Escaping the Scalpel

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In-depth evidence to change clinical practise for patients with a degenerative meniscal tear

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‘It’s all about mentelity’

Bibian Mentel (1972 - 2021)

Table of Contents

Chapter 1

General introduction

A meniscal tear is one of the most common knee injury.[6, 14] The menisci are important for the congruity in the knee.[8] They increase the contact area between the femoral condyles and tibia plateau, and decrease contact stress. The viscoelastic properties of the menisci make them important shock absorbers.[8] In younger adults the onset is often a traumatic, acute origin that is work or sports related.[6] However, as one gets older the viscoelasticity of menisci tissue decreases, causing an increased risk for a degenerative lesion.[7, 8] Degenerative meniscal lesions can even be an incidental finding in middle aged and older patients. In men and women between 50 and 59 years old with no history of knee pain, the prevalence of meniscus tears is 32% in men (95% Confidence Interval [CI]: 26% to 40%) and 19% in women (95% CI: 15% to 24%). Among 70 to 90 years old men and women the prevalence increases to 56% in men (95% CI: 46% to 66%) and 51% in women (95% CI: 42% to 60%).[7]

An overview of the evidence on treatment for degenerative meniscus tears

At the end of the last century arthroscopic knee surgery was the most frequently performed orthopedic treatment in patients with knee osteoarthritis or a degenerative meniscus tear.[24] The surgery either consisted of arthroscopic lavage and debridement for knee osteoarthritis or an arthroscopic partial meniscectomy (from now on: meniscus surgery) for patients with a meniscus tear.[5] However, the effectiveness of meniscus surgery compared nonsurgical treatment was not yet thoroughly studied.
This changed in the beginning of the 2000s, when a placebo-controlled trial investigated the effectiveness of arthroscopic surgery compared to placebo-surgery for knee osteoarthritis.[24] This study found no clinically relevant difference in patient reported pain and function between the placebo-surgery and the arthroscopic lavage and debridement.[24] Since 2007, when the evidence was incorporated the National Institute for Health and Care Excellence guidance, this study effectuated in an 80% reduction of arthroscopic lavage and debridement.[21] However, around the same time, from 2000 until 2012, we found an even larger increase in meniscus surgeries.[21] This shift towards meniscus surgery cannot be explained based on the grounds of evidence-based medicine, since high quality evidence on the effectiveness of this procedure was not yet available by that time.

The first randomized clinical trial on the effectiveness of meniscus surgery compared with nonsurgical management was published in 2007.[11] This study did not find a clinically relevant differences in patient reported knee function, patient reported knee pain and quality of life when comparing meniscus surgery followed by exercise-based physical therapy with exercise-based physical therapy alone over a period of 2 and 5 years.[11] The study concluded that meniscus surgeries was not superior to exercise-based physical therapy.[11]
Between 2013 and 2018 seven more RCT's published their results. Six of these studies concluded that meniscus surgery was not superior over exercise-based physical therapy for patient reported knee function [10, 12, 15, 20, 25, 35, 38]. In contrary, the study by Gauffin et al. [9] found significantly less pain after meniscal surgery compared with a structured exercise

program. However, this study found no significant differences in the subscales for symptoms, activities in daily life, sports and quality of life. Besides, the systematic reviews with meta-analysis of these studies resulted in statistically insignificant differences between the two treatments over a period of 1 and 2 years on pain, knee function and quality of life.[5, 37]

Interventions

Exercise-based physical therapy

The exercise-based physical therapy mainly focuses on regaining normal knee range of motion, improving strength of the upper leg, and knee stability.[17] The exercise protocols of the RCTs all consisted of a progressive exercise program but differed in duration, ranging from 6 to 12 weeks, and frequency, one to three times a week.[17] The exercise protocols used in the RCTs use a one-size-fits-all approach, i.e., all patients in a trial receive more or less the same exercise intervention. However, an exercise program tailored to the individual patient's needs and wishes may be more beneficial to reach the patients rehabilitation goals.[30]

Meniscus surgery

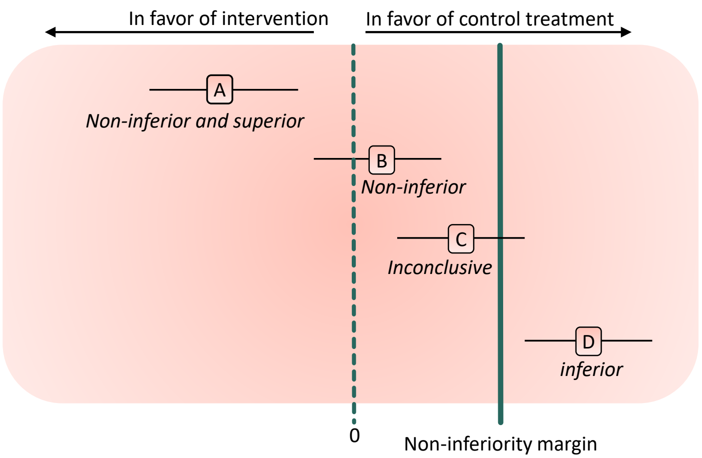
During the surgical procedure the orthopaedic surgeon removes the teared meniscus tissue until a stable rim is achieved. Patients are able to go home within hours after their surgery. Recovery takes 2 to 6 weeks and guidelines advise using a walking aid in the first week.[29] Post-operative exercises therapy, either self-guided or led by a physical therapist, may facilitate recovery.[29] Serious complications in arthroscopic knee surgery occur in 0.32% of the patients [3], which equates to approximately 210 patients with a degenerative meniscus tear per year in The Netherlands. These serious complications include pulmonary embolism and infections requiring additional surgery. Older patients are at higher risk for serious complications following arthroscopic knee surgery.[3] Another important disadvantages of meniscus surgery is the increased risk of developing knee osteoarthritis (OA) in the long-term.[22] As the effectiveness of meniscus surgery for degenerative meniscus tears is debated, both the risk for a serious complication and developing knee OA might be avoided if non-surgical interventions are prioritised.[2]

Clinical guidelines

In 2010 the first Dutch orthopedic evidence-based guideline on knee arthroscopy was published.[32] The guideline was updated in 2019.[31] Both the old and updated guidelines have similarities and differences. The most important similarities in the management of meniscus injuries is 1) the distinction between acute and degenerative meniscal tears and 2) to not performing MRIs on a routinely basis in patients over 50 years old with knee pain from a degenerative origin.[31, 32] The most striking difference is the available evidence on treatment effectiveness. [31, 32] Therefore, the old guideline does not make any statement on the treatment for degenerative meniscal tears.[32] Whereas, the current Dutch, but also international guidelines, recommend against surgical treatment for middle aged and older patients with a degenerative meniscus tear and nonsurgical management should last for at least 3 months.[1, 29, 31]

Despite that the guidelines recommend nonsurgical treatment, meniscus surgery is still frequently performed in middle aged and older patients with a meniscus tear.[4, 28] It seems that with 25.992 (75%) of the arthroscopic partial meniscectomies performed in patients over 40 years old in 2005, and still 20.833 (70%) in 2014, clinicians are not convinced by the evidence and uncertain about the quality of the current evidence.[3, 5] A non-inferiority design can fill this knowledge gap and provide high quality evidence that is need to empower clinicians in their evidence-based treatment decisions.[26]

Figure 2. Different examples of non-inferiority results and interpretation



A. The upper limit of the 95% confidence interval of the between-group difference is smaller than the non-inferiority margin and zero. The intervention is non-inferior and superior compared to the control treatment.

B. The upper limit of the 95% confidence interval of the between-group difference is smaller than the non-inferiority margin. The intervention is non-inferior compared to the control treatment.

C. The upper limit 95% confidence interval crosses the non-inferiority margin, therefore the between group difference is not smaller. The result is inconclusive.

D. The lower limit of the 95% confidence interval of the between-group is greater than the noninferiority margin. The intervention is inferiortothe control treatment

Methodological considerations

Noninferiority studies provide evidence whether an intervention (in this thesis: exercise-based physical therapy) is or is not less effective compared to the control treatment (in this thesis: meniscus surgery).[26] This study design is appropriate when the intervention has potential benefits over the control treatment. For instance, exercise-based physical therapy has a lower risk of complications, is less invasive and cheaper compared to meniscus surgery. Prior to the study a non-inferiority margin is defined, which indicates the threshold of clinical relevance for the outcome measure of interest. With noninferiority testing the between group difference (i.e. the mean difference and the upper limit of the 95% confidence intervals) is tested in respect to the non-inferiority margin, rather than with respect to zero.[26] Figure 2 displays an example of noninferiority figure and an explanation of the conclusions one can draw from these results.

Although results of RCTs are important to determine the effectiveness of treatments, they cannot always directly be implemented in clinical practice due to the experimental nature of an RCT that can result in a discrepancy between the study population and the general population seen in clinical practice, or due to healthcare policy rules and regulations. Besides, the RCT-based treatment recommendations do not account for the individual variation in treatment effect and are therefore not always applicable to the individual patient.[19] For instance, in the published trials an average of 24% (range 1.9 to 36%) of the patients underwent delayed meniscus surgery after initial physical therapy failed.[2] Published prognostic models cannot accurately predict treatment outcome or select subgroups of patients who benefit from either meniscus surgery or physical therapy.[16, 27, 34] With the growing interest in personalized medicine, professional guidelines for clinical prediction models have been established [23] and advanced statistical methods have been proposed to account for heterogeneity of treatment effects [18]. The TRIPOD statement is a guideline for multivariable prognostic models in which baseline variables are combined and the model is internally validate to correct for a possible overestimation of the models' accuracy.[23] Another, more advanced, approach is a Marker-by-Treatment analyses.[13, 19] This novel approach in orthopedic research, provides specific cut-off points for patient characteristics to determine which treatment, exercise-based physical therapy or meniscus surgery gives the best outcome.[19] This thesis will apply two prognostic techniques to RCT data, in order to strengthen the evidence base for treatment of patients with degenerative meniscus tears.

ESCAPE Trial

This thesis is an in-depth analyses and continuation of the ESCAPE trial. The ESCAPE trial is a multi-center randomized controlled trial with a noninferiority design comparing meniscus surgery with exercise-based physical therapy.[36] We enrolled patients for the ESCAPE trial in nine participating hospitals in The Netherlands. The inclusion and exclusion criteria are displayed in figure 3.[36]

Figure 3. Inclusion and exclusion criteria of the ESCAPE trial

Inclusion criteria
- MRI confirmes meniscus tear
- 45 to 70 years old
- Written informed consent

Exclusion criteria
- BMI >35 kg/m2,
- Locking of the knee or acute trauma needing surgery
- Prior knee surgery
- Injuries on the index knee:
  - Tear of anterior or posterior cruciate ligament
  - Severe OA of the knee
  - Lateral or posterolateral ligament complex injury
- Tumor suspicious of malignancy, on MRI
- Medical condition or treatment interfering with the study
- Drugs or alcohol abuse
- Patients unable to fill out the Dutch questionnaires

We collected the data between July 2013 and October 2020. The data contained of 1) Patients self-administered questionnaires on knee function, general physical health, pain in rest and during weight bearing, patient specific activities and quality of life. We collected the questionnaires at baseline and 3 months, 6 months, 1 year, 2 years and 5 years after enrolment. 2) We collected data on the medical costs and societal costs to evaluated the cost-effectiveness of meniscal surgery compared to exercise-based physical therapy. 3) We recorded the physical examination at baseline and after 3 months of enrolment containing range of motion of the knee, circumference of the thighs and calves, hydrops and specific meniscus tests (joint effusion, joint line tenderness, forced range of motion in full flexion and full extension, McMurray test, Thessaly test in 5 and 20 degrees of flexion and Duck Walk test. And last, imaging of the knee contained of an MRI at baseline and radiographs of the index knee at baseline, 2 years and 5 years.[36]
We based our sample size for noninferiority testing on a power of 90%, with an alpha of 0.05, a standard deviation of 18 points on the primary outcome knee function assessed with the International Knee Documentation Committee Subjective Knee Form (IKDC) (score ranged from 0-100; worst to best) and a clinically relevant difference of the IKDC based on the smallest detectable change of 8.8 point. To increase the power, we rounded this down to 8 points for the non-inferiority margin. We took a loss to follow-up of 10% and a 25% delayed meniscus surgery in the physical therapy group after 2 years into account. This calculation resulted in a total of 320 participants, 160 per group.[36]
Prior to this thesis, dr. V.A. van de Graaf wrote his thesis, titled "Changing our treatment of degenerative meniscal tears"[33] that included results from the ESCAPE trial. The conclusions from this thesis were:

- The IKDC is a reliable, valid and responsive measurement instrument for evaluating knee function in the treatment of degenerative meniscal tears.[33]
- In patients with a degenerative meniscal tears, exercise-based physical therapy is non-inferior and more cost-effective compared to meniscus surgery.[33]
- A survey among orthopaedic surgeons revealed that these surgeons could not reliably se-

lect those patients who are expected to benefit from meniscus surgery. Therefore, they should rely more on the evidence in their treatment decisions.[33]

- There is considerable evidence that exercise-based physical therapy should be proposed as treatment of first choice in patients with degenerative meniscal tears.[33]
- Avoidable meniscus surgeries will be performed in The Netherlands, as long as 1) the current evidence is not convincing to the orthopaedic surgeons, 2) the national and international guidelines are not consistent in their consensus for degenerative meniscus tears, and 3) the Dutch healthcare system does not differentiate between evidence-based and eminence-based financial reimbursement of healthcare.[33]
- Given the current widespread use of meniscus surgery, future research should focus on the subgroup of non-responders to physical therapy aiming to further reduce the numbers of unnecessary surgeries. [33]

Aiming to advance evidence-based practice for patients with degenerative meniscus tear, this thesis focused on predicting the response to the treatment, the difference between meniscus surgery and exercise-based physical therapy in important patient-specific activities in daily life and in longer term-outcomes.

Outline of this thesis

This thesis is an in-depth analyses and continuation of the ESCAPE trial, aiming to advance evidence-based practice for patients with degenerative meniscus tear. The primary outcome of the ESCAPE trial was patient-reported knee function. We assessed knee function using the IKDC, a valid and reliable measurement instrument for patients with a meniscus tear. In **Chapter 2** we investigated the Minimal Important Change (MIC) and responsiveness of the IKDC using the data obtained in the ESCAPE trial. These measurement properties are important to assess intervention effects in clinical trials. Previous clinical trials used generic patient-reported outcome measures that are regularly used in orthopedic research and clinical practice. However, when evaluating treatment effects, the patients' individual goals and activities in daily life also have to be taken into account, and may help the patient and physician in deciding the best treatment option. Therefore, in **Chapter 3** we used the patients' most important functional limitations in daily life as the outcome when comparing meniscus surgery with physical therapy in patients with a degenerative meniscus tear. To put the results in a clinically important perspective we determined the MIC of the outcome prior to the data analyses regarding the between-group difference.
To guide evidence-based treatment decisions for individual patients, we performed two prognostic studies. In **Chapter 4** we developed and validated prognostic models to identify those patients with a degenerative meniscus tear who will undergo surgery within 6 months and within 24 months following physical therapy. In **Chapter 5**, we introduced a novel prognostic approach in orthopedic research, a marker-by-treatment analysis. With this study we aimed to obtain specific cut-off points to identify whether meniscus surgery or physical therapy would yield the best outcome based on patient characteristics at baseline. In **Chapter 6**

we compared the effectiveness of arthroscopic partial meniscectomy and physical therapy in patients with a degenerative meniscus tear up to five years follow up, in terms of patient reported knee function and progression of knee OA.

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Chapter 2

Responsiveness and Minimal Important Change of the IKDC of Middle-Aged and Older Patients With a Meniscal Tear

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Abstract

Background: Responsiveness and the minimal important change (MIC) are important measurement properties to evaluate treatment effects and to interpret clinical trial results. The International Knee Documentation Committee (IKDC) Subjective Knee Form is a reliable and valid instrument for measuring patient-reported knee-specific symptoms, functioning, and sports activities in a population with meniscal tears. However, evidence on responsiveness is of limited methodological quality, and the MIC has not yet been established for patients with symptomatic meniscal tears.
Purpose: To evaluate the responsiveness and determine the MIC of the IKDC for patients with meniscal tears.
Methods: This study was part of the ESCAPE trial: a non-inferiority multicenter randomized controlled trial comparing arthroscopic partial meniscectomy with physical therapy. Patients aged 45 to 70 years who were treated for a meniscal tear by arthroscopic partial meniscectomy or physical therapy completed the IKDC and 3 other questionnaires (RAND 36-Item Health Survey, EuroQol-5D-5L, and visual analog scales for pain) at baseline and 6-month follow-up. Responsiveness was evaluated by testing predefined hypotheses about the relation of the change in IKDC with regard to the change in the other self-reported outcomes. An external anchor question was used to distinguish patients reporting improvement versus no change in daily functioning. The MIC was determined by the optimal cutoff point in the receiver operating characteristic curve, which quantifies the IKDC score that best discriminated between patients with and without improvement in daily function.
Results: Data from all 298 patients who completed baseline and 6-month follow-up questionnaires were analyzed. Responsiveness of the IKDC was confirmed in 7 of 10 predefined hypotheses about the change in IKDC score with regard to other patient reported outcome measures. One hypothesis differed in the expected direction, while 2 hypotheses failed to meet the expected magnitude by 0.02 and 0.01 points. An MIC of 10.9 points was calculated for the IKDC of middle-aged and older patients with meniscal tears.
Conclusion: This study showed that the IKDC is responsive to change among patients aged 45 to 70 years with meniscal tears, with an MIC of 10.9 points. This strengthens the value of the IKDC in quantifying treatment effects in this population.
Level of Evidence: Level II.

Introduction

Different patient-reported outcome measures (PROMs) have been developed and validated for patients with meniscal injuries. Many reflect the patients' perception of knee-specific symptoms, functioning, and sports activities, such as the KOOS (Knee injury and Osteoarthritis Outcome Score), the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), the Lysholm Knee Scoring Scale, the Western Ontario Meniscal Evaluation Tool (WOMET), and the International Knee Documentation Committee (IKDC) Subjective Knee Form.[1] It is important to use high-quality PROMs to obtain outcomes that are trustworthy.[15] The quality of PROMs mainly depends on their reliability, validity, and responsiveness as described by the Consensus-Based Standards for the Selection of Health Measurements Instruments (COSMIN).[16] The IKDC, a 1-dimensional questionnaire as proven by confirmatory factor analysis, was previously shown to have the highest reliability and validity in measuring the functional outcome after treatment of meniscal injuries as compared with the KOOS and WOMAC.[14, 27] The responsiveness, however, of most PROMs, including the IKDC, is not well documented, and limited evidence is available in the specific population of patients with a meniscal tear.[1] The COSMIN initiative defines responsiveness as ''the ability of a health related PROM to detect change over time in the construct to be measured.[16] Adequate responsiveness of a PROM is important to properly assess intervention effects in clinical trials. Aside from the responsiveness of a PROM, the interpretation of the changed score is essential in clinical practice. When changed scores are interpreted, the emphasis should be on the important change as perceived by the patient, represented by the minimal important change (MIC).[7] MIC is a measure that quantifies the smallest change score that patients perceive to be important.[4, 6, 7] It is relevant to know whether a measurement instrument is able to detect changes as small as the MIC value. This depends on the reliability and measurement error, often quantified as the smallest detectable change (SDC). When the SDC exceeds the MIC, an instrument cannot detect the MIC at the individual level on the basis of single measurements; when the SDC is smaller than the MIC, an instrument may detect statistically significant changes that lack clinical relevance. To ensure that observed changes are both statistically significant and clinically relevant, the change values have to exceed both the SDC and the MIC.[5] Devji and colleagues [6] acknowledged the importance of the MIC in the interpretation of a treatment effect. The MIC for the IKDC is not yet determined for patients with an isolated meniscal tear.[1] Knowledge of both the responsiveness and the MIC in this patient population is important for designing clinical trials and to discriminate between responders and nonresponders with regard to the treatment. Unknown responsiveness and MIC severely hamper the interpretation of clinical trial results and might explain why the preferred choice of treatment for meniscal tears is still a topic of debate, despite several randomized controlled trials, systematic reviews, and meta-analyses comparing arthroscopic partial meniscectomy with physical therapy.[13, 14, 24, 26] Because the IKDC has high reliability and validity for patients with a meniscal tear, this study focuses on the other main measurement property, responsiveness, and the measure of interpretability, the MIC.[14, 27] Specifically, we evaluated the responsiveness and MIC of the IKDC among middle-aged and older patients with meniscal tears.

Method

Population

This study was part of the ESCAPE trial, a noninferiority multicenter randomized controlled trial comparing arthroscopic partial meniscectomy with a nonoperatively treated control group receiving physical therapy.[24, 25] Between July 2013 and October 2015, 321 patients between 45 and 70 years of age with a symptomatic, nonobstructive, degenerative meniscal tear (confirmed per magnetic resonance imaging) were included. Exclusion criteria consisted of severe osteoarthritis (Kellgren-Lawrence 4), body mass index >35 kg/m2, locking of the knee, prior knee surgery, and knee instability attributed to anterior or posterior cruciate ligament rupture. Previous knee injuries (e.g., anterior cruciate ligament rupture) that can interfere with the treatment outcome were assessed on magnetic resonance imaging and excluded from the trial. Further details can be found in the study protocol.[25] The ESCAPE trial was approved by the Medical Ethical Committee (NL44188.100.13). All patients provided written informed consent for participation.

Treatment

Patients randomized to arthroscopic partial meniscectomy underwent surgery within 4 weeks after enrollment. The arthroscopic partial meniscectomy procedure started with a general assessment of the joint, whereupon the affected meniscus was partially removed, resulting in a stable and solid meniscus. Patients received standard written postoperative instructions. Participants were referred to physical therapy after arthroscopic partial meniscectomy if rehabilitation was not going according to the guideline of the Dutch Orthopaedic Association.[23] Physical therapy started 1 to 2 weeks after randomization. Patients in the physical therapy group participated in a supervised progressive exercise program consisting of 16 sessions of 30 minutes each (Appendix 1).[25]

Data Collection

Patients received self-administered questionnaires at baseline and 6 months after enrollment. Patients completed the questionnaires at home, either online or on paper. In the online questionnaires, no data were missing, as completion of each item was required to move on to the next item. When an item was missing in the paper-based questionnaires, the missing item was obtained by telephone. To enhance the response rate, up to 3 response reminders were sent to the patients. Details on patient inclusions, randomization, and follow-up are available in Appendix 2.

Table 1. Hypotheses with expected and calculated correlations

	Hypothesis	Expected r	Calculated r (95% CI)	P Value
1	The change in total IKDC score shows at least a very strong positive correlation with the change on the PCS of the RAND-36	≥0.7	0.74 (0.67 – 0.81)	<.001
2	The change in the items for activity of the IKDC (questions 8 and 9) shows a very strong positive correlation with the change on the dimension for PCS of the RAND-36	≥0.7	0.70 (0.61 – 0.78)	<.001
3	The change in the items for activity of the IKDC (questions 8 and 9) shows a very strong positive correlation with the change on the dimension for physical function of the RAND-36	≥0.7	0.72 (0.63 - 0.79)	<.001
4	The change in the items for pain of the IKDC (questions 1, 2 and 3) shows a very strong negative correlation with the change in VAS for pain during weight bearing.	≤-0.7	-0.68[b] (-0.76 – -0.59)	<.001
5	The change in the items for pain of the IKDC (questions 1, 2 and 3) shows a moderate to strong positive correlation with the change on dimension for bodily pain of the RAND-36	0.3≤ r <0.7	0.59 (0.51 – 0.69)	<.001
6	The change in VAS for pain at rest shows at least a moderate to strong negative correlation with the change in IKDC	-0.3≥ r >-0.7	-0.55 (-0.60 – -0.40)	<.001
7	The change in VAS for pain during weight bearing shows a moderate to strong negative correlation with the change in IKDC	-0.3≥ r >-0.7	-0.70[b] (-0.77 – -0.60)	<.001
8	The change in EQ-VAS shows moderate to strong moderate positive correlation with change in IKDC.	0.3≤ r <0.7	0.35 (0.21 – 0.43)	<.001
9	The change in total IKDC score shows a poor positive correlation with the change on the dimension for general health of the RAND-36	<0.3	0.04 (-0.06 – 0.17)	.49
10	The change in total IKDC score shows a poor positive correlation with the change on the MCS of the RAND-36	<0.3	-0.11[b] (-0.12 – 0.11)	.07

a EQ-VAS, EuroQol–Visual Analog Scale; IKDC, International Knee Documentation Committee; MCS, Mental Component Scale; PCS Physical Component Scale; RAND-36, 36-Item Health Survey; VAS, visual analog scale

b Hypothesis was not confirmed

Outcome Measures

Four PROMs that were evaluated were all translated and validated for the Dutch population.[8, 27, 28, 31] Sociodemographic information (age, sex, and body mass index) was collected at baseline. At follow-up, the same PROMs were administered, and an anchor question was added about the patients' assessment of change of functioning in daily activities. The IKDC was developed to measure knee-specific symptoms, function, and sports activity for patients with ligament or meniscal injuries.10 The IKDC consists of 19 items, of which 18 are converted into a total score. The answer to question 10a is not used for the overall score. Factor analysis confirmed the single dimension in a similar population.[27] The sum of these 18 items is converted into an IKDC score, ranging from 0 to 100 points. The minimum score of 0 points indicates that the patient is very limited in daily and sports activities, and the maximum score of 100 points indicates no restriction in functioning.[10] The IKDC was validated for patients with meniscal tears.[2, 27] The RAND 36-Item Health Survey (RAND-36) is a general health questionnaire that consists of 8 dimensions with a total of 36 questions.[31] From these 8 dimensions, 2 aggregated scores are calculated: the physical and mental component scores. These scores can be compared with the Dutch population with an average score of 50 points, in which higher scores represent better health. A study on its psychometric qualities concluded sufficient reliability and validity.[31] The EuroQol–5 Dimension–5 Level (EQ-5D-5L) is a generic measure of health often used to assess quality of life.[9] The questionnaire consists of 5 questions on mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Additionally, patients were asked to rate their general health on a visual analog scale (EQ-5D-VAS) for a score between 0 and 100, with 0 indicating the worst possible health status as perceived by the patient and 100 indicating the best. The EQ-5D-VAS is responsive for patients undergoing knee arthroscopy[17] and was the only EQ-5D item that we used for further analysis. Pain was assessed through 2 visual analog scales of 100 mm. Patients were asked to rate their pain at rest and during weightbearing activities in the previous week. The amount of pain was scored by marking on a line of 100 mm, with 0 indicating no pain and 100 indicating severe pain. The external anchor question "How did your function in daily activities change since the surgery/treatment of your knee?" was administered at 6 months after enrollment to determine the patient's perception of change in knee function after the treatment.[12] The question was scored on a 7- point Likert scale, ranging from very much worsened to very much improved.

Responsiveness

Responsiveness of the IKDC was assessed with hypothesis testing based on the correlations of absolute changed scores, as recommended by the COSMIN panel.[19] Ten hypotheses were formulated (see Table 1): 5 before data collection (hypotheses 1, 3, 5, 9, 10) and 5 after data collection but before data analysis (hypotheses 2, 4, 6-8). The expected correlations were predetermined per current literature, clinical experience, and consensus among the authors. Correlations were categorized as very strong ($r \geq 0.7$), strong ($0.5 \geq r < 0.7$), moderate ($0.3 \geq r < 0.5$), and weak ($r < 0.3$). The hypotheses were tested with the Pearson correlation coefficient for normally distributed data and the Spearman rank correlation coefficient for nonnormally distributed data. To demonstrate good responsiveness, ≥75% of the hypotheses should be confirmed.[16]

Minimal Important Change

The MIC was defined as the smallest change in outcome in the domain of interest as perceived beneficial by the patient.[4] The MIC value was established with an "anchor-based MIC distribution method," a blending of 2 methodologies: Specifically, an anchor-based method uses an external criterion to determine what patients consider important,[3] which is especially helpful in a study based on score distribution, given that distribution-based methods lack information on whether the observed changes are minimally important.[4] First, we analyzed the correlation between the changes in IKDC scores and the external anchor question. Next, if this correlation was >0.5, the study population was divided into changed and unchanged based on the external anchor question. The changed group comprised patients who reported to be very much, much, and slightly improved. The unchanged group included patients who reported to be unchanged. Patients who reported very much, much, or slight deterioration in daily functioning were excluded since we were comparing patients with and without important improvement. [4] The receiver operating characteristic (ROC) curve was used because it searches for the optimal cutoff points, irrespective of how much misclassification occurs. A graphic display of the anchor-based MIC distribution was plotted, as well as the ROC curve. [3] Sensitivity and specificity were determined for all potential cutoff points. The MIC value was determined by the optimal cutoff point—that is, with the smallest value of the sum of the proportions of misclassifications: (1 – sensitivity) + (1 – specificity).[3] In other words, the MIC was quantified by the IKDC score that best discriminated between patients with and without clinically relevant improvement.

Statistical Analyses

We used descriptive statistics to analyze the patients' demographics and tested all data for normality with the Kolmogorov-Smirnov test. The mean and SD were calculated for continuous normally distributed data ($P > .05$, Kolmogorov-Smirnov) and the median and interquartile range for continuous nonnormally distributed data ($P < .05$, Kolmogorov-Smirnov). Frequencies and percentages were used for categorical data. We calculated the changed scores by subtracting the baseline scores from the follow-up questionnaire scores. The percentage change scores are reported in Table 2, as it takes into account the scores at baseline. All analyses were performed with SPSS (v 22; IBM Corporation).

