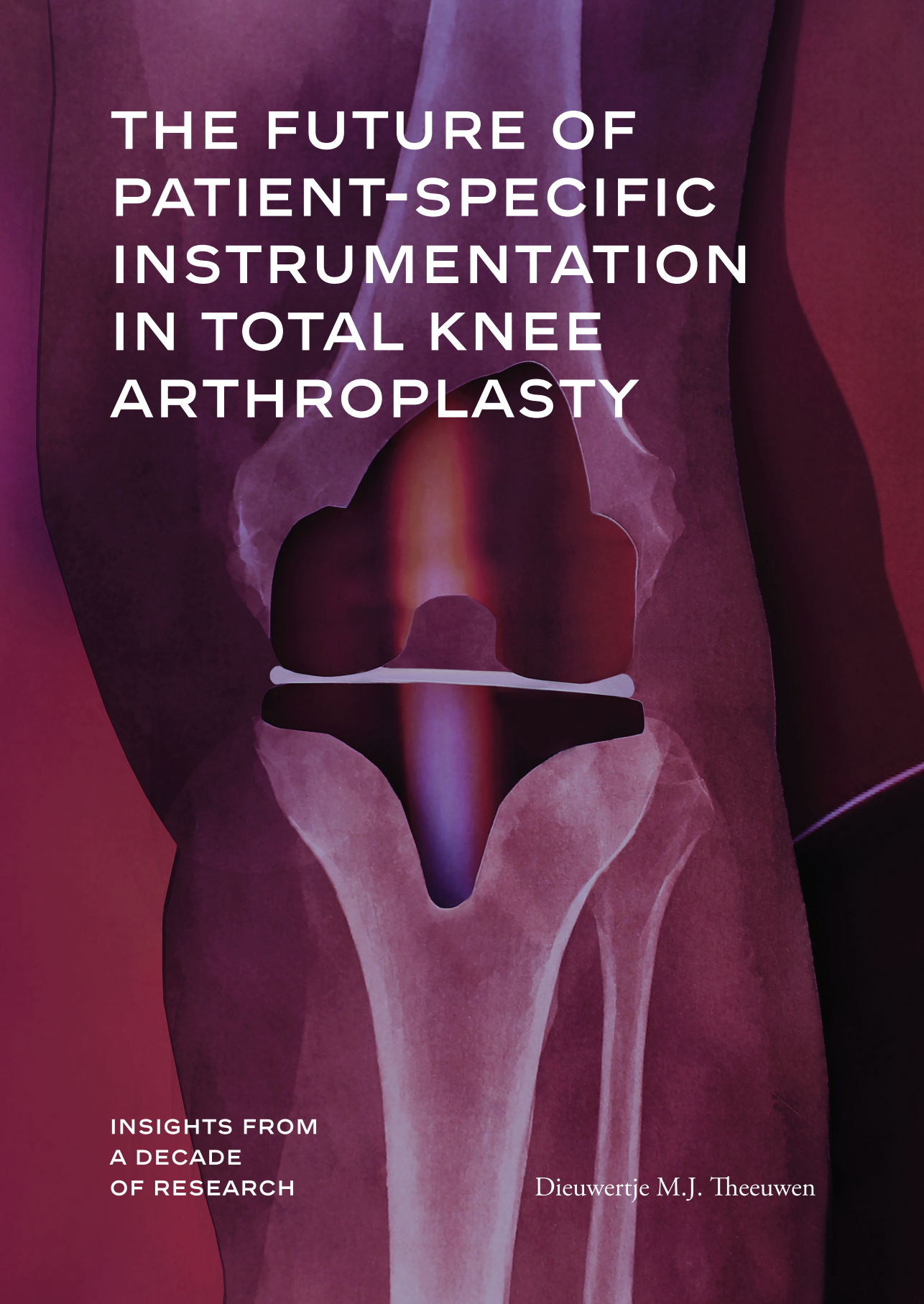
THE FUTURE OF PATIENT-SPECIFIC INSTRUMENTATION IN TOTAL KNEE ARTHROPLASTY



INSIGHTS FROM
A DECADE
OF RESEARCH

Dieuwertje M.J. Theeuwen

The Future of Patient-Specific Instrumentation in Total Knee Arthroplasty

Insights from a Decade of Research

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Design cover: Britt Berden & Marijn Hermans
Layout: Marlou van Uden
Printing: Ridderprint, www.ridderprint.nl

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The Future of Patient-Specific Instrumentation in Total Knee Arthroplasty

Insights from a Decade of Research

PROEFSCHRIFT

voor het behalen van de graad van Doctor aan de Universiteit Maastricht,

onder gezag van Rector Magnificus, prof.dr. Pamela Habibović,

overeenkomstig met het besluit van het College van Decanen,

te verdedigen in het openbaar op vrijdag 11 december 2026 om 13.00 uur

door

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CHAPTER 1

GENERAL INTRODUCTION

Introduction

1

Osteoarthritis

Osteoarthritis (OA) is a chronic degenerative disease commonly affecting the knee joints (1). It causes loss of articular cartilage and periarticular bone remodeling, leading to weight-bearing related pain, stiffness and functional impairment, resulting in significant decreases in the quality of life (2). OA of the knee joint is a major cause of disability in the worldwide population. In 2020, a worldwide pooled prevalence of 22.9% in individuals aged 40 and over was found, which corresponds to 654 million individuals and comes with a pooled incidence of knee OA of 203 per 10.000 person-years (3). Prevalence and incidence differ per region and increase with age. Women are more likely to develop knee OA than men, with relative risks described up to 1.5 (4). Other risk factors associated with the development of knee OA are overweight, obesity and a previous knee injury (5). For the Netherlands, the RIVM (the Dutch national institute for public health care and the environment) stated that the prevalence of OA will rise by 41% in the period 2015-2040 which will lead to a prevalence of 5.1% and 3.0% for respectively females and males (6).

The rising incidence of knee OA comes with increased medical costs, thereby placing a substantial economic burden on society (7). Not only the direct costs associated with knee OA pose a challenge. For example, OA is also a leading cause of sick leave among the working population (8). This not only impacts the health sector but also significantly affects economic productivity due to lost workdays and decreased workforce efficiency (9). Equally important, associations between OA and other diseases are described (10). Predominantly cardiovascular diseases, where people with OA are at increased risk of death (11). OA is also linked to patients' mental health status and cognition. It has an impact on the onset of dementia and cognitive impairment, and the prevalence of depression in OA is extensively documented (12,13). Giving these consequences of OA and the rising incidence, effective management of OA is expected to yield significant advantages in multiple areas. First line of treatment often consists of non-operative management aiming to alleviate symptoms, improve joint function and enhance quality-of-life. These treatment options include exercise therapy, weight loss, pharmacological pain relieve and orthotics (14). Patients with knee pain caused by advanced OA who continue to experience persistent pain despite conservative treatment are considered eligible candidates for total knee arthroplasty (TKA) (15).

Knee arthroplasty

Knee arthroplasty is a well-developed and cost-effective surgery for the treatment of OA of the knee joint. The history of TKA dates to the 1800s, but the first prosthesis that replaced both femoral and tibial surfaces dates back to 1950 (16). In the beginning, failure rates were high with poor long-term outcomes caused by inadequate restoration of the natural kinematics of the knee. An important breakthrough took place in 1970, with the development of a prosthesis

that replicated the shape of the distal femur, preserved the ligaments, and used a plastic insert on the tibial plateau. Ever since, prosthesis design, operative techniques, bearing properties and fixation techniques have been further developed to improve survival of the prosthesis and clinical outcome (17). Nowadays, TKA is a commonly used surgical procedure worldwide and numbers of procedures continue to increase. In Western countries, predictive models estimate an increase in TKA ranging from 43% to 143% by 2050 (18–21). Currently no TKA prediction models for future trends in the Netherlands are available, however, the number of TKA has increased by 23% over the past decade (22).

Despite developments and scientific research in the past decades, dissatisfaction rates up to 20% are described for TKA (23). Mainly persistent pain and functional limitation have been identified as major contributing factors to this issue (24). Additionally, expectations that a patient has about the outcome of the surgery, but may not be met, again influences dissatisfaction (25). Also, mild OA pre-operatively is considered a predictor for dissatisfaction rates after TKA. These patients gain less from their joint replacement and are more at risk for developing chronic pain after surgery (26). In addition, patients with short disease duration are also more likely to experience dissatisfaction after TKA (27). Furthermore, several studies have demonstrated that preoperative mental health status, such as the presence of anxiety, depression, or low life satisfaction, can significantly influence postoperative outcomes and patient satisfaction after TKA (28,29). Patients with poorer psychological well-being before surgery tend to report higher levels of pain, reduced functional improvement, and greater dissatisfaction after the procedure (30). These dissatisfaction rates after TKA come with greater costs when these patients are compared to satisfied patients, mainly during the first year after surgery (31).

Taking all of the above into consideration, substantial improvements in patient satisfaction following TKA are possible. It was long thought that malalignment of the prosthesis was an important factor contributing to dissatisfaction after TKA (23). Therefore, multiple surgical techniques have been developed to improve prosthesis alignment.

Computer-assisted navigation, patient-specific instrumentation and robotic-assisted surgery

To minimize the need for revisions and enhance clinical outcomes, surgeons aim for precise alignment of the prosthesis. Several surgical techniques have been developed and compared to conventional instrumentation (CI) for this purpose (32–34). Computer-assisted navigation systems were first developed in the early 1980s, and in the subsequent years, numerous navigation systems emerged. The aim of these navigated techniques was to improve accuracy and precision of the TKA component positioning, striving for a neutral lower limb alignment (35). Prior to the surgery, evaluation of the patient's knee joint using an imaging technique (X-ray or CT-scan) is performed. The collected information is then entered into the electronic computer system, upon which a comprehensive perioperative plan is developed. During the surgery, reference

points and sensors are placed on the bony surfaces feeding the computer system to accurately register the patient's anatomy. During the surgery, the navigation system continuously tracks the patient's anatomy and position of the surgical instruments. The information including the perioperative surgical plan is then displayed on a computer screen in the operation room. This real time feedback is used by the surgeon for making precise bony cuts and adequately positioning of the components (36,37). While some studies have reported enhanced component alignment with the use of navigation systems, evidence remains inconclusive regarding whether this improvement results in better clinical outcomes or increased long-term implant survival (37,38). In the early 2000s, patient-specific instrumentation (PSI) for TKA was introduced. PSI was developed with the hypothesis that it would lead to more adequate alignment of the prosthesis and a decline in operation time, blood loss and length of hospital stay when compared to CI. Therefore, survival rates and clinical outcome were expected to improve with the use of PSI (39). In PSI a CT- or MRI-scan of the knee joint is performed pre-operatively. With the use of advanced computer software, a personalized virtual preoperative plan is created, taking into account the ideal implant size, alignment and deformities of the patient's knee. This preoperative plan can be adjusted by the surgeon if needed. Following the surgeons' approval, patient-specific instruments are manufactured with a design that only fits one way on the native anatomy of the femur and tibia of the individual patient. The instruments are used for adequate pin positioning. After removal of the instruments, the pins are used for positioning of the standard cutting blocks (Figure 1-2) (40,41).

Extensive research has been conducted on this PSI, gaining increased insight into intra-operative results, alignment of the prosthesis and clinical outcome. Multiple studies describe the intra-operative results and radiological outcomes, often in comparison to CI. The use of PSI yielded notably reduced blood loss, potentially due to the avoidance of opening the medullary cavity, and significantly shorter operation times (42). However, these differences were minimal and frequently regarded as not clinically relevant. No distinct difference in the length of hospital stay was reported between PSI and CI (43–46). Regarding alignment improvement with PSI, the literature lacks consensus, some studies indicated improved alignment, while others reported outcomes comparable to CI (46–48). In the past decade, robotic-assisted surgery was developed to combine the expertise of a surgeon with the precision and guidance of a robotic system (49). During the surgery markers or trackers are placed on the bony surfaces. A robotic system equipped with sensors is used and provides real-time feedback regarding alignment and prosthesis component positioning, and helps to precisely execute the surgical plan (50). Studies with short follow-up periods have demonstrated that robotic-assisted surgery may achieve greater radiologic accuracy (51,52). Together, the above-mentioned surgical techniques aim to optimize accuracy, clinical outcomes and survival in TKA. Among them, PSI has shown potential advantages in surgical efficiency and alignment, without a significant difference in clinical outcomes and prosthesis survival over short- to mid-term follow-up (53,54). However, the long-term impact of PSI on prosthesis survival and clinical outcome remains to be established. To determine the role

of PSI in the future, it is essential to assess if PSI offers advantages over CI through long-term follow-up studies.



Fig1: preparation of the distal femur using personalized instruments



Fig2: preparation of the proximal tibia using personalized instruments

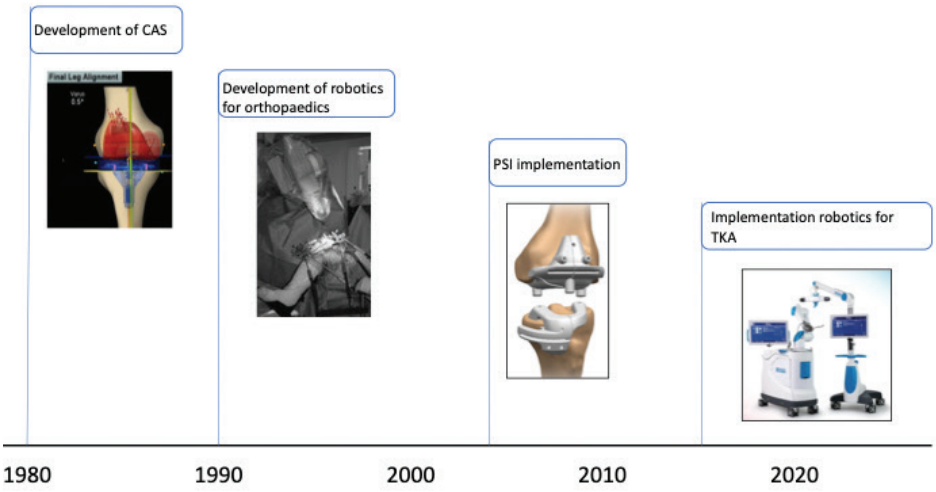

Fig3: surgical techniques developed for TKA over the years

CT- and MRI-based PSI

PSI utilizes preoperative CT- or MRI scans to develop a surgical plan, followed by the production and intraoperative use of custom instruments (55). Both CT- and MRI-scans are advanced and safe techniques. CT-scans have fewer contra-indications, especially for patients with metallic hardware around the knee joint or patients with claustrophobia. A CT-scan is also less sensitive to patient's movements duo to a shorter scanning process but it exposes patients to higher levels of radiation (56). The choice of imaging technique varies among PSI manufacturers, with CT-scans offering more detailed visualization of the bony surface but less clarity regarding the remaining articular cartilage compared to MRI. Research with short follow-up periods up to three months suggests that MRI-based PSI may exhibit fewer radiological outliers of coronal overall limb alignment than CT-based PSI. Moreover, CT-based PSI required longer operation time (57,58).

Pre-operative planning of PSI

During the preoperative phase of PSI, a technician utilizes the CT- of MRI scans to develop a virtual plan detailing implant size, resection, and implant positioning. This plan requires approval from the surgeon before the manufacturing of the guides can proceed (59). Previous literature described that the plan provided by the technician may differ from the plan approved by the surgeon (60). Such differences can result in variations in implant size, resection, and component positioning. Therefore, the surgeon's approval of the surgical plan plays a critical role during the preoperative phase (61).

Cost-effectiveness of PSI

More recently, focus had shifted from image modalities, alignment, clinical outcome and survival of the prosthesis to evaluating costs and cost-effectiveness of PSI compared to CI (62). Many studies focus on the costs of PSI compared to CI with differing results, where often only specific aspects of costs are analyzed (63). Examples of these specific costs are imaging costs, PSI production costs, operating time and sterilization costs. PSI was developed with the hypothesis that a decline in blood loss, shortened hospital stay, reduced operation time and reduction of surgical trays sterilization costs could lead to a decline in overall costs. However, only small differences were found without clinical significance (64). Overall, the comparison of costs revealed that PSI was more costly, mainly due to the manufacturing process of the instruments including the CT- or MRI-scan performed pre-operatively (63).

Radiological outliers and their influence on clinical outcome and survival of the prosthesis

Achieving optimal alignment after TKA and its impact on clinical outcomes and prosthesis longevity remains a topic of significant debate, particularly in light of the dissatisfaction rates reported after TKA procedures (65,66). The positioning of the prosthesis across different planes is planned pre-operatively. When planning for a neutrally mechanical aligned knee, postoperative

X-rays can reveal if the pre-planned alignment was successfully achieved. Deviations of more than 3° from this pre-planned alignment are considered as outlier. To prevent revision surgery, current literature suggests that maintaining a neutral mechanical axis remains the optimal guideline for TKA alignment (67). In the sagittal plane, femoral flexion between 0-3° and tibial slope between 0-7° are associated with reduced revision rates (68). Considering clinical outcome, the influence of varus- or valgus alignment in the coronal plane remains uncertain (69). Increased femoral flexion may result in flexion contractures while femoral component extension could contribute to anterior knee pain (70). A decreased tibial slope may reduce the range of motion (71).

Understanding the exact influence of alignment including possible deviations on clinical outcomes is important since surgical techniques, such as PSI, are often evaluated based on their ability to achieve optimal alignment.

The future of PSI in TKA

Although PSI has played a significant role in TKA for some time, there is still limited availability of data to define its optimal role in clinical practice. This begins in the pre-operative phase, where PSI involves the surgeon approving a virtual plan. The reliability of this process has not been previously studied. Also, this pre-operative virtual plan can be generated using either a CT- or MRI scan (57). No conclusive evidence has yet been published on the differences in clinical outcomes and survival between MRI- and CT-based PSI, with follow-up periods longer than three months. Given that further improvement in clinical outcome can still be expected after three months and that most revisions are performed several years after the index operation, longer follow-up periods are essential to provide more information on what imaging technique is superior in this regard (72,73). Additionally, there is a significant lack of evidence regarding the long-term outcomes of PSI. No studies have compared PSI and CI over follow-up periods longer than five years. Such long-term results are crucial for determining whether surgeons should continue using PSI in the treatment of knee osteoarthritis.

Overall, direct costs of PSI are generally considered higher due to the manufacturing process of the patient-specific instruments and the pre-operative CT- or MRI scans required (63). However, no comparison of cost-effectiveness between PSI and CI has been conducted, making it difficult to draw definitive conclusions about the cost-effectiveness of a PSI-based TKA.

In summary, based on the available literature, it can be concluded that PSI is a safe and reliable surgical technique within TKA. PSI demonstrates clinical outcomes and achieves pre-operative planned alignment comparable to CI, but it has not been proven to be superior. To date, no studies have investigated the long-term outcomes of PSI. These observations highlight the need for studies evaluating the long-term outcomes of PSI. In this thesis, several chapters are dedicated to assessing the long-term results of PSI in TKA. Moreover, this thesis aims to explore the question of what role PSI may play in the future of knee arthroplasty. An overview of the thesis aims and structure is presented below.

Aims and outline of this thesis

Chapters 2 and **Chapter 3** describe the assessment of differences in clinical outcome and survival of the prosthesis between CT- and MRI-based PSI at short- to midterm follow-up. MRI- and CT-based PSI have been compared regarding perioperative data and alignment of the prosthesis, but not regarding clinical outcome and survival of the prosthesis. We assessed if there are differences between MRI- and CT-based PSI, regarding clinical outcome and survival of the prosthesis, at 2- and 5-years postoperatively.

Chapter 4 describes the assessment of intra- and inter-observer reliability of approval and alteration of the virtual plan by the surgeon in MRI-based PSI. No intra- or inter-observer reliability of implant planning with PSI has been studied previously. In **Chapter 4**, four orthopedic surgeons performed standard pre-operative planning with MRI-based PSI for 120 cases and the intra- and inter-observer reliability was assessed.

Chapter 5 and **Chapter 6** present the evaluation of differences in clinical outcome and survival of the prosthesis between PSI and CI at long-term follow-up. To date, there is no literature available describing the long-term results of PSI. In **Chapter 5**, the results of a cohort study with 200 patients undergoing PSI TKA at 8-years follow-up were presented focusing on clinical outcome and survival of the prosthesis. **Chapter 6** is a continuation of a previously published, randomized multicenter study, where 180 patients were included and randomly assigned to either PSI-based TKA or CI. We analyzed the differences in clinical outcome and survival of the prosthesis between these PSI- and CI-TKA, 10 years after surgery.

Chapter 7 investigates the difference in cost-effectiveness between PSI and CI at long-term follow-up. Comparing cost-effectiveness of PSI to CI, in the literature no long-term comparison has been performed. Therefore, in this chapter the cost-effectiveness and cost-utility of PSI compared to CI was investigated from a hospital perspective.

In **Chapter 8** we assess how the cumulative number of postoperative radiological outliers affects clinical outcome and survival of the prosthesis. In the preceding chapters, comparisons between PSI and CI are frequently made by evaluating correct alignment, clinical outcome and revision rates. However, literature lacks consensus on the exact impact of multiple radiological outliers on clinical outcomes and survival of the prosthesis. In this chapter, we aim to assess the influence of the cumulative number of radiological outliers in one patient combined on clinical outcome and revision rates.

Finally, **Chapter 9** and **Chapter 10** present a comprehensive synthesis of the findings reported in the preceding chapters. These sections critically evaluate the results, outline recommendations for subsequent research projects, and discuss the potential applications and implications of the study's outcomes.

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CHAPTER 2

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COMPARABLE CLINICAL OUTCOME AND IMPLANT LONGEVITY AFTER CT- AND MRI-BASED PATIENT-SPECIFIC INSTRUMENTATION FOR TOTAL KNEE ARTHROPLASTY: A 2-YEAR FOLLOW-UP OF A RCT

Abstract

Purpose

Patient-specific instruments (PSI) are already widespread used in total knee arthroplasty (TKA). Either Computed Tomography (CT) scans or Magnetic Resonance Imaging (MRI) scans are used pre-operatively to create jigs to guide resection during surgery. This study is a sequel of previous work that showed significantly more radiological outliers for posterior slope when CT based guides were used. The aim of this study was to assess differences in revision rate and clinical outcome between the two groups at two years follow up.

Methods

At the 2-year follow-up 124 patients were analyzed in this prospective, randomized single-blind study. A survival analysis with revision of the TKA as endpoint was performed. Patients fulfilled four patient reported outcome measurements (PROMs). Scores on the questionnaires were compared between both groups at the different follow-up visits.

Results

At final follow-up, there was no significant difference in the survival rates of the CT- and MRI-based PSI surgery. Postoperatively the PROMs significantly improved within each group compared with the pre-operative values. There were no significant differences for the PROMs between both groups at the 2-years follow-up.

Conclusions

Although previous results showed more outliers regarding posterior slope for CT-based PSI's, no difference in revision rate or the outcome of PROMs were found at 2-year follow-up. Further research to determine what the influence is of radiological outliers on implant survival and clinical outcomes is necessary.

Introduction

Patient-specific instruments (PSI) are already widespread used in total knee arthroplasty (TKA) for several years. The technique uses computed tomography (CT) scans or magnetic resonance imaging (MRI) pre-operative to create jigs that have at best only one position on the native anatomy of the knee. The jigs are used to place pins on which the cutting blocks are positioned [16]. The differences in radiological outcome between PSI and conventional knee arthroplasty are little, most previous studies found comparable outliers in alignment between PSI and conventional total knee arthroplasty [3,19,20,22,28,31]

The method of image acquisition is not standardized among PSI manufacturers. Multiple studies examined the radiological differences between CT- and MRI-based PSI. The current literature suggest that MRI-based PSI show less radiological outliers than CT-based PSI [1,2,9,21,23,24,26,29].

Only one study has described the difference in clinical outcome between CT- and MRI based PSI. Their follow up was only three months and no clinical differences were found [21]. This is the first study that describes the differences in clinical outcome between MRI- and CT-based PSI with a follow up of more than three months.

This RCT is a sequel of a previously published study that compared intra-operative results and radiological outcomes between MRI- and CT based PSI [23]. Significantly more radiological outliers were found for posterior slope using the CT based guides. This suggests that MRI-based PSI is the preferred imaging modality when it comes to preventing radiological outliers.

These same patients have now been followed-up 2 years post operatively. The purpose of this study was to compare both clinical outcome and survival of the implant across groups. The following hypothesis was tested: there are no differences in revision rate and clinical outcome between MRI- and CT-based PSI for TKA at 2-years follow up.

Material & Methods

This single centre, prospective, randomised single-blind study with an allocation ratio of 1:1 was conducted from June 2014 till February 2015 at the Zuyderland Medical Centre, Sittard-Geleen in the Netherlands. The study was approved by the Independent Review Board (IRB Zuyd Heerlen, the Netherlands; IRB-Nr.13T147) and registered online at the Dutch Trial Register (www.trialregister.nl, Nr. NTR4734). Written informed consent was obtained from all participants. One hundred and thirty-seven patients were randomly assigned (www.randomizer.org) to two groups and were either operated with MRI- or CT-based Patient-Specific Instruments (PSI; Signature, Zimmer Biomet Orthopaedics, Warsaw, IN, USA) for total knee arthroplasty (TKA; cemented CR Vanguard system, Zimmer Biomet Orthopaedics, Warsaw, IN, USA). Four

experienced orthopaedic knee surgeons (EH,EJ,NK,RH) who all had undertaken at least 100 TKAs using PSI before the start of the study performed the surgical procedures.

Baseline conditions, randomization, surgical procedure, perioperative outcome (e.g., operation time, blood loss), proportion and fractions of outliers were described in a previous publication [23]. Regarding outliers for posterior slope (> 3 degrees deviation from planned position) 1 patient had excessive anterior slope and 8 patients more posterior slope compared to pre-operative planning. After completion of the 2-year FU, patients were unblinded for the type of imaging (CT or MRI) method that was used. An overview of the number of patients at the 2-year follow up, analysed in this study is presented in Fig. 1.

At a mean follow-up of 2.0 years (SD 0.3), 124 patients (88.5%): 44 men (31.4%) and 80 women (57.1.0%) were analyzed. Ten patients refused to attend the follow-up (MRI=7, CT=3) and three patients in the MRI-group deceased of causes unrelated to the surgery before the 2-years follow-up. Patient distribution is summarized in Figure 1. A survival analysis with revision of the TKA (partial or total revision) as endpoint was performed. At final follow up patients visited the outpatient clinic. AP and lateral x-rays were obtained to check for radiolucency, Patient-reported outcome measures (PROMs) were filled out and clinical evaluation was performed preoperatively, at 12 and 24 months postoperatively. The following PROMs were used: the 12-item Oxford Knee Score (OKS; 12–60, 12 being the highest score) [12,17] the Western Ontario and McMaster University Index (WOMAC; 0–100, 100 being the highest score), a visual analogue scale (VAS) for pain and the EuroQol (EQ-5D) [8]. For the EQ-5D, a single summary index was calculated, using the value set for The Netherlands [5,14]. Scores on the questionnaires were compared between both groups at the different follow-up visits.

