4)	31 (37.8)
Body Mass Index, kg/m²	24.3 (± 3.7)	25.0 (± 4.1)
Tegner score (0-10)	7.0 (± 2.3)	7.1 (± 2.0)
College education, no. (%)	30 (35.3)	36 (43.9)
Paid work, no. (%)	71 (83.5)	64 (78.0)
EQ-5D	0.74 (± 0.201)	0.75 (± 0.212)

Mean with standard deviation between parentheses or reported otherwise

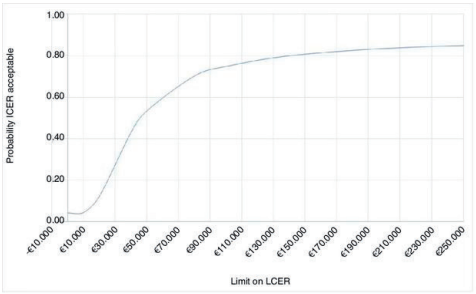
were relevant differences in baseline characteristics among the study groups. Costs and QALY's were summed over the 24 months study period using the information of all follow-up moments. Differences in QALY's measured by the differences between the two area under the curves over the 24 month period of the treatment arms were tested by a T-test between early reconstruction versus rehabilitation plus optional reconstruction.

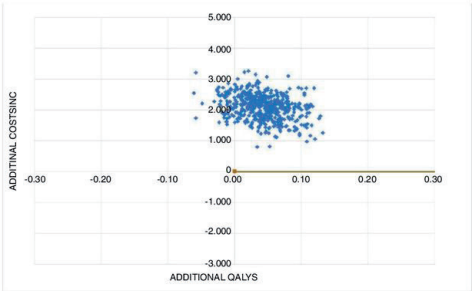
The uncertainty for costs and health effects was assessed by means of non-parametric bootstrapping, in which 5000 observations were randomly drawn from the available study. (21) The incremental costs and health effects for each bootstrap sample were displayed on a cost-effectiveness (CE) plane. An acceptability curve was drawn to indicate the probability that the cost-effectiveness ratio is acceptable, given various thresholds for the maximum willingness to pay for one QALY gained.

RESULTS

Patients

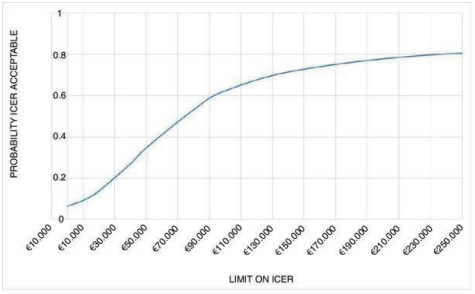
Baseline characteristics are presented in table 1, and did not differ among the study groups. In the randomized controlled trial 167 patients were included, of which 85 were randomized to the early ACL reconstruction (index) and 82 to the rehabilitation plus optional reconstruction. Of the 85 patients randomized to early ACL reconstruction (index), 3 patients were not reconstructed; one because of tomophobia and two because of negative instability testing under anesthesia. Of the 82 patients treated with rehabilitation and optional reconstruction, 41 patients (50%) eventually received reconstruction surgery during 2-year follow up. Follow up rates were considered high with 98 % among the different groups. The amount of missing values among the cost and quality of life data during follow-up was less than 20%.

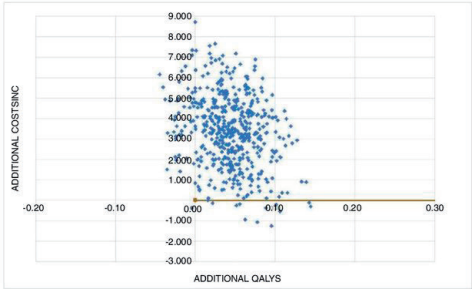




ICER= incremental cost-effectiveness ratio

Figure 1: Quality of life (EQ-5D) during follow up for patients treated with early reconstruction versus patients treated with rehabilitation plus optional reconstruction.





ICER= incremental cost-effectiveness ratio

Figure 2: Results of the cost-utility are depicted from the health care perspective. On the left the cost-effectiveness plane and on the right the acceptability curve.

Quality of life

For the period of 24 months patients in both treatment arms experience a quality of life between 0.72 and 0.84. Patients treated with an early reconstruction (n=85) have a total of 1.73 (SD 0.20) QALY and patients treated with rehabilitation plus an optional reconstruction (n=82) have a total of 1.69 (SD 0.21) QALY during the study period. On average, patients treated with an early reconstruction have a slightly better quality of life, as the difference is about 0.04 QALYs over the course of two years, see figure 1 (p-value = 0.18).

Costs

Medical costs were 6368 € (Standard Deviation (SD) 1630 €) in the early reconstruction group and 4267 € (SD 3011 €) in the rehabilitation plus optional reconstruction group. Productivity cost were 8489 € (SD 9659 €) in the early reconstruction group and 7214 € (SD 9137 €) in the rehabilitation plus optional reconstruction group, see table 3. Productivity costs due to paid work vary substantially across patients in both arms (see large SDs in table 3)

Table 2: Average costs per patient per treatment arm in Euros

	Early reconstruction (n=85)	Rehabilitation plus an optional reconstruction (n=82)
MEDICAL		
Hospital costs (SD)	4348 (1130)	2526 (1947)
Extramural costs		
- Sports medicine	23	44
- General practitioner	16	18
- Occupational medicine	33	19
- Physical therapist	1931	1650
Sum Extramural	2003 (1166)	1731 (1386)
Medication	16	10
1.Total costs from medical perspective (SD)	**6367 (1630)**	**4267 (3011)**
SOCIETAL		
absence paid work (SD)	5636 (7549)	4448 (6987)
presenteeism paid work (SD)	1480 (2931)	1262 (2624)
unpaid work(SD)	1373 (2636)	1504 (3045)
2.Productivity costs total (SD)	**8489 (9659)**	**7214 (9137)**
3.Direct non-medical costs (travel costs)	**94**	**79**
Total costs from societal perspective (1+2+3)	**14,951 (10004)**	**11,558 (10579)**

Table 3: Cost-utility results of early reconstruction versus rehabilitation plus optional reconstruction

	Medical perspective	Societal perspective
Incremental cost (in €)	2101	3393
Incremental QALYs	0.043	0.043
Incremental cost per QALY (ICER in €)	48,460	78,179

ICER=incremental cost-effectiveness ratio of early ACL reconstruction(index) versus rehabilitation plus an optional reconstruction in case of recurrent instability(comparator)

Cost-utility

Table 3 shows the results of the cost-utility analysis for both treatment regiments. Applying the medical perspective it takes 48.460 € to gain a QALY when performing early reconstruction instead of rehabilitation plus an optional reconstruction.

With the iMTA disease burden calculator we estimated patients loss of QALY around 5 % compared to healthy peers, which is estimated as a low burden of disease. (22) Given this low burden of disease patients experience after ACL rupture, the maximum willingness to pay in the Netherlands would be up to 20,000 €/QALY according to the Dutch Healthcare Institute.(10) The uncertainty analysis (bootstrapping) indicates that the probability that the cost-utility meets this standard is 12%. In case of a threshold of 50,000 € per QALY gained, this probability is 54%.

Using the societal perspective it takes 78.179 € to gain a QALY when performing early reconstruction compared to rehabilitation plus an optional reconstruction. In figure 2 the results of the cost-utility are depicted from the health care perspective. Early

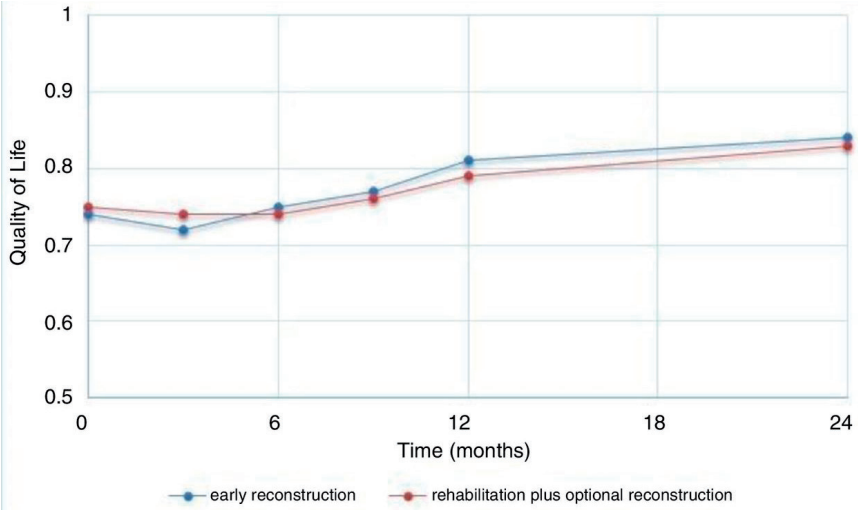


Figure 3: Results of the cost-utility are depicted from the societal perspective. On the left the cost-effectiveness plane and on the right the acceptability curve.

reconstruction led to better quality of life in 90 % of bootstrap replications (right side of the diagram) ; in 92 % of the replications early reconstruction led to a more expensive treatment (upper right quadrant). Almost all of the 10 % patients with a worse quality of life were more costly (upper left quadrant). The uncertainty analysis gives a 14% probability that incremental costs are lower than 20.000 € per QALY. In case of a threshold of 50.000 € per QALY gained, this probability is 35%. This is illustrated in the acceptability curve from the societal perspective (figure 3)

DISCUSSION

We are the first to analyze the cost-utility of two commonly used treatments for patients after ACL rupture with the use of actual patient data from a randomized controlled trial. Both treatments resulted in a relatively good quality of life. Patients treated with an early ACL reconstruction (index) experienced a slightly higher quality of life over the observed 24-month period. On the other hand early ACL reconstruction (index) leads to higher costs (both medical and non-medical). This resulted in a cost utility ratio of 48.460 €/QALY from the medical perspective and 78.179 €/QALY from the societal perspective.

As the quality of life of these patients is relatively good, the burden of disease is limited. Health related quality of life after ACL rupture is even better compared to a general population, probably due to the fact that ACL rupture more common in healthy and active individuals.(1) Given the low burden of disease patients experience after ACL rupture, the maximum willingness to pay would be up to € 20,000/QALY in the Netherlands,

according to the advice of the Dutch Healthcare Institute.(23) Uncertainty analysis gives a 12 % probability for the medical perspective and 14% for the societal perspective to meet this criterion, which is considered low. Therefore it is unlikely for early ACL reconstruction (index) to be cost-effective, compared to rehabilitation plus optional reconstruction, according to Dutch policy standards.

The early ACL reconstruction not being cost-effective is mostly caused by the low difference in QALY of 0.04 between both groups. This low difference in quality of life is in line with other clinical outcome measures used in the clinical study (amongst others the International knee documentation committee score (IKDC), Knee Injury and Osteoarthritis Outcome Score, and the Lysholm) and therefore we are confident that the difference between groups is not underestimated.(14)

In the rehabilitation plus an optional reconstruction in case of recurrent instability (comparator) group there are two distinct groups; patients who perform well with rehabilitation alone and patients with a delayed reconstruction. Patients who succeed with rehabilitation alone have the highest mean QALY (of 1.74 over two years) and lowest mean medical costs of 1988 euro and mean societal costs per patient of 7.223 €. Patients treated with a delayed ACL reconstruction have the lowest mean QALY (of 1.64 over two years) and highest mean medical costs of 6656 and mean societal costs of 16.111 € per patient.

If we are able to discriminate patients at an early stage that perform well with rehabilitation from those who don't, it is likely we decrease costs even more by reducing the number of patients who have two rehabilitation programs; one before the reconstruction and one after.

To estimate the willingness to pay for a specific condition is an ethical and political issue. We used the recommended method for calculating the burden of disease (proportional shortfall). A limitation of this method is that it only partially takes into account the patients' age. One could argue that a younger patient has more value on an ACL reconstruction, because he has more active life years to go.(24) But, given the relatively good quality of life these patients still have, it is still unlikely that direct reconstruction would then be considered cost-effective. Also we might be more reserved with an early ACL reconstruction in younger patients, because young and active patients have the highest risk of a new knee injury possibly and the young might be helped more in the long run with adjustment of their activity level.(8)

Von Essen et al (13) found that acute reconstruction resulted in less sick-leave days and fewer indirect costs to the individual and society and was cost-effective. But they did not take into account that 50 percent of patients treated with a rehabilitation program are doing well with this treatment and were not reconstructed after all.

Strengths of our study are the use of the largest multicenter randomized controlled trial for patients after ACL rupture, a high 2-year follow up rate of 98% and clear analysis of cost-utility by the latest standards.

Possible limitation of our study include the broad inclusion criteria; we used broad inclusion criteria (eg. 18-65 years of age and patients with all activity levels) and analyzed the groups as a whole. This leads to high level of generalizability, but might take away differences for certain subgroups. It is likely that in selected patient groups the procedure will be more cost-effective as, for example in the study of Stewart BA et al. found a cost-utility ratio of $ 22.702 per QALY gained in competitive athletes with the use of a decision tree analysis. (12)

Another limitation is the variability in costs as seen in the high SD especially in the societal costs and the relatively small patient numbers to perform the cost-effectiveness analysis.

In conclusion, an early ACL reconstruction(index) leads to a 0.04 increase in QALY over a period of 2 year compared to rehabilitation plus an optional reconstruction, but is with a cost of 48,460 € /QALY (medical perspective) to 78,179 € /QALY (societal perspective) not considered cost-effective for routine practice.

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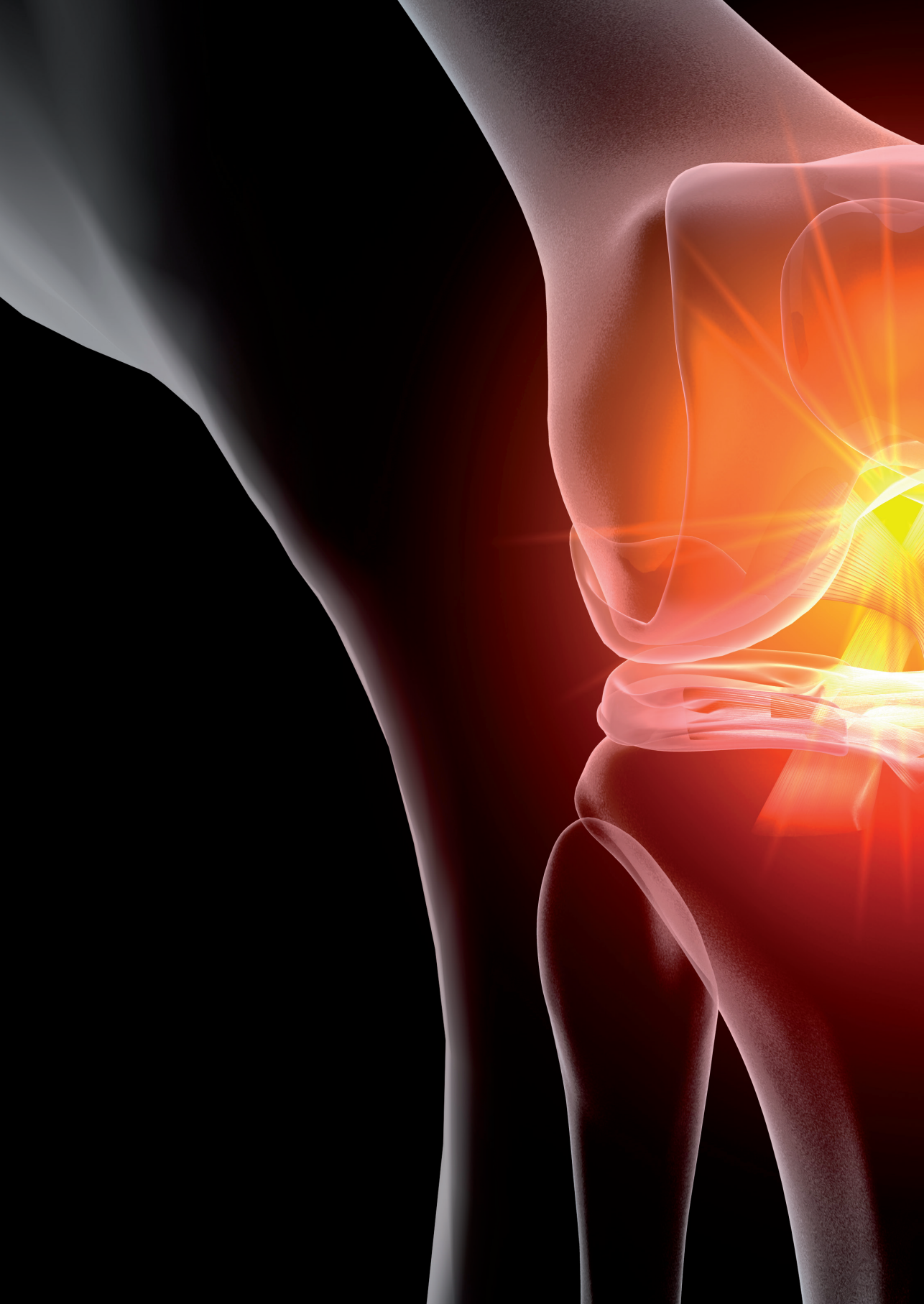

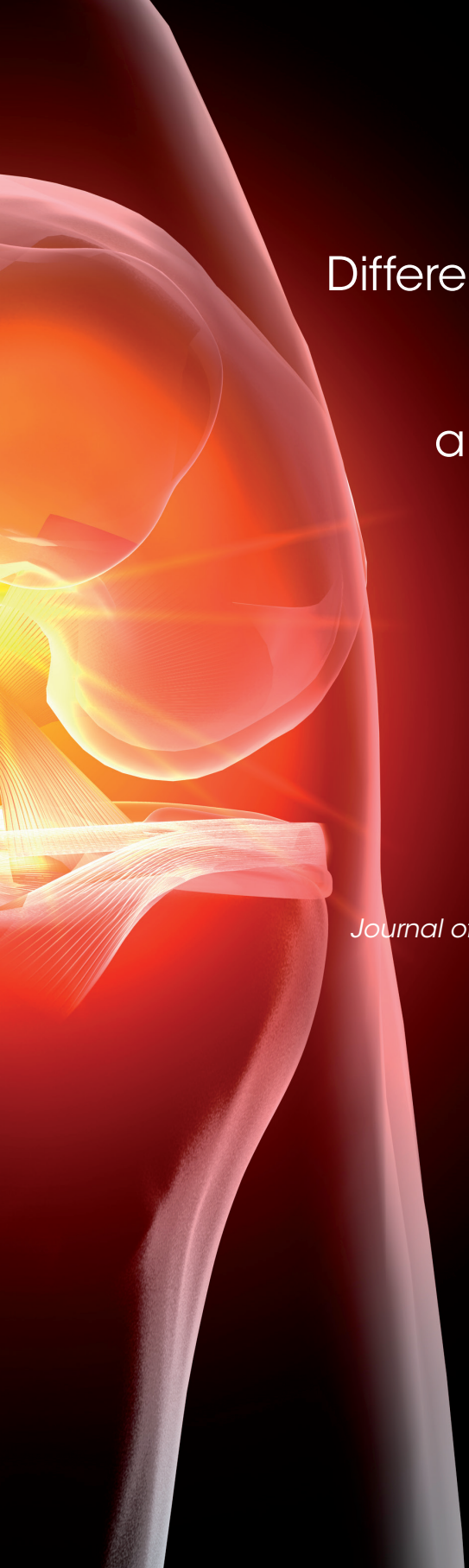

Chapter 4

Differences in knee geometry between ACL injured and non-injured: a matched case-control study of 168 patients

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ABSTRACT

Purpose Anterior cruciate ligament injury prevention programs can be more effective if we are able to select patients at risk for sustaining an ACL rupture. The purpose of this study is to identify radiographic differences in shape of the knee between patients with and patients without an ACL rupture.

Methods We compared the lateral view X-rays and Rosenberg view X-rays of 168 prospectively followed patients with a ruptured ACL to a control group of patients matched for gender with an intact ACL after knee trauma. Statistical shape modelling software was used to assess knee shape and find differences in anatomical landmarks between both groups.

Results On the Rosenberg view X-rays, we found five shape variants to be significantly different between patients with an ACL rupture compared to patients with an intact ACL after knee trauma. Overall, patients who had ruptured their ACL had smaller, flatter intercondylar notches, a lower lateral tibia plateau, a lower medial spike of the eminence and a smaller tibial eminence than control patients.

Conclusion Patients with an ACL rupture have smaller intercondylar notches and a smaller tibial eminences compared to patients with an intact ACL after knee trauma.

INTRODUCTION

Anterior cruciate ligament (ACL) rupture is a common, usually sports-related injury, with an annual incidence of approximately 5 to 8 per 10,000 persons in the general population(1-5). Rupture of the ACL has immediate consequences resulting in swelling of the knee and pain, but also long-term consequences, as there is an almost fourfold risk to progress to moderate or severe radiological osteoarthritis after ten years (6). Furthermore, in the young population ACL rupture has a direct impact on sport participation. It has been found for instance, that after ACL reconstruction 82% of the patients returned to some kind of sport participation, however only 63% returned to their preinjury sport level (5, 7, 8). Amongst young patients who return to their previous sports activity, the prevalence of second ACL injury may be as high as 30%.(9, 10). Also reports show that around 7% of patients need revision ACL surgery and around 3.4% of patients have ACL reconstructions on the contralateral side(11).

This had led to a rise of interest in the mechanism of ACL rupture, in risk factors and prevention of ACL rupture (12)and secondary ACL injury (13). Neuromuscular and proprioceptive prevention programs have been demonstrated to significantly reduce the prevalence of ACL ruptures in young athletes by approximately 50 % (12, 14-16). However these prevention programs can be more efficient if they focus on athletes who are at increased risk of sustaining an ACL rupture. Therefore it is essential to understand the mechanisms that lead to ACL rupture and to identify individuals with an increased risk of ACL rupture.

There is a relationship between shape of the knee and the need for reconstruction of the ACL after rupture(17). This has encouraged us to study the relationship between shape and rupture of the ACL more profoundly. Risk factors for ACL rupture can be categorized into anatomical, hormonal, neuro-mechanical and environmental. In the present study we focussed on osseous anatomical risk factors; Anatomical risk factors have previously been studied with focus on selected aspects of the anatomical properties of the knee. Anatomical factors that have been reported to be related to the risk of ACL rupture are increased tibial slope, decreased femoral notch size and smaller ACL size(18, 19). With the use of Statistical Shape Modeling (SSM), a sophisticated hypothesis generating methodology which identifies independent shape variants, it is possible to quantitatively describe the total morphology of a bone or joint. SSM reproduces all variation in shape that is present in the studied population.

SSM has been used earlier by our group to determine whether certain shape aspects are correlated to clinical outcome after ACL rupture(20). We found that operatively treated patients with good subjective outcome as evaluated by The International Knee Documentation Committee (IKDC) questionnaire had a smaller intercondylar notch and a smaller width of the intercondylar eminence compared to patients with worse outcome. Nonoperatively treated patients with good subjective outcome had a more pyramidal shaped intercondylar notch (.

The purpose of this current study was to identify radiographic differences in knee shape between patients with and patients without an ACL rupture by use of SSM.

PATIENTS AND METHODS

Cases

We included patients with a ruptured ACL from two previous series:, the KNALL (21)and the CAS-ACL study(22).

The KNALL (KNee osteoArthritis anterior cruciate Ligament Lesion) study is a prospective observational follow-up study of 154 patients with a recent ACL rupture, who were treated operatively or non-operatively. The inclusion period was from January 2009 to November 2010 with a follow-up period of two years. ACL rupture was diagnosed by physical examination and MRI. Patients were included from three participating hospitals.

The CAS-ACL study is a double-blinded randomized controlled trial of 100 patients who underwent ACL reconstruction. The study compared computer assisted ACL reconstruction with conventional ACL reconstruction (23). The inclusion period was from January 2007 to November 2009 with a follow-up period of two years. Of the 254 patients included in the two studies, 183 had both Rosenberg view and lateral view radiographs and were enrolled in the present study. Both studies were approved by our medical ethics committee (MEC-2006-223 and MEC-2008-068).

Controls

The control group consisted of patients identified retrospectively from the hospital records. They had consulted a trauma or orthopedic surgeon because of a knee trauma (median of 3 months and a range of 1-60 months between trauma and x-ray) with proven intact ACL on MRI and/or by arthroscopy. Hospital records from January 2003 till July 2013 were searched. Patients were included in the control group if they had both standard lateral view and Rosenberg view radiographs at the time of the first consult; were practicing sports (documented in our electronic patients files) before the injury (to be sufficiently exposed to rotational trauma) and had a Kellgren & Lawrence grade 0-1 at presentation (no radiological signs of osteoarthritis).