Table 2. Scores at Baseline and 6-Month Follow-up and the Changed Scores[a]

PROM: Subscale	Baseline	6-mo Follow-up	Changed Scores	Percentage Changed Scores
IKDC: total	45.7 ± 15.1	66.7 (50,6 to 78.2)	19.5 (3.5 to 31.3)	44.6 (7.1 to 82.8)
Rand-36				
PCS	37.7 ± 8.4	49.5 (41.8 to 54.2)	9.4 ± 9.6	25.8 (4.9 to 49.9)
MCS	52.9 (47.3 to 60.4)	55.3 (48.6 to 58.5)	-0.4 (-4.6 to 4.2)	-0.4 (-7.4 to 8.1)
PF	60 (45.0 to 75.0)	80.0 (60.0 to 90.0)	15.0 (0 to 30)	22.6 (0 to 70)
BP	42.9 (32.7 to 44.9)	77.6 (67.4 to 89.8)	32.7 (13.8 to 46.9)	77.3 (33.3 to 120)
GH	70.0 (60.0 to 80.0)	72.5 (65.0 to 85.0)	5 (-5 to 15)	6.5 (-6.7 to 25)
VAS for pain				
Rest	30.1 (5.8 to 56.1)	6 (0.0 to 24.1)	-18.9 (-36.9 to -1.9)	-82.0 (-100 to -17.5)
Weight bearing	60.9 (42.0 to 78.1)	16.5 (4.6 to 51.4)	-30.2 ± 32.8	-61.9 (-90.2 to -17.4)
EQ5D5L-VAS	78.1 (64.3 to 88.1)	82.6 (69.3 to 90.4)	3.1 (-7.6 to 11.6)	-3.8 (-8.9 to 15.7)

a Data are reported as median (interquartile range). For normally distributed data, values are reported as mean 6 SD. BP, bodily pain; EQ-5D-VAS, EuroQol–5 Dimension–Visual Analog Scale; GH, general health; IKDC, International Knee Documentation Committee; MCS, Mental Component Scale; PCS Physical Component Scale; PF, physical functioning; PROM, patient-reported outcome measure; RAND-36, 36-Item Health Survey; VAS, visual analog scale.

Results

In total, 321 patients were randomized in the ESCAPE study; however, 2 patients (1 in each treatment group) withdrew immediately after randomization. Of the remaining 319 patients, 298 (93.4%) returned the baseline and 6-month follow-up questionnaires. Baseline data of the 21 patients who did not complete the 6-month follow-up questionnaires were discarded. At baseline, the questionnaires (n = 298) contained 0.4% missing items. At follow-up (n = 298), 0.06% of the items were missing. Most patients (n = 279, 94%) completed both questionnaires online. Fifteen patients completed both questionnaires on paper, and 4 patients completed the first questionnaire online and the second on paper. Patient characteristics are shown in Table 3, with the mean and changed scores of the PROMs in Table 2.

II

Table 3. Baseline characteristics[a]

Characteristics	n (%) or Mean ± SD
Patients	298
Sex	
Male	148 (49.7)
Female	150 (50.3)
Age, y	57.5 ± 6.7
BMI, kg/m2	26.9 ± 3.9
Treatment	
APM	151 (50.7)
PT	147 (49.3)
Affected knee	
Left	136 (45.6)
Right	162 (54.4)
MRI: Affected meniscus	
Medial	245 (82.3)
Lateral	52 (17.4)
Both	1 (0.3)
Radiograph: Kellgren & Lawrence, n	281
0 – No OA n (%)	29 (9.7)
1 – Doubtful n (%)	147 (49.3)
2 - Minimal n (%)	95 (31.9)
3 - Moderate n (%)	10 (3.4)
4 – Severe n (%)[b]	0 (0)

Abbreviations: BMI, body mass index; MRI, Magnetic Resonance Imaging; APM, Arthroscopic Partial Meniscectomy; PT, physical therapy

a Data are reported as median and interquartile range unless otherwise indicated.

b Kellgren Lawrence grade 4 was an exclusion criterion

Responsiveness

Of 10 hypotheses, 7 (70%) were confirmed. The hypothesized and calculated correlation coefficients with the 95% CIs are shown in Table 1. For 2 unconfirmed hypotheses (hypotheses 4 and 7), the correlation coefficients deviated only slightly (0.02) from the predetermined threshold. Only hypothesis 10 differed from the predetermined direction, with a poor negative correlation while a poor positive correlation was expected.

Minimal Important Change

A strong correlation was found between the changed IKDC scores and the external anchor question ($r = 0.64$, $P<.001$). On the basis of the external anchor question, 217 patients (72.8%) reported to be changed and 48 (16.1%) unchanged. Patients who reported slight ($n = 21$, 7%), much ($n = 7$, 2.3%), or very much ($n = 3$, 1%) deterioration were excluded from the MIC analysis. Figure 1 shows the ROC curve. The optimal cutoff point was set at a sensitivity value of 79.7% and a specificity of 72.9%, resulting in an MIC of 10.9 points on the IKDC (range, 0-100 points). The anchor-based MIC distribution is displayed in Figure 2.

Figure 1. Receiver operating characteristic (ROC) curve, with optimal cutoff point

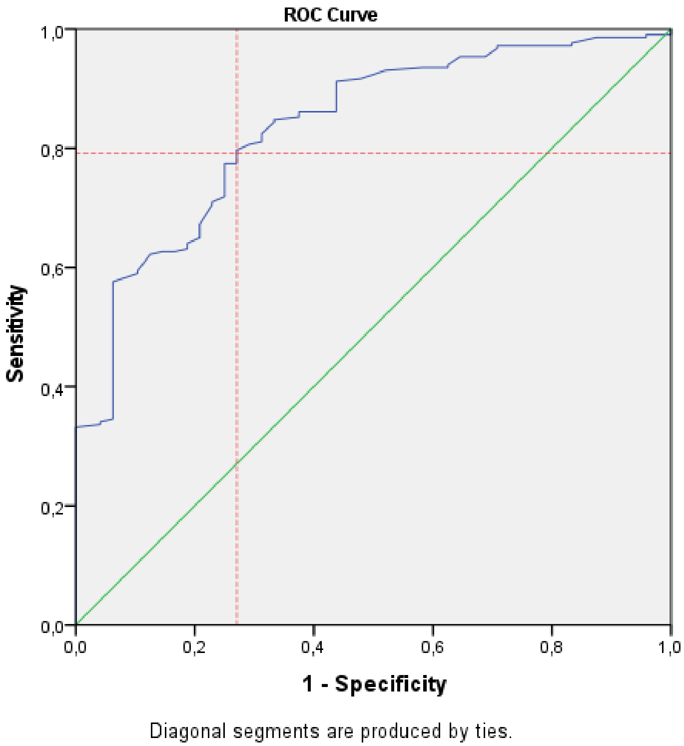
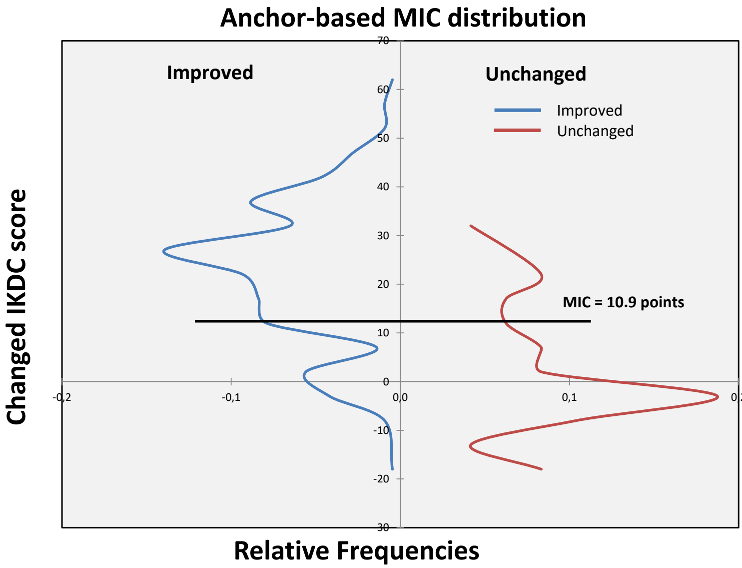


Figure 2. Anchor-based minimal important change (MIC) distribution. IKDC, International Knee Documentation Committee



Discussion

Responsiveness of the IKDC among patients 45 to 70 years old with symptomatic meniscal tears was confirmed in 7 of the 10 predefined hypotheses. One unconfirmed hypothesis demonstrated a weak negative correlation while a weak positive correlation was expected—namely, between change in IKDC score and the Mental Component Scale of the RAND-36. Two unconfirmed hypotheses (4 and 7) deviated only slightly in magnitude from the expected correlation. Therefore, we concluded that the IKDC was responsive in our population. Furthermore, we calculated an MIC of 10.9 points reflecting the minimal change in IKDC score that a patient considers important. This value contributes to the interpretation of change scores as a result of the treatment of patients with meniscal tears.

Comparison With the Literature

Irrgang et al. [11] established the MIC for the IKDC at 11.5 points and 20.5 points in a study population with various knee injuries, using the point on the ROC curve closest to the upper left corner. These values are both higher as compared with the MIC in our study. However, we determined the MIC as the optimal cutoff point, using the smallest value of the sum of the proportions of misclassifications. Furthermore, we found that the MIC exceeded the SDC of 8.8 points that was reported by Crawford et al.[2] Based on this SDC, there is 98% certainty that a change of 10.9 points was not due to measurement error.[21] Responsiveness of the IKDC was previously reported by 2 studies. Crawford et al. [2]analyzed responsiveness among 100 patients with meniscal injuries, and Irrgang et al. [11] analyzed the responsiveness of 207 patients with a variety of knee disorders. Both studies concluded adequate responsiveness, using the effect size without predefined hypothesis as a measure of responsiveness. This is considered a less suitable method, since it measures magnitude of change rather than quality of the measurement.[1, 5] Our results confirm that the IKDC is responsive to change based on recommended methodology.[18]

Strengths and Limitations

To our knowledge, this is the first study that determined the responsiveness and MIC of the IKDC among patients 45 to 70 years old with symptomatic meniscal tears, using predefined hypotheses with the expected magnitude and direction of the correlations. While previous studies investigating responsiveness with hypotheses testing used a general cutoff criterion of 0.5 for the expected correlations,[22, 29, 30] we defined more specific criteria to enhance the quality of our hypotheses. Another strength is that we utilized a large sample (n = 298) with >90% complete data. Third, with a relatively short interval (6 months), we are confident that patients could adequately recall any changes in physical functioning and that these changes were largely related to the treatment that they received. Fourth, we used the anchor-based MIC distribution for the calculation of the MIC to give more insight into the interpretation of the MIC. There were also limitations to this study. First, the data were retrieved from a randomized controlled trial, which could have led to selection bias. Second, the anchor question was not a true reflection of the construct measured by the IKDC. The anchor question focused on functioning in daily living, and the IKDC measures knee-specific symptoms, functioning, and activities. However, we found a strong correlation (r = 0.64) between the anchor question and change in IKDC score. The results of our study apply specifically to patients 45 to 70 years old with degenerative meniscal tears and can be different for patients with traumatic meniscal tears or other knee pathologies.

Implications of the Study

The results of this study contribute to the evidence regarding the measurement properties of the IKDC among patients with meniscal tears; the IKDC is also responsive to change in this population and is valid and reliable. An MIC of 10.9 was established, which strengthened the value of the IKDC for assessing patient-reported knee function. The MIC of 10.9 points was determined on a group level. These results can therefore be used on a group level, whether by policy makers to determine treatment per recipient or by researchers to compare different treatments.[4, 6, 7] The distinctive character of the MIC between "changed" and "unchanged," on a group level, makes it highly relevant for developing clinical prediction models. Furthermore, based on the sensitivity and specificity levels (79.7% and 72.9%, respectively) and the probability of the measurement error (2%), the MIC of 10.9 can also be applied to individual patients. [4, 6, 7]However, one should take the patient's characteristics into account when applying the MIC on an individual level.[20]

Conclusion

The IKDC was responsive to change, with an MIC of 10.9 points for middle-aged and older patients with a meniscal tear. This study has shown that the IKDC has good measurement properties to evaluate the treatment effect on meniscal injuries. Therefore, we recommend the use of the IKDC for middle-aged and older patients with degenerative meniscal tears.

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II

Chapter 3

Functional Outcomes of Arthroscopic Partial Meniscectomy Versus Physical Therapy for Degenerative Meniscal Tears Using a Patient-Specific Score

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Abstract

Background. It is unknown whether the treatment effects of partial meniscectomy and physical therapy differ when focusing on activities most valued by patients with degenerative meniscal tears.
Purpose. To compare partial meniscectomy with physical therapy in patients with a degenerative meniscal tear, focusing on patients' most important functional limitations as the outcome.
Methods. This study is part of the Cost-effectiveness of Early Surgery versus Conservative Treatment with Optional Delayed Meniscectomy for Patients over 45 years with non-obstructive meniscal tears (ESCAPE) trial, a multicenter noninferiority randomized controlled trial conducted in 9 orthopaedic hospital departments in the Netherlands. The ESCAPE trial included 321 patients aged between 45 and 70 years with a symptomatic, magnetic resonance imaging–confirmed meniscal tear. Exclusion criteria were severe osteoarthritis, body mass index >35 kg/m2 , locking of the knee, and prior knee surgery or knee instability due to an anterior or posterior cruciate ligament rupture. This study compared partial meniscectomy with physical therapy consisting of a supervised incremental exercise protocol of 16 sessions over 8 weeks. The main outcome measure was the Dutch-language equivalent of the Patient-Specific Functional Scale (PSFS), a secondary outcome measure of the ESCAPE trial. We used crude and adjusted linear mixed-model analyses to reveal the between-group differences over 24 months. We calculated the minimal important change for the PSFS using an anchor-based method.
Results. After 24 months, 286 patients completed the follow-up. The partial meniscectomy group (n ¼ 139) improved on the PSFS by a mean of 4.8 ± 2.6 points (from 6.8 ± 1.9 to 2.0 ± 2.2), and the physical therapy group (n ¼ 147) improved by a mean of 4.0 ± 3.1 points (from 6.7 ± 2.0 to 2.7 ± 2.5). The crude overall between-group difference showed a –0.6-point difference (95% CI, –1.0 to –0.2; P ¼ .004) in favor of the partial meniscectomy group. This improvement was statistically significant but not clinically meaningful, as the calculated minimal important change was 2.5 points on an 11-point scale.
Conclusion. Both interventions were associated with a clinically meaningful improvement regarding patients' most important functional limitations. Although partial meniscectomy was associated with a statistically larger improvement at some follow-up time points, the difference compared with physical therapy was small and clinically not meaningful at any follow-up time point.
Level of Evidence: Level I.

Introduction

For patients middle-aged and older with degenerative meniscal tears, previous randomized controlled trials have revealed no clinically relevant benefit of partial meniscectomy over nonoperative treatment such as physical therapy and sham surgery.[9, 11, 12, 14, 16, 22, 26, 31] When deciding on the best treatment for individual patients, their specific needs during activities of daily living should be taken into account. Additionally, the patient's perspective is important in treatment outcomes and is gaining attention in health care evaluation studies.[17] Past trials have investigated treatment effects using general, fixed-item patient-reported outcome measures (PROMs).[9, 11, 12, 14, 16, 22, 26, 31] The results of these studies were based on scores from the International Knee Documentation Committee (IKDC) subjective knee form, Knee injury and Osteoarthritis Outcome Score, and Western Ontario and McMaster Universities Osteoarthritis Index.[9, 11, 12, 14, 16, 22, 26, 31] These PROMs are validated for various patient populations, such as patients with anterior cruciate ligament (ACL) injuries, cartilage damage, and meniscal tears.[4, 13, 20] Although these fixed-item PROMs are adequate measures for health care evaluation studies, the items that are embedded in these PROMs do not take the variety of important daily life activities for individual patients into account.[2, 30] When using such fixed-item outcome measures, one assumes that all items are equally relevant for all patients.[30] Therefore, the scores of items that are less or not relevant for a patient can influence the overall results.[30] Additionally, these PROMs may not take into account an individual patient's rehabilitation goals. The patient's specific needs in daily life should be taken into account when evaluating treatment from a patient's perspective. A patient-specific instrument can be used in addition to the more generic, fixed-item PROMs. An instrument such as the Patient-Specific Functional Scale (PSFS; https://www.physiopedia.com/Patient_Specific_Functional_Scale) allows patients to select or propose those activities that are most relevant to them (i.e., patient-specific activities) and quantify the experienced difficulty in performing those activities because of their condition.[2, 5, 6] Middle-aged and older patients with a meniscal tear seem to overestimate the effectiveness of surgery in terms of participation in daily life activities such as walking and sports activities.[18] Research shows that 59% of these patients were too optimistic about their return to daily life and leisure activities after surgery.[19] The patient's overestimation of a surgical intervention could partly explain why meniscal surgery is still so frequently performed. Patient-specific activities have not yet been considered as part of the evaluation of treatment effects in those with a meniscal tear. Furthermore, assessing treatment effects using patient-specific activities can enhance treatment involvement, satisfaction, and perceived recovery.[23] This study compared the effectiveness of partial meniscectomy versus physical therapy on patient-specific activities over 24 months for middle-aged and older patients with degenerative meniscal tears.[27] We used the PSFS in addition to the fixed-item IKDC form, as previously published,[27] to assess differences between these treatments.

Method

Study design

For this study, we analyzed data of early surgery versus nonoperative treatment with optional delayed meniscectomy for patients aged ≥45 years with nonobstructive meniscal tears as part of the Cost-effectiveness of Early Surgery versus Conservative Treatment with Optional Delayed Meniscectomy for Patients over 45 years with non-obstructive meniscal tears (ESCAPE) trial, a multicenter randomized controlled trial comparing partial meniscectomy with physical therapy.[27] A medical ethics committee approved the ESCAPE trial in 2013, and the trial was registered at ClinicalTrials.gov (NCT01850719) and the Netherlands Trial Register (NTR3908).

Enrollment and Randomization

Patients for the ESCAPE trial were recruited from 9 participating hospitals in the Netherlands. Details on the inclusion/exclusion criteria and participant enrollment are described in the published study protocol. [27] In short, patients aged between 45 and 70 years with knee pain related to a meniscal tear (ie, pain experienced on the same side, medial or lateral, or both) were recruited for the trial. Meniscal tears were diagnosed by magnetic resonance imaging (MRI; 3.0 T) according to the ISAKOS grading system. If a participating surgeon considered a tear suitable for repair, the patient could not participate in the trial. Exclusion criteria were severe osteoarthritis (Kellgren-Lawrence grade of 4, significant osteophytes, joint-space narrowing, sclerosis, and abnormalities of bone ends)[15], body mass index >35 kg/m2 , locking of the knee[3], prior surgery to the index knee (with the exception of diagnostic arthroscopic surgery), and knee instability due to an MRI confirmed ACL or posterior cruciate ligament rupture. Patients were randomly allocated by computer to receive either partial meniscectomy or physical therapy in a 1:1 ratio with varying block sizes up to a maximum of 6. The randomization scheme was stratified by hospital and age (45-57 and 58-70 years). Participants, clinicians, and research staff were not blinded for treatment allocation during data collection. However, the researchers did perform statistical analyses on a blinded database. The database was unblinded for the interpretation of the results.

Interventions

Partial Meniscectomy. Patients assigned to the partial meniscectomy group underwent surgery within 4 weeks after randomization at the hospital of inclusion. Partial meniscectomy consisted of an intra-articular inspection of the knee joint according to standardized surgery protocols, including an assessment of the lateral and medial menisci, the ACL, and the chondropathy as well as a general classification of the level of degeneration. The surgeon partially removed the affected meniscal portion until a stable and solid meniscus was reached. Meniscal repair was not performed in this population. All patients received written perioperative instructions. Rehabilitation after discharge from the hospital consisted of a home exercise program. The patient received a consultation in the outpatient orthopaedic clinic 8 weeks after surgery. In agreement with Dutch Orthopaedic Association guidelines, patients were only referred to physical therapy when signs of abnormal recovery were present.[25]

Physical Therapy. Physical therapy started within 2 weeks after randomization. Patients were referred to preselected physical therapy clinics that participated in the trial. The treatment protocol consisted of a progressive exercise program of 16 sessions, each 30 minutes long, over a period of 8 weeks. Additionally, patients underwent the same home exercise program as the partial meniscectomy group. Patients with persistent symptoms either continued the physical therapy treatment beyond the prescribed 16 weeks or were referred for delayed surgery by their orthopaedic physician. A detailed description of the physical therapy protocol can be found in Appendix 1.

Data Collection

Our data were collected within the ESCAPE trial, as described in the trial study protocol.[27] We collected the data between July 2013 and October 2017. Patients completed self-administered questionnaires at baseline and at 3, 6, 12, and 24 months after enrollment, either online or on paper according to the preference of the patient. The baseline data for this study included patient characteristics, the level of osteoarthritis, and 3 PROM scores: the Dutch language equivalent of the PSFS, the IKDC form, and a visual analog scale (VAS) for pain during weight bearing. The IKDC is a PROM for knee-specific symptoms, function, and sports activity. This PROM was developed for patients with knee ligament or meniscal injuries.[13] The IKDC is a reliable and valid measurement instrument for patients with meniscal tears.[29] In this questionnaire, the minimum score of 0 points represents the worst knee function, and the maximum score of 100 points indicates no limitations in function. We assessed the patient's self-reported pain during weight bearing during the previous week at baseline. The pain intensity was scored using a VAS of 100 mm, with 0 indicating no pain and 100 indicating very severe pain. The VAS is the most reliable measure for degenerative knee pain.[1] This study assessed the baseline scores for the IKDC and VAS for potential confounding effects on the main outcome. The online questionnaires required completion of an item before continuing to the next item. For the paper questionnaires, the researcher obtained missing items by telephone. To enhance the response rate, the patient received up to 3 reminders. In case a patient was not able or willing to complete a questionnaire at a specific time point, efforts were made to collect data for the following time point(s).

Outcome

This study also focused on a secondary outcome measure of the ESCAPE trial: the Dutch-language equivalent of the PSFS. This Dutch-language questionnaire is also known as the Patient-Specific Complaint questionnaire, which is the term that we used in the ESCAPE trial protocol.[27] The Dutch-language equivalent of the PSFS assesses subjective functional status by measuring patients' perceived difficulty in performing activities that they value most in daily life and would like to improve. All patients selected a maximum of 3 activities. Patients could either choose from a predefined list of 28 activities or suggest their own. The perceived difficulty was quantified on an 11-point (0-10) numeric rating scale (NRS; online version) or on a 100- mm VAS (paper version). The VAS was subsequently converted into an NRS to match the measurement scale of the online questionnaire, with 0 indicating no difficulty and 10 indicating impossibility in performing that activity.[1] A mean score was calculated per patient by adding the difficulty scores for each activity and dividing this by the number of selected activities. The PSFS is an efficient and easy-to-administer measurement tool. The time to complete the PSFS is about 4 minutes. In addition, the PSFS is a reliable measurement tool in patients with knee dysfunction.[6] Before statistical analyses, we calculated the minimal important change (MIC) of the PSFS in our population, using an anchor-based method, to provide a context of clinical relevance.[7] The anchor question was the following: "How did your function in daily activities change since the surgery/treatment of your knee?" A detailed description of the methods and results for the MIC calculation can be found in Appendix 3.

Statistical Analysis

Specific activities that were listed by patients were evaluated in terms of frequencies using descriptive statistics. The overall PSFS difficulty score was analyzed by linear mixed-model analysis using both intention-to-treat and as-treated approaches. In the intention-to-treat analysis, patients were divided into 2 groups according to treatment allocation: partial meniscectomy and physical therapy. For the as-treated analysis, patients were divided into 3 groups: patients allocated to partial meniscectomy who underwent surgery, patients allocated to physical therapy who completed at least 16 physical therapy sessions, and patients allocated to physical therapy who underwent surgery during the study period. Patients allocated to partial meniscectomy who did not undergo surgery and patients allocated to physical therapy who did not complete the physical therapy protocol or undergo surgery were discarded from the as-treated analysis. In the linear mixed-model analysis with random intercepts, PSFS scores at all follow-up time points were included as dependent variables. The crude overall intervention effects were defined by a model with only the treatment group and the baseline score of the PSFS as independent variables. Time and time treatment interaction terms were added to specify crude intervention effects for each follow-up time point. Adjusted intervention effects were calculated using similar models and expanded with the following potential confounders as independent variables: level of osteoarthritis according to Kellgren-Lawrence classification,[15] baseline IKDC score, affected meniscus (medial, lateral, or both), body mass index (<25,25-30, or 31-35 kg/m2), age in years, affected leg, sex, and baseline VAS pain score. In all models, physical therapy was defined as the reference treatment. Adverse events from the ESCAPE trial were reported descriptively. All analyses were performed using SPSS Version 22 (IBM), and statistical significance was assessed at the .05 level.

Patient Involvement

A patient representative from the medical ethics committee (M.E.C.-U.) assessed the burden of the trial and patient information before the start of the ESCAPE trial. Furthermore, a representative of the Netherlands Patients Federation (J.K.) was added to the ESCAPE research group for this study and provided the authors with feedback on the study. Also, the representative advised us on an implementation strategy to translate the results to daily practice in orthopaedic and general health care.

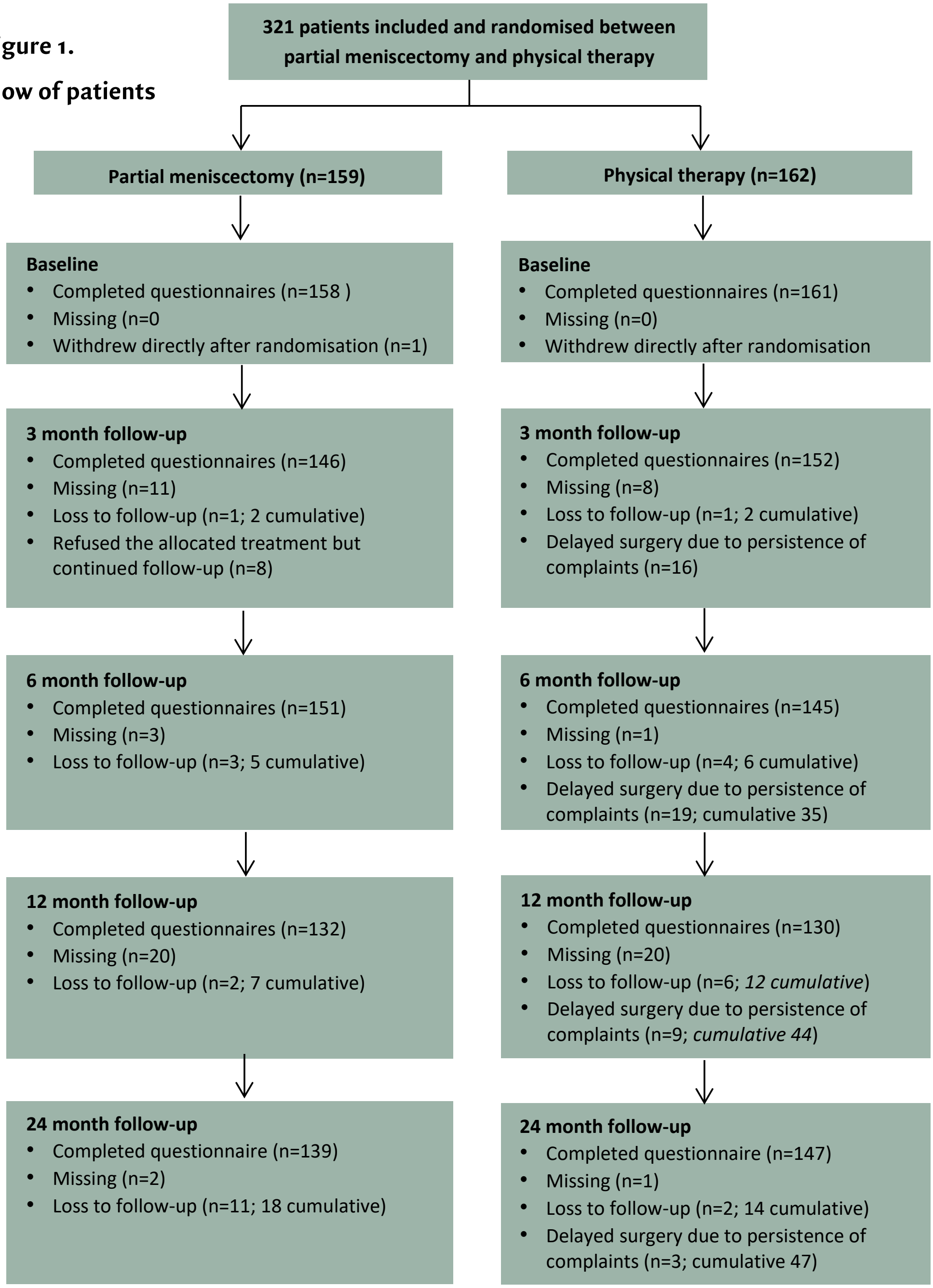
Results

Patients

Figure 1 shows a flowchart of the treatment allocation and patient follow-up. We included 321 patients in the ESCAPE trial, who were randomly assigned to either the partial meniscectomy (n = 159) or the physical therapy (n = 162) group. The PSFS was completed by 319 patients (99.4%) at baseline, 298 patients (92.8%) at 3 months, 296 (92.2%) at 6 months, 262 (81.6%) at 1 year, and 286 (89.1%) at 2 years, which was the primary time point. Baseline characteristics were similar in both treatment groups and are presented in Table 1. Patients selected a maximum of 3 (mean, 2.9 ± 0.4) activities that they experienced difficulty with and were most relevant to their daily life. The most frequently chosen activities in both groups were sports (12.4%), walking (10.3%), running (9.8%), standing for a long time (8.4%), and rising from a chair (7.4%). An overview of the frequencies and percentages of all activities for both groups is presented in Appendix 4.

Figure 1.

Flow of patients



The flowchart shows the follow-up data of all patients allocated to a treatment group. The number of missing patients refers to the patients that were missing for a specific follow-up time point. These patients continued participating in the remaining follow-up time points. Patients who dropped out from the trial were referred to as 'loss to follow-up'. Data of patients screened for eligibility were not available.