The study protocol was approved by the hospital's Independent Review Board (IRB, METC Z; File nr. 13T147) and registered online at the Dutch Trial Register (www.trialregister.nl, Nr. NTR4734). The trial was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all individual participants included in the study.

The statistical analyses were performed with the use of SPSS version 21.0 software (SPSS Inc., Chicago, USA). The primary study was powered with a 2-sided 5% significance level and a power of 80%. A sample size of 70 patients per group were included to detect a difference that was clinically acceptable (≤3° frontal femur component), in order to be able to reject the null hypothesis [23]. A survival analysis with revision of the TKA (partial or complete) as endpoint was performed. A generalised linear mixed model (GLMM) approach was used to take into account the repeated-measures design of the study in order to cope with any missing data collected before and at each follow-up and to cope with the range of variation in relation to the time frame the data was collected [7]. The GLMM contained both random and fixed variables, to estimate the effect of implant design on the trend of the different PROMs (dependent variables). For all analyses, a p-value was considered to be statistically significant at $p \leq 0.05$. Results are presented as mean (SD) or proportions (%).

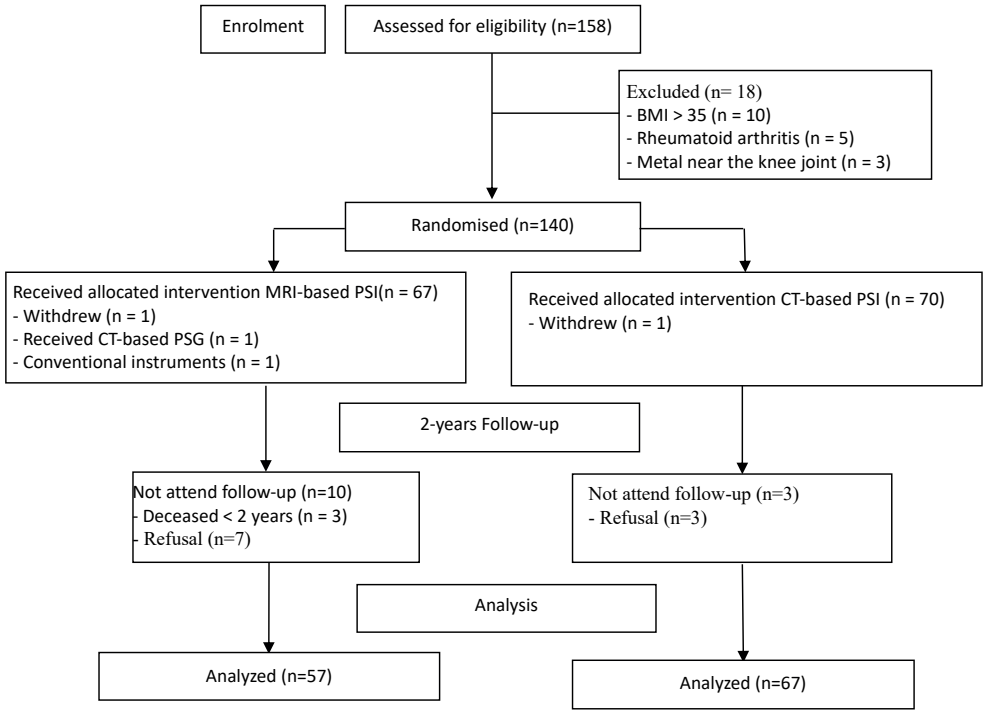

Figure 1: Patient distribution of the included patients at 2-year follow-up.

Results

At final follow-up, a total of 2 patients (1.4%) had undergone revision surgery. In one patient, 18 months postoperative, the bearing was revised to 3 sizes bigger (size 12 to 18) due to progressive valgus instability (CT-group) and in one other patient, 2 years postoperative, the bearing was broken due to an unknown cause (MRI-group). There was no difference in the survival rates of the CT- and MRI-based PSI TKA surgery (n.s.).

In two other patients, surgery was needed. In both patients a patella resurfacing button was placed. In one patient because of persistent pain due to degenerative patellofemoral arthrosis (CT-group) and in one other patient because of patella dislocation (MRI-group), 18 and 6 months after initial surgery respectively.

No radiolucent abnormalities were noted at any time point. Postoperatively the PROMs significantly improved within each group compared with the pre-operative values. There were no significant differences for the PROMs between both groups at 2-year follow-up (Table 1).

		MRI-based PSI n= 57 Mean SD (95% CI)	CT-based PSI n=67 Mean SD (95% CI)	p-value GLMM
OKS	**Pre**	34.9 7.2(32.6 – 37.2)	37.7 7.4 (35.4 – 39.9)	n.s.
	3-MTS	23.2 7.6 (20.8 – 25.6)	23.6 6.5 (21.6 – 25.6)	
	1-year	20.5 6.8 (18.4 – 22.6)	19.9 5.4 (18.3 – 21.5)	
	2-year	19.8 6.2 (17.9 – 21.7)	20.2 7.7 (18.0 – 22.5)	
WOMAC	**Pre**	63.2 20.5 (56.8 – 69.7)	59.0 24.7 (51.6 – 66.3)	n.s.
	3-MTS	84.2 15.2 (79.4 – 89.0)	80.9 16.6 (75.9 – 85.8)	
	1-year	85.0 16.4 (79.8 -90.2)	85.5 13.8 (81.4 – 90.0)	
	2-year	84.2 16.1 (79.1 – 89.3)	85.7 15.0 (81.2 – 90.1)	
VAS Pain Score	**Pre**	6.0 1.8 (5.5 – 6.6)	6.7 1.6 (6.2 7.2)	n.s.
	3-MTS	2.4 2.2 (1.7 – 3.1)	2.8 2.3 (2.1 – 3.5)	
	1-year	2.2 2.3 (1.5 – 3.0)	2.3 2.4 (1.5 – 3.0)	
	2-year	2.0 1.9 (1.4 2.6)	2.0 2.0 (1.4 – 2.6)	
EQ-5D	**Pre**	0.8 0.1 (0.8 – 0.8)	0.8 0.1 (0.8 – 0.8)	n.s.
	3-MTS	0.9 0.1 (0.8 – 0.9)	0.9 0.1 (0.8 – 0.9)	
	1-year	0.9 0.1 (0.9 – 0.9)	0.9 0.1 (0.9 – 0.9)	
	2-year	0.9 0.1 (0.9 – 0.9)	0.9 0.1 (0.9 – 0.9)	
EQ-5D VAS	**Pre**	68.1 19.1 (62.2 – 74.1)	61.9 18.5 (56.2 – 67.6)	n.s.
	3-MTS	78.1 16.0 (73.1 – 83.1)	71.6 19.9 (65.5 - 77.7)	
	1-year	76.7 16.2 (71.6 – 81.7)	74.0 16.4 (68.9 – 79.0)	
	2-year	74.0 23.0 (66.8 – 81.1)	75.8 14.2 (71.7 – 80.4)	

Table 1: Mean, standard deviation (SD), 95% confidence interval (CI) and p-values of the PROMs for the MRI- and CT-based group. 1

Discussion

The most important finding of the present study was that the short-term survival and clinical outcome with MRI-based PSI is comparable as that with CT-based PSI for TKA. No significant differences regarding the implant survival, clinical outcome and PROMs were found.

Revision of the bearing and placement of a patella button were the two revision procedures necessary. In one patient in the CT-group, 18 months postoperative, the bearing was revised to 3 sizes bigger because of progressive valgus instability. This patient had a postoperative biomechanical-axis outside the safe <3° varus from the neutral axis [23], which is associated with worse outcome [11]. A polyethylene insert exchange to a thicker dimension was performed. Postoperative knee instability represents the most common cause for revision TKA [6]. At the

onset of increasing pain after TKA, implant malalignment and/or non-articular causes should be the first consideration [13]. Revision surgery must take into consideration any component malalignment that may have primarily contributed to instability [6].

In the previous study [23], significantly ($p \leq 0.00$) more outliers (n=9, 13%) for both the anterior (n=1) and posterior slope (n=8) of the tibia component were observed in the CT-based PSI group compared to the MRI-based PSI group (0%). It is known that it is difficult to achieve an appropriate sagittal alignment of the tibial components with CT-based PSI [24]. In contrast with the MRI-based PSI, CT guides have an offset from the cartilage on the plateau and only make contact with the bone surface [23].

The impact of sagittal malalignment on the survival and clinical outcome of the prosthesis has not been described much yet. Available literature suggests that on the long-term a tibial slope of less than 0° or greater than 7°can result in more tibia component revisions [13]. Longer follow-up of this patient cohort is needed to analyse the future revision rate.

Few studies describe the controversial effects of outliers regarding slope on clinical outcome [15, 27]. A posterior slope of >3° may lead to impaired extension of the knee joint resulting in less satisfied patients [15]. A slope between 0-3° is believed to achieve maximal flexion of the knee which can cause instability and impaired flexion [27].

Recent systematic reviews revealed that CT-based PSI resulted in a significantly higher proportion of coronal plane outliers with regard to overall limb alignment (risk ratio: 1.67; 95% (CI): 1.03-2.72; P = 0.04) [29] while MRI-based PSI demonstrated a significantly lower risk of producing lateral femoral component outliers (OR 0.52, 95% (CI): 0.30-0.89, P = 0.02) [24]. The available literature on this topic is scarce. This is the first RCT comparing implant survival and clinical outcome of the TKA implant after a 2-year FU between MRI- and CT-based PSI TKA. This study showed that the early 2-years clinical results after TKA are equal for both scan modalities.

The results found in the present study are in line with others. Though, in those studies, PSI was compared with conventional instruments. Published long-term clinical results on PSI are scarce. The available literature on PSI showed that their early 2- and 5-year clinical results are equal to conventional instrumented TKA [4,18,25,30].

The strengths of this study are the number of patients (88.5 %) available for this 2-year follow-up. Furthermore, a mixed model approach was used to analyse the data. This is considered to be more appropriate for assessing repeated measurements in clinical trials [6].This study had some limitations. The most important limitation was the statistical power of this study. The initial study [23] was designed and powered for difference in the frontal femoral component; therefore, a type II error cannot be ruled out. Secondly, the PROMs used in the present study represent the best subjective measurements of clinical outcome after knee arthroplasty. The PROMs improved within each group compared with the preoperative values. However due to a lack of sensitivity to change, most of the used PROMs did not capture changes between both study groups after

a follow-up of 2-years [10]. It is known that PROMs remain inherently subjective, prone to an individual's interpretation and perception of joint functioning. In this study, the authors received several times the feedback from patients that they found it difficult to score the PROMs, especially in keeping other conditions or illnesses out of consideration that might have impaired mobility, general condition or quality of life. This emphasizes, that knee osteoarthritis alone only partially determines the overall score. Furthermore, only one PSI system from one manufacturer was used. Therefore, the results from this study could be inapplicable for other PSI systems from other manufacturers.

This is the first RCT comparing longevity and clinical outcome of the TKA implant after a 2-year FU between MRI- and CT-based PSI for TKA and therefore provides valuable insight into the type of scan modality to use, to create PSI for TKA.

Conclusion

Previous results showed more outliers regarding the slope for CT-based PSI's. In this sequel no differences were found regarding the survival rates and clinical outcome between the MRI- and CT-based PSI for TKA at the two years follow up. This suggests that MRI-based PSI is at least as good as CT-based PSI. It remains unclear to what extent significantly more outliers influences the implant survival and clinical outcomes in the long term. Literature regarding the mid- and long-term clinical follow-up comparing MRI- and CT-based PSI for TKA are scarce.

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CHAPTER 3

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Eur J Orthop Surg Traumatol. 2024;34(7):3529-34.

NO DIFFERENCES IN MID-TERM SURVIVAL AND CLINICAL OUTCOME BETWEEN CT- AND MRI-BASED PATIENT-SPECIFIC INSTRUMENTATION FOR TOTAL KNEE ARTHROPLASTY, A RANDOMIZED CONTROLLED TRIAL

Abstract

Purpose:

The purpose of this prospective randomized controlled trial was to compare the clinical outcome and the survival rate of total knee arthroplasty between CT- and MRI-based patient-specific instrumentation 5-years after initial surgery.

Methods:

At a mean follow-up of 5.8 years (SD 0.3), 98 patients (64% woman, loss to follow-up 28%) were included in this analysis. To assess the differences in clinical outcome, patients fulfilled PROMs preoperatively and at each follow-up moment. At final follow-up, the forgotten joint score was adjusted.

Results:

At final follow-up, no new patients underwent revision surgery in both groups. Regarding the clinical outcome, no statistically significant difference between the groups was found. The Forgotten Joint Score was only performed at final follow-up and showed no significant difference between both groups.

Conclusion:

At mid-term follow-up, survival rates between CT- and MRI-based patient-specific instrumentation did not show a significant difference. Regarding clinical outcome, only the EQ-5D-VAS ($p < 0.040$) showed a statistically significant difference over time, in favor of the MRI-group.

Introduction

In the treatment of advanced osteoarthritis of the knee joint, total knee arthroplasty (TKA) is the most commonly performed method [1]. Multiple techniques are developed for the optimization of pre-operative planning of TKA. Patient-specific instrumentation (PSI) is one of these methods [2-3]. This technique uses computed tomography (CT) scans or magnetic resonance imaging (MRI) preoperatively to create patient specific jigs. These jigs are used during surgery and have one possible position on the native anatomy of the knee joint [2]. The method of image acquisition is not standardized among the different PSI manufacturers. Previous studies with only short-term outcomes suggest that MRI-based PSI show less radiological outliers. No differences in the clinical outcome or survival of the prosthesis were found [4-9]. A recent systematic literature review and meta-analysis confirmed this finding [10]. To our knowledge, no randomized controlled trial (RCT) described the differences between CT- and MRI-based PSI concerning the clinical outcome and survival with mid-term follow-up. This RCT is a continuation of previously published studies that compared 137 patients who underwent TKA with either CT- or MRI-based PSI [5][9]. These same patients have now been followed up 5 years postoperatively. We hypothesized that there would be no statistically significant difference in implant survival rate and clinical outcome between CT- and MRI-based PSI at 5-years follow-up.

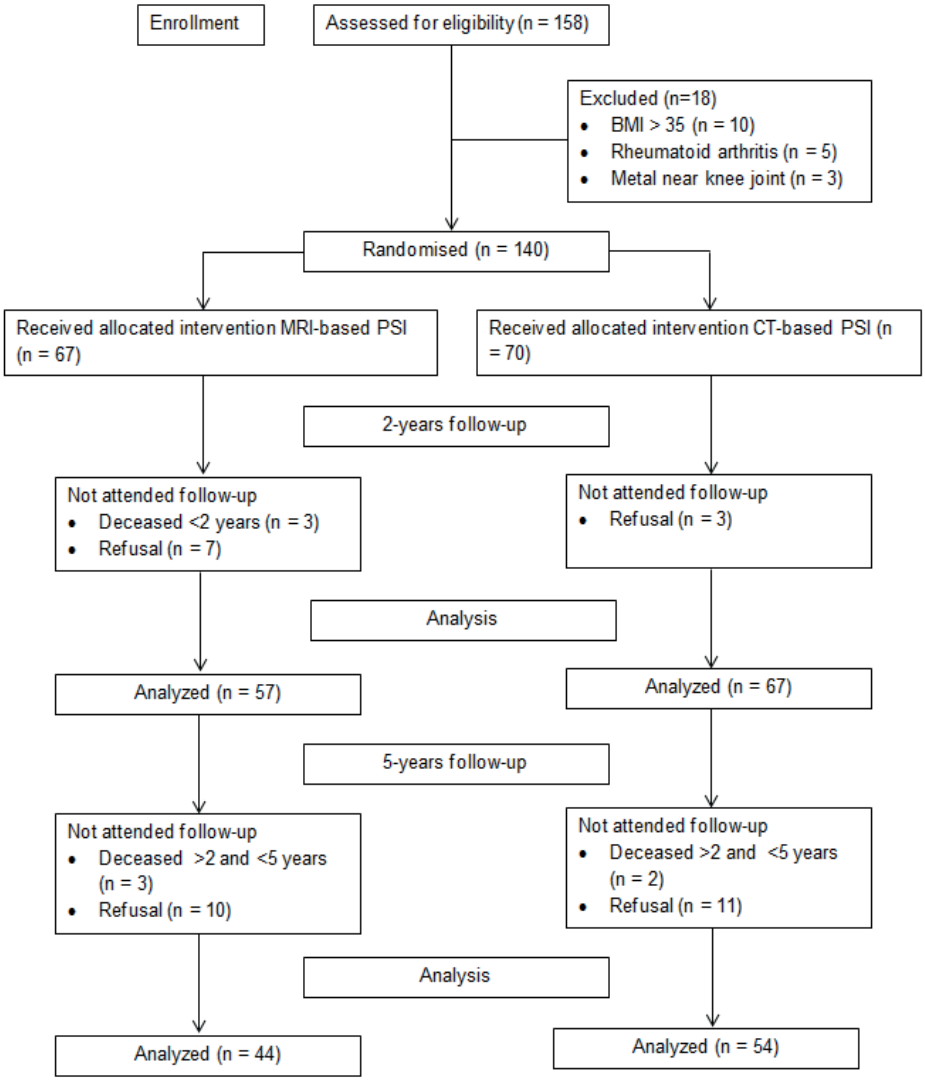

Figure 1: Patient distribution of the included patients at latest follow-up

Material and method

This single-centre, prospective, randomized, single-blind controlled trial was conducted from June 2014 till February 2015. A total of 137 knees in 137 patients were analysed in this study, randomized with an allocation of 1:1 and underwent TKA with either CT- or MRI-based PSI. Patients' recruitment, baseline characteristics, randomization, surgical procedure, peri-operative data and postoperative radiological outliers were described in detail in the first

article [9]. Subsequently, differences regarding clinical outcome and survival of the prosthesis at 2-years follow-up were defined in another article [5]. At a mean follow-up of 5.8 years (SD 0.3, 95% CI 5.71 - 5.88), 98 patients (64% women, 28% loss to follow-up) were included in this analysis. Eleven patients (MRI= 6, CT= 5) died of causes unrelated to the TKA surgery. Between the 2- and 5-years follow-up, 21 patients (MRI = 10, CT = 11) refused to participate any further, mostly since they did not want to fulfill the questionnaires. An overview of the number of patients at the latest follow-up, analyzed in this study is presented in figure 1. Due to the SARS-CoV-2 pandemic, collecting patients' data was performed differently compared to previous follow-up moments. Most patients were not able to, or allowed to visit the outpatient clinic. Therefore, no X-rays were obtained and no physical examination was performed. As an alternative all patients were contacted by phone to ask if revision surgery was performed. In addition, they received an envelope containing the different PROMs with the request to complete and return these forms. The PROMs used were: the 12-item Oxford Knee Score (OKS; 12-60, 12 being the highest score) [11], the Western Ontario and McMaster University Index (WOMAC; 0-100, 100 being the highest score) [12], a Visual Analogue Scale for pain (VAS; 0-100, 100 being the highest) [13], the Forgotten Joint Score (FJS-12; 0-100, 100 being the highest) [14] and the EuroQol (EQ-5D; 1,000 being the highest score). For the EQ-5D, a single summary index was calculated using the value set for The Netherlands [15]. Scores on the PROMs were compared between both groups at the different follow-up visits.

This study was approved by the Independent Review Board (IRB Zuyd Heerlen, the Netherlands; IRB-Nr. 13T14) and registered online at the Dutch Trial Register (Nr. NTR4734). Written informed consent was obtained from all individual participants included in the study.

Statistical analysis

The statistical analysis was performed using SPSS software version 26.0 (SPSS Inc., Chicago, Illinois). The primary study was powered with a two-sided 5% significance level and a power of 80%. Based on this calculation, 70 patients per group were included. Since no new patients underwent revision surgery, we did not perform a new survival analysis. A generalized linear mixed model (GLMM) was used to assess clinical outcome using PROMs with repeated-measures. For each item, the mean, 95%-CI and SD as well as the p-value for the latest follow-up and the p-value over time was calculated. A p-value was considered to be statistically significant when $p \leq 0.05$.

Results

At the final follow-up, one patient in the CT-group who already underwent revision surgery at 2-years follow-up underwent a new revision due to dissatisfying results caused by a continuance of experiencing pain and instability. No other revisions were performed in both groups.

Regarding clinical outcome, only the EQ-5D-VAS ($p < 0.040$) showed a statistically significant difference over time, in favor of the MRI-group (Table 1). The Forgotten Joint Score was only performed at the 5-year follow-up and showed no significant difference between both groups (Table 2).

	MRI-based PSI (n= 44) mean, SD, 95% C.I.	CT-based PSI (n= 54) mean, SD, 95% C.I.	p-value GLMM
OKS			
Pre	34.4, 7.2 (32.6-37.2)	37.7, 7.4 (35.4-39.9)	0.154 (n.s.)
3 months	23.2, 7.6 (20.8-25.6)	23.6, 6.5 (21.6-25.6)	
1 year	20.5, 6.8 (18.4-22.6)	19.9, 5.4 (18.3-21.5)	
2 years	19.8, 6.2 (17.9-21.7)	20.2, 7.7 (18.0-22.5)	
5 years	20.8, 8.5 (18.2-23.4)	23.4, 7.7 (21.1-25.6)	
WOMAC			
Pre	63.2, 20.5 (56.8-69.7)	59.0, 24.7 (51.6-66.3)	0.680 (n.s.)
3 months	84.2, 15.2 (79.4-89.0)	80.9, 16.6 (75.9-85.8)	
1 year	85.0, 16.4 (79.8-90.2)	85.5, 13.8 (81.4-90.0)	
2 years	84.2, 16.1 (79.1-89.3)	85.7, 15.0 (81.2-90.1)	
5 years	80.2, 20.2 (73.9-86.5)	75.5, 20.8 (68.5-80.5)	
VAS Pain score			
Pre	6.0, 1.8 (5.5-6.6)	6.7, 1.6 (6.2-7.2)	0.093 (n.s.)
3 months	2.4, 2.2 (1.7-3.1)	2.8, 2.3 (2.1-3.5)	
1 year	2.2, 2.3 (1.5-3.0)	2.3, 2.4 (1.5-3.0)	
2 years	2.0, 1.9 (1.4-2.6)	2.0, 2.0 (1.4-2.6)	
5 years	1.9, 2.4 (1.2-2.7)	3.0, 2.4 (2.2-3.7)	
EQ-5D			
Pre	0.8, 0.1 (0.8-0.8)	0.8, 0.1 (0.8-0.8)	0.838 (n.s.)
3 months	0.9, 0.1 (0.8-0.9)	0.9, 0.1 (0.8-0.9)	
1 year	0.9, 0.1 (0.9-0.9)	0.9, 0.1 (0.9-0.9)	
2 years	0.9, 0.1 (0.9-0.9)	0.9, 0.1 (0.9-0.9)	
5 years	0.9, 0.1 (0.9-0.9)	0.9, 0.1 (0.9-0.9)	
EQ-5D VAS			
Pre	68.1, 19.1 (62.2-74.1)	61.9, 18.5 (56.2-67.6)	0.040
3 months	78.1, 16.0 (73.1-83.1)	71.6, 19.9 (65.5-77.7)	
1 year	76.7, 16.2 (71.6-81.7)	74.0, 16.4 (68.9-79.0)	
2 years	74.0, 23.0 (66.8-81.1)	75.8, 14.2 (71.7-80.4)	
5 years	77.6, 16.2 (72.7-82.5)	66.3, 17.0 (61.4-71.2)	

Table 1: mean, standard deviation (SD) with confidence interval (C.I.) for the PROMs at different follow-up moments and p-values of the generalized linear mixed model (GLMM).

FJS-12	MRI-based PSI (n= 44) mean, SD, 95% C.I.	CT-based PSI (n= 54) mean, SD, 95% C.I.	p-value
5-years follow-up	68.6, 34.5 (58.1-79.1)	63.6, 28.0 (55.2-71.9)	0.480 (n.s.)

Table 2: Mean, standard deviation (SD), 95% confidence interval (CI) and p-values at 5 years follow-up for the Forgotten Joint Score (FJS-12).

Discussion

The most important finding of the present study was that at 5-years follow-up patients' satisfaction was comparable between those operated with use of CT- and MRI-based PSI for TKA. Only the EQ-5D-VAS showed a statistically significant difference between the groups in favor of the MRI-group. Baseline characteristics between both groups did not differ in the primary study. Possibly patients developed new comorbidities disproportionately between both groups, what could explain this difference. No new patients underwent revision surgery between 2- and 5-years follow-up. In the primary article, differences between both groups regarding adequate positioning of the prosthesis in the coronal and sagittal plane were described [9]. In the current literature these differences in postoperative alignment between comparable groups are well known [10][16]. Published mid- or long-term clinical results on PSI comparing CT- and MRI-based PSI are scarce. To our knowledge, there is only one other available study by Kang et al. that studied clinical outcome at two years follow-up between CT- and MRI-based PSI in a prospective RCT besides the previous study of this paper [17]. Although, this study reported similar outcomes to those in the present study, it reported on a posterior stabilized cemented total knee system while we used a cruciate retaining total knee system. To our knowledge, there are no previous articles describing differences in survival of the prosthesis at mid-term between both groups at any follow-up moment. Regarding the clinical outcome, we used multiple PROMs and at 5-years follow-up the FJS-12 was added. This scoring system assesses how natural the prosthesis feels after TKA and thus on what grade patients have "forgotten" they've had a joint replacement [14]. The FJS-12 is already increasingly reported as a PROM in the current literature. Recently, a validation study confirmed adequate measurement properties. This study shows the increased reliability of the measurement instrument and therefore it is a valuable addition to the present study [18-19]. Much discussion remains on whether PROMs are the most adequate measurement tool to assess clinical outcome after TKA [20-22]. The main reason for this discussion is that the majority of the commonly used PROMs after TKA only meet the minimal requirements for psychometric validity. Therefore, further validation studies are required to ensure a more reliable use of PROMs in the evaluation of TKA [23-24]. Besides PROMs, wearable motion sensors are increasingly used to assess the clinical outcome following TKA. These are believed to improve the understanding of recovery after surgery. At this moment, studies regarding wearable motion sensors lack consistency [25]. Further research is necessary and may consist of a combination of PROMs and wearable motion sensors for optimal evaluation of clinical outcome after TKA. At 5 years follow-up, no new patients underwent revision surgery. The primary article described significantly fewer outliers for only tibial slope with the MRI-based PSI [9]. A deviation of >3° from pre-operatively planned (for the Biomechanical-axis and the individual components) was considered an outlier. The current study suggests that a significant difference in outliers for tibial slope does not influence a difference in revision surgery at mid-term follow-up. In 2013, Kim et al. found that sagittal alignment of the tibial component between 0° and 7° leads to

better survival of the prosthesis [26]. The article described a mean time to failure of 9.8 years (range 8 to 12.6). This suggests that continued follow-up of our patient cohort is warranted to assess differences in the survival rate of the prosthesis at long- term. For better prediction of the survival of the femoral and tibial components, radio stereometric analysis (RSA) can be used to early detect migration of the components. This could lead to a more accurate comparison of two surgical techniques with both favorable outcomes regarding survival of the prosthesis. RSA can be considered in future studies comparing two surgical techniques. The strength of this study lies in the prospective randomized design with a response rate of 70% at mid-term follow-up. Furthermore, a GLMM was used to analyze the data and is considered to be the appropriate method for assessing outcome over time [27]. Since to our knowledge this study is the first randomized trial to access the differences between MRI- and CT-based PSI from the same manufacture with midterm follow-up, our results suggest that both methods are reliable and can be used in TKA surgery. A limitation of this study could be found in the fact that the power and sample size calculation was done for the clinical outcome at 2 years follow-up. Probably this present study was underpowered to detect a significant difference regarding survival of the prosthesis. Another noteworthy limitation is the fact that due to the pandemic, patients did not visit the outpatient clinic. Therefore, no radiological X-rays were taken and physical examination was not performed. It also led to an increased number of patients (n=21) that refused further participation and this may have increased the loss to follow-up. This information should be taken into account at the 10-years follow-up.

