Risk factors for long-term failure of orthopaedic medical devices

Taking advantage of RSA as an early detection tool

Koen van Hamersveld

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“Zonder jullie was ik ergens, maar gelukkig kan ik zwerven”

G. de Randamie (Sprokkeldagen, Tussen Licht en Lucht, 2007)

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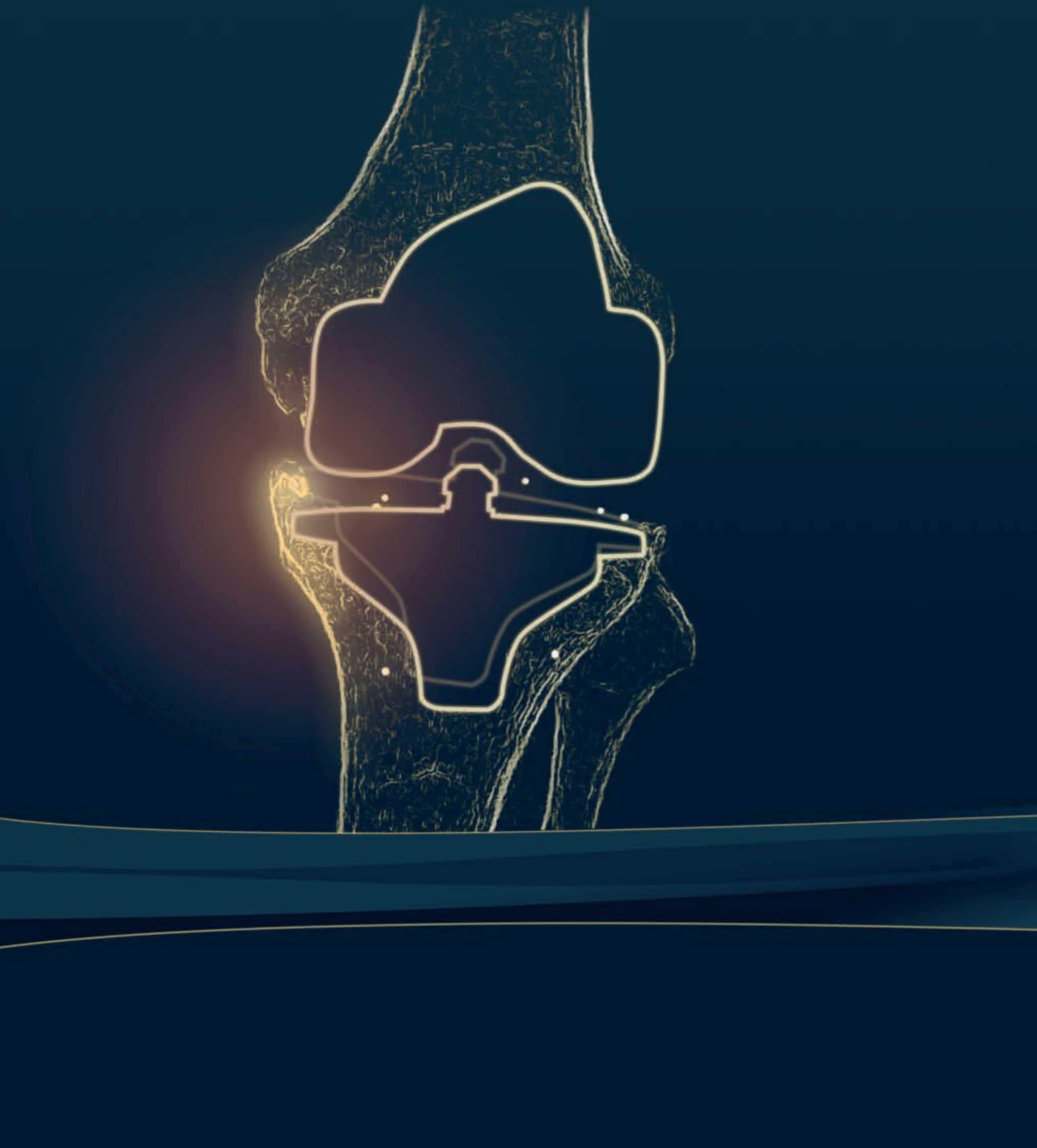

1 General introduction

Primary and revision total knee arthroplasty

Total knee arthroplasty (TKA) is currently the preferred treatment for patients suffering from refractory pain and limitations in daily activities associated with end-stage osteoarthritis of the knee. The demand for TKA is vastly increasing due to an aging society, obesity epidemic as well as the success of the procedure resulting in significant improvements in quality of life[1, 2]. The latest projections (which vary between models) have estimated an increase of 86-182%: from 680.000 procedures annually in 2014 in the United States up to 1.92 million procedures by 2030[2, 3]. Subsequently, the number of revision arthroplasties is also expected to rise dramatically given the revision burden of 5-10% (i.e., the ratio of revisions to the total number of arthroplasties), the limited lifespan of a prosthesis and continued increasing life expectancy of patients[4].

Revision surgery is however an expensive procedure requiring extensive resources, while patients are subjected to higher risks of perioperative morbidity and generally report less satisfying clinical results as compared with primary arthroplasty[5]. It is thus of vital importance to decrease the revision burden as much as possible. Revision surgery is generally only required if the patient outlives the life span of the implanted components or their fixation (which may depend on the patients' age, activity level, body habitus and on the implant materials and surgical proficiency[5]), or when complaints of instability, a periprosthetic fracture or deep surgical site infection cannot be controlled without removal of the components.

Infection and instability are major reasons for revision after TKA as reflected in the national arthroplasty registries[6-8]. However, aseptic loosening remains the leading cause of revision surgery[6]. Decades have passed with ongoing debates on implant design aspects[9], including the mode of fixation, conformity of the bearing and implant materials. Many design aspects have been fundamentally changed since the first total condylar design in continuous attempts to minimize the risk of loosening. Interestingly, abandoned concepts have been re-introduced as well after it became apparent that the reason for implant failure could be attributed to other causes. For example, early experimental designs with stemless uncemented tibial components have failed miserably, which was attributed to the uncemented technology rather than the absence of a stem[9]. Now that the technique and design of uncemented TKA has dramatically improved, there is a resurgence of interest in this technology[10].

In the past decades, there have been multiple examples of implants marketed as theoretically superior and subsequently implanted in thousands of patients before it became evident that the failure rates were much higher than anticipated and the implants turned out to be disastrous[11]. It is therefore of paramount importance that all implants introduced into the market have been rigorously tested in a stepwise manner, including preclinical studies and small, randomized clinical trials[12, 13]. The early clinical tests should preferably include methods associated with high accuracy, hence only requiring a limited number of patients[14]. Numerous studies have shown that radiostereometric analysis (RSA) is such a highly accurate tool that can detect early postoperative migration of the implanted components, which is predictive for the risk of late loosening long before clinical symptoms and other radiographic signs of loosening arise[11, 15-20].

Principles of radiostereometric analysis (RSA)

RSA is, amongst other purposes, used as a method to estimate prosthesis migration, defined as the change in position and orientation of a prosthesis with respect to the bone[20-22]. In order to do so, a stereo image is made at each follow-up moment by simultaneously obtaining two radiographs of the patient from a different angle. In marker-based RSA, tantalum markers inserted into the bone and added to the prosthesis define landmarks that are used for accurate calculations. In model-based RSA, the prosthesis itself is used as a marker, making prosthesis markers obsolete. By matching the prosthesis markers (in marker-based RSA) or virtual projections of a 3D surface model of the prosthesis (in model-based RSA) with the detected roentgen projections of the prosthesis, the position and orientation of the prosthesis is calculated[23]. The first step in migration calculation is the landmark transformation that aligns the bone markers in the follow-up moment (t1) with the bone markers in the reference moment (t0)[20]. This removes the "patient movement" between the different RSA acquisition moments (Figure 1).
The second step is the calculation of the change in position and orientation of the prosthesis between the reference moment and the follow-up moment. This change in position and orientation is thus relative to the bone markers.

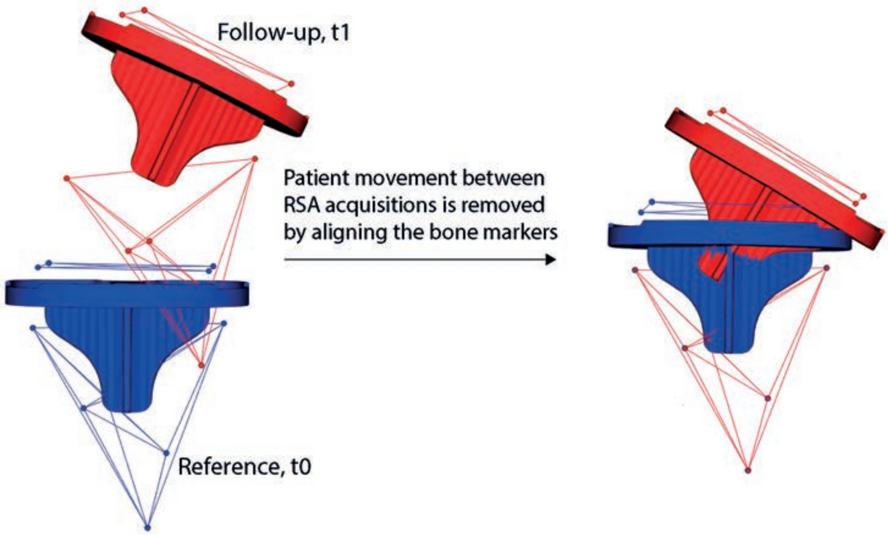

Figure 1. Transformation of the follow-up bone markers in the follow-up moment (t1) to the bone markers in the reference moment (t0) is performed (note that, in this example, the prosthesis migration is highly exaggerated for illustrative purposes).

The calculated migration describes a transformation of the prosthesis from the reference moment to the follow-up moment and is expressed as a series of rotations about the 3 orthogonal axes and translations along these axes (i.e., the x-axis is the transverse axis, the y-axis is the longitudinal axis, and the z-axis is the sagittal axis). The mathematics of RSA calculations are extensively described in Selvik[19] and Söderkvist and Wedin[24].

For individual points on the prosthesis (e.g., markers attached to the prosthesis, virtual markers or 3D surface model points) the translation along each axis can be calculated from the x-, y-, and z-coordinates of these points at t1 and t0. The point motion can be calculated based on Pythagoras' theorem:

$$point\ motion = \sqrt{(Tx2 + Ty2 + Tz2)}$$

In Figure 2 the point motion of 4 virtual markers on the tibia prosthesis is shown.

The point motion of the virtual markers from Figure 2 is:

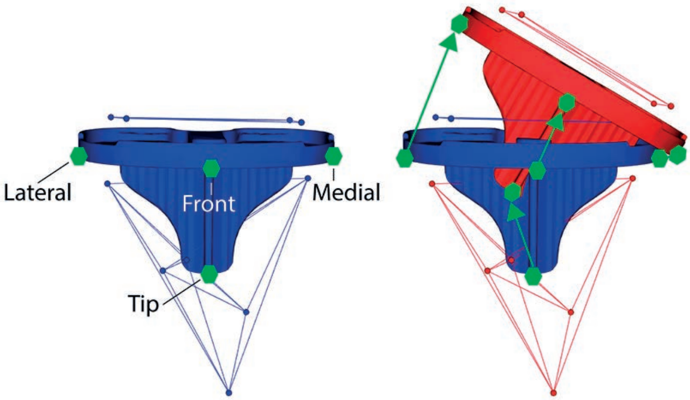

Figure 2. The change in position of 4 virtual markers on the tibia prosthesis model from t0 (blue) to t1 (red).

	x	y	z	Point motion (mm)
Front	10.41	19.89	0	22.45
Lateral	15.56	39.12	0	42.10
Medial	5.26	0.67	0	5.30
Tip	–6.15	24.33	0	25.09

The virtual marker with the largest point motion in this case is the "Lateral" marker. The virtual marker with the smallest point motion is the "Medial" marker. In this example, the tibia model rotates approximately around the medial edge of the prosthesis. Virtual markers close to this "true" rotation point have small point motions, and virtual markers at larger distances from this true rotation point have larger point motions. Maximum total point motion (MTPM), which is frequently used to summarize the migration of a prosthesis, is the length of the translation vector of the marker or virtual marker in a rigid body that shows the greatest migration. For model-based RSA, MTPM is the length of the translation vector of the point on the model that moved the most.

Contemporary thoughts and knowledge gaps on tibial component migration

Previous RSA studies have shown that every implant shows initial migration, which is usually benign and known as the prosthesis-settling phase. The magnitude of the initial migration varies between fixation types, with uncemented prostheses generally showing more initial migration than cemented prostheses[25]. Multiple studies have tried to establish early migration thresholds above which the physiological prosthesis-settling phase is deemed to be exceeded, and thus predictive for an unfavorable continuation of migration resulting in subsequent loosening. Ryd *et al.*[18] showed in a study with a variety of implants and fixation methods, that 'continuous' migration between one and two years of follow-up predicted later loosening. In that study, the cut-off MTPM value of continuous migration was 0.2 mm, and had a predictive power of 85% to correctly classify loosening implants. Pijls *et al.*[17] found an alternative cut-off value in a systematic review and meta-analysis. Of the investigated total knee prostheses (with specific type of fixation and type of insert) which showed revision rates for aseptic loosening of more than 10% after ten years follow-up in national arthroplasty registries, all had a mean MTPM of more than 1.6 mm at one-year follow-up as found in RSA studies. A later study showed that the latter threshold may already be used after six months of follow-up[26]. However, all of the abovementioned thresholds are based on both cemented and uncemented components from different brands, which limits the conclusions one can infer when analyzing the results for an individual patient with a specific type of implant. Despite that RSA was already introduced in 1974[19], there is thus a paucity of evidence on whether the migration profile of individual patient can be considered physiological (i.e., according to a normal prosthesis-settling phase) or should be considered pathological.

Outline of this thesis

In the first part of this thesis, the results of four randomized controlled trials (RCTs) are presented, each studying the effect of different design aspects on tibial component migration.

The first design aspect that was studied is the tibial component material. Historically, early tibial components were almost uniformly made of all-polyethylene[27]. The first-generation all-polyethylene designs often failed as a result of aseptic loosening, especially in comparison with the newly developed metal-backed modular[28]. Subsequently, the latter have been primarily used in the past decades. However, as the population in need for knee arthroplasty is rising dramatically, the associated healthcare costs are expected to rise accordingly. The latter may be reduced by using (newer) cost-saving all-polyethylene designs, which is one of the reasons for the renewed interest in such designs. However, all-polyethylene designs are still rarely used despite some evidence showing equivalent revision risks and clinical scores[28-30]. Studies evaluating (the risk of) aseptic loosening following all-polyethylene TKA, especially RSA studies, are thus scarce. In **chapter 2**, we evaluate the two-year results of an RCT comparing cemented condylar-stabilizing total knee prostheses with either an all-polyethylene or a metal-backed tibial component.

The second design aspect that was studied is the bearing concept. In an attempt to increase function and implant longevity, mobile-bearing TKA designs were developed in the late 1970s. This bearing theoretically minimizes contact stresses at the implant-bone interface, as well as polyethylene wear, which both should ultimately reduce the risk of aseptic loosening[31, 32]. However, contradicting evidence has been reported when comparing the clinical results with fixed-bearing designs[31-40]. Modern TKA designs, including the 'single-radius' prosthesis, are nowadays produced with improved quality of materials (in particular the polyethylene). Furthermore, the single-radius design reduces contact stresses and allows some axial rotation during deep flexion[41, 42]. The theoretical advantages of this single-radius TKA design may thus come close to the concepts of TKA designs with a mobile-bearing. There are however no studies comparing fixed-bearing and mobile-bearing single-radius prostheses. We therefore conducted an RSA trial, for which we present the medium-term follow-up results in **chapter 3**.

The third design aspect that was studied is the mode of fixation. 'Cement disease' was once thought to be the underlying cause of aseptic loosening following TKA[9]. The development of uncemented TKA designs subsequently started in the 1970s, but major experimental design flaws resulted in high failure rates of the uncemented components after which cemented TKAs remained the preferred mode of fixation[43]. However, some authors have raised concerns whether the cement-bone interface can endure the increased contact stresses as TKAs are now performed in younger, heavier and more active patients[25, 44]. This has caused a resurgence of interest in uncemented protheses, as they can provide a more durable, biologic fixation. The industry continuously introduces new biomaterials or application techniques in an attempt to improve bone ingrowth and thus influencing the biological fixation properties of the implants, which is the major cause of failure in the younger patient population[45]. *Peri-apatite* (PA) is one of those (relatively) new application techniques, which is, in contrast with standard 'line of sight' plasma sprayed hydroxyapatite (HA) coatings, a solution deposition technique of HA onto and into the 3D implant surface[46-52]. In **chapter 4**, we evaluate the effect of PA-coated TKA on five-year migration and compare the results with its cemented counterpart.

As most RCTs studying the impact of various design aspects typically report short-term results after two years of follow-up, the value of longer follow-up for such studies was studied while comparing the mode of fixation given the critical importance of rigid fixation in both the short- and long-term follow-up. In **chapter 5**, the results of a long-term RSA study are given in which we evaluate whether the observed short-term beneficial effect of PA-coating on uncemented tibial component migration is sustained over time, as compared with uncoated uncemented components. Furthermore, the concept of second postoperative year 'continuous migration' is evaluated, specifically for the uncemented prosthesis. It is unclear whether continuous migration in the second postoperative year in uncemented prostheses, can be prevented by a biological mediator at the implant surface such as hydroxyapatite which promotes osseointegration, leading to less mechanical implant failure or might that it may induce more loosening at mid-term due to dislodging of this coating . Given that the initial continuous migration phase in these uncemented components is longer than in cemented components, more long-term RSA follow-up studies are needed to determine what can be considered a 'safe' duration of this initial migration phase. The latter will also give more insight which short-term RSA cut-off values of migration can be used which are predictive for low revision rates of uncemented prostheses at long-term.