Table 1. Baseline Characteristics of Study Population[a]

	Partial meniscectomy (n=158)	Physical Therapy (n=161)
Demographics		
Age, y	57.6 ± 6.5	57.3 ± 6.8
Men, n (%)	78 (49.4)	80 (49.7)
Right knee, n (%)	88 (55.7)	81 (50.3)
BMI (kg/m2)	26.7 ± 3.8	27.2 ± 4.0
18.5-25, n (%)	56 (35.4)	53 (32.9)
25-30, n (%)	72 (45.6)	67 (41.6)
30-35, n (%)	30 (19.0)	41 (25.5)
Mechanical complaints,[b] n (%)	56 (35.4)	67 (41.6)
Imaging[c]		
Affected meniscus, n (%)		
Medial	126 (79.7)	136 (84.5)
Lateral	30 (19.0)	25 (15.5)
Both	2 (1.3)	0 (0.0)
Osteoarthritis grade (Kellgren-Lawrence classification),[d] n (%)	n =150	n =149
0 (none)	18 (12.0)	15 (10.1)
1 (doubtful)	81 (54.0)	74 (49.7)
2 (minimal)	45 (30.0)	55 (36.9)
3 (moderate)	6 (4.0)	5 (3.4)
4 (Severe)[e]	0 (0.0)	0 (0.0)
Patient-reported outcomes		
Kneefunction		
PSFS score (0-10; best to worse)	6.8 ± 1.9	6.6 ± 2.0
IKDC score (0-100; worse to best)	44.8 ± 16.6	46.5 ± 14.6
Pain	n =145	n =151
VAS score during activities (0-100; best to worse)	61.1 ± 24.5	59.3 ± 22.6

a Data are shown as mean ± SD unless otherwise indicated. IKDC, International Knee Documentation Committee; PSFS, Patient-Specific Functional Scale; VAS, visual analog scale.

b In contrast to locking of the knee joint, which was an exclusion criterion, mechanical complaints were allowed for inclusion.

c Meniscal tears were assessed on magnetic resonance imaging. d Osteoarthritis was assessed using standing radiographs of the knee in the anterior-posterior direction.

e Patients with a Kellgren-Lawrence grade of 4 on baseline radiographs were excluded from the trial.

Minimal Important Change of the PSFS

The anchor-based calculation resulted in an MIC of 2.5 points for our study population. A more detailed description of these results can be found in Appendix 3.

Intention-to-Treat Analysis

A total of 319 patients were included in the intention-to-treat analysis: 158 patients in the partial meniscectomy group and 161 patients in the physical therapy group. Group distributions per follow-up time point are reported in Table 2. From baseline to 24 months, the partial meniscectomy group improved a mean of 4.8 ± 2.6 points (from 6.8 ± 1.9 to 2.0 ± 2.2). The physical therapy group improved a mean of 4.0 ± 3.1 points (from 6.7 ± 2.0 to 2.7 ± 2.5) (Figure 2). The mixed-model analysis revealed a significant crude overall treatment effect on the PSFS score between partial meniscectomy and physical therapy of –0.6 points in favor of partial meniscectomy (95% CI, –1.0 to –0.2; P = .004). At the different follow-up time points, the between-group difference was also significant, except at 3 months (Table 2). Adjusting for confounders increased the intervention effect to –0.8 points in favor of partial meniscectomy (95% CI, –1.3 to –0.4; P < .001). The adjusted between-group difference was also statistically significant at all follow-up time points, except at 3 months (Table 2).

Table 2. Intention-to-Tr–Results of Mixed-Model Analysis

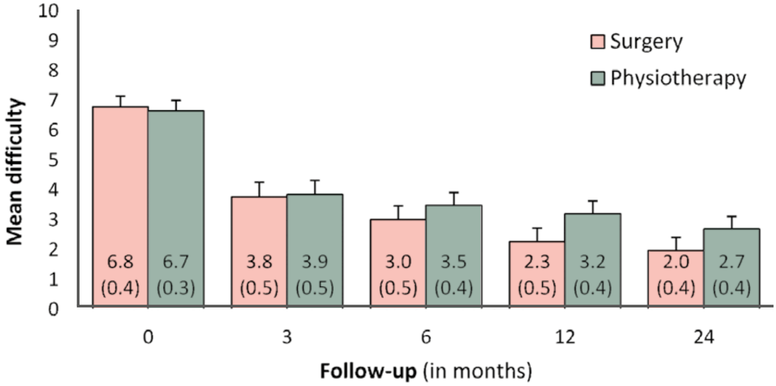
	n	Between-Group Difference[a] (95% CI)	P Value
Partial meniscectomy vs Physical therapy			
Crude[b]			
3 mo	146 vs 152	-0.2 (-0.7 to 0.4)	.596
6 mo	151 vs 145	-0.6 (-1.2 to -0.1)	.034
12 mo	132 vs 130	-1.0 (-1.6 to -0.5)	<.001
24 mo	139 vs147	-0.8 (-1.4 to -0.2)	.006
Overall	568 vs 574	-0.6 (-1.0 to -0.2)	.004
Adjusted[c]			
3 mo	146 vs 152	-0.4 (-1.0 to 0.2)	.184
6 mo	151 vs 145	-0.9 (-1.5 to -0.3)	.004
12 mo	132 vs 130	-1.2 (-1.8 to -0.6)	<.001
24 mo	139 vs 147	-0.8 (-1.3 to -0.2)	.006
Overall	568 vs 574	-0.8 (-1.3 to -0.4)	<.001

a Negative values indicate that the difference is in favor of partial meniscectomy.

b Crude analyses, only corrected for the baseline Patient-Specific Functional Scale score.

c Adjusted analyses, with additional correction for potential confounders.

Figure 2. Patients' perceived difficulty in performing activities



Mean Patient-Specific Functional Scale (PSFS) scores for each group at baseline and at 3, 6, 12, and 24 months. The mean difficulty scores per group were calculated as the mean of the overall PSFS score per patient, adding the scores for each activity and dividing this by the number of selected activities per patient. Data in parentheses and error bars indicate the 95% Confidence Intervals (CI).

As-Treated Analysis

A total of 294 patients were included in the as-treated analysis: 150 patients in the partial meniscectomy group, 97 patients in the physical therapy group, and 47 patients in the delayed partial meniscectomy group. Patients who had not undergone partial meniscectomy (n = 8) or who had not completed the physical therapy protocol (n = 17) were excluded from the as-treated analysis. Group distributions per follow-up time point are reported in Table 3. The crude overall difference on the PSFS score between partial meniscectomy and physical therapy was –0.2 points in favor of partial meniscectomy (95% CI, –0.8 to 0.2; P = .209). The crude effect was significant at the 12-month and 24-month follow-up (Table 3).

After adjusting for potential confounders, the overall difference increased to –0.6 in favor of partial meniscectomy (95% CI, –1.1 to –0.1; P = .025) (Table 3). The adjusted effect was also significant at the 12-month follow-up but not at 24 months (Table 3). We also observed a significant crude overall difference between the delayed partial meniscectomy group and the physical therapy group of 1.3 points (95% CI, 0.6-1.9;P < .001) in favor of the physical therapy group. Analyses of the separate follow-up time points showed that this difference was significant at all follow-up time points except at 24 months (Table 3). After adjusting for potential confounders, the effect remained significant only at 3 and 6 months (Table 3).

III

Table 3. As-Treated Results of Mixed Model Analysis

	Partial meniscectomy vs. Physical therapy			Delayed partial meniscectomy vs. Physical therapy		
	n	Between group difference[a] (95% CI)	P Value	n	Between group difference[a] (95% CI)	P value
Crude[b]						
3 mo	133 vs 91	0.3 (-0.3 to 1)	.31	43 vs 91	1.96 (1.1 to 2.8)	<.001
6 mo	144 vs 91	-0.3 (-0.9 to 0.4)	.386	40 vs 91	1.3 (0.4 to 2.2)	.005
12 mo	123 vs 81	-0.7 (-1.4 to -0.1)	.033	32 vs 81	1.1 (0.1 to 2.0)	.026
24 mo	133 vs 90	-0.6 (-1.3 to 0.0)	.049	40 vs 90	0.6 (-0.3 to 1.5)	.193
Overall	533 vs 353	-0.2 (-0.8 to 0.2)	.209	155 vs 353	1.3 (0.6 to 1.9)	<.001
Adjusted[c]						
3 mo	133 vs. 91	-0.1 (-0.7 to 0.6)	.843	43 vs 91	1.7 (0.8 to 2.6)	<.001
6 mo	144 vs. 91	-0.7 (-1.3 to 0.0)	.05	40 vs 91	1.1 (0.2 to 2.1)	.024
12 mo	123 vs. 81	-1.0 (-1.7 to -0.3)	.007	32 vs 81	1.0 (-0.01 to 2.0)	.053
24 mo	133 vs. 90	-0.7 (-1.3 to 0.02)	.059	40 vs 90	0.8 (-0.1 to 1.8)	.094
Overall	533 vs. 353	-0.6 (-1.1 to -0.1)	.025	155 vs 353	1.2 (0.5 to 1.9)	.001

a Negative values indicate that the difference is in favor of partial meniscectomy.

b Crude analyses, only corrected for the baseline Patient-Specific Functional Scale score.

c Adjusted analyses, with additional correction for potential confounders.

Adverse Events and Other Outcomes of the ESCAPE Trial

There were 17 participants (5.3%) who experienced a serious adverse event (partial meniscectomy: n = 9; physical therapy: n = 8). These serious adverse events included cardiovascular events (partial meniscectomy: n = 0; physical therapy: n = 2), neurological problems (partial meniscectomy: n = 1; physical therapy: n = 1), internal medicine conditions (partial meniscectomy: n ¼ 2; physical therapy: n = 1), (re)surgery on the affected knee (partial meniscectomy: n = 4; physical therapy: n = 1), and total knee replacement (partial meniscectomy: n = 2; physical therapy: n = 3). Other nonserious adverse events occurred in 13 patients (partial meniscectomy: n = 9; physical therapy: n = 4) including reactive arthritis (partial meniscectomy: n = 1; physical therapy: n = 0); extra consultations because of consistent knee pain (partial meniscectomy: n = 6; physical therapy: n = 2); pain in the back, hip, or foot (partial meniscectomy: n =[26] 2; physical therapy: n ¼ 0); and nonspecified adverse events (partial meniscectomy: n = 0; physical therapy: n = 2).[26]

The primary outcomes of the ESCAPE trial were published in separate articles. These outcomes included patient-reported knee function, pain, and general health as well as the cost-effectiveness of both treatments.[26, 28]

Discussion

In this study evaluating the treatment effect of degenerative meniscal tears focusing on activities most valued by individual patients, we found that patients with degenerative meniscal tears were mostly interested in improving in sports, walking, running, standing for a long time, and rising from a chair. Both partial meniscectomy and physical therapy resulted in a clinically relevant improvement over time on the individual patient's most important activities. Differences between partial meniscectomy and physical therapy were statistically significant but not clinically relevant.

To our knowledge, only 1 previous study has reported on patients' expectations after knee surgery.[19] In that study, patients undergoing partial meniscectomy were asked, before surgery, what their expectations were on return to leisure activities. This was compared with the actual outcome at 3 months after surgery. Less than half of the patients participated at the level that they expected, which resulted in a high proportion of patients who were unsatisfied with their knee function and level of participation. Patients were mainly overoptimistic about their return to light and recreational sports activities, which are categories that match the 3 most frequently selected activities (sports, walking, running) in our study population. Together, these studies provide clinicians and patients with a more realistic prognosis on recovery expectations for activities most valued by the patient.

When comparing partial meniscectomy with nonoperative treatment (i.e., physical therapy) for patients with a meniscal tear, previous trials have mainly focused on generic, fixed-item outcomes such as knee pain and function. [9, 11, 12, 14, 16, 26, 31]The results of this study support the findings from previous studies that there is no clinically relevant difference between partial meniscectomy and physical therapy for middle-aged and older patients with a meniscal tear.[9, 11, 12, 14, 16, 22, 26, 31] An important benefit of using patient-specific outcomes instead of generic outcomes is that the outcome reflects the relevant daily life and leisure activities for individual patients.[5] Therefore, this study strengthens the current guidelines on degenerative meniscal tears.[9, 11, 12, 14, 16, 21, 26, 31]

Strengths and Limitations

This study compared partial meniscectomy with physical therapy for symptomatic meniscal tears from a patient's perspective. The outcome measure focused on activities that were most valued by the patient, enhancing a patient-centered approach. We included a large sample of patients with symptomatic meniscal tears who were randomized between partial meniscectomy and physical therapy. The participation rate at 2-year follow-up was 89.1%.

In addition, we found that, of the list of 28 activities, 4 of the 5 most selected activities were equal in both intervention groups. The similarity in selected activities between both groups reduced the likelihood that the type of chosen activities influenced our results. This study has several limitations to report. First, participants, clinicians, and research staff were not blinded to the allocated treatment during data collection, and the patients' preferred treatment before randomization was not recorded. This increases the chance of observer and participant bias. However, statistical analyses were performed with a blinded database. Second, the sample size was determined by the power calculation of the ESCAPE trial. We determined the calculation on the primary outcome of the ESCAPE trial, namely, the IKDC form, and not specifically based on the PSFS. Third, patients were recruited if they experienced knee pain related to MRI-confirmed meniscal tears. However, we cannot guarantee that their knee pain was solely caused by the meniscal tear. Mild to moderate degenerative changes of the knee can also play a role in experienced knee pain.[8] Fourth, the PSFS is not validated in this specific population or in a similar population. Fifth, the physical therapy protocol that we used in the ESCAPE trial consisted of general incremental exercises for cardiovascular conditioning, coordination, balance, and closed–kinetic chain strength of the lower extremities rather than exercises that focused on the relevant activities selected by our patients. Tailoring physical therapy to the individual patient, by including specific exercises that target the specific activities that patients selected on the PSFS, may have further increased the efficacy of physical therapy. Last, the scoring of the activities differed between the online (NRS; 94% at baseline) and paper-based (VAS; 6% at baseline) questionnaires. The VAS scores were converted to NRS scores before data analysis. Although the VAS and NRS show high correlations in pain measurements for osteoarthritic knee pain, the correlation for the PSFS is unknown.[1]

III

Implications

While our results show a statistically significant difference in favor of partial meniscectomy, the difference between the partial meniscectomy and physical therapy groups was small.[10] In large samples, even very small differences between 2 groups can be statistically significant. However, statistical methods for significant differences do not account for clinical relevance.[10] When translating research results to clinical practice, we must consider clinical relevance instead of relying on statistical differences alone. However, research on clinically relevant differences between groups is lacking,10 let alone for group differences on the PSFS in patients with meniscal tears. The upper limit of the 95% CI of both the crude and adjusted between-group differences did not exceed the calculated MIC of 2.5 points. Also, regardless of the exact MIC value, it seems highly unlikely that the between-group difference of less than 1 point can be considered clinically relevant.[10] Although the calculated MIC of 2.5 points is in line with the 2.2 points on the PSFS reported in patients with cervical radiculopathy,[32] more research is necessary on the clinical relevance of the PSFS for quantifying treatment effects within patients and for comparing treatment effects between intervention groups.

Based on an MIC of 2.5 points on an 11-point scale, the PSFS might not be the recommended tool to detect small treatment effects at the group level. Nevertheless, the PSFS could potentially be valuable for physicians and physical therapists to evaluate treatment effects from the patient's point of view.[32]

Interestingly, our study results suggest that patients apparently only perceive relevant improvement when they experience substantially less difficulty during selected activities that matter most to them. In addition, we found a large variety in the specific activities that patients selected, as shown in Appendix 4. This indicates that a physical therapy program tailored to the individual patient's needs and wishes may be even more beneficial than the one-

size-fits-all strategy with general exercises used in our study.
A focus on patient-specific activities and realistic expectations when discussing treatment options with the patient may support the shared decision-making process and enhance treatment engagement in patients. Additional goal setting for each activity will further enhance treatment involvement, satisfaction, and perceived recovery.[23, 24]

Conclusion

This study found a statistically significant difference but no clinically relevant difference between physical therapy and partial meniscectomy in middle-aged and older patients with a meniscal tear, with outcomes focused on activities that the individual patients valued most. We therefore conclude that physical therapy should be suggested as a firstline treatment for middle-aged and older patients with a meniscal tear to improve specific daily life and leisure activities. Targeting physical therapy exercises to the specific activities that a patient values the most may even further enhance the physical therapy treatment effect.

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III

Chapter 4

In patients eligible for meniscal surgery who first receive physical therapy, multivariable prognostic models cannot predict who will eventually undergo surgery

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Abstract

Background. Although physical therapy is the recommended treatment in patients over 45 years old withdegenerative meniscal tear, 24% still opt for meniscal surgery.
Purpose. The aim was to identify those patients with a degenerative meniscal tear who will undergo surgery following physical therapy.
Methods. The data for this study were generated in the physical therapy arm of the ESCAPE trial, a randomized clinical trial investigating the effectiveness of surgery vs. physical therapy in patients of 45 to 70 years old, with a degenerative meniscal tear. At 6 months and 24 months patients were divided into two groups: those who did not undergo surgery, and those who did undergo surgery. Two multivariable prognostic models were developed using candidate predictors that were selected from the list of the patients' baseline variables. A multivariable logistic regression analysis was performed with backward Wald selection and a cut-off of $p<0.157$. For both models the performance was assessed and corrected for the models' optimism through an internal validation using bootstrapping technique with 500 repetitions.
Results. At 6 months, 32/153 patients(20.9%) underwent meniscal surgery following physical therapy. Based on the multivariable regression analysis, patients were more likely to opt for meniscal surgery within 6 months when they had worse knee function, lower education level and a better general physical health status at baseline. At 24 months, 43/153 patients (28.1%) underwent meniscal surgery following physical therapy. Patients were more likely to opt for meniscal surgery within 24 months when they had worse knee function and a lower level of education at baseline at baseline. Both models had a low explained variance (16% and 11%, respectively) and an insufficient predictive accuracy.
Conclusion. Not all patients with degenerative meniscal tears experience beneficial results following physical therapy. The non-responders to physical therapy could not accurately be predicted by our prognostic models.
Level of Evidence: Level III.

Introduction

Current guidelines state that physical therapy is the preferred first-line treatment in patients over 45 years of age with a degenerative meniscal tear.[15, 19] These guidelines are based on several randomized clinical trials (RCT) which demonstrated no clinically superiority of meniscal surgery over physical therapy in this population.[2, 4-7, 9, 12, 16, 17, 21, 25]However, not all patients experience beneficial results from physical therapy. An average of 24% (ranging between 1.9% and 36%) of patients randomized to physical therapy still opt for meniscal surgery following conservative management.[1]
Little information is available to predict at baseline the outcome of physical therapy in patients with a meniscal tear in both primary and secondary care, when a patient is referred by general practitioner to an orthopedic surgeon. In secondary care, the patient and orthopedic surgeon may choose for surgical management, or to start a physical therapist-led exercise program. Patients rely on the orthopedics surgeons' expertise to help decide on their treatment pathway. However, recent research showed that orthopedic surgeons were not able to predict whether patients would benefit from either meniscal surgery or physical therapy.[20] Patients with shorter symptom duration and more knee pain at baseline are more likely to undergo meniscal surgery following physical therapy.[8] However, this study did not report the accuracy of the association model. Also, the potential predictors with a continuous outcome were dichotomized before the logistic regression analysis. This makes it difficult to reliably predict which patients will undergo surgery following physical therapy based on the current literature.
Therefore, the aims of this study were to develop and internally validate multivariable clinical prognostic models to identify those patients who will undergo surgery following physical therapy.

Methods

Two prediction models were developed and internally validated for the outcome: meniscal surgery at 6 months and 24 months after initial physical therapy in middle aged and older patients with a symptomatic degenerative meniscal tear. The data for this study were generated in the physical therapy arm of the ESCAPE trial. The ESCAPE trial was a multi-centre RCT comparing meniscal surgery with physical therapy in patients over 45 years old with a degenerative meniscal tear.[21] The Medical Research Ethics Committees (MEC-U; NL44188.100.13) approved the ESCAPE trial. The trial was registered at clinincaltrials.gov (NCT01850719) and The Netherlands Trial Register (NTR3908). The current study was reported according to the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) statement.[11]

Participants

Patients aged between 45 and 70 years were referred by a general practitioner to the orthopaedic surgeon for diagnosis and treatment of their knee symptoms. All patients were diagnosed with a symptomatic degenerative meniscal tear. Besides that patients presented with symptoms, such as pain, the meniscal tear was confirmed on MRI. All patients were eligible for surgery and conservative treatment under the existing guidelines at the time. Patients who experienced a locked knee were excluded since this is an indication for surgery. In the ESCAPE-trial, patients were randomized to either immediate surgery or physical therapy. The physical therapy program consisted of a physical therapist-led standardized incremental exercise program containing of coordination/balance, closed kinetic chain strengths and cardiovascular exercises (see Appendix 1). The program was designed for 8 weeks with a total of 16 treatment sessions, each with a duration of 30 minutes.[21] As the Dutch health insurance does not cover PT, all 16 sessions were reimbursed by our research grant. If knee symptoms persisted following the physical therapy program (e.g., knee pain, limitations in daily activities or mechanical dysfunction), additional physical therapy sessions could be attended (not reimbursed by the study) or meniscal surgery, depending on a shared decision after consultation with the orthopaedic surgeon.All participants provided written informed consent.[22]

Outcome

The outcome was opting for meniscal surgery following physical therapy. Patients who attended less than 6 physical therapy sessions were excluded for the analyses. At both the 6 months and the 24 months follow up, the binary outcome was whether patients who were randomized to physical therapy treatment had undergone delayed surgery (1) or not (0).

Candidate predictor selection

From an extensive list of baseline variables assessed within the ESCAPE trial, candidate predictors were selected using a combination of three methods. First, a literature search was conducted to identify factors associated with the outcome after physical therapy treatment in patients with a meniscal tear. The search strategy can be found in Appendix 5. Second, an electronic survey was sent to an expert panel of orthopaedic surgeons (N=24), physical therapists (N=22) and patients (N=10) who were involved in the ESCAPE trial to identify the most relevant prognostic factors for physical therapy according to their opinion. The survey consisted of an extensive list of baseline variables assessed within the ESCAPE trial. Third, a univariable logistic regression analysis was conducted to include additional potential predictors in the prognostic models.

The selection of potential predictors contained of patients' demographics, patient reported outcome (PROM) measures and radiographic information on MRI and radiograph. Demographic information included age, sex, level of education and body mass index (BMI). PROMs consisted of the International Knee Documentation Committee Subjective Knee Form for knee function, the Visual Analogue Scale for pain during activities, the RAND-36 physical component scale for general physical health and patients' expectation on pain relieve with physical therapy at 6 months following physical therapy on a 7- point Likert scale, ranging from pain will be severely worse (1) to pain will be relieved completely (7). The radiographic information consisted of the Kellgren – Lawrence score for osteoarthritis, determined on a standing radiograph in Posterior-anterior direction. The information on MRI consisted of the tear location (medial, lateral or both) and the tear type according to the International Society of Arthroscopy, Knee Surgery and Orthopaedic Sports (ISAKOS) (longitudinal vertical, horizontal, radial, vertical flap, complex/degenerative, not able to classify).

A final selection of 10 potential predictors was made by the principle researchers of this study (JCAN, VAG, NWW and RWP). Then the potential predictors were ranked to decide which will be included in the model, based on the 10 events per potential predictor rule.[11] (see Appendix 6). A more detailed description of the selection procedures can be found in Appendix 5.

Statistical analysis

A complete case analysis was performed since the percentage of missing values was lower than 10%.[10, 18, 24]Before building the model, underlying assumptions of linearity between independent continuous variables and the outcome and multicollinearity for the potential predictors were checked.[3]

Two prognostic models were developed, one for the outcome at 6 months and one at 24 months, using a multivariable logistic regression analysis with Backward Wald Selection and a cut-off of $p<0.157$.[11, 18] The performance of the models was assessed by the explained variance, the calibration and the discriminative ability of the models.[3, 11, 18] The explained variance is determined by the Nagelkerke's R2 statistic, with a larger R2 indicating that a larger proportion of the variance can be explained by the model. Calibration, also called goodness of fit, was assessed by the Hosmer and Lemeshow test and calibration slope of the calibration plots.[3, 18] A good model fit was established when the Hosmer and Lemeshow test was not significant. The calibration slope indicates an over-, smaller than 1, or under fitting, larger than 1, of the model. The discriminative ability of the models was determined by the Area Under the Curve (AUC).[11, 18]An AUC between 0.6 and 0.8 was considered acceptable and a value of 0.8 or higher represents good discriminative ability of the model.[11] All statistical analyses were performed using IBM SPSS, version 22 (IBM Corp, Armonk, NY, USA).

To correct for the optimism in the prognostic model the final model was internally validated using bootstrapping technique with 500 repetitions.[11][3]The statistical software R-studio version 1.2.1335 (R-studio Inc., Boston, MA, USA) was used for the internal validation,. The correction factor from the bootstrapping was applied to the regression coefficients and performance measures.

Results

A total of 161 patients were allocated to physical therapy. Eight patients were excluded prior to data analysis because they attended less than 6 physical therapy sessions. At 6 months, 32 patients (20.9%) had undergone meniscal surgery. At 24 months, an additional 11 patients had undergone meniscal surgery, resulting in a total of 43 patients (28.1%). The baseline characteristics of both groups are presented in Table 1.

In the 28.1% of patients who underwent a meniscal surgery, 8 patients (18.6%) expected no relieve in pain (score 1 – 4) following physical therapy. In the patients who did not undergo surgery, 10 patients (9.1%) expected no relieve in pain following physical therapy.

Caption for Table 1. →

Data are presented as n (%) or mean (SD); NRS= Numeric Rating Scale, higher score indicates more pain; IKDC= International Knee Documentation Committee Subjective Knee Form, higher score indicates better knee function; RAND-36 PCS = physical component score of the RAND-36 questionnaire, higher score indicates better physical health status; OA = osteoarthritis; KL = Kellgren-Lawrence classification of knee osteoarthritis; n.s. = not significant.

a Statistical differences between the surgery after PT group and no meniscal surgery group was assesses by an independent-sample T test for continues data, or a chi-square test for binary and categorical data. P-values ≤ 0.05 were considered significant.

b Education level measured according to the International Standard Classification of Education (ISCED) score ranges from 1-7 with a higher score indicating higher level of education.

c Expectation of the pain score, 1 = pain will get severely worse and 6 = pain will be relieved completely.

d Grade of knee osteoarthritis was assessed by X-ray using the Kellgren and Lawrence scale (K&L).

e Patients with a KL classification of 4 on the baseline X-ray were excluded from the trial.

f Location of tear was assessed by Magnetic Resonance Imaging.

Table 1. Baseline characteristics per group for the models at 6 and 24 months

	Model at 6 months			Model at 24 months		
	No meniscal surgery	Meniscal surgery after PT	p-value[a]	No meniscal surgery	Meniscal surgery after PT	p-value[a]
Demographics	N=121	N=32		N=110	N=43	
Age in years	57.2 (6.8)	57.4 (7.0)	n.s.	57.7 (7.0)	56.4 (6.7)	n.s.
Women	63 (52.1%)	16 (50.0%)	n.s.	58 (52.7%)	21 (48.8%)	n.s.
Body Mass Index	27.0 (4.0)	27.6 (3.9)	n.s.	27.1 (4.1)	27.2 (3.7)	n.s.
Education Level (score is 1-7)[b]	4.8 (1.8)	3.8 (1.7)	0.05	4.8 (1.8)	4.0 (1.8)	0.02
Smoking (yes)	16 (13.2%)	3 (9.4%)	n.s.	14 (12.7%)	5 (11.6%)	n.s.
Patient reported outcomes						
Pain during activities (NRS; 0-100)	56.1 (22.4)	67.9 (21.1)	0.02	56.1 (22.2)	64.9 (22.5)	n.s.
Knee function (IKDC; 0-100)	48.8 (14.1)	39.6 (13.6)	<0.01	48.9 (14.2)	41.7 (14.2)	0.05
Physical health (Rand-36 PCS; 0-100)	38.7 (8.7)	36.2 (8.1)	n.s.	38.8 (8.7)	36.5 (8.4)	n.s.
Patient expectation			n.s.			n.s.
No pain relieve within 6 months	11 (9.1%)	7 (21.9%)		10 (9.1%)	8 (18.6%)	
Pain relieve within 6 months	110 (90.9%)	25 (78.1%)		100 (90.9)	35 (81.4%)	
Imaging Results						
OA score on radiograph (KL classification)[d]			n.s.			n.s.
0 - No OA	12 (9.9%)	2 (6.3%)		5 (4.5%)	0 (0%)	
1 – Doubtful	55 (45.5%)	16 (50%)		37 (33%)	10 (21.7%)	
2 - Minimal OA	45 (37.2%)	8 (25%)		35 (31.3%)	9 (19.6%)	
3 - Moderate OA	2 (1.7%)	2 (6.3%)		6 (5.4%)	1 (2.2%)	
4 – Severe OA[e]	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Affected meniscus[f]			n.s.			n.s.
Medial	93 (76.9%)	25 (78.1%)		86 (78.2%)	32 (74.4%)	
Lateral	19 (15.7%)	5 (15.6%)		17 (15.5%)	7 (16.3%)	
Both	9 (7.4%)	2 (6.3%)		7 (6.4%)	4 (9.3%)	

IV

Multivariable regression analyses

A complete case analysis was performed for both models with 153 cases. The model at 6 months confirmed all three candidate predictors as significant prognostic predictors: patient-reported knee function, education level and general physical health. Patients with worse knee function at baseline, a lower level of education and better self-reported general physical health had a higher probability of undergoing meniscal surgery. The results of the multivariable regression analyses, model performance measures and internal validation are presented in Table 2. The explained variance of the model was 16%, indicating that the predicted outcome can be explained for 16% by the predictors. The Hosmer and Lemeshow test was 0.12 and the mean calibration 0.003, indicating a good model fit. However, the calibration plot displayed an overestimation of the predicted outcomes for the model with a calibration slope of <1. The discriminative ability of the model was adequate with an AUC of 0.73. Internal validation resulted in a correction factor for the initial model's optimism of 0.90. The correction factor was applied to the regression coefficients and performance measures. The model at 24 months confirmed that worse patient-reported knee function and lower level of education were prognostic factors for undergoing meniscal surgery. Patients with worse knee function at baseline, a lower level of education had a higher probability of undergoing meniscal surgery. The results of the multivariable regression analyses, model performance measures and internal validation are presented in Table 2. The explained variance of the model was 11%, indicating that the predicted outcome can be explained for 11% by the predictors. The Hosmer and Lemeshow test was 0.48 and the mean calibration 0.002, indicating a good model fit. However, the calibration plot displayed an overestimation of the predicted outcomes for the model with a calibration slope of <1. The discriminative ability of the model was adequate with an AUC of 0.68. Internal validation resulted in a correction factor for the initial model's optimism of 0.82 for the regression coefficients and performance measures.