Conclusion

At mid-term follow-up, survival rates between CT- and MRI-based patient-specific instrumentation did not show a significant difference. Regarding clinical outcome, only the EQ-5D-VAS ($p < 0.040$) showed a statistically significant difference over time, in favor of the MRI-group. This suggests that both scan modalities are suitable for use in daily practice resulting in satisfied outcome.

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CHAPTER 4

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HIGH INTRA- AND INTER-OBSERVER RELIABILITY OF PLANNING IMPLANT SIZE IN MRI-BASED PATIENT-SPECIFIC INSTRUMENTATION FOR TOTAL KNEE ARTHROPLASTY

Abstract

Purpose

Patient-specific instrumentation (PSI) in total knee arthroplasty (TKA) uses individually designed disposable guides to determine intraoperative bone cuts. The manufacturer provides the surgeon with a proposed planning which can be modified and should be approved by the surgeon before the guides are produced. This study aims to assess the intra- and inter-observer reliability among preoperative planning by orthopaedic surgeons using PSI. The authors hypothesize a high intra- and inter-observer reliability in planning TKA using PSI.

Methods

Four orthopaedic surgeons modified and approved 40 preoperative MRI-based PSI plannings three times. The surgeons were blinded to their own and each other's results. Intra- and inter-observer reliability was obtained for planned implant size, resection, and position of the implant.

Results

Intra-observer reliability Intraclass Correlation Coefficients (ICC) were excellent for femoral and tibial implant size with a range of 0.948-0.995 and 0.919-0.988 respectively. Inter-observer reliability for femoral and tibial implant size showed an ICC range of 0.953-0.982 and 0.839-0.951 respectively. Next to implant size, intra- and inter-observer reliability demonstrated good to excellent agreement (ICC>0.75) for 7 out of 12 remaining parameters and 6 out of 12 remaining parameters respectively.

Conclusion

Preoperative planning of TKA implant size using MRI-based PSI showed excellent intra- and inter-observer reliability. Further research on comparison of predicted implant size preoperatively to intraoperative results is needed.

Introduction

Patient-specific instrumentation (PSI) in total knee arthroplasty (TKA) uses individually designed, disposable guides, to determine intraoperative bone cuts. Patient-specific preoperative 3D models for the femur and the tibia can be generated either from preoperative magnetic resonance imaging (MRI) or computed tomography scans (CT). A technician is able to make a default plan for the implant size and position using this data. The surgeon can make adjustments to all settings of the femur and tibia component, taking in mind each patient's anatomical variations. After the case is approved, the manufacturer produces disposable guides for intraoperative use. Previous literature has shown that the plan provided by the technician can differ from the approved plan by the surgeon [4, 10, 12]. Consequently, differences between the suggested and appropriate component size may occur. Therefore, the expertise of the surgeon is essential for evaluating and approving the planning provided by the manufacturer. Nonetheless, none of these studies evaluated the intra- or inter-observer reliability of the planning made by the surgeon.

Multiple other studies have been conducted to assess radiographic and clinical outcome of conventional TKA compared to PSI [6, 7, 14]. Other studies compared CT- to MRI-based PSI for TKA [1, 13, 16]. However, no literature exists on evaluating the reliability of the planning method itself by comparing repetitive preoperative planning within or between orthopedic surgeons. This comparison is of added value since it demonstrates whether TKA-planning using PSI is itself reliable. Therefore, the present study is designed to assess the intra- and inter-observer reliability among preoperative planning by orthopedic surgeons using PSI. The authors hypothesize that there is a high intra- and inter-observer reliability in planning TKA using PSI.

Material and Methods

The study group consists of all patients who underwent TKA in 2015 using PSI (Signature™ system, Zimmer-Biomet Inc., Warsaw, IN) based on a preoperative MRI in the Zuyderland Medical Center (Sittard-Geleen, the Netherlands). A total of 309 patients were included. From this cohort, 40 patients were randomly selected and anonymised by Materialise NV (Leuven, Belgium). The preoperative plan, in the default setting as suggested by Materialise NV, had to be evaluated, adjusted where necessary, and approved by the surgeon. Institutional review board (METC Z, Heerlen, the Netherlands) approval was obtained for this study (trial number 13-N-117).

Measurements

Four orthopaedic surgeons were each given three folders, within every folder the selected 40 cases in a random order. As a result, each surgeon performed standard preoperative planning three times

per case within two weeks. All surgeons were senior surgeons and had a minimum experience of three years with PSI for TKA. Only the manufacturer had information regarding matching case numbers until the evaluation of all approved plannings. For each case the following 14 parameters were planned: femoral size, femoral posterior medial resection, femoral mediolateral displacement, femoral distal medial resection, femoral flexion-extension, femoral varus-valgus, femoral rotation from epicondylar axis, tibial size, tibial anteroposterior displacement, tibial mediolateral displacement, tibial resection from highest point, tibial posterior slope, tibial varus-valgus, and tibial rotation.

Outcome measurements

The primary outcome measurements were intra- and inter-observer reliability of planned size component for the femur and tibia. The secondary outcome measurements were intra- and inter-observer reliability of all remaining planned measurements as described above.

Statistical analysis

All statistical analyses were performed using SPSS software version 25 (SPSS Inc., Chicago, Illinois). The Intra- and inter-observer reliability of all measurements were determined by Intraclass Correlation Coefficients (ICCs), using an absolute-agreement two-way mixed effects model for intra-observer reliability, and an absolute-agreement two-way random effects model for inter-observer reliability. ICC values less than 0.5 are indicative of poor reliability, values between 0.5 and 0.75 indicate moderate reliability, values between 0.75 and 0.9 indicate good reliability, and values greater than 0.90 indicate excellent reliability [9].

Results

Determination of femoral- and tibial implant size showed excellent agreement with ICCs for intra-observer reliability within a range of 0.948 - 0.995 and 0.919 - 0.988 respectively, as well as excellent ICCs for inter-observer reliability within a range of 0.953-0.982 and 0.839-0.951 respectively (Table 1). The maximum size change when an implant size was changed, when compared to other plannings within the same case, was 1 size for the femoral component and 2 sizes for the tibia component. The amount of adjusted implant sizes and differences between the implant sizes within the same case per surgeon are shown in Table 3.

Furthermore, intra- and interobserver reliability demonstrated excellent to good agreement (ICC>0.75) for 7 out of 12 remaining parameters, and 6 out of 12 remaining parameters respectively. A different agreement per surgeon, with an intra-observer reliability range from moderate to excellent (ICC range >0.5 - >0.9) was found in 2 out of 12 parameters, as well as in the range from poor to excellent (ICC range <0.5 - >0.9) (Figure 1 and Figure 2).

For 3 parameters (femoral rotation from the epicondylar axis, posterior tibial slope, tibial

rotation) no changes to the proposed planning were made by any of the surgeons, resulting in an intra- and inter-observer reliability ICC of 1.00.

Table 2 shows an overview per case of changes from proposed planning, and alterations within adjusted plannings. All modifications per surgeon are listed in Table 3.

	Intra ICC Surgeon 1	Intra ICC Surgeon 2	Intra ICC Surgeon 3	Intra ICC Surgeon 4	Inter ICC
Femoral distal medial resection	0.902 (0.842-0.943)	1.000	1.000	0.923 (0.874-0.956)	0.919 (0.881-0.950)
Femoral flexion extension	0.595 (0.423-0.742)	0.620 (0.451-0.760)	1.000	0.823 (0.724-0.895)	0.487 (0.369-0.624)
Femoral mediolateral displacement	1.000	0.987 (0.979-0.993)	1.000	1.000	0.997 (0.995-0.998)
Femoral posteromedial resection	1.000	1.000	1.000	1.000	0.998 (0.997-0.999)
Femoral rotation from epicondylar axis	1.000	1.000	1.000	1.000	1.000
Femoral size	0.987 (0.979-0.993)	0.990(0.983-0.994)	0.977(0.959-0.987)	0.966 (0.942-0.981)	0.970 (0.953-0.982)
Femoral varus/valgus	1.000	0.737 (0.604-0.840)	1.000	1.000	0.129 (0.065-0.231)
Tibial anteroposterior displacement	0.737 (0.604-0.839)	0.816 (0.715-0.891)	0.972 (0.954-0.984)	0.942 (0.905-0.967)	0.250 (0.160-0.379)
Tibial mediolateral displacement	0.900 (0.839-0.942)	0.754 (0.626-0.851)	1.000	0.384 (0.186-0.579)	0.177 (0.101-0.294)
Tibial posterior slope	1.000	1.000	1.000	1.000	1.000
Tibial resection from highest point	0.946 (0.911-0.969)	0.939 (0.901-0.965)	0.997 (0.994-0.998)	0.932 (0.889-0.961)	0.743 (0.584-0.851)
Tibial rotation	1.000	1.000	1.000	1.000	1.000
Tibial size	0.973 (0.955-0.985)	0.976 (0.959-0.987)	0.977(0.962-0.987)	0.935(0.867-0.967)	0.910 (0.839-0.951)
Tibial varus/valgus	1.000	0.560 (0.383-0.715)	1.000	1.000	0.081 (0.032-0.164)

Table 1: Intra- and inter-observer Intraclass Correlation Coefficients of surgical parameters in patient-specific TKA. Intraclass Correlation Coefficients (95%Confidence interval). Intra ICC, Intra-observer Intraclass Correlation Coefficients; Inter ICC, Inter-observer Intraclass Correlation Coefficients.

	Total number of cases adjusted from default plan n (%)	Adjusted plans within same case identical n
Femoral distal medial resection	16 (10%)	1
Femoral flexion extension	60 (37.5%)	22
Femoral mediolateral displacement	1 (0.6%)	N/A
Femoral posteromedial resection	1 (0.6%)	1
Femoral rotation from epicondylar axis	0 (0%)	N/A
Femoral size	52 (32.5%)	13
Femoral varus/valgus	4 (2.5%)	2
Tibial anteroposterior displacement	73 (45.6%)	2
Tibial mediolateral displacement	77 (48.1%)	2
Tibial posterior slope	0 (0%)	N/A
Tibial resection from highest point	96 (60%)	54
Tibial rotation	0 (0%)	N/A
Tibial size	63 (39.4%)	28
Tibial varus/valgus	19 (11.9%)	6

Table 2: Amount of adjusted cases combined for all surgeons. n, number of adjusted cases, or number of identical adjusted plans within same case; N/A, not applicable

	Surgeon 1		**Surgeon 2**		**Surgeon 3**		**Surgeon 4**	
	n (%)	Difference	n (%)	Difference	n (%)	Difference	n (%)	Difference
Femoral distal medial resection	7 (17.5%)	1 mm: 4 1.5 mm: 1 2 mm: 2	0 (0%)	N/A	0 (0%)	N/A	9 (22.5%)	0 mm: 1 1 mm: 3 1.5 mm: 2 2 mm: 3
Femoral flexion extension	18 (45%)	0 dg: 2 1 dg: 10 2 dg: 4 2.2 dg: 1 2.5 dg: 1	38 (95%)	0 dg: 20 0.5 dg: 15 1 dg: 3	0 (0%)	N/A	4 (10%)	0.7 dg: 1 0.8 dg: 1 1 dg: 1 1.5 dg:1
Femoral medio-lateral displace-ment	0 (0%)	N/A	1 (2.5%)	2.3 mm: 1	0 (0%)	N/A	0	N/A
Femoral postero-medial resection	0 (0%)	N/A	1 (2.5%)	0 mm: 1	0 (0%)	N/A	0	N/A

	Surgeon 1		Surgeon 2		Surgeon 3		Surgeon 4	
Femoral rotation from epicondylar axis	0 (0%)	N/A	0 (0%)	N/A	0 (0%)	N/A	0	N/A
Femoral size	8 (20%)	0 size: 2 1 size: 6	5 (12.5%)	1 size: 5	14 (35%)	0 size: 3 1 size: 11	25 (62.5%)	0 size: 8 1 size: 17
Femoral varus/valgus	0 (0%)	N/A	4 (10%)	0 dg: 2 0.5 dg: 2	0 (0%)	N/A	0 (0%)	N/A
Tibial antero-posterior displacement	35 (87.5%)	0 mm: 1 0.1-0.5 mm: 14 0.6-1.0 mm: 16 1.1-1.5 mm: 3 3.2 mm: 1	33 (82.5%)	0 mm: 1 0.1-0.5 mm: 14 0.6-1.0 mm: 15 1.1-1.5 mm: 3	1 (2.5%)	1.7 mm: 1	4 (10%)	0.7 mm: 2 0.8 mm: 1 1.5 mm: 1
Tibial medio-lateral displacement	37 (92.5%)	0 mm: 2 0.1-0.5 mm: 8 0.6-1.0 mm: 14 1.1-1.5 mm: 4 1.6-2.0 mm: 7 2.1 mm: 1 2.6 mm: 1	36 (90%)	0.1-0.5 mm: 15 0.6-1.0 mm: 13 1.1-1.5 mm: 6 1.6-2.0 mm: 2	0 (0%)	N/A	4 (10%)	2.5 mm: 1 2.6 mm: 1 6.2 mm: 1 7.3 mm: 1
Tibial posterior slope	0 (0%)	N/A	0 (0%)	N/A	0 (0%)	N/A	0 (0%)	N/A
Tibial resection from highest point	36 (90%)	0 mm: 27 2 mm: 9	40 (100%)	0 mm: 19 0.5 mm: 6 1 mm: 12 1.5 mm: 1 2 mm: 2	1 (2.5%)	1 mm: 1	19 (47.5%)	0 mm: 8 1 mm: 3 2 mm: 8
Tibial rotation	0 (0%)	N/A	0 (0%)	N/A	0 (0%)	N/A	0 (0%)	N/A
Tibial size	13 (32.5%)	0 size: 6 1 size 7	10 (25%)	0 size: 3 1 size: 7	7 (17.5%)	1 size: 7	33 (82.5%)	0 size: 19 1 size: 12 2 sizes: 2
Tibial varus/valgus	1 (2.5%)	1 dg: 1	17 (42.5%)	0 dg: 6 0.5 dg: 11	0 (0%)	N/A	1 (2.5%)	2 dg: 1

Table 3: Amount of adjusted cases and differences between adjusted plans within same case per surgeon. n, number of adjusted cases; N/A, not applicable

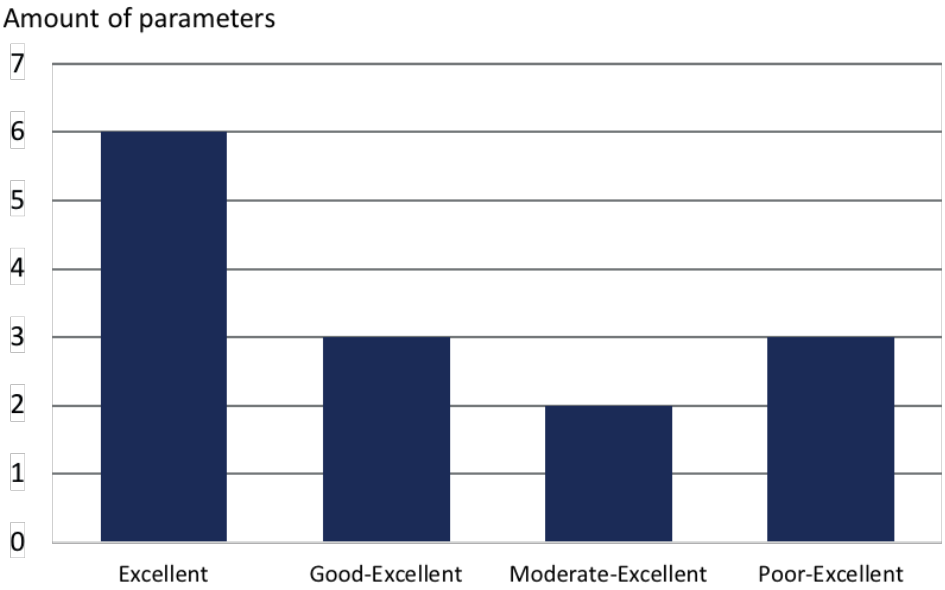

Figure 1: Number of parameters in each intra-observer reliability range

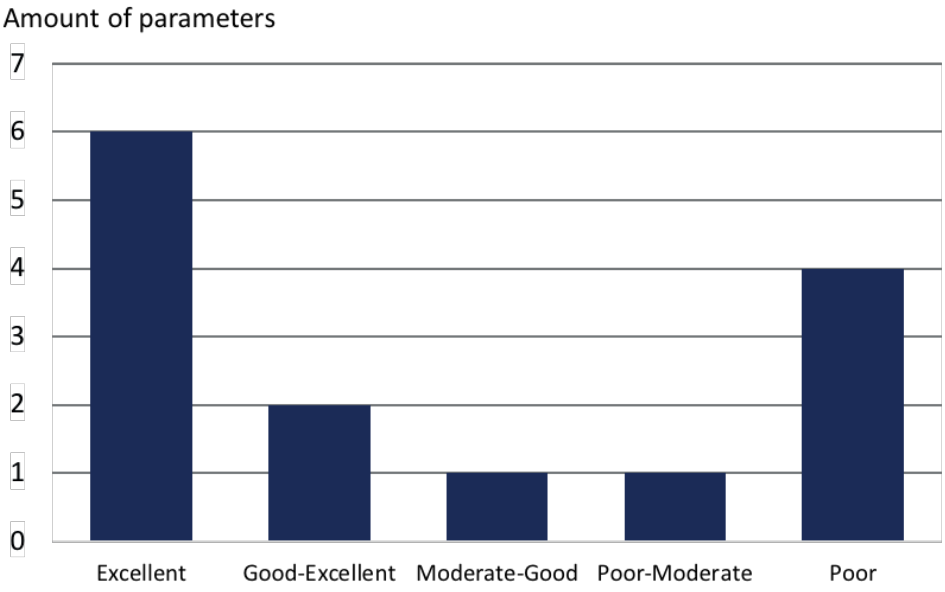

Figure 2: Number of parameters in each inter-observer reliability range

Discussion

This study shows that planning of TKA using PSI by different surgeons results in an excellent agreement for implant sizes between surgeons as well as in repeated planning by the same surgeon. Next to implant size, intra- and interobserver reliability demonstrated good to excellent agreement (ICC>0.75) for 7 out of 12 remaining settings and 6 out of 12 parameters respectively. Hence, it may be stated that PSI is a reliable method for planning of a TKA.

Previous studies have shown that PSI planning accurately predicts the implant size used intraoperatively [5, 8, 12]. The current study shows that planning of the implant size, within and between orthopaedic surgeons, is reliable. The maximum size difference was 1 implant size for the femur, and 2 implant sizes for the tibia, compared to the other plannings of the same patient.

Changes to the default plan can result in different implant sizes. Overall, more changes were made to the tibia than the femur. This may explain the greater difference in default and approved implant size for the femur and tibia: 1 size versus 2 sizes, respectively. TKA surgery can be planned more effectively by understanding the size change frequency of implants, in combination with intraoperative concordance to the preoperative plan. Consequently, when implant sizes can be accurately predicted, and planning implant sizes itself is reliable, the operating team will be able to minimize intraoperative implant size errors in advance. This may lead to improved operating room efficiency due to a decreased number of required operative trays (eq. reliable patient specific trays), less inventory planning, and possibly lowering hospital costs per TKA procedure. This may be of interest for future research.

Previous studies have emphasized that changes in the initial technician's plan were necessary to get an accurate preoperative planning of the implant sizes. Intraoperative alterations in implant size were significantly lower for the plans approved by the surgeon compared to the default plans provided by the technician [4, 10, 12]. Based on this previous literature, the expertise of the surgeon is thus essential for evaluating and approving the default planning provided by the manufacturer.

Intra- and inter-observer reliability ICC were 1.00 for femoral rotation from the epicondylar axis, posterior tibial slope, and tibial rotation because none of the surgeons modified these parameters. Due to general consensus on these parameters, less variation will occur, with a higher agreement as result. When there is less consensus on a certain parameter, more changes are made which will result in a lower agreement. Surgeon 3 made the fewest alterations to the proposed plannings, resulting in an excellent agreement (ICC > 0.90) for intra-observer reliability for all settings. Thus, high ICC can be caused by good agreement between adjusted plannings, or due to no alterations made to the proposed plan. Additionally, the adjustment of one parameter can derive alterations of other parameters. For example, an increase of resection might result in the need for a smaller implant size and adjustments in placement of the newly chosen implant size. Awareness of this effect is essential when interpreting the results of this article. This 'snowball

effect', as well as less consensus on certain parameters with more changes to the default planning and therefore more differences within and between surgeons, may explain why parameter such as femoral flexion/extension and tibial displacement showed less agreement.

Mechanical alignment technique is considered well performed when the overall limb alignment is within three degrees of neutral. Varus- and valgus angles for both femur and tibia showed modifications with a maximum of 0.5 and 2 degrees respectively. Given that the maximum difference of varus/valgus angles is 2 degrees within the same case, it is supposed that these changes are of no clinical importance. Moreover, adjustments to varus/valgus alignment are known to be dependent on the surgeon's philosophy for an anatomical-, (adjusted) mechanical-, or (restricted) kinematic alignment technique [2, 11]. A patient's specifications, such as findings from physical examination (for example preoperative leg axis, body mass index, and laxity) and previous medical history, can be determinative in the decision for a certain alignment.

Patient-specific characteristics uncontrollable by planning software, namely, ligamentous balancing and lower limb alignment, can require intraoperative changes. Therefore, correct matching of the pre-operative plan and intraoperative observations is a crucial factor in PSI-assisted TKA. In case of a mismatch, it is the surgeon's responsibility to consider a switch to conventional instrumentation. In previous literature intra-operative modifications were made to the pre-operative plan in 23% up to 36% of MRI-based and CT-based PSI-assisted TKA respectively. Most of these changes occurred due to a poor match between the pre-operative plan and intra-operative observations for the tibial component [3, 4, 15].

Furthermore, each surgeon has a 'personal touch' not only in planning, but also intraoperatively with his or her own preferences of additional releases, the decision whether or not recuts are needed, or the consideration to select a thicker insert in patients with a high BMI. Nonetheless, excellent agreement for implant sizes between surgeons and within surgeons was found in this study. Also, the agreement of implant size did not differ between the surgeons who made multiple changes to the proposed plans compared to the surgeon who made very little changes to the proposed plan.

This study has some limitations. Firstly, no power analysis for the number of surgeons, the number of patient cases, and repetitive measurements have been conducted. However, Koo et al. suggested as rule of thumb that researchers should obtain at least 30 heterogeneous samples and involve at least 3 observers whenever possible when conducting a reliability study [9]. Therefore, in the present study 40 patients were included and planned by 4 different orthopedic surgeons. Secondly, only one type of PSI was evaluated in this study. Other PSI planning systems may perform differently. Thus, these results may not be representative of all PSI technologies available. No comparison to the intraoperative results was made during this study; this study focused on the agreement of repeated planning by different surgeons - the correlation between the planned and placed implant has already been addressed in previous studies.

This study represents the first assessment of intra- and inter-observer reliability in PSI TKA. The study showed an excellent intra- and inter-observer reliability, among which implant sizes. This may contribute to more optimal and potentially effective preoperative planning of TKA surgery in the future. Therefore, this topic can be of interest for further research. Future research, with larger dataset measurements and different types of both MRI- and CT-based PSI, is necessary to further evaluate these results.

Conclusions

Preoperative planning of TKA implant size using MRI-based PSI showed excellent intra- and inter-observer reliability. Future research on comparison of predicted implant size preoperatively to intraoperative results is needed.

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CHAPTER 5

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Acta Orthop Belg. 2024;90(1):51-6.

FIRST LONG-TERM ANALYSIS OF SURVIVAL AND CLINICAL OUTCOME IN PATIENT-SPECIFIC INSTRUMENTATION FOR TOTAL KNEE ARTHROPLASTY: FOLLOW-UP OF A PROSPECTIVE COHORT STUDY

Abstract

Background

Patient-specific instrumentation (PSI) was introduced to improve post-operative alignment, and consequently the revision rate and clinical results after total knee arthroplasty (TKA). Short- to mid-term data are conflicting regarding these theoretical advantages of PSI. The purpose of this retrospective analysis was to evaluate the survival rate and clinical outcome in PSI TKA 8.4 years after initial surgery. To our knowledge, no other study investigated long-term follow-up of TKA procedures using PSI.

Materials and methods

From a total cohort of 184 consecutive patients (200 TKA) 136 patients (144 TKA, 72%) were prospectively analysed at a mean follow-up of 8.4 years (±0.4). A survival analysis with all-cause revision of TKA as endpoint was performed. Patient-reported outcome measures (PROMs) were obtained preoperatively and after 1-, 2-, 5-, and 8.4-years of follow-up. Differences between these moments of follow-up were analyzed.

Results

At final follow-up, 4 TKAs (2%) had undergone revision, all between 2-4 years after primary surgery. Reasons for revision were late infection, aseptic loosening, instability and polyethylene insert breakage. The median score of certain PROMs (WOMAC, VAS, EQ-index, EQ-VAS) decreased compared to previous follow-up scores but were significantly higher than preoperative scores.

Conclusions

After 8.4 years of follow-up, no additional revision surgery was performed compared to 5-years postoperatively. Certain PROMs at 8.4-year follow-up decreased compared to earlier moments of follow-up, but all PROMs improved compared to preoperative PROMs.

Introduction

Correct alignment of the femoral and tibial components in total knee arthroplasty (TKA) has a positive effect on the survival of the implant and short-term clinical results [1,2]. Malalignment of the components is associated with a reduction of the prosthesis' lifespan [2].

Over the past decade, as surgical techniques have evolved, patient-specific instrumentation (PSI) in TKA gained interest among orthopaedic surgeons as an alternative to traditional alignment instrumentation. With this technique, the patient's ideal prosthesis positioning is calculated based on magnetic resonance imaging (MRI) or computed tomography (CT) images of the patient's affected knee. This method was introduced in order to improve post-operative alignment, and consequently the revision rate and clinical results [3]. Despite the theoretical advantages, recent data are conflicting regarding the alignment accuracy and short-term clinical follow-up improvements of the PSI method as compared to conventional instrumentation [4, 5]. Short to midterm results show similar good clinical outcomes of PSI guided as compared to conventionally instrumented TKAs [4, 6, 7].