In the second part of this thesis, we attempt to find risk factors for loosening which may include implant design aspects, surgical alignment and patient characteristics. Since the primary studies were not powered to identify such risk factors, we pooled individual participant data of multiple RSA studies. Hence, statistical power increases as compared to studies, which use group-level data, as well as compared to meta-analyses using aggregated data[53].

In this thesis, the first issue to be addressed was whether it is justified to pool data from RSA studies using different RSA methods (i.e., marker-based and model-based RSA), as each method may introduce different types of measurement error. Furthermore, methodological differences between RSA methods may systematically affect migration results. **Chapter 6** describes the results of a comparison of two RSA methods, marker-based and model-based RSA used in a study of modular metal-backed components.

Besides design aspects of the prosthesis, the surgeon (surgical technique) has impact on migration of the prosthesis. The surgical alignment technique during TKA and its impact on implant longevity is still an issue of debate. Achieving neutral coronal alignment has historically been considered the optimal strategy, in which surgeons aim for the 'safe zone' of ± 3° from the neutral mechanical axis. However, studies have shown that the so-called constitutional (i.e., pre-morbid) alignment at the end of skeletal growth is not neutral in a large proportion of the general population[54]. Some authors have therefore advocated the use of alternative alignment techniques such as kinematic alignment, aiming to restore the knee to its pre-arthritic state rather than a standard neutral position[55-58]. There are studies suggesting that 'malalignment' may not necessarily result in increased prosthetic wear[59], and given that a relatively high rate of patients are not satisfied following TKA[60-62], the concept of kinematic alignment may potentially reduce patient dissatisfaction without compromising implant survivorship[63-65] which has subsequently been popularized by several groups of orthopaedic surgeons[66]. However, other authors have raised concerns on the long-term effects of intentionally aligning in varus or valgus, as the implants are designed for neutral mechanical alignment only[67]. With use of full-leg radiographs available in patients of three RSA studies, we focused on the effect of coronal alignment on tibial component migration in a pooled RSA study, for which the results are presented in **chapter 7**.

As described earlier in the introduction of this thesis, there is a paucity of evidence on whether the migration profile of an individual patient can be considered physiological or should be considered pathological. Furthermore, little is known on predisposing risk factors for tibial component migration. As a first step towards gaining more evidence, **chapter 8** describes the results of a meta-analysis on individual participant data pooled from 11 long-term RSA studies, evaluating different migration profiles and the effect of possible risk factors.

In **chapter 9**, the findings of this thesis are summarized and reflected on in a general discussion. Finally, future research recommendations are given.

This thesis thus aims to contribute to further evaluations regarding the effect of different implant design aspects on tibial component migration on a group level, whether results obtained from studies using different RSA techniques systematically differ or that it is justified to pool the outcomes of these studies, and ultimately to find risk factors for loosening in such pooled data sets, including not only implant design aspects, but also surgical alignment and patient characteristics.

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Part I

The effect of implant design on tibial component migration

2 Migration of all-polyethylene compared with metal-backed tibial components in cemented total knee arthroplasty: a randomized controlled trial

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Abstract

Background and purpose — With a rapidly increasing population in need of total knee arthroplasty (TKA), there is renewed interest in cost-saving all-polyethylene designs. Differences between metal-backed and all-polyethylene designs in initial component migration assessed by radiostereometric analysis (RSA), a proven predictor for late aseptic loosening, have been scantily reported. The purpose of this study was to compare implant migration and clinical outcomes of all-polyethylene tibial components *versus* metal-backed trays of similar geometrical shape.

Patients and methods — In this randomized controlled trial, 59 patients received a cemented Triathlon condylar-stabilizing implant (Stryker, Mahwah, NJ, USA) with either an all-polyethylene (n = 29) or a metal-backed tibial component (n = 30). RSA measurements and clinical scores (the Knee Society Score, Forgotten Joint Score, and Knee Osteoarthritis and Injury Outcome Score) were evaluated at baseline and postoperatively at 3, 12, and 24 months. A linear mixed-effects model was used to analyze the repeated measurements.

Results — A statistically significant difference in mean migration after 2 years was found in favor of the all-polyethylene group, with a mean maximum total point motion of 0.61 mm (95% CI 0.49–0.74) *versus* 0.81 mm (95% CI 0.68–0.96) for the metal-backed group (p = 0.03). However, this difference was smaller and not statistically significant after *post hoc* adjustment for surgeon effect. Both groups showed comparable improvements on all clinical outcome scores over time.

Interpretation — The Triathlon all-polyethylene tibial component showed less migration, suggesting a lower risk of late loosening as compared with its metal-backed counterpart. However, the found surgeon effect warrants further investigation.

Introduction

Metal-backed tibial components in total knee arthroplasty (TKA) have primarily been used since their introduction in the late 1970s, as clinical results were superior to the first generation of all-polyethylene tibial components[1]. With a rapidly increasing population in need of knee arthroplasty, the associated healthcare costs are expected to rise exponentially[2]. This triggered renewed interest in all-polyethylene designs as manufacturing such implants costs 20% to 50% less[1]. Meta-analyses comparing modern all-polyethylene and metal-backed tibial components show equivalent results in terms of risk for revision and clinical scores, yet all-polyethylene designs are still rarely used[3-5].

Given that first-generation all-polyethylene designs often failed secondary to aseptic loosening, many surgeons today are reluctant to use all-polyethylene components[5]. More evidence is thus needed on the fixation of today's all-polyethylene designs, preferably by radiostereometric analysis (RSA). None of the few RSA studies published to date has shown superiority of metal-backed designs over all-polyethylene designs[6-12]. Moreover, Hyldahl *et al.*[10] found lower initial migration in AGC all-polyethylene components (Biomet, Warsaw, IN, USA). They hypothesized that these—to some degree elastic—components may partly absorb eccentric forces, while the more rigid metal-backed design is thought to transform asymmetric load throughout the entire component, inducing adverse tensile forces.

With further improvements in implant design and quality of materials over the past decades, the clinical performance of either design could nowadays well outperform the other. We therefore conducted a randomized controlled trial in which we compared implant migration and clinical performance of a relatively new all-polyethylene tibial component with a similarly designed metal-backed tray of the Triathlon total knee prosthesis (Stryker, Mahwah, NJ, USA). The femoral component of this prosthesis is designed to rotate about a single axis during flexion, which should provide ligament isometry and a larger contact area throughout the range of motion[13]. Any remaining peripheral peak stresses that could compromise implant fixation might be better absorbed by the more elastic all-polyethylene design. Based on this theory, we hypothesized the all-polyethylene design to show less implant migration as compared with its metal-backed counterpart.

Patients and methods

This randomized controlled trial was conducted in Hässleholm Hospital, Sweden. All consecutive patients with primary osteoarthritis scheduled to undergo TKA between June 2014 and November 2014 were asked to participate. The main exclusion criterion was when regular postoperative visits for RSA and clinical evaluations were considered impractical, due to, for example, long travel time. A computer-generated randomization list was created by the study monitor (1:1 ratio with a block size of 20). Opening the sequentially numbered, opaque, sealed envelopes only on the day of surgery ensured concealment of treatment allocation. Patients remained blinded throughout follow-up, which was not the case for surgeons and observers performing clinical follow-up due to the marked difference in radiographic appearance between implant designs.

Prosthesis and surgical technique

Surgeries were performed by 2 experienced surgeons using standardized techniques according to the Triathlon knee system surgical protocol. All patients received condylar-stabilizing (i.e., with a deep-dished polyethylene insert) cruciate-retaining Triathlon total knee prostheses indicated for cemented fixation, with either modular metal-backed tibial components using highly cross-linked polyethylene inserts or monoblock all-polyethylene tibial components of similar geometrical shape made from conventional N2/Vac ultra-high molecular weight polyethylene. Both surgeons used a standard midline incision and medial parapatellar arthrotomy, preserved the posterior cruciate ligament and used pulsatile lavage prior to applying SmartSet GHV bone cement (DePuy CMW, Blackpool, UK) with the tibial keel uncemented in all procedures. No tourniquet was used and patellae were not resurfaced. For RSA purposes, 8 tantalum markers were inserted into the proximal tibial metaphysis and 5 markers were inserted (proximally) in the polyethylene insert at standardized positions (0.8 mm diameter; RSA Biomedical, Umeå, Sweden). Postoperatively, low molecular heparin (enoxaparin intramuscular 40 mg/day) was prescribed for 10 days and patients were stimulated to mobilize with immediate full weight-bearing.

Follow-up

Preoperatively, the Knee Society Score (KSS), Knee injury and Osteoarthritis Outcome Score (KOOS), and hip–knee–ankle angle (HKA) measurements (with varus < 180°) were assessed. Postoperative evaluations including RSA radiographs were performed on the first day after surgery. Subsequent RSA and clinical examinations including the KSS, KOOS, and the Forgotten Joint Score (FJS) were scheduled at 3 months, 1 year, and 2 years after surgery. The FJS questionnaire is a relatively new outcome measurement with increased discriminatory power in especially well-performing patients (i.e., able to detect small differences between good, very good, and excellent patients)[14, 15]. HKA measurements were repeated at 3 months' follow-up.

Radiostereometric analysis

To ensure similar measurement techniques between the radiolucent all-polyethylene design and the metal-backed design, marker-based RSA analysis was performed using the tantalum markers inserted at standardized positions in both designs. RSA radiographs were made in supine position with the knee in a calibration cage (Cage 10, RSA Biomedical, Umeå, Sweden) and analyzed using MB-RSA software version 4 (RSAcore, LUMC, Leiden, the Netherlands). The precision of the RSA setup was determined by taking "double examinations" at the 1-year follow-up and, as no actual migration is expected within the few minutes of time between examinations, is expressed as the upper limits of the 95% confidence interval (CI) around zero motion[16]. Levene's test for equality of variances was applied to test for differences in precision between modular (metal-backed) and monoblock (all-polyethylene) components. Positive directions along and about the orthogonal axes are according to the right-hand screw rule[17]. Migration was described as translation of the geometric center of the prosthesis markers and rotation about the geometric center of gravity. The maximum total point motion (MTPM), which is the length of the translation vector of the marker or virtual marker in a rigid body that has the greatest migration, was used as the primary outcome measure[16]. The direct postoperative RSA examination served as the reference for the migration measurements. Besides migration on a group level, the number of individual components showing "continuous migration," defined by Ryd *et al.*[18] as an increase in MTPM of 0.2 mm or more in the second postoperative year indicating an increased risk for aseptic loosening, are also reported. Marker stability and scatter values were within the limits of RSA guidelines[17].

Sample size

Earlier RSA studies using the Triathlon total knee prosthesis have shown measurement errors of less than 0.25 mm[19]. With an alpha of 0.05 and power of 80%, 17 patients were needed to detect a mean difference larger than 0.25 mm. To account for loss to follow-up, 30 patients were randomized to each group.

Statistics

All outcome measurements were analyzed according to the intention-to-treat principle using a linear mixed-effects model. This method accounts for the correlation of the repeated measurements in patients and deals effectively with missing values[20]. Treatment, time, and the interaction of time with treatment were modeled as fixed factors, patients were included as a random factor and a compound symmetry covariance structure was assumed. MTPM was log-transformed during statistical modeling to obtain a normal distribution, computed as log10(MTPM+1). Additionally, we conducted a *post hoc* sensitivity analysis to determine the effect of possible confounders on treatment by adding any baseline characteristic that was by chance not evenly distributed between groups as variables to the model, as well as their interaction with time. To analyze differences in mean migration along and about each orthogonal axis, only absolute values were used (as calculating the resultant of positive and negative displacement vectors requires all vectors to act on the same prosthesis)[21]. These outcome parameters were also log-transformed in a similar manner to MTPM to obtain normal distribution. Significance was set at $p < 0.05$ (IBM SPSS Statistics 23.0; IBM Corp, Armonk, NY, USA).

Ethics, registration, funding, and potential conflicts of interest

The trial was performed in compliance with the Declaration of Helsinki and Good Clinical Practice guidelines. The study was approved by the Regional Ethical Review Board in Lund prior to enrollment (entry no. 2013/434) and registered at isrctn.com (ID: ISRCTN04081530). Informed consent was obtained from all patients. Reporting of the trial was in accordance with the CONSORT statement. Stryker provided funds in support of the costs associated with RSA radiographs and extra clinical follow-up examinations. The sponsor did not take any part in the design, conduct, analysis, and interpretations stated in the final manuscript.

Results

Sixty patients were randomized of whom 1 patient withdrew from the study prior to surgery. This patient was not replaced, resulting in 29 patients receiving the allocated all-polyethylene components and 30 patients receiving allocated metal-backed components (Figure 1). At 2-year follow-up, the RSA images of 2 patients with metal-backed components could not be analyzed for technical reasons (1 stereo image had too few reference cage markers and 1 stereo image did not match). Both patients had low migration up to 1 year (MTPM < 0.3

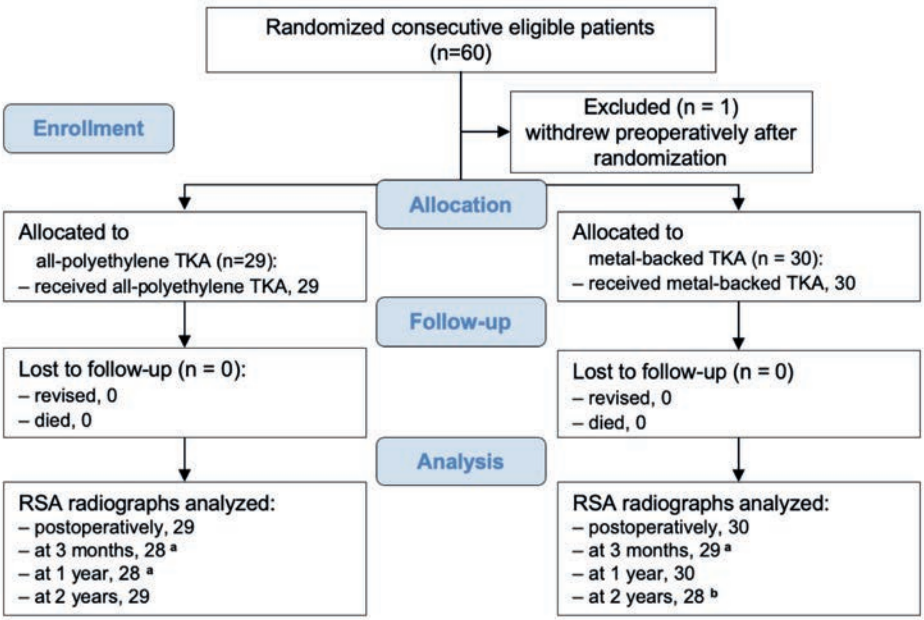

Figure 1. CONSORT flow diagram. TKA = total knee arthroplasty. [a] Missed follow-up; [b] Technical reasons, clinical follow-up only.

mm) and at 2-year follow-up no signs of loosening on conventional radiographs and good clinical scores. Due to chance, more females were randomized to the all-polyethylene group and surgeries were not evenly distributed between the two surgeons (Table I). Other than that, groups were comparable at baseline.

Table I. Baseline demographic characteristics

Outcome	All-polyethylene (n=29)	Metal-backed (n=30)
Age, mean (SD)	69 (5.5)	68 (5.6)
BMI, mean (SD)	28 (4.2)	29 (3.0)
Female sex, n	22	13
Ahlbäcks classification, n		
II	6	10
III	21	19
IV	2	1
HKA preoperative, n		
Varus (< 177°)	22	25
Neutral (177 - 183°)	5	3
Valgus (> 183°)	2	2
HKA postoperative, n		
Varus (< 177°)	4	7
Neutral (177 - 183°)	19	22
Valgus (> 183°)	6	1
Surgeon 1, n performed	20	14
Surgeon 2, n performed	9	16

HKA = hip–knee–ankle angle.

Radiostereometric analysis

The precision of the RSA setup was determined by making double examinations in 48 patients (of which 22 patients had metal-backed components) at one-year follow-up. The precision (expressed as the CI around zero motion) of transverse, longitudinal, and sagittal axis translation was 0.09 mm, 0.13 mm, and 0.11 mm, respectively; and of transverse, longitudinal, and sagittal rotation 0.15°, 0.12°, and 0.11°, respectively. There were no differences in precision between groups ($p > 0.15$ for all translations and rotations).

The results of the primary outcome MTPM showed a higher mean MTPM of 0.81 mm (CI 0.68–0.96) for the metal-backed group *versus* 0.61 mm (CI 0.49–0.74) for the all-polyethylene group after 2 years' follow-up ($p = 0.03$, Table II). In both groups, 4 prostheses showed continuous migration in the second postoperative year, ranging from 0.2 mm up to 1.5 mm (Figure 2). Most components showing continuous migration still had MTPM values < 1.5 mm at 2-year follow-up (Figure 2). The other RSA parameters revealed similar translations and rotations between groups at 2-year follow-up except for sagittal translation; the mean translation in the all-polyethylene group was 0.25 mm (CI 0.17–0.34) *versus* 0.43 mm (CI 0.34–0.52) for the metal-backed group ($p = 0.006$) (Table III, see Supplementary data).