Table 2. Prognostic models for meniscal surgery after initial PT treatment at 6 months and 24 months

Predictor	Beta[a]	Adjusted Beta[b]	OR (95% CI)	P-value[c]
Model at 6 months				
Knee function[d]	-0.06	-0.05	0.94 (0.90 - 0.98)	0.01
Education level[e]	-0.25	-0.23	0.78 (0.62 - 0.99)	0.04
General physical health[f]	0.05	0.05	1.05 (0.98 - 1.13)	0.15
Model at 24 months				
Knee function[d]	-0.03	-0.03	0.97 (0.94 -1.00)	0.03
Education level[e]	-0.17	-0.14	0.84 (0.69 - 1.03)	0.10
Model performance	**R2**	**AUC**	**Mean Calibration**	**H&L**
Model at 6 months				
Initial model	0.16	0.73	0.003	0.12
After internal validation[b]	0.14	0.71		
Model at 24 months				
Initial model	0.11	0.68	0.001	n.s.
After internal validation[b]	0.09	0.66		

Abbreviations: 95% CI= 95% confidence interval; OR= odds ratio; R2=Nagelkerke's R2; AUC= Area Under the Curve; H&L= Hosmer and Lemeshow test; n.s. = not significant.

a Positive Beta is indicative that a higher score results in a higher probability of undergoing a meniscal surgery; A negative coefficient indicates that this risk increased with lower score. Some multicollinearity between the predictors can explain apparent discrepancies with baseline table 1.

b Regression coefficients and performance measures for the model at 6 months were multiplied by the shrinkage factor of 0.90 retrieved from internal validation.

Regression coefficients and performance measures for the model at 24 months were multiplied by the shrinkage factor of 0.82 retrieved from internal validation.

c p-values lower than 0.157 are considered significant.

d Knee function measured with the International Knee Documentation Committee Subjective Knee Form (IKDC) score ranges from 0-100, a higher score indicates better knee function.

e Education level measured according to the International Standard Classification of Education (ISCED) score ranges from 1-7 with a higher score indicating higher level of education.

f General physical health measures with the RAND-36 Physical Component Score. Scores ranges from 0 to 100, higher score indicates better health status.

Discussion

Two prognostic models were developed and internally validated to predict which patients will undergo meniscal surgery following physical therapy in patients with a degenerative meniscal tear. Patients who experienced a better general physical health status (for the 6 months model), and had worse knee function and lower education level (for both the 6 and 24 months model) were more likely to undergo meniscal surgery. However, both models showed a low explained variance and had an insufficient predictive accuracy. Therefore, external validation of these models is not useful since the models cannot be used in clinical practice.

Predicting treatment outcome for patients with a meniscal tear remains challenging. Recently, a study investigated the ability of orthopedic surgeons to predict the outcome of physical therapy and the outcome of surgery in patients over 45 years with a symptomatic meniscal tear.[20] Orthopedic surgeons received baseline characteristics of the patient including demographic information about employment, age and BMI, PROMs on pain, knee function and mechanical dysfunction, and MRI results on tear type and location, and radiograph information on level of knee osteoarthritis. Similar to the results of this study, they found that orthopedic surgeons were also unable to accurately predict which patient would benefit from physical therapy based on the baseline characteristics.[20]

Multivariable prognostic prediction models have also been shown inaccurate in predicting the treatment outcome of initial meniscal surgery in a similar population.[13] The authors argued that treatment outcome cannot be accurately predicted in this population due to the combination of knee osteoarthritis and a meniscal tear, which is a common finding in middle aged and older patients.[13] Likewise, mild to moderate knee osteoarthritis was also found in our study in the majority of the patients.[21] This may have negatively impacted on the predictive ability of our models since patients might experience persistence of knee complaints due to overall degenerative knee pain instead of solely meniscal pain.[13] The current literature appears to report similar results as the current study which suggests that no subgroups can be identified who can benefit from surgery. The current study supports other literature that failed to identify subgroups of patients who can benefit from surgery.[13] The efficacy of physical therapy was not investigated in this study. However, given the absence of a clinically relevant benefit of surgery over conservative treatment [2, 4-7, 9, 12, 16, 17, 21, 25], and the lack of clear prognostic characteristics for treatment outcomes [13], clinicians should rely more on the current guidelines recommendingphysical therapy as the first-line treatment in patients with degenerative meniscal tears. [15, 19]

This study has some limitations. First, this study was not primary designed as a prognostic prediction model study. Using data collected within a RCT is suitable to develop prognostic models.[11] Nevertheless, it was a disadvantage that the variables, available for the development of the models, did not include some of the variables that were previously shown to be associated with the outcome. For instance, from the current literature the variable duration of symptoms was selected as prognostic factor.[8] However, duration of symptoms was not assessed in our study population and could therefore not be included in the model.[23] Second, the amount of candidate predictors was determined using the rule of 10 events per

potential predictor. Although this is an accepted method and recommended in the TRIPOD statement, some researchers suggest that the rule of thumb is too simplistic to determine an adequate sample size for multivariable prognostic models with a binary outcome.[14] In our study the sample size and amount of events was fixed since data were used that were collected within the ESCAPE trial. Therefore the amount of candidate predictors was determined on our sample size, instead of vice a versa. Nevertheless, the results of this study meet the criteria, a shrinkage factor of ≥0.9 that represents a small optimism in predictor effect estimates and a small absolute difference of ≤ 0.05 in the model's initial and adjusted Nagelkerke's R2, that Riley et al. proposed for an adequate sample size.[14] Last, the prescribed PT treatment was a standardized incremental exercise protocol.
With the current available evidence, it is impossible to identify which patient will require surgery following physical therapy. Instead, clinicians should recommend physical therapy as the first-line treatment for patients with degenerative meniscal tears, following the current guidelines [15, 19]

Conclusion

With this study, the course of conservative treatment could not be predicted and patients who are likely to undergo meniscal surgery in the short (i.e., 6 months) and long term (i.e., 24 months) following physical therapy could not be identified. Therefore, these models should not be externally validated and not used in clinical practice. Future research should focus on identifying specific prognostic factors for treatment selection, surgery or physical therapy, in this population.

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Chapter 5

An individualized decision between physical therapy or surgery for patients with degenerative meniscal tears cannot be based on continuous treatment selection markers. A marker-by-treatment analysis of the ESCAPE study

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Abstract

Background. Marker-by-treatment analyses are promising new methods in internal medicine, but have not yet been implemented in orthopedics.With this analysis, specific cut-off points may be obtained, that can potentially identify whether meniscal surgery or physical therapy is the superior intervention for an individual patient.
Purpose. This study aimed to introduce a novel approach in orthopedic research to identify relevant treatment selection markers that affect treatment outcome following meniscal surgery or physical therapy in patients with degenerative meniscal tears.
Methods. Data were analyzed from the ESCAPE trial, which assessed the treatment of patients over 45 years old with a degenerative meniscal tear. The treatment outcome of interest was a clinically relevant improvement on the International Knee Documentation Committee Subjective Knee Form at 3, 12 and 24 months follow-up. Logistic regression models were developed to predict the outcome using baseline characteristics (markers), the treatment (meniscal surgery or physical therapy), and a marker-by-treatment interaction term. Interactions with $p<0.10$ were considered as potential treatment selection markers and used these to develop predictiveness curves which provide thresholds to identify marker-based differences in clinical outcomes between the two treatments.
Results. Potential treatment selection markers included general physical health, pain during activities, knee function, BMI and age. While some marker-based thresholds could be identified at 3, 12 and 24 months follow-up, none of the baseline characteristics were consistent markers at all three follow-up times.
Conclusion. This novel in-depth analysis did not result in clear clinical subgroups of patients who are substantially more likely to benefit from either surgery or physical therapy. However, this study may serve as an exemplar for other orthopedic trials to investigate the heterogeneity in treatment effect. It will help clinicians to quantify the additional benefit of one treatment over another at an individual level, based on the patient's baseline characteristics.

Level of Evidence: Level II.

Introduction

Marker-by-treatment analyses are promising new methods in internal medicine [8], but have not yet been implemented in orthopedics. Results from randomized clinical trials (RCTs) do not account for the heterogeneity in treatment effect and therefore RCT-based treatment recommendations are not always applicable to the individual patient.[13, 18, 23] The more conventional prognostic models identify the association between a prognostic marker and a good or poor treatment response. However, to select the best treatment for an individual patient it is important to quantify the benefit of one treatment over the other.[8] Previous marker-by-treatment analysis provided clinicians an evidence based method to select the best treatment for ovulatory infertile women.[30] In middle aged and older patients with a meniscal tear, the results from RCTs show that meniscal surgery has no clinical advantage over non-surgical treatment (such as physical therapy) or placebo surgery. However, meniscal surgery is associated with higher societal and healthcare costs, and higher risk of serious adverse events.[2, 21, 28] The number of surgeries slowly decreases, but surgery is still regularly performed for degenerative meniscal tears.[20] This is partly explained by the belief among some orthopedic surgeons and patients that surgery is necessary to regain normal knee function in a subgroup of patients.[4] This view is based on a subgroup of non-responders to conservative treatment in RCTs.[1][10] Several studies recommend to explore the heterogeneity of treatment outcome to better understand underlying factors which influence individual treatment effects.[13, 18, 23] Previous studies tried to define these subgroups.[19, 25] However, neither multivariable prognostic models [16, 19] nor surgeons' personal predictions were able to accurately predict treatment outcome.[25]

With a marker-by-treatment analysis, the influence of baseline information on the treatment effect can be determined.[8, 13] These predictive factors, or treatment selection markers, represent baseline information regarding patient characteristics, physical and radiological examination findings or patient reported outcomes. The relevant interactions between the baseline characteristics (markers) and treatment outcome can be plotted in a marker-by-treatmentpredictiveness curve.[8] The analysis provides specific cut-off points that can potentially identify the superior intervention of two interventions. The baseline characteristics that can accurately differentiate between the outcome between interventions are considered relevant treatment selection markers. These treatment selection markers can guide personalized treatment choices, based on a patient's individual characteristics.[8]

Previous prognostic models were unable to accurately predict treatment outcome. Therefore, this study aimed to introduce this novel approach in orthopedic research and to identify relevant treatment selection markers that affect treatment outcome following meniscal surgery or physical therapy in patients with degenerative meniscal tears. Analyzing patient's baseline characteristics using this method can help clinicians to select the treatment that is potentially the most beneficial for an individual patient.

V

Method

The Medical Research Ethics Committees United (MEC-U; NL44188.100.13) approved the ESCAPE trial and the trial was registered (clinincaltrials.gov: NCT01850719 and The Netherlands Trial Register: NTR3908). All patients provided written informed consent before randomization.

To identify potential treatment selection markers, the data from the ESCAPE trial were used. The ESCAPE trial is a multi-center RCT comparing meniscal surgery with physical therapy in patients over 45 years old with a symptomatic degenerative meniscal tear who do not experience locking of the knee.[26] Patients were randomly allocated to meniscal surgery or physical therapy. Exclusion criteria were severe osteoarthritis (Kellgren and Lawrence score of 4, presenting significant osteophytes, joint-space narrowing, sclerosis, and bone ends abnormality)[11], a body mass index (BMI) >35 kg/m2, prior surgery to the index knee (with the exception of diagnostic arthroscopic surgery), or clinically relevant anterior or posterior cruciate ligament insufficiency. Meniscal surgery, in which the damaged part of the meniscus was removed was performed within 6 weeks after randomization. Physical therapy which consisted of a predefined incremental exercise protocol, consisting of 16 sessions during eight weeks (appendix 1).[27] For patients with persistent knee symptoms after the intervention, additional physical therapy sessions could be attended or a delayed meniscectomy could be planned, depending on a shared decision after consultation with the orthopedic surgeon. Further details of the interventions can be found in the study protocol of the ESCAPE trial.[26, 27]

Selection of baseline characteristics for treatment selection

Baseline characteristics were preselected as possible treatment selection markers from an extensive list of baseline variables that were available (appendix 7). First, a literature search was conducted to identify factors associated with the treatment outcome in patients with a meniscal tear. The search strategy can be found in appendix5. Second, an electronic survey was sent to an expert panel of orthopedic surgeons (n =24), physical therapists (n=22) and patients (n=10) who were involved in the ESCAPE trial to identify the most relevant treatment selection factors according to their opinion. The final selection of baseline characteristic that were analyzed as potential treatment selection markers consisted of variables with a continuous outcome that were identified by the literature and/or chosen by the expert panel as variables associated with the treatment outcome.[12]
Potential treatment selection markers included patients' demographics (age, education level, BMI), patient reported outcome measures (the International Knee Documentation Committee Subjective Knee Form (IKDC) for knee function, pain intensity during activities on a Visual Analogue Scale (VAS), the RAND-36 Physical Component Scale (PCS) for general physical health, and the patient's expectation for pain relief following treatment), and radiographic information (the Kellgren–Lawrence score for osteoarthritis,[11] determined on a weight bearing radiograph in a posterior-anterior direction.

Patient involvement

Ten patients were surveyed who were involved in the ESCAPE trial. The patients were asked to select relevant treatment selection factors according to their opinion. From the list of variables measured within the ESCAPE trial.

Treatment outcome

The treatment outcome of interest was a clinically relevant improvement on patient reported knee function. For short-term effects, 3 months was identified by the patients and clinicians as an important time-point. Long term effects were analyzed at 12 and 24 months.. Patient reported knee function was measured with the IKDC questionnaire.[7] The IKDC is a validated and reliable questionnaire with good responsiveness in patients with degenerative meniscal tears.[17, 29] Clinically relevant improvement was defined as an improvement exceeding the minimal important change (MIC) of the IKDC of 11 points for this patient population.[17] For this study, patients were divided into two groups at 3, 12 and 24 months follow-up: 1) patients who experienced a clinically relevant improved knee function (an improvement ≥11 IKDC points; i.e. good outcome) and 2) patients who did not experience a clinically relevant improved knee function (a deterioration or improvement <11 IKDC points; i.e. poor outcome).

Data processing and statistical analysis

For the preselected baseline characteristics with a continuous outcome, separate logistic regression models were developed (treatment selection models) to predict the outcome using 1) the baseline characteristic (marker), 2) the allocated treatment (meniscal surgery or physical therapy), and 3) a marker-by-treatment interaction term. Interactions with a p-value for association <0.1 were considered as potential treatment selection markers.[3, 22]
These potential treatment selection markers were further explored using predictiveness curves. These predictiveness curves present the risk on a poor outcome (no clinically relevant improved or deteriorated knee function) for both treatments. Furthermore, they also provide information on the performance of the potential treatment selection markers to guide treatment decisions, so called summary measures.[8] A detailed explanation of a predictiveness curve is provided in appendix 8. The performance of the potential treatment selection markers was analyzed under the assumption that physical therapy is the standard treatment as suggested by the current guidelines.[21, 24]

The summary measures provide information on:

1. **Marker positivity threshold**; the threshold value of the baseline score of the potential treatment selection marker. Above this value patients would receive a recommendation for physical therapy, below this value a recommendation for meniscal surgery;
2. **Marker positivity rate**; the proportion of patients with a marker value greater than the marker positivity threshold. For this proportion of the population, physical therapyhas an advantage over meniscal surgery;

3. **Marker negativity rate**; the proportion of patients with a marker score smaller than the marker positivity threshold. For this proportion of the population, meniscal surgery has an advantage over physical therapy and for this group standard care (i.e., physical therapy) would be recommended to change;
4. **Average benefit physical therapy**; the average benefit of physical therapyin patients with a marker value above the marker positivity threshold. This measure evaluates the effect of physical therapy compared to meniscal surgery on the marker outcome;
5. **Average benefit meniscal surgery**; the average benefit of meniscal surgery in patients with a marker value below the marker threshold. This measure evaluates the effect of meniscal surgery, if treatment decision was guided by the model, in terms of the expected decrease in patients with a poor outcome;
6. **Decrease in rate of poor outcome**, the estimated change in the outcome in our population if treatment decisions are guided by the model compared to the outcome when treated according to standard care (i.e. physical therapy). This measure is used to provide information on the decrease in percentage of patients with a poor outcome when treatment is decided on basis of the treatment selection models.

All analyses were performed based on the intention-to-treat data. The data analyses for the predictiveness curves were performed using R-studio, version 1.2.1335 and package 'Treatment selection' (R-studio Inc., Boston, MA, USA).[8]
The sample size was determined and calculated for the RCT in which the patients' data were collected. The details on the sample size calculations can be found in previous publications.[26, 27]

Results

Participants

Three-hundred and twenty-one patients were included in the study. The mean (SD) age was 57.5 (6.6) years, and 161 (50.5%) participants were female. A total of 158 patients were allocated to surgery and 161 to physical therapy. Both groups showed comparable baseline characteristics for the potential treatment selection markers (Table 1). Main results and a detailed flow chart of the ESCAPE trial were previously published.[26]
At 3 months follow-up, 57.0% (meniscal surgery) and 52.2% (physical therapy)of the patients were improved in knee function (>11 IKDC points). At 12 months, this was 70.3% (surgery) and 54.7% (physical therapy), and at 24 months, this was 70.9% (surgery) and 65.8% (physical therapy). This shows that over time more patients achieved a clinically important improvement in knee function. In the physical therapy arm, 43 patients (27%) received delayed meniscectomy within 24 months.

Table 1. Patients' baseline characteristics

	Surgery (n=158)	Physical therapy (n=161)
Demographics		
Age in years (SD)	57.6 (6.5)	57.3 (6.8)
Female (%)	80 (50.6)	81 (50.3)
Education level, high (%)	67 (42.4)	86 (53.4)
BMI (kg/m2) (SD)	26.7 (3.8)	27.2 (4.0)
Patient- reported outcomes		
Knee function on the IKDC (SD) 0-100, worse to best	44.8 (16.6)	46.5 (14.6)
General physical Health on the RAND-36 PCS (SD) 0-100, worse to best	37.6 (8.3)	37.9 (8.6)
Pain during activities on the VAS (SD) 0-100, best to worse	61.1 (24.5)	59.3 (22.6)
Expectation for pain relief (SD) 1-7, deterioration of pain to complete pain relief	5.6 (0.5)	5.3 (0.8)
Radiographic information[a]		
OA score on radiographs (K-L classification)[b] (%)		
0 - No OA	18 (12.0)	15 (10.1)
1 - Doubtful	81 (54.0)	74 (49.7)
2 - Minimal OA	45 (30.0)	55 (36.9)
3 - Moderate OA	6 (4.0)	5 (3.3)
4 - Severe OA[c]	0 (0%)	0 (0)
Tear location on MRI	n=158	n=161
Medial	126 (79.7)	136 (84.5)
Lateral	30 (19.0)	25 (15.5)
Both	2 (1.3)	0 (0)

Data are n (%) or mean (standard deviation (SD)).

Abbreviations:BMI=Body Mass Index; IKDC= International Knee Documentation Committee Subjective Knee Subjective Knee; PCS = Physical Component Score; VAS=Visual Analogue Scale; K-L=Kellgren-Lawrence classification; OA=Osteoarthritis; MRI= Magnetic Resonance Imaging.

a Surgery n= 150, Physical therapy n=149

b Grade of knee osteoarthritis was assessed by X-ray using the Kellgren and Lawrence scale (K&L).

c K-L grade 4 was an exclusion criterion for participation in the ESCAPE trial.

V

Treatment selection markers

Potential treatment selection markers at baseline were general physical health (p=0.01), pain during activities (p=0.02) and knee function (p=0.07) for the outcome at 3 months; BMI (p=0.05) and age (p=0.06) for the outcome at 12 months; and age (p=0.05) for the outcome at 24 months (Table 2).

Table 2. Logistic regression analyses for interaction between the baseline characteristics and treatment at 3, 12 and 24 months

	3 months (<MIC: 139 vs. ≥MIC: 174)[a]		12 months (<MIC: 80 vs. ≥MIC: 199)[a]		24 months (<MIC: 71 vs. ≥MIC: 218)[a]	
	Marker-by-treatment interaction		Marker-by-treatment interaction		Marker-by-treatment interaction	
Baseline characteristic	ORb (95% CI)	P value for interaction	ORb (95% CI)	P value for interaction	ORb (95% CI)	P value for interaction
Age	0.95 (0.89 – 1.02)	n.s. (0.14)	0.93 (0.84 – 1.00)	0.06*	0.92 (0.84 - 0.10)	0.05*
Education level (1-7)	1.02 (0.41-2.50)	n.s. (0.97)	0.65 (0.22 – 1.90)	n.s. (0.43)	1.01 (0.34 – 3.02)	n.s. (0.98)
BMI	0.93 (0.83 – 1.05)	n.s. (0.24)	0.86 (0.75 – 0.10)	0.05*	0.94 (0.82 – 1.09)	n.s. (0.41)
Knee function on the IKDC (0-100)	1.04 (0.10 – 1.07)	0.07*	1.01 (0.97 – 1.05)	n.s. (0.52)o	1.03 (0.99 - 1.08)	n.s. (0.16)
General physical health on RAND-36 PSC (0-100)	1.08 (1.02 – 1.15)	0.01*	1.05 (0.99 - 1.12)	n.s. (0.11)	1.04 (0.97 – 1.11)	n.s. (0.30)
Pain intensity during activities on VAS (0-100)	0.97 (0.95 – 0.10)	0.02*	0.99 (0.96 – 1.01)	n.s. (0.25)	0.10 (0.97 – 1.02)	n.s. (0.79)
Expectation of pain relief (1-7)	1.31 (0.63 – 2.71)	n.s.(0.47)	0.88 (0.38 – 2.06)	n.s. (0.77)	1.62 (0.65 – 4.07)	n.s. (0.30)
Knee osteoarthritis on K-L scale (0-4)[c]	0.71 (0.27 – 1.85)	n.s. (0.48)	0.99 (0.32 – 3.11)	n.s. (0.99)	1.22 (0.39 – 3.87)	n.s. (0.74)

Abbreviations: MIC = minimally important change; OR = Odds Ratio; CI = confidence intervals; IKDC= International Knee Documentation Committee Subjective Knee; RAND-36 PCS = Physical Component Scale for or general physical health; BMI = body mass index; K-L= Kellgren-Lawrence scale.

Marker-by-treatment interactions per follow-up moment are shown.

a (n=<MIC vs. n=≥MIC)For each follow-up moment the distribution of patients who experienced MIC in knee function (improvement ≥11 IKDC points) and patients who did not experience a MIC in knee function (changed IKDC score <11 points) is reported. The reference treatment is physical therapy. Data was available of 313 patients at 3 months, 279 patients at 12 months and 289 patients at 24 months.

b For each marker-by-treatment interaction, the OR shows the relative change per unit increase in the marker and we reported the 95% CI of the OR. An OR ≥1 indicates the value is in favor of physical therapy. The p-values expressed whether the marker-by- treatment interaction is significant (p≤0.1).

c We analyzed educational level, expectation of pain relief an K-L score as a continuous variable in the logistic regression analyses

*indicates the baseline characteristics that are potential treatment selection markers

Prediction curves for potential treatment selection markers

These potential treatment selection markers were further explored with predictiveness curves. Figures 1-5 show the predictiveness curves at 3, 12 and 24 months for the following markers: general physical health, knee function, pain intensity during activities, age and BMI.

Figures 1-5 Marker-by-Treatment predictiveness curves for the outcome at 3, 12 and 24 months

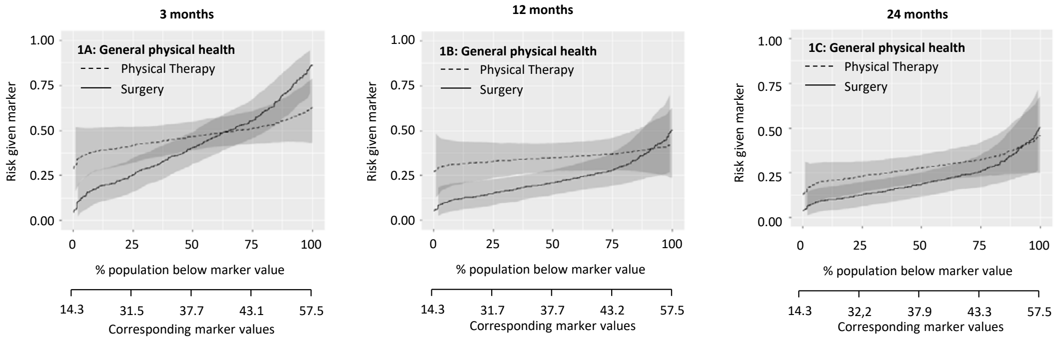

Fig 1: Patients with a score above the threshold would improve more from physical therapy. The marker-by-treatment interaction at 3 months is significant (p=.01) with a corresponding marker positivity threshold of 40.7 points. At 12 and 24 months follow-up the marker-by-treatment interactions are no longer significant (12 months p = .11; 24 months p = .30). Therefore, general physical health is not useful for treatment selection on the longer term.

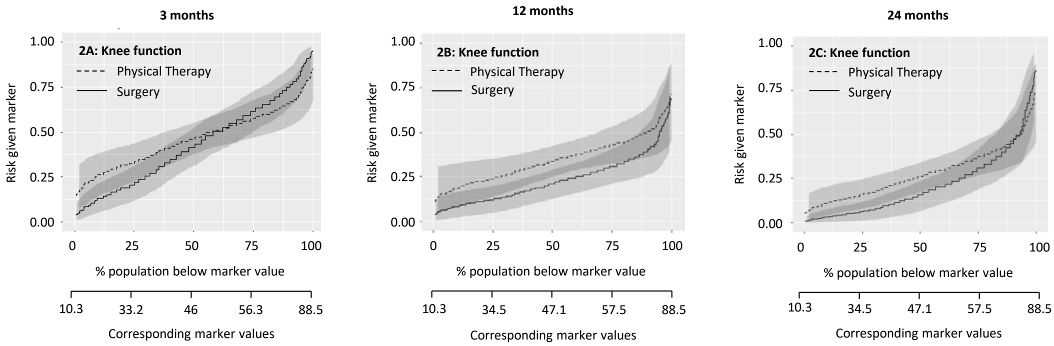

Fig 2: Patients with a score above the threshold would improve more from physical therapy. The marker-by-treatment interaction at 3 months is significant (p = 0.07) with a corresponding marker positivity threshold of 50.6 points. At 12 and 24 months follow-up the marker-by-treatment interaction are no longer significant (12 months p= 0.52; 24 months p = 0.16). Therefore, knee function is not useful for treatment selection on the longer term.

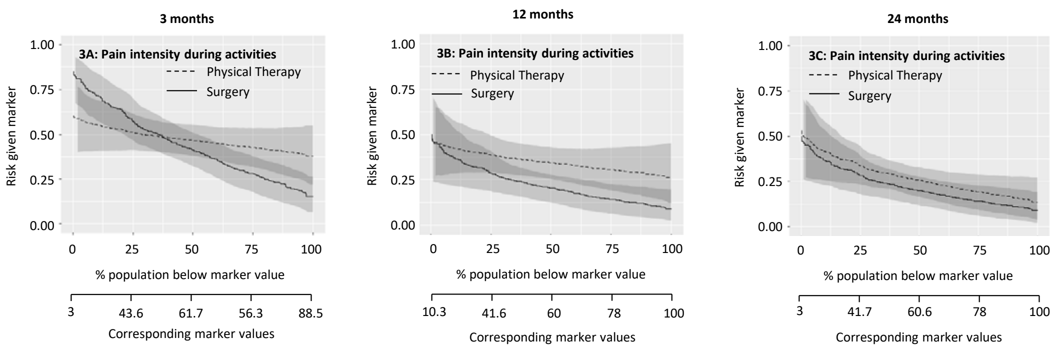

Fig 3: Patients with a score above the threshold would improve more from physical therapy. The marker-by-treatment interaction at 3 months is significant (p = 0.07) with a corresponding marker positivity threshold of 50.6 points. At 12 and 24 months follow-up the marker-by-treatment interaction are no longer significant (12 months p= 0.52; 24 months p = 0.16). Therefore, knee function is not useful for treatment selection on the longer term.

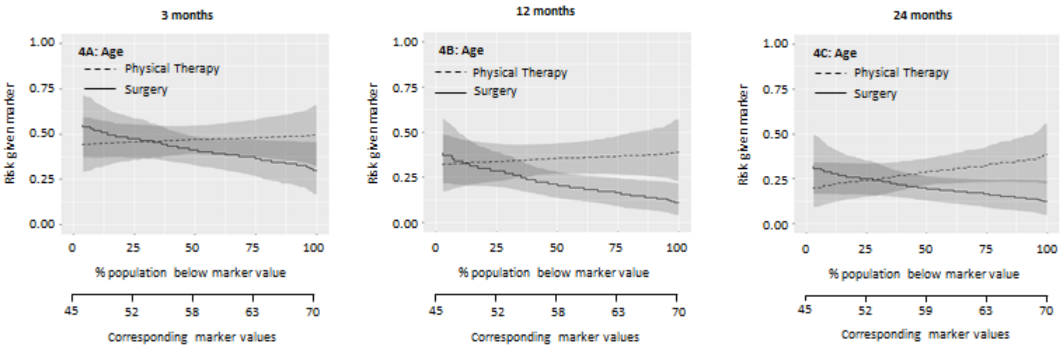

Fig 4: Patients with a score above the threshold would improve more from meniscal surgery. The marker-by-treatment interaction for the marker age is not significant at 3 months (p = 0.14). However, At 12 and 24 months follow-up the marker-by-treatment interaction are significant (12 months p = 0.06; 24 months p = 0.05). The corresponding marker positivity threshold at 12 months follow-up is 49 years old and at 24 months follow up the marker positivity threshold is 53 years old.