To our knowledge, there is only limited evidence reporting on implant survival and long-term clinical outcomes up to 5 years after a PSI procedure [8]. Additionally, no studies have been performed observing these patients for a follow-up period of over 5 years. Multiple authors emphasized the importance of long-term analysis of clinical outcome and implant survival after PSI TKA [4, 6, 8]. This is even more relevant given the substantial rise in TKA procedures performed in a younger, and therefore, more active patient population [9, 10].

This study is a continuation of previously published articles that evaluated surgical data, radiological alignment, implant survival and clinical outcomes at earlier follow-up moments in a cohort of 184 patients (200 TKAs) who received TKA using PSI [11, 12].

Materials and methods

A total of 200 PSI TKAs were performed in 184 patients with end stage osteoarthritis. Data were collected prospectively and consisted of the following parameters: revision incidence and clinical functioning scores preoperatively and postoperatively at 1-, 2-, 5-, and 7-to-9 (mean= 8.4 ±0.4) years. Criteria for exclusion in this patient cohort are described in a previous study [12]. Patients were operated between July 2009 and March 2011. Baseline characteristics are listed in Table 1.

The Signature™ system (Biomet Inc., Warsaw, IN) was used in this cohort and Vanguard™ (Biomet, Inc., Warsaw, IN) implants were inserted. Pre-operative preparation, operative procedure and postoperative management was performed as described previously by Boonen et al [13].

Survival of prosthesis at 8.4-year follow-up was collected from electronic patient files. Additionally, specific questionnaires were sent to all patients by mail to prevent missing data due to possible revision treatments in other institutions. All revision or implant removal interventions were recorded together with the reason for revision and the revised component (insert, femoral component, tibial component or total revision). An overview of the number of patients at each of the analysed follow-up moments and the reasons for exclusion, is presented in Figure 1.

The clinical functioning scores consisted of the following questionnaires: the Western Ontario and McMaster Osteoarthritis Index (WOMAC; 0 to 100, 0 being the worst and 100 the best possible outcome) [14], the Oxford Knee Score (OKS; 12 to 60, with 12 being the worst and 60 being the best possible outcome) [15], the Pain Visual Analogue Score (VAS; 0 to 10, 0 representing no pain and 10 representing the worst pain imaginable), the EuroQol (EQ-5D-3L; 1 to 3 on all 5 domains and combined into one calculated index value), and the EQ-Visual Analogue Scale (EQ-VAS; on a vertical VAS, 0 representing worst imaginable health state and 100 representing the best imaginable health state) [16].

The same array of questionnaires was used preoperatively and at the other postoperative follow-up time points. The scores were evaluated and compared between the different moments of follow-up. Additionally, for the 8.4-year follow-up the Forgotten Joint Score-12 (FJS-12; 0 to 100, 0 being the worst and 100 being the best possible outcome) has been evaluated to assess the degree of patients' awareness of their artificial joint [17].

This study was approved by the hospital's ethics committee (METC Z, Heerlen, the Netherlands; trial number 13-N-102).

All statistical analyses were performed using SPSS software (SPSS inc., Chicago, Illinois). Descriptive statistics were used to evaluate the baseline characteristics and the data regarding patient reported outcome measures (PROMs). Baseline data were not normally distributed; therefore, the observed PROMs are presented as median including the range. Wilcoxon signed-rank tests were performed to determine whether significant differences are present between follow-up observations. p values below 0.05 were considered statistically significant.

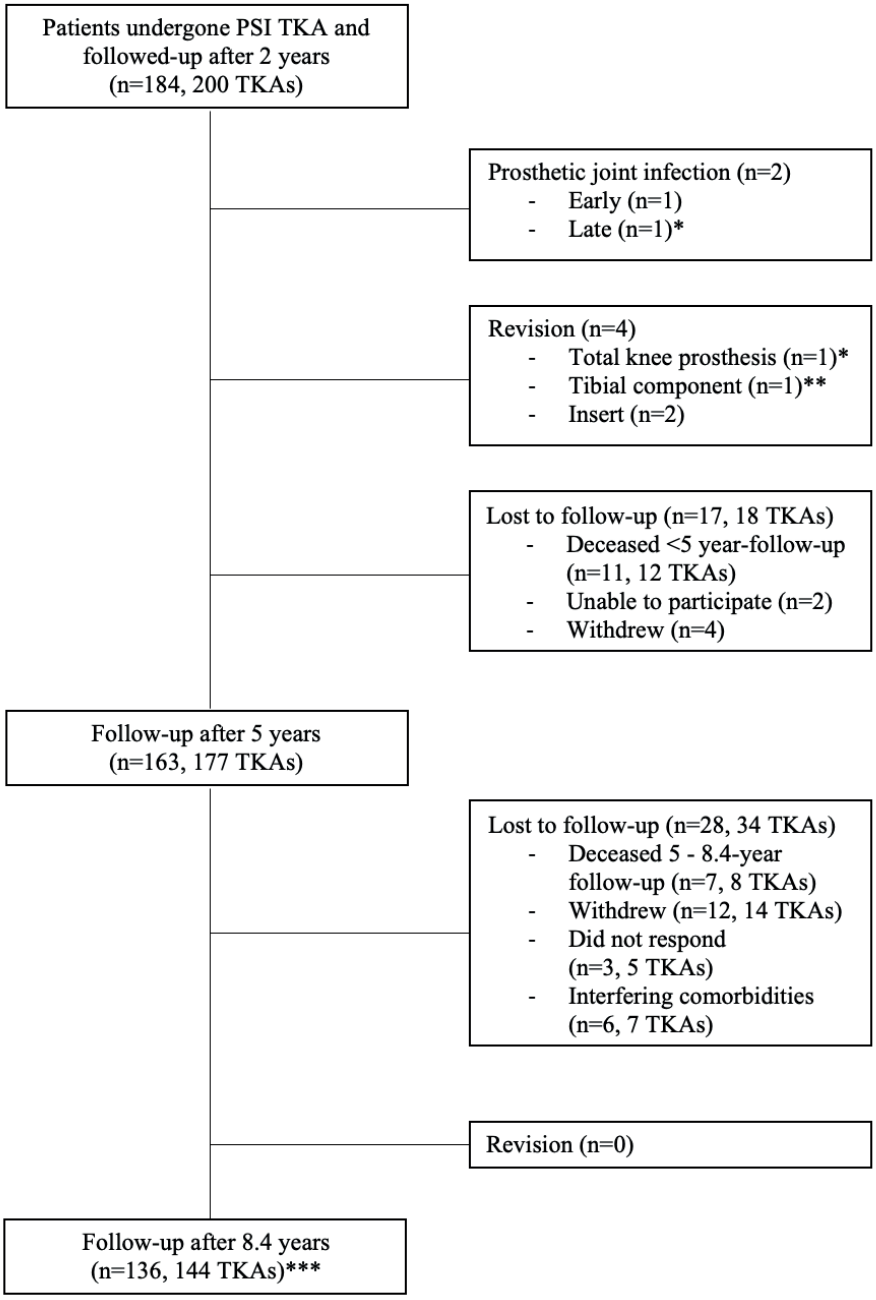

Figure 1. Diagram of the included patients at the 2-, 5- and 8.4-year follow-up

*Occurred in same patient

**Patient still included for prosthesis of contralateral knee

***One patient excluded at 5-year follow-up was successfully included at the 8.4-year analysis

Results

At a mean follow-up of 8.4 years (± 0.4), 144 patients (72%) with a mean age of 73.7 years (± 7.8) were analysed. Additional baseline characteristics are presented in Table 1. Figure 1 shows detailed information of evaluated patients at final follow-up.

At final follow-up, four patients (4 TKAs, 2%) had undergone revision surgery (Table 2). All revisions occurred in a follow-up range of 2 to 4 years. Indications for the revisions are described by Schoenmakers et al. [11]. Summarized description of the individual revision cases is shown in Table 2.

PROMs measured preoperatively and at each follow-up time point are shown in Table 3. The medians of all observed PROMs showed significant improvement at the 8.4-year follow-up compared to preoperative values ($p<0.005$). The median of the WOMAC, VAS, EQ-index, and EQ-VAS at final follow-up differed compared to one or more previous follow-up observations, as described in Table 3. The OKS did not significantly change between individual follow-up time points.

Characteristics	Value
Females, n (%)	80 (55.6%)
Median age at surgery date, years (Range)	66 (48-84)
Median follow-up, years (range)	8.3 (7.7-9.1)
ASA1, n (%)	77 (53.5)
ASA2, n (%)	62 (43.1)
ASA3, n (%)	5 (3.5)
BMI median (range)	29.1 (19.8-45.0)
Prosthesis side left/right	56/88

Table 1: Baseline characteristics

Side	ASA	BMI	Age (years)	Time until revision (years)	Type of revision	Cause of revision
Left	2	30	73	2.1	Tibial component revision	Aseptic loosening
Left	2	25	77	2.2	Total revision	Secondary prosthetic join infection
Right	1	28	54	2.5	Insert exchange	Collateral instability
Left	2	31	71	3.7	Insert exchange	Posttraumatic polyethylene insert breakage

Table 2: Characteristics of the individual revision cases

	Preoperative	1-year postoperative	2-year postoperative	5-year postoperative	8.4-year postoperative
WOMAC	57.0 (0-93)	90.5 (23-100)	90.0 (27-100)	90.0 (18-100)	82.3 (4.2-100)*
OKS	39.0 (21-56)	19.5 (12-47)	19.0 (12-45)	18.0 (12-55)	18.0 (12-53)
VAS	7 (0-10)	2 (0-10)	2 (0-9)	1 (0-10)	1 (0-8.5)***
EQ-index	0.788 (0.615-1.000)	0.874 (0.638-1.000)	0.874 (0.593-1.000)	0.874 (0.595-1.000)	0.874 (0.600-1.000)*
EQ-VAS	60 (0-100)	80 (0-100)	80 (0-100)	80 (0-100)***	75 (0-100)**
FJS12	-	-	-	-	67.75 (0-100)

Table 3: Results at follow-up time points presented as median scores and range
WOMAC, Western Ontario McMaster Universities Osteoarthritis index; OKS, Oxford Knee score; VAS, Pain Visual Analogue Score; EQ-index and EQ-VAS, EQ-5D-3L; FJS12, Forgotten Joint Score
*Significant difference compared to all previous follow-up moments (1-, 2-, and 5-year follow-up)
**Significant difference compared to 1- and 2-year follow-up moments
***Significant difference compared to 1-year follow-up moment

Discussion

The main finding of this study was that all-cause revision of TKA occurred in 4 patients (2%). All implant revisions occurred during the period between 2- and 4-year follow-up. PROMs at final follow-up significantly improved compared to the preoperative values.

To keep loss to follow-up to a minimum and still have a substantial follow-up period, the cohort was analysed at this time point instead of waiting until the 10-years follow-up. Increase in decease rate and invalidating comorbidities is expected due to an ageing cohort.

The results on prosthesis survival at final follow-up are in line with literature on conventional TKA. The 2% failure rate is minimally lower than results reported for conventional TKA after comparable follow-up [18, 19]. Specified for similar prosthesis design, the failure rate does not differ from our results, ranging between 2.2% and 3.3% [18, 20, 21]. These findings suggest no alteration in long-term survival with the use of PSI. Long-term follow-up of RCTs are necessary to clarify these findings. A randomized analysis by Schotanus et al. [8] reported no significant difference in survival after 5 years comparing conventional- to PSI TKA. Additionally, multiple short-term radiographic RCTs [22-24] and case series [25] analysing PSI have been published. Unfortunately, mid- to long-term follow-up of these cohorts have not yet been published. The absence of additional implant revisions after 4 years in our cohort is as expected since these findings seem to follow a general course of prosthesis failure after conventional TKA [18]. During the first 3 postoperative years infection and instability cause a strong increase in revisions, while in the following few years the failure incidence stabilizes relatively. After 10 years the incidence increases again, mainly due to an increase in aseptic loosening and polyethylene wear [18].

In conventional TKA, septic and aseptic loosening are the most common reasons for revision, ranging between 15-30% of all revision cases [26, 27]. The septic and aseptic loosening cases in this study, representing both 25% of the total number of revisions, are as expected. However, revision caused by instability and insert breakage has been observed much less in the literature compared to this study [26, 27]. The authors believe that this cohort can be too small to adequately compare revision after PSI TKA with conventional TKA. With only 4 revisions, the impact of a single revision is disproportionate and could over-represent a less common cause of revision.

Boonen et al. [12] published the radiographic alignment analyses of this cohort, and discussed that the number of outliers using PSI are in line with literature on PSI TKA. In this study, 2 out of 4 revisions had postoperative malalignment of the prosthesis (>3° deviation from planned alignment). One of these patients, with a mechanical axis malalignment of 7.2° varus, suffered a broken insert after trauma. The insert was exchanged after which the patient was satisfied regarding its clinical functioning. The other patient had a mechanical axis malalignment of 3.6° valgus and suffered from lateral instability postoperatively. Although the insert was replaced with a larger size, the stability did not improve. Eventually, a total system revision to a semi constrained prosthesis was considered but not performed for this patient.

The observed results on clinical functioning are in line with results described in literature on conventional TKA [28-30]. The decrease of the WOMAC and EuroQol scores could be a consequence of the ageing cohort, since aging and an associated health decline are correlated with lower PROMs [31]. The marginal decrease in VAS is considered as not clinically significant.

PSI was introduced to improve alignment after TKA, and therefor result in better clinical functioning with less revisions [3, 32]. Regarding prosthesis survival and clinical outcomes, in the current literature PSI does not seem to show advantages over conventional TKA. Studies with short- to mid-term analyses show similar results with no difference in postoperative alignment, clinical functioning or prosthesis survival [8, 33, 34, 35, 36]. Moreover, PSI is more expensive compared to conventional TKA. The pre-operative MRI scan and fabrication costs of the patient-specific cutting jigs are higher than the costs saved by reduction of operation time [37, 38]. Slover et al. [39] calculated that a revision reduction of 50% would be necessary for PSI to be cost-effective. To date, this criterium is not met. Currently, studies are launched to assess patient-specific cutting jigs designed from x-ray images. This method has the potential to greatly reduce costs compared to MRI- or CT-based PSI [40]. Future studies are needed to analyse the accuracy of this technique and whether or not this could lead to a better cost-effectiveness.

The most important strength of this study is the well-described cohort with analysis of clinical outcome and prosthesis survival over 3 successive time points, with relatively little lost to follow-up. Moreover, this study is the first to report results of over 5 years follow-up and is among the largest study currently available on follow up of PSI TKA. The most important limitation was the absence of a control group. This makes it challenging to compare this PSI cohort with

conventional instrumented TKA. A randomized controlled design would be preferable in future research. Secondly, only one PSI system was used. It is unclear if our results automatically apply to other PSI-systems. At last, although no new revisions were performed between the last two follow up moments, x-rays were not assessed for the presence of radiolucency which could be a predictor for future revisions.

Conclusions

After 8.4 years of follow-up, no additional revision surgery was performed compared to 5-years postoperatively. Certain PROMs at 8.4-year follow-up decreased compared to earlier moments of follow-up, but all PROMs were significantly higher compared to the preoperative values. Future research is needed to evaluate possible advantages of PSI TKA compared to conventional TKA, preferably with a randomized controlled design.

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CHAPTER 6

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PATIENT-SPECIFIC INSTRUMENTATION IMPROVED CLINICAL OUTCOME AND IMPLANT SURVIVAL BUT IS NOT SUPERIOR COMPARED TO CONVENTIONAL TOTAL KNEE ARTHROPLASTY: 10 YEARS FOLLOW-UP OF A MULTICENTER DOUBLE BLIND RANDOMIZED CONTROLLED TRIAL

Abstract

Purpose

Patient-specific instrumentation (PSI) is a commonly used technique designed to improve mechanical alignment in total knee arthroplasty (TKA) and was therefore believed to lead to better clinical outcome and implant survival rates compared to conventional instruments (CI). To date, long term results comparing these two techniques are not available.

Methods

This study is a 10-year follow-up of a previous double-blind multicenter randomized controlled trial where PSI was compared to CI. Patients with osteoarthritis of the knee that were candidates for TKA were included. Exclusion criteria were metal near the knee-, ankle- or hip joint, patients with contra-indications for an MRI-scan and patients who had previous knee surgery (except arthroscopic meniscectomy). Clinical outcomes were assessed using Patient Reported Outcome Measures (PROMs) and the analysis was performed with a general linear mixed model for repeated measurements. Kaplan-Meier curves were used to compare revision rates. X-rays were obtained and examined by two individual reviewers for any signs of loosening of the components.

Results

At a mean follow-up of 10.1 (SD 0.1) years, 129 patients (loss to follow-up 23%) were analyzed in this trial. No statistically significant difference between the two groups were found for any of the PROMs and revision rates were comparable, 6 in the PSI-group and 3 in the CI-group (p=0.29). Two x-rays in the PSI-group showed a radiolucent line of the femoral component.

Conclusion

At 10-year follow-up, PSI does not lead to better clinical outcome or survival of the prosthesis compared to CI.

Introduction

The number of total knee arthroplasty (TKA) procedures are still increasing [18]. Meanwhile, dissatisfaction rates after TKA ranges between 15 and 25 percent up to 2 years after surgery.

Over the past decades advanced surgical techniques for TKA have been developed in order to improve alignment, clinical outcome and survival of the prosthesis. Examples of surgical techniques that have been compared to conventional instrumentation (CI) are navigated TKA, patient-specific instrumentation (PSI) and robotic assisted TKA. Although some trials suggest better alignment of the prosthesis with these new techniques compared to, no clear prove has been delivered that these techniques lead to improved clinical outcome and implant survival rate [4, 22, 23, 24].

PSI is one of these surgical techniques used in TKA where preoperative MRI- or CT-scans are done to create a patient specific 3D digital plan of the TKA replacement. As compared to CI, some of the first trials reported better alignment of the prosthesis with these techniques, but this has not translated in improved clinical outcome or implant survival rate up to 5 years after surgery. No studies with follow-up periods over 5 years are available [4, 5, 16, 17, 25, 29].

This study is a continuation of a previous double-blind, multicenter RCT comparing PSI to CI, demonstrating the results of the 10-year follow-up [4, 5, 25]. The main goal of this study is to analyze whether there are any significant differences regarding clinical outcome and implant revision rate between PSI and CI with follow-up periods over ten years. It was hypothesized that PSI will show comparable outcomes compared to CI.

Material and Method

Between September 2010 and March 2013, 180 patients were recruited and included in this multicenter double blind randomized controlled trial. All patients provided oral and written informed consent. Two hospitals (St. Anna Hospital Geldrop and Zuyderland Medical Centre, both in the Netherlands) included 90 patients each and randomization was stratified to hospital. A more detailed description of the in- and exclusion criteria, the randomization process, the operation technique, surgical outcome, the postoperative enhanced recovery protocol and baseline conditions were described in the previous manuscripts [4, 5, 25].

At the 2-year follow-up visit, when primary outcome data were collected, patients were unblinded. The same implant (Vanguard, Zimmer-Biomet, Warsaw, IND; cemented, cruciate retaining) was used in all patients. Both groups underwent an MRI-scan pre-operatively. A neutral mechanical axis, neutral position of the femoral and tibial component in the coronal plane, 3 degrees flexion and 3 degrees posterior slope for the femoral and tibial components in the sagittal plane were obtained. In the CI-group femoral flexion and tibial slope were set at neutral instead of 3 degrees.

Patients were excluded from the follow-up if they withdrew from the study, were no longer capable of participating (e.g. due to Parkinson's disease) or passed away during the follow-up period. Patients who underwent revision surgery were excluded for the analysis of the PROMs. PROMs were obtained preoperatively, at three months and at 1-, 2- 5- and 10-year follow-up. These comprised of the: 12-item Oxford Knee Score (OKS: 0-48: 0 being the worst outcome) [15], the Western Ontario and McMaster Osteoarthritis Index (WOMAC: scored 0-100, 0 being the worst outcome) [2], pain visual analogue score (VAS: 0-10, 0 being painless) [10], the EuroQol-index (EQ-5D-index, 3L version: 0 being the worst outcome) and EuroQol-Visual Analogue Scale (EQ-5D-VAS: 0 the worst imaginable health status) [9]. At the 10-year follow-up the Forgotten Joint Score (FJS: 0-100, 0 being the most aware of having a joint prosthesis) was added [6].

PROMs were sent out to patients by mail due to the COVID-19 pandemic. The patients were requested to complete the separate questionnaires and send their response back in an envelope provided by the hospital. Electronic health records were checked if patients underwent revision surgery. In addition, antero-posterior (AP) long-leg digital radiographs and sagittal- and frontal radiographs were taken. Due to the COVID-19 pandemic not all patients were willing to visit the hospital, therefore not all participants had an X-ray. Implant interfaces and radiolucent lines (more than 1mm compared to the first postoperative X-ray) have been examined and measured independently by two reviewers (DT and ID). To determine whether radiolucent lines were progressive, x-rays were compared to x-rays from the 5-year follow-up.This study was approved by the Institutional Medical-Ethical Review Committee under trial number 12-N-139.

Statistical analysis

The first study was powered on the difference in KSS at 2-years follow-up. Statistics were performed on SPSS (IBM statistics version 25.0). Data is presented as mean (SD) or in percent (N). A general linear mixed model with the PROMs as dependent and time, group and time*group-interaction as independent fixed factors was used to examine if there was a difference over time between the different groups for each PROM. P-values <0.05 were considered statistically significant. For displaying the difference in revision rate between PSI and CI, Kaplan-Meier curves were used. A per protocol analysis was performed.

Results

At a mean follow-up of 10.1 years (SD 0.1, minimum of 10), 129 patients (71.7%) were analyzed. The distribution of the patients is displayed in figure 1. The present study population was 53% female (n=69) and 60.6 (8.1) years old at time of surgery.

All PROMs showed a statistically significant improvement over time. No statistically significant difference over time were found between the PSI- and CI-group for any of the PROMs

(WOMAC, p=0.43; OKS, p=0.81; VAS, p=0.71; EQ5D, p=0.34; EQ5D VAS, p=0.09). Forgotten joint scores did not differ between groups at 10-year follow-up (p=0.90). A display of PROM improvement and comparison is given in figure 2.

Between 5- and 10-year follow-up, 5 new revisions were performed: one revision in the CI-group due to persistent patellofemoral pain, four revisions in the PSI-group; one due to patellofemoral pain, one late acute hematogenous infection, one case of persistent instability and one case of loosening of the tibial component. A display of TKA survival is given in figure 3. The cause of revision at previous follow-up moment were described in a previous publication [32]. In total, 6 (6.6%) revisions were performed in the PSI-group and 3 (3.3%) in the CI-group (p=0.29). In total 10% of TKA needed revision.

In Figure 4, we show that individual responses measured at 10-years as compared to 5-years post-surgery also did not differ between groups. Interestingly, ~15% of patients report a decrease of >10 points on the OKS, indicating clinical relevance. This observation is consistent across all PROMs and comparable for PSI and CI.

A total of 109 patients (84%) analyzed in this study had an X-ray 10-years after surgery. Two patients showed a new radiolucent line without any complains, both of the femoral component and both in the PSI-group.

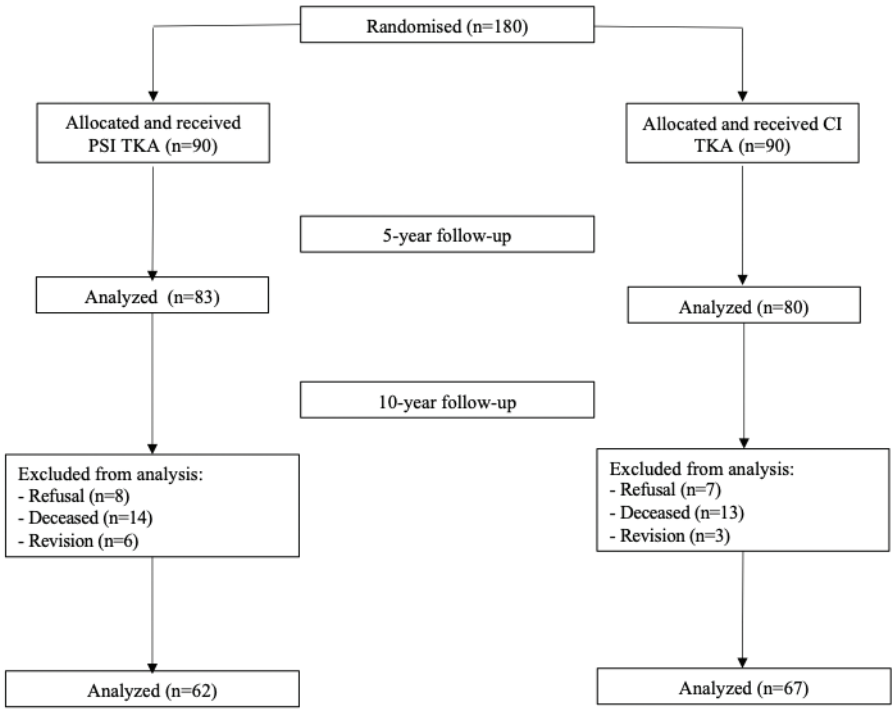

Figure 1: patients' distribution

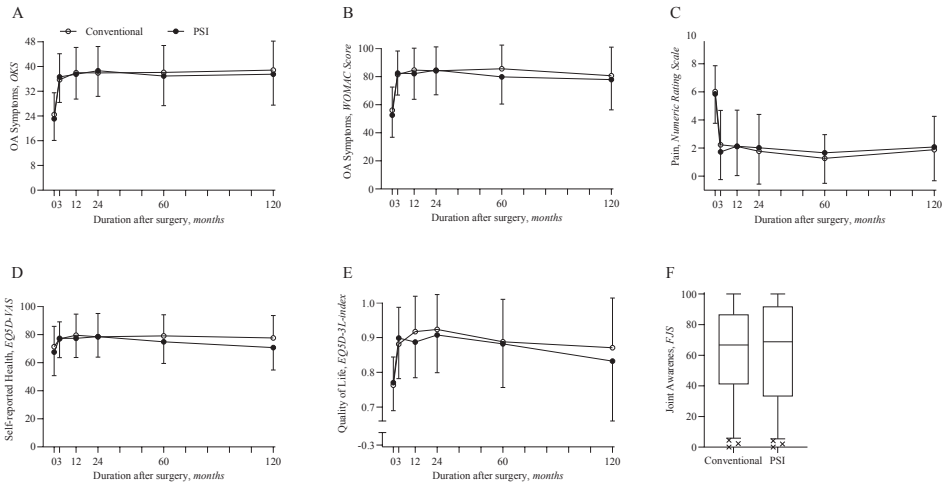

Figure 2: Difference between patient-specific instrumentation (PSI) and conventional instruments (CI) over time for each patient-reported outcome measures (PROM). (a) OKS (= Oxford knee score), (b) WOMAC (= Western Ontario and McMaster Universities Osteoarthritis Index), (c) pain numeric rating scale, (d) EQ5D-VAS, (e) EQ5D, and (f) FJS (= forgotten joint score).