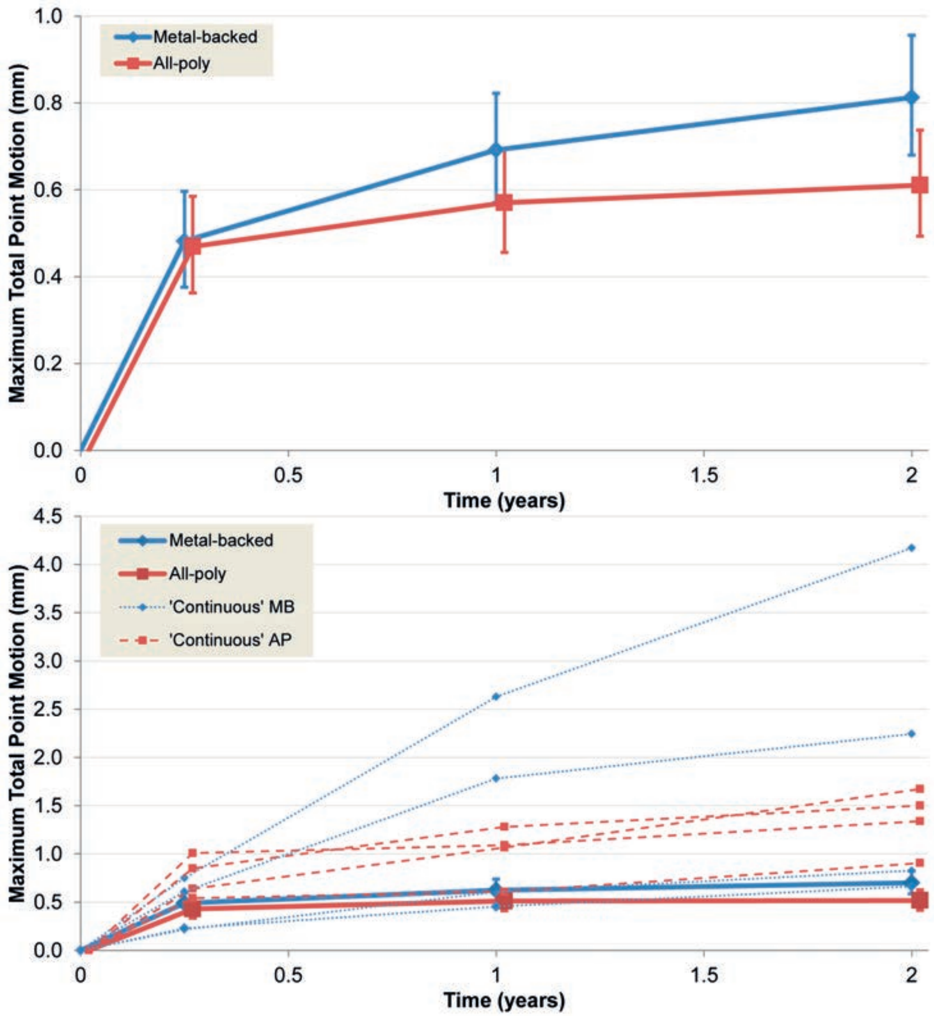

Figure 2. RSA analysis results of maximum total point motion (MTPM). Top: mean and 95% confidence interval for the groups; bottom: mean and 95% confidence interval for the same groups excluding 8 individual components showing continuous migration of > 0.2 mm in the second postoperative year. These individual components are illustrated as 4 dashed blue lines (metal-backed) and 4 dashed red lines (all-polyethylene).

Table II. RSA migration analysis of mean Maximum Total Point Motion (logMTPM values are back-transformed in original scale in millimeters), as provided by the mixed-effects model

	All-polyethylene (95% CI)	Metal-backed (95% CI)	p-value
3 months	0.47 (0.36 to 0.59)	0.48 (0.38 to 0.60)	
1 year	0.57 (0.46 to 0.69)	0.69 (0.57 to 0.82)	
2 years	0.61 (0.49 to 0.74)	0.81 (0.68 to 0.96)	0.03

In the *post hoc* sensitivity analysis (adjusting for a possible effect of the unevenly distributed covariates sex and surgeon), a statistically significant surgeon effect was found on migration; the mean logMTPM difference between surgeons at 2-year follow-up was 0.13 (CI 0.09–0.17, $p < 0.001$); sex had no statistically significant effect on migration (Table IV, see Supplementary data). Although all-polyethylene components showed on average less migration in both surgeon groups, the difference with metal-backed components was, in contrast with the primary analysis, not statistically significant anymore when adjusting for the surgeon effect ($p = 0.2$) (Figure 3 and Table IV, see Supplementary data).

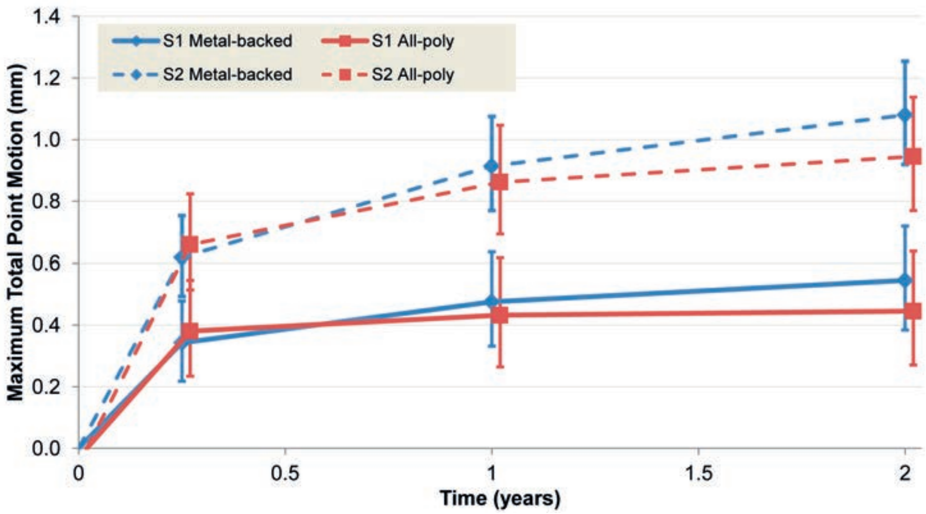

Figure 3. *Post hoc* sensitivity analysis results of maximum total point motion stratified by surgeon. The solid lines are the mean and 95% CI of the treatment group*s* of surgeon 1 (S1) and the dashed lines of surgeon 2 (S2).

Clinical results and adverse events

The KSS score and all patient-reported outcome scores (KOOS and FJS) showed comparable improvements over time between groups (Table V, see Supplementary data).

Several adverse events occurred (all in patients of the metal-backed group, except for the last patient described below). One patient suffered from peroneal nerve dysfunction directly postoperatively, which partially resolved. Two venous thrombo-embolisms occurred within 3 months (1 deep-vein thrombosis and 1 pulmonary embolism) requiring temporary pharmacologic treatment. One patient experienced persistent anterior knee pain with patellar maltracking for which a medial patellofemoral ligament reconstruction was performed 14 months after the primary surgery (all components remained in situ). The patient continued to participate in the study showing moderate clinical scores at 2-year follow-up. Lastly, 1 patient (a 67-year-old female with an all-polyethylene component) sustained a supracondylar femur fracture of the ipsilateral leg following a fall accident 15 months after the primary surgery. She was initially treated using a lateral distal femoral locking plate, but this was converted to an intramedullary nail due to plate failure after 2 months. At 2 years' follow-up, the patient and her knee functioned well with excellent clinical scores, no signs of loosening of the femoral component and a stable tibial component migration pattern similar to the group average.

Discussion

The results of the primary outcome of this study confirm our hypothesis that all-polyethylene components show statistically significantly lower migration after 2 years of follow-up compared with metal-backed trays of similar geometrical shape. However, smaller, non-significant differences were found after adjustment for surgeon effect in the *post hoc* analysis. As high initial migration is predictive for late aseptic loosening[18, 22], our results suggests that by using a Triathlon all-polyethylene tibial component the risk of late loosening is at least comparable with, if not less than, that of its metal-backed counterpart.

Whereas the first-generation all-polyethylene TKA designs often failed due to loosening, our findings support a growing body of evidence that modern all-polyethylene designs are performing at least equally as well as metal-backed TKA designs[3-5]. Previous RSA studies have shown all-polyethylene designs of various manufacturers to have comparable implant migration to its metal-backed counterpart[6-12]. Depending on the cementing technique, Hyldahl *et al.*[10, 11] found comparable or lower migration of all-polyethylene components owing to the "teeter-totter" effect (i.e., tensile forces on the opposite side of the implant upon peripheral compressive loading). This adverse effect on migration was found to be greater when the tibial stem of the more rigid metal-backed tray was not cemented. As the tibial components in our study were only horizontally cemented, this could explain the higher migration of the metal-backed components in our study too.

Although there is a strong association between high initial migration and late loosening, it remains unclear how to optimally define "high" migration when comparing the performance of different implants[23]. The found difference in mean MTPM suggests superiority of the all-polyethylene components over the metal-backed components. On the other hand, 4 components showed continuous migration in the second postoperative year in both groups, thus the number of individual components considered at risk for loosening is equal between groups. Furthermore, in the sensitivity analysis (adjusting for surgeon effect), results within each surgeon group appeared to be still in favor of the all-polyethylene components, but the differences were smaller and not significant anymore. The found surgeon effect highlights that, even today with all of the instrumentation available to promote standardization of surgical procedures, meticulous performance of each surgical step can improve the outcome, at least on a subclinical level. The results of the sensitivity analysis should, however, be regarded with caution due to multiple testing and an insufficient sample size for stratification by surgeon. It would be of interest if future RSA studies further explore this surgeon effect by randomizing patients to 2 or more surgeons using identical implants.

Most RSA studies have used maximum total point motion as the primary outcome to predict the occurrence of aseptic loosening[18, 22, 24]. Recently, however, Gudnason *et al.*[25] advocated the use of other RSA parameters as the main predictor for loosening as MTPM has its limitations. One of the limitations is that one cannot infer the direction of migration of the MTPM values alone, resulting in uncertainty concerning the failure mechanism. But as motion implies a biological effect, which is expected to be greatest at the point of maximum motion[17], merely expressing migration in fixed directions (e.g., anterior/posterior tilt) would in our opinion underestimate this effect in combined directions (e.g., subsidence into the medial-posterior tibial plateau with internal rotation). Another limitation of MTPM is that any movement between the polyethylene insert and the metal tray influences MTPM in marker-based RSA if polyethylene markers are used to represent the tibial component. Although improved locking mechanisms of modern fixed-bearing designs should prevent the insert from moving with respect to the metal tray, one should be aware of this phenomenon as previous studies have shown such movements to occur in older fixed-bearing designs, resulting in unreliable RSA measurements in the transverse plane[26-28]. It is therefore possible that the found difference is partly caused by movements between the modular components of the metal-backed design, rather than actual migration of the metal tray. One way to overcome this potential problem is to use model-based RSA measurements, but since all-polyethylene components are radiolucent, model-based RSA was only a possibility in the metal-backed trial arm. Given the known differences in precision between marker-based and model-based analysis[29], the current study was set up to use only marker-based RSA in both arms, rather than using different RSA methods in each arm. Furthermore, double examinations showed comparable precision between designs in all directions, indicating that the modular insert is most likely securely fixed within the tray. The influence of such movements on MTPM is therefore expected to be negligibly small.

In summary, a statistically significantly lower mean migration after 2 years was found in favor of the Triathlon all-polyethylene design, which may put patients at lower risk of aseptic loosening as compared with its metal-backed counterpart. However, smaller, non-significant differences in migration were found after adjustment for surgeon effect in the *post hoc* analysis. This unexpected surgeon effect warrants further investigation.

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Supplementary data

Table III. RSA migration analysis of mean absolute translation and rotation along and about each orthogonal axis (log-values are back-transformed in the original scale)

	All-polyethylene (95% CI)	Metal-backed (95% CI)	p-value
Translation along transverse axis (mm)			
3 months	0.14 (0.09 to 0.20)	0.20 (0.14 to 0.25)	
1 year	0.14 (0.09 to 0.20)	0.22 (0.16 to 0.28)	
2 years	0.19 (0.14 to 0.25)	0.25 (0.19 to 0.31)	0.2
Translation along longitudinal axis (mm)			
3 months	0.12 (0.08 to 0.15)	0.11 (0.08 to 0.15)	
1 year	0.13 (0.09 to 0.16)	0.13 (0.10 to 0.17)	
2 years	0.10 (0.07 to 0.14)	0.15 (0.12 to 0.19)	0.08
Translation along sagittal axis (mm)			
3 months	0.19 (0.11 to 0.27)	0.19 (0.12 to 0.27)	
1 year	0.24 (0.16 to 0.32)	0.36 (0.27 to 0.45)	
2 years	0.25 (0.17 to 0.34)	0.43 (0.34 to 0.52)	0.006
Rotation about transverse axis (degrees)			
3 months	0.38 (0.27 to 0.49)	0.21 (0.12 to 0.30)	
1 year	0.48 (0.38 to 0.60)	0.38 (0.28 to 0.49)	
2 years	0.47 (0.36 to 0.59)	0.45 (0.34 to 0.57)	0.8
Rotation about longitudinal axis (degrees)			
3 months	0.18 (0.11 to 0.25)	0.19 (0.12 to 0.26)	
1 year	0.20 (0.13 to 0.27)	0.24 (0.17 to 0.31)	
2 years	0.20 (0.13 to 0.27)	0.29 (0.22 to 0.37)	0.09
Rotation about sagittal axis (degrees)			
3 months	0.26 (0.18 to 0.33)	0.23 (0.16 to 0.31)	
1 year	0.32 (0.25 to 0.41)	0.28 (0.21 to 0.36)	
2 years	0.34 (0.26 to 0.42)	0.33 (0.25 to 0.41)	0.8

Table IV. *Post hoc* sensitivity analysis of log-transformed maximum total point motion (logMTPM)

	Mean difference in logMTPM between groups (95% CI)	p -value
Treatment effect (reference: all-polyethylene)		
3 months	-0.012 (-0.055 to 0.032)	
1 year	0.013 (-0.031 to 0.057)	
2 years	0.029 (-0.016 to 0.074)	0.2
Sex effect (reference: male)		
3 months	0.008 (-0.037 to 0.053)	
1 year	0.017 (-0.028 to 0.062)	
2 years	0.026 (-0.019 to 0.072)	0.3
Surgeon effect (reference: surgeon 1)		
3 months	0.080 (0.037 to 0.129)	
1 year	0.114 (0.070 to 0.157)	
2 years	0.129 (0.085 to 0.173)	< 0.001

Table V. Functional outcomes, values are mean and standard error in points, unless otherwise stated. The p-values indicate testing the between-group mean difference of improvement between baseline and 2-year follow-up

	All-polyethylene	Metal-backed	Difference in progression between groups (95% CI)	p-value
KSS Knee Score				
Preoperative	32.3 (2.9)	30.1 (2.8)		
3 months	85.6 (2.4)	78.3 (2.4)		
1 year	94.4 (1.8)	92.7 (1.7)		
2 years	91.9 (2.1)	93.4 (2.1)	3.7 (-4.6 to 12)	0.4
KSS Function Score				
Preoperative	58.8 (2.8)	57.5 (2.8)		
3 months	75.9 (2.6)	76.3 (2.6)		
1 year	90.1 (2.0)	87.3 (1.9)		
2 years	88.3 (2.8)	86.7 (2.7)	-0.3 (-8.3 to 7.7)	0.9
KOOS – Symptoms				
Preoperative	46.7 (2.5)	41.8 (2.5)		
3 months	51.6 (2.3)	51.7 (2.3)		
1 year	59.4 (2.6)	57.1 (2.5)		
2 years	62.1 (3.5)	61.8 (3.5)	4.6 (-5.9 to 15)	0.4
KOOS – Pain				
Preoperative	38.7 (3.3)	38.3 (3.4)		
3 months	69.8 (3.0)	60.5 (3.0)		
1 year	84.5 (3.0)	80.2 (2.9)		
2 years	79.2 (3.4)	83.2 (3.3)	4.5 (-5.5 to 14)	0.4
KOOS – ADL				
Preoperative	44.8 (3.3)	42.1 (3.3)		
3 months	69.9 (2.6)	64.2 (2.6)		
1 year	81.8 (2.7)	79.6 (2.7)		
2 years	79.4 (3.0)	80.5 (2.9)	3.8 (-5.4 to 13)	0.4
KOOS – Sports				
Preoperative	7.8 (1.9)	7.4 (2.0)		
3 months	19.5 (3.1)	21.7 (3.1)		
1 year	48.4 (4.3)	36.5 (4.2)		
2 years	41.5 (4.7)	41.3 (4.7)	0.2 (-13 to 14)	1.0
KOOS – QOL				
Preoperative	35.6 (1.5)	32.1 (1.6)		
3 months	46.1 (2.4)	44.5 (2.4)		
1 year	57.5 (2.8)	55.2 (2.7)		
2 years	57.5 (3.8)	57.8 (3.8)	3.7 (-7.3 to 15)	0.5
FJS				
3 months	38.4 (4.3)	30.9 (4.3)		
1 year	61.8 (4.8)	55.9 (4.7)		
2 years	56.9 (5.2)	57.5 (5.2)	8.1 (-5.4 to 21)	0.2

KSS = Knee Society Score, KOOS = Knee injury and Osteoarthritis Outcome Score, FJS = Forgotten Joint Score.

3

Migration and clinical outcome of mobile-bearing *versus* fixed-bearing single-radius total knee arthroplasty: a randomized controlled trial

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Abstract

Background and purpose — Mobile-bearing total knee prostheses (TKPs) were developed in the 1970s in an attempt to increase function and improve implant longevity. However, modern fixed-bearing designs like the single-radius TKP may provide similar advantages. We compared tibial component migration measured with radiostereometric analysis (RSA) and clinical outcome of otherwise similarly designed cemented fixed-bearing and mobile-bearing single-radius TKPs.