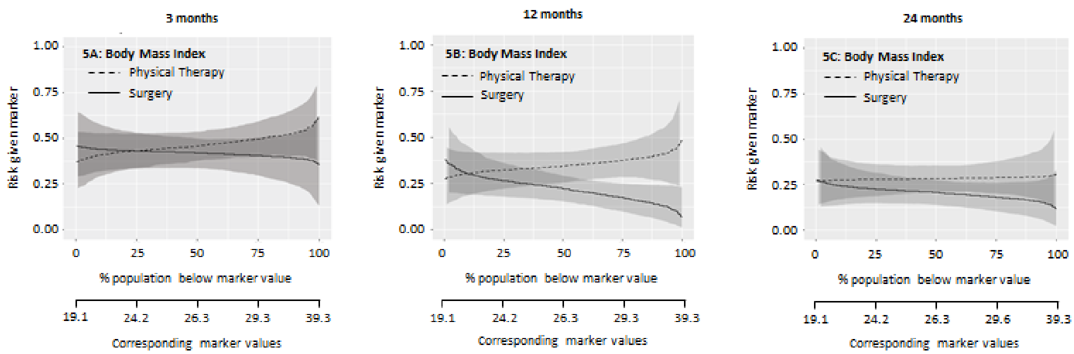

Fig 5: Patients with a score above the threshold would improve more from meniscal surgery. The marker-by-treatment interaction for Body Mass Index is not significant at 3 months (p = 0.24). At 12 follow-up the marker-by treatment interaction is significant (p = 0.05) with corresponding marker positivity threshold of 22.3. However, at 24 months follow-up the marker-by-treatment interaction are no longer significant (p = 0.41). Therefore, Body Mass Index is not useful for treatment selection on the short and long term.

Abbreviations: PT = physical therapy; APM = arthroscopic partial meniscectomy (surgery)

Predictiveness curves present the risk for individual patients, with a certain marker score, at the outcome of interest due to the given treatment.

On the X-axis is the proportion of patients displayed that score below the corresponding marker value. The corresponding marker value is the raw marker score.

On the Y-axis is the risk for the individual patient at the outcome with physical therapy and arthroscopic partial meniscectomy displayed.

The sloping lines in Figure 1 indicate that the risk of poor outcome increases with higher levels of baseline general physical health. This applies to both treatments. The intersection in Figure 1a indicates that at 3 months, patients with baseline values below 40.7/100 were more likely to benefit from surgery and patients with baseline values above 40.7/100 were more likely to benefit from physical therapy. The curves at 12 and 24 months follow-up were sloping less, indicating a similar risk of poor outcome across baseline values. Figure 2 shows a similar pattern for the marker knee function. The curves at 12 and 24 months run largely parallel, indicating that the effect of this baseline marker was similar for both treatments. The lines sloping down in Figure 3 indicate that the risk of poor outcome decreased with higher levels of pain at baseline. The intersection in Figure 3a indicates that at 3 months, patients with baseline VAS scores below 53.9/100 were more likely to benefit from surgery and patients with baseline VAS scores above 53.9/100 were more likely to benefit from surgery. No such intersection indicating a potentially relevant cut-off for baseline pain was observed at 12 and 24 months. For age and BMI, all curves were rather horizontal, but diverging with increasing baseline marker values with half of them reaching statistical significance. This indicates that the benefit of surgery compared to physical therapy was largest for patients with highest age and BMI. For all markers the predictiveness curves were inconsistent over time. The summary measures of the predictiveness curves are presented in Table 3. This provides information on marker positivity threshold, average benefit physical therapy, average benefit surgery, marker positivity rate, marker negativity rate and decrease in rate of poor outcome.

Caption for Table 3.

→

The proportions are given in percentages (95% Confidence Interval)

Abbreviation: NA = not available, no marker positivity threshold as the line do not cross each other)

The score ranges from 0 to 100, with 100 representing the best possible knee function.

Interpretation (example): For general physical health at 3 months, 36.8% (95% CI: 5.4 to 66.1) of the patients scored higher than the threshold value of 40.7 points (marker positivity rate), representing the cut-off point for a better outcome from physical therapy. Patients with a score above this threshold had an average 10.1% (95% CI 1.1 to 20.6) better outcome from physical therapy as compared to those treated with surgery (average benefit physical therapy). A total of 63.2% (95% CI 33.5 to 94.6) of the patients scored lower than the threshold (marker negatively rate). These patients had an average 13.1% (95% CI 4.1 to 22.9) better outcome from surgery as compared to those treated with physical therapy (average benefit surgery). If treatment would be based on general health, there would be an 8.3% (95% CI 1.5 to 16.4) reduction in poor outcomes at 3 months if all patients with a RAND-36 score below 40.7 would receive surgery (decrease in rate of poor outcome).

Table 3. Summary measures of predictiveness curves for pain during activities

	3 months	12 months	24 months
General physical health			
Marker positivity rate	36.8% (5.4 – 66.1)	8.9% (0.0 – 36.5)	7.3% (0.0 – 48.5)
Marker negativity rate	63.2% (33.5 – 94.6)	91.1% (62.7 – 100)	92.7% (51.2 – 100
Marker positivity threshold	40.7	51.0	52.0
Average benefit Physical Therapy	10.1% (1.1 – 20.6))	0.3% (0.0 – 15.7)	1.8% (0.0 – 14.1)
Average benefit Surgery	13.1% (4.1 – 22.9)	13.8% (5.2– 24.1)	8.4% (1.8 – 17.5)
Decrease in rate of poor outcome	8.3% (1.5 - 16.4)	12.6% (3.8 – 22.5)	7.7% (1.3 – 16.7)
Knee function			
Marker positivity rate	37.9% (-0.1 – 85.5)	0% (0.0 – 38.4)	8.7 (0.1 – 54.4)
Marker negativity rate	62.1% (14.2 – 100)	100% (60.2 – 100)	91.3% (44.6 – 99.9)
Marker positivity threshold	50.6	NA	65.5
Average benefit Physical Therapy	6.0% (0.0 – 15.0)	0.1% (0.1 – 10.8)	5.8% (0.1 – 17.0)
Average benefit Surgery	8.9% (1.0 – 18.6)	11.3% (3.1 – 21.9)	8.2% (1.4 – 17.6)
Decrease in rate of poor outcome	5.5% (0.1 – 14.5)	11.3% (2.0 – 21.6)	7.4% (1.0 – 16.5)
Pain intensity during activities			
Marker positivity rate	62.8% (30.7 – 97.6)	99.2% (63 – 100)	99.9% (0.1 – 99.9)
Marker negativity rate	37.2% (2.0 – 68.6)	0.8% (0.0 – 36.6)	0.1% (0.1 – 100)
Marker positivity threshold	53.9	9.3	NA
Average benefit Physical Therapy	11.0% (0.3 – 22.4)	1.4% (0.0 – 14.0)	0% (0.0 – 12.2)
Average benefit Surgery	12.2% (2.7 – 23.7)	12.7% (3.8 – 23.9)	5.2% (0.0 – 16.7)
Decrease in rate of poor outcome	7.7% (0.9 – 16.8)	12.6% (3.1 – 22.7)	5.2% (0.0 – 15.6)
Age			
Marker positivity rate	67.4% (19.8 – 100)	88.8% (60.5 – 99.9)	72.2% (48.7 – 99.9)
Marker negativity rate	32.6% (0.0 – 79.3)	11.2% (0.1– 39.5)	27.8% (0.1 – 50.9)
Marker positivity threshold	54.0	49.0	53.0
Average benefit Physical Therapy	5.0% (0.0 – 16.7)	4.1% (0.0 – 14.4)	5.5% (0.0 – 17.0)
Average benefit Surgery	9.5% (1.2 – 20.4)	14.8% (6.5 – 25.7)	12.8% (4.3 – 22.0)
Decrease in rate of poor outcome	6.4% (0.3 – 16.2)	13.2% (0.5 – 23.7)	9.3% (2.8 – 18.2)
Body Mass Index			
Marker positivity rate	75.7% (6.3 – 99.9)	90.3% (52.7 – 100)	99.0% (30.8 – 100)
Marker negativity rate	24.3% (0.1 – 93.7)	9.7% (0.0 – 46.9)	1.0% (0.0 – 68.9)
Marker positivity threshold	24.2	22.3	19.6
Average benefit Physical Therapy	3.2% (0.0 – 13.6)	4.4% (0.0 – 12.7)	0.5% (0.0 – 8.7)
Average benefit Surgery	7.3% (0.1 – 19.2)	14.8% (6.7 – 25.1)	8.0% (1.3 – 18.3)
Decrease in rate of poor outcome	5.5% (0.1 – 16.1)	13.4% (5.4 – 23.6)	7.9 (0.4 – 17.9)

V

Discussion

The important finding of the present study was that the identification of potential treatment selection markers did not result in clear clinical subgroups of patients who are substantially more likely to benefit from either surgery or physical therapy. Therefore, treatment decisions for patients with degenerative meniscal tear cannot be based on these treatment selection markers evaluated in the current study.

The published randomized clinical trials that evaluated surgical to conservative treatment for degenerative meniscal tears revealed small and clinically non-meaningful benefits of meniscal surgery over physical therapy in patients with degenerative meniscal tears for patient reported knee function.[5, 6, 9, 15, 26, 32] However, due to potential heterogeneity in treatment effects, this does not necessarily imply that individual patients cannot have a clinically relevant improvement from meniscal surgery compared to physical therapy.[23]

The present study revealed that the average benefit that individual patients would experience from meniscal surgery is small (ranging from 5.2% to 14.8%) if treatment would be based on these markers. Similar to the results from the RCTs, the increased benefit that some patients may experience from meniscal surgery compared to physical therapy is not convincing since these benefits were small and not consistently present on all follow-up moments.

No studies were found that have analyzed the variation in treatment effect for a musculoskeletal disorder based on RCT baseline data of their patients by performing a marker-by-treatment analysis. One cohort study on prognostic factors was identified and found worse outcomes at 1 and 2 years after surgery in case of complex tears, larger extrusion, cartilage injuries, and larger meniscal excision but without comparison to physical therapy.[14] In another, computer-based, prediction model in a similar population multivariable prognostic models were investigated to identify a subgroup of patients who might benefit from meniscectomy.[19] The multivariable prognostic models did not accurately predict treatment outcome after 1 year of surgery, and the study did not consider specific cut-off points that can potentially differentiate between the outcomes from the two treatments. In another study the orthopedic surgeons' prediction ability for treatment outcome in patients with degenerative meniscal tears was analyzed for both physical therapy and meniscectomy.[25] Similar to the current findings, neither of these prediction studies were able to identify any subgroup of patients who might benefit from a meniscectomy or physical therapy on the longer term.[25]

To our knowledge, this is the first RCT-based marker-by-treatment analysis that assessed the differential treatment effect of potentially relevant baseline variables for predicting clinically relevant improvement of knee function in patients with a degenerative meniscal tear. For treatment decision making, this type of prediction studies may be favorable over more common multivariable prediction studies.[8] Marker-by-treatment analyses focus on predicting the difference in outcomes between the two treatments, rather than only predicting the outcome for one treatment. Therefore, the analyses help clinicians and patients select the best treatment to optimize the outcomes. The selection markers deemed relevant by patients in this study aim to direct the choice of treatment based on specific baseline characteristics and the corresponding marker cut-off values.

Several limitations should be mentioned. First, the observed treatment thresholds did not account for potential adverse events resulting from surgery as an alternative to physical therapy. In other words, treatment benefit from surgery is overestimated because the risk of surgical complications is neglected.[2] Second, due to trial-based approach, the available baseline characteristics were restricted. Some potentially important predictors, such as objective knee function, muscle strength, the duration of symptoms,[10] could not be included in our analyses. Although these factors may be viewed as relevant for treatment outcome, prior prognostic models that did include these variables could also not accurately predict treatment outcome in this population.[19][10] Trials that included these prognostic variables are recommended to perform a marker-by-treatment analysis including these variables. Also, the trial-based approach might have resulted in an insufficient power for marker-by-treatment analysis due to the size of the RCT cohort. Third, the primary interest concerned the cut-off point on a predictiveness curve that distinguishes between a better outcome after surgery or after physical therapy based on a patient's baseline score. Therefore, only continuous variables could be included, and dichotomous and categorical variables such as sex, joint line tenderness and tear type were not addressed.

Clinical implications

In general, marker-by-treatment analyses determine whether baseline characteristics can be used in making treatment decisions for individual patients. The predictiveness curves and performance measures of these predictiveness curves show the amount of benefit that individual patients will have from a treatment, if the treatment decision for that patient is based upon the treatment selection marker.[8] A threshold value is derived that differentiates between a favorable outcome for either of the compared treatments. Although such thresholds are rather uncommon to use as treatment decision tool in clinical practice, this information can be of high value to clinicians and policy makers who are seeking evidence based decision tools to weigh treatment benefit for individual patients against the risk of adverse events and healthcare costs.[13] So, instead of using mean outcomes of RCTs to make treatment decisions, patients and clinicians can potentially base their treatment decision for an individual patient upon the treatment selection marker.

In patients with degenerative meniscal tears our marker-by-treatment analyses only revealed specific baseline characteristics that showed a small increase in a better treatment outcome after meniscal surgery for each follow-up time point. As the combination of characteristics varies among patients, combining these potential selection markers may be more accurate. Future research, combining the individual data from the published RCTs in an individual patient data meta-analysis,[31] may be able to identify any of these subgroups and could steer towards an even more individualized approach.

The opinion that surgery is necessary to regain normal knee function in selected patients is not supported by our study or previous scientific evidence in which subgroups have been unable to be identified.[4, 19, 25] Therefore physical therapy is recommended as initial treatment for all patients with degenerative meniscal tears.

Conclusion

A marker-by-treatment analysis was successfully conducted in orthopedic research. No subgroups were found in this study that benefit more from surgery throughout the follow-up period. Physical therapy should be considered first choice treatment in all patients over 45 years old with degenerative meniscal tears who do not experience locking of the knee.Although the treatment selection markers had clear thresholds, none of the markers maintained a predictive effect over time. Therefore, treatment decisions for patients with degenerative meniscal tear cannot be based on the treatment selection markers studied in this trial.

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Chapter 6

Effect of Physical Therapy vs Arthroscopic Partial Meniscectomy in People With Degenerative Meniscal Tears. Five-Year Follow-up of the ESCAPE Randomized Clinical Trial

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Abstract

Importance There is a paucity of high-quality evidence about the long-term effects (ie, 3-5 years and beyond) of arthroscopic partial meniscectomy vs exercise-based physical therapy for patients with degenerative meniscal tears. OBJECTIVES To compare the 5-year effectiveness of arthroscopic partial meniscectomy and exercise-based physical therapy on patient-reported knee function and progression of knee osteoarthritis in patients with a degenerative meniscal tear.

Design, setting, and participants A noninferiority, multicenter randomized clinical trial was conducted in the orthopedic departments of 9 hospitals in the Netherlands. A total of 321 patients aged 45 to 70 years with a degenerative meniscal tear participated. Data collection took place between July 12, 2013, and December 4, 2020.

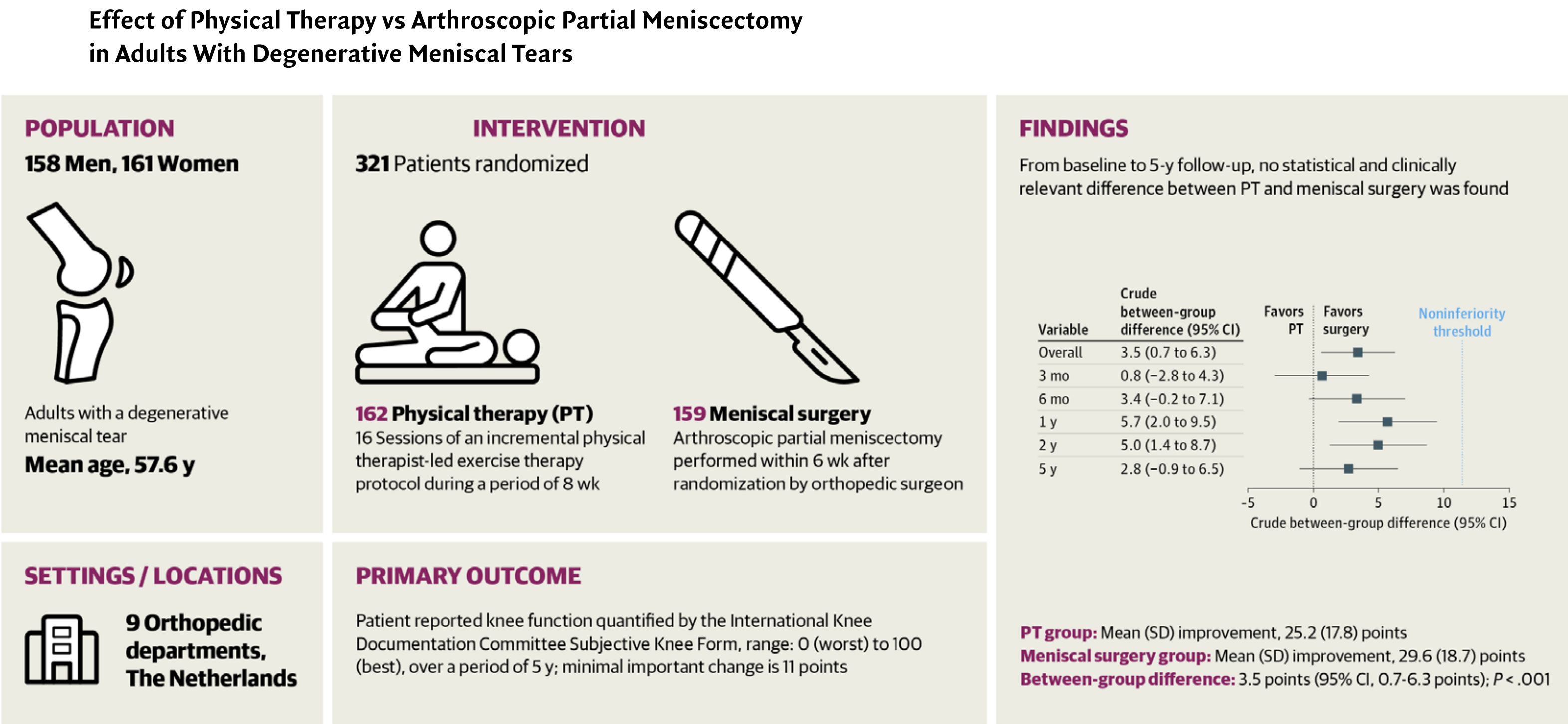
Interventions Patients were randomly allocated to arthroscopic partial meniscectomy or 16 sessions of exercise-based physical therapy.

Main outcomes and measures The primary outcome was patient-reported knee function (International Knee Documentation Committee Subjective Knee Form (range, 0 [worst] to 100 [best]) during 5 years of follow-up based on the intention-to-treat principle, with a noninferiority threshold of 11 points. The secondary outcome was progression in knee osteoarthritis shown on radiographic images in both treatment groups.

Results Of 321 patients (mean [SD] age, 58 [6.6] years; 161 women [50.2%]), 278 patients (87.1%) completed the 5-year follow-up with a mean follow-up time of 61.8 months (range, 58.8-69.5 months). From baseline to 5-year follow-up, the mean (SD) improvement was 29.6 (18.7) points in the surgery group and 25.1 (17.8) points in the physical therapy group. The crude between-group difference was 3.5 points (95% CI, 0.7-6.3 points; $P < .001$ for noninferiority). The 95% CI did not exceed the noninferiority threshold of 11 points. Comparable rates of progression of radiographicdemonstrated knee osteoarthritis were noted between both treatments.

Conclusions and relevance In this noninferiority randomized clinical trial after 5 years, exercise-based physical therapy remained noninferior to arthroscopic partial meniscectomy for patient-reported knee function. Physical therapy should therefore be the preferred treatment over surgery for degenerative meniscal tears. These results can assist in the development and updating of current guideline recommendations about treatment for patients with a degenerative meniscal tear.

Trial registration ClinicalTrials.gov Identifier: NCT01850719



Visual abstract

Noorduyn JCA, van de Graaf VA, Willigenburg NW, et al. Effect of Physical Therapy vs Arthroscopic Partial Meniscectomy in People With Degenerative Meniscal Tears: Five-Year Follow-up of the ESCAPE Randomized Clinical Trial. JAMA Netw Open. 2022;5(7):e2220394. doi:10.1001/jamanetworkopen.2022.20394

VI

Introduction

Randomized clinical trials (RCTs) and their aggregated data in systematic reviews show that arthroscopic partial meniscectomy has no clinically meaningful patient benefit compared with exercise therapy in patients with a degenerative meniscal tear in the first 2 years of follow-up.1-8 These findings have been embedded in recently updated guidelines.9-11

Long term trial results (i.e., 3 – 5-years follow-up) of arthroscopic partial meniscectomy vs exercise therapy for patients with degenerative meniscal tears have been published.12-16 These studies have consistently reported a lack of clinically relevant differences between partial meniscectomy and exercise therapy on important patient-reported outcomes, such as knee function. While these results are consistent, debate still exists on the progression of osteoarthritis (OA) after meniscal surgery.17-19 The long term trial results have reported conflicting data with respect to this outcome.12-16 The RCT conducted by Shivonen et al. (2020) found that arthroscopic partial meniscectomy is associated with a slight increased risk of radiographic knee OA compared to exercise therapy.15 The study by Katz et al. (2020) found a 5 times higher risk for total knee replacement (i.e., the treatment for end-stage knee OA) after surgery compared to exercise-based physical therapy.14 However, the trials by Herrlin et al. (2013), Berg et al. (2020) and Sonesson et al. (2020) that compared surgery with exercise therapy found no clinically relevant difference between the 2 treatments for OA progression.12,13,16

Although the current evidence suggests nonoperative management is best in patients with degenerative meniscal tears, it has not yet led to a substantial reduction of meniscal surgeries for this population.20 Additional evidence from RCTs on the long term outcomes (i.e., 5 years and beyond) of patients with degenerative meniscal tears is likely to further clarify the role of surgery and exercise in the management of meniscal tears.

The primary aim of this study is to compare patient-reported knee function at the 5 year follow-up after arthroscopic partial meniscectomy and exercise-based physical therapy in patients with a degenerative meniscal tear. The secondary aim was to assess the progression of radiographic and symptomatic knee OA. We hypothesized that exercise-based physical therapy is noninferior to arthroscopic partial meniscectomy over a period of 5 years.

Methods

Design

We performed a 5-year follow-up assessment of patients in the ESCAPE trial, a multicenter RCT comparing arthroscopic partial meniscectomy with exercise-based physical therapy. 6,21 The primary end point of the ESCAPE trial was at 2 years. The published protocol and 2-year results paper contain a detailed description of the design and methods of the trial, including the sample size calculation. We added our 5-year follow-up statistical analysis plan to the trial registration on October 6, 2021, before data analyses commenced. The Medical Ethical Committee–United approved the ESCAPE trial in 2013, including the data collection for the 5-year follow-up. All patients provided written informed consent prior to participating in the trial. We followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Participants

We recruited patients from 9 participating orthopedic departments of secondary and tertiary care hospitals in the Netherlands. Patients had to be between ages 45 and 70 years and have a symptomatic, degenerative, magnetic resonance imaging–confirmed meniscal tear. We excluded patients with a locked knee or trauma requiring acute surgery, associated injuries on the index knee (symptomatic partial or total anterior or posterior cruciate ligament rupture), severe structural knee OA (grade 4 on the Kellgren-Lawrence [KL] Grading Scale), or a body mass index greater than 35 (calculated as weight in kilograms divided by height in meters squared). Patients did not receive financial compensation for participating in the study. The 16 physical therapy sessions were compensated for patients allocated to physical therapy because this therapy is not reimbursed by the basic Dutch health insurance. A more detailed description of the selection criteria is presented in the protocol.21

Randomization and blinding

We enrolled all patients between July 2013 and November 2015. The 5-year follow-up evaluation was completed in December 2020. We randomized patients to meniscal surgery or exercise-based physical therapy using a computerized randomization schedule with a 1:1 ratio and varying block sizes up to a maximum of six. The randomization scheme was stratified by hospital and age (45-57 and 58-70 years). Due to practical considerations patients, clinicians, and research staff, with the exception of the radiologist in charge of examining the radiographs, were not blinded to treatment allocation during data collection. We, however, performed the analyses and interpreted the results based on data that were blinded for treatment allocation. We unblinded the treatment allocation after we reached consensus on the interpretation of the results.

Intervention

Arthroscopic Partial Meniscectomy

Patients allocated to arthroscopic partial meniscectomy received arthroscopic partial meniscectomy within 4 weeks after randomization at the hospital of inclusion. The arthroscopic partial meniscectomy included a standardized intra-articular inspection of the knee joint, including assessment of the lateral and medial meniscus, the anterior cruciate ligament, the level of chondropathy, and a general classification of the level of cartilage degeneration. The surgeon removed the affected part of the meniscus until a stable and solid meniscus remained. The costs for surgery were covered by the patients' health insurance. After surgery, all patients received written postoperative instructions, including a home exercise program. Eight weeks after surgery, patients visited the outpatient orthopedic clinic for a clinical consultation. According to the guidelines of the Dutch Orthopedic Association, we referred patients for physical therapy only in case of delayed recovery.10

Exercise-based physical therapy

Patients allocated to physical therapy were referred to participating physical therapy practices and started exercise therapy within 2 weeks of randomization. The treatment protocol consisted of a physical therapist–led incremental exercise program over a period of 8 weeks, consisting of 16 sessions of 30 minutes each. If knee symptoms persisted following the physical therapy program (eg, knee pain, limitations in daily activities, or mechanical dysfunction), the patient could attend additional physical therapy sessions or opt for arthroscopic partial meniscectomy based on a shared decision after consultation with the orthopedic surgeon. A detailed description of the physical therapy protocol can be found in Appendix 1.

Data collection

Patients completed self-administered questionnaires at baseline and 3 months, 6 months, 1 year, 2 years and 5 years after enrolment. Weight-bearing radiographs were performed at baseline and 5-years follow-up.
Patients completed the questionnaires either online or on paper, according to their preference. Baseline data included patient characteristics, the level of OA assessed on radiographs and several patient-reported outcome measures (details below). Each item in the questionnaires required an answer to limit missing data. For the paper-based questionnaires, the researcher tried to retrieve missing items by telephone. To optimize the response rate, patients received up to three reminders. In case a patient was not able or willing to complete a questionnaire at a specific time point, efforts were made to collect data for the subsequent time points.

Primary outcome measure

The primary outcome was the difference between the surgery group and physical therapy group in patient-reported knee function, quantified by the International Knee Documentation Committee Subjective Knee Form (IKDC) questionnaire over a period of 5-year. The IKDC questionnaire assesses knee-specific symptoms, function and sports activity, and was developed for patients with knee ligament or meniscal injuries.22 In patients with a meniscal tear, the IKDC is a reliable, valid and responsive measurement instrument to assess knee function.23,24 The score ranges from 0, representing worst knee function, to 100, indicating no limitations in functioning. The minimal important change for people with degenerative meniscal tears is 11 points.23

Secondary outcome measures

Secondary outcomes included the progression of knee OA assessed on radiographic images and additional patient-reported outcomes. All radiographic images were taken with the patient in a standing position and with an anterior-posterior view. An experienced radiologist (R.A.v.d.D.) blinded to treatment allocation performed all radiographic evaluations to assess the presence and grade of knee OA using the KL scale, ranging from 0 (no knee OA) to 4 (severe knee OA),25 as well as the Osteoarthritis Research Society International (OARSI) atlas sum score26, a semiquantitative instrument which assesses the severity of joint space narrowing and osteophytes in knee OA.

We specifically chose to discriminate between radiographic knee OA, looking only at the structural changes of cartilage tissue, and symptomatic knee OA, combining structural changes on radiograph with the patient experienced symptoms.

Radiographic knee OA

Using the OARSI atlas sum score, we assessed the severity of knee osteophytes at baseline and at 5-year follow-up for the medial and lateral femoral condyle, and medial and lateral tibia plateau. Joint space narrowing was assessed for the medial and lateral compartment. The severity for each item was scored with an ordered categorical grade (Grade 0: normal; Grade 1: mild change in joint space or osteophytes; Grade 2: moderate change in joint space or osteophytes and Grade 3: severe change in joint space or osteophytes). We calculated a sum score by adding the scores of all items. We defined radiographic knee OA if at least one of the following criteria was met: 1) joint space narrowing Grade 2 or higher; 2) sum of osteophyte Grades $\geq$2; or 3) Grade 1 joint space narrowing in combination with one or more grade 1 osteophyte(s).12

To determine the progression of knee OA between baseline and 5-year follow-up we used the OARSI sum score (ranging from 0-18) of the 6 items. Patients who underwent partial or total knee replacement surgery received the score of end-stage knee OA (OARSI score of 3 for the involved components).