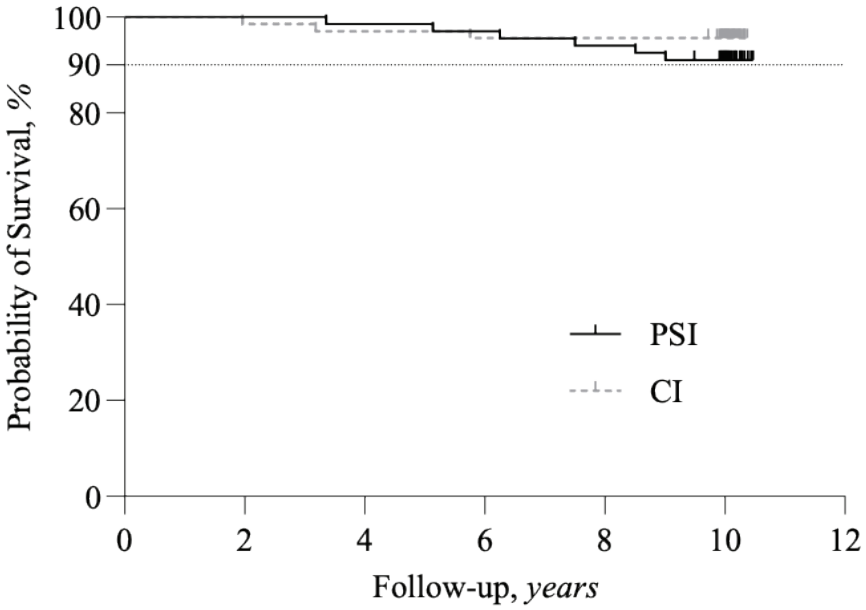

Figure 3: Kaplan–Meier survival curve comparing patient-specific instrumentation (PSI) to conventional instruments (CIs).

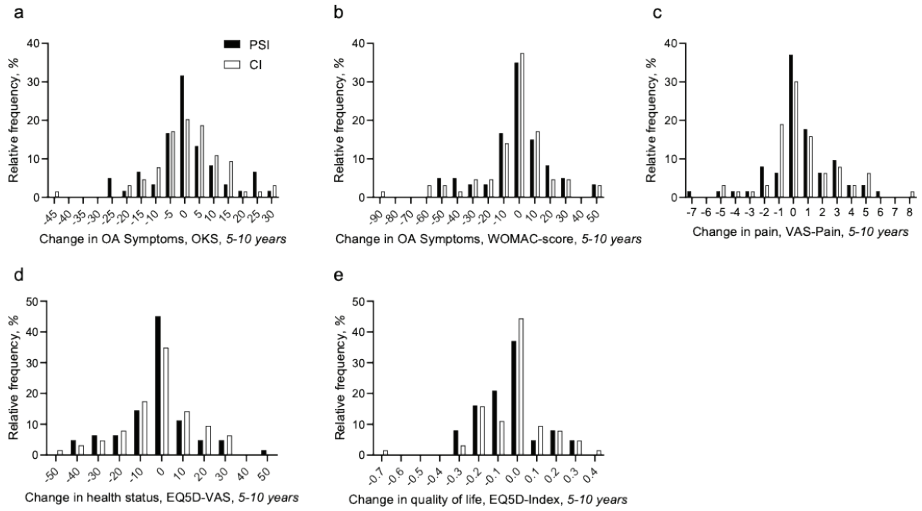

Figure 4: Delta scores from 5 to 10 years after surgery for each patient-reported outcome measures (PROM) for both, patient-specific instrumentation (PSI) and conventional instrument (CI). (a) Change in OA symptoms, OKS 5-10 years. (b) Change in OA symptoms, WOMAC 5-10 years. (c) Change in pain, VAS-Pain, 5-10 years. (d) Change in health status, EQ5D-VAS, 5-10 years. (e) Change in quality of life, EQ5D- index, 5-10 years.

Discussion

The most important finding of the present study is that at 10-year follow-up there is no significant difference in clinical outcomes or revision rate between PSI and CI for TKA.

Based on the data, it is clear that the initial theoretical claims that PSI offers more precise alignment and therefor better clinical outcomes, cannot be validated with the present data. Nonetheless, specific groups or specific indications for surgery such as patients with posttraumatic osteoarthritis or patient who undergo revision of hemi-arthroplasty to TKA might still benefit from the use of PSI [26, 27]. Further long-term studies where the use of PSI in these specific groups is compared to CI are therefore necessary.

Although studies on this subject with longer follow-up periods are scarce, our findings on clinical outcome are in line with the literature available. Previous studies comparing PSI to CI with midterm follow-up reported no differences regarding clinical outcome, but only one study was of randomized design [13,20]. Retrospective cohort studies without the use of a control group reported excellent satisfaction and functional score of PSI with follow-up up to 8 years, similar to this study [21, 39]. The lack of available literature with follow-up periods of more than 5 years immediately confirms the importance and strength of the present study.

A review of the literature concluded that PSI may benefit indeed a decline in outliers for the axial alignment of the femoral component while different results between the studies exist [11]. In our primary analyses, a significant difference in outliers for the alignment of the femoral component in the sagittal plane was found, in favor of the CI-group [4]. Summarizing, to date, there is no clear evidence that PSI leads to a better aligned knee prosthesis compared to CI. Subsequent, this does not lead to a decline in revision rate for the PSI-group, confirmed by our finding in the current study. With respect to the second claim on PSI resulting in less blood loss and faster operating times, only small gains in blood loss, surgery time and duration of hospital stay, were found with PSI compared to CI [4, 11]. Given these outcomes, the remaining question to be answered is whether PSI is cost-effective when compared to CI. Recently a systematic review and meta-analysis was published focusing of cost-effectiveness of PSI versus CI [7]. It was found that, considering operation room time and tray sterilization, PSI cost less. However, regarding the total costs per patient including imaging- and production costs, PSI is more expensive compared to CI.

In line with the literature available, our study does not show any clinical or survival advantages with the use of PSI over CI at 10-year follow-up. The same holds true for studies comparing CI with navigation. The explanation might lay in the fact that all techniques were used to obtain a neutral mechanical alignment. From recent literature, we now know that reconstructing every patient to a neutral leg axis by performing 90-degree cuts to the mechanical axis of the femur and the tibia might not be the optimal solution [19]. Future research should therefore primarily focus on the difference between alignment philosophies and the influence it has on clinical outcome and survival of the prostheses.

The most important strength of this study is that on this subject it is the first randomized controlled design with longer than midterm follow-up what makes it of great added value to the current literature. This study population is the largest of an RCT known on this subject, with relatively low loss to follow-up 10 years after surgery.

However, the study had multiple limitations. The most important limitations of this study were that the study population is most likely too small to detect statistically significant differences regarding survival of the prosthesis and a per protocol analysis was performed which could have led to selection bias. Second, the loss to follow-up resulted in a diminished amount of data for the analysis. Third, revision surgeries may be performed in other hospitals unknown to the investigators and potentially inducing bias in the results.

In this study a single PSI-system was used which improves the quality of this study, however the results may be less applicable for other systems. According to the current literature, PROMs are believed to represent the best available tools to objectively assess functional outcome and physical performance after primary TKA [3]. The OKS and WOMAC in particular have been identified as the best performing condition-specific PROMs for patients who have undergone primary

TKA [14]. The FJS is found to have good construct validity and test-retest reliability with low ceiling effect. This confirms the added value of this PROM in this current study [1, 31].

Conclusion

At 10-year follow-up, PSI does not lead to better clinical outcome or survival of the prosthesis compared to CI. Therefore, also taken into account the extra costs, it cannot be considered a new golden standard or a replacement for CI. Future research should provide better understanding of factors that influence patient satisfaction and revision rates after TKA.

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CHAPTER 7

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J Exp Orthop. 2025;12(4):e70447.

HIGHER COST, COMPARABLE OUTCOMES: A HEALTH ECONOMIC EVALUATION OF PATIENT-SPECIFIC INSTRUMENTATION VS. CONVENTIONAL INSTRUMENTATION FOR TOTAL KNEE ARTHROPLASTY IN A DUTCH AGING POPULATION

Abstract

Purpose

The demand for treatment of knee osteoarthritis is rising as the population ages. To optimize outcomes of total knee arthroplasty (TKA), several innovative techniques have been introduced, including patient-specific instrumentation (PSI). While these developments may improve clinical outcomes, they are often associated with higher healthcare costs. The present study aimed to evaluate the long-term cost-utility of PSI compared to conventional instrumentation (CI) for TKA, from a hospital perspective.

Methods

A multicenter randomized controlled trial including 180 patients was conducted in 2010, with 45 patients in each treatment arm per center. For the current economic evaluation, data from one participating center (n = 90) were analyzed. Patients were assigned to receive either PSI or CI TKA and completed EQ-5D-5L questionnaires preoperatively and at 5- and 10-year follow-up. Utility scores and Quality-Adjusted Life Years (QALYs) were derived from these questionnaires. Hospital records provided cost data, which were indexed to 2023 values. Incremental cost-effectiveness ratios (ICERs) were calculated as cost per QALY gained.

Results

At final follow-up, 23 patients (26%) were lost due to death (n = 15, 17%) or withdrawal (n = 8, 9%). The cohort included 58% females with a mean age of 67 years. QALY gains did not differ significantly between groups at either follow-up point. Mean total costs were €10,722.58 per patient for PSI and €10,063.89 for CI, with PSI exceeding CI by €658.69. This translated into an ICER of €14,856.07/QALY after 5 years and €12,836.66/QALY after 10 years for PSI, compared to €13,932.24/QALY and €12,550.40/QALY, respectively, for CI.

Conclusion

Both PSI and CI TKA improved quality of life at 5 and 10 years postoperatively. However, PSI incurred higher costs without demonstrating additional clinical benefit. From a hospital perspective, CI remains the more cost-effective approach.

Introduction

Total knee arthroplasty (TKA) is one of the most commonplace surgeries performed worldwide, with over 1 million cases performed in 2021 (10). The number of cases per year was predicted to increase and had increased over the past decade (27). In the Netherlands, the burden of hip and knee osteoarthritis (2015-2017) was estimated to be € 26.9 million based specifically on sick leave within the workforce (1,13)

The direct medical costs for osteoarthritis in the Netherlands was estimated at € 1.1 billion in 2019 (18). These numbers have led to preventative measures being undertaken, such as education on lifestyle related factors of osteoarthritis from a government level. However, the increase of surgical intervention has also been observed with 42.000 hospitalizations for osteoarthritis in 2020 (19). Not only in the Netherlands but also in the United States a massive increase of TKA has been noted. Epidemiologic analyses of the United States showed that the increase for TKA is expected to be 139% by 2040 and 469% by 2060 (27). The demand for TKA thus remains on the rise.

Historically, dissatisfaction rates up to 20% have been reported for TKA (8). Recent evidence, however, suggests that this rate is closer to 10% (8). These rates have led orthopedic surgeons and researchers to strive for optimal and accurate placement of TKA, to improve clinical outcome (25). To optimize prosthetic alignment, patient-specific instrumentation (PSI) has been introduced for TKA (25). The theory behind PSI was that a 3-dimensional (3D) reconstruction was made of the knee and subsequently a 3D-printed jig was produced, to use intraoperatively as an alignment tool. This tool would ensure more accurate alignment and therefore improved clinical results. However, this advancement has demonstrated no significant difference in clinical outcomes when compared to conventional instrumentation (CI) for TKA (23,32). Most new technological developments for TKA add additional costs to the procedure, due to the additional required equipment. Nevertheless, if these developments ensure better clinical outcomes, despite their higher costs, they could be cost-effective regardless. As these new technological improvements have emerged over the past decades, an increased interest in costs, cost-effectiveness and cost-utility has been noted. Many studies have investigated differences in monetary costs of PSI and CI, with differing results (9). Most studies conclude that PSI is more costly compared to CI, mainly due to the manufacturing of the 3D-printed jigs used intraoperatively, and the magnetic resonance imaging (MRI) necessary for jig production. Notwithstanding, PSI has proven to be more efficient with decreased operating room (OR) time (4) and decreased operating tray usage (2). These differences influence the procedure costs. Currently, no long-term studies directly evaluate the cost-effectiveness of PSI with CI TKA.

The hypothesis of this study was that PSI for TKA is more costly than CI for TKA due to additional manufacturing and imaging costs, despite less OR time and tray usage. The expected effect of the interventions was hypothesized to be similar, as clinical studies have shown no

clinical significant difference in patient reported outcome measures for both techniques (26, 5). We therefore investigated the difference in cost-effectiveness of PSI TKA versus CI TKA 5- and 10-years postoperatively, from a hospital perspective.

Materials and methods

Study design and participants

In 2010, a randomized controlled trial (RCT) recruited a total of 180 patients, of which 90 at the Zuyderland Medical Centre, the Netherlands (26,5). This single center trial was registered under the ABR registration number: NL31469.096.10. The study was performed in accordance with the declaration of Helsinki, version 2008 (29). In this study patients from our center were analyzed: 45 patients received TKA using CI and 45 patients received TKA using PSI. The other center was excluded due to inaccessibility to their costing data. The patients were followed up at the 1-, 2-, 5- and 10-year mark. The inclusion criteria of the primary study were as follows: patients with disabling osteoarthritis, that were candidates for unilateral TKA (5). The exclusion criteria included: patients with metal near the knee, ankle or hip joint; patients unable to undergo MRI-imaging, and patients who had previously undergone knee surgery (excluding arthroscopic meniscectomy) (5). The baseline characteristics of the original study included: male/female gender (40/50, p-value n.s.), mean age (65 years, SD 8.8, p-value 0.001), and mean Body Mass Index (29.5, p-value n.s.) (5).

At the time of study conduction, no in-trial economic analysis was performed. Thus, the current study was performed retrospectively from a hospital perspective. Earlier follow-up dates were not included in the study, as the quality-of-life results could have been affected by ongoing recovery and difference in effect were not expected based on the study results. For this current study, the CHEERS 2022 reporting standard and guidance for health economic evaluations was used (6).

Randomization, blinding, and data collection

Randomization was computer generated. More detailed information on the randomization process can be found in the original article (5). The patients as well as the researchers were blinded to the type of intervention; at the 2-year follow-up patients were unblinded. Preoperatively and 1-, 2-, 5-, and 10-years postoperatively the patients received EQ-5D-5L (Dutch tariff) questionnaires to assess quality of life after TKA (12). These were filled in at the outpatient clinic or sent by post. The forms were entered into the electronic data capture system.

Outcomes

For the cost-effectiveness analysis, the EQ-5D-5L was used as the primary outcome. This is a standardized instrument which assesses five different aspects of health (12). These aspects include mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. These five

aspects can be scored as no-, slight-, moderate-, severe-, and extreme- problems/unable to do. Additionally, the patients had to score their overall health from 0-100, with 0 meaning the worst imaginable health and 100 meaning the best imaginable health. The estimated benefit from the EQ-5D-5L was transformed into the number of gained or lost QALYs by calculating the index values (19). These values ranged from 0 to 1.000, with 0 being death and 1.000 being perfect quality of life. Patients lost to follow-up due to death thus received the utility 0. The index values can be calculated using an online tool (14). These index values were used to calculate the delta quality-adjusted life year (Δ QALY) during the follow-up years. This was calculated by subtracting the utility measured preoperatively with the utility measured during the different follow-up years, and dividing this value by the number of years it is counted over. By doing this, the mean gain or loss in utility was determined over the course of one year. It was assumed that the changes over this time period were linear.

Costs

The analysis *was* performed from a hospital perspective. All costs were presented in euros (€). 2023 was used as the reference year. The calculation of costs related to the surgery were split into three separate categories: preoperatively, intraoperatively and postoperatively. Preoperative costs included costs of initial presentation at the outpatient clinic, standard X-ray imaging and/or MRI (for the PSI group), production of the PSI mold, preoperative health assessment, preoperative lab work, and preparation of the surgical trays. For the intraoperative category, all relevant data correlating to the surgery was calculated. This included the knee prosthetic itself, OR usage costs and time. The OR time cost was not available in our center. The pricing for OR time was therefore based on the Dutch reference pricing (16). The postoperative costs were attributed to standard postoperative care (a single X-ray of the knee the first day after surgery, and a personal session with a physiotherapist), length of hospital stay costs and revision surgery during the follow-up.

The Δ costs were calculated for each separate category. The Δ total cost were calculated for all abovementioned cost categories together. To preserve the costing integrity of our center, an indication of costs based on the reference prices of healthcare costs in the Netherlands were presented in Table 1. These were available from the Dutch manual for costs for economic evaluation in the healthcare sector: methodology and references prices, version 2024 (16).

Specific, detailed data were not available on the costs of healthcare staff, such as cooking- and cleaning staff, residents, specialists and nurses. These were not taken into account when performing the current analysis.

Cost category	Reference price in the Netherlands in euros (€)
Intake at outpatient clinic	€ 120
Magnetic resonance imaging (MRI) of the knee	€ 264
Standard X-ray of the knee	€ 82.17
Costs of OR time, defined per minute	€ 11.09
Costs of admittance in the hospital, defined per day	€ 644

Table 1: An overview of costs retrieved from the publicly available online manual for reference pricing in the Netherlands in euros (16). Not all of the costs as described in the materials and methods are given in this table. Only available costs from the manual. The actual costs of our center were not given to ensure integrity. The costs given in this table are indicative of costs in our center. Abbreviations: MRI (Magnetic Resonance Imaging), OR (Operating Room)

Analysis of data

ICER was calculated by subtracting the mean total costs of the PSI group from the CI group, divided by the mean QALY of the PSI group subtracted from the CI group (ΔTotal Cost / Δ QALY) (19).

For the cost-effectiveness analysis, discount rates of 3% for costs and 1.5% for effects were applied in accordance with Dutch guidelines for economic evaluations (22). The ICER was calculated for base case (with and without discounting), the upper and lower bounds of the confidence intervals and worst- and best-case scenarios for both follow-up periods. To emulate a best- and worst-case analysis, either +10% or -10% cost and either +10% or -10% QALY gain was applied for PSI and CI.

ICER is interpreted with the cost-effectiveness plane (3). This plane is divided into four quadrants: northwest (NW), northeast (NE), southwest (SW), southeast (SE). These quadrants represent: increased cost with less effect (NW), increased cost with more effect (NE), decreased cost and less effect (SW), decreased cost and more effect (SE). The National Institute for Health in the Netherlands (ZorgInstituut Nederland) advises a cost-effectiveness threshold of up to €50,000 per QALY gained for health interventions related to osteoarthritis based on a proportional shortfall of 0.41 (31). Therefore, any ICER that falls under the threshold is regarded as cost-effective within the cost effectiveness plane. In addition, a sensitivity analysis was performed by calculating the ICER when comparing PSI TKA to CI TKA. No subgroup analysis was performed.

Statistical analysis

All data was analyzed using IBM SPSS version 29. To analyze the effect of missing data on QALY and cost/QALY analysis, the 'missing complete at random' (MCAR) test was used (13). If data was MCAR, mean imputation was used due to normally distributed data. A significance level of $p \leq 0.05$ (95% Confidence Interval (Ci)) was used to determine significance. As quality of life was not normally distributed, a nonparametric bootstrap sampling method with 1000 replications was used to assess statistical significance of the differences between the two treatment groups.

Bootstrapping was not used for the cost outcomes as the hospital perspective of this analysis ensured fixed costs which are linear during the follow-up period.

Results

Baselines

At baseline, among the 90 included in the study, 58% patients were female. During the follow-up, 23 patients (26%) were lost to follow-up due to death (n= 15, 17%) or withdrawal (n= 8, 9%). The mean age was 69.2 years for the PSI group and 65.4 years for the CI group. Figure 1 displays a flowchart of the follow-up of patients during the past 10 years. Table 2 displays the baseline characteristics at time of inclusion.

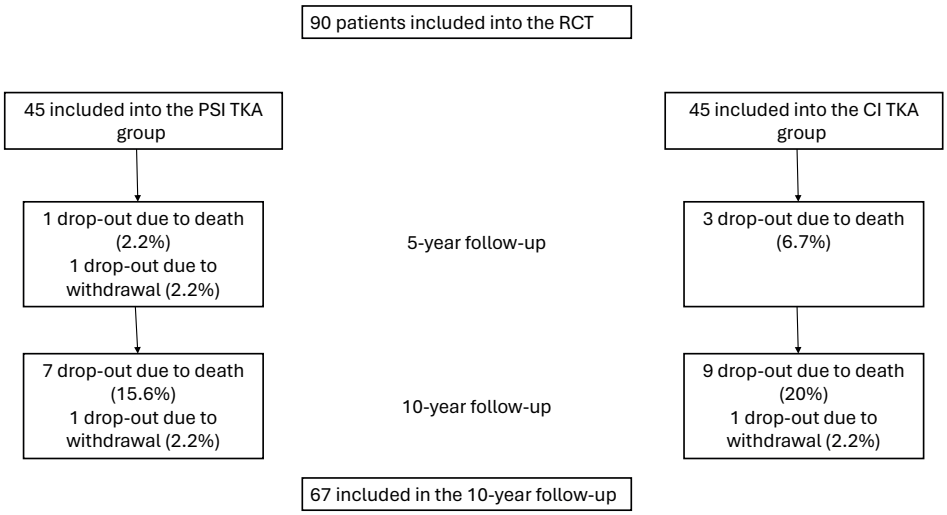

Figure 1: patient drop-out rates during the 10-year follow-up period. All reported deaths were not related to the study intervention. Abbreviations: TKA (Total Knee Arthroplasty), CI (Conventional Instrumentation), PSI (Patient-Specific Instrumentation).

	PSI (n= 45)	CI (n= 45)	Significance between groups (p-value)
Age (years)	69.2 (SD ± 8.53, 95% CI 66.6-71.7)	65.4 (SD ± 9.6, 95% CI 62.5-68.3)	0.512
Height (meters)	1.67 (SD ± 0.08, 95% CI 1.65-1.70)	1.70 (SD ± 0.09, 95% CI 1.67-1.73)	0.072
Weight (kg)	83.3 (SD ± 11.9, 95% CI 79.7-86.9)	81.9 (SD ± 14.5, 95% CI 77.5-86.3)	0.663
BMI (kg/m^2)	29.4 (SD ± 4.0, 95% CI 28.3-30.7)	28.2 (SD ± 3.7, 95% CI 27.1-29.3)	0.062

Table 2: baseline characteristics patient population at time of inclusion. The means of following outcomes were calculated for the cohort, at time of inclusion: age in years, height in meters, weight in kg and BMI in kg/m2. The results are presented as means with standard deviations (±) and 95% confidence intervals (Ci). Statistical significance was determined at a p-value of $p \leq 0.05$. No statistically significant differences were found at baseline, as demonstrated in this table. Abbreviations: PSI (Patient Specific Instrumentation), CI (Conventional Instrumentation), BMI (Body Mass Index) and CI (Confidence Interval).

Missing data

Little's MCAR test showed a significance of p=0.096 for missing data of the EuroQol-5D for the entire follow-up period. The missing data was random.

Quality of life

A complete overview of the mean QALY gain for the total population, PSI group, and CI group after 5- and 10-years can be found in table 3. The table includes standard deviations and 95% confidence intervals (CI). All mean utilities and significance thereof are reported in the original studies and corresponding follow-up studies (4, 5, 26,28). No statistically significant differences were found between PSI and CI TKA for the amount of gained QALYs/year, 5- and 10-years postoperatively ($p \geq 0.05$). The data is additionally presented in table 3 with standard deviations and confidence intervals.

	Total QALY gain (PSI and CI)		QALY gain PSI		QALY gain CI		p-value
5-years postoperative	0.72 (± 0.48, 95% CI 0.62-0.82)	n = 80	0.72 (± 0.53, 95% CI 0.56-0.88)	n = 37	0.72 (±0.44, 95% CI 0.59-0.85)	n = 43	0.308
10-years postoperative	0.82 (±1.19, 95% CI 0.56-1.06)	n = 67	0.83 (SD ± 0.86, 95% CI 0.57-1.09)	n = 32	0.80 (±1.46, 95% CI 0.36-1.24)	n = 35	0.166

Table 3: baseline characteristics patient population at time of inclusion. The means of following outcomes were calculated for the cohort, at time of inclusion: age in years, height in meters, weight in kg and BMI in kg/m2. The results are presented as means with standard deviations (±) and 95% confidence intervals (Ci). Statistical significance was determined at a p-value of $p \leq 0.05$. No statistically significant differences were found at baseline, as demonstrated in this table. Abbreviations: PSI (Patient Specific Instrumentation), CI (Conventional Instrumentation), BMI (Body Mass Index) and CI (Confidence Interval).

Total costs

For PSI TKA, the total costs were €10,722.58 per patient. For CI TKA, the total costs were €10,063.89 per patient. In total, the usage of PSI TKA costs €658.69 more than CI TKA per patient. Total costs are the standard costs for the entire pathway of care; these do not differ at the 5- and 10-year follow-up period.

Preoperative costs

These costs included the costs of standard pre-operative workup, imaging, mold production. All preoperative costs combined amounted to €971.66 less for CI TKA.

Intraoperative costs

The total OR cost and cost of the prosthetic itself is equal for PSI and CI TKA. This amounts to €0 difference between the two techniques. The main difference between the two techniques intraoperatively is the OR time and tray use. The number of surgical trays used for PSI TKA were 5 large trays and 4 small trays. For CI TKA, 7 large trays and 3 small trays were used. The difference in cost for the sterilization of these trays is €132.93 more for CI TKA. From the cohort of patients, the reduced OR time for PSI TKA was a mean of 11 minutes per case. OR costs were defined as €11.09 per minute (4). This amounted to a difference of €254.92 less for PSI TKA for intraoperative costs.

Postoperative costs

These costs included the costs of the hospital stay and standard postoperative care. The mean length of hospital stay for PSI TKA was 4.3 days. The mean for CI TKA was 4.4 days. This amounted to a total postoperative cost of €58.05 less for PSI TKA.

Revision rates

No difference was found in the number of revisions performed between the two groups. For the CI group one revision was reported due to lateral knee pain. For the PSI group one revision was performed due to aseptic tibial plateau loosening. Both patients received revision in the first year after surgery. Revisions were accounted for in the sensitivity analysis by adding their costs to the initial costs of care.

Cost-utility

With discounting, the cost-utility measure for PSI TKA was €13,839.20/QALY gained after 5-years and €11,156.02/QALY gained after 10-years. With discounting the cost-utility measure for CI TKA was €12,989.06/QALY gained after 5-years and €10,863.36/QALY gained after 10-years.