Patients and methods — RSA measurements and clinical scores were assessed in 46 randomized patients at baseline, 6 months, 1 year, and annually thereafter up to 6 years postoperatively. A linear mixed-effects model was used to analyze the repeated measurements.

Results — Both groups showed comparable migration ($p = 0.3$), with a mean migration at 6-year follow-up of 0.90 mm (95% CI 0.49–1.41) for the fixed-bearing group compared with 1.22 mm (95% CI 0.75–1.80) for the mobile-bearing group. Clinical outcomes were similar between groups. One fixed-bearing knee was revised for aseptic loosening after 6 years and 2 knees (1 in each group) were revised for late infection. Two knees (1 in each group) were suspected for loosening due to excessive migration. Another mobile-bearing knee was revised after an insert dislocation due to failure of the locking mechanism 6 weeks postoperatively, after which study inclusion was preliminary terminated.

Interpretation — Fixed-bearing and mobile-bearing single-radius TKPs showed similar migration. The latter may, however, expose patients to more complex surgical techniques and risks such as insert dislocations inherent to this rotating-platform design.

Introduction

Mobile-bearing total knee prostheses (TKPs) were developed in the late 1970s in an attempt to increase function and improve implant longevity. The bearing was designed to articulate with both a congruent femoral component and a flat non-constrained tibial component, thereby minimizing both contact stresses at the implant–bone interface and polyethylene wear, which should ultimately reduce the occurrence of mechanical loosening[1, 2].

The first—implant developer—long-term survival studies of such designs showed promising high survival rates and good clinical performance[1, 3-5]. Contrarily, no superior results compared with fixed bearings were seen in a number of trials, large registry-based studies and meta-analyses[2, 6-10]. Several trials assessing the migration pattern with radiostereometric analysis (RSA) found no superiority of either design on tibial component fixation[11-14] and even questioned whether the mobile bearing truly stays mobile in vivo[15]. Furthermore, mobile-bearing arthroplasty is considered technically more challenging as less optimal ligament balancing increases the risk of insert dislocations, requiring revision surgery[16-18]. Nevertheless, the mobile-bearing design is marketed as an appealing choice for especially young and active patients who demand maximum function and implant longevity [2, 14, 19].

Over time, modern TKPs have substantially improved in design, quality of materials (particularly the polyethylene) and fixation methods. In contrast to most conventional designs that have several axes of femoral rotation during flexion, the femoral component of the 'single-radius' TKP rotates about a single axis and should thereby reduce contact stress[20, 21]. The fixed-bearing variant of this single-radius design allows for some axial rotation during deep flexion with minimal constraint forces[20]. Thus, the theoretical advantages of this fixed-bearing single-radius design might come close to the concepts of mobile-bearing designs, but without the associated risks like insert dislocations.

There are to our knowledge no studies comparing mobile-bearing and fixed-bearing single-radius TKPs, except for a previous report on 1-year migration and kinematics on the first 20 patients of this trial[21]. We now present medium-term follow-up results of all included patients and compare tibial component migration and clinical out-comes of similarly designed mobile-bearing and fixed-bearing cemented single-radius TKPs.

Patients and methods

This randomized controlled trial was conducted at the Leiden University Medical Center (an academic tertiary referral center) between April 2008 and February 2010. Patients received either mobile-bearing or fixed-bearing components of an otherwise similarly designed cemented posterior stabilized Triathlon TKP (Stryker, Mahwah, NJ, USA). The rotating-platform mobile-bearing design additionally has a locking O-ring, which allows axial rotation about a central post[21]. The arthroplasties were performed by three experienced knee surgeons or under their direct supervision, using the appropriate guidance instruments following the manufacturer's instructions. In all patients, the components were cemented first, after which the insert was mounted. Pulsatile lavage of the osseous surface was undertaken before applying bone cement (Palacos R cement, Heraeus-Kulzer GmbH, Hanau, Germany). For more details regarding patients, randomization and prostheses, see Wolterbeek *et al.*[21].

Follow-up

Baseline characteristics, including the Knee Society Score (KSS) and hip–knee–ankle angle (HKA) measurements (with varus < 180°) were assessed 1 week before surgery. Postoperative evaluations including RSA radiographs were performed the first or second day after surgery, before weight bearing. Subsequent RSA and clinical examinations including KSS scores were scheduled at 6 months, 1 year and annually thereafter. HKA measurements were repeated at the 1-year follow-up.

Radiostereometric analysis

To accurately measure tibial component migration, radiostereometric analysis measurements were performed according to the RSA guidelines[22]. At each examination, the patient was in a supine position with the calibration cage (Carbon Box, Leiden, The Netherlands) under the table in a uniplanar setup. Migration was analyzed using Model-based RSA, version 4 (RSAcore, LUMC, Leiden, the Netherlands). Positive directions along and about the orthogonal axes are: medial on transverse (x-)axis, cranial on longitudinal (y-)axis and anterior on sagittal (z-)axis for translations and anterior tilt (x-axis), internal rotation (y-axis) and valgus tilt (z-axis) for rotations[23]. The maximum total point motion (MTPM), which is the length of the translation vector of the point on the tibial component that has moved most, was defined as the primary outcome.

Sample size

RSA measurement error of less than 0.5 mm was expected[23]. If the true difference in MTPM between fixed-bearing and mobile-bearing TKPs is 0.5 mm, 17 patients were required to detect this difference with alpha 0.05 and power 0.80. To account for loss to follow-up, the intention was to randomize 20 patients to each group.

Statistics

The original primary endpoint[21] was registered as a difference in MTPM between groups after 1-year follow-up on the first 20 enrolled patients. For this medium-term follow-up analysis, we changed the primary endpoint—prior to data analysis—to a difference in MTPM between groups of all included patients after 6 years of follow-up, as 6-year data were available at the time of data analysis. To provide unbiased comparisons between groups, the main approach to analyze the results was the intention-to-treat analysis (groups according to allocation). In case of switches between groups so that patients were not treated as randomized, thereby diluting the treatment effect, an as-treated analysis (groups according to received type of prosthesis) was also performed.

The first postoperative radiographs were taken as reference for the migration measurements. We used repeated measures analysis of variance with a linear mixed-effects model to analyze the migration measurements. This is the recommended technique to model repeated measurements as it takes the correlation of measurements performed on the same subject into account and includes all patients in the analysis while dealing effectively with missing values[24-26]. The difference in migration between groups is only tested once after 6-year follow-up to safeguard against multiple testing and is modelled as a function of time and the interaction of time with type of prosthesis (fixed effects). A random-intercepts term is used (random effect) and remaining variability is modelled with a heterogeneous autoregressive order 1 covariance structure. For revised and lost cases, RSA measurements were included in the analysis up to the last follow-up. MTPM was log-transformed during statistical modelling as it was not normally distributed.

The secondary (clinical) outcomes, namely KSS scores, flexion, and extension, were analyzed with a similar linear mixed-effects model. The standard errors of KSS knee score and extension were corrected via the sandwich estimator using a generalized estimating equations approach, as these outcome measures were not normally distributed and a log-transformation did not result in a normal distribution. To illustrate the directions of migration, descriptive data of the translations and rotations along and about the orthogonal axes are presented but not tested for significance.

IBM SPSS Statistics 23.0 (IBM Corp, Armonk, NY, USA) was used for all analyses, and significance was set at $p < 0.05$.

Ethics, registration, funding, and potential conflicts of interest

The trial was performed in compliance with the Declaration of Helsinki and Good Clinical Practice guidelines, and approved by the local ethics committee prior to enrollment (entry no. P07.205, retrospectively registered at ClinicalTrials.gov, NCT02924961). All patients gave informed consent. Reporting of the trial was in accordance with the CONSORT statement. This study was partially funded by a single unrestricted grant from Stryker. The sponsor did not take any part in the design, conduct, analysis, and interpretations stated in the final manuscript.

Results

Fifty-two knees were eligible in 48 patients (Figure 1). 6 patients (3 of both groups) were excluded due to an insufficient number of bone markers placed in the proximal tibia, resulting in unmeasurable RSA images. Thus 23 fixed-bearing and 23 mobile-bearing TKPs could be used in the intention-to-treat analysis. During the 6-year follow-up, 5 patients died, 4 revisions were performed (see below), 1 patient withdrew dissatisfied with his knee function, and 9 patients withdrew or refused to visit the clinic for reasons not related to the knee prosthesis. This resulted in 299 valid RSA radiographs used for the migration analysis. Baseline characteristics did not differ between groups (Table I).

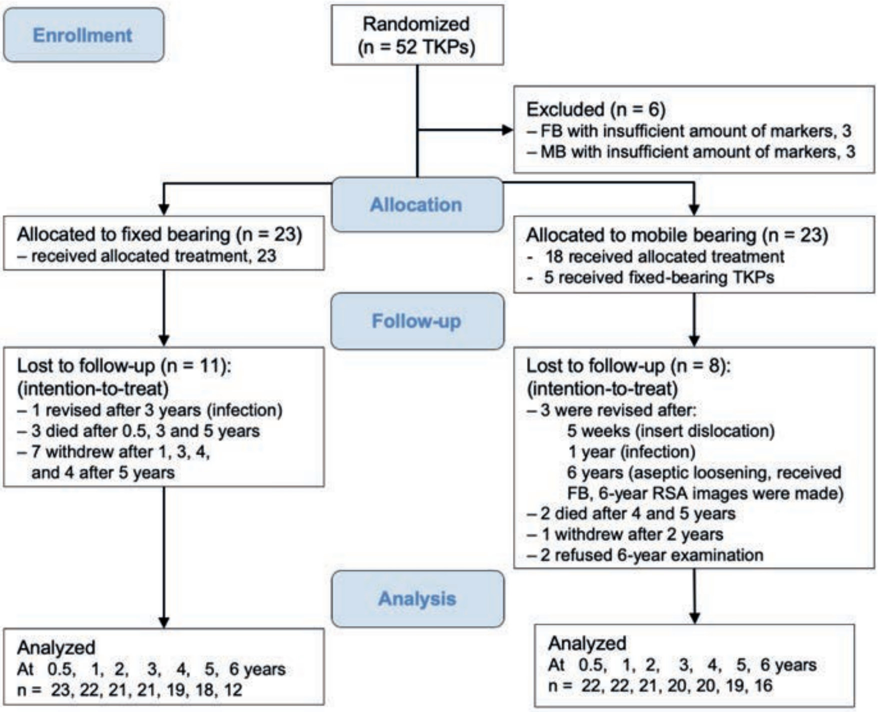

Figure 1. CONSORT flow diagram. FB = fixed-bearing, MB = mobile-bearing, TKPs = total knee prostheses.

Table I. Baseline demographic characteristics. Values are mean (SD) unless otherwise indicated

Outcome	Fixed-bearing (n=23 TKPs)	Mobile-bearing (n=23 TKPs)
Age	68.0 (9.6)	67.5 (10.1)
BMI	30.1 (6.2)	29.8 (6.2)
Female sex, n	16	19
Diagnosis, n		
Osteoarthritis	17	13
Rheumatoid arthritis	5	10
Haemophilic arthropathy	1	0
ASA classification, n		
I	3	2
II	17	15
III	3	6
Hip–knee–ankle angle		
Preoperative	177 (6)	180 (8)
Postoperative	178 (4)	178 (4)
Knee Society Score		
KSS Knee Score	49.3 (8.9)	47.2 (18.3)
KSS Function Score	45.7 (22.6)	35.9 (21.8)

ASA = American Society of Anesthesiologists.

RSA and clinical outcomes

The precision of RSA measurements was assessed with 34 double examinations (Table II). There were no statistically significant differences in mean migration between groups during 6 years of follow-up (Figure 2 and Table IV, see Supplementary data). Migration remained similar between groups when excluding five components with high migration profiles (Figure 2).

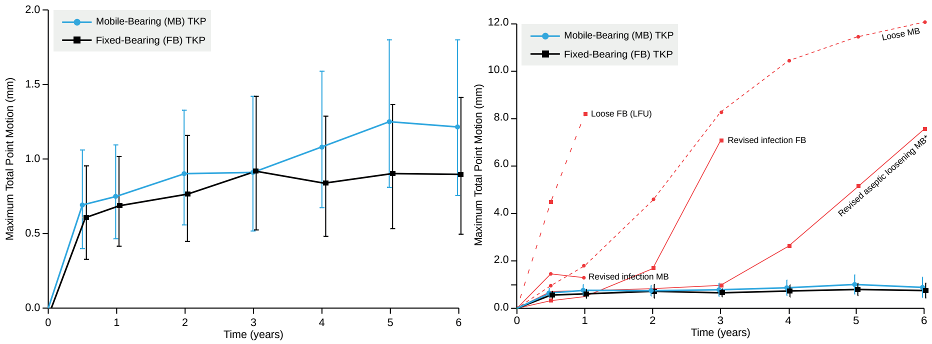

Figure 2. Mean maximum total point motion and 95% CI for the groups alone **(top)** and mean and 95% CI for the groups with solid red lines for the revised components and dashed red lines for the components suspected for loosening excluded from the groups **(bottom)**. One component revised due to a mobile-bearing insert dislocation is not shown separately, as this complication occurred before 6 months of follow-up. *Analyzed as mobile-bearing TKP in intention-to-treat analysis but received fixed-bearing TKP. LFU = lost to follow-up.

Table II. Precision of RSA measurements (upper limits of the 95% CI around zero motion)

Tibial component	Transverse	Longitudinal	Sagittal
Translation (mm)	0.05	0.04	0.14
Rotation (°)	0.21	0.45	0.11

Both groups showed comparable translations and rotations along and around the 3 orthogonal axes, and high migration of individual components was seen in almost any direction (Figure 3). Five components showed excessive migration (Figure 2 and Figure 3), of which 2 were revised for septic loosening (late infections of a mobile-bearing knee with *Staphylococcus aureus* after 1 year and a fixed-bearing with a *Candida albicans* after 3 years) and 1 fixed-bearing (randomized in the mobile-bearing group) was revised for aseptic loosening after 6 years (Table III #35, see Supplementary data). The other 2 were suspected for aseptic loosening of which 1 mobile-bearing knee was postponed for revision surgery (Figure 4, see Supplementary data) and 1 fixed-bearing, placed in an 81-year-old female with osteoarthritis, was lost to follow-up after 1 year. This patient visited the outpatient clinic after 6 years of follow-up with severe knee complaints, showing a progressive varus alignment of the tibial component (HKA 174° at 1 year *versus* 168° at the 6-year follow-up), but refused further RSA examinations and treatment (other than a knee brace) due to age and comorbidities. The secondary outcome scores (KSS scores, flexion, and extension) showed no statistical differences in improvement over time between the two groups (Table V, see Supplementary data).

Adverse events

Besides the 5 components with excessive migration already stated, 1 patient withdrew due to dissatisfaction. This 47-year-old man with secondary osteoarthritis due to hemophilic arthropathy had a preoperative knee flexion of 85° and a flexion contracture of 15°; postoperatively, his knee flexion did not improve after receiving a fixed-bearing design. One mobile-bearing knee was revised due to an insert dislocation, which occurred 5 weeks after surgery (Figure 5, see Supplementary data). Dislocation of a Stryker mobile bearing was not described in the literature at that time and thus necessitated thorough investigations. Patient inclusion was put on hold until the manufacturer had evaluated the reason for this insert dislocation. Incorrect intraoperative mounting of the insert on the tibial post possibly damaged the tibial insert locking mechanism, although the exact cause of the failed locking mechanism remains unclear. For this reason, patient recruitment of this study was stopped preliminarily after 18 out of the intended 20 mobile-bearing TKPs were implanted.

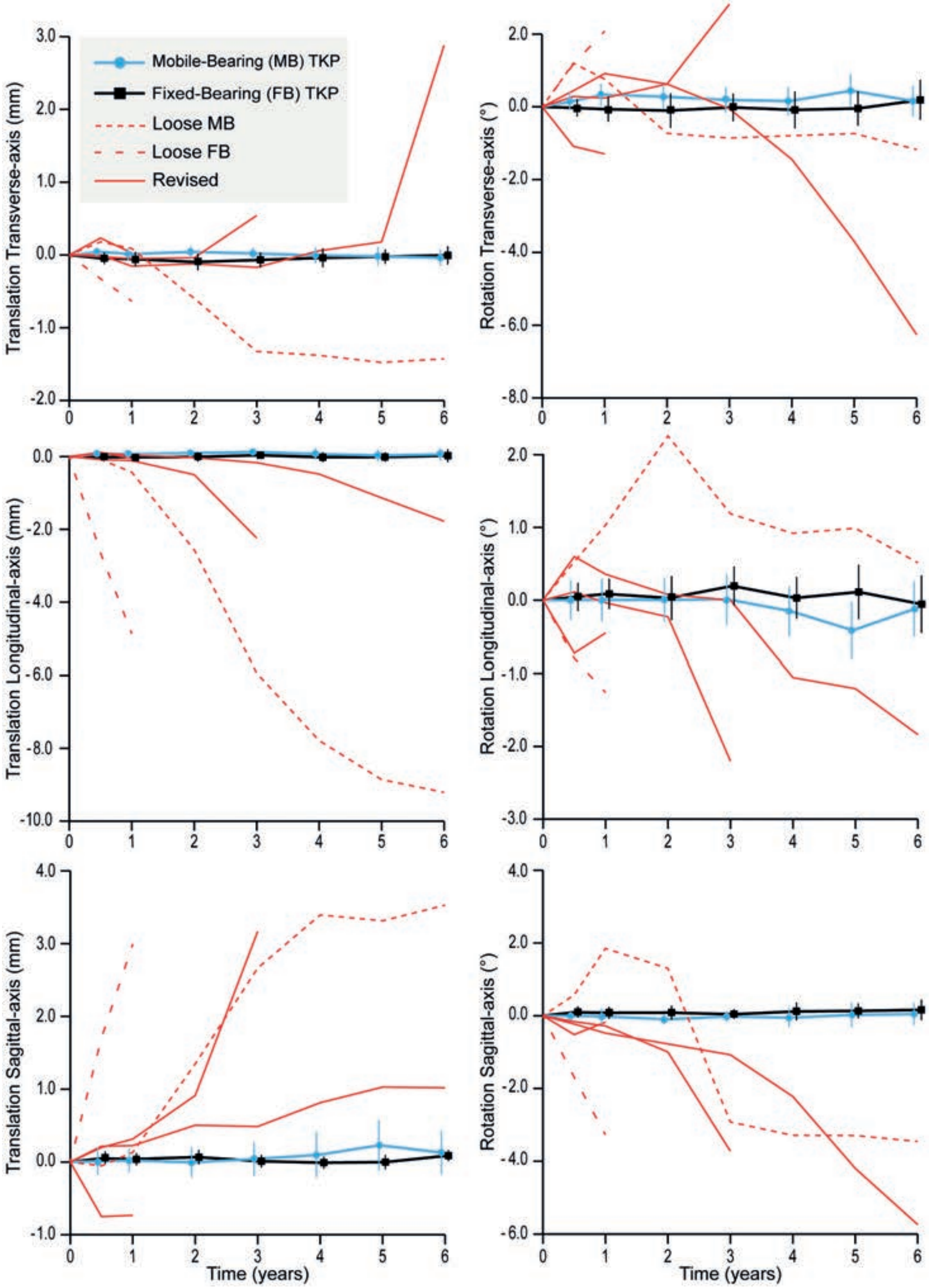

Figure 3. Descriptive data showing the translations in mm **(left side)** and rotations in degrees **(right side)** of the transverse axis **(top)**, longitudinal axis **(middle)** and sagittal axis **(bottom)** for both groups (mean and 95% CI). Similar to Figure 2, the revised components (solid red lines) and the 2 components suspected for loosening (dashed red lines) are drawn separately.