Control patients and cases were matched for gender. For age our patients were matched with a control patient older of age, to ensure that these patients were sufficiently at risk for ACL rupture. Of all patients found in the database, 168 control patients were matched to 168 patients with a ruptured ACL. See figure 1. We were unable to match all patients due to younger age, since we wanted to only include older control patients. Fifteen control patients were younger than the matches from the ACL ruptured group.

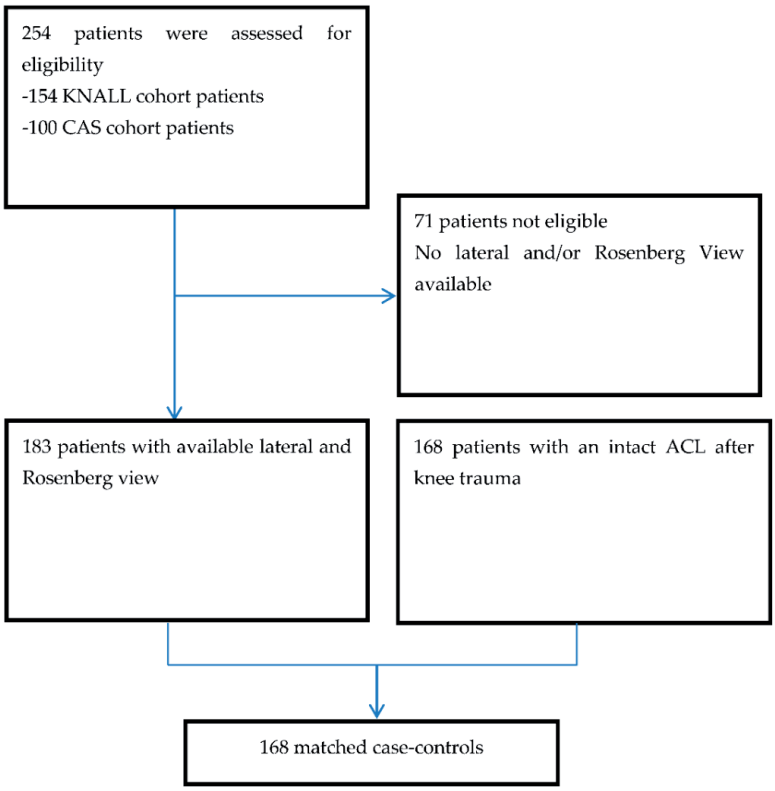

Figure 1: Flowchart of the selected patients included in the study. KNee osteoArthritis anterior cruciate Ligament Lesion (KNALL); Computer Assisted Surgery (CAS).

X-rays and Statistical Shape Modelling

The radiological measurements were performed on standard non-weight bearing lateral view radiographs and Rosenberg view radiographs. The Rosenberg view is a weight-bearing posteroanterior radiograph taken at 45 ° flexion of the knee (24). We have chosen to include the Rosenberg view x-rays because it gives a better view of the intercondylar notch and gives better insights in the shape of the femur.

With statistical shape modelling (SSM) (25) it is possible to quantify the general shape of the knee joint on the radiographs. This method is unique because it deconstructs nearly all variation in shape into a limited number of quantitative measures that each describes distinct shape variants. SSM has been used in studies of a possible association between knee shape variants and osteoarthritis (26, 27). On the radiographs, we outlined the distal femur, the proximal tibia and fibula (ASM tool kit, Manchester University, Manchester, UK).

The shape of the distal femur and proximal tibia were defined by 60 landmark points for the lateral view and 25 landmark points for the Rosenberg view, that were placed along the surface of the bone on the x-rays. Each point was placed on the same location in each

image to allow comparison between shapes, for the exact placement of each landmark point, see the addendum. Statistical shape modelling transforms the set of points into a statistical shape model, which comprises a number of shape variants that together explain 95 % of variation in shape of the individual knee of the study population. SSM represents relative variation in shape, independent of differences in size of the joint. In this way, the method corrects errors caused by variation in magnification or in the size of the patient's knee.

Intra-observer reliability was assessed by randomly selecting 25 Rosenberg view x-rays of patients with a ruptured ACL and 25 Rosenberg view x-rays of patients with an intact ACL which were annotated a second time after 2 weeks.

The description of which shape aspects a variant represents was determined at a consensus meeting, which consisted of an orthopaedic surgeon with extensive experience in treating ACL ruptures, an expert on statistical shape modelling, the first authors and the principle investigator.

Statistical analysis

We used logistic regression analysis to study the association between each shape variant and whether or not patients had a ruptured ACL. As dependent variable we used whether or not a patient had an ACL rupture (yes or no) and as independent variables we selected the different variants. We applied Bonferroni correction for multiple testing. We investigated if there was a significant effect of the x-ray protocol on knee shape, by comparing the shape models of the x-rays taken in the three participating hospitals. Furthermore, we analyzed if correction for age changed the outcomes. All Statistical analyses were performed with IBM SPSS Statistics for Windows (Version 20.0. Armonk, NY: IBM Corp).

RESULTS

Patients

The study population consisted of 2 groups of 168 patients; each group consisted of 119 males and 49 females. The mean age of the 168 patients after ACL rupture was 31 (± standard deviation (SD) 7,4) years and of the control group 38 (± sd 12) year (Table 1). The diagnoses of the control patients is shown in table 3. The mean time between trauma and radiograph was 1.0 months for the ACL injured and 6.9 months for the control group.

SSM

SSM produced 30 variants for the Rosenberg view and 24 variants for the lateral view x-rays. After we applied Bonferroni correction for multiple testing, we considered a p-value of 0.0017 for the Rosenberg view (0.05/30=0.00167) and a p-value of 0.0021 for the lateral view (0.05/24=0.0021) as statistically significant.

Table I: Baseline Deomgraphic Variables

	ACL injured (n = 168)	Control group (n = 168)
Age, year	31 ± 7.4	38 ± 7.4
BMI, kg/m2	24.5 ± 3.4	24.7 ± 3.2
Female n (%)	49 (29.1)	49 (29.1)
Mean time in months between trauma and radiograph	1.0	6.9

Data are expressed as mean ± standard deviation
BMI, body mas index

Table 2: Shape variants associated with ACL rupture

	Odds ratio	95% C.I.	Sig.
Variant 1	2.2	(1.7 – 2.8)	.001
Variant 3	1.8	(1.4 – 2.3)	.001
Variant 6	2.1	(1.6 – 2.7)	.001
Variant 10	1.5	(1.2 – 1.8)	.001
Variant 17	1.4	(1.1 – 1.8)	.0015

Table 3: Diagnosis of control patients

Diagnosis, n (%)		
Medial meniscus tear	57	(33.9)
Lateral meniscus tear	32	(19)
Cartilage lesion	15	(8.9)
Bone contusion	11	(6.5)
Collateral ligament lesion	7	(4.2)
No intra-articular lesions	46	(27.4)

On the Rosenberg views five variants were significantly associated with rupture of the ACL (see Table 2). For the lateral view x-rays, none of the variants were statistically significantly associated with rupture of the ACL.

We analyzed whether the protocols of the X rays differed in the period of time of which the x-rays were taken. We didn't find a significant difference between the three hospitals, nor did we find a significant difference in time. Correction for age did not alter the outcomes, therefore we did not correct for age.

The intra observer ICC of the placement of the points was considered good to excellent with a range of 0.48-0.97 and 89% above the 0.7;

Description of the variants

Below we present a description of the variants significantly associated with ACL rupture. The software produces graphics, of which the extremes (+2SD and -2SD) for each variant are shown in figure 2 on the left and right side. In the middle an overlay is presented. Higher variants describe more subtle shape aspects, e.g. the variation in shape represented in variant 17 is a much more subtle than the variation represented by variant 1.

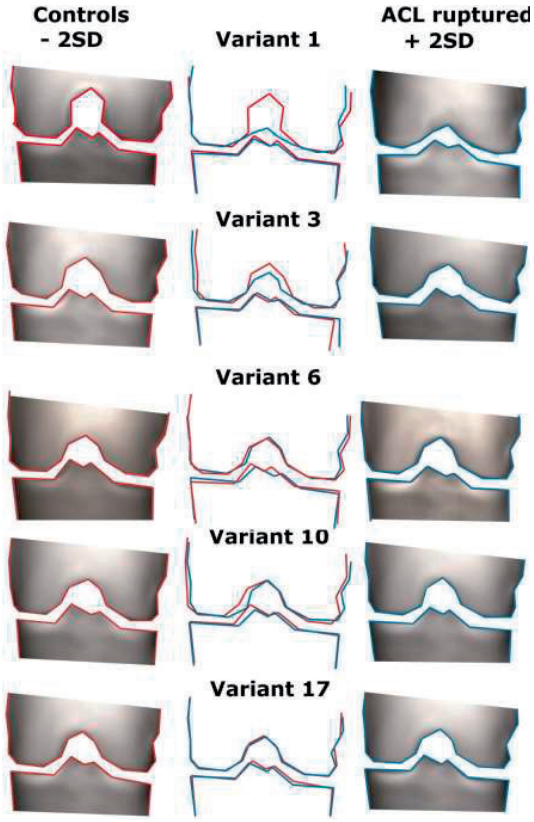

Figure 2: Graphic outcomes of statistic shape modeling: five variants that are significantly different for patients with intact and ruptured ACL. On the left and right sides are the two extremes (+/– 2.5 SD); in the middle is the overlay of both sides. SD = Standard.

Variant 1

Variant 1 describes a variation in height of the intercondylar notch. Positive values represent a more flattened intercondylar notch. Patients with an ACL rupture had flatter intercondylar notches than control patients.

Variant 3

Variant 3 shows a variation in width and height of the intercondylar notch. Positive values represent a smaller intercondylar notch. Patients with an ACL rupture had smaller intercondylar notches than control patients.

Variant 6

Variant 6 represents the size of the footprint of the ACL on the tibial eminence. Positive values represent a smaller tibial eminence. Patients with an ACL rupture had a smaller tibial eminence than control patients.

Variant 10

Variant 10 outlines the footprint of the ACL on the tibia and also the width of the tibial eminence and the width of the intercondylar notch. Positive values represent a smaller tibial eminence and a smaller intercondylar notch. Patients with ACL rupture had a smaller tibial eminence and a smaller intercondylar notch.

Variant 17

Variant 17 depicts a very subtle difference. Positive values represent a lower height of the lateral tibial plateau and the lower medial spike of the tibial eminence. Patients with an ACL rupture had a lower lateral tibia plateau and a lower medial spike of the intercondylar eminence.

DISCUSSION

The most important finding of the present study is that aspects of bony morphology on the Rosenberg view X-ray of the knee joint were different between patients with a ruptured ACL and a matched control group. Our findings indicate that smaller, a flatter intercondylar notch, a lower lateral tibia plateau, a lower medial spike of the eminence and a smaller tibial eminence is more common in patients who ruptured their ACL compared to control patients. Lower body strength exercises (Nordic hamstring, lunges and heel-calf raise) are not performed by all (professional) athletes, but have proven to reduce the risk of ACL rupture (28). If we are able to identify patients at higher risk for ACL injury, injury prevention programmes will be even more effective. Our results could, for example, be used during sports medical screening: Most professional athletes already undergo x-rays of the knee in the medical screening process.

The results of our study are consistent with studies in the past, which also found the femoral notch size, and the notch width index related to ACL rupture (29, 30). However, these previously conducted studies where primarily focused on anterior-posterior x-rays, while we used the Rosenberg view x-rays. The study of van Diek et al.(31) found no differences in morphology between patients with an ACL rupture and a control group in measurements with MRI. Though, another MRI study performed by Whitney et al (32) found a decreased femoral notch width to be related to ACL rupture. This was also a case-control study. A smaller femoral notch and smaller tibial eminence are related to smaller ACL size (33, 34). It is plausible that a smaller ACL could be less strong compared to a larger sized ACL. The ACL is the main structure to prevent the bony relatively instable lateral compartment from rotatory dislocation, i.e. rotation anterior of the tibia relative to femur. The finding of a lower lateral tibia plateau in ACL patients could inspire to the theory that these patients have even worse bony stability regarding in the lateral compartment, which could be a risk factor for ACL injury.

On the Lateral view x-rays, we did not find an association between shape variants and ACL rupture. Earlier, it has been demonstrated that the femoral condyle configuration (35) and the posterior tibial slope (PTS) (36-38) are related to increased stress on the ACL, but it is not known, if this is connected to a higher risk of ACL rupture. .

We understand that all the odds ratios are relative small, but all the provided variants show a significant relationship to an ACL rupture, with odds ratio's comparable to that of other studies investigating anatomical variants of the knee(18, 31). Further research could focus primarily on the shape variants found in this study and see if these results can be reproduced. Furthermore, prospective studies should be performed to see if, with these risk factors, the prevalence of ACL ruptures can be reduced.

A drawback of SSM is that it is not immediately clear what a shape variant specifically represents as is the case with predefined morphological measures and it does not provide us with a measurable cut of point yet. We used an expert consensus meeting to determine which shape aspects were captured in each variant.

The strength of our study is the use of a large study population of 336 patients, who all practiced sports. An advantage of SSM is that the various variants represent relative variation in shape, independent of differences in size of the joint. In this way the method reduces errors caused by variation in magnification.

We used Rosenberg and standard lateral view X-rays for our analyses. In 1997 Shelbourne et al(39) already advocated the use of Rosenberg view X-rays, because of the standardized protocol. The advantage of the use of x-rays is that they are easily obtained, relatively cheap and have a low patient radiation dose and thus are ideal for identifying risk factors for sustaining an ACL rupture on large groups of asymptomatic patients.

An interesting sequel of this research would be to compare the differences in bony morphology between patients with and without a re-rupture after ACL reconstruction. This could help the clinician in giving patient individualized information on risk of re-rupture.

Clinical relevance

This hypothesis generating research is a step forward in identifying and also excluding anatomical risk factors for sustaining an ACL rupture. Screening programs for professional athletes could focus on the intercondylar notch and tibial eminence as a risk factor. For example, it is well known that females are at higher risk for sustaining an ACL rupture. Gender is a not changeable determinant, yet training programs focus on female athletes. When our results are confirmed in future studies, screening programs could also focus on these determinants and include patients with a higher risk of sustaining an ACL in their training programs. These studies should try to find easy useable measurements, which can be used by every clinician in daily practice. In the past, research stated that the tibial slope could also be a determinant for sustaining an ACL rupture, however, it is not known, if this is connected to a higher risk of ACL rupture. Our research did not find similar results.

Excluding potential risk factors is also important because research should focus on risk factors that are more likely to be associated with sustaining ACL rupture.

Conclusion

This study indicates that a smaller, a flatter intercondylar notch, a lower lateral tibia plateau, a lower medial spike of the eminence and a smaller tibial eminence is more common in patients who ruptured their ACL compared to control patients.

Further research should focus on ways to implement these differences in bony morphology in prevention programs to prevent ACL rupture in an individual who is at greater risk for sustaining ACL rupture.

Perspective

With this current study, we used a hypothesis generating program to find anatomical risk factors for sustaining an ACL rupture. Previous research has shown that knee injury prevention programs have been proven effective (16). With this study, we possibly found risk factors for sustaining an ACL rupture, which in the future should be used to secelt athletes at greater risk for sustaining ACL injury, and thereby making these programs more cost effective. In the past, research stated that the tibial slope could also be a determinant for sustaining an ACL rupture(40), however, our research does not support this. This could be due to variantion in the methods used between these studies and our current studies. Excluding potential risk factors is also important because research should focus on risk factors that are more likely to be associated with sustaining ACL rupture.

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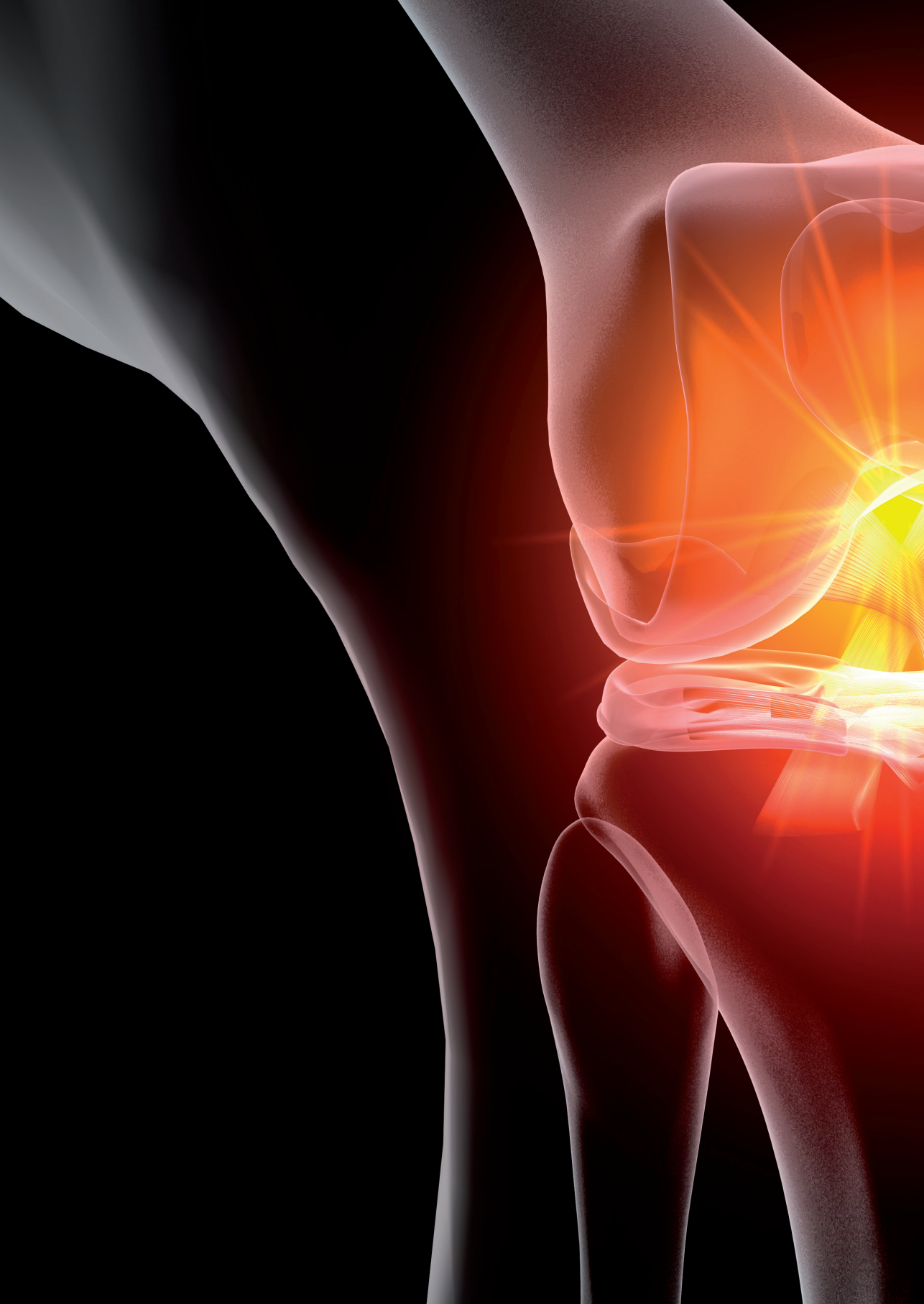

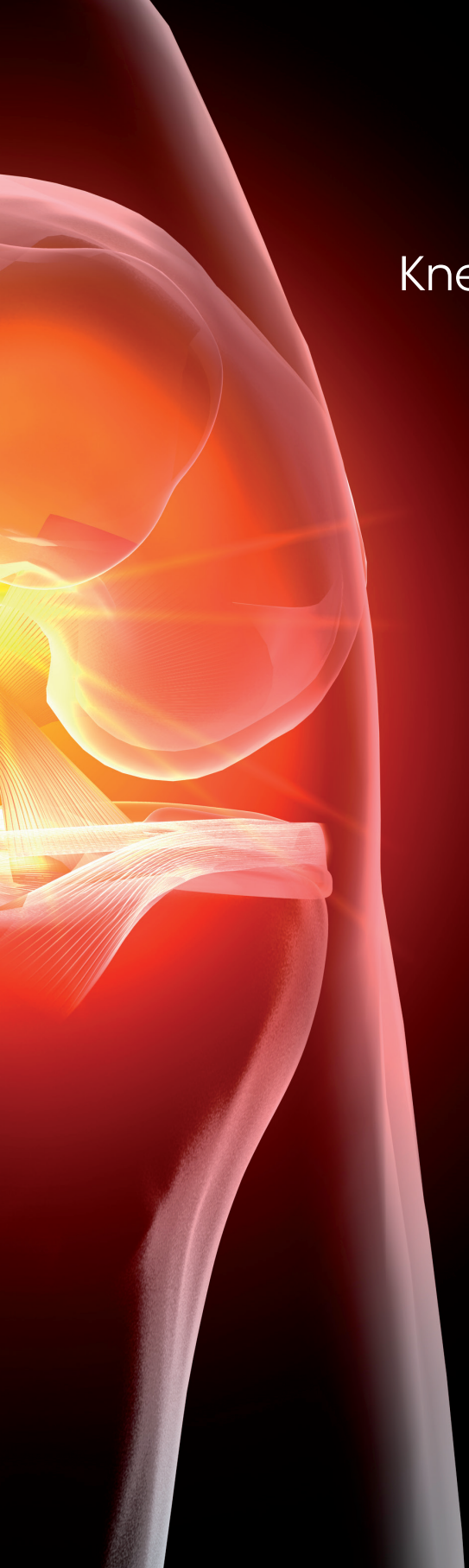

Chapter 5

Knee shape might predict clinical outcome after an anterior cruciate ligament rupture

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ABSTRACT

Objective We have investigated whether shape of the knee can predict the clinical outcome of patients after an anterior cruciate ligament rupture.

Methods We used statistical shape modelling to measure the shape of the knee joint of 182 prospectively followed patients on lateral and Rosenberg view radiographs of the knee after a rupture of the anterior cruciate ligament. Subsequently, we associated knee shape with the International Knee Documentation Committee subjective score at two years follow-up.

Results The mean age of patients was 31 years (21 to 51), the majority were male (n = 121) and treated operatively (n = 135). We found two modes (shape variations) that were significantly associated with the subjective score at two years: one for the operatively treated group ($p = 0.002$) and one for the non-operatively treated group ($p = 0.003$). Operatively treated patients who had higher subjective scores had a smaller intercondylar notch and a smaller width of the intercondylar eminence. Non-operatively treated patients who scored higher on the subjective score had a more pyramidal intercondylar notch as opposed to one that was more dome-shaped.

Conclusion We conclude that the shape of the femoral notch and the intercondylar eminence is predictive of clinical outcome two years after a rupture of the anterior cruciate ligament.

INTRODUCTION

Rupture of the anterior cruciate ligament (ACL) is a common sports-related injury. The annual incidence is estimated at five per 10 000 persons in the general population. (1) ACL rupture can lead to complaints of instability in the short term, which negatively influences the quality of life and level of sporting activity. In the long term, an ACL rupture is associated with an increased risk of osteoarthritis, which varies from 13% to 48%, depending on secondary injuries. (2) At present clinical outcome after an ACL rupture is not predictable. (3) Additional injuries to the knee might forecast a less successful outcome after an ACL rupture according to a population-based register. (4) However, these supplementary injuries cannot be used to give an individual patient a clear prediction on their expected clinical outcome. The availability of objective predictors would aid the provision of accurate information for patients as to what they might expect. A study of 100 patients by Fridén et al. demonstrated that a more spherical shape of the femoral condyles was predictive of failure of non-operative treatment. (5) However, conventional radiographs were used with lines drawn on them by the researcher. This manual method provided a low inter-observer correlation coefficient and they had no patient reported outcome measures (PROMs), basing their end point on whether patients underwent an ACL reconstruction. (6) Another measure of anatomical shape is the tibial slope. (7) Using the same patients and outcome measures, Kostogiannis et al found that reconstructed knees were over-represented where there were extremely low tibial slope angles. (7) The shape of the knee can be assessed using radiographs and generally after a knee injury, a radiograph will have been obtained. Because of this widespread availability and low cost, it would be very useful if the radiographs could be used to predict outcomes after an ACL rupture. Our objective was to evaluate whether the shape of the knee on the presenting radiographs can predict clinical outcomes of patients after an ACL rupture.