ICER and Sensitivity analysis

A sensitivity analysis was performed by calculating the ICER when comparing PSI TKA to CI TKA. As utilities were not significantly different in all scenarios, ICUR was not calculated in the current study. The analysis, as illustrated in figure 2, delineates the positioning of the calculations across the various quadrants of the cost-effectiveness plane. Base case analysis showed that PSI is more expensive and more effective after 5- and 10-years, situating in the NW of the cost-effectiveness plane in figure 2. This indicates a higher cost with a higher QALY gain. The sensitivity analysis showed that the cost-effectiveness of PSI improves if QALY gains are higher but worsens if clinical outcomes worsen. The cost-effectiveness of CI remains favorable; however, it contains considerable variability in the sensitivity analysis, attributable to fluctuations in the estimated effect bounds. In other words, if CI performs better or worse clinically, it has more effect on the cost-effectiveness than that it would for PSI. This indicates that the cost-effectiveness of CI is highly sensitive to postoperative quality-of-life outcomes obtained after 5- and 10-years. This analysis showed that in the best-case both PSI and CI showed improved cost-effectiveness, so both situating in the NE quadrant of figure 2. CI showed an increased cost-effectiveness than PSI in the best case. In the worst case both interventions present a decrease in cost-effectiveness, situated in the NW quadrant, but more for PSI when compared to CI. True cost-effectiveness is situated in the SE quadrant. If CI performs at its lowest bounds, PSI could hypothetically be situated here after 10-years.

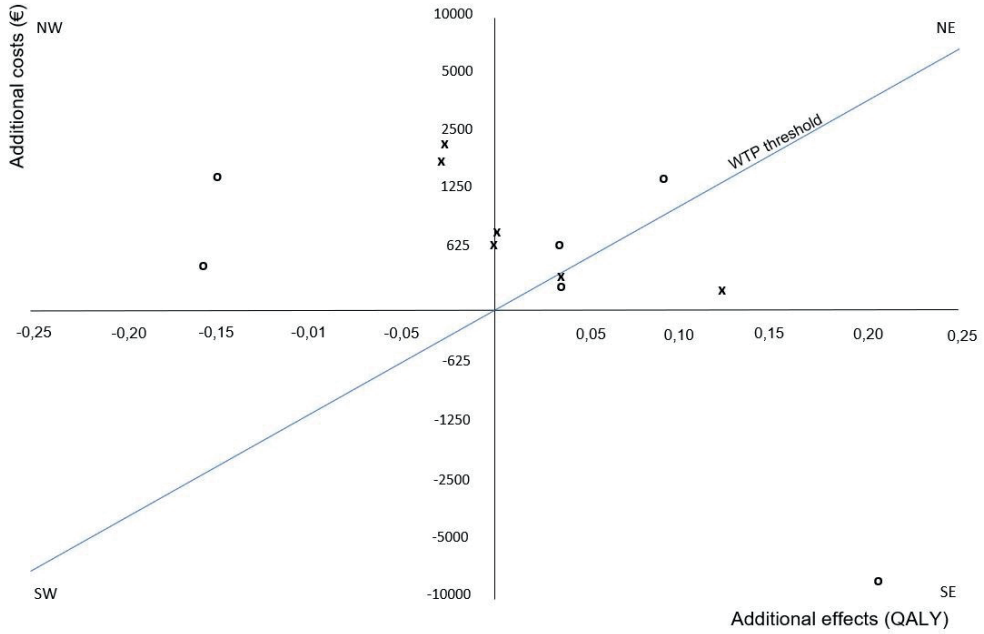

Figure 2: Cost-effectiveness plane comparing PSI TKA to CI TKA in different scenarios.This figure shows a scatter plot of the sensitivity analysis including discounting scenarios, upper- and lower bounds and the best- and worst-case scenarios when comparing PSI to CI TKA in a timeframe of 5- and 10-years postoperatively. The plot compares additional costs in different scenarios to different effects (QALY). The plot shows multiple scenarios under the WTP threshold (€50.000). All scenarios (base case as well as best- and worst- case) in the 5-year follow-up are indicated by 'x'. All scenarios in the 10-year follow-up are indicated by 'o'. Abbreviations: WTP (willingness to pay), NE (northeast), NW (northwest), SE (southeast), SW (southwest), QALY (quality adjusted life year).

Discussion

The aim of the present study was to compare cost-effectiveness of PSI and CI TKA. The main finding was that PSI TKA costs €658.69 more per procedure than CI TKA if all applicable costs, from a hospital perspective, are considered. PSI TKA was less cost-effective after 5- and 10-years.

Comparable literature is scarce, but the current presented results are reflective of other results published in Europe. Räsänen et al. presented a cost per QALY of €13,995, 1 year after primary CI TKA (21). Furthermore, Schilling et al. presented their estimate of 0.77 of QALY gain 7-years after CI TKA in 2016 (21,24). This data on cost per QALY and QALY gain 5- to 10-years after primary TKA corresponds to the presented data which was derived from our center.

Cost-effectiveness also depends on the willingness to pay threshold. In the Netherlands the threshold is up to €50,000 per QALY gained for health interventions related to osteoarthritis

(31). In the current study the cost per QALY for both PSI and CI TKA are within this range and could therefore both be accepted as cost-effective interventions. Additionally, the ICER 10-years after PSI falls within this range, and therefore PSI could be considered cost-effective after 10-years. Reports have shown that PSI TKA can be a useful tool in anatomically challenging cases. Mainly, in cases where intramedullary alignment tool use is not possible or when there are posttraumatic anatomical changes (17). The PSI method offers surgeons an alternative guidance option. The increased cost per patient case could therefore have its value in specific situations.

This study has a few limitations. Firstly, the cost-effectiveness analysis was performed from a single hospital perspective. Unfortunately, calculations performed from this perspective do not offer insight into the effects of TKA after hospitalization. The possible cost-benefit of return to work, care burden and overall health-benefits with improved mobility have not been taken into account in our analysis. Due to this, the current analysis did not give a full overview of the societal impact of the intervention. TKA has been shown to improve quality of life, with increased mobility and decreased pain being the main attributing factors (7, 20). This in turn ensures increased return to work and sports of up to 90% one year postoperatively. This could have major cost-effectiveness implications for all types of TKA, which should be the focus of future research. Another limitation is that the RCT on which this study was based, was performed in 2010. Although the clinical outcomes are expected to be similar now, this has an implication on the costs. For instance, the length of hospital stay in 2010 was 4.2 days, while it is currently 2 days due to pathway optimization (11). Additionally, change in the current pathways has impact on staff costs, which were not available for the current analysis as mentioned in the materials and methods. This impacts total costs and thus cost-effectiveness. So, while costs were converted and discounted from 2010 to 2023, the current analysis might give a slight skewed view on the total cost outcome.

Furthermore, the hospital costs were derived from a single center which makes this analysis site-specific. Secondly, as patients age the EQ-5D utility scores are expected to worsen linearly (30). As a result, the present analysis could include outliers in utility scores which are not attributed to the TKA, but to overall decline in perceived health (15).

The strength of this analysis was that it presents data which was collected over the course of 10-years. As of now, no cost-utility analysis over this period of time is available for PSI and/ or CI TKA. Additionally, the data was missing completely at random, which indicates that there is little bias within calculated QALYs. Lastly, the analysis aimed to look at many different variables that influence costs within the hospital, to create valid evidence based on a single hospital setting.

Conclusion

PSI and CI TKA ensure an increased quality of life 5- and 10-years postoperatively in an aging population. From a hospital perspective, PSI TKA is less cost-effective at 5- and 10-years

postoperative. Since PSI TKA is not proven to be significantly clinically superior to CI TKA, and it is more costly per patient case, its use should be considered carefully.

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CHAPTER 8

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THE INFLUENCE OF THE NUMBER OF RADIOLOGICAL OUTLIERS ON THE SURVIVAL AND CLINICAL OUTCOME OF TOTAL KNEE ARTHROPLASTY

Abstract

Introduction

After total knee arthroplasty (TKA), dissatisfaction rates are described up to 30%. Optimal alignment of the prosthesis in TKA is believed to improve clinical outcome and survival rates. Radiological outliers after TKA are used to define this alignment. Limited evidence is available on the cumulative effect of these outliers on survival or clinical outcome. The purpose of this study is to assess whether the amount of postoperative femoral and/or tibial radiological outliers, measured in different planes, influences the survival and clinical outcome after TKA.

Methods

Prospective data were used from a previously published randomized trial, with a mean follow-up of 5 years after surgery. Data of 168 patients who received TKA were assessed. Patients were divided into four groups: 0, 1, 2 or ≥3 postoperative radiological outliers of the femoral and/or tibial component in different planes (e.g. frontal, sagittal). Revision rates were analyzed and clinical outcome was assessed using PROMs. The study used a general linear model for repeated measures to compare the difference of each questionnaire over time between the groups.

Results

No statistically significant differences were found between patients with 0, 1, 2 or ≥3 outliers regarding improvement of postoperative PROMs. Data was underpowered to detect a possible relationship between the number of outliers and the survival of the prosthesis.

Conclusion

The number of postoperative radiological outliers did not influence clinical outcome after TKA. High-powered studies are needed to examine the influence of these outliers on survival rates.

Introduction

In the treatment of severe end-stage osteoarthritis (OA), joint replacement has proven to be one of the most successful surgical procedures [1][2][3]. Over the past decades, the rate of total knee arthroplasty (TKA) has increased worldwide and is expected to grow even further [4]. Nevertheless, dissatisfaction rates after TKA rise up to 30% [5][6][7]. Multiple operative techniques have been developed to achieve the best results regarding clinical outcome and survival rates of the prosthesis. Patient-specific instrumentation (PSI), computer- and robotic-assisted surgery for TKA are all developed in the pursuit of optimal alignment of the tibial and femoral components. It is believed that this optimal alignment improves clinical outcome and survival rates [8][9]. Many studies have described the results of these techniques by measuring the occurrence of postoperative radiological outliers (>3 degrees deviation from pre-operative planning) [10][11][12][13][14][15][16][17]. The outliers of the tibial and femoral component are measured in different planes (e.g. frontal, sagittal). Available literature on the influence of the number of these outliers combined on the clinical outcome and survival of the prosthesis is limited. The current study is a continuation of a previously published study on the 5-years follow-up in TKA surgery. In that study, PSI was compared to conventional TKA regarding clinical outcome and survival of the prosthesis, conducted as a randomized controlled trial. This study compared the clinical outcome, in terms of PROMs, and survival of the prosthesis after TKA between patients with different amounts of postoperative radiological outliers. It was hypothesised that the cumulative number of postoperative radiological outliers negatively influences the clinical outcome and survival of TKA.

Methods

In this multicentre prospective study, data was used from the 5-years follow-up of a previously published study [17][18]. The primary study was approved by the institutional review boards of both hospitals (File nr. 10-T-21) and informed consent from all patients was obtained. This randomized, double-blind controlled trial compared TKA procedures with use of PSI to the conventional surgical method. A total of 180 patients were enrolled between September 2010 and March 2013 at the Zuyderland Medical Center (Sittard-Geleen, the Netherlands) and St. Anna Hospital (Geldrop, the Netherlands). Inclusion criteria were patients with disabling osteoarthritis of the knee, candidate for total knee arthroplasty. Exclusion criteria were osteosynthesis or other metal near the knee, ankle or hip joint, the inability to undergo an MRI-scan and previous knee surgery (except arthroscopic meniscectomy). The same cemented cruciate retaining implant was used in both groups (Vanguard TKA System, Zimmer Biomet Orthopaedics, Warsaw, IN, USA). All procedures were performed by experienced orthopaedic knee surgeons with >10 years of experience with conventional TKA who performed at least 100 TKA's using PSI. For all patients the position of the prosthesis was planned pre-operatively. In the frontal plane the goal was to

obtain a neutral mechanical axis and neutral position of the femoral and tibial components (90° cut to mechanical axis of both femur and tibia). When using PSI, a femoral flexion and posterior slope of 3° was obtained in the sagittal plane. When using conventional TKA, femoral flexion and posterior slope were set at 0° [17]. Six-weeks postoperatively, all patients received weight bearing AP long-leg radiographs and standard lateral radiographs. On the long-leg radiographs, deviations of more than 3° from a neutral mechanical axis (180°) and more than 3° varus or valgus position of the tibial or femoral component were regarded as outliers. On the lateral radiographs, values that differ more than 3° from pre-operatively planned femoral flexion and posterior slope were regarded as an outlier. In this current study patients were allocated to different groups, based on the cumulative number of postoperative radiologic outliers. The first group consisted of patients with no radiological outliers. The second, third and fourth group consisted of patients with 1, 2 or ≥3 radiological outliers, respectively. To measure clinical outcome after TKA all patients completed the questionnaires described below pre-operatively, at 3 months follow-up and at 1-, 2- and 5-years follow-up. First the Dutch version of the Oxford Knee Score (OKS) scored from 12 to 60, with 12 being the best possible outcome and 60 being the worst possible outcome [19]. Second, the Dutch version of the Western Ontario and McMaster osteoarthritis index (WOMAC) scored from 0 to 100 with 0 being the worst outcome and 100 being the best outcome [20]. Next a visual analogue scale (VAS-pain) for pain [21] and the EuroQol (EQ-5D, 3L version) [22]. For the EQ-5D a single summary index was used. An index of 1 represents perfect health. To assess survival of the prosthesis, patients' files were checked if revision surgery was performed.

Statistical analysis

The analyses were performed with the use of SPSS (IBM statistics version 25.0). An ANOVA test was done to determine if there was a difference between the groups pre-operatively. Thereafter, a general linear model for repeated measurements was used to examine if there was a difference over time between the different groups for each questionnaire. P-values <0.05 were considered statistically significant.

Results

In this current study we used data from the 5-years follow-up of a previous RCT [17]. Measurement method of outliers on radiographs was described in the previous article. Patients' characteristics including the occurrence of the number of outliers are described in table 1. Table 1 also shows that most outliers were measured in the sagittal plane for both femoral and tibial component. Lost to follow-up of this trial was described in the previous article [18]. Loss to follow-up for the specific groups in the current study was 1 patient in the group with no outliers, 3 patients in the group with 1 outlier, 3 patients in the group with two outliers and 2 in the group with ≥3 outliers. Finally, 168 patients were included in this study. There was no statistically

significant difference over time between the groups for each questionnaire assessed (Table 2). Results for each questionnaire are presented separately in figures 1-5.

At final follow-up, 5-years postoperatively, a total of 4 patients had undergone revision surgery. Two patients in the group with 1 outlier; one revision of the tibial component to one size smaller due to lateral knee pain and one placement of a patella button for patellofemoral complains. The other two patients underwent revision due to persistent knee pain, one in the group with 2 outliers and one in the group with 3 outliers. No revisions were performed due to instability of the knee joint.

Participants		168
Men:women (%)		66:102 (39:61%)
Mean age		71.8 (range 52.5-87.6)
Mean follow-up		4.6 years (range 4.4 – 4.8)
Number of outliers per patient (%)	Patients with 0 outliers	40 (24%)
	Patients with 1 outlier	55 (33%)
	Patients with 2 outliers	49 (29%)
	Patients with ≥3 outliers	24 (14%)
Outliers per radiological outcome (%)	HKA	49 (21%)
	FFC	28 (12%)
	FTC	13 (6%)
	LFC	80 (35%)
	LTC	60 (26%)

Table 1: patient characteristics. HKA = hip knee angle. FFC = frontal femoral component. FTC = frontal tibial component. LFC = lateral femoral component. LTC = lateral tibial component

PROMs	N	Significance of difference over time between groups (statistically significant different when p<0.05)
WOMAC	138	0.436
OKS	137	0.174
VAS-pain	143	0.368
EQ5D	136	0.233
EQ5D-VAS	135	0.223

Table 2: Significance of difference in number of outliers over time, statistically significant different when p<0.05. WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index. OKS = Oxford Knee Score. VAS = Visual Analogue Scale. EQ5D = Euroqol 5D.

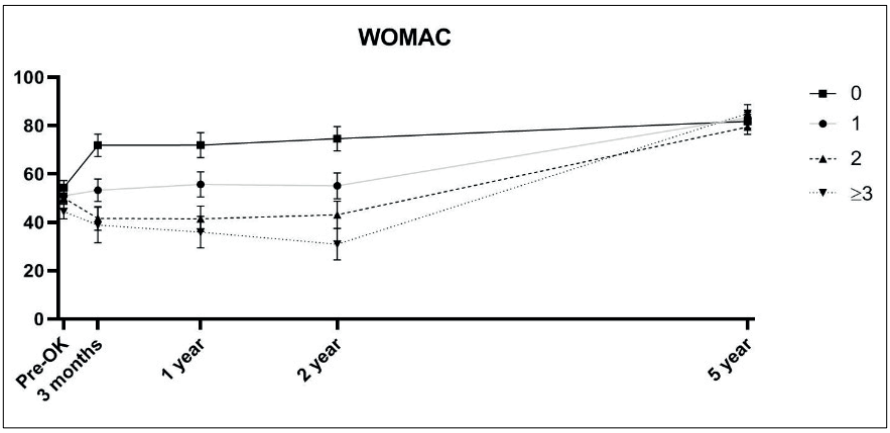

Figure 1: Scores on WOMAC for each group over time.

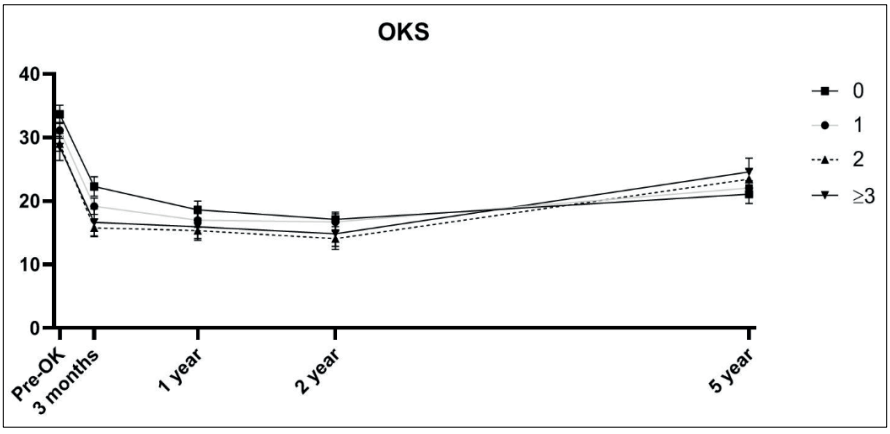

Figure 2: Scores on OKS for each group over time.

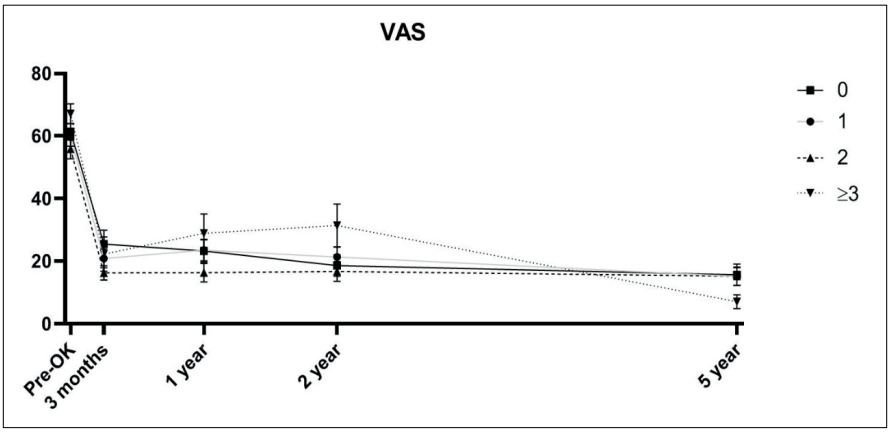

Figure 3: Scores on VAS for each group over time.

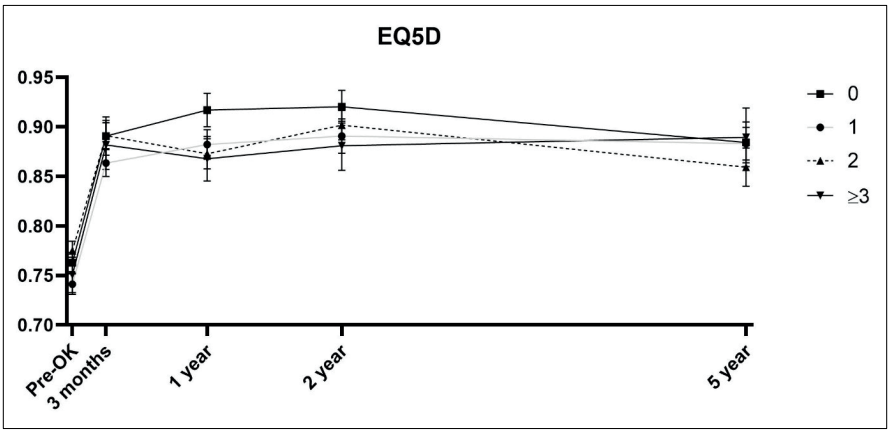

Figure 4: Scores on EQ5D for each group over time.

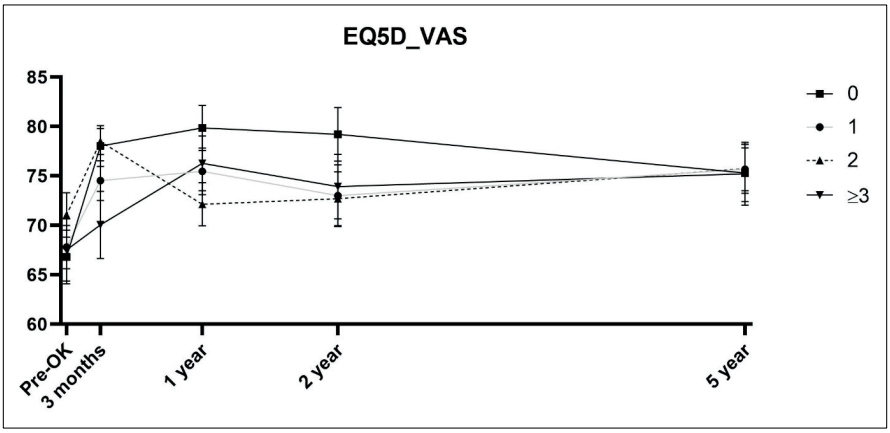

Figure 5: Scores on EQ5D_VAS for each group over time.

Discussion

The main finding of this study is that the cumulative number of postoperative radiological outliers does not influence clinical outcome after TKA over time. No statistically significant differences were found over time for any of the PROMs between the different groups. In our population, rate of revision was low and therefore underpowered to assess the influence of the number of outliers on the survival of the prosthesis. Although this study showed no statistically significant difference over time for any of the PROMs, it is remarkable that for the WOMAC, EQ-5D and EQ-5D-VAS the group with no outliers shows better results up to 2-years follow-up compared to the other groups. At 5-years follow-up, this difference is no longer visible. An explanation could be that improvement after TKA is most seen up to one or two years postoperatively with

relatively unchanged improvement up to 5-years [23][24][25]. This suggests that TKA with fewer outliers leads to a different postoperative improvement of clinical outcome. To the best of our knowledge, there are no previous studies that describe the influence of the cumulative number of different radiological outliers in one and the same patient. However, a few studies assessed the influence of one outlier on clinical outcome. Within these studies, the influences of radiological outliers on clinical outcome were limited. For example, varus alignment of >3°, measured in the frontal plane, was found to not negatively influence clinical outcome [26][27]. The results were obtained by measuring only mechanical long leg axis and not the femoral and tibia component, as done in the present study. Besides, both studies divided their study population in multiple groups which led to relatively small groups and could therefore influence outcome due to underpowered sample size. Nevertheless, the current study reports equal results regarding varus alignment and clinical outcome. Previous studies found that increased femoral flexion, measured in the sagittal plane, could lead to dissatisfaction rates and possible flexion contracture whereas extension of the femoral component could lead to anterior knee pain [28] [29]. Although these differences were not statistically significant different, adequate positioning of the femoral component in the sagittal plane is still of crucial importance to prevent for unsatisfactory results. Regarding the influence of radiological outliers of the tibial component on clinical outcome for the sagittal plane, one study suggest one study suggests that decreased tibial slope can lead to decreased range of motion [30]. Another study reported that maintaining native posterior slope within 4° correlates with superior PROMs [31]. Compared to the current study, we only found one previous study that examined the influence of different outliers combined on clinical outcome. For each plane, the height of the outlier in degrees was determined. These numbers were added up which led to the cumulative error of all outliers. Trends were identified for better function with good sagittal and coronal tibial alignment while low cumulative error leads to better clinical outcome. The difference with the current study is that the cumulative error of the different planes was assessed, while we assessed the cumulative number of planes that have an outlier. Limitations were that only one measurement tool (KSS) was used to assess clinical outcome [32]. Regarding survival of the prosthesis, the present study was underpowered. Nevertheless, the reported revisions were seen in all the outlier groups (1, 2 and >3 outliers respectively). A review of the literature concluded that a neutral mechanical axis remains the optimal guide to alignment of TKA, suggesting that adequate positioning is crucial to prevent for revisions [33][34]. When analyzing in detail the role of varus alignment, higher failure rates were found for varus alignment less than 0° and more than 3°. Reports on valgus outliers showed no statistically significant differences on clinical outcome or revision rate [35][36]. As present in our study, 4 patients underwent revision surgery where 3 patients had an outlier of the femoral component in the sagittal plane, namely increased femoral flexion. In the previous literature, for the sagittal plane only one study stated that a femoral alignment of 0-3° and tibial slope of 0-7 ° leads to a decreased revision rate [37]. In the current study we only used PROMs to assess clinical outcome. Controversy exists whether PROMs are the most reliable method to evaluate clinical

outcome of TKA [38]. A recurring limitation is the fact that a large number of the PROMs that are currently used lack essential evidence of their measurement properties. Previous studies also described that the limitation of PROMs can be a result of the ceiling effects [39]. Besides PROMs, forgotten joint score (FJS-12) is increasingly used to measure patient satisfaction after TKA surgery. When comparing TKA to total hip arthroplasty (THA), TKA patients reported remarkably lower FJS-12 scores [40]. Considering these outcomes, it underlines the importance of understanding more about the causes of unsatisfying results after TKA where dissatisfaction rates up to 30 percent are described [41]. High variation exists between studies in the assessment of clinical and functional outcome after TKA. Although PROMs are the most commonly adopted outcome measure, performance-based outcome measures, for example range of motion and 6-min-walk test, can be of added value [42]. The main advantage of the current study is that by our knowledge no previous study assessed the influence of the number of outliers in multiple planes in a RCT. Limitations of this study were the retrospective setting and the fact that the study was underpowered to assess a significant difference in revision rate. This can be explained by the fact that data from a previous published study were used [17,18]. This study was powered in order to assess a different hypothesis and using data from a previous study can therefore be considered as a limitation.

Larger study populations are needed to assess the influence of the number of outliers on the survival of the prosthesis. Since several studies describe a statistically significant relationship between an outlier and the survival of the prostheses, it can be argued that this relationship might even be more pronounced for the cumulative number of outliers. Longer follow-up is therefore mandatory.

8 Conclusions

The cumulative number of postoperative radiological outliers did not influence clinical outcome after TKA. Higher-powered studies are needed to examine the influence of these outliers on survival rates.