As-treated analysis

Intraoperatively, 1 of the surgeons (who performed 37 of the study procedures) deemed 5 knees unsuitable for the allocated mobile-bearing insert and fixed-bearing components were used instead. The as-treated population therefore included 28 fixed-bearing and 18 mobile-bearing TKPs (see Figure 1). The reasons for the deviations and the outcome in these patients are given in Table III (see Supplementary data). All primary and secondary outcome results were comparable in the as-treated analysis and subsequently did not alter conclusions (Tables IV–V, see Supplementary data).

Discussion

While migration measured by RSA and clinical outcomes of mobile-bearing and fixed-bearing designs of the single-radius TKP were comparable after 6 years, some of the complications experienced are inherent to the mobile-bearing design. In 5 cases, suboptimal gap balancing during mobile-bearing surgery resulted in the decision to switch to fixed-bearing TKPs, as is recommended in the literature[27]. Especially if bone resections and soft-tissue releases are performed conservatively in cases with compromised (peri-)articular tissue, insertion of the mobile bearing onto the central post of the baseplate in a perpendicular vertical manner can be technically challenging. Forcing the insert onto the post from a different angle can damage the locking mechanism, which possibly occurred in 1 procedure and, if so, instigated an insert dislocation necessitating revision surgery. Several explanations have been suggested for the discrepancies between the theoretically expected superior outcome and actual clinical results of mobile-bearing TKPs. First, it is questionable whether the mobile-bearing component truly is mobile in vivo. Garling *et al.*[15] performed a fluoroscopic study using a different rotating-platform TKP (NexGen LPS, Zimmer Biomet, Winterthur, Switzerland) and found limited rotation of the mobile bearing. Among other explanations, the authors hypothesized that this might be caused by (1) polyethylene-on-metal impingement due to a mismatch of the location of the fixed pivot point in the rotating-platform design and the actual tibiofemoral rotation point, or (2) due to fibrous tissue formation between the mobile bearing and the baseplate[15]. However, in a previous report on a subset of our study population[21], kinematic analysis with step-up and lunge motions showed that overall the mobile-bearing insert followed the femoral component movement as intended by its design, but not in all patients. Second, dislocation of the mobile bearing is a serious complication requiring revision surgery. Historically, this complication was mainly seen in the old mobile meniscal-bearing designs[7], while insert dislocations in rotating-platform designs are rare nowadays[17, 28, 29]. At the time (2008–2010) of patient inclusion for the current study, there were no reports on dislocation of the mobile-bearing insert with similar locking mechanisms as used in the Triathlon TKP. Thus our study was stopped awaiting results of thorough investigations. A case report on a bearing dislocation was later reported, describing failure of the locking O-ring identical to the Triathlon locking mechanism[30]. Testing the mode of failure during revision surgery in our case resulted in similar conclusions: once the O-ring of the insert has been damaged, flexing the knee can lead to lift-off and anterior dislocation of the insert. This was most easily observed while testing the knee intraoperatively with external rotation force. Third, several authors have addressed the effect of surgical procedure volumes, with superior results being attained by high-volume centers[31-34]. Good clinical results reported in single-surgeon series may not be realized in low-volume centers or centers treating patients with diverse demographic factors[7]. In our academic center, all participating surgeons were experienced in performing both mobile-bearing and fixed-bearing total knee arthroplasties and often performed surgery in patients with secondary osteoarthritis due to rheumatoid arthritis and other inflammatory diseases, which was also the case in a high proportion of the included patients. Nevertheless, the number of adverse events observed in this study was much higher than reported in other clinical (RSA) studies performed in our center. Although this could be due to chance, a learning-curve effect with this new design may have contributed to some of the complications and intraoperative decisions to deviate from the randomized treatment allocation.

A limitation of this study is that patient inclusion was prematurely terminated for patient safety after the mobile-bearing dislocation, before reaching the intended 20 patients in this study arm. This did not compromise the number of patients needed to have sufficient power on the primary outcome in the first 5 years of follow-up, as only 17 patients were required according to the sample size calculation. This was not the case at 6 years (with less than 17 TKPs available for analysis in both groups). However, as the patients lost in the sixth post-operative year had stable migration patterns, it is unlikely that migration at 6 years would substantially differ from the pattern depicted in Figure 2. Contrarily, results of the clinical outcomes should be interpreted with caution, given the lower accuracy and precision of these measurements. However, large meta-analysis studies comparing mobile-bearing with fixed-bearing TKPs found no differences in clinical outcomes either[8, 10]. Another limitation is the duration of follow-up. Although early tibial component migration measured through RSA is a proven predictor of late loosening[35, 36], one can hypothesize about various mechanisms affecting migratory patterns at different time intervals. However, results of an RSA study with long-term follow-up (> 10 years) revealed no changes in migration patterns of mobile-bearing and fixed-bearing prostheses after the first 2 years[13].

In summary, fixed-bearing single-radius TKPs showed similar migration compared with the mobile-bearing TKPs, while the latter may expose patients to more complex surgical techniques and risks such as insert dislocations inherent to this rotating-platform design.

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Supplementary data

Table III. Characteristics of patients with deviation in allocated randomization group

Case	Patient	Reason for deviation	Outcome
#1:	Female, 55 y, osteoarthritis, BMI 35, HKA 179°, lateral plate from valgus-producing HTO (2001) in situ	Ligament balancing difficulties, additional bone-cuts needed and inferior lateral compartment after plate-removal	Migration pattern stable. Functionally satisfied with high KSS scores
#5:	Female, 72 y, osteoarthritis, BMI 38, HKA 174°, previously valgus-producing HTO (1994) and staple removal (2005)	Difficulties with ligament balancing, exposure and mobilization of tibia due to previous surgical procedures	Migration pattern stable. Functionally satisfied, high KSS Knee Scores, KSS Function Score compromised due to ataxia
#16:	Female, 72 y, osteoarthritis, BMI 26, HKA 171°	Tight soft tissue requiring undesirable additional releases around fragile soft bone	Migration pattern stable. Functionally satisfied with high KSS scores
#32:	Female, 78 y, rheumatoid arthritis, BMI 20, HKA 191°	Minimal releases and exposure possible due to soft bone and fragile soft tissue affected by rheumatoid arthritis	Migration pattern stable. Medium to high KSS scores up until 4 years. Patient died after 4 years due to respiratory health problems
#35:	Female, 52 y, osteoarthritis, BMI 34, HKA 168°	Bilateral procedure, first knee was an uncomplicated mobile-bearing design, second knee was tight with difficult releases while the epidural block wore off	Continuous migration after three years, progressive varus alignment with low to medium KSS scores. Revision due to aseptic loosening after 6 years

HKA = pre-operative hip–knee–ankle angle (varus < 180°), HTO = High tibial osteotomy.

Table IV. RSA migration analysis of mean Maximum Total Point Motion (MTPM) with lower and upper limits of 95% CI (log values are back-transformed in the original scale in mm).

Factor		Fixed-bearing	Mobile-bearing	p-value
Intention-to-treat	6 months	0.61 (0.32–0.95)	0.69 (0.39–1.06)	
	1 year	0.69 (0.41–1.02)	0.75 (0.46–1.09)	
	2 years	0.77 (0.45–1.16)	0.90 (0.56–1.33)	
	3 years	0.92 (0.52–1.42)	0.91 (0.51–1.41)	
	4 years	0.84 (0.48–1.29)	1.08 (0.67–1.59)	
	5 years	0.90 (0.53–1.37)	1.25 (0.81–1.80)	
	6 years	0.90 (0.49–1.41)	1.22 (0.75–1.80)	0.3
As-treated	6 months	0.65 (0.38–0.97)	0.64 (0.31–1.05)	
	1 year	0.71 (0.45–1.01)	0.73 (0.41–1.12)	
	2 years	0.80 (0.50–1.16)	0.89 (0.51–1.38)	
	3 years	0.93 (0.56–1.38)	0.88 (0.44–1.46)	
	4 years	0.89 (0.55–1.31)	1.06 (0.61–1.65)	
	5 years	1.00 (0.64–1.44)	1.18 (0.70–1.80)	
	6 years	1.04 (0.64–1.53)	1.08 (0.59–1.72)	0.9

Table V. Secondary outcomes. Values are mean (standard error) unless otherwise specified

	As-treated				Intention-to-treat			
Factor	Fixed-bearing	Mobile-bearing	Difference in progression between groups (95% CI)	p-value [a]	Fixed-bearing	Mobile-bearing	Difference in progression between groups (95% CI)	p-value [a]
Flexion (°)								
Preoperative	111 (3)	112 (4)			111 (3)	112 (3)		
1 year	113 (2)	119 (3)			114 (2)	117 (2)		
6 years	113 (3)	119 (3)	5 (-6 to 16)	0.4	111 (3)	119 (3)	7 (-4 to 18)	0.2
Extension (°) [b]								
Preoperative	-4 (1)	-3 (1)			-4 (1)	-3 (1)		
1 year	-0 (1)	0 (1)			-0 (1)	-0 (1)		
6 years	0 (1)	-3 (2)	-4 (-8 to 1)	0.1	-0 (1)	-1 (1)	-2 (-6 to 1)	0.2
KSS Knee Score								
Preoperative	48 (2)	49 (4)			49 (2)	47 (4)		
1 year	86 (3)	90 (3)			86 (3)	89.4 (2.2)		
6 years	91 (4)	95 (2)	3 (-11 to 16)	0.7	92 (5)	93.2 (2.1)	3 (-11 to 17)	0.7
KSS Function Score								
Preoperative	44 (6)	35 (8)			46 (7)	36 (7)		
1 year	67 (5)	58 (6)			69 (6)	57 (6)		
6 years	54 (6)	39 (7)	-6 (-26 to 13)	0.5	54 (7)	43 (6)	-2 (-21 to 18)	0.9

[a] p-values indicate testing the mean between group differences of improvement after 6 years of follow-up derived with a linear mixed-effects model analysis (data of all follow-up measurements are used to test for differences). [b] Negative extension means no full extension possible.

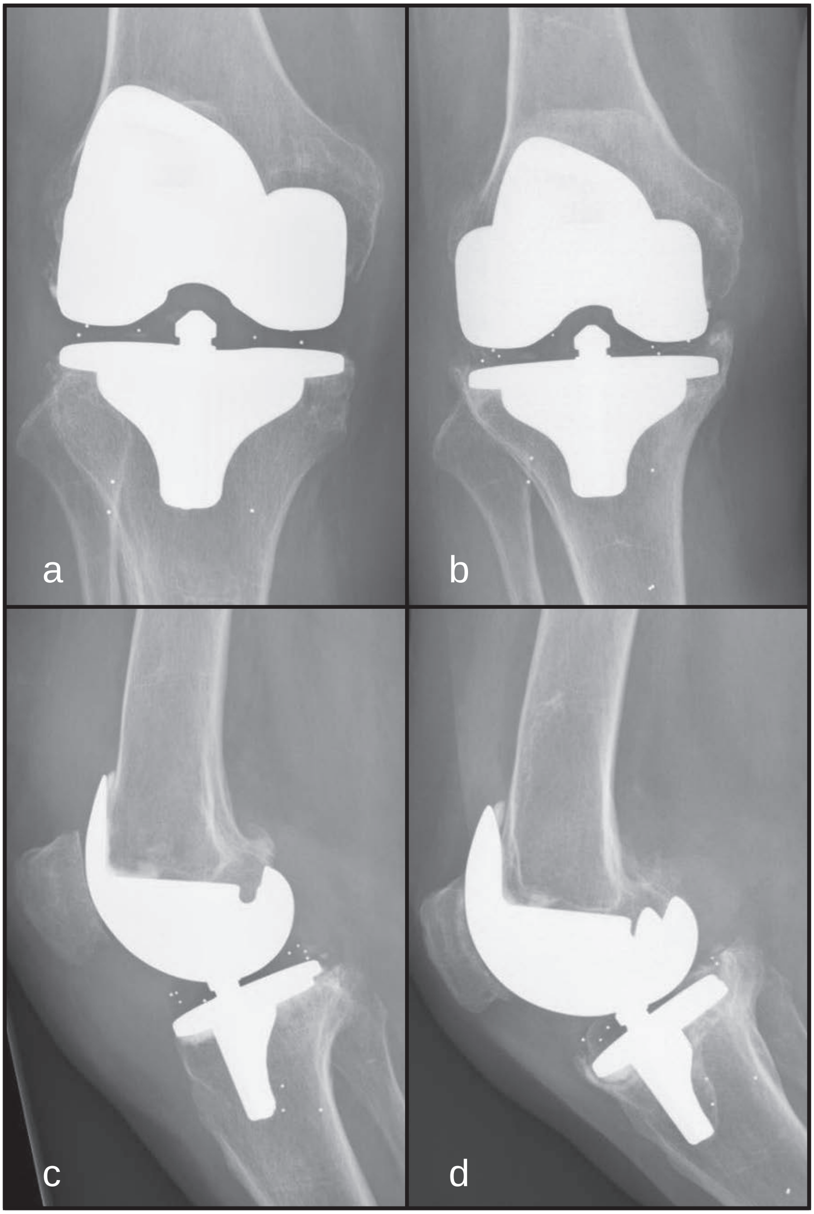

Figure 4. Mobile-bearing TKP suspected for aseptic loosening in a 72-year-old woman with rheumatoid arthritis. Revision surgery was postponed due to refractory stasis dermatitis around the knee. Anteroposterior radiographs **(a)** 3 months and **(b)** 6 years follow-up, lateral radiographs **(c)** 3 months and (d) 6 years follow-up. Note the varus tilt of 3.5° (b), anterior translation of 3.5 mm **(d)** and subsidence of 9.2 mm (both b and d) of the tibial component.

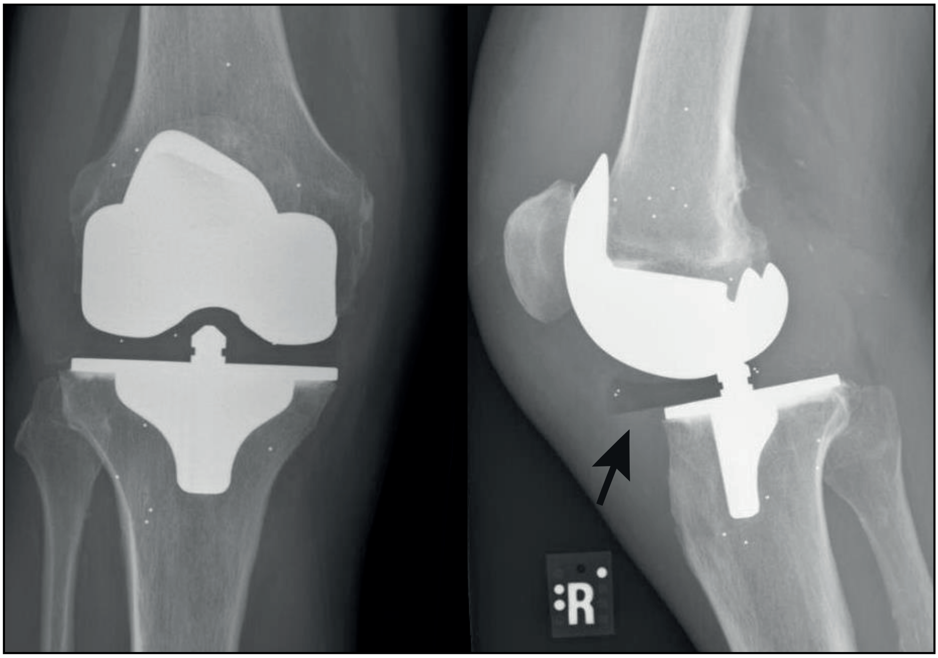

Figure 5. Insert dislocation of the mobile-bearing insert in a 66-year-old man with osteoarthritis. The antero-posterior radiograph **(a)** shows no abnormalities, the lateral radiograph **(b)** shows anterior displacement of the insert (black arrow).