PATIENTS AND METHODS

Patients were identified from two previously conducted prospective studies at the Erasmus MC Department of Orthopaedic Surgery; the Knee steoarthritis anterior cruciate Ligament Lesion (KNALL) and the Computer Assisted Surgery for Anterior Cruciate Ligament injury (CAS-ACL) study. (8,9)

The KNALL is a prospective observational study of 154 patients with a recent ACL rupture, who were treated either operatively or non-operatively. The inclusion period of the KNALL study was from January 2009 to November 2010 with a follow-up period of two years. The CAS-ACL study is a double-blinded randomised clinical trial of 100 patients, for whom ACL reconstruction was indicated. The study compared computer-assisted ACL reconstruction with conventional ACL reconstruction. (9) The inclusion period of the CAS-

ACL study was from January 2007 to November 2009, with a follow-up period of two years. Radiographs, patient characteristics and International Knee Documentation Committee (IKDC)-subjective score at baseline and at the two years follow-up were obtained. (10) Both studies were approved by the medical ethics committee and a written consent was obtained from all patients. For the present study, we selected those patients for whom we had lateral and Rosenberg view radiographs, IKDC- subjective-score and two years of follow-up. (11) The combination of the KNALL study and the CAS-ACL study created a database of 257 patients. Of these patients, a total of 182 fulfilled the inclusion criteria, of whom 135 had been treated operatively (74.2%) and 47 non-operatively (Fig. 1). All participants had a complete primary ACL rupture and a mean age of 31 years (21 to 51) in the absence of any injury to the posterior cruciate ligament. The demographic data, time to reconstruction and IKDC-subjective scores of the patients is provided in Table I. The radiological measurements were performed on non-weight bearing, standard lateral and Rosenberg view radiographs. The Rosenberg view is a weight-bearing posterior-anterior radiograph taken at 45° flexion of the knee. (11) With statistical shape modelling (SSM) it is possible to quantify the general shape of the knee joint on the radiographs. (12) This method is unique because it deconstructs nearly all variation in shape into a limited number of quantitative measures that each describes distinct shape variants. In a recent study by our group, SSM was employed to see whether knee-shape variants were associated with the development of osteoarthritis. (13) From the radiographs, we outlined the shape of the distal femur and the proximal tibia and fibula with the use of SSM software (ASM tool kit, Manchester University, Manchester, United Kingdom). (12) The shapes were defined by 60 landmarks on the lateral view and 25 landmarks on the Rosenberg view, which were placed along the contour of the bone in the image. Each point was placed at the same location in each image to allow comparison between shapes. The researcher who placed the points was blinded to the clinical outcome of the patient. Principal component analysis was used to transform the set of point co-ordinates into the statistical shape model, which comprises a number of shape variants (modes) that together explain 95% of variation in shape of the knees in the study population. The description of a definition of a mode was determined at a consensus meeting, which consisted of an orthopaedic surgeon with extensive experience in treating ACL ruptures (DEM), an expert on statistical shape modelling (JHW) and the first two authors of this study (VE, KSRvK). Intraobserver reliability was assessed by randomly selecting 26 knees which were annotated a second time after four weeks. Our primary outcome score was the IKDC-subjective score at two-years follow-up. The IKDC-subjective Knee Form was designed to measure symptoms and limitations in function and sporting activity due to impairment of the knee for every knee-related injury. (14, 15) In a review of available outcome measurements for ligament injuries of the knee, Johnson and Smith and Van Meer et al found that the IKDC-subjective knee form is the preferred measurement tool for monitoring patients after an ACL rupture, particularly in the short term. (10, 16)

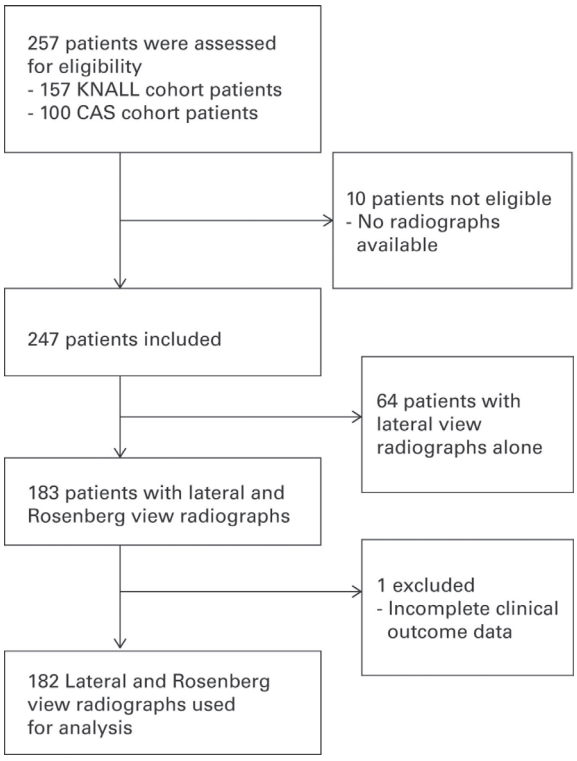

Figure 1: Flowchart of the selected patients included in the study. KNee osteoArthritis anterior cruciate Ligament Lesion (KNALL); Computer Assisted Surgery (CAS).

Statistical analysis

The association between separate modes with the IKDC-subjective score at two-years follow-up was analysed using linear regression analyses. We performed a separate analysis for the operatively and non-operatively treated patients. IKDC-subjective score was used as dependent variable and the different modes as independent variables. We selected all the modes with a p-value < 0.05 with the use of univariate analyses and considered them as modes, with a possible association with the IKDC-subjective score at two years. A p-value < 0.01 was considered significant. We adjusted for known confounders for the IKDC-subjective score such as BMI, age and gender and the IKDC-subjective score at inclusion. (17-19) Reliability of positioning of the landmarks was tested by assessing intra-class correlation coefficient (ICC) with a two-way random model for absolute agreement. All statistical analyses were performed with IBM SPSS Statistics v.20.0 (IBM, Armonk, New York).

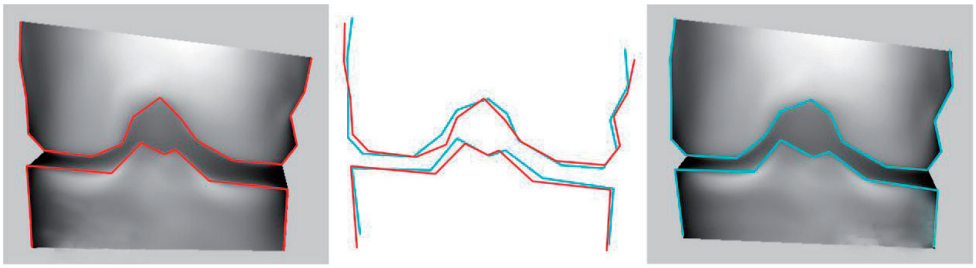

Figure 2: Digital images of the extreme shape variables for mode 9 represented as -2.5 standard deviation (SD) (left) and +2.5 SD (right).

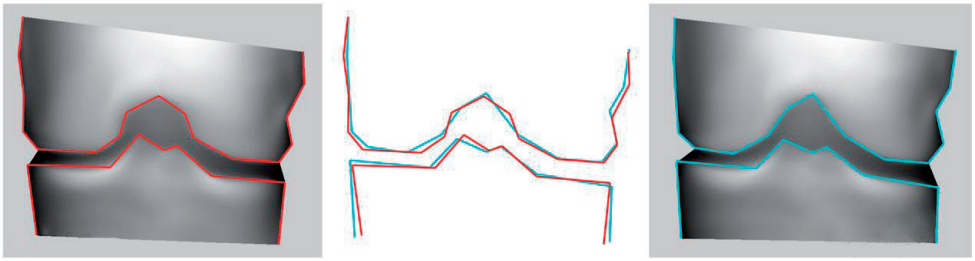

Figure 3: Digital images of the extreme shape variables for mode 15 represented as -3.0 standard deviations (SD) (left) and +3.0 SD (right).

RESULTS

There was no statistical difference in mean IKDC-subjective after two years between the operatively treated and the non-operatively treated group of patients, 85.9 (SD 13.5) and 85.4 (SD 12.7), respectively ($p = 0.835$) (Table I). The SSM provided 20 modes for the lateral radiographs (mode 0 to mode 19) and 28 modes for the Rosenberg view (mode 0 to mode 27). Tables II and III represent the modes and their correlation coefficients with $p < 0.05$. The intra-observer ICC was considered good, with a mean of 0.805 (0.48 to 0.97), 89% above the 0.7; the ICC was below the 0.7 for only three modes. With multivariate analysis we found five modes with $p < 0.05$ for the lateral view which had an association with the IKDC-subjective scores (Mode 4: $p = 0.02$; mode 6: $p = 0.013$; mode 7: $p = 0.026$; mode 8: $p = 0.042$; mode 10: $p = 0.039$). For the Rosenberg, we found five modes with $p < 0.05$ which had an association with the IKDC-subjective scores (mode 9: $p = 0.002$; mode 12: $p = 0.045$; mode 14: $p = 0.032$; mode 21: $p = 0.047$; mode 22: $p = 0.014$). In the univariate analyses, only mode 9 on the Rosenberg view was significantly predictive of the clinical outcome at two years ($p = 0.002$). Mode 9 describes the width of the intercondylar eminence and the width of the intercondylar notch, the variation in shape for mode 9 is shown in Figure 2. Patients with a smaller intercondylar eminence and a smaller intercondylar notch, scored higher on the IKDC subjective at two years. We found one mode with $p < 0.05$ for the lateral

Table I: Patient characteristics and clinical outcome. Data shown as mean value (range) (IKDC, International Knee Documentation Committee)

	Operative (n = 134)	**Non-operative (n = 48)**	**p-value**
Age	30 (21 to 51)	33 (21 to 47)	0.012
Weight (kg)	77 (52 to 123)	78 (52 to 125)	0.677
Height (cm)	178 (159 to 197)	175 (158 to 197)	0.062
Body mass index	24 (18 to 38)	25 (21 to 41)	0.209
Female	n = 43	n = 16	0.331
Time to reconstruction (mths)	17 (1 to 180)	-	-
IKDC-subjective for	57.3 (19.5 to 9 3.1)	58.8 (18.4 to 97.7)	0.617
IKDC-subjective form (two-years follow-up)	85.9 (36.8 to 100)	84.9 (51.7 to 100)	0.835

Table 2: Modes of the Rosenberg radiograph and correlation with clinical outcome. P-values are corrected for confounders for the International Knee Documentation Committee score (mean body mass index, age, gender and IKDC-subjective score at baseline)

	Non-operatively treated patients		**Operatively treated patients**	
	R^2	**p-value**	**R^2**	**p-value**
Mode 9			0.153	0.002
Mode 12			0.094	0.045
Mode 14			0.101	0.032
Mode 15	0.357	0.003		
Mode 20			0.092	0.050
Mode 21			0.093	0.047
Mode 22			0.118	0.014

Table 3: Modes of the lateral radiograph and correlation with clinical outcome. P-values are corrected for confounders for the International Knee Documentation Committee (IKDC) score (mean body mass index, age, gender and IKDC-subjective score at baseline)

	Non-operatively treated		**Operatively treated**	
	R^2	**p-value**	**R^2**	**p-value**
Mode 4			0.108	0.020
Mode 6			0.116	0.013
Mode 7			0.103	0.026
Mode 8			0.093	0.042
Mode 10			0.095	0.039
Mode 17	0.249	0.041		

view which had an association with the IKDC-subjective score (mode 17: $p = 0.041$). For the Rosenberg view, we found two modes with $p < 0.05$ which had an association with the IKDC-subjective scores (mode 5: $p = 0.019$; mode 15: $p = 0.003$). In the univariate analyses only mode 15 on the Rosenberg view was significantly predictive of the clinical outcome at two years ($p = 0.003$). Mode 15 describes the shape of the intercondylar notch with the variation demonstrated in Figure 3. Patients with pyramid-shaped intercondylar notch,

similar to the A shape as described by Van Eck et al20 scored higher on the IKDC-subjective score at two years compared with a more dome-shaped intercondylar notch.

DISCUSSION

The main finding of this prospective cohort study was that two specific shape variants of the knee are predictive of clinical outcome two years after an ACL rupture; mode 9 in the operatively treated group and mode 15 in the non-operatively treated group. Mode 9 represents a variation in the width of the intercondylar notch and the intercondylar eminence. A smaller intercondylar notch and a smaller intercondylar eminence predicted a better clinical outcome for patients who underwent operative reconstruction on the IKDC-subjective score at two years follow-up. Mode 15 represents a variation in steepness of the intercondylar notch in the non-operatively treated group. A possible explanation for our finding is that patients with a smaller intercondylar notch also had a smaller size of their native ACL. (18) In this way, the graft used in ACL reconstruction bears more resemblance to the native ACL. Consistent with this idea is that patients with a larger notch have a relatively smaller graft compared with their native ACL and there is more of a mismatch between graft and notch size. Several studies in the past suggested that a larger graft is less likely to fail. (21-23) An explanation for the fact that mode 15 can predict clinical outcome after non-operative treatment for patients after ACL rupture, is that patients with a pyramid-shaped notch have a larger contact area between femur and tibia. In this way, the femur and tibia have a more intrinsically stable construction and such a patient may be able to reach a higher level of function despite the ligament rupture. Our method to assess the shape of the knee with SSM creates modes. These modes are a combination of variation in different aspects of the shape. The advantage of SSM is that it objectively creates a set of shape variants that explain 95% of the variation. (24) Nevertheless, it is not possible with SSM to extract the factor that contributes the greatest amount to the mode. It is possible that if we only take one contributing factor out of mode, then any correlation is lost. Previous studies also focused on other anatomical variants thought to be predictive of outcome after an ACL rupture, such as the tibial slope and the sphericity of the femoral condyle on the lateral radiograph. (5, 7) Our study could not confirm the influence of these shape variants on clinical outcome. On the lateral view radiograph, no mode was predictive of clinical outcome after an ACL rupture. The difference between our findings and the previously published studies might be explained by the use of different outcome measures and another method being used to assess the shape of the knee. Previous studies used reconstruction of the ACL as an outcome measure, whereas we used a validated PROM. The strengths of this study are the use of a large group of prospectively followed patients and the use of radiographs for depicting the shape of the knee. The benefits of the use of radiographs are that they are widely available and relatively inexpensive. A limitation of this

study is that the knee is a complex three-dimensional joint, of which some shape variations are attributable to a combination of the lateral and the Rosenberg projections. We tried to fully outline the important contours of the femur, tibia and fibula aided by the placement of the landmarks. An advantage of SSM is that the various modes represent relative variation in shape, independent of differences in size of the joint, such that the method reduces errors caused by variation in magnification. In conclusion, this study demonstrates that two shape variants can predict a better score on the IKDC-subjective score at two years, one for the operatively treated group and one for the non-operatively treated group. Our results suggest that in the future, clinicians will identify the shape of the knee when informing patients with an ACL rupture on what they might expect their clinical outcome to be.

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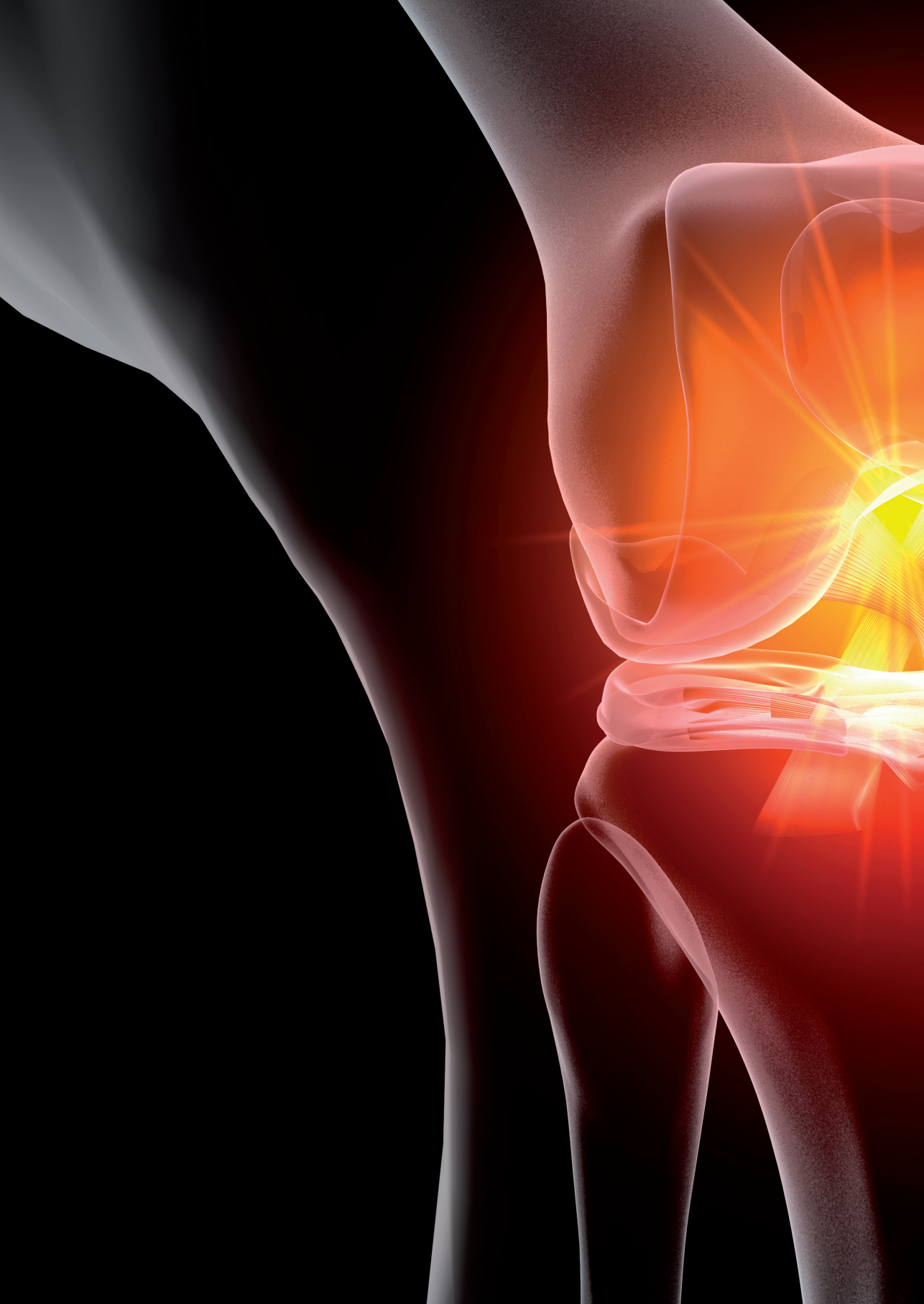

Chapter 6

Factors related to the need for surgical reconstruction after anterior cruciate ligament rupture: a systematic review of the literature

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ABSTRACT

Objectives To summarize and evaluate research on factors predictive of progression to surgery after nonoperative treatment for an anterior cruciate ligament (ACL) rupture.

Background Anterior cruciate ligament rupture is a common injury among young, active individuals. Surgical reconstruction is often required for patients who do not regain satisfactory knee function following nonsurgical rehabilitation. Knowledge of factors that predict the need for surgical reconstruction of the ACL would be helpful to guide the decision-making process in this population.

Methods A search was performed for studies predicting the need for surgery after nonoperative treatment for ACL rupture in the Embase, MEDLINE (OvidSP), Web of Science, CINAHL, Cochrane Central Register of Controlled Trials, PubMed, and Google Scholar digital databases from inception to October 2013. Two reviewers independently selected the studies and performed a quality assessment. Best-evidence synthesis was used to summarize the evidence of factors predicting the need for surgical reconstruction after nonoperative treatment for an ACL rupture.

Results Seven studies were included, 3 of which were of high quality. Based on these studies, neither sex (strong evidence) nor the severity of knee joint laxity (moderate evidence) can predict whether, soon after ACL injury, a patient will need ACL reconstruction following nonoperative treatment. All other factors identified in this review either had conflicting or only minimal evidence as to their level of association with the need for surgical reconstruction. Noteworthy is that 1 high-quality study reported that the spherical shape of the femoral condyle was predictive of the need for ACL reconstruction.

Conclusion Sex and knee joint laxity tests do not predict the need for ACL reconstruction soon after an ACL rupture. Independent validation in future research will be necessary to establish whether knee shape is a predictive factor.

INTRODUCTION

Anterior cruciate ligament (ACL) rupture is a common injury, with an estimated incidence of 4 new cases per 10000 people yearly. (27) Anterior cruciate ligament rupture has a high impact not only on the personal life of the individual, who must undertake a long recovery period, but also on society, owing to loss of productivity and medical costs.(3, 9, 16)

In past decades, many studies of various treatment options post–ACL rupture have been published. (12, 21, 22) Nonoperative management of ACL ruptures has been shown to result in good clinical outcomes in the short, medium, and long term. (2, 4, 15, 24)

For example, a recently published randomized controlled trial by Frobell and colleagues indicated that clinical outcomes 5 years postinjury in patients successfully treated nonoperatively were comparable to outcomes in those treated with surgical reconstruction. (15) The study found no increased risk of osteoarthritis or meniscal surgery and no significant difference in patient function, activity level, quality of life, pain, symptoms, and general health between surgical and nonsurgical treatment of an ACL tear.

These data suggest that a large portion of individuals will reach a good level of function without reconstruction of the ACL. However, a significant proportion of patients who are not satisfied with their knee function, either because they are unable to reach a desired sports activity level or because of recurrent givingway episodes, will opt to undergo ACL reconstruction. Unfortunately, ACL reconstruction is not always successful, as indicated by Ardern et al, who, based on their review of the literature, reported that only 63% of individuals return to sports after ACL reconstruction. (1)

The 2012 ACL injury guidelines from the Dutch Orthopaedic Association recommend that symptomatic instability of the knee after ACL injury that is not reduced after an intense physiotherapeutic exercise program or after adjustment in activity level is a good indication for surgical reconstruction. (25) However, a potential risk of failed nonoperative treatment post–ACL rupture is the possibility of recurrent giving-way episodes, which may lead to secondary injuries to the meniscus and cartilage. (14, 18, 30) It should be noted that secondary injuries may also occur after surgical ACL reconstruction. (15)

The clinical decision to manage ACL rupture operatively or nonoperatively is usually based on the patient's preinjury activity level, fear of not being able to return to a previous level of sport ability, clinical knee instability test outcomes, age, and individual preference. (6, 19, 23, 31)

However, the predictive value of these factors to select the most appropriate management strategy post–ACL rupture is unclear. Identifying prognostic factors that could be used soon after the ACL injury to determine which individuals would be unlikely to succeed with nonoperative treatment could be useful in determining the need for surgical reconstruction of the ACL.

The purpose of this systematic review was to summarize the literature on prognostic factors identifying which patients require surgical reconstruction post–ACL rupture.

METHODS

Study Selection

A systematic search for relevant articles was performed in the Embase, MEDLINE (OvidSP), Web of Science, CINAHL, Cochrane Central Register of Controlled Trials, PubMed, and Google Scholar digital databases from inception to October 2013. The primary search phrases were anterior cruciate ligament, rupture, and nonoperative.

A full overview of the search criteria can be found in the APPENDIX.

The articles were assessed for eligibility by 2 reviewers (V.E. and M.R.) independently, using the inclusion criteria listed below. Additionally, the reference lists of the selected articles were manually searched to identify any additional articles of potential interest.

To be included, studies had to meet all of the following criteria: (1) to report the statistical association between a patient related factor and requirement for ACL reconstruction after nonoperative treatment of a complete, primary ACL rupture; (2) to verify a complete ACL rupture arthroscopically (gold standard test) or by a combination of physical examination and magnetic resonance imaging; (3) to be written in English, German, Italian, Spanish, French, or Dutch; (4) to be a randomized controlled trial, prospective, retrospective, or case-control study (not a systematic review or meta-analysis); (5) to have a follow-up period of at least 12 months; and (6) to have a sample size of at least 20 participants. Disagreement on inclusion was resolved by discussion or a final decision by a third reviewer (J.V.) if necessary.

Quality Assessment

The methodological quality of the included articles was evaluated with a quality assessment form that consisted of 11 items relevant to prognostic studies, such as the validity and reliability of determinants, selected outcome measures, and the statistical analysis. This form was composed in advance, based on existing quality assessment tools.(5, 7, 29)

Two reviewers (V.E. and M.R.) independently performed the quality assessment of the selected articles. Disagreement was resolved by discussion or a final decision by a third reviewer (J.V.) if necessary.