Symptomatic knee OA

We planned to assess symptomatic knee OA at the 5-year follow-up but found no consensus on cutoff values for symptomatic knee OA in the literature. We therefore introduced a pragmatic definition based on radiographic images and the Patient Acceptable Symptom State of the Knee Osteoarthritis Outcome Score-Physical Functioning Short-Form (KOOS-PS) score (range, 0 [best] to 100 [worst] physical functioning). The KOOS-PS is a reliable, valid, and responsive measurement instrument to assess physical functioning in patients with knee OA.27,28 Symptomatic knee OA was considered to be present in patients with both a KL score greater than or equal to 225 and KOOS-PS score exceeding the Patient Acceptable Symptom State of 52.8 points for people with knee OA.29 The data manager (E.J.K.) combined the KL score, assessed by the radiologist, and the patientreported KOOS-PS score into a symptomatic knee OA (yes or no) score using syntax coded in SPSS (IBM SPSS).

Additional patient-reported outcomes

Additional patient-reported outcomes were (1) pain intensity during activities, assessed for the preceding week and scored using a visual analog scale ranging from 0 (no pain) to 100 (worst imaginable pain); (2) physical function using the KOOS-PS; and (3) quality of life, assessed with the EuroQol 5 Dimension 5 Level, which is a widely used instrument for health-related quality-of-life based on 5 dimensions: mobility, self-care, daily activities, pain/discomfort, and depression/anxiety.30 These 5 dimensions were combined into a health state. The index score ranges from 0 (death) to 1 (best quality of life). We assessed pain intensity and quality of life at baseline, 3 months, 6 months, 1 year, 2 years, and 5 years and physical function using the KOOS-PS only at the 5-year follow-up.

Adverse events and additional knee surgery

The adverse events up to the 2-year follow-up were previously reported.6 In the 5-year follow-up questionnaire, we asked patients: “Did you have additional knee surgery performed on your affected knee in the last 3 years?” If yes, patients were asked to specify the type of surgery (arthroscopic partial meniscectomy, total knee replacement, partial knee replacement, cartilage surgery, or other). We reported these additional knee surgeries descriptively.

Sample Size Calculation

We calculated the study sample size before the trial in 2013. The sample size was calculated for the primary end point, which was the 2-year follow-up. We based our sample size on an SD of 18 points on the IKDC questionnaire, a power of 90%, a 2-sided α of .05, and a non-inferiority margin of 8 points on the IKDC questionnaire. With an anticipated 20% loss to follow-up and a 25% delayed arthroscopic partial meniscectomy rate after 24 months, 160 participants per treatment group were needed.

Statistical Analysis

We used descriptive statistics to report baseline characteristics of the study population and frequencies of further surgeries, partial or total knee arthroplasties, and patients who received delayed surgery following physical therapy. Similar to our previous analyses6 and as recommended for clinical trials, we analyzed 5-year follow-up data using the intention-to-treat principle. In the intention-to-treat analysis, patients were analyzed in 2 groups according to their randomly allocated treatment. To test for robustness of the results regarding knee function and radiographic knee OA, we also performed an as-treated analysis. For this process, we divided patients into 3 groups: (1) patients allocated to arthroscopic partial meniscectomy who underwent surgery, (2) patients allocated to physical therapy who completed 16 or more physical therapy sessions, and (3) patients allocated to physical therapy who underwent arthroscopic partial meniscectomy during the 5-year follow-up. Patients who did not undergo their allocated treatment (either surgery or completion of physical therapy) were excluded from the as-treated analysis.

We analyzed a continuous outcome measure using linear mixed-model analyses with a random intercept. We defined the overall crude intervention effects by a model with only treatment group and the baseline value of the outcome as independent variables. We added time and time-by-treatment interaction terms to specify crude intervention effects for each follow-up time point.

Adjusted intervention effects were calculated using similar models expanded with the following potential confounders as independent variables6: level of OA at baseline using the KL classification,25 baseline pain during weight bearing, body mass index at baseline (<25, 25-30, or >30-35), and sex. In all models, physical therapy was defined as the reference treatment. We tested for noninferiority based on a 1-sample z test with respect to the noninferiority threshold of 11 points and 1-sided level of 0.025. Statistical significance was assessed at the .05 level for secondary outcome measures. Significant P values indicate noninferiority, ie, the upper limit of the 95%CI of the between-group difference does not exceed the noninferiority threshold of 11 points. We report the secondary outcomes for knee OA descriptively. All analyses were performed using SPSS, version 27 (IBM SPSS).

Results

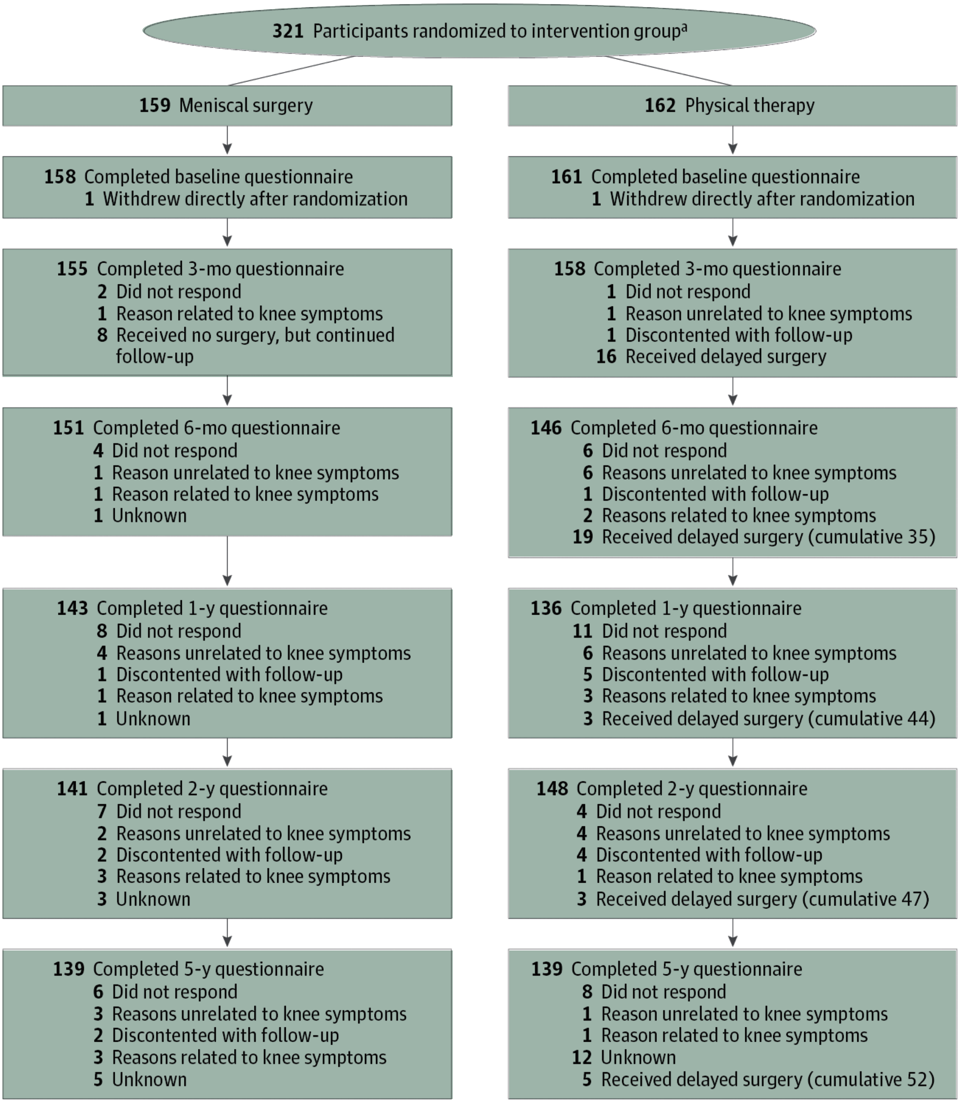
Patients

We included and randomized a total of 321 patients (mean [SD] age, 58 [6.6] years; 161 women [50.2%], 160 men [49.8%]) to either surgery (n = 159) or physical therapy (n = 162). Directly after randomization, 1 patient in each group withdrew from participation. After 5 years, 278 participants (87.1%) completed the follow-up: 139 in each group, with a mean follow-up time of 61.8 months (range, 58.8-69.5 months). In the surgery arm, a total of 19 patients (12.0%) did not complete the follow-up at 5 years. In the physical therapy arm, a total of 22 patients (13.6%) did not complete the follow-up at 5 years. In 4 patients (1 physical therapy vs 3 surgery), the loss to follow-up was related to the lack of knee symptoms. Other reasons for loss to follow-up were patients did not respond to the questionnaires and reminders (8 physical therapy vs 6 surgery), patients did not wish to
complete the follow-up (0 physical therapy vs 2 surgery), the reason was unrelated to knee symptoms (1 physical therapy vs 3 surgery), or the reason was unknown (12 physical therapy vs 5 surgery).

Figure 1 presents the patient flow through the trial, and Table 1 reports the baseline characteristics for the surgery and physical therapy groups. The groups had similar baseline characteristics. During the follow-up period, 52 of 162 participants (32.1%) in the physical therapy group underwent delayed arthroscopic partial meniscectomy due to persistence of knee symptoms: 44 patients within the first 2 years of follow-up and 5 patients within the last 3 years of the trial (Figure 1).

In the as-treated analyses, we excluded a total of 25 participants (7.8%): 8 allocated to surgery withdrew from surgery and 17 allocated to physical therapy did not adhere to the treatment protocol. The as-treated analysis therefore included the data of 150 participants in the surgery group, 92 participants in the physical therapy, and 52 participants in the delayed surgery group.

Figure 1. Flow of Patients



a The number of patients screened for eligibility was not available. The flow diagram represents separate time points instead of a mathematical flow

Table 1. Baseline characteristics

	Meniscal surgery group (n=158)	Physical therapy group (n=161)
Demographics		
Age, mean (SD), y	57.6 (6.5)	57.3 (6.8)
Sex		
Men	78 (49.4%)	80 (49.7%)
Women	80 (50.6%)	81 (50.3%)
Treated knee, right side	88 (55.7%)	81 (50.3%)
Education level high[a]	67 (42.4%)	86 (53.4%)
BMI, mean (SD)	26.7 (3.8)	27.2 (4.0)
18.5-25	56 (35.4%)	53 (32.9%)
25-30	72 (45.6%)	67 (41.6%)
30-35	30 (19.0%)	41 (25.5%)
Mechanical problems[b]	56 (35.4%)	67 (41.6%)
Imaging		
Affected meniscus on MRI		
Medial	126 (79.7%)	136 (84.5%)
Lateral	30 (19.0%)	25 (15.5%)
Both	2 (1.3%)	0 (0%)
OA score on radiographs images, No.	n=148	n=146
OARSI sum score, mean (SD)	1.9 (1.5)	2.1 (1.6)
KL classification[c]		
0 (no OA)	18 (12.0%)	15 (10.1%)
1 (doubtful)	81 (54.0%)	74 (49.7%)
2 (minimal OA)	45 (30.0%)	55 (36.9%)
3 (moderate OA)	6 (4.0%)	5 (3.3%)
4 (severe OA)[d]	0 (0%)	0 (0%)
Patient-reported outcomes, mean (SD)		
IKDC score	44.8 (16.6)	46.5 (14.6)
Pain during activities	61.1 (24.5)	59.3 (22.6)

Abbreviations: BMI=Body Mass Index, MRI = Magnetic resonance imaging, OA = Osteoarthritis, OARSI = Osteoarthritis Research Society International, KL=Kellgren-Lawrence classification, IKDC=International Knee Documentation Committee.

a Educational level was measure according to the International Standard Classification of Education (ISCED) and dichotomized to low (ISCED level 0-3; eg. Early childhood education, primary education or high school) or high (ISCED level 4-8; eg. Any education beyond high school, including bachelor's, master's, or doctoral degree).

b In contrast to locking of the knee joint, which was an exclusion criterion, mechanical complaints such as catching and clicking of the knee, were allowed for inclusion.

c Osteoarthritis was assessed using standing radiographic images of the knee in the anterior-posterior direction

d Patients with a Kellgren-Lawrence grade of 4 on baseline radiographic images were excluded from the trial.

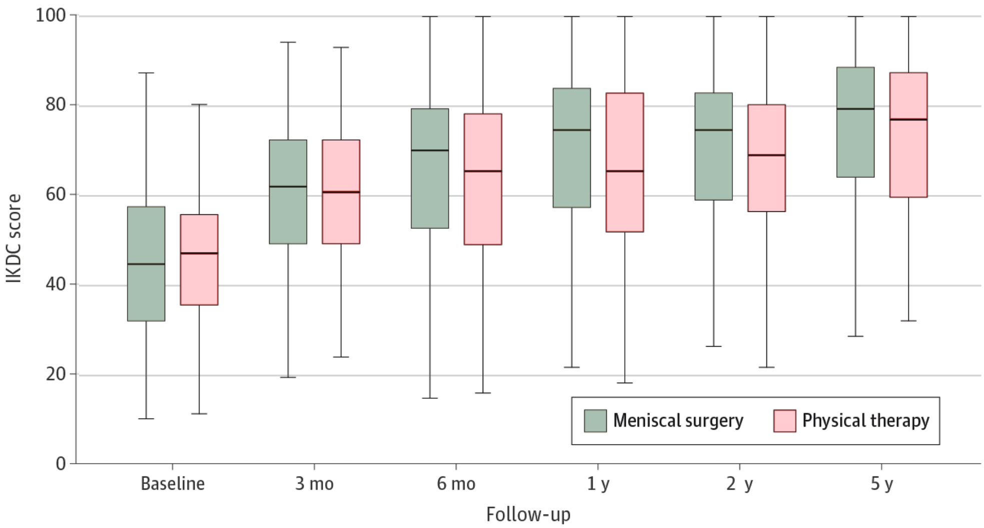
Primary outcome measure – Patient reported knee function

Intention-to-treat analysis

The crude and adjusted between-group differences in effect between physical therapy and arthroscopic partial meniscectomy for knee function overall and at each time point are reported in

Table 2, and the knee function box plots in each group at each time point are displayed in Figure 2.

Figure 2 International Knee Documentation Committee (IKDC) Subjective Knee Form Questionnaire Scores During Follow-up



The IKDC score for knee function per time point, shown with the box representing the IQR and median score indicated as the line within the box. The error bars indicate the 95% CIs.

Over the 5 years of follow-up, the overall crude between-group difference was 3.5 points (95% CI, 0.7-6.3 points; P < .001 for noninferiority) and was 3.8 points (95% CI, 0.8-6.8; P < .001 for noninferiority) after adjusting for confounding factors. From baseline to the 5-year follow-up, the surgery group had a mean (SD) improvement of 29.6 (18.7) points (from 44.8 [16.6] to 74.7 [18.4] points), and the exercise-based physical therapy group had a mean improvement of 25.1 (17.8) points (from 46.5 [14.6] to 73.1 [17.7] points) on the IKDC questionnaire score for knee function.

The crude mixed-model analysis found a mean between-group difference in patient-reported knee function on the IKDC at the 5-year follow-up of 2.8 points (95% CI, −0.9 to 6.5 points; P < .001 for noninferiority). After adjusting for confounders, there was a mean between-group difference of 3.4 points on the IKDC questionnaire (95% CI, −0.7 to 7.4 points; P < .001 for noninferiority). A positive between-group value indicates greater mean improvement on the IKDC questionnaire in the surgery group compared with the physical therapy group. However, the between-group differences are significantly smaller than the noninferiority threshold of 11 points, indicating that physical therapy is not inferior to arthroscopic partial meniscectomy.

Figure 3A shows crude between-group differences, and Figure 3B presents adjusted between-group differences at all follow-up time points, relative to the noninferiority threshold of 11 points on the IKDC questionnaire. Because none of the 95% CIs crossed this noninferiority threshold, no clinically meaningful difference between physical therapy and surgery was observed.

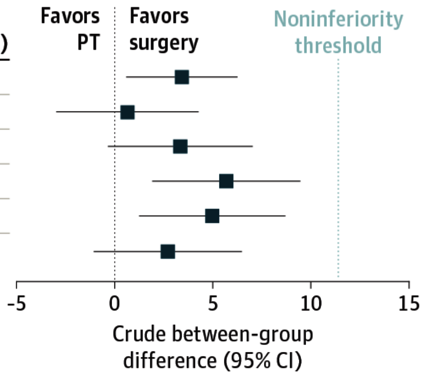
As-treated analysis

The overall crude difference between physical therapy and arthroscopic partial meniscectomy on the IKDC questionnaire score was 2.4 points (95% CI, −0.8 to 5.5 points; P < .001 for noninferiority) and the difference between physical therapy and delayed surgery was −3.8 points (95% CI, −8.2 to 0.6 points; P < .001 for noninferiority). A positive value indicates greater improvement on the IKDC questionnaire in the arthroscopic partial meniscectomy group compared with the physical therapy group, and a negative between-group value indicates greater mean improvement on the IKDC questionnaire in the physical therapy group compared with the delayed surgery group. These between-group differences were significantly different from the noninferiority threshold, indicating that physical therapy was not inferior to arthroscopic partial meniscectomy. The crude and adjusted intervention effects for all time points are presented in Table 2.

Figure 3. Between-Group Intervention Effects Indicated With International Knee Documentation Committee (IKDC) Subjective Knee Form Questionnaire for Physical Therapy (PT) vs Surgery

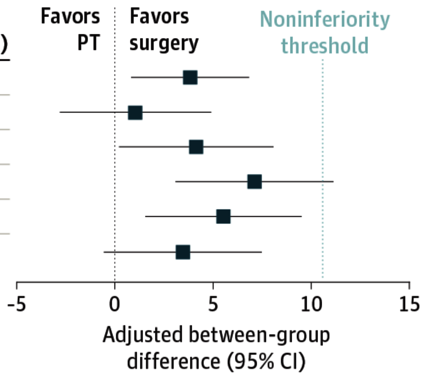
A Knee function: crude intervention effect

Variable	Crude between-group difference (95% CI)
Overall	3.5 (0.7 to 6.3)
3 mo	0.8 (-2.8 to 4.3)
6 mo	3.4 (-0.2 to 7.1)
1 y	5.7 (2.0 to 9.5)
2 y	5.0 (1.4 to 8.7)
5 y	2.8 (-0.9 to 6.5)



B Knee function: adjusted intervention effect

Variable	Adjusted score between-group difference (95% CI)
Overall	3.8 (0.8 to 6.8)
3 mo	1.0 (-2.9 to 4.8)
6 mo	4.1 (0.1 to 8.0)
1 y	7.1 (3.0 to 11.1)
2 y	5.5 (1.5 to 9.5)
5 y	3.4 (-0.7 to 7.4)



Crude (A) and adjusted (B) noninferiority threshold refers to the minimal important change on the IKDC questionnaire (11 points). The squares indicate the between-group differences with 95% CIs. A positive value indicates greater improvement on the IKDC questionnaire in the arthroscopic partial meniscectomy group compared with the physical therapy group. Because none of the 95% CIs in the crude intervention effect crossed this noninferiority threshold, no clinically meaningful difference between physical therapy and surgery was observed.

Table 2. Crude and Adjusted Between-Group Differences in Effect for Knee Function Overall and at Each Time Point

	Intention-to-treat analyses		As treated analyses[c]			
	Surgery vs Physical therapy		Surgery vs Physical therapy		Delayed Surgery vs. Physical therapy	
	Between group difference[a] (95% CI)	P-value for non inferiority[b]	Between group difference (95% CI)	P-value for non inferiority[b]	Between group difference (95% CI)	P-value for non inferiority[b]
Crude						
3 months	0.8 (-2.8 to 4.3)	<.001	-2.4 (-6.4 to 1.7)	<.001	-9.1 (-14.6 to -3.6)	<.001
6 months	3.4 (-0.2 to 7.1)	<.001	2.1 (-2.0 to 6.2)	<.001	-5.4 (-11.2 to 0.3)	<.001
1 year	5.7 (2.0 to 9.5)	.003	5.7 (1.6 to 9.9)	.007	-0.6 (-6.5 to 5.4)	<.001
2 years	5.0 (1.4 to 8.7)	.001	4.1 (-0.1 to 8.3)	.001	-2.5 (-8.3 to 3.2)	<.001
5 years	2.8 (-0.9 to 6.5)	<.001	3.0 (-1.2 to 7.1)	<.001	2.3 (-3.7 to 8.2)	.002
Overall[d]	3.5 (0.7 to 6.3)	<.001	2.4 (-0.8 to 5.5)	<.001	-3.8 (-8.2 to 0.6)	<.001
Adjusted						
3 months	1.0 (-2.9 to 4.8)	<.001	-2.3 (-6.7 to 2.0)	<.001	-9.7 (-15.7 to -3.7)	<.001
6 months	4.1 (0.1 to 8.0)	<.001	2.6 (-1.8 to 7.1)	<.001	-6.1 (-12.4 to 0.2)	<.001
1 year	7.1 (3.0 to 11.1)	.028	6.6 (2.1 to 11.1)	.028	-2.4 (-8.9 to 4.2)	<.001
2 years	5.5 (1.5 to 9.5)	.003	4.0 (-0.5 to 8.5)	.001	-4.6 (-10.9 to -1.7)	<.001
5 years	3.4 (-0.7 to 7.4)	<.001	3.1 (-1.4 to 7.6)	<.001	0.9 (-5.5 to 7.4)	.001
Overall[d]	3.8 (0.8 to 6.8)	<.001	2.2 (-1.2 to 5.6)	<.001	-4.9 (-9.6 to -0.2)	<.001

a In the as-treated model, we analyzed patients in 3 groups: (1) patients allocated to the surgery group who received surgery, (2) patients allocated to the physical therapy group who completed the physical therapy protocol without having surgery during the follow-up period, and (3) patients randomized to the physical therapy group who had a delayed surgery during follow-up. We excluded patients from the as-treated analysis who were randomized to surgery but did not have surgery and those who were randomized to physical therapy but did not complete the physical therapy protocol and did not have delayed surgery.

b The between-group difference at different time points and as an overall effect corrected only for International Knee Documentation Committee (IKDC) score at baseline. Positive values imply that patients did better with surgery or delayed surgery. However, none of these values indicated a clinically relevant difference.

c P values for noninferiority based on a 1-sample z test with respect to the noninferiority threshold of 11 points and 1-sided α level of .025. Significant P values indicate that the between-group difference is significantly different with respect to the noninferiority threshold of 11 points.

d Overall estimate refers to the overall IKDC score between groups including all time points.

Table 2. Crude and adjusted intervention effects for knee function

Secondary outcomes

Radiographic knee OA

At baseline, we analyzed the radiographic images of 294 patients (surgery group, n = 146; physical therapy group, n = 148). At the 5-year follow-up, 222 radiographic images were available (surgery, n = 112; physical therapy, n = 110). We found that at 5 years of follow-up, radiographic knee OA, assessed by the OARSI sum score ranging from 0 (best) to 18 (worst), progressed by at least 1 point in 61 patients (49.2%) in the surgery group and 63 patients (50.8%) in the physical therapy group. We found a mean (SD) progression of 1.1 (2.2) points in the surgery group (from 1.9 [1.5] to 3.0 [2.6]) and 1.1 (2.1) points in the physical therapy group (from 2.1 [1.6] to 3.4 [2.7]) from baseline to 5 years. The between-group difference of 0.1 points (95% CI, −0.5 to 0.7; P = .78) was not significantly or clinically meaningful.
Table 3 presents an overview of radiographic outcomes and patient reported outcome measures at 5 years. We found a progression of at least one point on the OARSI sum score in 52% (n=42) of the physical therapy group and in 54% (n=61) of the surgery group and in 70% (n=21) of the delayed surgery group. We found no difference (p=0.156) between the three groups in progression of the OARSI sum score from baseline to 5 years. The mean (SD) progression in the surgery group was 1.1 (2.2) points, in the physical therapy group 0.8 (2.1) points and in the delayed surgery group with a progression of 1.7 (2.2) points, out of a maximum of 18 points.

Symptomatic knee OA

We found symptomatic knee OA in 6 patients; 4 in the surgery group and 2 in the physical therapy group. An overview of radiographic outcomes and patient-reported outcomes at 5 years can be found in Table 3.

Additional patient-reported outcomes and surgeries

From baseline to 5 years, we found no differences between the two treatment groups in pain, general physical health and quality of life. Besides the delayed meniscal surgeries performed in the physical therapy group (n = 52), additional knee surgeries were performed in 17 patients (n=5 surgery; n=12 physical therapy). Table 3 gives an overview of these patient-reported outcomes and additional surgeries.

Table 3. Five year outcomes for both treatment groups

	Meniscal surgery group	Physical therapy group
Patient reported outcome	n= 139	n= 139
IKDC score	74.7 ±18.4	73.1 ±17.7
Pain during activities	19.0 ±25.0	20.0 ±24.0
KOOS-PS	19.9 ±16.8	22.5 ±15.0
EQ-5D-5L	0.87 ±0.15	0.87±0.14
Knee OA on radiographs	n=112	n=110
OARSI sum score	3.0 ±2.6	3.4 ±2.7
Progression on OARSI		
Baseline – 5 years	1.1 ±2.2	1.1 ±2.1
KL classification[c]		
0 - No OA	8 (7.1%)	8 (7.3%)
1 - Doubtful OA	44 (39.3%)	39 (35.5%)
2 - Minimal OA	31 (27.7%)	33 (30.0%)
3 - Moderate OA	18 (16.1%)	18 (16.4%)
4 - Severe OA[d]	11 (9.8%)	12 (10.9%)
Symptomatic knee OA yes (%)	4 (3.6%)	2 (1.9%)
Additional knee surgeries[e]		
Delayed surgery	NA	52
Meniscal re-surgery	2	6
TKP or UKP	3	4
Cartilage surgery	0	1
Arthroscopic inspection	0	1

Data are n (%) or mean ± SD.

Abbreviations: IKDC=International Knee Documentation Committee, KOOS-PS = Knee Osteoarthritis Outcome Score – physical function short form, EQ-5D-5L = EuroQol 5 Dimension 5 Level, OA=Osteoarthritis, OARSI = Osteoarthritis Research Society International, KL=Kellgren-Lawrence classification, TKR = total knee replacement, UKP = Unicompartal knee prosthesis.

e In the PT group 12 patients underwent additional knee surgery, other than delayed surgery. However, of these 12 patients, 10 patients first had a delayed surgery.

Discussion

Results of this 5-year follow-up of the ESCAPE trial showed that exercise-based physical therapy is not inferior to arthroscopic partial meniscectomy with respect to knee function during 5 years of follow-up in patients with a degenerative meniscal tear. Furthermore, we found comparable rates of progression of radiographic and symptomatic OA between both treatments.

The improvement in knee function experienced by patients in the ESCAPE trial over the first 2 years was maintained at the 5-year follow-up.[6,8] In addition to patient-reported knee function, we found small comparable radiographic changes of the tibiofemoral joint in both treatment groups.

Our findings on patient-reported knee function are consistent with previously published trials reporting 5-year follow-up results for patient-reported knee function and pain.[12-16] Our crossover rate (patients undergoing delayed surgery after initial physical therapy) of 32% was lower compared with the 38% crossover rate in the study of Katz et al.[14] but higher compared with the crossover rates of 20% reported by Berg et al. [12] and 25% reported by Sonesson et al.[16] In our study, the as-treated results indicate that patients who received delayed surgery negatively influenced the mean knee function in the physical therapy group. In addition, after undergoing delayed surgery, the patients in the crossover group did not experience better knee function compared with those in the physical therapy group. This finding puts the added value of arthroscopic partial meniscectomy under debate, but we could not compare our as-treated results because this factor was not reported in the current literature. [12-16] However, when looking at knee OA, we found 2 studies suggesting an increased risk of knee OA following surgery compared to no surgery.[14,15] Shivonen et al.[15] found that arthroscopic partial meniscectomy was associated with a slight increased risk for knee OA compared to non-operative management.[15] Katz et al.[14] reported that patients in the surgery group had a 5 times higher risk for a total knee replacement, the intervention for end-stage knee OA, compared to patients who only had exercise-based physical therapy.[14] However, other recent trials reporting their 5-year data reported no significant difference in radiographic deterioration between both treatment groups.[12,13,16] These latter findings are consistent with our results.

Furthermore, we checked for confounding effects within our primary outcomes, and our adjusted analyses are in line with our primary unadjusted results. Previous studies investigated specific patient characteristics and combinations of characteristics to estimate treatment outcome and possible subgroups of patient who will benefit more from surgery compared with physical therapy.[31-34] However, none of these studies were able to find such a subgroup of patients. This finding is in line with ours, showing that physical therapy is non-inferior to arthroscopic partial meniscectomy in patients with degenerative meniscal tears. The RCTs that reported their results on the progression of knee OA following meniscal treatment have limited power to draw conclusions that can influence clinical practice. Pooling these data using individual patient data meta-analysis will provide more reliable results. Future research should focus on pooling the 5-year data on knee function and knee OA from separate trials to strengthen clinical guidelines. In addition, investigating the effectiveness of exercise-based physical therapy compared with a wait-and-see policy or no treatment can strengthen policy makers to invest in physical therapy and enhance further de-implementation of arthroscopic partial meniscectomy for degenerative meniscal tears. Another option would be an experiment in which nonresponders to exercise therapy are randomized into a surgery group vs a radiofrequency ablation of the genicular nerve group. In patients with knee OA, radiofrequency ablation of the genicular nerve shows promising results in sham-controlled trials and may reduce the need for surgery based on pain.35

Other additional research should focus on facilitators and barriers for deimplementing arthroscopic partial meniscectomy. Such studies might provide insight into why so many patients opt for delayed arthroscopic partial meniscectomy following physical therapy and identify deimplementation strategies that could be tested. For instance, a natural experiment among hospitals reported that a strict evidence-based policy on knee arthroscopy in patients aged 50 years can result in a 60% decrease of arthroscopies compared with a usual-care policy.36 Another successful deimplementation strategy is to regulate the public financial reimbursement of knee arthroscopies.37

Limitations

This study has limitations. First, during the 5-year follow-up, 52 patients (32%) from the physical therapy group underwent delayed arthroscopic partial meniscectomy—most patients (n = 44) within the first year of follow-up and only 5 patients within the last 3 years of the trial. These numbers demonstrate that not all patients experience satisfying results following physical therapy. Second, we did not register all patients' reasons for not responding to our questionnaire or radiograph invitation. We assume that the COVID-19 pandemic would be one of the reasons why people did not attend the 5-year follow-up. Nevertheless, our response rate was high (87%). Third, radiographic sensitivity for change in knee OA is lower compared with the sensitivity of magnetic resonance imaging, and therefore magnetic resonance imaging would be preferred over radiographic images.38 To minimize the patient burden and study costs, we obtained radiographic images instead of magnetic resonance imaging. However, we used validated measures for OA, radiographic findings were reported by a single radiologist, and we adhered to the study protocol. A second assessor would have reduced the potential risk of observer bias in our radiographic data. However, our pragmatic approach was chosen because the radiographic data were not part of our primary outcome. This approach reflects clinical practice, and blinding the assessor strengthened the comparison between treatments. Fourth, we did not register noninvasive additional treatments for knee pain. Fifth, there is a potential risk of selection bias due to some loss to follow-up. However, we performed randomization, our missing data were equally distributed over both treatment arms (19 physical therapy and 22 arthroscopic partial meniscectomy), and the mixed-model analysis takes missing data into account using maximum likelihood estimation. Therefore, we believe it is unlikely that the missing values affected our results. Sixth, the number of patients screened for eligibility was not available.