4

Fixation and clinical outcome of uncemented peri-apatite-coated *versus* cemented total knee arthroplasty: five-year follow-up of a randomized controlled trial using RSA

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Abstract

Aims — The optimal method of tibial component fixation remains uncertain in total knee arthroplasty (TKA). Hydroxyapatite coatings have been applied to improve bone ingrowth in uncemented designs, but may only coat the directly accessible surface. As peri-apatite (PA) is solution deposited, this may increase the coverage of the implant surface and thereby fixation. We assessed the tibial component fixation of uncemented PA-coated TKAs *versus* cemented TKAs.

Patients and Methods — Patients were randomised to PA-coated or cemented TKAs. In 60 patients (30 in each group), radiostereometric analysis of tibial component migration was evaluated as the primary outcome at baseline, three months post-operatively and at one, two and five years. A linear mixed-effects model was used to analyse the repeated measurements.

Results — After five years of follow-up, one (cemented) component was revised due to ligament instability. Overall, uncemented PA-coated tibial components migrated significantly more ($p = 0.003$), with the mean maximum total point motion (MTPM) at five years being 0.62 mm (95% confidence intervals (CI) 0.49 to 0.76) for cemented tibial components and 0.97 mm (95% CI 0.81 to 1.15) for PA-coated tibial components in TKA. However, between three months and five years the cemented TKAs migrated significantly more ($p = 0.02$), displaying a MTPM of 0.27 mm (95% CI, 0.19 to 0.36) *versus* 0.13 mm (95% CI, 0.01 to 0.25) for PA-coated tibial components. One implant in each group was considered at risk for aseptic loosening due to continuous migration after five years of follow-up, albeit with different migration patterns for each group (i.e. higher initial migration but diminishing over time for the PA-coated component *versus* gradually increasing migration for the cemented component).

Conclusion — The tibial components of PA-coated TKAs showed more overall migration compared with the tibial components of cemented TKAs. However, *post hoc* analysis showed that this difference was caused by higher migration of PA-coated components in the first three months, after which a stable migration pattern was observed. Clinically, there was no significant difference in outcome between the groups.

Introduction

Development of uncemented designs in total knee arthroplasty (TKA) started in the 1970s as aseptic loosening was thought to be caused by 'cement disease'[1]. Consistently good long-term survival of cemented TKAs in the decades thereafter shifted the attention, with cemented TKAs being the preferred option. However, concerns have been raised whether the cement-bone interface can endure increased stress now that arthroplasties are performed in increasingly younger, heavier and more active patients[2, 3]. Furthermore, studies have shown a loss of cement-bone interlock due to trabecular resorption as well as deformation and degradation of the cement mantle over the years[4-6].

Uncemented TKAs, at least in theory, can provide strong long-term biological fixation due to bone ingrowth[3, 7, 8]. However, early generations of uncemented designs failed due to experimental modifications of the implant design (e.g. use of screws and metal-backed patellar components)[9]. Consequently, many surgeons are reluctant to perform uncemented TKAs: only 5% of the procedures are uncemented in Sweden[10]; 5% (including hybrid) in England, Wales, Northern Ireland and the Isle of Man[11]; 14% in Australia[12]; and 20% in Canada[13]. Recent meta-analyses comparing the benefit of cemented with cementless fixation show contradictory results depending on selection of trials and outcome measurements[2, 5, 8].

Several biomaterials, like osteoconductive hydroxyapatite (HA) coatings, have been applied to improve bone ingrowth in uncemented TKAs[14-16]. Most HA coatings are plasma sprayed onto the porous implant surface area, thereby only coating the substrate surface in the direct 'line of sight'[17]. In contrast, peri-apatite (PA) HA is solution deposited, which increases the coverage of HA onto the 3D implant surface[18]. The PA-coating is relatively thin with a thickness of 20 μm compared with 50 μm to 75 μm for most HA-coatings[16, 18]. Several studies reported a beneficial effect of PA-coating compared with only porous-coated tibial components with less subsidence and earlier stabilisation[17, 19-21]. Despite cement fixation being the reference standard, there are, to our knowledge, no randomised trials in humans comparing the fixation of PA-coated components with cemented components. We therefore conducted a single blinded, randomised controlled trial to assess the effect of uncemented PA-coated TKAs compared with cemented TKAs on fixation and clinical outcome. We used radiostereometric analysis (RSA) to accurately measure early migration of the tibial component and its predictive value of future loosening as primary outcome[22, 23]. As uncemented prostheses typically show higher initial migration compared with cemented prostheses, the present manuscript is the first to report the short-term outcomes of this trial using five-year follow-up data, rather than the usual two-year data to be able to determine accurately full stabilisation of individual components[3, 24-26].

Patients and Methods

From March 2009 to July 2010, all consecutive patients scheduled to undergo TKA due to primary osteoarthritis at Hässleholm Hospital (Sweden) were asked to participate in this randomised, controlled trial. The study was approved by the local ethics committee (entry no. 445/2005) and registered at ClinicalTrials.gov (NCT02525601, originally part of NCT00436982) before enrolment. Main exclusion criteria were active infection, active malignant disease or not being able to comply with the post-operative scheduled evaluations and prescribed rehabilitation (for example due to long travel time). After informed consent, patients were randomised using a sealed envelope technique and remained blinded to the allocated treatment throughout the entire follow-up. Randomisation was performed using a computer-generated randomisation list and only revealed to the surgeons on the day of surgery.

All patients received a Triathlon implant (Stryker, Mahwah, New Jersey) using either the cemented version (with Refobacin Bone Cement R, Biomet Inc., Warsaw, Indiana) or the uncemented PA-coated version. For both versions, cruciate retaining chrome-cobalt components of similar geometrical shape, with a tibial delta shaped stem and highly crossed-linked polyethylene inserts were used. The only difference with the cemented components is that the undersurface of both the femoral and tibial uncemented components are porous-coated to facilitate bone ingrowth, consisting of (PA-coated) cobalt-chromium sintered beads with a porosity of 35% and mean pore size of 425 μm. All TKAs were performed by three experienced knee surgeons (STL, MM and CFN). Antibiotic prophylaxis (2 g cloxacillin intravenously 15 to 45 minutes before surgery) and tranexamic acid (10 mg/kg intravenously administered prior to incision) were given. A standard midline incision and medial parapatellar arthrotomy was used to enter the joint. No tourniquet was used. Necessary soft-tissue releasing was undertaken with the posterior cruciate ligament retained. The prosthesis was implanted using the appropriate guidance instruments according to manufacturer's instructions. When bone cement was used, pulsatile lavage of the osseous surface was undertaken before applying the cement. Patellar resurfacing was not conducted on any of the patients. A total of eight to nine tantalum markers (0.8 mm diameter; RSA Biomedical, Umeå, Sweden) were inserted into the proximal tibial metaphysis and five markers in the polyethylene tibial insert. Thromboembolic prophylaxis was given for ten days, using low molecular heparin (enoxaparin intramuscular 40 mg/day). Mobilisation was similar for both groups and included immediate bearing of full weight on the day of surgery.

Pre-operatively, the following measurements were conducted: Knee Society Score (KSS)[27]; Knee injury and Osteoarthritis Outcome Score (KOOS)[28]; hip-knee-ankle angle (HKA) measurements (varus < 180° and valgus > 180°)[29]; and severity of osteoarthritis according to the Ahlbäck classification[30]. Post-operative evaluations including conventional radiographs and RSA radiographs were performed after weight-bearing was achieved (on the first postoperative day in all cases). Subsequent examinations were performed at three months, one year, two years and five years post-operatively. RSA was performed in supine position with the knee in a calibration cage (Cage 10, RSA Biomedical).

Migration was analysed using UmRSA software v6.0 (RSA Biomedical). Positive directions along and about the orthogonal axes are, according to RSA guidelines: medial on transverse axis, cranial on longitudinal axis and anterior on sagittal axis for translations and anterior tilt (transverse axis), internal rotation (longitudinal axis) and valgus tilt (sagittal axis) for rotations[31]. Migration was described as translation of the geometric centre of the prosthetic markers and rotation of the rigid body defined by the prosthetic markers about this geometric centre of gravity. The length of the translation vector of the marker (or virtual marker in a rigid body) that has the greatest migration, i.e. the maximum total point motion (MTPM), was used as the primary outcome measure[32]. The post-operative RSA examination served as the reference for the migration measurements. The precision of the local RSA setup as measured by 15 double examinations, described as 1.96 × standard deviation (SD) (i.e. 95% confidence interval (CI)),32 was 0.10 mm, 0.10 mm and 0.09 mm for transverse, longitudinal and sagittal translation, respectively; and 0.20°, 0.20° and 0.24° for transverse, longitudinal and sagittal rotations, respectively. Implants showing continuous migration (more than 0.2 mm of migration (MTPM) in the second post-operative year) are generally considered at risk for aseptic loosening[23, 33]. This threshold was set at 0.3 mm between two and five years[24]. Subsequently, implants with continuous migration in the second post-operative year are considered stabilised if the migration was less than 0.3 mm between two and five years. The mean error of rigid body fitting of the RSA markers was below 0.2 mm. The upper limit for the condition number was set at 100. A high level of precision of migration measurements of the tibial component relative to the bone was thus achieved and marker stability and scatter values were within the limits of RSA guidelines[31].

Statistical analysis

From previous RSA studies, the migration of Triathlon TKAs within the first two years was around 1.0 mm (SD 0.5)[20]. Based on this finding, we undertook a sample size calculation. If the true difference of migration between cemented and PA-coated TKAs is 0.5 mm, we would need 17 patients per group to detect this difference with 80% power and alpha set at 0.05. To account for possible dropouts, 30 patients were randomised to each group.

Mean values and SDs are presented for measured variables; point estimates are presented including the 95% CI. Data were analysed following the intention-to-treat analysis principle. For the primary outcome MTPM, a linear mixed-effects model was used, which deals effectively with missing values during follow-up. MTPM was log-transformed (logMTPM), computed as log10(MTPM+1), given its non-normal distribution. The mean progression of logMTPM is modelled as a function of time and the interaction of time with the type of implant fixation. For the random-effects structure, a random-intercepts term is used and remaining variability is modelled with a heterogeneous autoregressive order 1 covariance structure using R Software version 3.2.3 with nlme package (R foundation for Statistical computing, Vienna, Austria). To safeguard against multiple testing, differences in migration between groups were only tested for the primary outcome MTPM at two-year follow-up (as prespecified in the protocol) and at final (five-year) follow-up. RSA data describing the direction of migration (i.e. translation along and about the three orthogonal axes) were not tested for significance, but descriptive data is presented to illustrate the directions of migration. *Post hoc* testing was performed to assess between group differences in migration with three months and one year as a baseline to test a possible difference in migration beyond the first post-operative period. A Bonferroni corrected p-value < 0.05 was considered significant. Secondary outcomes (flexion, extension, KSS and KOOS scores) were analysed with a similar mixed-effects model. If the data were non-normally distributed, a log-transformation was performed. If this did not result in a normal distribution, a comparable generalised estimating equations (GEE) approach was used to correct the standard errors via the sandwich estimator. The latter was needed for knee extension and the KSS knee score. IBM SPSS Statistics 23.0 (IBM, Armonk, New York) was used for all secondary outcome measures.

Results

A total of 76 patients were randomised, 16 of which – those operated on between 4 September 2009 and 16 November 2009 – were excluded due to unknown problems with the RSA calibration box, resulting in unmeasurable post-operative RSA images (Figure 1). As expected, the baseline demographic characteristics were similar in the two randomised groups (Table I). Each of the 60 remaining patients were due to have five RSA examinations, giving a possible total of 300 RSA measurements. After five years, five patients were lost to follow-up; two of these patients moved out of the region, two withdrew due to health problems (pulmonary embolism and cardiopulmonary comorbidities, both after one year), and one patient withdrew after two years for reasons unrelated to his knee (family circumstances). One other patient underwent knee revision due to ligament instability. None of the patients died during follow-up. In all lost and revised patients, 12 RSA examinations could not be made. A further ten RSA examinations were missing and two were invalid due to non-matching stereo images, resulting in 276 valid RSA analyses.

RSA migration measurements. Descriptive RSA migration data of the tibial components are presented in Table II. Uncemented PA-coated components migrated significantly more at all follow-up measurements, with a mean migration (MTPM) at five years of 0.62 mm (95% CI 0.49 to 0.76) for the cemented group and 0.97 mm (95% CI 0.81 to 1.15) for the PA-coated group ($p = 0.003$) (Figure 2; Table III). However, differences were primarily due to a large difference in migration in the first three months. The PA-coated group showed almost no migration from three months onwards (Figure 2; Table III). *Post hoc* testing showed more migration in the cemented group between three months and two years (p = 0.037), and between three months and five years (p = 0.020) (Table III). There were no significant differences between groups from one-year onwards as both groups showed almost no migration (Table III).

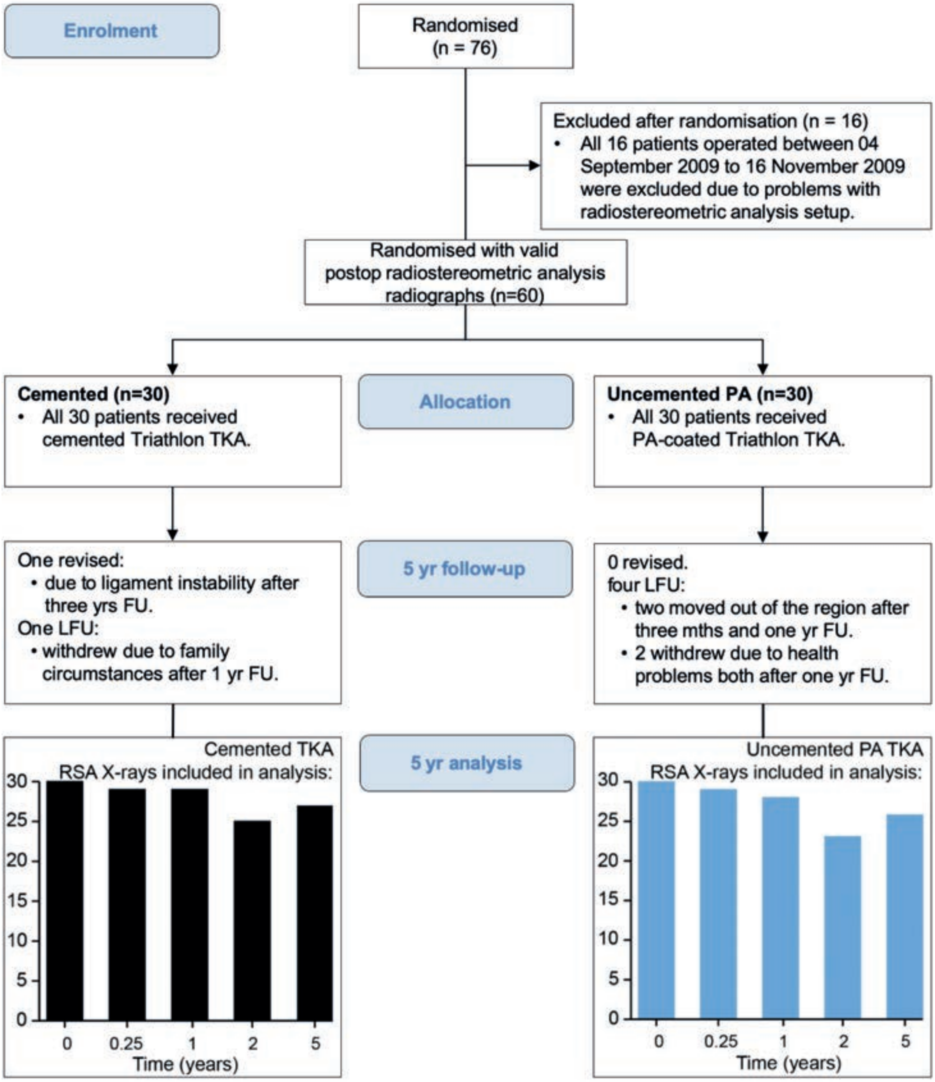

Figure 1. CONSORT flowchart. FU = follow-up, LFU = lost to follow-up, TKA = total knee arthroplasty.

Table I. Baseline demographic characteristics for the two groups of patients

	Cemented (n = 30)	Uncemented PA (n = 30)
Mean age, yrs (SD)	65.7 (6.3)	66.8 *(9.1)*
Mean BMI, kg/m2 (SD)	28.6 (3.6)	28.0 *(3.3)*
Female gender, n (%)	13 *(43.3)*	19 *(63.3)*
Previous knee surgery, n (%)		
None	22 *(73.3)*	23 *(76.7)*
Joint debridement	2 *(6.7)*	2 *(6.7)*
Meniscectomy	4 *(13.3)*	5 *(16.7)*
Other	2 *(6.7)*	0 *(0.0)*
Ahlbäcks grade, n (%)		
II	8 *(26.7)*	5 *(16.7)*
III	20 *(66.7)*	18 *(60.0)*
IV	2 *(6.7)*	7 *(23.3)*
ASA classification, n (%)		
I	7 *(23.3)*	10 *(33.3)*
II	22 *(73.3)*	17 *(56.7)*
III	1 *(3.3)*	3 *(10.0)*
Mean hip-knee-ankle angle, ° (SD)		
Pre-operative	173.2 (5.6)	175.3 (6.3)
Post-operative	180.5 (3.5)	179.9 (3.4)

PA = peri-apatite, BMI = body mass index, ASA = American Society of Anesthesiologists.