Studies were considered to be of high quality when all of the following items were scored as adequate: data were collected prospectively, consecutive patients were included, outcome and predictive factors were measured objectively, aims of the study were clearly stated, and a description of inclusion and exclusion criteria was provided.

Data Extraction

The main characteristics of the studies, outcome measures, and factors predicting outcome and their relationship with the outcome measures were extracted by 1 reviewer (V.E.).

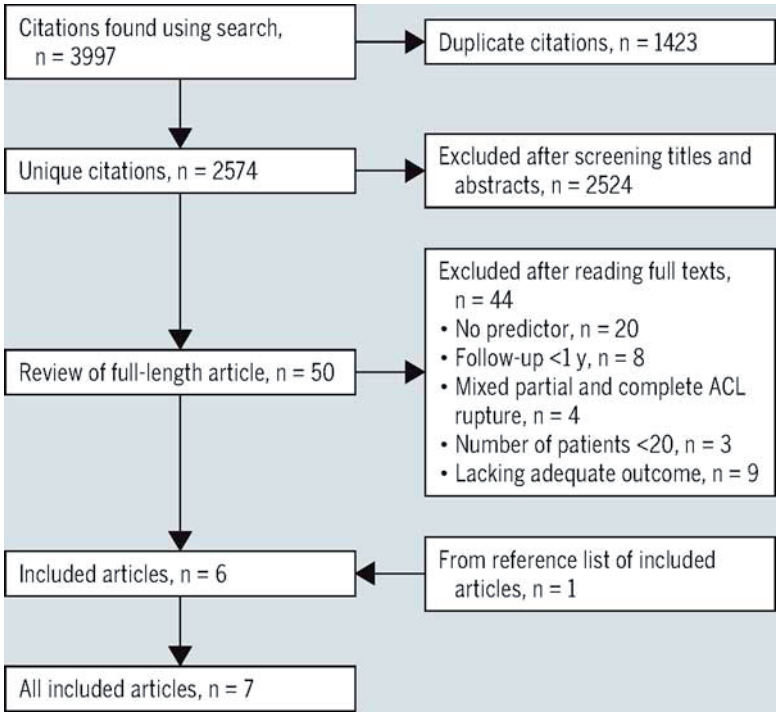

Figure 1: Flow chart of articles included in the literature review. Abbreviation: ACL, anterior cruciate ligament.

Best-Evidence Synthesis

Because the measures and follow-up times of the included studies were considered heterogeneous, the data were not statistically pooled. Instead, a best-evidence synthesis was used to outline the evidence available on factors predicting the outcome of nonoperative treatment after ACL rupture, and the following ranking of evidence was formulated in accordance with the method of van Tulder et al.: (32)

1. Strong evidence: 2 or more studies with high-quality results and generally consistent findings in all studies (75% or more of the studies reported consistent findings)
2. Moderate evidence: 1 high-quality study and 2 or more low-quality studies and generally consistent findings in all studies (75% or more of the studies reported consistent findings)
3. Limited evidence: 1 high-quality study or low-quality studies and generally consistent findings (75% or more of the studies reported consistent findings)
4. Conflicting evidence: conflicting findings (less than 75% of the studies reported consistent findings)
5. No evidence: no studies could be found

RESULTS

Search

The database search produced a total of 3997 articles, of which 50 (1.3%) were found to be appropriate after screening the title and abstract. Of these 50 articles, 44 were subsequently excluded after reading the full text because they did not meet the inclusion and exclusion criteria, leaving 6 articles (8, 13, 17, 20, 26, 28) to be included in the systematic review. Manual search of the reference lists of these 6 articles identified 1 extra article(FIGURE). (10) Disagreement on inclusion/ exclusion was resolved by discussion between the 2 assessors in all cases.

Included Studies

Table 1 gives an overview of the 7 studies retained for this review, consisting of 5 prospective cohort studies (8, 13, 20, 26, 28) 1 matched control study (17), and 1 prospective nonrandomized trial(10). All studies were published between 1993 and 2012 and solely included patients with a primary ACL rupture. The number of patients in the studies varied from 69 to 146, with a mean follow-up ranging from 1.1 to 15.7 years. The mean age of the included patients varied from 25 to 42 years. The studies were heterogeneous with regard to preinjury activity level (TABLE 1).

Quality Assessment

Three (43%) of the 7 included articles fulfilled the criteria for high-quality studies. (13, 20, 26) An overview of the quality assessment is provided in TABLE 2. Disagreement was resolved by discussion between the 2 assessors in all cases.

Factors Examined

Factors associated with eventual ACL reconstruction after nonoperative treatment are provided in TABLE 3.

Patient Characteristics

In 4 studies,(8, 13, 20, 26) the influence of patient characteristics on an eventual reconstruction after nonoperative treatment for ACL rupture was investigated. We found strong evidence that sex does not influence the risk of a reconstruction after nonoperative treatment for an ACL rupture. Limited evidence was found that height and weight do not influence the likelihood of a reconstruction. Conflicting evidence was found for the influence of age: the study by Eitzen et al (8) reported that patients who progressed to reconstruction were significantly younger, whereas 2 other high-quality studies (13, 20) found that age had no significant influence.

Table 1: Characteristics of the Included Studies

	Eitzen et al[8]	Fithian et al[10]	Fridén et al[13]	Grindem et al[17]	Kostogiannis et al[20]	Moksnes et al[26]	Neuman et al[28]
Sample, n	145	146	99	69	94	102	94
Age, y*	25.9 (14–47)	41.5 ± 12.4	25 (14–40)	27.9 ± 7.3	25.1 (14–43)	27.2 ± 8.6	26 ± 8.0
Female, %	52	55	41	46	41	45	42
Follow-up, y*	1.2	6.6 (3–10)	5 (3–6)	1.1 ± 0.1	15 (12–20)	1.1 ± 0.2	15.7 ± 1.4
Predictors	Age, sex, knee laxity, questionnaires, hop tests, medial collateral ligament injury, quadriceps strength index, activity level	Combination of predictors	Body weight, height, age, femoral condyle shape	Activity level, sports frequency, laxity, meniscal/ cartilage injury, questionnaires, hop tests, sex	Age, sex, activity level, knee laxity	Combination of tests	Knee laxity
Time between trauma and baseline measurement, d	59.8	<28	Unknown	74 (mean)	<10	82 (mean)	<10
Reason for surgery	Unknown	Unknown	Giving way An unacceptable activity level	Unknown	Patient's lack of acceptance of knee disability	Combination of factors	Frequent giving way Unacceptable function or activity level
Preinjury activity level	66% Hefti level I 34% Hefti level II	Tegner 6 (median)	Recreational sports or competed on a low to moderate level	54% Hefti level I 46% Hefti level II	Tegner 7 (median; range, 3–9)	68% Hefti level I 32% Hefti level II	Tegner <7, 41% Tegner ≥7, 59%

*Values are mean, mean (range), or mean 6 SD.

Table 2: Quality Assessment of the Studies Included in the Review*

	Question†										
Quality/Study	**1**	**2**	**3‡**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
High quality§											
Kostogiannis et al[20]	1	1	1	1	1	0	1	1	1	0	0
Moksnes et al[26]	1	1	1	1	1	1	1	0	1	0	0
Fridén et al[13]	1	1	1	1	1	0	0	1	1	0	0
Low quality‡											
Grindem et al[17]	1	0	0	1	1	1	1	1	1	0	1
Neuman et al[28]	1	1	0	1	1	0	1	1	1	0	1
Eitzen et al[8]	0	1	1	1	1	1	1	0	0	0	0
Fithian et al[11]	0	1	1	1	1	1	1	1	0	0	0

*0 is inadequate, 1 is adequate.

†(1) Inclusion of consecutive patients? Did the authors state: "consecutive patients" or "all patients during period from … to…." or "all patients fulfilling the inclusion criteria"? (2) Prospective collection of data? Did the authors state: "prospective" or "follow-up"? (3) Unbiased assessment of the study outcome and determinants/predictor? To be judged as adequate, the following 2 items had to be positive: (1) outcome and determinants had to be measured independently; and (2) both for cases and for controls, the outcome and determinants had to be assessed in the same manner. (4) A clearly stated aim? Did the authors have a "study question" or "primary aim" or "objective"? The question addressed should be precise and relevant in the light of available literature. To be scored adequate, the aim of the study should be coherent with the introduction section of the paper. (5) A description of inclusion and exclusion criteria? Did the authors report the inclusion and exclusion criteria? (6) Was the inclusion process transparent? Did the authors report how many eligible patients agreed to participate? (7) Were the determinants used accurate (valid and reliable)? For studies in which the determinant measures are shown to be valid and reliable as part of the study, an adequate score is provided. For studies that refer to other work that demonstrates the determinant measures are accurate, an adequate score is provided. (8) Follow-up period? Judged adequate if the follow-up period was considered sufficiently long to allow the assessment of the main outcome (minimum of 1 year). (9) Loss at follow-up? Judged adequate if the following 2 aspects were met: (1) losses of patients at follow-up were reported, and (2) the loss at follow-up was less than 20%. (10) Calculation of the sample size? Is there any information about the sample-size calculation? (11) Adequate statistical analyses? To be judged as adequate, the following 3 aspects had to be met: (1) there must be a description of the relationship between the predictor and outcome or a description of the comparison (with information about the statistical significance); (2) there must be adjustment for the following confounders: age and gender (if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses, the question should be answered inadequate); and (3) variance (eg, SD, confidence interval) of the reported outcomes was reported.

‡Questions 1–3 were necessary for high quality.

Physical Examination

Relationships between clinical tests and an eventual reconstruction after nonoperative treatment for an ACL rupture were evaluated in 4 studies (1 high-quality study(20) and 3 low-quality studies(8, 17, 28)). There is moderate evidence that tests for knee joint laxity (1 high-quality study(20) and 3 low-quality studies(8, 17, 28)), such as the pivot shift, Lachman test, and the KT1000 arthrometer (MEDmetric Corporation, San Diego, CA), do not predict an eventual reconstruction after nonoperative treatment. One high-quality study reported that concurrent injury to the medial collateral ligament is not predictive of later reconstruction. (20)Also, limited evidence was found that the presence of an injury to the meniscus or cartilage at the time of initial physical examination has no influence on the

Table 3: Factors Associated With Eventual Reconstruction of the ACL After Nonoperative Treatment*

Determinant	Positive Association†	Negative Association‡	No Association§	Best-Evidence Synthesis
Patient characteristics				
Age		8	**13,20**	Conflicting evidence
Body weight			**13**	Limited evidence for no association
Height			**13**	Limited evidence for no association
Sex (female)			8,**13,26**	Strong evidence for no association
Physical examination				
Laxity			8,17,**20,**28	Moderate evidence for no association
Quadriceps strength index			8	Limited evidence for no association
Hop tests			8,17	Limited evidence for no association
Meniscal/cartilage/MCL damage			8,17	Limited evidence for no association
Activity level				
Preinjury activity level	8		**20**	Conflicting evidence
Other factors				
Spherical shape of the femoral condyle	**13**			Limited evidence for a positive association
Predictive model A			**26**	Limited evidence for no association
Predictive model B¶			10	Limited evidence for no association
Predictive model C#	8			Limited evidence for a positive association

Abbreviation: MCL, medial collateral ligament.

*Numbers refer to the studies from the References section that were included in the review. Studies in bold are considered to be of high quality.

†An increase in the determinant leads to an increased likelihood of patients eventually needing reconstruction surgery.

‡An increase in the determinant leads to a decreased likelihood of patients eventually needing reconstruction surgery.

§No correlation was found between determinant and the eventual need for reconstruction surgery.

Consisted of 6-meter timed hop test, Knee Outcome Survey activities of daily living subscale, global rating of knee function assessed by a visual analog scale, and number of episodes of giving way.

¶Consisted of sports hours per year and the difference in anterior/posterior laxity between the injured and noninjured knees, assessed with the KT1000 arthrometer.

#Consisted of patients' age, activity level, giving-way episodes, Knee Outcome Survey activities of daily living subscale, International Knee Documentation Committee Subjective Knee Form 2000 score, 6-meter timed hop test, and quadriceps strength index.

need for eventual reconstruction after nonoperative treatment. (8, 17) There was limited evidence from 1 low-quality study that quadriceps strength deficit is not a significant predictor of a failed nonoperative treatment. (8) Finally, 1 low-quality study reported that 4 different hop tests independently do not significantly predict whether a patient will eventually need ACL reconstruction. (8)

Activity Level

Conflicting evidence was found for the influence of the preinjury activity level on the likelihood of requiring surgical ACL reconstruction. The study by Eitzen et al. determined that there were significantly more high-level athletes in the group of patients requiring an eventual ACL reconstruction. (8) On the other hand, Kostogiannis et al. did not find a difference in preinjury activity level between patients who eventually went through to surgery and those who did not. (20)

Other Factors

There is limited evidence from 1 high quality study that a more spherical shape of the femoral condyle, as measured from a lateral knee radiograph, predicted patients who needed surgical reconstruction of the ACL. (13)

Three studies (1 of high quality (26) and 2 of low quality (8, 10)) investigated whether the need for surgical reconstruction after nonoperative treatment could be predicted by a combination of patient characteristics, scores on self-report questionnaires, and physical examination findings. Eitzen et al. found that a combination of baseline characteristics could significantly distinguish between those patients who needed ACL reconstruction and those who did not ($P<.001$). (8)

The best predictive model for ACL reconstruction incorporated younger age, higher preinjury activity level, multiple giving-way episodes, lower score on the Knee Outcome Survey activities of daily living subscale (KOS-ADL), lower score on the International Knee Documentation Committee Subjective Knee Form 2000, lower limb symmetry index on the 6-meter timed hop test, and a lower quadriceps strength index. The other 2 studies found no correlation between their model and an eventual ACL reconstruction. (10,26)

In 2 other studies (10, 26), no predictive value was found for either the algorithm developed by Fitzgerald et al. (11) (1 highquality study) or the surgical risk factor criteria (10) (1 low-quality study) on the need for later ACL reconstruction. The algorithm developed by Fitzgerald et al. (11) classifies patients as potential copers if they meet all the following criteria: (1) hop test index of 80% or greater for the timed 6-meter hop test, (2) KOS-ADL score of 80% or greater, (3) global rating of knee function of 60 or greater, and (4) no more than 1 episode of giving way since the injury. The surgical risk factor criteria label individuals as high, medium, or low risk of late surgery based on preinjury hours of sports participation, arthrometer measurements, and patient age. (10)

DISCUSSION

In this systematic review, we summarized the available literature on factors predicting which patients may need reconstructive surgery after nonoperative treatment for an ACL rupture. Strong (8, 13, 26) and moderate (8, 17, 20, 28) evidence showed that sex and the

amount of knee joint laxity on primary physical examination, respectively, cannot predict whether a patient will progress to surgery after nonoperative treatment for an ACL rupture. The latter is especially noteworthy because laxity is often used in clinical decision making to opt for reconstruction. (10) Among the selected studies, there was limited evidence for only 1 factor that was able to predict patients who would progress to surgery after nonoperative treatment: the spherical shape of the femoral condyle, as described in a high-quality study by Fridén et al.(13) It is remarkable that this relationship has not been researched more extensively, as the shape of the femoral condyle is easily determined in clinical practice by measuring the condyle height and depth on radiographs and calculating a quotient. A potential explanation is that a more rounded condyle may promote greater displacement between the articular surfaces. However, a predictive association shown in a single study is not sufficient to influence clinical practice and, consequently, independent validation is necessary.

Three studies examined whether a combination of factors could predict the need for ACL reconstruction. In the first study, Moksnes et al. did not find the combination of a functional test (6-meter timed hop test), a self-report questionnaire (KOS-ADL), the subjective rating of the knee function using a visual analog scale, and clinical instability (number of giving-way episodes) predictive of requiring ACL reconstruction.(26) In a separate study, Fithian et al. determined that a combination of the amount of hours in sports participation per year and the amount of knee joint laxity did not predict the need for ACL reconstruction. (10) Finally, Eitzen et al. found a model that could predict 43% of the variance in whether or not patients would require ACL reconstruction.(8) The model consisted of younger age, higher activity level, more episodes of giving way, a lower KOS-ADL score, lower score on the International Knee Documentation Committee Subjective Knee Form 2000, lower limb symmetry index on the 6-meter timed hop test, and a lower quadriceps strength index.

The current study, to our knowledge, is the first to systematically review the literature on factors that may be associated with the need for surgical reconstruction after nonoperative treatment for an ACL rupture. Progression to surgery may be easily identified as an outcome measure, but it is not as objective as the results of some of the validated questionnaires, and may be subject to bias. Both patient and surgeon might make the decision for a reconstruction based on previous experiences or outcome of similar individual cases. In the studies included in the present review, the criteria for surgery were not reported and might not be similar. Also, because of the unclear indications for surgery, the question remains whether factors predictive for surgery are really patient-bound factors that increase the need for surgery or whether they reflect dogmatic theories in clinical practice.

A limitation of this review is the limited number of applicable studies. Despite extensive search, only 7 studies met the criteria for inclusion, of which only 3 were classified as high-quality studies.

It is also noteworthy that 6 of the 7 studies were performed by 2 research groups: 3 from a research group based in Oslo, Norway and 3 from a research group based in Lund,

Sweden. These 6 studies differed in sample population, predictors, and outcome measures; therefore, all were included in this review.

It was not possible to pool the results of the studies included in this review because of the heterogeneity of prognostic factors and the different time points used in measuring the prognostic factors. Instead, a best-evidence synthesis, which involves classification into high- and low-quality studies, was used. Such subdivision of studies is somewhat arbitrary, but to make this process as transparent as possible, the quality assessment is shown in TABLE 2.

This review included a comprehensive search for published studies on factors potentially associated with the need for reconstruction surgery after nonoperative treatment for ACL rupture, and the limited number of studies identified highlights the paucity of evidence. While a large proportion of patients (49%-85% after 5-year follow-up) after an ACL rupture seem to cope well with nonoperative treatment, based on the current evidence, we were not able to predict at an individual level whether a patient would require reconstruction surgery after nonoperative treatment. (13,15) Therefore, rehabilitation should be considered the primary treatment after ACL rupture.

CONCLUSION

This review highlights that the evidence available on factors predicting the need for ACL reconstruction after nonoperative treatment for an ACL rupture is scarce. However, based on the limited literature available, this review found strong evidence that sex and moderate evidence that knee joint laxity are not good predictors. All other factors identified in this review either had conflicting or minimal evidence as to their level of association with the need for surgical reconstruction. One high-quality study reported that the shape of the femoral condyle may be associated with an eventual reconstruction after nonoperative treatment.

Well-designed prospective studies of patients with an ACL rupture are needed to identify factors predicting who is less likely to benefit from nonsurgical management post–ACL rupture and who should therefore be treated surgically. Also, to make the pooling of data possible in the future, greater standardization is required in the assessment of baseline features and treatment outcomes after an ACL rupture. Based on the lack of clear predictors for failure of nonoperative treatment after an ACL rupture, we advise clinicians to be reserved in advising patients directly to opt for operative treatment.

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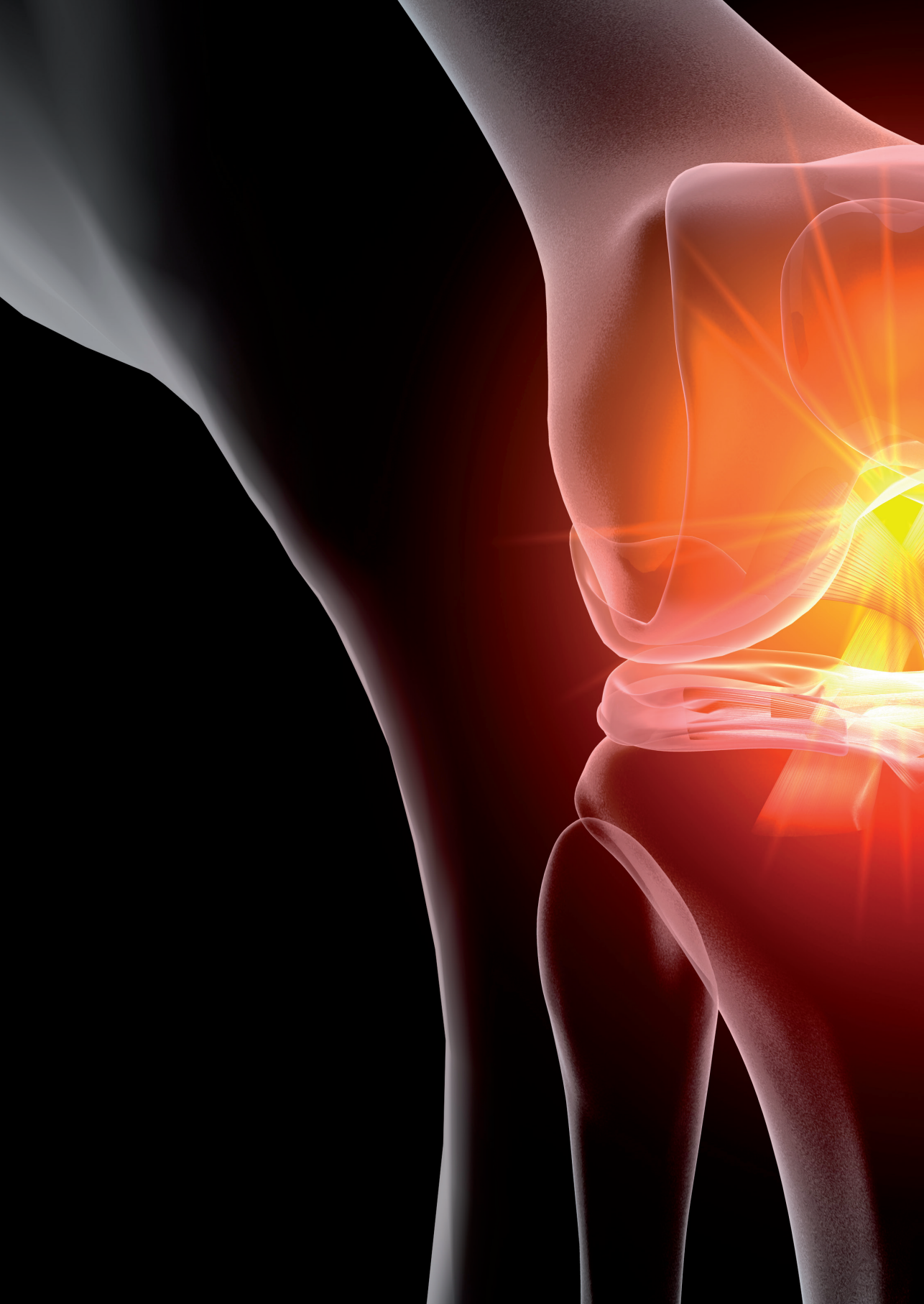

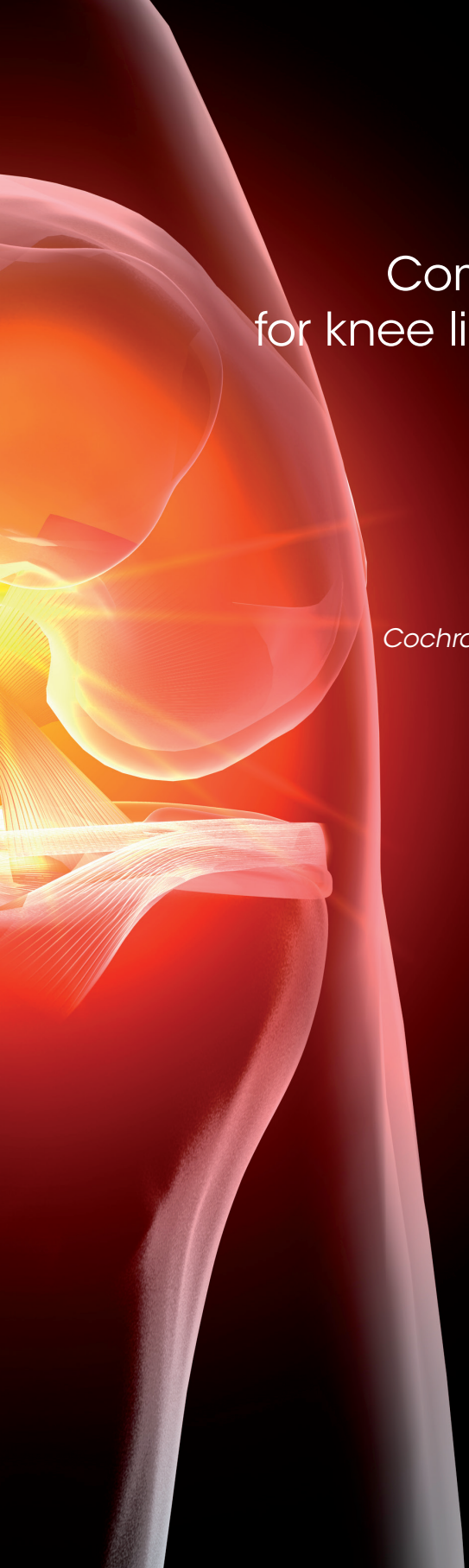

Chapter 7

Computer-assisted surgery for knee ligament reconstruction

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ABSTRACT

Background Anterior cruciate ligament (ACL) reconstruction is one of the most frequently performed orthopaedic procedures. The most common technical cause of reconstruction failure is graft malpositioning. Computer-assisted surgery (CAS) aims to improve the accuracy of graft placement. Although posterior cruciate ligament (PCL) injury and reconstruction are far less common, PCL reconstruction has comparable difficulties relating to graft placement. This is an update of a Cochrane review first published in 2011.