Conclusions

This RCT found that exercise-based physical therapy was not inferior to arthroscopic partial meniscectomy over a period of 5 years for self-reported knee function. We observed a small and comparable progression of knee OA in both groups. Findings from this trial further support the recommendation that exercise-based physical therapy should be the preferred treatment over surgery for degenerative meniscal tears.

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VI

Chapter 7

General Discussion

Key findings

This thesis contributes to the evidence based care of patients with a degenerative meniscus tear.
In patients with a degenerative meniscus tear the International Knee Documentation Committee Subjective Knee Form (IKDC) is a reliably and valid Patient Reported Outcome Measure (PROM) to evaluate patient reported knee function[30], and is also responsive to change (**Chapter 2**).[15] The interpretability of a PROM helps clinicians, researchers and policy makers to put the results from randomized clinical trials (RCT) into a clinically relevant perspective. We successfully determined the minimal important change (MIC) of two patient reported outcome measures, the IKDC (**Chapter 2**) and the Patient Specific Functioning Scale (PSFS) (Chapter 3).[13, 15] Based on the MIC of the PSFS, we found no clinically relevant difference between physical therapy and meniscus surgery when focusing on activities that the individual patients valued most (**Chapter 3**).[13]
In our RCT 28% (n=43 out of 153) of the patients in the physical therapy group underwent delayed meniscus surgery. For patients opting for meniscus surgery following initial physical therapy, a worse patient reported knee function, in combination with a better general health and lower education level are predictors for poor recovery (**Chapter 4**).[14] However, our prognostic models did not accurately predict which patients will undergo meniscus surgery following initial physical therapy. In line with other conventional prognostic models aiming to predict treatment outcome in patients with a meniscus tear, treatment cannot be based on these prognostic models.[8, 18] Therefore, we introduced a novel approach in musculoskeletal research by conducting a marker-by-treatment analysis (**Chapter 5**).[17] This analyses provides specific cut-off points for a single prognostic factor, such as a PROM or patient characteristic. These cut-off points help clinicians and patients to make an evidence based choice between two treatments, and choose the one with the most benefit for the individual patient. However, a patient cannot be defined by only one prognostic factor. Therefore, it can be important to combine multiple prognostic factors in one marker-by-treatment analysis before this can be applied to individual patients in clinical practice.
The treatment effect for patient reported knee function over a period of 5 years revealed that physical therapy remained non-inferior to meniscus surgery (**Chapter 6**).[16] Besides, based on the literature we hypothesized a faster progression of knee osteoarthritis (OA) in patients undergoing meniscus surgery, compared to physical therapy. Overall we found a small progression of knee OA that was comparable between both groups (**Chapter 6**).[16]

Comparison with literature

The current guidelines for degenerative meniscal tears recommend against meniscus surgery as initial treatment.[22] These treatment recommendations are based on RCT results. However, treatment effects measured within RCTs do not take the individual variation in treatment effect into account. Therefore, it is not always applicable to the individual patient.[9] This might explain why meniscus surgery is still widely performed in the Netherlands within this population.[20] Several studies attempted to determine specific subgroups of patients who will benefit more from meniscus surgery compared to physical therapy.[8, 18, 27] These studies use different research methods, such as a survey among international orthopedic surgeons[27], association models[8] and multivariable prediction models[18]. Nevertheless, results show that orthopedic surgeons could not reliably select patients who are expected to benefit from meniscus surgery.[27] And also statistical prognostic models, based on specific patient characteristics and combinations of patient characteristics could not accurately predict treatment outcome.[8, 18, 27] In line with these studies, our multivariable prediction model and marker-by-treatment analyses, can also not accurately make evidence-base treatment choices on patients' characteristics. Therefore the treatment should be based on the clinical guidelines.[14, 17]

Moreover, it seems that patients over-estimate the effect of meniscus surgery.[19] Adequate patients expectations of recovery time and participation in daily life activities are important because it is associated with requesting surgical treatments and it is related to the treatment outcome. Patients over 55 years, opting for meniscus surgery, expected shorter recovery times and higher levels of participation in leisure activities after surgery.[19] Setting realistic treatment expectations and goals can enhance the patient-reported treatment outcome.[12, 26] The PSFS is a PROM that evaluates patient specific activities.[2] Patients and clinicians can use this PROM to evaluate the treatment, based on the patients' most important activities in daily life. In our study we first calculated the MIC of the PSFS.[13] We found a MIC of 2 points, this can help clinicians to put treatment results in a clinically relevant perspective.[13] Second, in our study we found no clinically relevant difference between meniscus surgery and exercise-based physical therapy over a period of 2 years when evaluating the treatment using the patients' specific activities.[13] Physical therapists can use these most important activities in daily life when developing a patient-specific exercise program and evaluate treatment outcome.[26]

However, mostly RCTs evaluated treatment effect using patient reported knee function. A total of five RCTs on degenerative meniscus tears first reported the 2-year or 3-year follow-up results and later also their 5-year follow-up results.[1, 3-7, 10, 23-25] They all found that the improvement in patient-reported knee function over the first two or three years maintained at 5-year follow-up.[1, 5, 7, 23, 25] This is in line with the results of the ESCAPE trial.[16, 28] One of the major strengths of the ESCAPE trial, in comparison with the other five RCTs, is the non-inferiority design. We used the MIC of the IKDC (determined in chapter 2) to set the non-inferiority threshold in our 5-year follow-up analyses.[15] We investigated whether the between-group difference differed statically from the non-inferiority threshold. Analyses showed that the between-group difference and the upper limit of the 95% CI did not exceed the non-inferiority threshold. We therefore concluded that exercise-based physical therapy is statistically and clinically not inferior to meniscus surgery (see figure 1 in the introduction for an explanation on how to interpret non-inferiority results).[16]

Implementing our research results into clinical practice

Additional to this thesis, we developed and implemented a shared decision e-tool for degenerative meniscal tears. Healthcare professionals and patients can use the e-tool to enhance shared decision making. Shared treatment decisions between healthcare professionals and patients can lead to more patient empowerment, higher satisfaction and less surgeries.[11, 21]

This e-tool was developed with a multidisciplinary team consisting of a patient representative, orthopaedic surgeons, a general practitioner, physical therapists and researchers. It includes evidence based information on what meniscus surgery and non-surgical treatments, (i.e., exercise therapy, pain medication and weight lose) contains, the advantages and disadvantage of surgical and non-surgical treatments and expected treatment outcomes, based on the results of recently published RCTs. Besides, it includes questions about the patients' preferences and treatment expectations. The treating healthcare professional can use the information on patients preferences and expectations in establishing a shared treatment plan.[14]

In my opinion it is key to provide unambiguously information throughout the entire healthcare chain. Therefore, we implemented the e-tool in both primary and secondary care practices. Patients over 45 years old with knee complaints, who consulted one of the participating general practitioners, physical therapist or orthopedic physicians, received the shared-decision e-tool when a meniscal tear was expected after physical examination. Despite the healthcare provider, all patients now receive the same information in layman's terms. This enables patients to form an evidence-based opinion in choosing the best suitable treatment. In patients with a degenerative meniscal tear, I believe this can enhances effective evidence-based healthcare and reduce unnecessary meniscal surgeries.

Implications for clinical practice, future research and healthcare policy

Even though the evidence and clinical guidelines recommend against meniscus surgery, meniscus surgery is still fully reimbursed by the basic healthcare insurances, apart from an yearly individual contribution of €385,- for medical expenses. While in the Netherlands, physical therapy for meniscus tears is currently not financially reimbursed by the basic healthcare insurances. Therefore physical therapy is not equally accessible for every Dutch citizen. This may cause a delay in de-implementing meniscus surgery for degenerative meniscus tears. Future research should focus on finding facilitators and barriers to de-implement meniscus surgeries. These facilitators and barriers can then be used to develop specific de-implementation strategies. Further de-implementing meniscus surgeries results in evidence-based, and value-based healthcare. The trial-based economic evaluation of the ESCAPE trial, published in 2019, found that not only the medical costs but also the societal costs of physical therapy are non-inferior to those of meniscus surgery.[30] Besides the budget impact analysis shows that reducing meniscus surgery by 50% in patients with a degenerative meniscus tear in the Netherlands will reduce the total societal costs by € 92.5 million over a period of 5 years. Therefore, exercise-based physical therapy should be the preferred treatment in patients with a degenerative meniscus tear.

But first, physiotherapy should be equally accessible to every Dutch citizen. Dutch policy makers claim that the current evidence is not convincing enough to expand the current basic health insurance with physical- and exercise therapy. The question is whether the current insurance policy keeps patients from choosing nonsurgical interventions over surgical interventions? In my opinion, this is the case. The findings reported in this thesis can be used by policy makers to determine effectiveness of physical therapy for degenerative meniscal tears and possible consequences for the healthcare insurance claim.

Furthermore, future research can concentrate on interventions tailored to the patients specific needs. The current published RCTs comparing meniscus surgery with exercise-based physical therapy used a general, one-size-fits-all, exercise protocol. [3, 4, 6, 10, 32] The general exercise programs do not take the individual, social and environmental factors in daily life into consideration. Future studies should investigate the effectiveness and cost-effectiveness of personalized exercise-based physical therapy compared to a wait-and-see policy or compare a home-based e-health exercise to a physical therapist-led exercise program. An exercise program tailored to the individual needs of a patient in daily life, work and leisure activities can further enhance treatment outcome and patient satisfaction. Investigating the impact of physical therapy on the patients' functioning in daily life and in societal context will lead to more high quality evidence which policymakers can use in their rationale on evidence-based physical therapy towards politics and health insurances.

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Chapter 8

Summary of this Thesis
&
Nederlandse samenvatting
(Dutch summary)

What we already know

- It is important to use patient reported outcome measures (PROMs) with adequate measurement properties when evaluating treatment effects.
- Randomised clinical trials show no clinically relevant difference between meniscus surgery and exercise-based physical therapy in patients with degenerative meniscus tears over a period of 2 years.
- Despite exercise-based physical therapy being the recommended treatment, meniscus surgery is still widely performed.
- In clinical trials between 1.9 and 36% of patients randomized to physical therapy still opt for meniscus surgery following conservative management.
- Surgeons cannot identify which patients will benefit from meniscus surgery based on their characteristics at baseline.

What we found

- The International Knee Documentation Committee Subjective Knee Form (IKDC) is responsive to change among patients aged 45 to 70 years with meniscus tears, with a Minimal Important Change (MIC) of 10.9 points (**chapter 2**).
- The lack of clinically important difference between meniscus surgery and exercise-based physical therapy also applies to a PROM based on specific activities that individual patients value most (**chapter 3**).
- Patients who opt for meniscus surgery following exercise-based physical therapy (non-responders) could not accurately be predicted by thoroughly designed multivariable prognostic models (**chapter 4**).
- With our novel approach in orthopedic research we evaluated treatment selection markers, which appeared not helpful for guiding treatment choices (**chapter 5**).
- The lack of clinically relevant differences in patient reported and radiographic outcomes between physical therapy and surgery in patients with a degenerative meniscus tear is consistent over 5 years of follow-up (**chapter 6**).

Implications for future research

- Barriers and facilitators for further de-implementation of arthroscopic partial meniscectomy for degenerative meniscal tears should be explored.
- Effectiveness of exercise-based physical therapy tailored to the patients' specific needs compared to a wait-and-see policy is needed to further investigate the effectiveness of exercise-based physical therapy.

Summary of this thesis

This thesis is an in-depth analysis and continuation of the ESCAPE trial, aiming to advance evidence-based practice for patients with degenerative meniscus tears. The ESCAPE trial is a non-inferiority randomized clinical trial comparing meniscus surgery with exercised-based physical therapy in patients with a degenerative meniscus tear.[9, 10] We included 321 patients, aged 45 to 70 years, with a degenerative meniscus tear.[9] The primary outcome was patient reported knee function, assessed using the IKDC.[9, 10] Secondary patient reported outcomes were general health, pain in rest, pain during activities, patient specific activities and quality of life.[10] We collected the patient reported data at baseline, 3 months, 6 months, 1 year, 2 years and 5 years after randomization. Additional secondary outcomes were knee osteoarthritis assessed by radiographs at baseline, 2 years and 5 years. After two years of follow up, the ESCAPE trial found no significantly and clinically important difference on patient reported knee function between the two treatments.[9]
Important measurement properties of health related outcome measures to evaluate and interpret treatment outcome are the responsiveness and the minimal important change (MIC).[1, 2] The IKDC is a reliable and valid instrument for measuring patient-reported knee-specific symptoms, functioning, and sports activities in a population with meniscus tears.[11] However, evidence on responsiveness is of limited methodological quality, and the MIC has not yet been established for patients with symptomatic meniscus tears. Therefore, in **Chapter two** [6] we evaluated the responsiveness and determine the MIC of the IKDC for patients with meniscus tears. Responsiveness was evaluated by testing ten predefined hypotheses about the relation of the change in IKDC with regard to the change in the secondary patient-reported outcomes. An external anchor question was used to distinguish patients reporting improvement versus no change in daily functioning. The MIC was determined by the optimal cutoff point in the receiver operating characteristic curve, which quantifies the IKDC score that best discriminated between patients with and without improvement in daily function. Data from all 298 patients who completed baseline and 6-month follow-up questionnaires were analyzed. Responsiveness of the IKDC was confirmed in 7 of 10 predefined hypotheses about the change in IKDC score with regard to other patient reported outcome measures. This study showed that the IKDC is responsive to change among patients aged 45 to 70 years with meniscus tears, with an MIC of 11 points. This strengthens the value of the IKDC in quantifying treatment effects in this population.
Patient-specific activities have not yet been considered as part of the evaluation of treatment effects in those with a meniscus tear. In **chapter three** [4] we compared meniscus surgery with exercise-based physical therapy in patients with a degenerative meniscus tear, focusing on patients' most important functional limitations as the outcome. We obtained the Patient Specific Functioning Scale (PSFS) questionnaire at baseline, 3, 6, 12 months and 2 years. Patients selected their three most important activities from a list of 28 and rated the experienced difficulty for each activity on a numeric rating scale from 0 (no difficulty) to 10 (impossible to perform). We calculated which activities in daily life patients were most often limited and therefore wanted to improve. PSFS scores were calculated as the mean difficulty scores of the three selected activities per patient. We used crude and adjusted linear mixed-model

analyses to reveal the between-group differences over 2 years. We also calculated the MIC for the PSFS using an anchor-based method. This resulted in a MIC of 2.5 points for our study population. At the 2 year follow-up, 286 patients (surgery=139, physical therapy =147) completed the PSFS, resulting in a response rate of 89%. The most frequently chosen activities in both groups were: sports, walking , running, and standing for a long time. Both groups had a mean PSFS score of 6.7 at baseline and improved significantly over the 2 year follow-up period, the surgery group showed an improvement of 4.8 ± 2.6 points and the physical therapy group improved by 4.0 ± 3.1 points. The crude overall between-group difference showed a difference of 0.6 point (95% CI, –1.0 to –0.2; p = .004) between both groups. Although statistically significant, this difference between meniscus surgery and physical therapy in terms of patients specific activities is not clinically meaningful.

In the current guidelines exercise-based physical therapy is the recommended treatment in patients over 45 years old with a degenerative meniscus tear. However, between 1.9 and 36% of the patients randomized to physical therapy still opt for meniscus surgery. In **chapter four** [5] the aim was to identify those patients with a degenerative meniscus tear who still undergo surgery after random allocation to exercise-based physical therapy. At 6 and 24 months patients who were initially randomly allocated to physical therapy were divided into two groups: those who did not undergo meniscus surgery, and those who did. Two multivariable prognostic models were developed using candidate predictors that were selected from the list of the baseline patient characteristics. A multivariable logistic regression analysis was performed with backward Wald selection and a cut-off of $p < 0.157$.[3] For both models the performance was assessed and corrected for the models' optimism through an internal validation using a bootstrapping technique with 500 repetitions. We found that 32 out of 153 patients (20.9%) underwent meniscus surgery following physical therapy within 6 months and 43 out of 153 patients (28.1%) underwent meniscus surgery following physical therapy within 24 months. Based on the multivariable regression analysis, patients were more likely to opt for meniscus surgery within 6 months when they had worse knee function, lower education level and a better general physical health status at baseline. At 24 months, patients were more likely to opt for meniscus surgery when they had worse knee function and a lower level of education at baseline. Both models had a low explained variance (16% and 11%, respectively) and a poor discriminative ability. The non-responders to physical therapy could not accurately be predicted by our prognostic models.

To select the best treatment (i.e. meniscus surgery or exercise-based physical therapy) for an individual patient it is important to quantify the expected benefit of one treatment over the other. In **chapter 5** [8] we introduced a novel approach in orthopedic research to identify relevant treatment selection markers that may affect treatment outcome in patients with degenerative meniscus tears. The treatment outcome of interest was whether patients improved more than 10.9 (the MIC determined in chapter 2) on the IKDC at 3, 12 and 24 months follow-up. First, we developed logistic regression models to predict the outcome using baseline characteristics (markers), the treatment (meniscus surgery or physical therapy), and a marker-by-treatment interaction term. We considered interactions with $p<0.10$ as potential treatment selection markers. We used these to develop predictiveness curves which provide thresholds to identify marker-based differences in clinical outcomes between the two treatments. We found that general physical health, pain during activities, knee function, BMI and age were potential treatment selection markers. While some marker-based thresholds could be identified at 3, 12 and 24 months follow-up, none of the baseline characteristics were consistent markers at all three follow-up times. This novel in-depth analysis did not result in clear clinical subgroups of patients who are substantially more likely to benefit from either surgery or physical therapy.

Finally, in **chapter 6** [7] we compared longer term (i.e., 5-years) effectiveness of meniscus surgery and exercise-based physical therapy on patient reported knee function and progression of knee osteoarthritis in patients with a degenerative meniscus tear. We assessed patient-reported knee function on the IKDC over 5 years follow-up based on the intention-to-treat principle, with a non-inferiority threshold of 11 points (based on the MIC determined in chapter 2). Out of the 321 included patients, 278 (87.1%) completed the 5-year follow-up. The mean (SD) improvement was 29.6 (18.7) points in the surgery group and 25.1 (17.8) points in the exercised-based physical therapy group. The between-group difference was 2.8 points (95%CI: -0.9 to 6.5; p-value for non-inferiority <0.001) and the confidence interval did not cross the non-inferiority threshold of 11 points. Exercise-based physical therapy resulted in non-inferior patient-reported knee function, and therefore should be the preferred treatment over surgery for degenerative meniscus tears.

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Nederlandse samenvatting van het proefschrift

Een degeneratieve meniscusscheur is een meniscusscheur die vaak geleidelijk aan ontstaat. Naarmate we ouder worden kan de meniscus minder elastisch worden waardoor het makkelijker kan scheuren. Dit noemen we een degeneratieve meniscusscheur.
Bij mensen met een degeneratieve meniscusscheur was een kijkoperatie van de knie, waarbij het gescheurde deel van het meniscus weg word gehaald (vanaf nu: meniscusoperatie), de standaardbehandeling. Meerdere onderzoeken van het hoogste wetenschappelijk niveau (gerandomiseerde klinische studies) hebben in de afgelopen jaren aangetoond dat een meniscusoperatie ten opzichte van een fysiotherapeutische behandeling geen relevant verschil geeft in de behandeluitkomsten. Deze onderzoeken samen gaven aanleiding om de richtlijnen waarop zorgverleners hun behandeling baseren aan te passen. De huidige richtlijn voor een degeneratieve meniscusscheur stelt dat er als eerste behandeloptie niet voor een meniscusoperatie moet worden gekozen. Maar in de praktijk worden er toch nog veel meniscusoperaties uitgevoerd. Een mogelijke verklaring hiervoor is dat onderzoeksresultaten op groepsniveau niet altijd toepasbaar zijn op een individuele patiënt in de praktijk. Daarnaast waren ook de behandeluitkomsten op de langere termijn (na 5 jaar) nog niet bekend.
De ESCAPE-studie vormt de basis voor de totstandkoming van mijn proefschrift. Met de ESCAPE-studie is onderzocht of fysiotherapie niet minder effectief is dan een meniscusoperatie bij patiënten tussen de 45 en 70 jaar met een degeneratieve meniscusscheur. Het onderzoek is uitgevoerd tussen 2013 en 2020 in 9 Nederlandse ziekenhuizen. Deelnemende patiënten werden willekeurig verdeeld (dit word randomisatie genoemd) tussen fysiotherapie (oefenprogramma van 16 sessies onder leiding van een fysiotherapeut) of een meniscusoperatie. In totaal hebben 321 patiënt meegedaan aan het onderzoek, de meniscusoperatiegroep bevat 159 patiënten en de fysiotherapiegroep bevat 162 patiënten. De belangrijkste uitkomstmaat van het onderzoek is de patiënt gerapporteerde uitkomst voor kniefunctie die wordt gemeten met de IKDC-vragenlijst. Dit is een betrouwbaar meetinstrument voor het meten van patiënt gerapporteerde kniefunctie. De score van de IKDC loopt van 0 (zeer slechte kniefunctie) tot 100 (zeer goede kniefunctie).
Het was nog onduidelijk of de IKDC-vragenlijst ook daadwerkelijk een relevante verbetering in kniefunctie kan meten. Ook het aantal punten dat een patiënt moet verbeteren op de vragenlijst om het als ‘echte’ verbetering te ervaren was onbekend. Dit zijn belangrijke eigenschappen van een meetinstrument voor het interpreteren van behandel- en onderzoeksuitkomsten. In **hoofdstuk 2** zijn de responsiviteit van de IKDC en het minimale relevante verschil (Minimal Important Change, MIC) onderzocht. Responsiviteit is het vermogen van de IKDC om een relevante verandering te meten voor de patiënt gerapporteerde kniefunctie. Het minimale relevante verschil is het aantal punten verbetering op de IKDC waarna wordt verwacht dat een patiënt ook daadwerkelijk een verbetering in kniefunctie ervaart. Dit onderzoek toont aan dat de IKDC een relevante verandering over de tijd kan meten, en dus responsief is voor de patiënt gerapporteerde kniefunctie. Daarnaast toont het onderzoek aan dat een verbetering van tenminste 10.9 punten op de IKDC door de patiënt als verbetering van de kniefunctie wordt ervaren.
In **hoofdstuk 3** wordt de meniscusoperatiegroep vergeleken met de fysiotherapiegroep op

basis van de activiteiten die voor individuele patiënten belangrijk zijn in het dagelijks leven (een secundaire uitkomstmaat van de ESCAPE-studie. We gebruiken hiervoor het meetinstrument patiënt specifieke klachten (PSK). Dit meetinstrument wordt vaak gebruikt om fysiotherapeutische zorg te evalueren in de praktijk maar is nog niet eerder gebruikt in meniscusonderzoek. Het geeft inzicht in de mate van klachten die de patiënt ervaart bij het uitvoeren van activiteiten die voor hem of haar belangrijk zijn in het dagelijks leven. Patiënten kiezen 3 activiteiten, zoals wandelen, sporten, traplopen etc., en geven aan elke activiteit een score van 0 (geen moeite met de activiteit) tot 10 (erg veel moeite met de activiteit). Patiënten hebben de PSK ingevuld voor de behandeling na 3, 6 maanden 1 en 2 jaar. Dezelfde 3 activiteiten die voor de behandeling werden gekozen kwamen terug bij de vervolg meetmomenten. Voordat de twee groepen met elkaar zijn vergeleken is eerst de minimale relevante verandering van de PSK voor onze doelgroep bepaald. Bij een verbetering van 2.5 punt ervaart de patiënt ook daadwerkelijk verbetering in het uitvoeren van de activiteit. De meest gekozen activiteiten in beide groepen waren: sporten, lopen, hardlopen en langdurig staan. Voorafgaand aan de behandeling hadden beide groepen een PSK score van 6.7 punten. Twee jaar na de behandeling zagen we een gemiddelde verbetering van 4.8 (standaard deviatie [SD] ± 2.6) punten bij de meniscusoperatiegroep en van 4.0 (SD ± 3.1) punten bij de fysiotherapie groep. Het verschil tussen de groepen, bepaald doormiddel van statistische analyse waarin alle tussenliggende meetmomenten zijn meegenomen, is 0.6 punten (95% betrouwbaarheidsinterval –1.0 tot –0.2; p = .004) in het voordeel van de meniscusoperatie groep. Rekening houdend met het minimale belangrijke verschil van 2.5 punten op de PSK, concluderen wij dat er geen klinisch relevant verschil bestaat tussen fysiotherapie en een meniscusoperatie voor patiënt specifieke activiteiten.

Echter, in eerdere wetenschappelijke onderzoeken die een meniscusoperatie vergelijken met fysiotherapie zien we dat een deel van de patiënten (verschillend van 1.9% tot 36%) die fysiotherapie kregen daarna alsnog geopereerd worden. **Hoofdstuk 4** gaat in op de vraag of voorafgaand aan de behandeling kan worden voorspeld welke patiënten na een fysiotherapiebehandeling alsnog een meniscusoperatie zullen ondergaan. De onderzoeksdata van de ESCAPE-studie zijn gebruikt om twee statische voorspelmodellen te ontwikkelen. Eén voor de uitkomst na 6 maanden en één voor de uitkomst na 2 jaar. Deze voorspelmodellen bepalen op basis van een combinatie van patiëntkarakteristieken de kans dat een patiënt alsnog een meniscusoperatie ondergaat na de fysiotherapiebehandeling. Daarnaast bepaalde we of de voorspelling nauwkeurig genoeg is om het in de praktijk toe te kunnen passen. Gebruikte patiëntkarakteristieken waren: leeftijd, geslacht, body mass index (BMI), opleidingsniveau, mate van pijn voor de behandeling, kniefunctie voor de behandeling, algemene fysieke gezondheid, de patiënt verwachting, mate van knie artrose en de locatie van de meniscusscheur. In de ESCAPE-studie zijn binnen 6 maanden 32 van de 153 patiënten (20.9%) in de fysiotherapiegroep alsnog geopereerd. Het voorspelmodel laat zien dat patiënten met een slechte kniefunctie, een laag opleidingsniveau en een betere fysieke gezondheid een grotere kans hadden om binnen 6 maanden alsnog geopereerd te worden. Na 2 jaar zijn 43 van de 153 (28.1%) patiënten uit de fysiotherapiegroep alsnog geopereerd. Het voorspelmodel toont aan dat patiënten met een laag opleidingsniveau en een slechte kniefunctie een grotere kans hebben om binnen 2 jaar alsnog een operatie te ondergaan na fysiotherapie. De nau-

wkeurigheid van beide modellen is matig. Op basis van deze twee voorspelmodellen kunnen we voorafgaand aan de fysiotherapiebehandeling niet met genoeg zekerheid voorspellen of een patiënt alsnog een meniscusoperatie zal ondergaan. We raden het daarom niet aan om deze twee voorspelmodellen in de praktijk te gebruiken.
Om in te schatten bij welke behandeling (fysiotherapie of een meniscusoperatie) een patiënt het meeste baat heeft, wordt er in **hoofdstuk 5** een nieuwe analyse in orthopedisch onderzoek geïntroduceerd. Een zogenaamde selectiemarker analyse. Selectiemarker analyses kunnen, op basis van patiënteigenschappen, bepalen welke behandeling de beste uitkomst geeft voor de individuele patiënt. We hebben gekeken welke selectiemarkers invloed hebben op de behandeluitkomst van patiënten met een degeneratieve meniscusscheur. Hiermee zouden we specifieke behandelkeuzes kunnen maken gebaseerd op de eigenschappen van de individuele patiënt. Voor de uitkomstmaat kniefunctie op 3 maanden, 1 en 2 jaar hebben we met behulp van statistische analyse relevante selectiemarkers geselecteerd. Voor deze relevante selectiemarkers zijn voorspelgrafieken gemaakt die het verschil tussen de twee behandelingen voorspellen. Relevante selectiemarkers voor de behandeluitkomst op 3 maanden zijn fysieke gezondheid, pijn en kniefunctie. Op 1 jaar zijn dit BMI en leeftijd, en op 2 jaar is leeftijd een relevante selectiemarker. De voorspelgrafieken van 3 maanden laten zien dat patiënten met een matige tot goede fysieke gezondheid (afkappunt ≥40.7 punten, range 0-100) meer baat hebben van fysiotherapie. Patiënten met een gemiddeld tot hoge pijnscore (afkappunt ≥53.9 punten, range 0-100) of een gemiddeld tot goede kniefunctie (afkappunt ≥50.6 punten, range 0-100) zouden meer baat hebben bij een meniscusoperatie. Echter, op langere lange termijn houden deze uitkomsten geen stand. Ondanks duidelijke afkappunten voor drie selectiemarkers, geeft deze methodiek met selectiemarkers geen aanleiding om voor individuele patiënten af te wijken van de huidige richtlijnen. De beste behandeling voor de individuele patiënt blijft lastig te voorspellen, ook met de selectiemarker analyse.
Als laatste zijn in **hoofdstuk 6** de behandeluitkomsten van fysiotherapie en een meniscusoperatie na 5 jaar met elkaar vergeleken. Om te bepalen of fysiotherapie niet minder effectief is dan een meniscusoperatie hanteren we een drempelwaarde van 11 punten op de hoofduitkomstmaat kniefunctie. Deze drempelwaarde is gebaseerd op de minimale relevante verandering die we in hoofdstuk 2 hebben bepaald. Van de 321 patiënten die aan de ESCAPE studie mee doen hebben in totaal 278 (87%) patiënten de dataverzameling na 5 jaar voltooid. Op de hoofduitkomstmaat kniefunctie verbeterde de meniscusoperatiegroep 30.0 punten (van 44.7 ±16.6 naar 74.7 ±18.4) en de fysiotherapiegroep verbeterde 26.6 punten (van 46.5 ±14.6 naar 73.1 ±17.7). Na 5 jaar toonde de statistische analyse een verschil tussen de groepen aan van 2.8 punten (95% CI -0.9 - 6.5; p-waarde voor noninferiority <.001) in het voordeel van de meniscusoperatie groep. Statistische analyse toont aan dat dit kleine verschil significant kleiner is dan de drempelwaarde van 11 punten. Hieruit concluderen wij dat fysiotherapie niet minder effectief is dan een meniscusoperatie voor patiënten met een niet-obstructieve degeneratieve meniscusscheur.