Table II. Radiostereometric analysis migration measurements

	3 mths		1 yr		2 yrs		5 yrs	
	Cemented	PA	Cemented	PA	Cemented	PA	Cemented	PA
Mean translation, mm (SD)								
Transverse	0.00 (0.15)	0.03 (0.39)	-0.07 (0.31)	-0.05 (0.41)	-0.11 (0.33)	0.01 (0.44)	-0.09 (0.35)	-0.05 (0.52)
Longitudinal	-0.01 (0.13)	-0.26 (0.30)	-0.01 (0.17)	-0.20 (0.29)	-0.02 (0.18)	-0.17 (0.29)	0.02 (0.24)	-0.13 (0.30)
Sagittal	0.04 (0.14)	-0.05 (0.34)	0.01 (0.26)	-0.09 (0.37)	-0.04 (0.27)	-0.12 (0.36)	-0.03 (0.36)	-0.08 (0.40)
Mean rotation, ° (SD)								
Transverse	0.00 (0.23)	-0.52 (0.76)	-0.16 (0.43)	-0.52 (0.79)	-0.32 (0.65)	-0.62 (0.82)	-0.45 (1.18)	-0.45 (0.77)
Longitudinal	0.04 (0.15)	0.15 (0.31)	0.03 (0.22)	0.15 (0.35)	0.03 (0.24)	0.13 (0.40)	-0.06 (0.25)	0.11 (0.29)
Sagittal	0.04 (0.24)	0.01 (0.76)	0.10 (0.34)	0.05 (0.85)	0.08 (0.36)	0.02 (0.80)	0.07 (0.52)	0.10 (0.96)
Mean MTPM, mm (SD)*	0.34 (0.18)	0.90 (0.44)	0.54 (0.33)	0.97 (0.44)	0.58 (0.35)	0.96 (0.53)	0.68 (0.50)	1.00 (0.56)

*p-values of mean maximum total point motion (MTPM) values derived from a linear mixed-effects model analysis are stated in Table III. PA = peri-apatite.

Continuous migration of > 0.2 mm MTPM in the second post-operative year was seen in three PA-coated components and one cemented component. Between two and five years of follow-up, one of the PA-coated components showed 0.39 mm of migration, the other two PA-coated components and the cemented component stabilised (i.e. showed less than 0.3 mm of migration). One other cemented component was stable up to two years, after which high migration of 1.32 mm was seen (Figure 2). Migration measurements of the components with continuous migration were not affected by measurement errors as the condition numbers and mean errors were consistent over time and well within limits.

The components with high migration predominantly rotated about the transverse axis (all posterior tilt) and sagittal axis (both varus and valgus tilt) in both groups. However, lateral, medial and posterior translation was also seen (Figure 3). There were no differences in mode of failure between groups. The difference in migration between groups seen in the first three months is primarily due to subsidence and posterior tilt of the PA-coated components, which stabilised beyond three months (Figure 3). Varus and valgus tilt were seen in both pre-operatively varus and valgus aligned knees; subgroup analysis yielded no differences, as the study was not sufficiently powered for subgroup analysis.

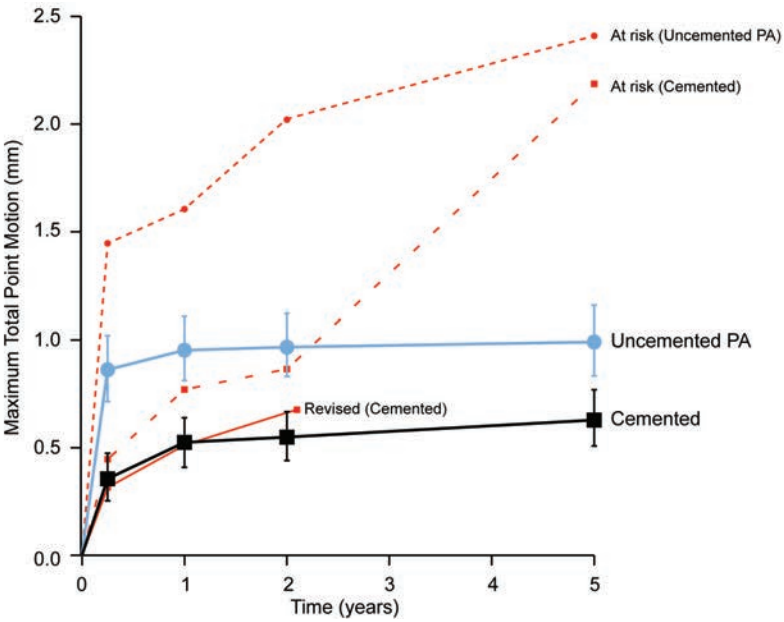

Figure 2. Maximum total point motion during the five years of follow-up (mean and 95% confidence interval for the groups in the original scale in mm, derived from the linear mixed-model analysis). The individual lines excluded from the groups are shown for one revised (ligament instability) and two high migrating components at risk for aseptic loosening.

Clinical results

Post-operatively, no significant differences in improvement in flexion, extension, KSS Knee Score, KSS Function Score and all KOOS subscales were found between groups (Table IV).

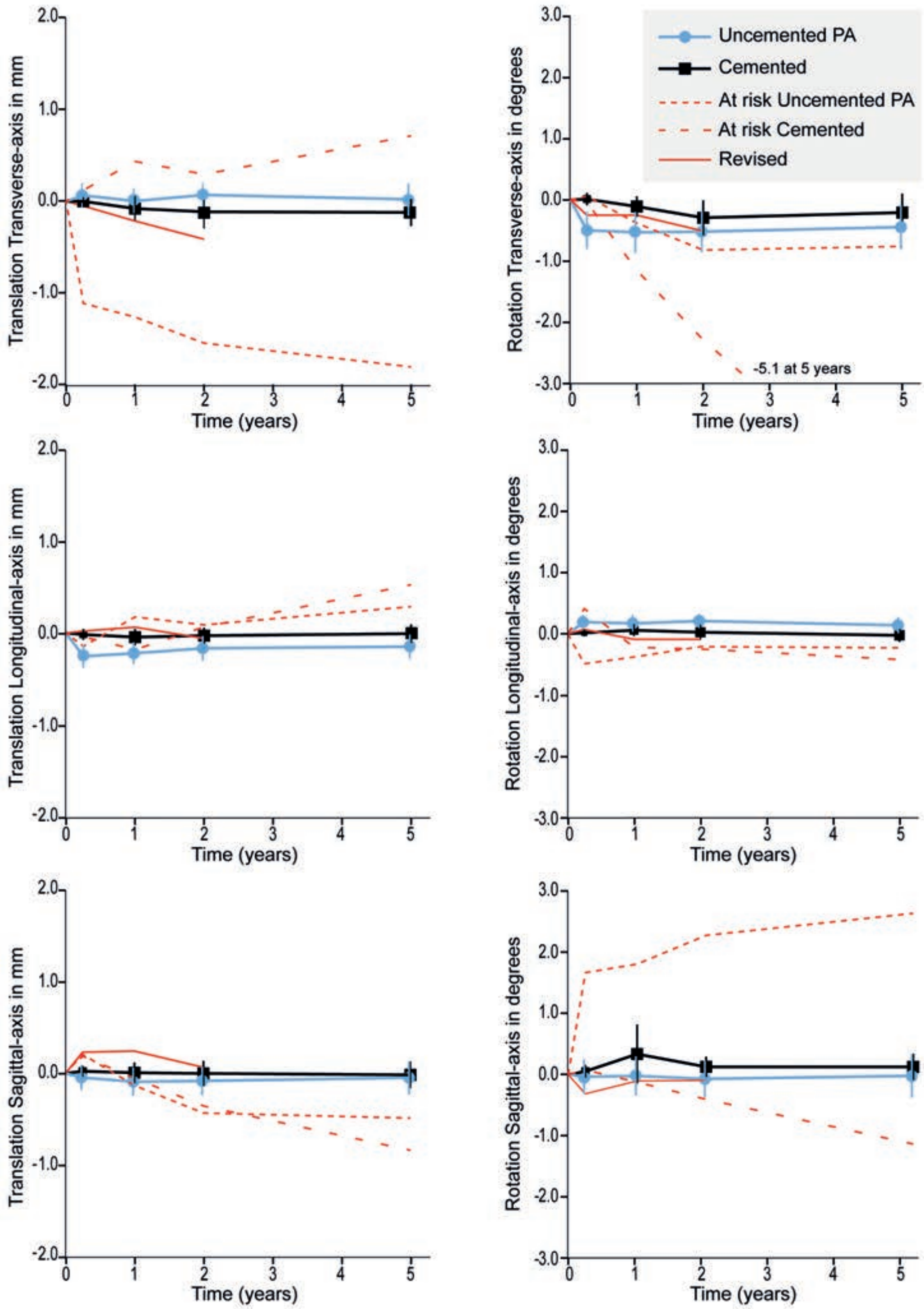

Figure 3. Translations in mm **(left side)** and rotations (°) **(right side)** of the transverse axis **(top)**, longitudinal axis **(middle)** and sagittal axis **(bottom)** for both groups (mean and 95% confidence intervals, descriptive data). The individual lines excluded from the groups are shown for one revised and two high migrating components at risk for aseptic loosening.

Table III. RSA migration analysis of maximum total point motion (MTPM) in the cemented group and the uncemented PA-coated group (back-transformed in the original scale in mm) with different time points as baseline, as derived from a linear mixed-effects model analysis

Baseline	Duration	Cemented, mean MTPM, mm (95% CI)	Uncemented PA, mean MTPM, mm (95% CI)	p-value*
Post-operative as baseline	3 mths	0.34 (0.23 to 0.47)	0.84 (0.69 to 1.01)	NS
	1 yr	0.50 (0.39 to 0.63)	0.93 (0.78 to 1.09)	NS
	2 yrs	0.53 (0.42 to 0.66)	0.95 (0.81 to 1.11)	0.000
	5 yrs	0.62 (0.49 to 0.76)	0.97 (0.81 to 1.15)	0.003
Three-months as baseline	1 yr	0.16 (0.09 to 0.23)	0.09 (-0.01 to 0.18)	NS
	2 yrs	0.19 (0.12 to 0.26)	0.11 (0.01 to 0.20)	0.037
	5 yrs	0.27 (0.19 to 0.36)	0.13 (0.01 to 0.25)	0.020
One-year as baseline	2 yrs	0.03 (-0.02 to 0.08)	0.02 (-0.05 to 0.09)	0.721
	5 yrs	0.11 (0.04 to 0.19)	0.04 (-0.06 to 0.14)	0.421

*The (Bonferroni-corrected) p-values stated in this column indicate testing the between-group mean differences with different baselines at two and five years of follow-up, as derived from a linear mixed-effects model analysis. PA = peri-apatite, NS = not stated.

Adverse events

One cemented TKA was revised after three years due to ligament instability. No other revisions were performed. One patient in the cemented group had a deep vein thrombosis during hospital admission. One patient in the PA-coated group suffered a myocardial infarction ten months after discharge but continued to participate in the study. Patients with components showing high migration are clinically still asymptomatic; no revisions due to aseptic loosening have been performed yet.

Table IV. Functional outcome compared between the two groups

	Cemented	Uncemented PA	p-value*
Mean flexion, º (SD)			
Pre-operative	116.3 (9.6)	116.0 (12.3)	NS
1 yr	121.3 (12.3)	122.6 (10.1)	NS
5 yrs	127.6 (10.0)	125.8 (8.5)	0.514
Mean extension, º (SD) †			
Pre-operative	-0.8 (7.0)	-1.8 (5.9)	NS
1 yr	-0.3 (2.9)	-0.3 (1.3)	NS
5 yrs	-0.3 (1.3)	0.0 (0.0)	0.656
Mean KSS – Knee Score (SD)			
Pre-operative	36.5 (11.8)	37.9 (8.5)	NS
1 yr	93.1 (7.7)	95.0 (5.1)	NS
5 yrs	94.3 (11.7)	91.2 (13.6)	0.297
Mean KSS – Function Score (SD)			
Pre-operative	57.3 (13.1)	62.5 (14.4)	NS
1 yr	90.2 (13.0)	94.8 (9.9)	NS
5 yrs	90.0 (12.8)	86.4 (20.9)	0.089
Mean KOOS – Symptoms (SD)			
Pre-operative	37.8 (14.5)	45.9 (13.6)	NS
1 yr	81.3 (15.8)	82.5 (16.2)	NS
5 yrs	82.1 (14.5)	86.6 (13.2)	0.307
Mean KOOS – Pain (SD)			
Pre-operative	29.9 (10.2)	38.7 (9.7)	NS
1 yr	83.2 (15.2)	83.4 (15.5)	NS
5 yrs	84.3 (15.1)	86.1 (17.9)	0.114
Mean KOOS – ADL (SD)			
Pre-operative	35.5 (11.5)	43.5 (11.5)	NS
1 yr	82.7 (17.6)	82.1 (16.3)	NS
5 yrs	80.5 (17.2)	82.9 (17.2)	0.193
Mean KOOS – Sports (SD)			
Pre-operative	3.1 (7.1)	6.0 (9.3)	NS
1 yr	44.1 (23.1)	41.0 (19.7)	NS
5 yrs	37.9 (28.7)	38.5 (25.6)	0.719
Mean KOOS – QOL (SD)			
Pre-operative	29.6 (5.5)	33.4 (8.8)	NS
1 yr	54.6 (13.2)	58.3 (12.8)	NS
5 yrs	71.0 (22.8)	74.0 (19.2)	0.867

*The p-values stated in this column indicate testing the between-group mean differences of improvement between baseline and five years of follow-up, derived with a linear mixed-effects model analysis. Note that three-months and two-year values are not stated, but results from all follow-up measurements were used in the linear mixed-effects model to test for differences. †Negative extension means no full extension possible. PA = peri-apatite, NS = not stated, KSS = Knee Society Score, KOOS = Knee injury and Osteoarthritis Outcome Score, ADL = Activities of Daily Living, QOL = Knee-related Quality of Life.

Discussion

The present study shows that uncemented PA-coated tibial components migrate more compared with cemented components over five years of follow-up. However, this difference was caused by higher migration of PA-coated components in the first post-operative weeks (i.e. settling into the bone bed). From three months onwards, the migration in both groups showed minor progression especially in the PA-coated group, suggesting a durable biological fixation might have been achieved despite high initial migration.

Both excessive initial migration in the first year, as well as high continuous migration after one year is believed to be detrimental to implant fixation and longevity[23, 34]. Yet, in most uncemented tibial trays, high initial migration in the first months appears benign and merely part of a typical biphasic migration pattern followed by stabilisation[3, 24-26, 35]. Long-term RSA studies have shown that despite substantial initial migration, highly porous and hydroxyapatite-coated uncemented components remain firmly fixated to the bone up to at least ten years of follow-up[25, 26]. In contrast, cemented tibial trays typically display little initial migration in the first months as the cement provides instant fixation, is capable of filling irregularities of the cut surface of the prepared tibial bone and evenly distributes weight[3, 36]. Continuous bone resorption at the cement-bone interface may, however, prohibit stabilisation[3]. In our study, the migration pattern suggests stabilisation of uncemented PA-coated components within three months, while cemented components appear to continue to migrate up to one year of follow-up or even longer. Carlsson et al[37] found similar migration patterns over five years of follow-up and hypothesised that cemented TKAs would eventually show more migration than the hydroxyapatite coated TKAs. Unfortunately, no long-term follow-up data are published to confirm this. The Australian registry reported comparable implant survival rates up to seven years of follow-up of cemented (97.0%) and uncemented (96.7%, not discriminating between porous-coated or PA-coated) Triathlon CR implants[12]. Given these comparable rates and the results of our study, we agree with Henricson and Nilsson[25], who concluded that the magnitude of the initial migration is not as important as the migration pattern over time, particularly for implants relying on bone ingrowth. However, future registry reports with long-term results should confirm our prediction that PA-coated implants achieve a durable biological fixation. Furthermore, future research should also focus on whether peri-apatite clinically provides any benefit over conventional 'line of sight' hydroxyapatite coating techniques.

A strength of this study is that both the cemented and the PA-coated components were of similar geometrical shape, thus differences in migration can be fully attributed to the mode of fixation. Three earlier RSA studies comparing the effect of cemented *versus* cementless fixation on migration used different designs between groups, with modular stemmed tibial trays in cemented components and either monoblock trays with two pegs[25, 33] or modular trays with a short stem and multiple spikes in uncemented components[3].

Several limitations can be noted. First, migration was based on markers inserted in the polyethylene insert. Previous studies have demonstrated small movements in the transverse plane between the polyethylene insert and the metal tray in fixed bearing TKAs[38, 39]. Nilsson et al[39] conclude that when measuring marker-based migration of modular tibial components, only out-of-plane measurements are reliable. In our study, however, a similar tibial tray and locking mechanism was used in both groups, thus insert migration with respect to the tibial tray, if any, is expected to be similar. Furthermore, the migration predominantly comprised of transverse and sagittal rotations moving out of the transverse plane. Second, the study was underpowered to perform subgroup analysis on preoperative alignment. Dunbar et al[33] reported a significant difference in rotation about the sagittal axis depending on the pre-operative alignment of the knee. They found that pre-operatively aligned varus knees tilted into valgus and *vice versa*, but only in the uncemented Trabecular Metal knees (Zimmer Biomet, Warsaw, Indiana). Previous studies have shown that pre-operative varus or valgus alignment is associated with a lower bone mineral density in one compartment and that this might influence component migration[40, 41]. Pooling data of several RSA studies, while properly adjusting for slight differences in implant design, may increase the power to further explore these failure mechanisms. Third, because cement can be seen on radiographs, migration measurements could not be blinded, making it a single blinded study. However, a single straightforward and therefore objective interpretation of RSA data can be expected when using standardised analysing methods in accordance with the RSA guideline[26, 32].