Objectives To assess the effects of computer-assisted reconstruction surgery versus conventional operating techniques for ACL or PCL injuries in adults.

Search methods For this update, we searched the Cochrane Bone, Joint and Muscle Trauma Group Specialised Register (from 2010 to July 2013), the Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 5, 2013), MEDLINE (from 2010 to July 2013), EMBASE (from 2010 to July 2013), CINAHL (from 2010 to July 2013), article references and prospective trial registers.

Selection criteria We included randomized controlled trials (RCTs) and quasi-randomized controlled trials that compared CAS for ACL or PCL reconstruction versus conventional operating techniques not involving CAS.

Data collection and analysis Two authors independently screened search results, assessed the risk of bias in the studies and extracted data. Where appropriate, we pooled data using risk ratios (RR) or mean differences (MD), both with 95% confidence intervals (CI).

Main results The updated search resulted in the inclusion of one new study. This review now includes five RCTs with 366 participants. There were more female than male participants (70% were female); their ages ranged from 14 to 53 years. All trials involved ACL reconstructions performed by experienced surgeons.Assessing the studies' risk of bias was hampered by poor reporting of trial methods, and consequently several studies were judged to be 'unclear' for several types of bias. One trial presenting primary outcome data was at high risk of detection bias from lack of clinician blinding and attrition bias from an unaccounted loss to follow-up at two years.We found moderate quality evidence (three trials, 193 participants) of no clinically relevant difference between CAS and conventional surgery in International Knee Documentation Committee (IKDC) subjective scores (self-reported measure of knee function; scale of 0 to 100 where 100 was best function). Pooled data from two of these trials (120 participants) showed a small, but clinically irrelevant difference favouring CAS (MD 2.05, 95% CI -2.16 to 6.25). A third trial (73 participants) also found minimal difference in IKDC subjective scores (reported MD 0.2).We found low quality

evidence (two trials, 120 participants) showing no difference between the two groups in Lysholm scores, also measured on a scale 0 to 100 where 100 is best function (MD 0.25, 95% CI -3.75 to 4.25). We found very low quality evidence (one trial, 40 participants) showing no difference between the two groups in Tegner scores. We found low quality evidence (three trials, 173 participants) showing the majority of participants in both groups were assessed as having normal or nearly normal knee function (86/87 with CAS versus 84/86 with no CAS; RR 1.01, 95% CI 0.96 to 1.06).Similarly, no differences were found for our secondary outcome measures of knee stability, loss in range of motion and tunnel placement. None of the trials reported on re-operation.No adverse post-surgical events were reported in two trials (133 participants); this outcome was not reported by the other three trials.CAS use was associated with longer operating times compared with conventional operating techniques: the mean difference in operating times reported in the studies ranged between 9 and 27 minutes.

Authors' conclusions From the available evidence, we are unable to demonstrate or refute a favourable effect of CAS for cruciate ligament reconstructions of the knee compared with conventional reconstructions. However, the currently available evidence does not indicate that CAS in knee ligament reconstruction improves outcome. There is a need for improved reporting of future studies of this technology.

BACKGROUND

Description of the condition

The anterior and posterior cruciate ligaments (ACL and PCL) are located within the knee joint. These connect the femur(thigh bone) to the tibia (shin bone) and play a crucial stabilising role. The ACL restrains the anterior translation (forward movement) of the tibia relative to the femur. The PCL restrains posterior translation (backward movement) of the tibia relative to the femur. Both are also important for varus/valgus (sideward) and rotational stability of the knee joint during movement.

ACL injury is a common orthopaedic problem with an annual incidence of approximately 200,000 cases per year in the US(AAOS 2007). It often results from an abrupt change in direction or rapid deceleration during sports, typically football or skiing. As well as knee instability, an ACL rupture can give rise to recurrent episodes of the knee 'giving way' and pain (Noyes 1983), and can result in discontinuation or limitation of sporting activities (Barrack 1990a; Barrack 1990b). Although the natural history is not clearly defined, the ACL injury predisposes the knee to chronic instability and further damage, such as meniscal tears, with a consequent impairment to quality of life (Mohtadi 1998). An ACL injury may also predispose to early osteoarthritis (Daniel 1994; Meuffels 2009;Sherman 1988).

PCL injury is less common, comprising 1% to 20% of knee ligament injuries. It is most often sustained through a direct blow to the anterior part of the tibia in a traffic accident(e.g. a dashboard injury, in which the lower leg of the flexed knee hits the dashboard) or after athletic trauma (in which an athlete receives a blow to the anterior surface of the tibia) (Schulz 2003). Complaints after a PCL injury can include instability or knee pain, especially patellofemoral, and, in the long term, this injury can lead to progressive osteoarthritis and functional limitations (Margheritini 2002).

DESCRIPTION OF THE INTERVENTION

An ACL rupture with recurrent knee instability is most often treated with a tendon graft reconstruction, which involves reconstruction of the damaged ligament using a strip of tendon, often from the patient's knee (the patellar tendon or hamstring). In most cases, the surgery is done arthroscopically. As well as in the type of graft, there is much variation in surgical methods used in practice. Two commonly used types of reconstruction are the traditional single bundle reconstruction and the double bundle reconstruction, which represents the more anatomical approach. There is continuing uncertainty about which is the better of these two methods (Tiamklang 2012), and which are the best methods and devices for fixing the graft (Zeng 2013).

The primary goal of surgery is to restore a stable knee without incurring extra morbidity. Approximately 100,000 ACL reconstructions are performed annually in the

US (AAOS 2007). PCL reconstruction is usually reserved for more complex knee injuries (Peccin 2005). Navigation systems have been introduced to surgery, including orthopaedic surgery (Zafagnini 2010). These systems are known as computer-assisted surgery (CAS) or computer-assisted orthopaedic surgery (CAOS). The most common types use images acquired pre-operatively by fluoroscopic computed tomography (CT) or intra-operatively by fluoroscopy (dynamic X-rays) or an image-free system using pre-specified anatomical landmarks.

During surgery, the CAS system uses infrared feedback, enabling orientation of the surgical instruments relative to the anatomical structures of interest. In cruciate ligament reconstruction, CAS has the potential to optimize the preparation for grafting, which involves drilling into the femur and tibia to form a bone tunnel, and subsequent placement of the graft. The system also has the capacity to monitor femur and tibia positions and movements. With this information, knee stability and range of motion can be optimized during surgery.

For a clinically successful outcome, an accurate graft placement is considered essential. This is accomplished by an exact and reproducible tunnel placement. Although the anatomic attachment sites of the ACL and PCL have been well described, these vary to a great degree between individuals. The optimal bone tunnel placement for ACL and PCL grafts also remains controversial. Current surgical practice focuses on placing the bone tunnels within the anatomic insertion sites of the native ACL and PCL (anatomic placement). Given the individual variation in anatomy, defining a universal optimal position is not possible, thus an individualized approach is necessary (Meuffels 2012). The surgeon visualizes and chooses the most appropriate tunnel position based on their experience combined with identification of the anatomical landmarks for the femoral and tibial side. For instance, for the femoral tunnel position, the ACL footprint is used if visible and, if possible, is combined with the bony contour of the medial side of the lateral femoral condyle and the height and depth of the medial side of the femoral condyle. The size and shape of the femoral condyle or intercondylar notch, or both, can then be used to determine the appropriate tunnel position by visualizing the angle and height or by measuring and marking the central position of the femoral tunnel aperture.

How the intervention might work

Malposition of the graft can lead to limited range of motion, impingement of and damage to the graft, instability and re-injury. The most common cause of technical failure of cruciate ligament reconstruction is the misplacement of the bone tunnel (Giffin 2001; Morgan 2012; Nakagawa 2007). CAS could potentially give a more anatomically reproducible ACL or PCL reconstruction with an exact bone tunnel placement, which could potentially improve outcome by increasing knee stability and lowering the risk of complications, especially those associated with limited range of motion and knee discomfort. However, CAS requires a longer operating time, an extra investment in the necessary equipment and the additional

fixation of navigation probes to the patient's leg. As with every new development, using CAS involves a learning curve for the experienced surgeon. However, compared with traditional surgical techniques, using CAS may shorten the learning curve for the novice surgeon (Schep 2005).

Why it is important to do this review

Cruciate ligament reconstruction is a very common orthopaedic procedure. The pressure to implement technological advances is unrelenting. Thus, it is important to review the current evidence systematically comparing the effects of computer-assisted knee ligament reconstruction versus conventional surgery for the reconstruction of the ACL or PCL deficient knee. The previous version of this review, published in 2011, concluded there was insufficient evidence to advise for or against the use of CAS. This absence of evidence and the rapid development and use of computer techniques, made it important to do an update of this review in order to ensure that treatment decisions are made on the most up-to-date and reliable evidence.

Objectives

To assess the effects of computer-assisted reconstruction surgery compared with conventional operating techniques for ACL or PCL injuries in adults.

To investigate possible effect modification by:

1. the type of system used for CAS: for example, intraoperative use of X-rays, pre-operative use of radiology (CT, magnetic resonance imaging (MRI), X-rays), intraoperative landmarks or bone morphing (this is using data such as intraoperative acquisition of points on the bone surface, to compute the shape (geometrical features) of the bone to aid surgical planning);
2. the type of ligament reconstruction: ACL or PCL or both.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) and quasi-randomized controlled trials (for example, allocation by hospital record number or date of birth) that compared CAS with conventional operating techniques.

Types of participants

Skeletally mature people undergoing reconstruction of the ACL, PCL or both ligaments. We included trials including skeletally immature people, based on age, provided that these were few and balanced between groups.

We included studies involving a policy of surgical treatment of other concomitant soft-tissue knee injuries, such as meniscal tears, in the same operation as cruciate ligament reconstruction provided this applied to both groups.

Types of interventions

Reconstruction of the ACL or PCL, or both using either CAS or conventional techniques. There was no exclusion based on the type of graft or the method of graft fixation.

Types of outcome measures

Primary outcomes

Validated self-reported health and quality of life measures, including knee-specific measures

These could include, for example, 36-item Short Form (SF-36), Tegner scale (Tegner 1985), Lysholm scale (Lysholm 1982), International Knee Documentation Committee (IKDC) subjective part (Irrgang 2001), the Cincinnati knee scales (Noyes 1989), Knee injury and Osteoarthritis Outcome Score (KOOS) (Roos 1998), and the ACL Quality of Life outcome measure (Mohtadi 1998).

Note: in the next update, we plan to separate out joint-specific and generic measures of function and quality of life.

Measures of objective assessment of overall knee function

International Knee Documentation Committee (IKDC) objective part (Hefti 1993). The IKDC 2000 forms can be accessed at IKDCforms.

Secondary outcomes

Objective measures of knee function

These measures of specific aspects of knee function could include, for example, range of motion, static stability (measured by arthrometric (for instance KT 1000 or 2000) or other stability assessment devices, strength (Cybex muscle testing or equivalent).

Technical and anatomical outcomes

- Tunnel positions and positioning of the graft
- Development of radiological osteoarthritis

Adverse post-surgical events

- Re-rupture of the ACL
- Infection
- Venous thromboembolism

Measures of resource use

- Duration of surgery
- Radiological screening time
- Re-operation
- Formal economic evaluation

Timing of outcome measurement

We assessed the effect of the interventions in the short term (within six months of ACL/PCL reconstruction), intermediate term (between six months and two years of ACL or PCL reconstruction) and long term (more than two years after ACL or PCL reconstruction).

Search methods for identification of studies

Electronic searches

For this update, we searched the Cochrane Bone, Joint and Muscle Trauma Group Specialised Register (from 2010 to July 2013), the Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 5, 2013), MEDLINE (from 2010 to July 2013), EMBASE (from 2010 to July 2013) and CINAHL (from 2010 to July 2013). Details of the search strategies used for the previous version of the review are given in Meuffels 2011.

In MEDLINE (PubMed), the first two levels of the optimal trial search strategy (Higgins 2006) were modified slightly and combined with the subject specific search. The complete search strategy is shown in Appendix 1. The search strategies that were used in The Cochrane Library (Wiley Online Library), EMBASE (Embase.com) and CINAHL (EBSCO online) are also shown in Appendix 1.

We also searched the WHO International Clinical Trials Registry Platform and the Current Controlled Trials Meta Register (both July 2013) for ongoing and recently completed trials.

Searching other resources

We checked the bibliographies of relevant papers identified. Where appropriate and possible, we contacted the corresponding authors of studies identified by the search strategies to obtain other relevant studies not previously included for review.

Data collection and analysis

Selection of studies

Two review authors (VE and DM) independently assessed potentially eligible trials identified by the search strategy.

Data extraction and management

One review author (VE) and an associate with expertise in systematic reviews (Belle van Meer: BM) used pre-piloted data extraction forms to independently extract the data of the

newly included trial. They compared the data extracted for this study to achieve consensus. We resolved any differences by discussion. We contacted the trial authors for missing data.

Assessment of risk of bias in included studies

One review author (VE) and an associate with expertise in systematic reviews (BM) independently assessed the risk of bias of the newly included study using the same version of The Cochrane Collaboration's 'Risk of bias' tool as previously (Higgins 2008). For the item 'blinding', we assessed blinding of 1. participant-reported outcomes, 2. outcomes assessed by a physician and 3. Radiological outcomes. In additional to the items from the five domains listed in the tool (sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting), we also assessed bias relating to differences in the surgeon's experience with the techniques being compared (performance bias). We considered other sources of bias that were not addressed in the domains of the tool in the category 'other sources of bias'; for this category, the review authors judged whether the study was apparently free of other problems that could put it at a high risk of bias.

Measures of treatment effect

For each study, we calculated risk ratios (RR) with accompanying 95% confidence intervals (CI) for dichotomous outcomes, and mean differences (MD) with 95% CI for continuous outcomes.

Dealing with missing data

We contacted trial investigators for missing data. Where appropriate, we performed intention-to-treat analyses to include all participants randomized to the intervention groups. We investigated the effect of drop-outs and exclusions by conducting worst-scenario and best-scenario analyses. If missing standard deviations could not be derived from CI data or retrieved from the study authors, we did not impute standard deviations for the analyses.

Assessment of heterogeneity

We examined forest plots visually for heterogeneity and considered the Chi^2 test and I^2 statistic.

Assessment of reporting biases

Should there be sufficient studies (at least 10) available in a future update, we plan to assess publication bias by examining a funnel plot. However, we checked prospective clinical trial registers to help us assess publication bias. We compared the method descriptions of the included studies with the actual reported outcomes in the results section to assess selective outcome reporting bias.

Data synthesis

If the participants, interventions, outcomes and the timing of the outcome measurements were sufficiently similar, we pooled the results using a fixed-effect model. In the presence of clinical or methodological heterogeneity, we planned to use the random effects model. If necessary in future, we will calculate standardized mean differences for pooling data when outcomes are measured in different units or scales.

Subgroup analysis and investigation of heterogeneity

Should there be sufficient data in future updates, we plan, where appropriate, to explore heterogeneity using subgroup analyses by the type of lesion (ACL, PCL or both) and by CAS system used (CAS systems with or without pre-operative use of fluoroscopy, or preoperative use of radiological data as X-rays, CT or MRI).

We will investigate whether the results of subgroups are significantly different by inspecting the overlap of CI values and by performing the test for subgroup differences available in Review Manager 5 software (RevMan 2012).

Sensitivity analysis

In future updates, we plan, where appropriate, to conduct sensitivity analyses to explore the effects of various aspects of trial and review methodology, including the effects of missing data, whether allocation was concealed and differences in surgeon's experience with CAS and standard methods of ACL reconstruction.

Quality assessment

We used the GRADE approach to assess the quality of evidence relating to our primary outcomes and adverse post-surgical events (Section 12.2,Higgins 2011);this informed our Summary of findings for the main comparison.

RESULTS

Description of studies

Results of the search

In the first version of this review (Meuffels 2011),the search resulted in 517 records, of which five articles reporting four RCTs were included in the review. As two reports appeared to report the same study (Endele 2009; Mauch 2007a), with the same methods being performed at the same hospital in the same time interval (recruitment: December 2003 to April 2004), we considered them as one study (Mauch 2007). There was one ongoing trial (former study ID: Meuffels). The new searches for this update, run in July 2013, identified 202 articles: Cochrane Bone, Joint and Muscle Trauma Group Specialised Register (4), CENTRAL (23), MEDLINE (22), EMBASE (137), CINAHL (16), international registries of

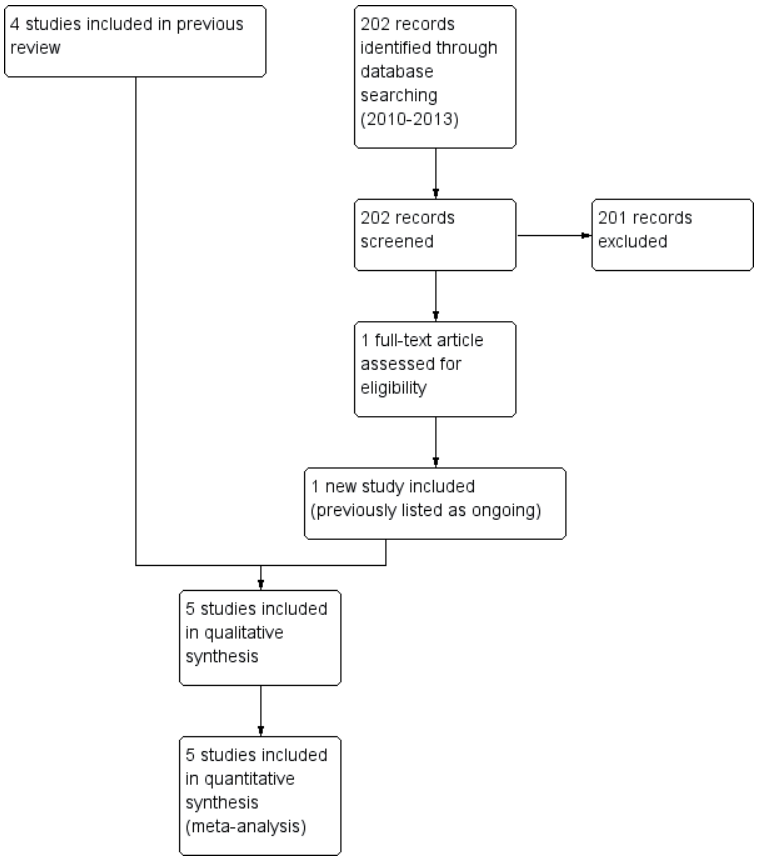


Figure 1: Study flow diagram

prospective RCTs and handsearches (0). Of these, a published report of the RCT formerly listed as ongoing was found (Meuffels 2012). There are no excluded or ongoing trials or studies waiting assessment. A flow diagram summarising the study selection process is shown in Figure 1.

Included studies

We included five studies, conducted in single centres in France (Chouteau 2008), the Czech Republic (Hart 2008), Germany (Mauch 2007), The Netherlands (Meuffels 2012), and France (Plaweski 2006). Details of each study are shown in the Characteristics of included studies table. All included studies compared computer assisted ACL reconstruction with conventional surgery. No study involved PCL reconstruction.

Participants

The included studies reported data from 366 participants (262 males and 104 females). The ages of the participants included in the review ranged from 14 to 53 years. Three

studies included participants younger than 18 years of age (Chouteau 2008; Hart 2008; Plaweski 2006). Separate outcome data on these skeletally immature participants were not available, but, since the numbers of participants in this category were low and were balanced between groups, we included these studies in this review. All participants in the five studies underwent ACL reconstruction.

Interventions

All five included studies compared computer-assisted ACL reconstruction with conventional surgery. However, the studies differed in the type of CAS used and in the techniques used for the conventional reconstruction. Chouteau 2008 and Meuffels 2012 used a CAS system that made use of intra-operative radiographic images to template the preferred femur and tibial tunnel placement. Both Hart 2008 and Mauch 2007 used the imagefree OrthoPilot (Braun-Aesculap) system to aid in selecting the femoral and tibial tunnel placement. The image-free system of Surgetics using the Julliard protocol (Praxim) was used in Plaweski 2006.

All studies used devices to aid in tunnel placement. The tibial aperture of the tunnel was chosen using a guided cannulated aiming device (Acufex) in three studies (Mauch 2007; Meuffels 2012; Plaweski 2006). Mauch 2007 and Meuffels 2012 placed the tunnel at 7 mm and Plaweski 2006 at 6 mm anterior to the PCL on the tibia.

Neither Chouteau 2008 nor Hart 2008 described the tibial tunnel placement in sufficient detail. For the conventional femoral tunnel placement, Hart 2008 and Mauch 2007 planned the tunnel position by positioning the femur at the 10.30 o'clock position on the right side and 1.30 o'clock position on the left side. Meuffels 2012 planned a slightly more horizontal position aimed at the 10 o'clock position for the right knee and 2 o'clock position for the left knee. Plaweski 2006 planned the femoral tunnel in a slightly more vertical position with the femur at 11 o'clock on the right side and 1 o'clock on the left side. Chouteau 2008 did not describe the type of femoral placement.

Plaweski 2006 used a four-stranded hamstring autograft to reconstructthe ACL. Meuffels 2012 used a single-bundle, transtibial technique using either bone-patellar-tendon-bone (BPTB) or looped semitendinosus-gracilis autograft. The three remaining studies used BPTB autografts. A miscellaneous array of fixation techniques (press-fit, interference screw and extra-cortical fixation) were used.

Outcomes

In Chouteau 2008, outcomes were assessed at a mean of 2.2 years (range 1 to 4.5 years). Meuffels 2012 reported only on tunnel position one day after operation. In the other three studies, long-term outcomes at two or more years post-operatively were reported.

Functional assessment of the participant's ACL reconstructed knee was assessed by the IKDC subjective score and the Lysholm score in two studies (Hart 2008; Mauch 2007), and by the post-operative IKDC knee examination grade in three studies (Chouteau 2008;

Mauch 2007; Plaweski 2006).No study addressed return to previous activity level or generic quality of life measures.

The IKDC objective score was assessed by Chouteau 2008, Mauch 2007, and Plaweski 2006.

Secondary outcomes were reported infrequently, and when reported, the authors used different measurement tools for the same type of outcome, for instance, femoral and tibial aperture tunnel position. Meuffels 2012 used three-dimensional (3D) positioning of the intra-articular femoral and tibial tunnel apertures as depicted with a CT scanner. All other included studies reported tibial tunnel position on the lateral X-ray. Mauch 2007 also added MRI measurement of the tunnel position and of the graft quality. The measurements that were used consisted of absolute or relative measurements from the anterior to the posterior tibial plateau or looked at the position in relation to the Blumensaat's line (roof of the intercondylar notch) in full extension.

Femoral position was assessed using the triangle method by Chouteau 2008, the quadrant method by Mauch 2007 on X-ray and by Meuffels 2012 on the 3D CT scanner, and the relative position towards the Blumensaat's line and the lateral femoral condyle by Hart 2008 and Plaweski 2006.

Stability measurements were assessed separately by the pivot-shift and Lachman test by Plaweski 2006, and the pivot-shift by Hart 2008. Range of motion loss was reported for Chouteau 2008.

Two trials reported on adverse post-surgical events (Hart 2008; Plaweski 2006).

None of the included studies performed an economic evaluation, but the MD between the groups in length of operation was reported by all studies. None of the studies reported the need to abandon the CAS or to alter the CAS proposed tunnel placement.

Risk of bias in included studies

Overall, it was difficult to judge risk of bias or the methodological quality of the five included studies due to poor reporting. The results of the risk of bias assessment are shown in Figure 2 and Figure 3.