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CHAPTER 9

GENERAL DISCUSSION

This thesis evaluated both midterm and long-term clinical outcomes, prosthesis survival, and cost-effectiveness of patient-specific instrumentation (PSI). PSI is compared to conventional instrumentation (CI) in total knee arthroplasty (TKA), with a particular focus on differences between CT- and MRI-based PSI. Additionally, the reliability of preoperative virtual implant planning and the impact of postoperative radiological outliers on clinical outcomes were investigated. The following discussion integrates the major findings of the work presented in this thesis, critically examines their implications for clinical practice and future research in orthopedic surgery, and specifically addresses the aims that were originally outlined in this thesis. Each aim will be discussed separately.

Differences in clinical outcome and survival of the prosthesis between CT- and MRI-based PSI at short- to midterm follow-up

When using PSI in TKA, first, a CT- or MRI-scan is performed for all patients. To date, according to the current literature, none of the imaging modalities is considered the gold standard (1–4). In **Chapter 2** and **Chapter 3**, differences between CT- and MRI based PSI at 2- and 5-years after surgery were assessed, focusing on clinical outcome and revision rates. These studies were a continuation of a previously published randomized controlled trial (RCT) where differences in alignment between CT- and MRI-based PSI were studied, and only for posterior slope a statistically significant difference in radiological outliers was found in favor of MRI-based PSI (5). At 2- and 5-years after surgery, no differences in survival of align the prosthesis were found. For clinical outcome, only for the EQ-5D 5-years after surgery, a significant difference was found in favor of the MRI-group. This may be related to comorbidity that influences quality of life following TKA (6). The significant difference observed may therefore potentially be explained by the development of new comorbidities in the years following the knee replacement, which could differ between the CT- and MRI-group. All other PROMs at 2- and 5-years follow-up did not show any significant difference. To make a definitive determination of which imaging modality can be considered the gold standard, additional factors need to be taken into account. In the current literature there is no health-economic evidence comparing CT-based to MRI-based PSI in TKA. However, direct costs, including prices of diagnostic procedures, are determined by the Dutch Healthcare Authority (NZa), where in public hospitals costs of an MRI scan of the knee differ from €287-317 and costs of a CT-scan of the knee differ from €48-55 (7). These numbers suggest that when cost-effectiveness is taken into account, there may be a preference for CT-based PSI. In addition, patients may experience a CT scan as less burdensome (8). MRI scans involve significantly longer acquisition times and are often poorly tolerated by patients with claustrophobic tendencies (9). On the other hand, CT-scans lead to a small increase in lifetime risk of radiation-induced malignancies. To put things in the right perspective, these risks are comparable to a transatlantic flight (10,11).

The data presented in this thesis demonstrated that both CT- and MRI-based PSI are accurate methods that lead to good clinical outcomes and excellent survival of the prostheses up to

midterm follow-up. How to determine which technique to use will depend on the availability of imaging techniques in different settings and may therefore vary between countries and care facilities. If PSI is to remain part of TKA in the future, its continued use should be supported by comprehensive cost-effectiveness analyses to guide an evidence-based choice between CT- and MRI-based PSI.

Intra- and inter-observer reliability of approval and alteration of the virtual plan by the surgeon in MRI-based PSI

After imaging, the next step in the workflow of PSI for TKA would be pre-operative virtual planning. The pre-operative plan provided by the manufacturer can be modified and should be approved by the surgeon before the guides are produced (12). These pre-operative corrections and approval by the surgeon are essential steps of the PSI process (13). Once the plan is approved, the implant size to be used intraoperatively can be predicted with high accuracy (14). In **Chapter 4**, the first assessment of intra- and inter-observer reliability of planned implant size, resection, and position of the implant in MRI-based PSI was assessed.

For pre-operative planning of TKA implant size of the tibial and femoral component, MRI based-PSI showed an excellent intra- and inter-observer reliability. These findings demonstrate that the preoperative process involving surgeon approval of the virtual plan is a safe and valid method to predict implant size. For planning of intra-operative resection, two femoral resection parameters showed excellent agreement and tibial resection showed moderate agreement. Six alignment parameters were assessed, three (femoral rotation, tibial rotation and tibial slope) with excellent-, one (femoral flexion/extension) with moderate- and two (femoral varus/valgus and tibial varus/valgus) with poor agreement. In this study, neutral alignment was pursued in all patients. Later in this discussion, we will return to the differences between alignment techniques. Hypothetically, since all surgeons aimed for neutral alignment, only limited variability in preoperative planning was expected since the same alignment was planned in every individual case. However, if in the future there is a shift towards personalized alignment approaches, there will be considerable and arguably larger 'gray areas' within each alignment strategy as compared to mechanical alignment. This can lead to a difference in preoperative planning between different surgeons and therefore consequently may influence the inter-observer reliability. To address this, future research should evaluate inter- and intra-observer reliability within the context of different alignment philosophies. Although intraclass correlation coefficients for these alignment concepts have not yet been established, such analyses would provide valuable insight into the reproducibility of personalized planning approaches.

Differences in clinical outcome and survival of the prosthesis between PSI and CI at long-term follow-up

PSI and CI are both widely performed surgical techniques in TKA (15). Differences between PSI and CI focusing on perioperative results, alignment and short- to mid-term clinical outcome

have been extensively analyzed before. Systematic reviews and meta-analysis suggest that PSI indeed improves alignment in one or more radiological planes, but no improvement of clinical outcome or survival compared to CI was found (16–18). Moreover, the reduction of surgical time and blood loss with the use of PSI was found not to be clinically relevant (19,20). Therefore, at the start of the studies in this thesis, the debate about what surgical technique is the preferred method, remained a critical point of discussion, with no available literature comparing PSI- and CI TKA after longer follow-up periods. In this thesis, this long-term follow-up of differences in clinical outcome and survival between PSI and CI is a main topic further discussed in **Chapter 5** and **Chapter 6**. In a cohort study in **Chapter 5**, survival and clinical outcome of PSI TKA 8.4 years after surgery were analyzed. At final follow-up, over time all PROMs in this study showed significant improvement compared to pre-operative values and 2% of the patients underwent revision surgery. In **Chapter 6**, the first long-term results of our multicenter RCT comparing PSI to CI were presented. Mean follow-up was 10.1 years. No significant differences in survival rates were found between PSI and CI, with survival rates of 92% for PSI and 94% for CI. Analyzing clinical outcome, no significant differences over time between the PSI- and CI-group were found for any of the PROMs.

Long-term survival

No previous studies have reported on the long-term differences in the need for revision surgery between PSI and CI, or on the long-term survival of PSI alone. When interpreting results of survival analyses it is important to point out that there are many factors apart from alignment or surgical technique that can influence survival, including patient characteristic e.g. age, sex and comorbidities (21). When analyzing survival, studies may differ in terms of which indications for re-operation are considered revision surgery, and therefor studies can be difficult to compare. In **Chapter 5**, patients who underwent a second operation due to any cause were considered as a case where revision surgery was performed. There was a total of four cases that underwent revision surgery. One with aseptic loosening, one with secondary prosthetic join infection, one with collateral instability and one with posttraumatic polyethylene insert breakage. In **Chapter 6**, again all causes were included. This led to a total of four cases in the CI-group, two with persistent pain with revision of tibia and/or femur, one with persistent patellofemoral pain with placement of a patellar button and one with collateral instability. For the PSI-group, a total of five revisions were performed. One with persistent pain and revision of tibia and femur, one due to patellofemoral pain with placement of a patellar button, one late acute hematogenous infection, one case of persistent collateral instability and one case of aseptic loosening of the tibial component. Frequently in the literature, as well as in our own studies, all reasons for revision have been included in survival analyses. However, when assessing the influence of a surgical technique on implant survival, the reason for revision should ideally be related to the surgical technique itself. In the case of, for example, a late acute hematogenous infection, this relationship is unlikely. Therefore, for future research to draw more accurate conclusions

regarding the association between a surgical technique and survival, a more selective inclusion of revision reasons in the analysis will be necessary.

Existing literature does not describe the long-term survival of PSI and comparing our results to other studies was therefore not feasible. However, several studies have described the long-term survival of CI alone (22). In **Chapter 5** and **Chapter 6**, a cruciate retaining (CR) Vanguard prothesis with a cementing technique was used in all patients. In **Chapter 6** this applied to both the PSI- and CI-group. Studies specifically focusing on the same Vanguard prostheses used in this thesis, reported survival rates at 10-years follow-up between 94-98% and 87% 15 years after surgery. In these studies, again all causes for revision were included (22–25). Retrospective studies analyzing survival of CR TKA from different manufactures with inclusion of any cause for revision surgery, showed 10-years survival ranging from 91-99%, 15-years survival of CR TKA ranging between 88-100% and 20-years survival of 87% (26–29). The aforementioned studies demonstrate that data focusing on the same type or the same brand of prosthesis report results at 10-years follow-up comparable to those observed in this thesis for both PSI- and CI-TKA. Given the absence of radiological- and alignment differences between PSI an CI, it is expected that patients included in the studies in this thesis will demonstrate a survival curve comparable to that reported in previous studies.

The same holds true for different prosthesis brands. A systematic review including large registry studies and multiple prothesis brands reported comparable survival rates at 10-years follow-up and a pooled survival of 82% 25 years after surgery (30). Since the survival curve up to 10 years after surgery is comparable to our study, and differences between prosthesis designs and surgical technique are relatively small, it is likely that the population in our study will follow a similar survival trend after longer follow-up periods.

Long-term clinical outcome

Prior research has evaluated both implant survival and long-term clinical outcomes following TKA. Comparable to **Chapter 5** and **Chapter 6**, often the Knee Society Score (KSS) and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) are used for measuring patient satisfaction (31,32). Previous research has shown that these and other PROMs often reach a plateau within 1–2 years postoperatively (33). Research on a similar Vanguard prosthesis demonstrated outcomes at 10 years postoperatively that were consistent with those reported in this thesis (24,25). Moreover, studies focusing on the same CR prosthesis from different manufactures generally report comparable results of KSS and WOMAC, although a mild decline in outcomes has been observed between 5 and 10 years postoperatively (23,26,29). Because in this thesis both patients with PSI- and CI-TKA show similar clinical outcomes compared to previous studies, it is unlikely that significant changes will develop at longer follow-up periods. Moreover, as the population ages, additional new factors are likely to influence PROMs. Possible differences, eg in comorbidities, can emerge over time. Therefore, it is believed that even with extended follow-up, for instance 15 or 20 years, it would be difficult to draw

evidence-based conclusions regarding differences in clinical outcomes between PSI- and CI-TKA. For this reason, a longer follow-up period is expected not to be of added value.

Comparisons involving larger cohorts of patients receiving PSI prostheses from different manufacturers could provide greater insight. In the Netherlands, operative data from joint replacements are recorded in the LROI registry (34). This allows large-scale comparisons of perioperative differences between patients, such as preoperative characteristics or the use of a cemented technique. Unfortunately, the specific surgical technique, including PSI or CI, was only recently added. Future analyses of this registry could provide additional information, including comparison of PSI- and CI-TKA on a large scale but also differences in multiple PSI brands. Important sidenote on registry data is the inherent limitations we have to deal with when interpreting these results. Variability in data entry, limited detail on surgical planning or intraoperative decisions and limited detail of outcomes are limitations to consider. Still, they can provide a valuable complementary perspective to the findings presented in this thesis and may help confirm that our results are applicable to other PSI brands.

Conclusion

Summarizing, based on the available literature and the findings in this thesis, no differences were found between PSI- and CI-TKA regarding clinical outcome and survival of the prosthesis up to 10-years follow-up. From this, we can conclude that PSI- and CI-TKA, where in both techniques a cemented CR prosthesis was used, lead to comparable outcomes. The absence of differences between the PSI- and CI-TKA suggests that any potential differences may be too small to detect, and potentially not clinically relevant. This might be explained by the fact that although there is a difference in pre-operative planning, the same prosthesis, alignment strategy, cementing technique and postoperative protocol is used in PSI- and CI-TKA. Although PSI involves the use of a guide, both PSI and CI require the intraoperative placement of pins over which the cutting block is positioned. From this step onward, the surgical procedures for PSI and CI are identical. In this thesis, with a 10-year follow-up, no differences were observed between PSI and CI for a cemented CR prosthesis, and it is not expected that extended follow-up would reveal any significant differences between PSI and CI. For this reason, it is not recommended to focus future research on studies comparing PSI and CI with even longer follow-up periods.

Difference in cost-effectiveness between PSI and CI at long-term follow-up

Evaluating the cost-effectiveness of TKA interventions has become increasingly important in guiding healthcare decision-making. Cost-effectiveness analysis helps to determine the value of different surgical techniques by balancing their costs against clinical outcomes, survival rates and quality of life improvements (35). Cost-utility analysis extends this framework by relating costs to health-related quality of life, commonly expressed in quality-adjusted life years (QALYs). It evaluates the additional cost required to gain one extra year of life in optimal or improved health attributable to the intervention (36). As new technologies such as PSI emerge, cost-analyses are

essential for implementing these techniques into routine clinical practice (37). In **chapter 7**, the cost-utility from a hospital perspective of PSI compared to CI for TKA was investigated. Data from the same study population presented in **Chapter 6** was used. A critical note is that the primary study was not powered to detect a difference in costs after 10 years. However, over these years, increasing attention was directed towards costs-analysis. Given current knowledge, additional data that are known to influence cost-effectiveness could have been collected. Future research should take collecting these data into consideration

Both PSI and CI demonstrate improvement in quality of life five and ten years postoperatively. From a hospital perspective, PSI TKA came with higher costs per patient and reduced cost-effectiveness. Since this study was performed only from a hospital perspective, it is not possible to provide a complete overview of the difference in cost-effectiveness. Comparison of costs after hospitalization (e.g. return to work, visiting other healthcare providers, care burden and overall health-benefits) were not included. However, given that **Chapter 6** demonstrated no difference in clinical outcomes between PSI and CI-TKA, it is not expected to find significant differences in costs after hospitalization. Furthermore, our findings did not demonstrate that PSI implementation decreased the hospital's stock of prosthetic components. Given that **Chapter 4** showed that a preoperative virtual plan can accurately predict implant sizes, this is a remarkable finding. Theoretically, if implant sizes can be predicted reliably, it should also be possible to make more accurate estimates of the number of each prosthesis size that needs to be kept in stock. From a logistical standpoint however, matching prosthetic inventory with predicted PSI implant sizes was challenging, mainly because PSI was not the standard approach for every patient.

In addition, the time that surgeons spend on approval of the pre-operative plan was not included in the comparison. Mean planning time for orthopedic surgeons using PSI is 8±4 minutes (38). Assuming a surgeon has five surgeries scheduled in one day, this could result in up to an additional hour spent on preoperative planning, a time commitment that is not required when CI is used. If this preparation time is considered paid working hours, it also contributes to higher costs associated with PSI. Furthermore, the present findings are likely relevant to other public hospitals in the Netherlands. Given that private clinics may operate under a different business model, caution should be exercised before projecting the here acquired results to such settings. The same applies to healthcare institutions abroad. Besides just discussing costs, it is also important nowadays to look at sustainability and carbon footprint (39,40). The production and use of medical devices contribute significantly to gas emissions (mainly carbon dioxide), thereby indirectly harming global health (41). The production of PSI guides is likely to be less environmentally sustainable compared to CI. Facts are that the process includes a pre-operatively CT or MRI-scan (including a hospital visit for the patient), production of the PSI guides and their shipment to hospitals. Future research examining these sustainability differences between PSI and CI could provide additional insights and help validate these assumptions.

In conclusion, while PS- and CI-TKA results in comparable long-term clinical outcomes and survival of TKA, PSI was associated with higher hospital costs and reduced cost-effectiveness. Although this study was conducted from a hospital perspective and differences may therefore exist between institutions, these findings underscore the need for careful consideration when surgeons choose PSI over CI.

The influence of the cumulative number of postoperative radiological outliers on clinical outcome and survival of the prosthesis

Several chapters of this thesis focus on differences in prostheses designs or surgical techniques where comparisons are based on radiological outliers. Outliers are quantified as deviations greater than 3° from preoperative planning. These studies all examined the impact of a single outlier in one radiological plane (e.g. coronal or sagittal outliers of the femoral or tibial component) on clinical outcome (42–45). Overall, studies demonstrated no consistent results, with several reporting that radiological outliers had no significant influence on clinical outcomes. A few studies, however, indicated that a valgus limb alignment, increased femoral flexion, or decreased tibial slope might be associated with poorer clinical outcomes (44–47). The influence of the cumulative number of outliers across multiple radiological planes has not been previously assessed. In **Chapter 8**, we investigated whether a higher number of postoperative radiological outliers negatively affects clinical outcomes. Patients were divided into four groups. The first group consisted of patients with no radiological outliers. The second, third and fourth group consisted of patients with 1, 2 or ≥3 radiological outliers, respectively. PROMs were compared between the groups. There was no statistically significant difference found over time between the groups for each PROMs. This shows that the cumulative number of postoperative radiological outliers did not influence clinical outcome after TKA.It is important to note that the previous studies describing the impact of a single outlier in one radiological plan, similar to **chapter 8** in this thesis, were designed with the goal of achieving mechanical alignment. For several decades, a deviation of more than 3° from this mechanical axis has been regarded as an outlier in the assessment of TKA (48). This threshold emerged from early studies in which neutral mechanical alignment was defined as 0°-3°, based on the assumption that a mechanically neutral limb was essential for optimal load distribution and long-term implant survival (49). Consequently, the 3° cut-off has become a widely adopted cut-off point. However, the validity of this traditional threshold has increasingly been questioned in contemporary literature. Studies have demonstrated that deviations exceeding 3° do not necessarily lead to inferior clinical outcomes or reduced implant survival (50,51). Nowadays, new alignment techniques challenge the universality of the 3° cut-off point even further. These new and personalized alignment strategies aim to achieve postoperative alignment more closely to the patient's native preoperative alignment (52,53). They suggest that the relationship between mechanical alignment and clinical outcome may be more nuanced than originally proposed (54).

Given all these new insights, it is increasingly uncertain whether the 3° cut-off point from a neutral aligned TKA remains an appropriate criterion for distinguishing correctly from incorrectly aligned TKA's. If this cut-off point is revised, it will also affect the interpretation of the results presented in **Chapter 8.** In this chapter for example more than 3° varus was considered and outlier, while according to new alignment philosophies this might be considered as an appropriate postoperative alignment that partially preserves the patient's native anatomy. For future research, and according to the personalized alignment philosophies, it may be of interest to evaluate postoperative alignment not relative to a neutral mechanical axis, but relative to the patient's preoperative limb alignment. When the discrepancy between preoperative and postoperative alignment becomes sufficiently large, it may be classified as an outlier. However, consensus must first be established regarding the preferred alignment technique and the degree of deviation that should be considered an outlier. Once such a definition is in place, the influence of the cumulative number of outliers can again be analyzed.

The future role of PSI in TKA

Ultimately, the question remains whether in the future there is a place for PSI in TKA.

In this thesis, PSI and CI across multiple domains were evaluated, with a particular focus on clinical outcome, prosthesis survival, alignment and cost-effectiveness. The assessment of these domains ultimately contributes to answering the question whether surgeons should continue using PSI in the future. However, assessing these domains, and thereby making a thorough comparison between PSI and CI, comes with its difficulties and limitations.

Assessment of clinical outcome

For clinical outcome, to make an accurate statement about the differences between two surgical techniques, appropriate and validated measurement tools must be used. PROMs continue to be regarded as the gold standard for assessing clinical outcomes following TKA. However, there remains debate in the literature whether PROMs are the most appropriate tool for assessing clinical outcome (55). Multiple PROMs differ in their content, where some focus on generic health and others are disease- or joint-specific (56–59). To ensure that a PROM is meaningful and accurate, it must be validated in the appropriate language and must also demonstrate good reliability, validity, and responsiveness (60). Multiple studies have assessed PROMs after TKA and found limited evidence for their psychometric properties (55). Some PROMs did meet the minimal requirements for psychometric validation but none have been validated for all measurement properties (61,62). Since these PROMs are still the golden standard to assess clinical outcome, the question raises whether we should explore alternative measurement tools. Other measurement instruments that have already been analyzed include performance-based assessments and the use of wearable sensors (63,64). To date, these methods have not demonstrated superiority over PROMs. However, performance-based assessments may provide reliable supplementary information including kinematic characterization (65). Additionally,

wearable sensors enable the assessment of gait function after TKA, something that is not achieved through the exclusive use of PROMs as measurement tool (66). Combining these different assessment modalities may provide a more comprehensive understanding of clinical outcomes following TKA, including the comparison between PSI and CI (66,67).

Analyzing survival of the prosthesis

Next to clinical outcome, one of the critical measures used to evaluate the success of TKA is the survival rate of the prosthesis, defined as the time until revision surgery is required. A survival analysis is believed to provide valuable insights into the quality of an implant and is therefore frequently used to compare different surgical techniques and implant designs, for example PSI and CI (28). In most revision cases, the indication for revision is clear and defined in guidelines or local protocols, such as in cases of infection, implant loosening or periprosthetic fractures (68). For other reasons for revision, such as instability and persistent pain, the outcome of the revision is more difficult to predict, and surgeons may differ in their opinions and motivations regarding whether the revision should be performed (69,70). This highlights the importance of studies with a randomized design. It may also be beneficial in studies to compare only revisions for which a clear indication for revision existed. One could further argue that analyses should focus primarily on aseptic loosening of the prosthesis. This means excluding deep infections or periprosthetic fractures, because these outcomes are mostly influenced by factors beyond prosthesis design and alignment of the prosthesis.

In the multicenter RCT in Chapter 6, a clear difference in number of revisions between two hospitals was observed, particularly in cases where the indications were associated with less predictable outcomes. Examples include changing to a larger insert in case of instability or adding a patellar button for persistent pain. Differences in revision rates between hospitals are not unique to our institution. Researchers must be aware of this when comparing two surgical techniques, as we have done for PSI and CI in Chapter 6 (71).

Alignment philosophies

Finally, when evaluating a surgical technique, alignment plays a major role. In the case of PSI, this new technique was developed with the hypothesis that it would lead to better mechanical alignment, therefor better clinical outcome and eventually improvement of survival of the prosthesis (72). With regard to alignment, the question arises: what is the optimal alignment that should be pursued? Before evaluating alignment, it is essential to first establish consensus on what the preferred alignment technique is. In this thesis, in all chapters where surgical procedures were compared, the goal was to achieve mechanical alignment, also described as neutral alignment. Mechanical alignment is a surgical technique aimed at positioning the prosthetic components so that the load-bearing axis of the lower limb is restored to a neutral alignment (73). This is typically achieved by aligning the femoral and tibial components perpendicular to their respective mechanical axis, regardless of whether there was a preoperative varus or valgus limb alignment.

The goal is to evenly distribute forces across the knee joint, and was therefore thought to improve clinical outcome and optimize implant longevity.

Alignment and implant positioning have become central to the ongoing debate, with surgeons increasingly exploring more personalized approaches to TKA (52,53). Kinematic alignment, for example, seeks to recreate the patient's pre-arthritic joint line orientation and limb alignment, with the goal of restoring natural knee kinematics and improving patients' satisfaction (74). Functional alignment, on the other hand, focuses on balancing the soft tissues and achieving optimal joint stability and patellar tracking, rather than solely relying on bony landmarks (75). Both kinematic and functional alignment techniques have been explored as alternatives to traditional mechanical alignment, with the aim of improving patient satisfaction and long-term implant survival. To avoid confusion, these various alignment techniques that deviate from the mechanical alignment principle are collectively referred to in the current literature as personalized alignment (73,76). Despite hopeful predictions, the current literature has not been able to confirm that personalized alignment leads to better clinical outcomes or implant survival in TKA compared with mechanical alignment (54,74,77). Moreover, the results do not indicate that personalized alignment leads to inferior clinical outcomes or reduced implant survival compared to mechanical alignment (78). Therefore, personalized alignment can be used safely, but mechanical alignment cannot yet be dismissed as a golden standard and the debate about the preferred alignment technique continues. Studies comparing long-term implant survival between mechanical and personalized alignment are not yet available. Such studies would be of particular interest, as the underlying principle of mechanical alignment is that a neutral load-bearing axis of the limb supports optimal prosthesis survival (79). Long-term follow-up studies could therefore provide valuable insights into which alignment strategy may ultimately become the gold standard. For now, books are not closed yet on the debate over which alignment technique is most suitable for one specific patient and it remains one of the most important current research questions in TKA surgery.

The choice between achieving mechanical or personalized alignment, also influences the comparison between PSI and CI. Some studies in the current literature suggest that PSI may offer certain advantages over CI in achieving personalized alignment (80). A common criticism of CI is the limited intraoperative control over bony resections, whereas the use of 3D-printed cutting guides in PSI may provide greater precision (80). This highlights the importance of establishing a consensus on the definition of the preferred alignment technique. Only thereafter, a meaningful discussion is possible on whether PSI of CI is best suited to correctly obtain the desired alignment.

Final considerations on PSI

All of the above should be taken into consideration when evaluating PSI. At this moment, the choice between PSI and CI should be based on the studies available that assessed alignment, clinical outcome and survival of PSI with the measurement properties that are currently used.

The findings in this thesis have shown that with long term follow-up periods, PSI leads to comparable patient satisfaction and survival compared to CI, when achieving neutral alignment. More-over, PSI leads to higher costs per patient with reduced cost-effectiveness. Today, when the appropriate cases are selected, there may potentially be indications where PSI is preferable. For example, CT-based PSI for patients with posttraumatic knee deformities, osteosynthesis around the knee joint or revision surgery (12,81,82). In the future, PSI could play a specific role if the preferred alignment of the prostheses shifts more toward personalized alignment techniques. Nowadays, in Western countries including the Netherlands, there is an increasing use of robotics, which entails significant investment costs (83,84). Although consensus in the literature has not been obtained yet, robotics are believed to achieve more accurate alignment (compared to what was planned pre-operatively) and play an important role in the functional alignment philosophy. Should functional alignment become the gold standard for TKA, PSI may offer a viable solution for its implementation in non-Western countries, even in resource-limited settings.

Overall, the work collected in this thesis did not demonstrate a general superiority of PSI over CI. PSI comes, however, with significantly higher costs. In the present day, based on the available literature and findings in this thesis, it cannot be confirmed that PSI should be preferred above CI in all TKA cases. For now, only when the appropriate cases are selected, PSI may indeed have a place as an alignment tool in TKA.

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CHAPTER 10

IMPACT PARAGRAPH

PSI has been used by surgeons for over a decade, and has undergone the typical cycle of innovation (1). This cycle refers to the process that new technologies go through. Typically, the cycle begins with a new technology, often driven by industry, that is introduced as a potential solution for a clinical challenge, e.g. achieving optimal alignment. The first studies often report favorable outcomes. Such initial positive results generally generate enthusiasm among a group of "believers" who begin to implement the technique more widely in clinical practice. This is a remarkable process in which a new technique is applied directly, without first conducting solid scientific research before the product is brought to the market. With a growing utilization of the new technology, studies with larger patient populations are conducted, which frequently show smaller or no clinically significant differences when compared to conventional methods. As a result, the popularity of the innovation may decrease. During the last phase, long-term clinical outcomes and cost-effectiveness analyses become available, providing a more comprehensive understanding of any added value of such new technology. Currently, robotic TKA is undergoing the same process (1).