De conclusie van dit proefschrift luidt:
Een fysiotherapeutische behandeling heeft de voorkeur boven een meniscusoperatie bij patiënten met een degeneratieve meniscusscheur die geen slotklachten ervaren.

Chapter 9

Appendices

List of abbreviations

ACL	Anterior cruciate ligament
APM	Arthroscopic Partial Meniscectomy
AUC	Area Under the Curve
BMI	Body Mass Index
CI	Confidence interval
COSMIN	Consensus-Based Standards for the Selection of Health Measurements Instruments
EQ-5D-5L	EuroQol–5 Dimension–5 Level
EQ-5D-VAS	EuroQol–5 dimension-Visual Analog Scale
ESCAPE	Cost-effectiveness of early surgery versus conservative treatment with optional delayed meniscectomy for patients over 45 years with non-obstructive meniscal tears
H&L	Hosmer and Lemeshow
IKDC	International Knee Documentation Committee Subjective Knee Form
ISCED	International Standard Classification of Education
KL	Kellgren and Lawrence scale
KOOS	Knee injury and Osteoarthritis Outcome Score
KOOS-PS	Knee Osteoarthritis Outcome Score-Physical functioning Short from
MCS	Mental Component Scale
MEC-U	Medical Ethical Committee - United
MIC	minimal important change
MRI	magnetic resonance imaging
n.s.	not significant
NA	Not available
NRS	numeric rating scale
OA	osteoarthritis
OARSI	Osteoarthritis Research Society International
OR	Odds Ratio
PASS	Patiënt acceptable symptom state
PCS	Physical Component Scale
PROMs	patient-reported outcome measures
PSFS	Patient-Specific Functional Scale
PT	Physical therapy
RAND-36	36-Item Health Survey
RCT	randomized clinical trials
ROC	Receiver operating characteristic
SD	Standard deviation
SDC	smallest detectable change
TRIPOD	Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis
VAS	Visual Analog Scale
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
WOMET	Western Ontario Meniscal Evaluation Tool

Appendix 1

Physical therapy exercise program

Time (week)	Exercises	Repetitions or time
0-8	Stationary cycling for warming up and cooling down or cardiovasculair training	15 min or longer gradually increase intensity
0-8	Pully or dynaband, strapped around ankle uninjured side. Stand on injured side and keep balance, Step with uninjured side forward, backwards and sideways	3x12 reps each direction
0-4	Calf raises on a leg press machine	3x12 reps
0-8	Hamstrings: standing hip extension in a "multi-hip" trainings device	3x12 reps
0-4	Keeping balance on a balance board, use both feet	
0-8	Climbing stair , walking, acceleration, running, Jumping. According to the patients activity level	10 min
5-8	Calf raises standing on one leg 3x12 reps	
1-8	Leg press, place feet high enough for the shinbones to become in a horizontal plane and the knee starting at 110˚ flexion, unilateral	3x12 reps
5-8	Squats (according the needs of the patient) In which a knee flexion > 90° is not allowed	3x12 reps
5-8	Balance board on one foot challenge with throwing a ball	3 min
5-8	Elliptical machine for warming up and cooling down or cardiovascular training	10 min or longer

The exercise program contained 16 supervised sessions during 8 weeks

For all exercises is it important to keep the patients individual needs and limitations focused by using the ICF. The uninjured side is also less trained as usual and therefore both sides should be trained.

Besides training of the lower extremity, "core stability" training is of importance for good posture positioning and moving. The active rehabilitation program is designed around cardiovascular (circulation), coordination and balance, and closed chain strength exercises.

Shearing forces in the knee are less using closed chain exercises compared to open chained exercises. The closed chain exercises activate both agonists and antagonists around the knee joint resulting in a direct rotatory movement and prevent in shearing forces seen by open chained exercises.

Home exercise program

In addition, a home exercise program was provided to all participants. It consisted of one leg standing during 60 seconds and a step-down exercise comprising 3, 9, 10 repetitions, twice a week.

Appendix 2

Patient inclusion and follow up

321 patients randomly assigned to intervention groups

Arthroscopic partial meniscectomy	Physical therapy
159 Arthroscopic partial meniscectomy	162 Physical therapy
158 completed baseline questionnaire	161 completed baseline questionnaire
151 completed 6 months questionnaire	147 completed 6 months questionnaire

Appendix 3

Minimal Important Change of the PSFS

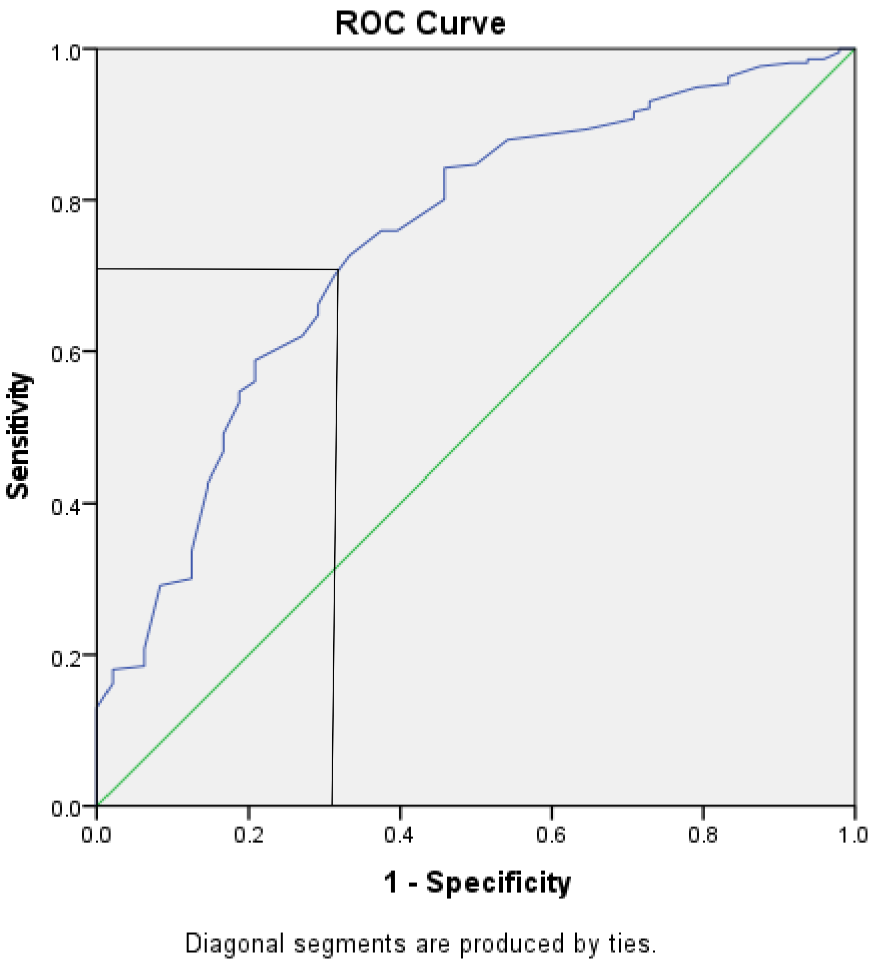
Method

The minimal important change (MIC) is defined as the smallest change in PSFS score that patients perceive as a beneficial change. We determined the MIC value using an anchor-based method as it uses a external criterion to determine what patients consider important. The external anchor question that we used reads as follows: "How did your function in daily activities change since the surgery/treatment of your knee?". Patients answered the question on a 7-likert scale range from: my function was very much improved, much improved, slightly improved, neutral, slightly deteriorated, much deteriorated, very much deteriorated. Before calculating the MIC we first analyzed the correlation between the changes in PSC scores and the external anchor question. Next, if this correlation was above 0.5, the study population was divided into changed and unchanged, based on the external anchor question. The changed group were patients who reported to be very much, much, and slightly improved. The unchanged group were patients who reported to be unchanged. We excluded patients who reported very much, much or slight deterioration in daily functioning since we are comparing patients with important improvement versus patients without important improvement.

We used the Receiver Operating Characteristic curve (ROC) method because it searches for the optimal cut-off points, irrespective of how much misclassification occurs. A graphic display of the ROC-curve was plotted. We then determined the sensitivity and specificity for all potential cut-off points and determined the MIC value by the most optimal cutoff point; i.e. with the smallest value of the sum of the proportions of misclassifications {[1 – sensitivity] + [1 – specificity]}. In other words, the MIC was quantified by the PSFS score that best discriminated between patients with and without clinically relevant improvement.

Results

The correlation between the changed PSFS score and the anchor question was 0.5. We then devided the population between changed (n=216) and unchanged(n=48). The ROC-curve has en area under the curve of 0.744, the graph is diplayed below.



We determined the optimal cutoff at a sensitivity value of 72.7% and a specificity of 66.7%, resulting in a MIC of 2.5 points on the PSC (ranging from 0-10 points).

Appendix 4

Frequencies and percentages of all activities

	Total		Surgery		Physiotherapy	
Activity	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage
Sports	114	12,4	60	12.9	54	11.9
Walking	95	10,3	49	10.6	46	10.1
Running	90	9,8	50	10.8	40	8.8
Standing for a long time	77	8,4	37	8.0	40	8.8
Rising up from a chair	68	7,4	37	8.0	31	6.8
Turning over in bed	55	6,0	23	5.0	32	7.0
Getting in/out of a car	53	5,8	23	5.0	30	6.6
Lying in bed	51	5,5	32	6.9	19	4.2
Cycling	45	4,9	26	5.6	19	4.2
Heavy labour in and outside your home	45	4,9	21	4.5	24	5.3
Sitting for long periods	28	3,0	15	3.2	13	2.9
Carrying out your job	28	3,0	18	3.9	10	2.2
Picking-up an object from the floor	27	2,9	11	2.4	16	3.5
Rising up from bed	26	2,8	10	2.10	16	3.5
Driving a car or bus	25	2,7	12	2.6	13	2.9
Carrying out hobbies	18	2,0	9	1.9	9	2.0
Carring out household labour	14	1,5	5	1.1	9	2.0
Other activities	13	1,4	7	1.5	6	1.3
Traveling	11	1,2	3	0.6	8	1.8
Standing	10	1,1	2	0.4	8	1.8
Light labour in and outside your home	8	0,9	4	0.9	4	0.9
Lifting	6	0,7	1	0.2	5	1.1
Sexual activities	3	0,3	3	0.6	0	0
Sitting on a chair	2	0,2	1	0.2	1	0.2
Walking around the house	2	0,2	1	0.2	1	0.2
Carrying an object	2	0,2	2	0.4	0	0
Going out	2	0,2	1	0.2	1	0.2
Visiting friends and family	1	0,1	1	0.2	0	0

Appendix 5

Detail description of selecting candidate predictors

From an extensive list of baseline variables assessed within the ESCAPE trial we selected candidate predictors using a combination of three methods. First, we conducted a literature search to identify factors associated with the outcome for physical therapy in patients with a meniscal tear.
To identify studies on prognostic factors, a search strategy was developed with the assistance of an independent librarian. We searched the database of PubMed in March 2019. Two researchers (JCAN and MT) independently selected the studies that identified factors associated with treatment outcome in patients with meniscal tears. We included a study for our candidate predictor selection if one of the researchers selected the article based on the title and abstract containing information on predictive factors for the outcome of physical therapy for patients with a meniscal tear. Both researchers then read the full text article and excluded studies that reported on a different study population or that did not report any predictive factors for the treatment outcome of physical therapy. The selected studies were evaluated on the level of evidence by the Grading of Recommendations, Assessment, Development and Evaluations (GRADE). Finally, we identified all possible predictors from the selected studies that were also measured within the ESCAPE trial.

Search strategy:
Search (((("Meniscus"[Mesh] OR menisc*[tiab]) AND (tear*[tiab] OR injur*[tiab] OR lesion*[tiab] OR rupture*[tiab])) AND ("Conservative Treatment"[Mesh] OR "Rehabilitation"[Mesh] OR "Physical Therapy Modalities"[Mesh] OR "Physical Therapy Department, Hospital"[Mesh] OR "Exercise"[Mesh] OR "Exercise Movement Techniques"[Mesh] OR "Exercise Therapy"[Mesh] OR "Physical Therapy (Specialty)"[MeSH] OR rehabilitati*[tiab] OR physiotherap*[tiab] OR ((physical[tiab] OR conservative[tiab]) AND (therapy[tiab] OR therapies[tiab] OR activity[tiab] OR activities[tiab] OR treatment*[tiab] OR management*[tiab])) OR exercis*[tiab] OR training*[tiab]) AND ("Epidemiologic Studies"[Mesh] OR cohort[tiab] OR (case[tiab] AND (control[tiab] OR controll*[tiab] OR comparison[tiab] OR referent[tiab])) OR risk[tiab] OR causation[tiab] OR causal[tiab] OR "odds ratio"[tiab] OR etiol*[tiab] OR aetiol*[tiab] OR "natural history"[tiab] OR predict*[tiab] OR prognos*[tiab] OR outcome[tiab] OR course[tiab] OR retrospect*[tiab]))) AND ((("Patient Satisfaction"[Mesh] OR patient satisfaction[tiab] OR satisfaction[tiab])) OR (cross over) OR (IKDC[tiab] OR outcome*[tiab] OR KOOS[tiab] OR WOMAC[tiab]))

Second, we sent an electronic survey to the orthopaedic surgeons (n=24) and physical therapists (n=22) who were involved in the ESCAPE trial. We gave the respondents 4 weeks, in which we sent 3 reminders, to respond to our survey. A total of 12 orthopaedic surgeons (50%) and 5 physical therapists (23%) completed the survey. Additionally, 10 patients from the ESCAPE trial completed the survey by phone with the assistance of a researcher (MT) to clarify medical jargon.
The survey contained all baseline variables measured in the ESCAPE trial. The respondents received written instructions to select all clinically relevant prognostic factors for the treatment outcome, in their opinion. We then ranked the list of predictors by percentage and se-

lected the 10 most chosen prognostic factors.
Third, we conducted an univariate logistic regression analysis preselection. We considered a predictor as significant with a p-value of 0.05 or lower. The principle researchers of this study (JCAN, VAG, NWW and RWP) made a final selection of 10 potential predictors.

Appendix 6

Table of candidate predictors and selection procedure

	Selection procedure of candidate predictor			
Candidate Predictor	Literature[a]	Expert panel survey[b]	Univariate analysis[c]	Principle researchers' ranking of predictors[d]
Knee function*	Yes[2-4]	56%	P<0.01	1
Education level*	No	56%	P<0.01	2
General physical health*	Yes[5]	42%	P=0.09	3
Body Mass Index**	Yes[6]	85%	P=0.20	4
Pain during activities	Yes[6]	78%	P<0.01	5
Knee arthrosis	Yes[7]	46%	P<0.68	6
Knee effusion	No	63%	P=0.57	7
Age	No	56%	P=0.96	8
Patient's expectation	No	-	P=0.09	9
Mechanical complaints	No	-	P=0.36	10

* These candidate predictors were included in the initial multivariable prognostic model at 6 months

** BMI was added to the selected candidate predictors in the initial multivariable prognostic model at 24 months

a Identification of candidate predictors from the current literature on factors for prognosis of physical therapy in patients with a meniscal tear.

b Identification of relevant prognostic factors by the expert panel of orthopaedic surgeons, physical therapists and patients, thru an online survey. The numbers indicate the percentages of the expert panel that selected the variable as relevant predictor for the prognosis of physical therapy in patients with a meniscal tear.

c Univariate logistic regression analysis was conducted to included additional prognostic factors. $P \leq 0.05$ was considered significant.

d The principle researchers of this study made a final ranking of 10 potential predictors based on whether the prognostic factor could be influenced by physical therapy, clinical relevance, the applicability in the clinical setting and aiming to cover all components of the biopsychosocial model.

IX

Appendix 7

List of variables measured in the ESCAPE trial

Patients' demographics
- Age*
- Sex
- BMI*
- education level*
- Smoking status
- Employment

Physical examination
- McMurray test
- Range of motion
- Joint effusion
- Duck walk test
- Thessaly test
- Pain at full flexion
- Pain at full extension
- Jointline tenderness
- Circumference Femur

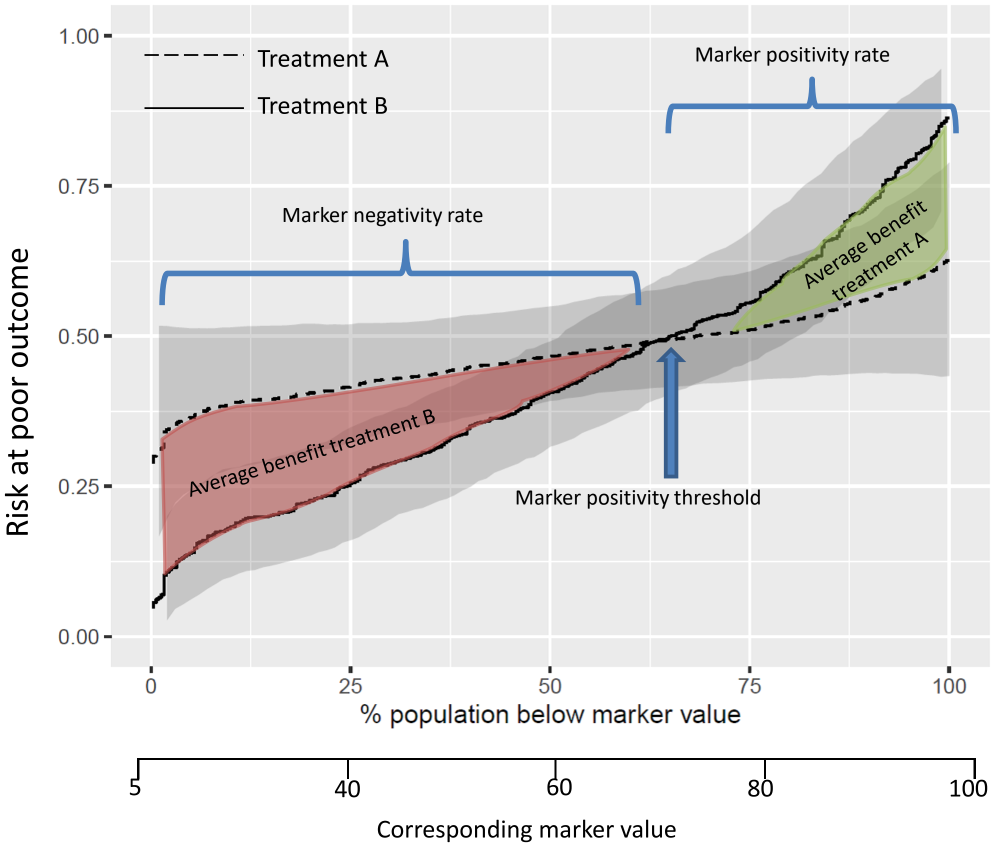
Radiographic information (X-ray and MRI
- Grade of osteoarthritis of the knee*
- Rupture of Anterior cruciate ligament in medical history
- Presence of bakers' cyct

Patient reported outcome measures
- Patient specific functioning scale
- RAND-36 for general health*
- Tegner activity scale
- International Knee Documentation Committee Subjective Knee Form (IKDC) for knee function*
- Euroqol 5 dimension, 5 level (EQ5D5L)
- Pain intensity in rest on a Visual Analogue Scale (VAS)
- Pain intensity during activities on VAS*
- Patients' expectation for pain relief following treatment*

Variables marked with an asterisk were selected as potential treatment selection markers.

Appendix 8

An example of a predictiveness curve with summary measures



$$\text{Decrease in rate of outcome} = \frac{\text{Marker positivity rate} * \text{Average benefit treatment B}}{100}$$

Predictiveness curves present the risk for individual patients, with a corresponding marker value, at the outcome of interest due to the given treatment. This example uses fictitious numbers and provides a manual to interpret the study results that are presented in the manuscript.

In this example treatment A is the reference treatment. The outcome is a dichotomous outcome, corresponding to a poor outcome. The graph displays the risk at a poor outcome.

The **X-axis**, the proportion of patients with a value or score below the corresponding marker value. The corresponding marker value is the value of that marker scored by an individual patient.

The **Y-axis**, represents the risk for the individual patient at a poor outcome when undergoing treatment A or treatment B.
Marker positivity threshold, the intersection of both treatments, in this example the corresponding marker value is 75;
Marker positivity rate, the proportion of patients with a marker score greater than the marker positivity threshold, in this example this is the case in 40% of the patients. For this proportion of patients treatment A has an advantage over treatment B;
Marker negativity rate, the proportion of patients with a marker score lower than the marker positivity threshold, in this example this is the case in 60% of the patients. These patients have a higher risk at a poor outcome due to the standard treatment A. For this proportion of the population, treatment recommendation would change;
The **average benefit of treatment A**. In this example the average benefit of treatment A is 10%. This means that we would expect an average decrease of 10% of patients with a poor outcome due to treatment A.
The **average benefit of treatment B**. In this example the average benefit of treatment B is 15%. This indicates that we would expected an average decrease of 15% of patients with a poor outcome due to treatment B.
The **decrease in rate of outcome** is the reduction in poor outcome when patients avoid treatment A and follow treatment recommended by the model. This is calculated by multiplying the marker negativity rate of 60% with the average benefit of treatment B for this subgroup of 15%, divided by 100. In this example, this has the value of 60%*15% / 100 = 9%. This means an almost 9% reduction in poor outcomes when all patients with a baseline score exceeding the marker positivity threshold are given treatment B.

Chapter 10

List publications
Acknowledgement / Dankwoord
About the author

List of publications

This thesis

Responsiveness and Minimal Important Change of the IKDC of Middle-Aged and Older Patients With a Meniscal Tear. *Am J Sports Med, 2019.*
JCA Noorduyn, VA van de Graaf, LB Mokkink, NW Willigenburg & RW Poolman; ESCAPE Research Group.

Functional Outcomes of Arthroscopic Partial Meniscectomy Versus Physical Therapy for Degenerative Meniscal Tears Using a Patient-Specific Score. *Ort. J Sports Med. 2020.*
J.C.A. Noorduyn, T. Glastra van Loon, V.A. van de Graaf, N.W. Willigenburg, I.K. Butter, G.G.M. Scholten-Peeters, M.W. Coppieters & R.W. Poolman; ESCAPE Research Group.

In patients eligible for meniscal surgery who first receive physical therapy, multivariable prognostic models cannot predict who will eventually undergo surgery. *KSSTA, 2021.*
J.C.A. Noorduyn, M.M.H. Teuwen, V.A. van de Graaf, N.W. Willigenburg, M. Schavemaker, R.A. van Dijk, G.G.M. Scholten-Peeters, M.W. Heymans, M.W. Coppieters & R.W. Poolman; ESCAPE Research Group.

An individualized decision between physical therapy or surgery for patients with degenerative meniscal tears cannot be based on continuous treatment selection markers. A marker-by-treatment analysis of the ESCAPE study. *KSSTA, 2022*
J.C.A Noorduyn, V.A. van de Graaf, N.W. Willigenburg, G.G.M. Scholten-Peeters, B.W. Mol, M.W. Heymans, M.W. Coppieters & RW Poolman; ESCAPE Research Group.

Physical therapy is not inferior to arthroscopic partial meniscectomy for degenerative meniscal tears. Conclusions based on five-year follow up evaluation of the ESCAPE study. *JAMA NO, 2022*
J.C.A Noorduyn, V.A. van de Graaf, N.W. Willigenburg, G.G.M. Scholten-Peeters, E.J. Kret, R.A van Dijk, R. Buchbinder, G.A. Hawker, M.W. Coppieters & R.W. Poolman; ESCAPE Research Group

Other

How to assess femoral and tibial component rotation after total knee arthroplasty with computed tomography: a systematic review. *KSSTA. 2016*
De Valk EJ, Noorduyn JCA, Mutsaerts EL.

Cost-effectiveness of Early Surgery versus Conservative Treatment with Optional Delayed Meniscectomy for Patients over 45 years with non-obstructive meniscal tears (ESCAPE study): protocol of a randomised controlled trial. *BMJ Open. 2016*
van de Graaf VA, Scholtes VA, Wolterbeek N, Noorduyn JCA, Neeter C, van Tulder MW, Saris DB, de Gast A, Poolman RW; Escape Research Group.

What Is the Diagnostic Accuracy of the Duck Walk Test in Detecting Meniscal Tears? *Clin Orthop Relat Res. 2017*
Van der Post A, Noorduyn JCA, Scholtes VAB, Mutsaerts ELAR.

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van de Graaf VA, Noorduyn JCA, Willigenburg NW, Butter IK, de Gast A, Mol BW, Saris DBF, Twisk JWR, Poolman RW; ESCAPE Research Group.

How do the costs of physical therapy and arthroscopic partial meniscectomy compare? A trial-based economic evaluation of two treatments in patients with meniscal tears alongside the ESCAPE study. *Br J Sports Med. 2020*
van de Graaf VA, van Dongen JM, Willigenburg NW, Noorduyn JCA, Butter IK, de Gast A, Saris DBF, van Tulder MW, Poolman RW; ESCAPE Research Group.

Can even experienced orthopaedic surgeons predict who will benefit from surgery when patients present with degenerative meniscal tears? A survey of 194 orthopaedic surgeons who made 3880 predictions. *Br J Sports Med. 2020*
van de Graaf VA, Bloembergen CH, Willigenburg NW, Noorduyn JCA, Saris DB, Harris IA, Poolman RW; ESCAPE Research Group.

Arthroscopic partial meniscectomy versus physical therapy for traumatic meniscal tears in a young study population: a randomised controlled trial. *Br J Sports Med. 2022*
van der Graaff SJA, Eijgenraam SM, Meuffels DE, van Es EM, Verhaar JAN, Hofstee DJ, Auw Yang KG, Noorduyn JCA, van Arkel ERA, van den Brand ICJB, Janssen RPA, Liu WY, Bierma-Zeinstra SMA, Reijman M.

Honors and awards

2017 First prize for best poster, national physical therapy conference (Dag van de Fysiotherapeut).
Preliminary results of the 1 year follow-up of the ESCAPE trial

2018 First prize for best abstract, annual OLVG science fair (OLVG wetenschapsdag).
Primary results of the 2 year follow-up of the ESCAPE trail

2019 First prize for best poster, World Congress of Physical Therapy.
Comparing surgical versus conservative treatment of meniscal tears: a novel approach focusing on patient-specific activities

2021 Runner-up best publication, annual OLVG science fair (OLVG wetenschapsdag).
Functional Outcomes of Arthroscopic Partial Meniscectomy Versus Physical Therapy for Degenerative Meniscal Tears Using a Patient-Specific Score.

2022 Golden award for best free paper in orthopedic science, EFORT conference.
Physical therapy is not inferior to arthroscopic partial meniscectomy for degenerative meniscal tears. Conclusions based on five-year follow up evaluation of the ESCAPE study

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Dear Foster, my big sister since 2005. You take me on adventures and I love all of them. From Berlin, Germany to Berlin, New Jersey. From Brooklyn, New York to Jamaica and so on. It's about time that we start building our transatlantic bridge. What will our next adventure be? (Make sure to double check with me so that I end up in the same place as you).

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About the author

Julia Catharina Anita Noorduyn was born on January 13th 1988 in Capelle aan den IJssel, the Netherlands. After graduating high school (Libanon lyceum, Rotterdam) in 2005 she attended Villanova University (Pennsylvania, United States of America) to study Liberal arts and Science and to play division I field hockey. However, after one (amazing) year abroad she decided to pursue her dream in becoming a physical therapist (at the Olympics…). She obtained her bachelor's degree in physical therapy at the Hogeschool Utrecht, after which she continued with a pre-master and master degree in Human Movement Science at Vrije Universiteit, Amsterdam. During this time she started working as a physical therapist in a private practice in de Jordaan, Amsterdam (Amsterdam Fysio).
While writing her master thesis on spinal cord injuries at the rehabilitation center of Amsterdam (Reade), she developed a preference for inpatient rehabilitation over outpatient care and she desired to combine physical therapy with research. In the summer of 2013 Julia started working as a physical therapist at a local hospital in Amsterdam (OLVG oost). A year later she got the opportunity to combine clinical practice with a position as junior researcher at the orthopedic research department of OLVG (JointResearch) for the ESCAPE study. After 4 years of including patients, collecting data, reporting preliminary results for the ESCAPE study and coordinating several other orthopedic studies she received funding for her PhD projects. In 2022 she finished her PhD thesis and started a new position as senior advisor paramedical care at Zorginstituut Nederland.