Allocation

We judged two trials at low risk of bias relating to random sequence generation: Mauch 2007 drew lots and Meuffels 2012 used a computer-generated procedure (block randomization using a variable block size). We judged the other three trials, which did not provide any details on their methods of sequence generation, at unclear risk of bias. We rated Meuffels 2012, which confirmed independent administration of allocation, and Plaweski 2006, where sealed envelopes were opened just before surgery, at low risk of bias relating to allocation concealment. No details were provided by the other three trials, which we judged at unclear risk of selection bias relating to allocation concealment.

figure 2: Risk of bias summary: review authors' judgements about each risk of bias item for each included study (Empty cells = not applicable).

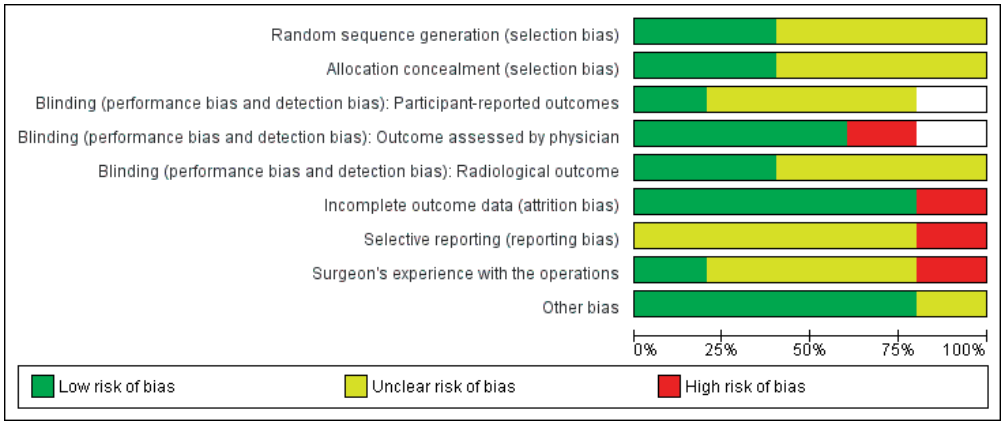


figure 3: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Blinding

We assessed blinding for trial participants, surgeons and outcome assessors. In a surgical trial, the surgeon cannot be blinded.

Participant (patient) blinding was described in Hart 2008, which we judged at low risk of bias. We rated the risk of detection bias related to participant-reported outcome assessment as unclear in three trials (Chouteau 2008; Mauch 2007; Plaweski 2006). (To 2014, Meuffels 2012 has not reported these outcomes.)

The outcome assessor for physician-reported outcomes was blinded or independent in three trials (Chouteau 2008; Hart 2008; Plaweski 2006), but not in Mauch 2007; we judged this at high risk of detection bias for these outcomes. (To 2014, Meuffels 2012 has not reported these outcomes.)

Assessment of radiological outcomes was blinded in two trials (Mauch 2007; Meuffels 2012), which we judged at low risk of detection bias. We judged the other three trials as being at unclear risk of this bias.

Incomplete outcome data

Four studies described loss to follow-up or had no loss to follow-up for the outcomes reported and so were assessed as being at low risk of bias in this domain. Mauch 2007 did not describe loss to follow-up; however, 13 participants were not mentioned in the later report of this trial (Endele 2009). We assessed this trial as being at high risk of attrition bias.

Selective reporting

We considered Meuffels 2012 to be at high risk of selective reporting bias because only placement was reported despite the fact participant-reported outcomes and physical examination were recorded. However, the trial authors have assured the independent reviewers for this study that these results will be published in a separate publication. It was unclear whether there was selective reporting in any of the other included studies.

Other potential sources of bias

There was an unclear risk of performance bias relating to surgeon experience in Chouteau 2008, Mauch 2007, and Hart 2008. We considered Plaweski 2006 at high risk of performance bias because the study's start coincided with the introduction of CAS into the department. We judged Meuffels 2012 at low risk of performance bias as the surgeons had prior experience with CAS.

We judged that all trials with the exception of Mauch 2007 were at low risk of any other bias. There was a possible bias in Mauch 2007 relating to the lack of acknowledgement of the earlierreport of this trial in the later report and the omission of 13 participants from investigations in the later report.

Effects of interventions

Primary outcomes

1. Self-reported health and quality of life measures (knee function and generic)

Pooled data from two studies showed no statistically significant difference between the groups in the subjective IKDC score at two or more years' follow-up (MD 2.05, 95% CI -2.16 to 6.25; 120 participants; Analysis 1.1) (Hart 2008; Mauch 2007). This difference is not clinically relevant; as supported by findings from Greco 2010.Although for cartilage defects rather than ACL reconstruction, Greco 2010 estimated the minimum clinically important difference for the subjective IKDC score was 6.3 at six months and 16.7 at 12 months. Chouteau 2008 (73 participants) also found no significant difference in the mean IKDC subjective score between 1 and 4.5 years' follow-up (89.7 versus 89.5); no standard deviations were reported for this outcome.

Two studies reported Lysholm scores (Hart 2008; Mauch 2007). Pooled data showed no significant difference between the two groups (MD0.25, 95% CI-3.75 to 4.25; 120participants; Analysis 1.2).

One study found no significant difference in Tegner level of activity scores (0 to 10: highest level of activity) between the two groups (MD -0.35, 95% CI -1.81 to 1.11; 40 participants at 2-year follow-up;

Analysis 1.3) (Mauch 2007).

2. International Knee Documentation Committee Knee Examination Grade (objective score)

Three studies reported the IKDC knee examination grades at final follow-up (Chouteau 2008; Mauch 2007; Plaweski 2006). There was no statistically significant difference between CAS and conventional reconstruction in those knees with normal or nearly normal grades (86/87 versus 84/86; RR 1.01, 95% CI 0.96 to 1.06; 173 participants; Analysis 1.4). The knees of the other three participants were graded as abnormal.

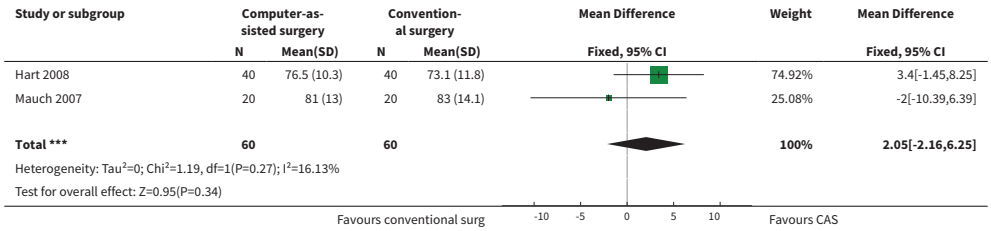
Secondary outcomes

Other objective measures of knee function

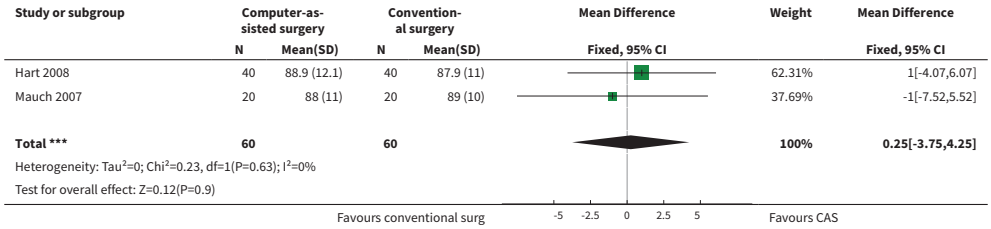
Rotational stability was measured using the pivot shift test, which was dichotomised as either negative (0) or positive (+, ++, +++). Three studies provided data; there was no statistically significant difference between the two groups in those knees with a normal (negative) pivot shift test at follow-up (RR 1.06, 95% CI 0.91 to 1.22; 180 participants; Analysis 1.5) (Hart 2008; Mauch 2007; Plaweski 2006).

Reported arthrometric testing was performed with a KT-1000 in two studies (Chouteau 2008; Hart 2008), and with a Telos device at 200 Newtons in one study (Plaweski 2006). None of the trials found significant differences between the two groups (Appendix 2).

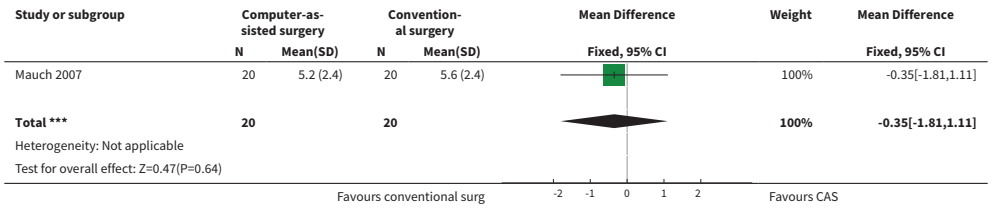
We found no reports of strength outcomes (Cybex muscle testing or equivalent).



Analysis 1.1: Comparison 1 Computer-assisted surgery versus conventional surgery, Outcome 1 Functional status at 2 years or more: IKDC subjective (score 0 to 100: best function).



Analysis 1.2: Comparison 1 Computer-assisted surgery versus conventional surgery, Outcome 2 Functional status at 2 years or more: Lysholm score (score 0 to 100: best function).



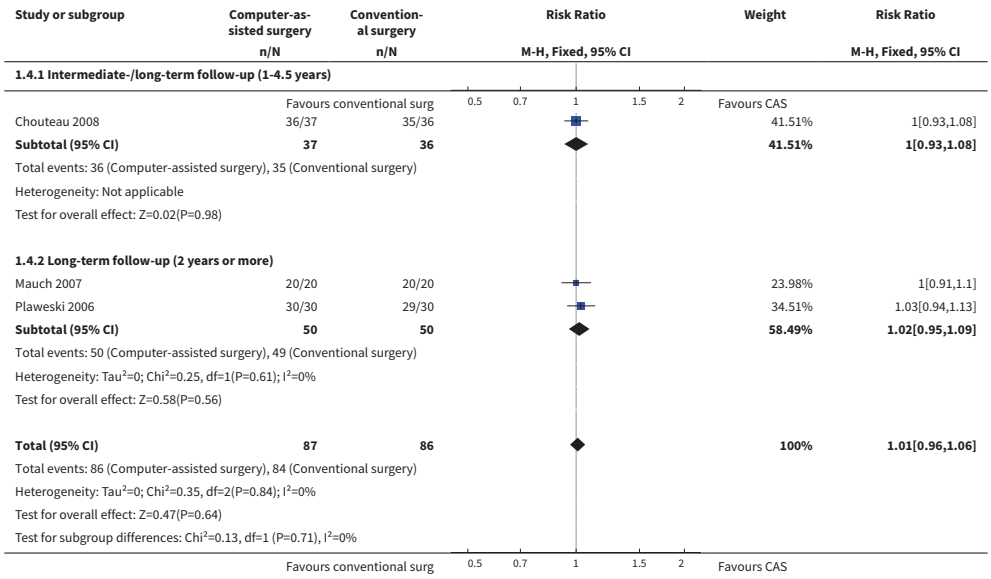
Analysis 1.3: Comparison 1 Computer-assisted surgery versus conventional surgery, Outcome 3 Functional status at 2 years or more: Tegner activity level (score 0 to 10: best result).

Chouteau 2008 reported two participants with some loss of range of motion in the CAS group and three in the control group.

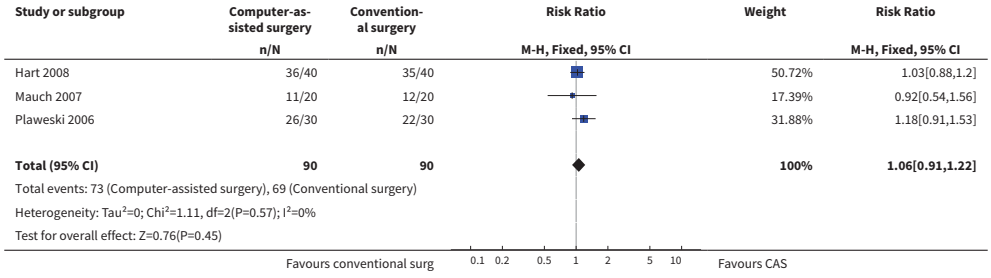
Technical and anatomical outcomes

Tunnel placement is an important aspect of ACL reconstruction surgery. All five studies reported the tibial tunnel position visualised on post-operative imaging acquired by X-ray images.

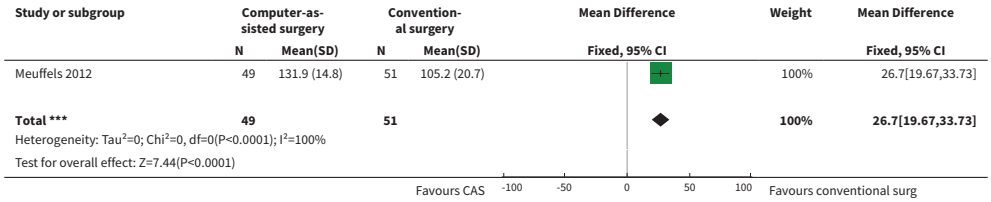
Meuffels 2012 assessed tibial tunnel placement with the use of 3D CT. Mauch 2007 used X-ray images and visualised tibial tunnel position using MRI measurement methods. The three remaining studies used X-ray images. This made pooling of the tunnel placement position data impossible. No significant differences were reported for overall placement between the two groups in any of the five trials (Appendix 3).



Analysis 1.4: Comparison 1 Computer-assisted surgery versus conventional surgery, Outcome 4 IKDC knee examination grade normal (grade A) or nearly normal (grade B).



Analysis 1.5: Comparison 1 Computer-assisted surgery versus conventional surgery, Outcome 6 Length of operation (minutes).



Analysis 1.6: Comparison 1 Computer-assisted surgery versus conventional surgery, Outcome 5 Negative (normal) pivot shiL test at 2 years or more.

Chouteau 2008, Hart 2008, and Plaweski 2006 also reported the femoral tunnel position on post-operatively acquired X-ray images. Meuffels 2012 assessed femoral tunnel placement with the use of 3D CT. Mauch 2007 visualised the femoral tunnel on postoperatively acquired MRI. Chouteau 2008 showed a significantly more accurate tunnel placement for the femur in favour of the CAS group. None of the other studies showed a statistically significant difference between CAS and the conventional ACL reconstruction groups (Appendix 4).

None of the trials reported on outcomes relating to the development of radiological osteoarthritis.

Adverse post-surgical events

Hart 2008 reported that there was no re-rupture of the ACL, loss of motion, infection or venous thromboembolism in either group. Plaweski 2006 did not observe any infection, clinical thromboembolic events or haematoma requiring intervention. There was no specific reporting of post-operative complications in the other three trials.

Measures of resource use

Reported additional operating time for the CAS groups was 9.3 minutes in Chouteau 2008, 11 minutes in Hart 2008, 15 minutes in Mauch 2007, 26 minutes in Plaweski 2006, and 27 minutes in Meuffels 2012. This difference was statistically significant in Meuffels 2012 (131.9 versus 105.2 minutes; MD 26.70 minutes, 95% CI 19.67 to 33.73 minutes; Analysis 1.6). The difference was also reported to be statistically significant in Plaweski 2006 (mean operating times: 78 minutes (range 40 to 120 minutes) in the CAS group versus 52 minutes (range 30 to 65 minutes) for the conventionally treated participants; reported P value = 0.03). Chouteau 2008 also reported radiological screening time in the CAS group of "15 ± 5" seconds.

We found no data on frequency of re-operation. No formal economic evaluations were identified.

DISCUSSION

ACL reconstruction is one of the most frequently performed orthopaedic interventions, especially in the young active population. An improved surgical outcome has the potential to reduce time lost from work or athletic activity and additional suffering. This systematic review examined the evidence from RCTs for computer-assisted ACL surgery.

Summary of main results

We included five RCTs (366 participants) who underwent ACL reconstruction. The trials were heterogeneous but all involved ACL lesions eligible for ACL reconstruction.

We found moderate quality evidence (three trials, 193 participants) showing no statistically significant or clinically relevant differences between CAS versus conventional surgery in IKCD subjective scores (self-reported measure of knee function).

We found low quality evidence (two trials, 120 participants) showing no difference between the two groups in Lysholm scores. We found very low quality evidence (one trial, 40 participants) showing no difference between the two groups in Tegner scores. We found low quality evidence (three trials, 173 participants) showing the majority of participants in both groups were assessed as having normal or nearly normal knee function. No adverse post-surgical events were reported in two trials; this outcome was not reported by the other three trials. Similar findings of an absence of differences applied to reports of other secondary outcome measures such as knee stability and tunnel placement.

Therefore, apart from a consistently and significantly increased operating time (between 9.3 and 27 minutes longer)for participants randomized to CAS, no difference in outcome of CAS versus conventional ACL reconstruction was detected.

Overall completeness and applicability of evidence

The applicability of the results from this review is strengthened by the studies having been performed by research groups from different countries, and by the diversity in the CAS ACL reconstruction systems used. However, incomplete reporting of results and heterogeneity hampered the drawing of firm conclusions regarding the effect of CAS. Since all five included trials were on ACL reconstruction, we can draw no conclusions about PCL reconstruction.
All included trials were single-bundle ACL reconstructions, performed with a transtibial approach forthe femoral placement of the tunnel. A transtibial approach can hinder the ideal placement of the femoral tunnel because of restrictions imposed by the shape and orientation of the tibial tunnel. To circumvent this problem, current practice has seen greater use of an accessory anteromedial portal. However, both the CAS ACL reconstruction and the conventional ACL reconstruction were single-bundle ACL reconstructions aiming at an anteromedial bundle femoral position, which is possibly less hindered by a transtibial tunnel.

Another issue is the use of different methods to evaluate tunnel position. The studies of Mauch 2007 and Meuffels 2012 used 3D techniques (MRI and CT) to evaluate the tunnel position, whereas the other studies used conventional X-rays. Imaging techniques using 3D images are superior in depicting tunnel placement over two-dimensional imaging techniques and might be less accurate in detecting differences between the two treatment groups (Meuffels 2011a).

The study groups were quite similar to large cohorts presented in national registries (Kvist 2014; Rahr-Wagner 2013). The mean age of the participants ranged in the included studies from 26 to 34 years of age and the majority of participants were male. These participant characteristics are in accordance with the national registries from Sweden and Denmark. The vast majority of grafts recorded in both national registries are hamstrings

(more than 80% of the operations); three of our five studies used predominantly BPTB grafts and two studies used hamstring grafts.

All studies were performed by ACL surgeons or surgical groups with ample experience in reconstructive procedures. Only one study reported the experience level with CAS of the participating surgeons. It is difficult to judge if the high experience level of the surgeons only left a very small margin for improvement by, for instance, the additional help of CAS. It is conceivable that less experienced orthopaedic surgeons may derive more benefit from the use of CAS technology, including in terms of a training intervention, with a potential for improved clinical outcomes for the person. However, this has not been researched.

All CAS systems used were systems using infrared (either active (transmitting) or passive (reflecting)). However, the systems were homogeneous in the technique used to determine the desired tunnel position.

A complete analysis of the effect of the CAS system for these knee ligament reconstructions can only be given when the intra-operative goal can be measured with a universal validated objective gold standard, such as for optimal graft placement. 3D CT is a validated measurement tool for the placement of the tunnel, but there is no consensus on the ideal placement (Meuffels 2011a). The present outcome measures (rotational stability measurements and radiological measurements for tunnel placement and osteoarthritis) are limited in their ability to measure small but possibly significant clinical differences for short-term and longer-term outcome. In other words, the responsiveness of these related ACL reconstructed knee scores may be insufficient to identify improvements or differences that could be clinically important.

Quality of the evidence

We included only randomized clinical trials as these are considered to have the lowest risk of bias compared with other study designs. However, assessment of the risk of bias was hampered by poor reporting. Therefore, we were mainly unclear about the risk of bias. In terms of our primary outcomes, Mauch 2007 was at high risk of bias relating to attrition bias for all outcomes, and also at high risk of bias relating to outcome assessment by physician. The included studies were small and possibly underpowered to determine an absence of difference between the two treatments. Only the study of Meuffels 2012 performed a power analysis in advance; the number of participants was sufficient to conclude that CAS is not superior to conventional surgery in terms of tunnel placement.

We assessed the evidence available for the primary outcomes and adverse post-surgical events using GRADE. We downgraded the level of evidence for the IKDC subjective score by one level for serious study limitations, mainly reflecting high risk of attrition bias in Mauch 2007. Although the numbers of participants from two trials in the meta-analysis were small (120 participants), the results from a third trial were consistent. Thus, we judged the evidence to be of moderate quality, which means that further research is likely to have an important impact on our confidence in the estimate of effect and may change

the estimate. We downgraded the level of evidence for the Lysholm score by one level for serious study limitations, mainly reflecting high risk of attrition bias in Mauch 2007, and by one level for imprecision. We downgraded the level of evidence for the Tegner score by one level for serious study limitations, mainly reflecting high risk of attrition bias in Mauch 2007, and by two levels for imprecision given that these data were from one trial only. We downgraded the level of evidence for IKDC objective assessment (number with normal or nearly normal grades) by one level for serious study limitations, mainly reflecting high risks of bias in Mauch 2007, and one level for imprecision, since the very few participants failed to attain normal or nearly normal grades. Thus, we judged the evidence to be of low quality for both the Lysholm score and IKDC objective assessment of knee function, which means that 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.

Potential biases in the review process

We conducted a comprehensive search strategy. In an effort to locate all relevant trials, we conducted sensitive searches across a comprehensive list of electronic databases. We performed citation tracking and searched for unpublished studies through clinical trials registers. However, it is still possible that we missed some trials. Despite our efforts to contact authors, this review is limited by the availability of data from the included studies. As explained, we concluded that Endele 2009 reported the two-year follow-up results of Mauch 2007 based on the considerable similarity in methods, including identical period of recruitment. Even if this turned out to be an incorrect assumption, the difference in the outcomes reported by the two reports meant that there was no loss of evidence available to this review.

In the first version of our review, we modified our types of outcome measures, which was thus a 'post hoc' modification and susceptible to 'selective reporting bias'. We have kept the revised list of outcomes but plan to revisit this list before our next update to make a better distinction between patient-reported measures relating to knee function and overall quality of life.

Agreements and disagreements with other studies or reviews

To our knowledge, this was the first published systematic review on this specific topic. Since the first version of this review, another systematic review has been published (Cheng 2012). The conclusion of Cheng 2012 is that there were no differences between CAS and conventional treatment with regard to knee stability and functional assessment during short-term follow-up. Although Cheng 2012 does not include Meuffels 2012 and presents the two trial reports of Mauch 2007 as separate trials, their findings are in keeping with our review, which found no evidence of any differences in knee function at long-term follow-up.

There has also been a review looking at CAS and total knee prosthesis implantation, which did not show any significant differences in clinical outcome but did show, in some instances, that there are fewer outliers when using CAS (Bauwens 2007).

Our review was inconclusive on this point, possibly because all included studies in our review compared CAS with conventional ACL reconstructions performed by experienced ACL surgeons. This

might have reduced the differences expected between the groups because of an already accurate ACL reconstruction, with fewer outliers due to the surgeons' greater experience.

Authors' Conclusions

Implications for practice

There is insufficient evidence from randomized controlled trials to draw conclusions about the effectiveness of computer-assisted surgery (CAS) for knee ligament reconstructions compared with conventional reconstruction surgery. The currently available evidence does not indicate that CAS in knee ligament reconstruction improves outcome.

Implications for research

The reporting of the existing studies assessing the effects of CAS anterior cruciate ligament (ACL) reconstruction is generally poor, which hampers proper assessment of their methodological quality and the interpretation of results. Before further uptake of this technology, more rigorous studies are needed to establish whether CAS should play an important role in ACL reconstruction. Future studies should follow the Consolidated Standards of Reporting Trials (CONSORT) guidelines for reporting of randomized trials (Moher 2010), use adequate methods of randomization with adequate concealment of allocation of the participants to treatment groups, use an adequate sample size, blind the participants and outcome assessors to treatment allocation, include reliable and validated outcome measures, and be of sufficient duration to assess medium- and long-term effects.

Although the emphasis should remain on clinically important outcomes, we also advise research into the ideal anatomic placement of the aperture of the femoral and tibial tunnel. A validated and reliable reference standard is needed for this and should be used in further research as well as to inform graft placement and future approaches for CAS.