The question remains whether there is a better or smarter way to implement a new technology within orthopedic surgery. There is a clear need for structured and evidence-based strategies for implementation. A possible approach is to introduce the new technique initially in only a few large hospitals or clinical centers. In such settings, large patient cohorts allow for adequate evaluation of whether the new technique is safe and effective, and whether it indeed leads to improved outcomes. This leads to controlled and prospective data collection, allowing real-world validation to take place before large-scale implementation. Attention should also be given to cost-effectiveness from the beginning. Only after positive results have been demonstrated should the technology be adopted on a wider scale. Ideally, and where financially possible, this whole process should involve minimal dependence on industry support.

Completion of the cycle should ultimately answer the fundamental question of what factors truly contribute to improved patient satisfaction following TKA. The existing literature is still overly focused on implant design and alignment precision as primary factors determining clinical success. It remains debatable whether the type of prosthesis that is implanted is primary responsible for clinical success (2). Consequently, there is a need to shift attention towards other elements that may substantially influence patient recovery and short-, mid-, and long-term satisfaction. Growing evidence suggests that patient-related factors, such as preoperative expectations, the perioperative experience and postoperative support, may be at least equally important for outcomes (3–6). Also, there is considerable variability among patients, for whom the affected joint represents only one aspect of a complex individual case. For example, the literature has already shown that a patient's preoperative mental health status influences postoperative clinical outcomes (7). All of this requires accurate patient selection, preoperative education including effective expectation management and renewed postoperative management strategies (8,9). Collectively, the underlying determinants of patient dissatisfaction following TKA remain largely unclear. Findings from this thesis, together with prior studies, demonstrate

that the implementation of new or seemingly improved surgical techniques is insufficient to resolve this issue. There is a need for a shift in future research that takes a broader perspective on this question. This should include greater focus on personalized care pathways, expectation management, and digital health interventions that support recovery and may enhance patient satisfaction (10,11). Mobile applications represent a form of digital health intervention that may offer several advantages. In the postoperative setting, patients can be monitored more closely in their home environment and receive personalized advice regarding physical activity. Through an integrated AI-driven chatbot, patients may also obtain answers to their questions. Previous studies have even suggested that chatbot responses can be perceived as even more empathetic than those provided by human clinicians (12). Future studies will need to determine whether these applications indeed improve patient satisfaction. Furthermore, in the long term, patients can also continuously contribute additional health data in these apps, such as information on the development of comorbidities. This ongoing input creates a richer database, which can substantially enhance the accuracy and reliability of long-term outcome assessments. Such more efficient data collection can also include the integration of step counters or more frequent completion of PROMs. To enable large-scale data implementation, it is crucial that different applications are compatible with each other, rather than each hospital department developing its own system. A broader approach could even involve linking data from such applications to national registries, such as the LROI. All of this, however, must be accompanied by a critical focus on patient data security. Patients may perceive the collection of such information as an invasion of privacy, or express concerns about data safety.

As patient satisfaction gains an increasing focus in healthcare, there is a shift towards viewing patients not only as receivers of care, but as active consumers within the healthcare system. This change is driven by multiple factors, including the availability of digital health tools, greater access to medical information, and an increased use of shared decision-making, which enables patients to make more informed choices regarding their healthcare (13). These developments come with additional challenges. Healthcare professionals and institutions carry a collective responsibility to balance patient satisfaction with the broader public interest, particularly in light of rising healthcare costs. While improving patient satisfaction is clearly important, it is equally essential to ensure that such developments do not result in increased costs without corresponding improvements in health outcomes (14). Given these considerations, it is crucial for future research to adopt a more holistic perspective, integrating patient satisfaction with principles of sustainability and value-based care. Such an approach should look for strategies that improve the patient experience, while simultaneously optimizing the use of healthcare resources and minimizing unnecessary costs. In this way, healthcare systems can better provide healthcare with delivering high-quality, cost-effective services.

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CHAPTER 11

SUMMARY
NEDERLANDSE SAMENVATTING

This thesis investigates the mid- and long-term results of patient-specific instrumentation (PSI) in total knee arthroplasty (TKA). PSI was introduced to improve component positioning and optimize surgical workflow, yet its (long-term) clinical value remains debated. The influence of imaging modality (CT versus MRI), the reliability of PSI preoperative planning, implant survival and clinical outcome up to ten years after surgery, cost-effectiveness, and the clinical relevance of radiological alignment outliers were all evaluated. By integrating findings from randomized trials and cohort studies, this work aims to contribute to a more evidence-based and critical implementation of PSI in daily surgical practice.

Chapter 2 examined whether the imaging modality used for PSI affects clinical outcomes and implant survival two years postoperatively. In a prospective randomized trial, 137 patients were allocated to MRI- or CT-based PSI, of whom 124 were analyzed at two years follow-up. PROMs (Oxford Knee Score, WOMAC, VAS pain, EQ-5D, EQ-5D VAS) improved significantly in both groups, with no significant differences between MRI- and CT-based PSI. Only two revisions occurred, equally distributed. Radiological evaluation showed no loosening. In conclusion, short-term clinical outcomes and survival were comparable between both imaging modalities. **Chapter 3** reports the five-year follow-up of this cohort (98 patients, mean follow-up 5.8 years). No additional revisions occurred. PROMs remained comparable between both groups, except for a small difference in EQ-5D VAS in favor of MRI-based PSI. These findings indicate that MRI- and CT-based PSI result in similar mid-term clinical outcomes and implant survival.

Chapter 4 focused on the reliability of the preoperative planning process for PSI TKA. Four experienced orthopedic surgeons independently reviewed and modified MRI-based plans on three separate occasions. The surgeons were blinded to their own previous assessments and those of their colleagues. Intra- and interobserver reliability for implant size was excellent, and good to excellent agreement for most alignment parameters was found. Variability was mainly attributable to surgical preference and anatomical interpretation. Overall, PSI planning proved to be reproducible and consistent, while underlining the importance of surgical expertise.

Chapter 5 and **Chapter 6** focus on the long-term results of PSI TKA. **Chapter 5** presents a prospective cohort study of 200 PSI TKAs in 184 patients with a mean follow-up of 8.4 years. PROMs were collected preoperatively and at multiple postoperative intervals. Implant survival was 98%, with all revisions occurring within the first four years. All PROMs showed improvement compared to baseline, although slight declines over time were observed, likely related to aging and developing comorbidities. Clinical outcomes and survival were comparable to results of conventional instrumentation (CI) described in the literature, concluding good mid- to long-term results for PSI. **Chapter 6** describes a randomized controlled trial comparing PSI with CI with a mean follow-up of 10.1 years (129 patients analyzed). No significant differences were found in PROMs or implant survival between the groups. These results demonstrate that the theoretical advantages of PSI over CI do not translate into superior long-term clinical outcomes or reduced revision rates.

Chapter 7 evaluated cost-effectiveness from a hospital perspective at five and ten years postoperatively. Quality-adjusted life years (QALYs), derived from EQ-5D-5L data, were similar for PSI and CI. However, PSI incurred higher total costs, primarily due to preoperative imaging and production of patient-specific guides, despite some perioperative efficiencies. Consequently, PSI found to be less cost-effective at both time points.

Chapter 8 examined whether the cumulative number of radiological outliers influences clinical outcome and implant survival up to five years after TKA. Patients were stratified according to the number of outliers across multiple planes. No significant associations were found between the number of outliers and PROMs or revision rates. These findings question the clinical relevance of radiological deviations as a predictor for clinical outcome and survival.

Collectively, the overall conclusion from the work in this thesis is that PSI does not provide superior clinical outcomes, implant survival, or cost-effectiveness compared with CI at long-term follow-up. While PSI is a reliable and reproducible planning tool and yields durable results, its routine use as a superior alternative or new gold standard for TKA is not supported by current evidence. Careful and selective application of PSI may remain justified in specific clinical scenarios.

Dit proefschrift onderzoekt de middellange- en langetermijnresultaten van patiëntspecifieke instrumentatie (PSI) bij totale knieartroplastiek (TKA). PSI werd geïntroduceerd om de positionering van componenten te verbeteren en de chirurgische workflow te optimaliseren. De (langetermijn) klinische waarde bleef echter onderwerp van discussie. De invloed van de beeldvormingstechniek (CT versus MRI), de betrouwbaarheid van de preoperatieve planning, implantaatoverleving en klinische uitkomsten tot tien jaar na de operatie, kosteneffectiviteit en de klinische relevantie van radiologisch afwijkende alignement werden geëvalueerd. Door bevindingen uit gerandomiseerde studies en cohortonderzoeken te integreren, beoogt dit werk bij te dragen aan een meer evidence-based en kritische implementatie van PSI in de dagelijkse operatieve praktijk.

Hoofdstuk 2 onderzocht of de bij PSI gebruikte beeldvormingstechniek invloed heeft op klinische uitkomst en implantaatoverleving twee jaar postoperatief. In een prospectieve gerandomiseerde studie werden 137 patiënten toegewezen aan MRI- of CT-gebaseerde PSI, van wie er 124 werden geanalyseerd twee jaar postoperatief. PROMs (Oxford Knee Score, WOMAC, VAS-pijn, EQ-5D, EQ-5D VAS) verbeterden significant in beide groepen, zonder significante verschillen tussen MRI- en CT-gebaseerde PSI. Er traden slechts twee revisies op, gelijk verdeeld over beide groepen. Radiologische evaluatie toonde geen tekenen van loslating. Concluderend was de klinische uitkomsten en implantaatoverleving vergelijkbaar tussen beide technieken. **Hoofdstuk 3** beschrijft de follow-up van dit cohort 5 jaar postoperatief (98 patiënten, gemiddelde follow-up 5,8 jaar). Er traden geen aanvullende revisies op. De PROMs bleven vergelijkbaar tussen beide groepen, met uitzondering van een klein verschil in EQ-5D VAS ten gunste van MRI-gebaseerde PSI. Deze bevindingen tonen aan dat MRI- en CT-gebaseerde PSI vergelijkbare klinische uitkomsten en implantaatoverleving opleveren 2- en 5 jaar postoperatief.

Hoofdstuk 4 richtte zich op de betrouwbaarheid van het preoperatieve planningsproces voor PSI. Vier ervaren orthopedisch chirurgen beoordeelden en corrigeerden onafhankelijk van elkaar MRI-gebaseerde planningen op drie afzonderlijke momenten. De chirurgen waren geblindeerd voor hun eerdere beoordelingen en die van hun collega's. De intra- en interobserver betrouwbaarheid voor implantaatgrootte was excellent, en voor de meeste uitlijningsparameters werd goede tot excellente overeenstemming gevonden. Variabiliteit was voornamelijk toe te schrijven aan chirurgische voorkeur en anatomische interpretatie. Over het geheel genomen bleek de PSI-planning reproduceerbaar en consistent, waarbij het belang van chirurgische expertise werd onderstreept.

Hoofdstuk 5 en **Hoofdstuk 6** richtten zich op de langetermijnresultaten van PSI. **Hoofdstuk 5** beschrijft een prospectieve cohortstudie van 200 PSI-TKA's bij 184 patiënten met een gemiddelde follow-up van 8,4 jaar. PROMs werden preoperatief en op meerdere postoperatieve tijdstippen verzameld. De implantaatoverleving bedroeg 98%, waarbij alle revisies binnen de eerste vier jaar plaatsvonden. Alle PROMs verbeterden ten opzichte van de uitgangssituatie, hoewel in de loop der tijd lichte dalingen werden waargenomen, waarschijnlijk gerelateerd aan veroudering

en het ontstaan van comorbiditeiten. Klinische uitkomsten en overleving waren vergelijkbaar met resultaten van conventionele instrumentatie (CI) zoals beschreven in de literatuur, hetgeen wijst op goede middellange- tot langetermijnresultaten voor PSI. **Hoofdstuk 6** beschrijft een gerandomiseerde gecontroleerde studie waarin PSI werd vergeleken met CI met een gemiddelde follow-up van 10,1 jaar (129 geanalyseerde patiënten). Er werden geen significante verschillen gevonden in PROMs of implantaatoverleving tussen beide groepen. Deze resultaten tonen aan dat de theoretische voordelen van PSI ten opzichte van CI zich op lange termijn niet vertalen in superieure klinische uitkomsten of lagere revisiepercentages.

Hoofdstuk 7 evalueerde de kosteneffectiviteit vanuit ziekenhuisperspectief vijf en tien jaar postoperatief. Quality-adjusted life years (QALY's), afgeleid van EQ-5D-5L-gegevens, waren vergelijkbaar voor PSI en CI. PSI ging echter gepaard met hogere totale kosten, voornamelijk door preoperatieve beeldvorming en de productie van patiëntspecifieke instrumenten, ondanks enige perioperatieve efficiëntiewinst. PSI was derhalve op beide tijdstippen minder kosteneffectief.

Hoofdstuk 8 onderzocht of het cumulatieve aantal radiologische alignement afwijkingen invloed heeft op klinische uitkomsten en implantaatoverleving tot vijf jaar na TKA. Patiënten werden verdeeld op basis van het aantal afwijkingen in meerdere vlakken. Er werden geen significante associaties gevonden tussen het aantal afwijkingen en PROMs of revisiepercentages. Deze bevindingen plaatsen vraagtekens bij de klinische relevantie van radiologische afwijkingen als voorspeller van klinische uitkomst en overleving van de prothese.

Gezamenlijk leiden de resultaten in dit proefschrift tot de conclusie dat PSI geen superieure klinische uitkomsten, implantaatoverleving of kosteneffectiviteit biedt ten opzichte van CI bij langetermijnfollow-up. Hoewel PSI een betrouwbaar en reproduceerbaar planningsinstrument is en vergelijke resultaten als CI oplevert, wordt het routinematig gebruik als superieur alternatief of nieuwe gouden standaard voor TKA niet ondersteund door de huidige evidentie. Een zorgvuldige en selectieve toepassing van PSI kan in specifieke klinische scenario's gerechtvaardigd blijven.

CHAPTER 12

DANKWOORD
BIOGRAPHY
LIST OF PUBLICATIONS

Dit proefschrift was nooit tot stand gekomen zonder de hulp van velen die mij dierbaar zijn. Ik wil iedereen die heeft bijgedragen en mij heeft gesteund enorm bedanken, en een aantal mensen in het bijzonder.

Als eerste wil ik graag mijn promotieteam bedanken. **Prof. dr. Tim Welting**, beste Tim, dankjewel voor jouw positieve aanwezigheid binnen het promotieteam en jouw kritische blik, die dit proefschrift naar een hoger niveau heeft getild. Als tweede bedank ik mijn copromotoren en steunpilaren vanaf het begin van het eerste artikel uit dit proefschrift, **Bert** en **Martijn**. Uiteraard wil ik jullie bedanken voor jullie bijdrage aan dit proefschrift, maar zeker niet minder voor alle jaren van fijne samenwerking, gezelligheid en gekkigheid, de tripjes naar Hamburg en Lyon, de goede gesprekken en jullie voortdurende interesse in mij als persoon. Jullie vormen een rode draad in mijn carrière tot nu toe en daar ben ik jullie enorm dankbaar voor.

Daarna wil ik mijn geweldige paranimfen bedanken, op wie ik enorm trots ben en voor wie ik dankbaar ben dat ze vandaag naast mij staan. Lieve **Ilse**, we zijn al meer dan 30 jaar vriendinnen en wat mij betreft komt daar nog zeker 2x30 jaar bij. Dankjewel dat je al jaren zo'n lieve vriendin voor mij bent en mij altijd het gevoel geeft dat je trots op mij bent en mij steunt. Je bent altijd in voor gezelligheid maar ook voor een eerlijk en goed gesprek. Onze vriendschap is mij ontzettend veel waard. Lieve **Wieteke**, mijn grote zus, uiteraard sta jij vandaag naast mij als paranimf. Niet alleen steun je mij in alles wat ik doe, maar je hebt door de jaren heen ook letterlijk alle artikelen gelezen en waardevolle feedback gegeven. Ik ben megatrots op jou en op alle bizarre dingen die je nu al hebt bereikt, maar ook op de persoon die je bent en de band die we samen hebben. Onbeschrijfelijk blij met jou in mijn leven.

Lieve **Britt** en **Marijn**, jullie vormen het talentvolle designteam van dit boekje, maar zijn bovenal twee geweldige en waardevolle vriendinnen. Jullie bijdrage aan het ontwerp maakt dit boekje nog specialer. Dankjewel voor jullie input, enthousiasme en jarenlange vriendschap.

Alle hoofdstukken in dit proefschrift zouden niet tot stand zijn gekomen zonder de medewerking van vele **coauteurs**. Enorm veel dank hiervoor. Speciale dank aan **Isobel** en **Daphne**, niet alleen voor de fijne samenwerking, maar ook voor de fijne momenten en gesprekken daaromheen.

Gedurende mijn opleiding tot orthopedisch chirurg ben ik werkzaam geweest in verschillende ziekenhuizen en heb ik overal een heerlijke tijd gehad. Hiervoor wil ik alle collega's door de jaren heen bedanken. Om te beginnen wil ik de **vakgroep Chirurgie in het Catharina Ziekenhuis Eindhoven** bedanken. Hoewel COVID soms wat roet in het eten gooide, kijk ik terug op een heel leerzame en fijne periode bij jullie. Daarna wil ik de **vakgroep Orthopedie van het Zuyderland Medisch Centrum** en in het bijzonder (oud)opleiders **Edwin Jansen, Emil van Haaren** en **Ide Heyligers** bedanken**.** Bij jullie begon ik als ANIOS en ging ook dit promotietraject van start. Vervolgens werd ik aangenomen voor de opleiding en keerde ik terug als AIOS. Het werkplezier bij jullie was een belangrijke reden voor mij om voor een toekomst binnen de orthopedie te kiezen. Vervolgens veel dank aan de **vakgroep Orthopedie van het Máxima Medisch Centrum**

en in het bijzonder aan opleiders **Rob Janssen** en **Hans Hendriks**. Twaalf jaar geleden kwam ik voor het eerst bij jullie als coassistent, vervolgens als semiarts en AIOS, en afgelopen jaar als kers op de taart voor een etalagestage. **Rob**, graag wil ik jou speciaal bedanken voor jouw steun en het zelfvertrouwen dat je mij hebt gegeven, waardoor deuren voor mij zijn geopend. Speciaal wil ik ook **Marijn van den Besselaar** en **Thijn Fuchs** bedanken voor het voeden van mijn interesse in knie-, voet- en enkelpathologie, maar vooral voor de fijne samenwerking, met name op de operatiekamer. Als laatste bedank ik de **vakgroep Orthopedie van het Maastricht Universitair Medisch Centrum** en in het bijzonder (oud)opleiders **Mark van den Boogaart** en **Peter Feczko.** Dankjewel voor jullie steun in de laatste fase van mijn opleiding en voor jullie bijdrage aan mijn ontwikkeling tot volwaardig orthopedisch chirurg. Daarnaast speciale dank aan het 'voetenteam', **Erwin Peters** en **Joris Hermus**, voor jullie steun en de vele leermomenten. Tot slot speciale dank aan al het personeel van de **Annadal Kliniek** voor de fijne samenwerking en gastvrijheid. Het was altijd een feest om een dag bij jullie te mogen opereren.

De personen die misschien wel de grootste stempel hebben gedrukt op mijn opleiding de afgelopen jaren, zijn alle **collega A(N)IOS.** Met velen van jullie zat ik in hetzelfde schuitje: een promotietraject afronden tijdens de opleiding. Het wederzijdse begrip, het samen kunnen sparren en af en toe (soms regelmatig) even zeuren zijn van grote waarde geweest bij het afronden van dit proefschrift. Nu, aan het einde van mijn opleiding, kijk ik terug op een geweldige tijd die we samen met alle A(N)IOS hebben gehad. Hiervoor wil ik iedereen enorm bedanken. Een aantal mensen wil ik graag in het bijzonder vermelden. In 2017 begon ik als ANIOS in het Zuyderland, samen met **Mark** en onder andere **Simon** en **Jeroen** als onze steunpilaren. Het is een periode waaraan ik met heel veel plezier terugdenk en die niet hetzelfde was geweest zonder jullie. Enorm bedankt! Vervolgens heb ik samen met **Frank** de vooropleiding getrotseerd. Frank, dankjewel dat je door de jaren heen zo'n fijne collega en vriend bent geweest. Daarnaast wil ik ook de rest van mijn lichting speciaal bedanken. **Misha**, mijn lieve collega, huisbaas, personal trainer en goede vriend. Je hebt de afgelopen jaren veel voor mij betekend. **Michaël**, geen feestje zonder jou. Jouw positiviteit en zorgeloosheid zijn een verademing. Lieve **Alexandra**, gedurende de opleiding was jij mijn collega, cursus- en reisgenoot, vriendin en powervrouw aan mijn zijde. Dankjewel voor jouw ongefilterde en verfrissende mening en jouw doorzettingsvermogen. Beide zijn goud waard.
Met veel plezier denk ik terug aan alle cursussen en congressen die ik de afgelopen jaren samen met collega-AIOS heb bijgewoond, zowel in Nederland als in het buitenland. Deze waren echt een cadeautje en ik hoop jullie hier de komende jaren nog vaak te treffen. Enkele speciale herinneringen verdienen een aparte vermelding. Ten eerste de kampeertrip door de Alpen richting ESSKA Milaan samen met **Alexandra** en **Sander**. Ten tweede de 'familievakantie' naar de sneeuw in Davos voor de AO advanced met **Michaël**, **Ruud** en **Sem**. Tot slot speciale dank aan het ESSKA-team voor de leuke en memorabele tijd in Parijs, Milaan en Praag. Op naar Göteborg!

Heel veel dank aan mijn vriendinnen die het leven extra leuk maken en die ik graag allemaal wil noemen. Lieve vriendinnen uit Sevenum: **An, Britt, Doreen, Floor, Hilde, Ilse, Lizzy en Marijn.** Samen met jullie opgroeien en het leven ontdekken was een groot feest. Dankjewel voor de ontelbare herinneringen die we samen hebben. Ik ben dankbaar dat ik jullie nog steeds in mijn leven heb. Dankjewel aan alle Terra's: **Carolien, Celine, Fabiënne, Fleurine, Iris, Laura, Marlou, Nieke en Zoë**. Wat hebben wij een heerlijke tijd gehad in Maastricht en in alle jaren daarna, tot en met vandaag! Onze vriendschap en alle herinneringen zijn mij zeer dierbaar. Samen staan we sterk! Dankjewel aan al mijn huisgenootjes door de jaren heen. Ten eerste **Katja en Anouk.** Jarenlang hebben wij als zusjes geleefd en nog steeds zijn jullie enorm belangrijk voor mij. Dankjewel voor de heerlijke jaren in alle huizen waar we samen hebben gewoond, voor de ontelbare herinneringen en vooral voor de bijzondere vriendschap die we nog altijd hebben. Lieve **Chrissy**, aan het begin van mijn opleiding was ik huisloos en nam jij mij in huis. Jaren later ben je een van mijn beste vriendinnen. Dankjewel dat je zo'n fijne vriendin voor mij bent, voor jouw zorgzaamheid, jouw feestvreugde en alle fijne gesprekken die we samen hebben. Lieve **Sabine**, Bienie, jij was mijn allereerste huisgenootje in Maastricht. Je bent altijd in voor gekkigheid maar ook voor een goed gesprek. Gezien je aan de andere kant van het land woont, duurt bijkletsen soms een hele dag, maar wat mij betreft blijven we dit voor altijd doen. Lieve **An**, we begonnen als maatjes bij de vooropleiding en nu zijn we onder andere biosvriendinnen. Ik ben heel blij met onze vriendschap. Lieve **Nicole**, dankjewel dat je zo'n lieve vriendin bent, altijd voor iedereen klaarstaat en dat we alles met elkaar kunnen delen.

Dank aan mijn lieve schoonfamilie uit België: **Hadewych, Paul, Laurens** en **Lien, Matthias** en **Stefanie**. Dankjewel voor jullie interesse, medeleven, steun, gastvrijheid en het heerlijke eten dat we in Achel altijd voorgeschoteld krijgen.

Dankjewel aan alle ooms, tantes, neven en nichten van de **familie Wijnen** en de **familie Theeuwen** voor jullie interesse en betrokkenheid bij mij en mijn carrière tot nu toe. Speciale dank aan **peetoom Jos** en **tante Jacquelien**, **peettante Riet** en **ome Toon**, en uiteraard **Des**.

Lieve pap en mam, uiteraard gaat er heel veel dank en lof naar jullie. Lieve **mam**, je bent altijd betrokken, trots en ondersteunend bij alles wat wij meemaken, ondernemen en bereiken. Lieve **pap,** dankjewel dat je altijd voor ons klaarstaat. Letterlijk niets is te veel gevraagd. Dankjewel dat je ons steunt en zo trots op ons bent. Jullie aanwezigheid bij mijn verdediging is alles!

Allerliefste **Alexander**, je bent het liefste en mooiste mensje dat ik ken. Ik prijs mij onwijs gelukkig met jou in mijn leven. Dankjewel voor jouw oneindige liefde en steun, niet alleen bij het afronden van dit proefschrift, maar echt bij alles. I love you!

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Dieuwertje Theeuwen was born on 1 September 1991 and grew up in Sevenum, where she lived until the age of 18. In 2009, she graduated from high school and began studying Health and Life at Vrije Universiteit Amsterdam. In 2010, she was accepted into the medical degree programme at Maastricht University. After completing her bachelor's degree, she spent some time in Australia, after which she completed her master's degree and graduated in 2017.

In 2017, she started working as a medical doctor (ANIOS) in the Department of Orthopaedics and Traumatology at Zuyderland Medical Centre. It was here that she began conducting scientific research, and the first publication from this thesis appeared in 2019. In the same year, she was also accepted into the orthopaedic surgery residency programme, which she started on 1 January 2020. In the following years, she worked as a resident in orthopaedic surgery (AIOS) at various teaching hospitals in the region, namely Catharina Hospital Eindhoven, Zuyderland Medical Centre, Máxima Medical Centre and Maastricht University Medical Centre. Alongside her clinical work, she continued her scientific research activities at Zuyderland Medical Centre, which led to a formal PhD project and this thesis.

Throughout her residency, her enthusiasm for the treatment of knee, foot and ankle conditions continued to grow. To further develop her expertise in ligamentous and sports-related knee injuries, she attended several specialized courses and completed a six-month elective rotation at Máxima Medical Centre in 2026. Her interest in the treatment of foot and ankle conditions also continued to grow. Through courses and clinical rotations at various hospitals, she further expanded her expertise and interest in minimally invasive techniques, arthroscopic treatment of ankle injuries, and forefoot and hindfoot surgery. On 26 December 2026, she will officially complete her orthopaedic surgery residency and will further focus on the conservative and surgical treatment of knee, foot and ankle conditions as an orthopaedic surgeon.

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