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* Indicates the major publication for the study

Participant or population: People, primarily adults, undergoing ACL reconstruction surgery

Settings: Inpatient

Intervention: Computer-assisted reconstruction surgery

Comparison: Conventional operating techniques

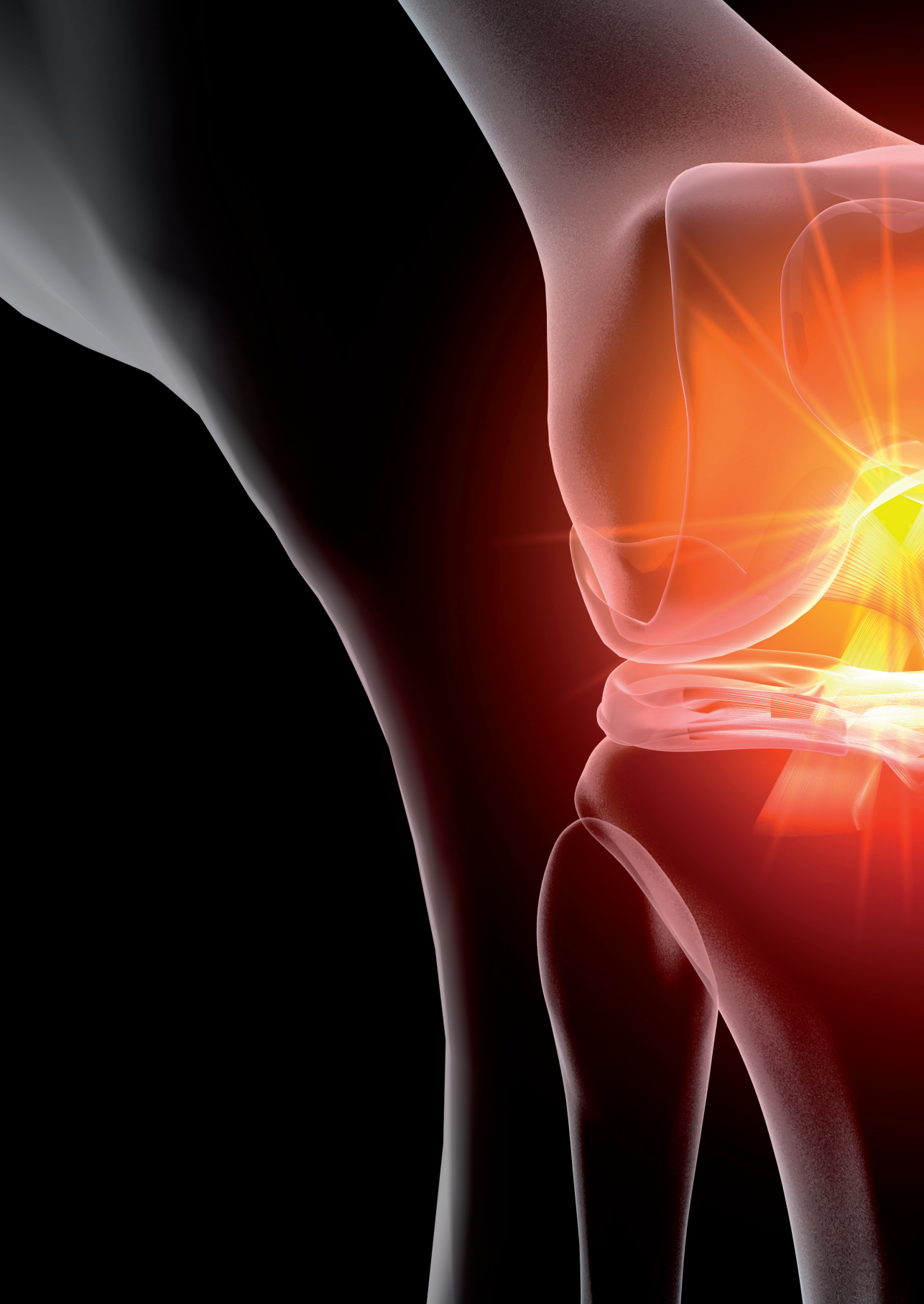
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Conventional operating techniques	Computer-assisted reconstruction surgery				
Functional status at 2 years or more: subjective IKDC score (score 0 to 100: best function)	The mean IKDC subjective score ranged across control groups from 73.1 to 83	The mean IKDC subjective score in the intervention groups was **2.05 points higher** (-2.16 to 6.25)[1]	-	120 (2 studies)	⊕⊕⊕⊖[2] **moderate**	A third trial (73 participants) reported almost identical scores in the 2 groups at between 1 and 4.5 years' follow-up: 89.7 versus 89.5
Functional status at 2 years or more: Lysholm score (score 0 to 100: best function)	The mean Lysholm score ranged across control groups from 87.9 to 89	The mean Lysholm score in the intervention groups was **0.25 points higher** (-3.75 to 4.25)	-	120 (2 studies)	⊕⊕⊖⊖[3] **low**	-
Functional status at 2 years or more: Tegner activity score (score 0 to 10: highest activity)	The mean Tegner score was 5.58	The mean Tegner score was **0.35 points lower** (-1.81 to 1.11)	-	40 (1 study)	⊕⊖⊖⊖[4] **very low**	-
IKDC knee examination grade normal (grade A) or nearly normal (grade B) - Intermediate/long-term follow-up (1 to 4.5 years)	976 per 1000[5]	986 per 1000 (937 to 1036)	RR 1.01 (95% CI 0.96 to 1.06)	173 (3 studies)	⊕⊕⊖⊖[6] **low**	Conversely only 3/173 knees were graded as abnormal
Adverse post-surgical events	See comment	See comment	Not estimable	140 (2 studies)	See comment	2 trials reported no events. The other 3 trials did not report this outcome. None reported on re-operation

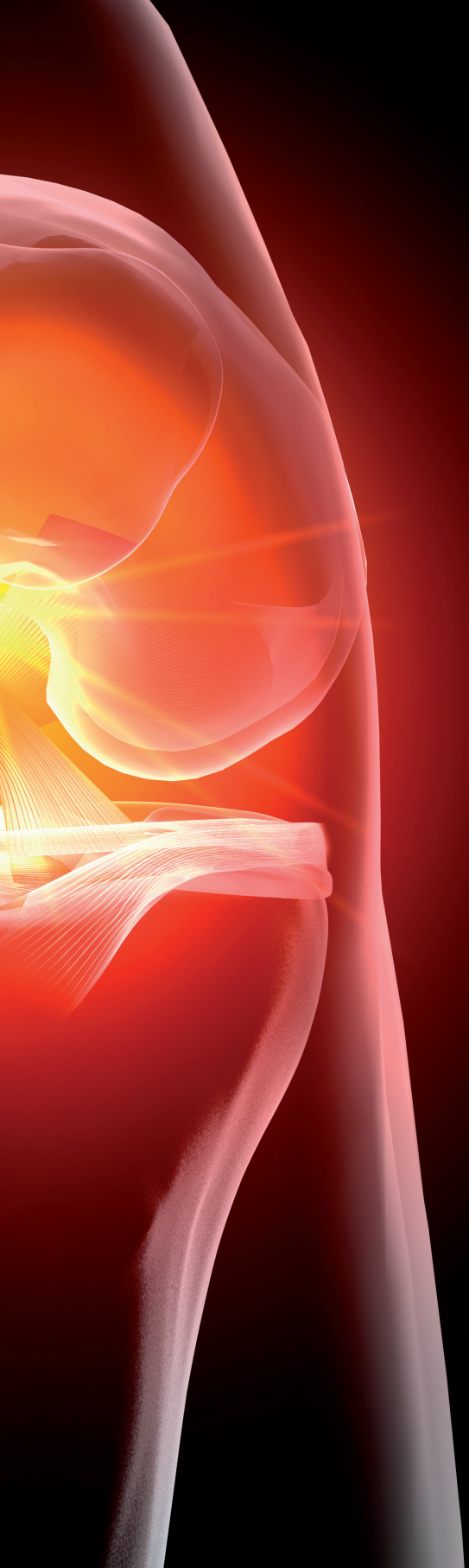
* The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **ACL:** anterior cruciate ligament; **CI:** confidence interval; **IKDC:** International Knee Documentation Committee; **PCL:** posterior cruciate ligament; **RR:** risk ratio
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.
1. The 95% confidence intervals not include a clinically relevant difference. The minimum clinically important difference for the subjective IKDC score was estimated to be 6.3 at 6 months and 16.7 at 12 months for people with focal cartilage defects 2. The quality of evidence for the subjective IKDC was downgraded 1 level for serious study limitations 3. The quality of evidence for the Lysholm score was downgraded 1 level for serious study limitations and 1 level for imprecision 4. The quality of evidence for the Tegner score was downgraded 1 level for serious study limitations and 2 levels for imprecision 5. Basis for assumed risk was the mean incidence for the 3 contributing trials 6. The quality of evidence for the IKDC objective assessment (number with normal or nearly normal grades) was downgraded 1 level for serious study limitations and 1 level for imprecision
• Figures • Tables Summary of findings for the main comparison. Computer-assisted reconstruction surgery compared with conventional operating techniques for ACL or PCL injuries in adults Comparison 1. Computer-assisted surgery versus conventional surgery Summary of findings for the main comparison. Computer-assisted reconstruction surgery compared with conventional operating techniques for ACL or PCL injuries in adults

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Functional status at 2 years or more: IKDC subjective (score 0 to 100: best function) **Show forest plot**	2	120	Mean Difference (IV, Fixed, 95% CI)	2.05 [-2.16, 6.25]
2 Functional status at 2 years or more: Lysholm score (score 0 to 100: best function)**Show forest plot**	2	120	Mean Difference (IV, Fixed, 95% CI)	0.25 [-3.75, 4.25]
3 Functional status at 2 years or more: Tegner activity level (score 0 to 10: best result)**Show forest plot**	1	40	Mean Difference (IV, Fixed, 95% CI)	-0.35 [-1.81, 1.11]
4 IKDC knee examination grade normal (grade A) or nearly normal (grade B)**Show forest plot**	3	173	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.96, 1.06]
4.1 Intermediate-/long-term follow-up (1-4.5 years)	1	73	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.93, 1.08]
4.2 Long-term follow-up (2 years or more)	2	100	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.95, 1.09]
5 Negative (normal) pivot shift test at 2 years or more**Show forest plot**	3	180	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.91, 1.22]
6 Length of operation (minutes)**Show forest plot**	1	100	Mean Difference (IV, Fixed, 95% CI)	26.70 [19.67, 33.73]

Summary of findings for the main comparison. Computer-assisted reconstruction surgery compared with conventional operating techniques for ACL or PCL injuries in adults

Comparison 1. Computer-assisted surgery versus conventional surgery





Chapter 8

General Discussion

In this general discussion I will discuss the optimal treatment for anterior cruciate ligament (ACL) rupture; the strengths but also the limitations of the studies presented in this thesis will be addressed, as well as the implications for daily practice and recommendations for further research.

STUDY POPULATION

ACL rupture is a common (1) and substantial injury to the knee, which causes serious morbidity (2) with large socio-economic impact. (3) In spite of the impact of the injury on the knee, not all ACL ruptures are recognized and some patients after ACL rupture will never see an orthopaedic surgeon. (4) This is mainly explained by a mild natural course in some patients. (4) The population of patients who present themselves to the orthopaedic surgeon is heterogeneous, with regard to age, activity level, symptoms, expectations and timing of presentation to the outpatient clinic. (5) For example, one young professional soccer player may visit an orthopaedic surgeon shortly after a first trauma with a painful and swollen knee and the request for an ACL reconstruction, while another patient in her mid-thirties presents months after the first trauma with recurrent instability but a preference for primary rehabilitation. At this moment the most optimal treatment for the individual is still unknown. In the COMPARE study we randomized patients after recent ACL rupture into either an early ACL reconstruction or to a rehabilitation programme optionally followed by an ACL reconstruction in case of complaints. We included patients aged 18 - 65 years of age, and with an acute (within two months after the initial trauma) complete primary ACL rupture (chapter 2). Patients with a history of ACL injury of the contralateral knee, or a dislocated bucket handle lesion of the meniscus with an extension deficit were excluded. In this manner we constituted a relative homogeneous study population of which we thought the question of immediate or delayed surgery is especially relevant.

However, of the 282 eligible patients, 115 patients declined to participate which makes generalizability of our outcomes for this particular target population questionable. The main reason for not participating was a strong preference of the patient for either primary ACL reconstruction or primary rehabilitation. In the inclusion process patients were excluded when they had a clear preference for one of both treatments, and our experience was that this preference was evenly distributed to both treatments once the patients were presented to us as eligible patients for the study.

Although a rehabilitation programme followed by optional ACL reconstruction is recommended by the Dutch guideline “ACL injury” (6), immediate ACL reconstruction is the most common management in the Netherlands (7) in orthopaedic clinical practice. A preference of the orthopaedic surgeon for primary ACL reconstruction might therefore have diminished the total of presented eligible patients, because they were already operated or on the waiting list before we were able to recruit them. However, in our study

all participating orthopaedic surgeons were instructed and committed themselves to participation to the study. With a regular and administrative extensive check of all eligible patients that were diagnosed in the orthopaedic outpatient clinic with an ACL rupture, we attempted to limit the amount of missing's.

MANAGEMENT OPTIONS

In the current Dutch guideline "ACL injury", recommendation for treatment choice for the individual patient is mainly based on expert opinion, because strong scientific evidence is lacking. (6) The guideline recommends to start with an exercise program supervised by a physical therapist. In case of symptomatic knee instability, which still is present after physiotherapy, and/or reduction of the activity level (with the aim to limit symptomatic knee instability), an ACL reconstruction is recommended. (6, 8) The current practice is, however, that the majority of patients (estimated 40-100% depending on age and gender) diagnosed with an ACL rupture in the orthopedic outpatient clinic undergo an ACL reconstruction within the first year and this overall percentage has increased over the past 25 years. (1, 7) So far, the only RCT available on the treatment options delayed ACL reconstruction or immediate ACL reconstruction has been published in 2010. (9) This KANON study compared structured rehabilitation plus early ACL reconstruction and structured rehabilitation with the option of later ACL reconstruction if needed. Patients aged 18-35 who presented themselves to the emergency department with recent rotational knee trauma, ACL insufficiency on physical exam, a Tegner activity score of 5-9 before injury were included in the study and the primary outcome score was change from baseline to the 2 years in the average score on four subscales of the Knee injury and Osteoarthritis Outcome Score (KOOS) score. (9)

This KANON study showed equal outcomes for both treatment options after a two and five years follow-up with respect to patient reported outcome measure, radiographic osteoarthritis and meniscus surgery. (9, 10) Still, whether an early surgical reconstruction or primary non-operative treatment is the most optimal treatment for a patient with an ACL rupture is debated in the field of orthopedics. (11-14) Several authors emphasized some limitations of the KANON study such as the use of the KOOS sum score as the primary outcome, and the expectancy that the percentage of patients eventually in need of an ACL reconstruction is likely to increase with time. (15-17)

Like the group of Lund University that published the KANON study, we also had identified the knowledge gap on preferred treatment for patients after ACL rupture. Our study (COMPARE study, chapter 2 and 3) was already ongoing when the KANON study was published, but we studied exactly the same research question. However, some differences were apparent. First, the inclusion of a larger number of patients (167 in our study versus 121 in the KANON study) might make the results more precise. Secondly, the multicenter design of our COMPARE study, improves the generalizability of our study results compared

to the KANON study. Thirdly, our inclusion criteria were somewhat broader (see below). Fourthly, there was a more strict and standardized indication for ACL reconstruction in the KANON study, namely presence of symptomatic instability and a positive pivot shift test while in our study this was based on a shared decision making after 3 months. These differences might also increase the generalizability of the results of our study. Finally, we used the International Knee Documentation Committee Subjective knee from (IKDC) as primary outcome instead of the KOOS sum score like the KANON study did.

During the study it appeared that we had a low loss to follow-up rate of 2 %, and 4% protocol violations, which strengthens the validity of our outcomes. In the KANON study also a minimal loss to follow up rate is mentioned.

As reported in chapter 2 we found in the COMPARE study that 50 % of patients allocated to rehabilitation plus optional delayed ACL reconstruction underwent a reconstruction within two years. This is largely in line with the KANON study, who found after 2-years of follow-up 39% of the patients underwent a delayed ACL reconstruction and after 5-years this was increased to 51%. (9, 10) Compared to our study, the study population of the KANON study was younger (approximately 5 years) and had a higher pre-injury sport level (Tegner of 9 compared to 7). The fact that less patients in the KANON study opted for delayed ACL reconstruction after two years of follow-up seems to be contradicted by the fact that they were younger and more active. The clinical experience is that young patients with a high pre-injury activity level more often opt for an early ACL reconstruction. (1) One possible explanation for this discrepancy might be the more standardized and possibly more strict indication for ACL reconstruction in the KANON study, namely presence of symptomatic instability and a positive pivot shift test compared to shared decision making after 3 months in the COMPARE study as stated before.

The primary outcome measure in our study was the International Knee Documentation Committee Subjective knee from (IKDC), while in the KANON study this was the KOOS sum score. The KOOS sum score was defined as the average of four of the five KOOS subscales covering pain, symptoms, difficulty in sports and recreational activities, and quality of life. The IKDC-score is considered to be a more appropriate questionnaire for patients after ACL rupture, with a higher responsiveness and better construct validity, even than the sub scores of the KOOS. (18, 19) In our study we saw after three months follow-up that the IKDC score was significantly and clinically relevant higher in favour of the rehabilitation plus optional delayed ACL reconstruction group, and that at the 2 years follow-up this difference was reversed in favour of the early ACL reconstruction group but of uncertain clinically relevance.

The early ACL reconstruction group had a statistically significant better KOOS sport subscale score (81.4 with SD of 22.6 versus 73.0 with SD of 24.9) and better KOOS quality of life subscale score (77.0 with SD of 20.5 versus 65.8 with SD of 22.4) at two-year follow-up in our study, compared to the rehabilitation plus optional delayed ACLR group. The KOOS scores of the other subscales and the sum score were similar for both groups. The KANON

study did not find any difference at two years follow-up between the both groups on the subscales of the KOOS score or their primary outcome. (9)

In our study we see more serious adverse events in the early ACL reconstruction group; 3 ruptures of the contralateral ACL occurred, compared to 1 in the rehabilitation plus optional delayed ACL reconstruction group. Four re-ruptures occurred in the early ACL reconstruction group and 2 in the rehabilitation plus optional delayed ACL reconstruction group.

With the results of the COMPARE and the KANON study, we now have 2 high-quality, randomized controlled trials which conclude that a treatment strategy of early ACL reconstruction is not or hardly superior to rehabilitation and optional ACL reconstruction. In both studies at least 50 % of the patients treated with rehabilitation and optional reconstruction did not need ACL reconstruction. This should encourage clinicians and patients to favour rehabilitation as the initial treatment followed by optional reconstruction in case of instability.

Another information source to support the treatment decision-making is the use of cost-effectiveness of the different treatment options. With the overall increasing health care costs, value calculations are becoming more and more important. We evaluated the cost-effectiveness of both treatment strategies in the COMPARE study as reported in chapter 3. Both treatment strategies resulted in a relatively good quality of life as measured with EQ-5D with minor differences between both groups. Patients treated with an early ACL reconstruction experience a slightly higher quality of life in the study period after an initial drop after the ACL reconstruction. In the COMPARE study we found that early ACL reconstruction leads to higher costs (both health care and societal perspective). Based on these results we concluded that it is unlikely that early ACL reconstruction is cost-effective, compared to rehabilitation plus optional reconstruction, according to Dutch policy standards. This can be explained by the ratio of a large between group difference in medical and non-medical costs and a small difference in gained quality of life. So based on these value calculations, it also is worthwhile to start the treatment of the ACL injured patient with rehabilitation therapy.

PREDICTION OF OUTCOME OF THE MANAGEMENT OPTIONS

Although our and the earlier KANON study showed that at least 50% of the patients with an acute ACL rupture does not need a surgical ACL reconstruction, it also means that almost 50% of the patients in the rehabilitation group opted for a delayed reconstruction indicating that these patients did not do satisfactory well with conservative treatment.

Till date it is unknown which patient will be capable of restoring adequate knee stability, for sports and daily activities, by means of non-operative management and who will require surgical reconstruction. Patients who will not be capable to restore adequate

knee stability by means of physical therapy, will have an indication for a delayed surgical reconstruction. Consequently, if receiving delayed surgery these patients will have two rehabilitation periods, before (3-6 months) and after surgery (9-12 months). In the COMPARE study we additionally described the following groups regarding the primary outcome: early surgical reconstruction of the ACL, non-operative treatment and delayed surgical reconstruction after unsuccessful rehabilitation. We found that the group of patients who underwent a delayed ACL reconstruction showed a worse recovery by means of the IKDC score and worse quality of life (EQ-5D) compared to the other two groups after two years of follow-up. However, it should be taken into account that patients who had delayed surgery, had a shorter duration of follow-up after surgery and might not have yet completed their full rehabilitation period. Of the 41 patients treated with rehabilitation and delayed reconstruction, 7 patients received this surgery in the second year of follow-up. For these patients more recovery is still expected.

Because of the selection based on “indication” it is not known whether the group with delayed reconstruction would have been better off with an early reconstruction. However, it would be beneficial to be able to recognize these patients in the acute stage. Our systematic review on factors predictive of progression to surgery after non-operative treatment (chapter 4) illustrates the lack of predictive rules.

Moreover, if an ACL reconstruction is considered, not all patients have satisfactory clinical outcome following such an ACL reconstruction. It also would be worthwhile to identify these patients before the treatment choice has been made. So, which variables are predictive of less satisfactory or poor results following an ACL reconstruction? So far only limited to moderate evidence of these predictive variables is available. Persistent subjective instability, an extension deficit pre-operatively, a strength deficit of hamstrings and or quadriceps of over 20 % compared to the contralateral leg, cartilage and or meniscal damage, continued participation in “high-risk pivoting sports”, and leg malalignment are reported to lead to less good to poor clinical outcome of reconstruction surgery (level 3 evidence based on one clinical trial or non-comparative study). (6) A longer period between the ACL rupture and the reconstruction is reported to increase the risk of meniscal and/or cartilage damage. (level 2 evidence based on one randomized double blind trial with good study quality and an adequate number of participants or 2 non-randomized clinical trials). (6, 20)

THE ORTHOPAEDIC SURGEONS’ AND PATIENTS’ PREFERENCE

In daily practice the orthopaedic surgeon and the patient come to a shared decision what the most optimal treatment will be for the individual patient. (21) Shared decision making (SDM) has been defined as: ”an approach where clinicians and patients share the best available evidence when faced with the task of making decisions, and where patients are

supported to consider options, to achieve informed preferences". (22) The orthopaedic surgeon and the patient both can have preferences for a treatment. As a support for the shared decision the 2014 clinical guideline in the United States reports there is moderate evidence supporting surgical reconstruction in active young adult (18-35) patients with an ACL tear and there is limited evidence for non-operative treatment after ACL rupture for less active patients with less laxity. (23) The 2012 and updated 2018 Dutch guideline on treatment after ACL rupture states that an ACL reconstruction is to be recommended if patient have symptomatic instability not improving after rehabilitation and/or activity modification.(8) However, our review in 2015 (chapter 6) and in a recent review the lack of evidence to guide treatment decision is illustrated. (24, 25)

Because there is limited to no scientific evidence of prognostic factors of both treatment options, the preference of an orthopaedic surgeon is mainly expert opinion or driven by own clinical experiences. Based on own observations and discussions in clinical practice, the used factors in daily practice by orthopaedic surgeons as well as by patient summarized in table 1.

In our systematic review we found that we cannot use age (strong evidence) and the severity of knee joint laxity (moderate evidence) to predict whether a patient will need an ACL reconstruction. Of all other identified factors conflicting or minimal evidence was available. (chapter 4)

Return to sports represents a common orthopaedic dilemma, both in patients treated with rehabilitation as in patients treated with ACL reconstruction. On the one hand, orthopaedic surgeons aim to restore clinical function for patients and help them to regain pre-traumatic activity level. On the other hand there is a high risk of subsequent ACL rupture (up to 30%) and associated injuries (up to 52%) of the knee. (25-27) Of the wish to return to pre-trauma activity level can be said, that 55% of the patients will return to this activity level after ACL reconstruction, and 81 % of patients return to some kind of sport. (28) Moreover, patients who return to pivoting sports have an increased re-rupture risk, probably due to abuse of the knee. The risk for new ACL rupture in the COMPARE study was 8.2% (ipsi- and contralateral rupture combined after ACL reconstruction). This is in accordance with 8.1% of patients with a new ACL rupture after reconstruction in the Swedish registry study. (29) Patients with a higher risk of ACL re-rupture are younger patients (fourfold increased risk for < 16 years old versus > 35 years old), playing soccer before initial injury and time between injury and primary surgery (two to threefold increased rate for ACL reconstruction <90 days versus > 365 days). (29)

Another common used argument for the preference of ACL reconstruction is the orthopaedic surgeons' intention to prevent secondary injury to cartilage and meniscus caused by recurrent instability moments. In our study we found that the number of secondary meniscal and cartilage injuries in both groups was similar, namely 45 % meniscal tears in both groups and 27 % cartilage injury in the early reconstruction group versus 20% in the rehabilitation plus optional reconstruction group (chapter 2). This suggests that

Table 1: Overview of common considerations for the decision of reconstruction surgery in ACL inured patients derived from own observations in clinical practice

The orthopaedic surgeons' preference	**The patients' preference**
Early ACL reconstruction	Early ACL reconstruction
- Meniscal injuries that need suturing or chondral lesions that need fixating	- Subjective instability
- Age	- Wish to return to pre-trauma activity (sport) level
- Subjective instability and/or instability on physical examination	- Influence of social contacts and role models
- Preference of the patient	- The belief that it is better 'to fix what is broken' for the long-term
- High pre-trauma activity level	
- Prevention of secondary injury to cartilage and meniscus	
- Anxiety to lose patients to colleague orthopaedic surgeons (loss of income and/or respect)	
Primary rehabilitation therapy	Primary rehabilitation therapy
- Contra-indications for surgery (high BMI, smoking, other co-morbidities)	- Anxiety for surgery
- Uncertainty whether a patient can endure the rehabilitation after ACL reconstruction	- Long rehabilitation period after ACL reconstruction
- High risk of re-rupture of the ACL in certain patient groups, such as adolescent males	- Willingness to adapt the activity level

a delayed reconstruction does not increase the risk of secondary injury to meniscus or cartilage, which is consistent with previous studies. (9, 10, 30) It is possible that with a longer follow up this difference will arise as reported for the 5 year follow up of the KANON study, where patients treated with rehabilitation and optional delayed ACL reconstruction had significant more meniscus surgery. (10)

IMPLEMENTATION AND PROPOSED FUTURE RESEARCH

The COMPARE study, performed in another country, using a multicentre approach, provides crucial confirmation of the results of the previous KANON study. Based on these studies the initial treatment of patients with an acute ACL rupture should be non-operative by rehabilitation therapy. The publication of the KANON study apparently did not affect the treatment decision making, as the number of ACL reconstructions is still increasing worldwide, especially in young women there is an increase of 120% in the last decade. (1, 7, 31, 32) It is a well-known challenge to implement a paradigm shift in abandonment of standard surgical care. Public perception is one of great confidence in medicine and surgical interventions. Surgeons and professional athletes have created an image of ACL

reconstruction as a standard procedure, with a 9-month recovery path with minor risk of side effects. However, the results of both the KANON and our COMPARE study show that reconstruction might be unnecessary in at least half of the patients.

The publication of the results of the KANON study ten years ago, has not led to changes in the treatment of ACL injury. As the numbers of ACL constructions are still increasing, future research should focus how the results of both studies should be implemented in daily practice. Nowadays 40-100% of all patients with an ACL rupture will undergo a surgical reconstruction. (1) The de-implementation (abandonment) of this current standard-care will be necessary, and will be a great challenge. We need more formal knowledge on what kind of factors or preferences (as presented in table 1) both patients and orthopedic surgeons mainly base their decision for surgery. Moreover, an implementation strategy has to be developed based on analysis of the likely barriers and facilitators. (33)

In addition, in case the initial delayed surgery is implemented and we are able to predict the non-copers, a randomized study where we compare immediate surgery and delayed surgery in this group, would reveal whether immediate surgery in this specific group is favorable.

Further, more research should be done to enhance evidence based personalized treatment. We know that a certain amount of patients with an ACL rupture are able to return to their pre-injury (sport) activity level without a surgical ACL reconstruction. On the other hand, some patients need a surgical reconstruction after non-successful physical therapy. As earlier stated, these patients will need two rehabilitation periods beside the surgical reconstruction. So, it could be highly efficient to predict the most optimal treatment for the individual patient as soon as the diagnosis has been made. Based on the data of the COMPARE and the KANON study a prediction model should be developed that predict what the most optimal treatment choice will be for the individual patient. This will help the patient and physician to choose the most optimal treatment for the patient. Thereafter the additional value of this treatment model or algorithm should be compared with the current daily practice. We recently started inclusion for this study “Which patient with an anterior cruciate ligament rupture will need a surgical reconstruction?”(Dutch trial register 8637).

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Summary

Optimal treatment after anterior cruciate ligament (ACL) rupture remains unclear. Treatment can consist of an early surgical reconstruction of the ACL or a rehabilitation plus an optional ACL reconstruction in case of secondary instability. The overall aim of this thesis was to provide more clarity on optimal treatment for patients after ACL rupture.

In chapter 2 we present the clinical outcome of the COMPARE study; our multicentre, randomized controlled trial. We randomized 167 patients to either an early reconstruction or rehabilitation plus an optional reconstruction. Patients were evaluated at 3, 6, 9, 12 and 24 months. Primary outcome was the difference in International Knee Documentation Score (IKDC) during 24 months between groups. Of the 167 included patients 85 were randomized to early ACL reconstruction and 82 to rehabilitation plus optional ACL reconstruction. Among patients with acute ACL rupture, surgical reconstruction alone, compared with rehabilitation plus optional surgical reconstruction, resulted in improved patients' perception of symptoms, knee function and ability to participate in sports at 2 year follow-up that was statistically significant but of uncertain clinical importance. Study interpretation should consider that 50% of the patients randomized to the rehabilitation group did not need surgical reconstruction.

In chapter 3 we evaluated the cost-effectiveness of both treatments used in the COMPARE study: early ACL reconstruction versus rehabilitation plus an optional reconstruction. A cost-utility analysis was performed to compare treatments during two years follow-up. Cost-effectiveness was calculated as incremental costs per Quality adjusted life year (QALY) gained, using two perspectives: the healthcare perspective and the societal perspective. The uncertainty for costs and health effects was assessed by means of non-parametric bootstrapping. Maximum willingness to pay to increase a QALY for a patient is estimated to be € 20.000 in the Netherlands for a patient with a low burden of disease. An early ACL reconstruction(index) leads to a 0.04 increase in QALY over a period of 2 year compared to rehabilitation plus an optional reconstruction, but is with a cost of 48,460 € /QALY (healthcare perspective) to 78,179 € /QALY (societal perspective) not considered cost-effective for routine practice with the former mentioned limit of € 20.000 euro.

In chapter 4 we attempted to identify radiographic differences in knee geometry between patients with and without ACL rupture after knee trauma. These differences could be used to classify patients into a higher risk for ACL rupture and help selecting patients in need of a prevention programme. We compared lateral view X-rays and Rosenberg view X-rays of 168 prospectively followed patients with a ruptured ACL to a control group of patients matched for gender with an intact ACL after knee trauma. Statistical shape modelling software was used to assess osseous knee geometry and find differences in

anatomical landmarks between both groups. On the Rosenberg view X-rays, we found five shape variants to be significantly different between patients who tore their ACL compared to patients with an intact ACL after knee trauma. Overall, patients who ruptured their ACL have smaller intercondylar notches and a smaller tibial eminence than control patients.

In chapter 5 we have investigated whether shape of the knee can predict the clinical outcome of patients after an ACL rupture. We used statistical shape modelling to measure the shape of the knee joint of 182 prospectively followed patients on lateral and Rosenberg view radiographs of the knee after a rupture of the ACL. Subsequently, we associated knee shape with the International Knee Documentation Committee subjective score at two years follow-up. The mean age of patients was 31 years (21 to 51), the majority were male (n = 121) and treated operatively (n = 135). We found two modes (shape variations) that were significantly associated with the subjective score at two years: one for the operatively treated group ($p = 0.002$) and one for the non-operatively treated group ($p = 0.003$). Operatively treated patients who had higher subjective scores had a smaller intercondylar notch and a smaller width of the intercondylar eminence. Nonoperatively treated patients who scored higher on the subjective score had a more pyramidal intercondylar notch as opposed to one that was more dome-shaped. We concluded that the shape of the femoral notch and the intercondylar eminence is predictive of clinical outcome two years after a rupture of the ACL.

In chapter 6 we present our systematic review on factors related to the need for surgical reconstruction after ACL rupture. A literature search was performed for studies predicting the need for ACL reconstruction after failed nonoperative treatment for patients with an ACL rupture. Two reviewers independently selected the studies and performed a risk of bias assessment. Best-evidence synthesis was used to summarize the evidence of factors predicting the need for surgical reconstruction after non-operative treatment for an ACL rupture. Seven studies were included, 3 of which were of high quality. Based on these studies neither sex (strong evidence) nor the severity of knee joint laxity (moderate evidence) can predict whether, soon after diagnosis of an ACL rupture, a patient will need ACL reconstruction following nonoperative treatment. All other factors identified in this review either had conflicting, minimal or no evidence as to their level of association with the need for surgical reconstruction. Noteworthy is that 1 high quality study reported that the spherical shape of the femoral condyle was predictive of the need for ACL reconstruction. Independent validation in future research will be necessary to establish whether knee shape is a predictive factor.

In chapter 7 we present the update of the Cochrane review on computer assisted surgery for knee ligament reconstruction. ACL reconstruction is one of the most frequently performed orthopaedic procedures. The most common technical cause of reconstruction failure is graft malpositioning. Computer-assisted surgery (CAS) aims to improve the accuracy of graft placement. Although posterior cruciate ligament (PCL) injury and reconstruction are far less common, PCL reconstruction has comparable difficulties

relating to graft placement. This was an update of a Cochrane review first published in 2011. For this update, we searched the Cochrane Bone, Joint and Muscle Trauma Group Specialised Register (from 2010 to July 2013), the Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 5, 2013), MEDLINE (from 2010 to July 2013), EMBASE (from 2010 to July 2013), CINAHL (from 2010 to July 2013), article references and trial registers. We included randomized controlled trials (RCTs) and quasi-randomized controlled trials that compared CAS for ACL or PCL reconstruction versus conventional operating techniques not involving CAS. Two authors independently screened search results, assessed the risk of bias in the studies and extracted data. Where appropriate, we pooled data using risk ratios (RR) or mean differences (MD), both with 95% confidence intervals (CI). The updated search resulted in the inclusion of one new study. This review now includes five RCTs with 366 participants.

We found moderate quality evidence (three trials, 193 participants) showing no statistically significant or clinically relevant differences between CAS versus conventional surgery in IKCD subjective scores (self-reported measure of knee function).

We found low quality evidence (two trials, 120 participants) showing no difference between the two groups in Lysholm scores. We found very low quality evidence (one trial, 40 participants) showing no difference between the two groups in Tegner scores. We found low quality evidence (three trials, 173 participants) showing the majority of participants in both groups were assessed as having normal or nearly normal knee function. No adverse post-surgical events were reported in two trials; this outcome was not reported by the other three trials. Similar findings of an absence of differences applied to reports of other secondary outcome measures such as knee stability and tunnel placement.

Therefore, apart from a consistently and significantly increased operating time (between 9.3 and 27 minutes longer) for participants randomized to CAS, no difference in outcome of CAS versus conventional ACL reconstruction was detected.

PhD portfolio Summary

Name PhD student: V. Eggerding	Promotor:	Prof. dr. S.M.A. Bierma-Zeinstra
Erasmus MC Department: Orthopaedic surgery	Copromotoren:	Dr. M. Reijman
		Dr. D.E. Meuffels

PhD training

In depth courses	**Year**	**ECTS**
Introduction to Data-analysis (NIHES)	2011	1.0
Health economics	2011	0.7
Endnote	2011	0.2
Basiscursus regelgeving en organisatie voor klinische onderzoekers (BROK)	2012	1.5
English Biomedical Writing and Communication course	2012	2.0
Methodologie van patiëntgebonden onderzoek en voorbereiding subsidie aanvragen	2012	0.3
Gezondheidsrecht	2018	0.5

Podium presentations	**Location**	**ECTS**
De vorm van de knie kan de klinische uitkomst voorspellen na een voorste kruisbandruptuur.	*Najaarsvergadering NOV 2013*	1.0
Kan de vorm van de knie een voorste kruisbandruptuur voorspellen?	*NVA jaarcongres 2014*	1.0

Awarded with the Eijkelaarsaward

Kan de vorm van de knie een voorste kruisbandruptuur voorspellen?	*NOV voorjaarsvergadering 2014*	1.0
Leidt een operatieve of conservatieve behandeling na een voorste kruisbandruptuur tot de beste klinisch uitkomst? Een multicenter gerandomiseerde studie	*NOV jaarvergadering 2019*	1.0

Awarded with the van Rens award

Operative versus Nonoperative Treatment for Acute Anterior Cruciate Ligament Tears: A Multicenter Randomized Trial	*ISAKOS congress 2019 (Cancun, Mx)*	1.0
Operative versus Nonoperative Treatment for Acute Anterior Cruciate Ligament Tears:A Multicenter Randomized Trial	*EFORT congress 2019 (Lisboa, Pt)*	1.0
Operative versus Nonoperative Treatment for Acute Anterior Cruciate Ligament Tears: A Multicenter Randomized Trial	*NVA jaarcongres 2019*	1.0

Awarded with the eijkelaarsaward		
Reconstruction or Primary non-operative treatment for Anterior cruciate ligament rupture? A multicentre Randomized Controlled trial	*Virtual EFORT congress 2020*	1.0
Poster presentation .		
Reconstruction or Primary non-operative treatment for Anterior cruciate ligament rupture? A multicentre Randomized Controlled trial	Virtual EFORT congress 2020	1.0

Teaching activities	**Year**	**ECTS**
Lecturing		
Webinar JBJS-JOSPT : to operate or not is still the question	2018	1.0
Supervising practicals and excursions, tutoring		
Minor orthopaedic sports traumatology, 3rd year medical students	2011, 2012, 2018	0.9
Supervising Master's theses medical students		
Defining predictors of successful conservative therapy after an ACL rupture R. R. Molders	2012	3.0
Knee shape is related with an ACL rupture: a matched case-control study K.S.R. van Kuijk	2013	3.0
Why do patients with initial non-operative treatment for ruptured ACL progress to surgical reconstruction S.P.G. Kraanen	2018	1.5

List of publications

Eggerding V, Reijman M, Scholten RJ, Verhaar JA, Meuffels DE.
Computer-assisted surgery for knee ligament reconstruction.
Cochrane Database Syst Rev. 2014 Sep 3;(9):CD007601. PMID: 25180899

Eggerding V, van Kuijk KS, van Meer BL, Bierma-Zeinstra SM, van Arkel ER, Reijman M, Waarsing JH, Meuffels DE.
Knee shape might predict clinical outcome after an anterior cruciate ligament rupture.
Bone Joint J. 2014 Jun;96-B(6):737-42. PMID: 24891572

Eggerding V, Meuffels DE, Bierma-Zeinstra SM, Verhaar JA, Reijman M.
Factors related to the need for surgical reconstruction after anterior cruciate ligament rupture: a systematic review of the literature.
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Why anterior cruciate ligament ruptures fail non-operative treatment – an exploratory analysis of the COMPARE trial
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Nederlands Samenvatting

Een gescheurde voorste kruisband is een groot knieletsel, welke vaker voorkomt bij jonge sporters. Op korte termijn kan dit leiden tot instabiliteit en op de lange termijn tot artrose. De optimale behandeling voor de individuele patiënt na een gescheurde voorste kruisband blijft onduidelijk. Behandeling kan bestaan uit een vroegtijdige reconstructie van de voorste kruisband of een oefenprogramma onder begeleiding van de fysiotherapeut gevolgd door een reconstructie van de voorste kruisband als sprake is van terugkerende instabiliteit.
In dit proefschrift werden verschillende aspecten van de behandeling onderzocht. Hiervoor werd een multicenter gerandomiseerde studie opgezet, de COMPARE studie. Patiënten van 18 tot 65 jaar met een gescheurde voorste kruisband in de afgelopen 2 maanden werden gevraagd om deel te nemen. Deze patiënten werden vervolgens ofwel behandeld met een vroegtijdige reconstructie of een revalidatie van minimaal 3 maanden optioneel gevolgd door een reconstructie indien sprake was van instabiliteit of onvermogen tot terugkeer naar sport. Patiënten werden voor 2 jaar gevolgd met behulp van klinische uitkomstmaten.

In **hoofdstuk 2** presenteren we de klinische uitkomsten van de COMPARE studie. In totaal zijn 167 patiënten behandeld met ofwel een vroegtijdige reconstructie of een revalidatie met een optionele reconstructie. De metingen werden verricht op baseline en na 3, 6, 9, 12 en 24 maanden follow-up. Primaire uitkomstmaat van de studie was het verschil in International Knee Documentation Score (IKDC) gedurende 24 maanden tussen de beide groepen. In totaal werden 85 patiënten gerandomiseerd voor een vroegtijdige reconstructie en 82 patiënten voor een revalidatie optioneel gevolgd door een reconstructie. Er was na 2 jaar studietijd een statistisch significant verschil in het voordeel van de vroegtijdige reconstructie groep, maar dit verschil is dusdanig klein dat het niet klinisch relevant is. Van belang bij de interpretatie van de studieresultaten is dat 50 % van de patiënten in de revalidatiegroep geen reconstructie hebben ondergaan.

In **hoofdstuk 3** hebben we met de uitkomsten van de COMPARE studie de kosteneffectiviteit van beide behandelstrategieën na een acuut gescheurde voorste kruisband vergeleken. Voor de beoordeling van kosteneffectiviteit berekenen we de QALY, quality adjusted life year. Een QALY staat voor één levensjaar in goede gezondheid. De kosteneffectiviteit werd berekend door de extra kosten per QALY te bepalen vanuit 2 perspectieven; het zorgperspectief en het maatschappelijk perspectief. In Nederland is voor aandoeningen met een beperkte ziektelast het maximale bedrag wat men bereid is om te betalen voor een QALY € 20.000. Patiënten die werden behandeld met een vroegtijdige reconstructie hebben een toename van 0.04 QALY gedurende 2 jaar vergeleken met patiënten die werden behandeld met een

revalidatie en mogelijke reconstructie. De kosten vanuit zorgperspectief waren 48,460 €/QALY en vanuit maatschappelijk perspectief 78,179 €/QALY en, gezien de eerder genoemde grens van 20,000 €/QALY, niet als kosteneffectief beschouwd.

In **hoofdstuk 4** hebben we met behulp van statistische modeleren van de vorm van de knie, vormvariaties van de knie kunnen identificeren tussen patiënten die een gescheurde voorste kruisband hebben ten opzichte van patiënten die geen gescheurde voorste kruisband hebben na een knieletsel. Deze vormverschillen kunnen gebruikt worden om mensen met een groter risico op een gescheurde voorste kruisband te identificeren. We vergeleken de röntgenfoto's van 168 patiënten met een gescheurde voorste kruisband met 168 patiënten met een intacte voorste kruisband. Groepen werden gekoppeld voor geslacht. Met behulp van software voor vormanalyse werden beide groepen vergeleken. Patiënten met een gescheurde voorste kruisband hadden een kleinere inkeping (notch) tussen beide femurcondylen en kleinere verhevenheid (eminentia) van de tibia.

In **hoofdstuk 5** hebben we met gebruik van de zelfde software onderzocht of de anatomische vorm van de knie de klinische uitkomst na een gescheurde voorste kruisband kan voorspellen. We hebben 182 patiënten vergeleken en geëvalueerd of er een samenhang met de klinische uitkomst (gemeten met de IKDC score) was na 2 jaar. Gemiddelde leeftijd van de patiënten was 31 jaar, de meerderheid was man en de meerderheid werd behandeld met een voorste kruisband reconstructie. Patiënten behandeld met een voorste kruisband reconstructie hadden een hogere IKDC score bij een kleinere femorale notch en een kleinere eminentia van de tibia. Patiënten die niet werden behandeld met een voorste kruisband reconstructie, hadden een betere klinische uitkomst na 2 jaar als ze een meer piramidevormige notch hadden ten opzichte van een koepelvormige vorm. De vorm van de femorale notch en de eminentie van de tibia kan de klinische uitkomst voorspellen na een gescheurde voorste kruisband.

In **hoofdstuk 6** presenteren we een systematisch overzicht van in de literatuur beschikbare kennis over factoren die samenhangen met de noodzaak voor een reconstructie na een gescheurde voorste kruisband. In totaal werden 7 studies in het overzicht geïncludeerd, waarvan 3 van methodologisch hoge kwaliteit. Op basis van deze studies was duidelijk dat vroeg na de diagnose gescheurde voorste kruisband, geslacht (sterk bewijs) en de ernst van laxiteit (matig bewijs) van de knie niet kan voorspellen of een patiënt een voorste kruisband reconstructie nodig heeft. Alle andere factoren in het review hadden tegenstrijdig bewijs, minimaal of geen bewijs. Opmerkenswaardig is 1 studie van hoge kwaliteit, welke melding maakt dat er een relatie is tussen de ronding van de femurcondyl op een zijwaartse röntgenfoto en de noodzaak van een reconstructie van de voorste kruisband.

In **hoofdstuk 7** presenteren we een update van het artikel over computerondersteuning tijdens de operatie voor reconstructie van kniebanden uit 2011. Een veelvoorkomend technische oorzaak van falen van een bandreconstructie is suboptimale plaatsing. Met computerondersteuning proberen we tot een nauwkeurigere plaatsbepaling te komen bij bijvoorbeeld voorste en achterste kruisbandreconstructies. De update leidde tot inclusie van 1 nieuwe studie, waardoor nu 5 gerandomiseerde studies met in totaal 366 deelnemers werden geïncludeerd. Er werd matig kwaliteit bewijs gevonden dat het gebruik van computer ondersteuning geen meerwaarde heeft op de klinische uitkomst gemeten met IKDC vergeleken met de traditionele navigatie. Voor de klinische uitkomstmaten Lysholm (beperkte kwaliteit bewijs) en activiteiten niveau gemeten met Tegner score (beperkte kwaliteit) bleek computernavigatie ook geen meerwaarde te hebben. Al met al werd er behoudens een langer operatietijd met computerondersteuning geen verschil in uitkomsten gevonden tussen de operaties met of zonder computer ondersteuning.

Curriculum Vitae

Vincent Eggerding werd geboren op 17 februari 1983 te Leiderdorp. Hij groeide op in Leimuiden en haalde in 2001 zijn diploma op het gymnasium van het Herbert Vissers College. Aansluitend startte hij met de studie geneeskunde aan het VU medisch centrum te Amsterdam. De studie geneeskunde sloot hij af met een onderzoeksstage aan the University of Illinois at Chicago in 2006. Na onder andere een keuze co-schap orthopedie in het Spaarne Gasthuis en oudste co-schap heelkunde in het Kennemer Gasthuis ontving hij in 2008 zijn artsendiploma cum laude.

Vervolgens startte hij als arts niet in opleiding heelkunde in het Kennemer Gasthuis. In 2011 kon hij starten met een promotieonderzoek op de afdeling orthopedie van het Erasmus MC. Het opzetten van de COMPARE studie naar behandelstrategieën voor patiënten met een voorste kruisbandruptuur. Dit onderzoek heeft geleid tot dit proefschrift en werd onder andere gepresenteerd op de ISAKOS (International Society of Arthroscopy, Knee Surgery and Orthopaedic Sports Medicine), EFORT (European Federation of Orthopaedics and Traumatology), NOV (Nederlandse Orthopedische Vereniging) en NVA (Nederlandse Vereniging van Arthroscopy). In 2014 en 2019 werd zijn presentatie op het jaarcongres van de NVA beloond met de Eijkelaarsprijs en in 2019 werd zijn presentatie op het jaarcongres van de NOV met de professor van Rens prijs.

In 2014 kon worden begonnen met de opleiding tot orthopedisch chirurg. De vooropleiding vond plaats in het Amphia Ziekenhuis te Breda onder begeleiding van professor dr. Lyckle van der Laan. Het academische deel van zijn opleiding orthopedie heeft hij gevolgd in het Erasmus MC onder leiding van dr. Koen Bos en zijn perifere deel in het Elisabeth Tweesteden Ziekenhuis te Tilburg onder begeleiding van dr. Taco Gosens.

In 2020 heeft Vincent zijn opleiding tot orthopedisch chirurg afgerond en is hij in 2021 gestart als fellow Spine in het Zuyderland Ziekenhuis te Heerlen onder begeleiding van Wouter van Hemert, Pieter Tilman en Inez Curfs.

Vincent is woonachtig in Sambeek met zijn vrouw Manon en drie kinderen Gwen (2016), Simon (2018) en Guus (2021).

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