In conclusion, PA-coated tibial components showed more initial migration compared with cemented components. However, *post hoc* analysis showed that a stable migration pattern was observed from three months onwards, especially in the PA-coated group, suggesting subsequently durable biological fixation might have been achieved. Clinically, there was no significant difference in outcome between the two methods of fixation.

Take home message:

- Compared with cemented tibial components, PA-coated tibial components show higher initial migration as part of a biphasic migration pattern, characteristic for uncemented components.
- Despite high initial migration of PA-coated tibial components, a stable migration pattern was achieved.
- Both the number of tibial components showing continuous migration and the clinical outcomes were comparable between cemented and PA-coated TKAs.

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5

Peri-apatite coating decreases uncemented tibial component migration: long-term RSA results of a randomized controlled trial and limitations of short-term results

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Abstract

Background and purpose — Biological fixation of uncemented knee prostheses can be improved by applying hydroxyapatite coating around the porous surface via a solution deposition technique called Peri-Apatite (PA). The 2-year results of a randomized controlled trial, evaluating the effect of PA, revealed several components with continuous migration in the second postoperative year, particularly in the uncoated group. To evaluate whether absence of early stabilization is diagnostic of loosening, we now present long-term follow-up results.

Patients and methods — Sixty patients were randomized to PA-coated or uncoated (porous only) total knee arthroplasty of which 58 were evaluated with radiostereometric analysis (RSA) performed at baseline, at 3 months postoperatively and at 1, 2, 5, 7, and 10 years. A linear mixed-effects model was used to analyze the repeated measurements.

Results — PA-coated components had a statistically significantly lower mean migration at 10 years of 0.94 mm (95% CI 0.72–1.2) compared with the uncoated group showing a mean migration of 1.72 mm (95% CI 1.4–2.1). Continuous migration in the second postoperative year was seen in 7 uncoated components and in 1 PA-coated component. All of these implants stabilized after 2 years except for 2 uncoated components.

Interpretation — Peri-apatite enhances stabilization of uncemented components. The number of components that stabilized after 2 years emphasizes the importance of longer follow-up to determine full stabilization and risk of loosening in uncemented components with biphasic migration profiles.

Introduction

Early migration of tibial components, which can be accurately measured with radiostereometric analysis (RSA), has been shown to predict future aseptic loosening[1, 2]. Uncemented components typically display a biphasic migration pattern with high initial migration before stabilization[3-5], while cemented components are initially more stable as the cement provides instant fixation, yet continuous bone resorption at the cement–bone interface may result in continuous migration[6, 7]. Given the importance of stabilization in the first months after implantation, one method to improve bone ingrowth after uncemented total knee arthroplasty (TKA) is the application of osteoconductive hydroxyapatite (HA) coatings[8, 9].

Most HA coatings are plasma sprayed onto the porous beaded implant surface area. Plasma spraying is a "line of sight" technique and therefore only able to coat the substrate surface[10]. Contrarily, Peri-Apatite HA (PA) (Stryker, Mahwah, NJ, USA) is an alternative technique to deposit HA from an aqueous solution at room temperature, thereby increasing the coverage of HA onto the 3D beaded implant surface[11]. However, without the effect of high temperatures up to 20,000 °C associated with plasma spraying, the HA remains pure and 100% crystalline, while a lower crystallinity has been shown to improve the bioactivity and resorption profile of HA[11, 12]. In addition, the adhesion of the relatively thin PA layer (of 20 µm compared with 50–75 µm for most HA coatings) is fragile when touching the coated metal during implantation and, like any HA coating, might delaminate or release particles over time[13, 14]. Only a few randomized RSA studies have assessed the short-term (2-year follow-up) effect of PA on uncemented tibial component migration[10, 15-17]. All trials concluded that the PA coating appears to improve stabilization up to 2 years after implantation. However, no studies have examined long-term migration profiles of PA-coated tibial components. It is therefore unknown whether the found short-term effect on component fixation is sustained over time. Furthermore, in the short-term report of the current study[17], a number of both uncoated and PA-coated components showed continuous migration in the second postoperative year. It is unclear whether this leads to future aseptic loosening or if this high initial migration is merely part of a migration pattern typical for uncemented components. We therefore now report 10-year follow-up results of this double-blinded, randomized controlled trial comparing implant migration measured with RSA and clinical results of PA-coated with uncoated uncemented TKAs.

Patients and methods

Study design

Full details of the design and patient selection of this randomized controlled trial have been described previously[17]. In short, all consecutive patients scheduled to undergo TKA due to primary osteoarthritis from July 2007 until February 2008 in Hässleholm Hospital (Sweden) were asked to participate. 60 patients were randomized in a 1:1 ratio. Patients received either "PA-coated" (applied on both the femoral and tibial component) or "uncoated" components of an otherwise identical (fully) uncemented cruciate retaining Triathlon total knee prosthesis (Stryker, Mahwah, NJ, USA). The porous undersurface (in both versions) consisted of cobalt-chromium sintered beads with a porosity of 35% and mean pore size of 425 μm. Highly cross-linked polyethylene inserts were used in all cases.

At all follow-up points, the Knee Society Score (KSS) and the Knee injury and Osteoarthritis Outcome Score (KOOS) were obtained. Both patients and observers performing clinical follow-up and RSA measurements remained blinded to the allocated group during the entire follow-up period.

Radiostereometric analysis

RSA radiographs were made on the first day after surgery when weight bearing was achieved. Subsequent examinations were performed after 3 months, 1 year, 2, 5, 7, and 10 years. RSA radiographs were performed in supine position with the knee in a calibration cage (Cage 10, RSA Biomedical, Umeå, Sweden). RSA measurements were analyzed using UmRSA software (v6.0, RSA, Biomedical, Umeå, Sweden). Positive directions along and about the orthogonal axes are according to RSA guidelines[18]. Migration was described as translation of the geometric center of the prosthesis markers and rotation of the rigid body defined by the prosthesis markers about this geometric center of gravity. The length of the translation vector of the marker or virtual marker in a rigid body that has the greatest migration, i.e., the maximum total point motion (MTPM), was used as the primary outcome measure[19]. The first postoperative RSA examination served as the reference for the migration measurements. Individual components with "continuous migration," defined by Ryd *et al.*[1] as an increase in MTPM of 0.2 mm or more in the second postoperative year, were classified as "loose." This threshold was set at 0.1 mm per year after 2-year follow-up according to the modified continuous migration criterion[1]. Consequently, implants classified in the second postoperative year as loose were considered stabilized if the migration was less than 0.1 mm/year between 2-year and final follow-up[4, 20]. The precision of the local RSA set-up after the 2-year follow-up period, specified as the 95% confidence interval (CI) around zero motion, and measured with 15 double examinations[19], was 0.10 mm, 0.10 mm, and 0.09 mm for transverse, longitudinal, and sagittal translations; 0.20°, 0.20°, and 0.24° for transverse, longitudinal, and sagittal rotations, respectively. The mean error of rigid body fitting of the RSA markers was below 0.35 mm and the upper limit for the condition number was set at 120, complying with the suggested limits of the RSA guidelines[19]. The mean condition number was 40 (CI 37–42) and 51 (CI 49–54) for the implant and tibial markers, respectively.

Statistics

Given the high accuracy of RSA measurements, only 17 patients were needed in each group to detect a decrease in migration from 1.0 to 0.5 ± 0.5 mm with 80% power and alpha set at 0.05, as described previously[17]. Thirty patients were randomized to each group to account for possible dropouts. The original primary outcome reported by Molt and Toksvig-Larsen[17] was a difference in migration (MTPM) after 2 years of follow-up. For this long-term outcome report, the primary outcome was a difference in MTPM after 10 years of follow-up as registered at ClinicalTrials.gov (ID: NCT03198533). Data were analyzed according to the intention-to-treat principle. A linear mixed-effects model was used for all repeated measurements to effectively deal with missing values within patients during follow-up. As MTPM is always a positive vector, normal distribution was only obtained after log-transformation (logMTPM), computed as log10(MTPM+1). Differences in mean progression of logMTPM between groups were modeled as a function of time and the interaction of time with treatment. A random-intercepts term was used and remaining variability was modelled with a heterogeneous autoregressive order 1 covariance structure. Secondary outcomes (RSA translations and rotations, flexion, extension, KSS, and KOOS scores) were analyzed with a similar mixed-effects model. Differences in mean migration along and about each orthogonal axis were calculated using log-transformed absolute values (as the resultant of positive and negative displacement vectors requires all vectors to act on the same prosthesis)[21]. Given the non-normal distribution of knee extension and the KSS knee score (not resulting in a normal distribution after a log transformation), a comparable generalized estimating equations (GEE) approach was used to correct the standard errors via the sandwich estimator. *Post hoc* testing was performed to estimate between-group differences in MTPM using 3 months, 1 year, and 2 years as the reference. IBM SPSS Statistics 24.0 (IBM Corp, Armonk, NY, USA) was used for all outcome measures; a p-value < 0.05 was considered significant.

Ethics, registration, funding, and potential conflicts of interest

The trial was performed in compliance with the Declaration of Helsinki and Good Clinical Practice guidelines. This trial was approved by the local ethics committee prior to enrollment (entry no. 445/2005) and registered at ClinicalTrials.gov (new ID: NCT03198533, originally registered in 2007 as a sub-study of NCT00436982). Informed consent was obtained from all patients. Stryker provided funds in support of the costs associated with RSA radiographs and extra clinical follow-up examinations. The sponsor did not take any part in the design, conduct, analysis, and interpretations stated in the final manuscript.

Results

Sixty patients were randomized, of which 1 patient in each group was excluded on the day of surgery. Baseline characteristics were similar (Table I). During follow-up, 3 knees were revised (2 infections and 1 loosening, see adverse events), 7 patients died, 14 patients refused further follow-up due to the burden of coming to the clinic at high age or moving out of the region, and 2 patients could not be analyzed reliably for technical reasons (Figure 1). Of the 2 cases with unreliable measurements, 1 had insufficient bone markers available causing high condition numbers (up to 216) after 1 year; reversed RSA migration results showed stable minor translations, and this patient had no knee complaints and no signs of loosening on conventional radiographs. The other case had unreliable measurements after 5 years (condition number of 135) due to over-projection of the femoral component and this component was revised after 10 years for mechanical failure (see below).

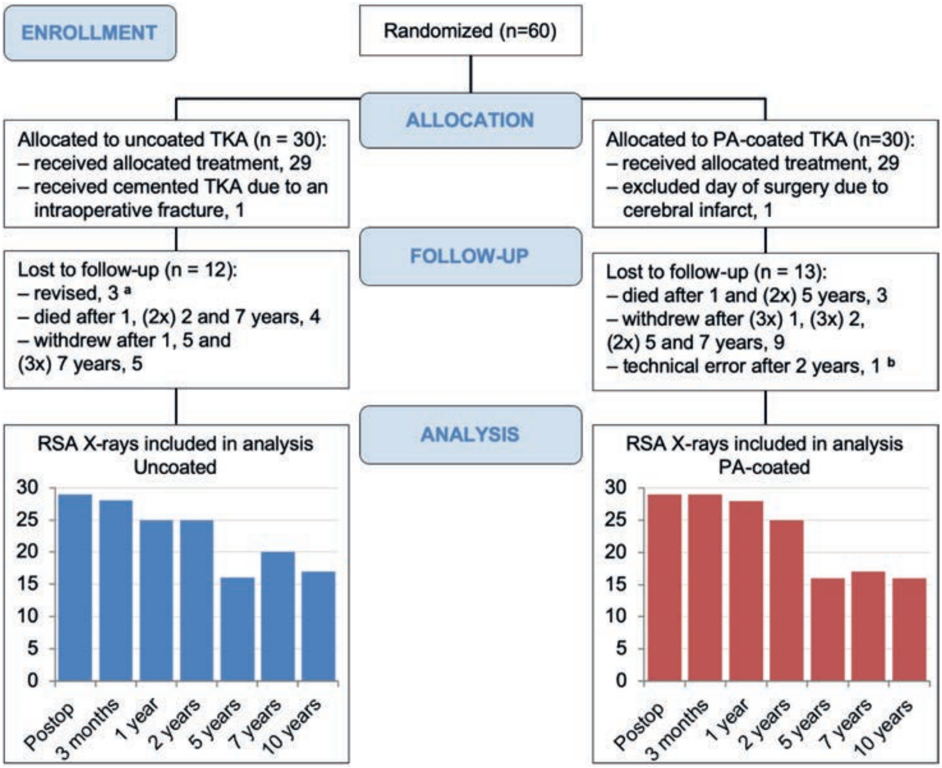

Figure 1. CONSORT flow diagram. TKA: total knee arthroplasty. [a] revised after 3 months (early infection), 1 year (late infection), and 10 years (mechanical failure). [b] clinical follow-up only, see text.

Table I. Baseline demographic characteristics. Values are mean (SD) unless otherwise specified

	Uncoated (n=29)	PA-coated (n=29)
Age	67 (6.8)	65 (8.1)
Body mass index	30 (4.3)	30 (4.9)
Female sex (n)	16	17
Previous knee surgery (n)		
None	22	25
Joint debridement	1	1
Meniscectomy	5	2
Other	1	1
Ahlbäcks grade (n)		
II	12	6
III	15	22
IV	2	1
ASA classification (n)		
I	8	6
II	20	21
III	1	2
Hip–knee–ankle angle		
Preoperative	175 (5.0)	176 (6.2)
Postoperative	179 (2.8)	179 (3.2)

RSA migration measurements

PA-coated components stabilized earlier as compared with uncoated components, resulting in a lower mean migration at 10 years: 0.94 mm (CI 0.72–1.2) for the PA-coated group and 1.7 mm (CI 1.4–2.1) for the uncoated group ($p < 0.001$). Over time, differences in migration between groups were seen in almost any direction (Table II). Most of the difference in migration was already seen at 1 year, as the PA-coated components stabilized within the first 3 months while the uncoated components stabilized after 1 year of follow-up (Figure 2). *Post hoc* analysis showed that when using different baselines, no statistically significant between-group mean differences were seen from 1 year onwards ($p = 0.1$) and from 2 years onwards ($p = 0.7$) (Table III, see Supplementary data).

Between 1 and 2 years of follow-up, 7 uncoated components showed more than 0.2 mm MTPM and were suspected for loosening, compared with 1 in the PA-coated group. Five of the 7 uncoated components stabilized, while 2 did not: 1 (clinically still asymptomatic patient) showed continuous migration of 0.14 mm/year up to 10-year follow-up (Figure 3, see Supplementary data) and 1 showed continuous migration of 0.11 mm/year up to 7-year follow-up who, despite having progressive complaints, refused to visit for 10-year follow-up (Figure 4, see Supplementary data). One uncoated component that was initially classified as loose was lost to follow-up but showed full stabilization at final (5-year) follow-up. One uncoated component was revised after 10 years as the patient had increasing pain and instability due to mechanical failure (see below). The PA-coated component initially classified as loose was stabilized at 5-year follow-up. None of the PA-coated components classified as stable showed continuous migration at any follow-up measurement beyond 2 years.

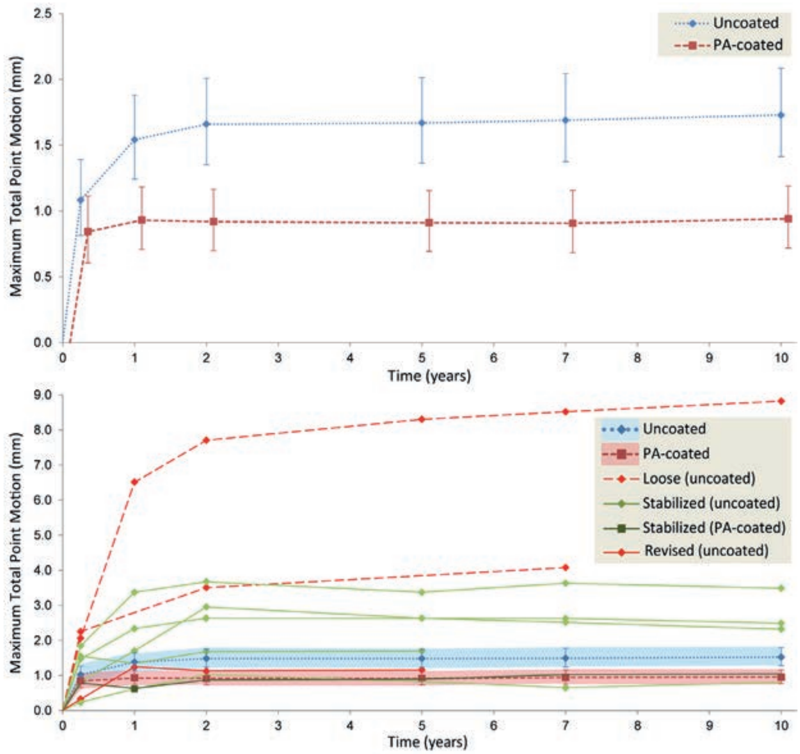

Figure 2. Maximum total point motion (back-transformed in the original scale in mm) during 10 years of follow-up: **(top)** the mean and 95% CI for the groups and **(bottom)** the mean and 95% CI for the groups and separate lines for the components showing continuous migration in the second postoperative year (in green the stabilized components after 2 years, in dashed red the components failing to stabilize after 2 years and suspected for aseptic loosening, and in solid red the revised component).

Table II. RSA migration measurements in absolute mm or degrees (95% CI) (log-transformed values are back-transformed in the original scale)

	1 year		2 years		10 years		
	Uncoated	**PA-coated**	**Uncoated**	**PA-coated**	**Uncoated**	**PA-coated**	**p-value[a]**
Translations (mm)							
Transverse	0.4 (0.28–0.49)	0.3 (0.21–0.40)	0.4 (0.33–0.54)	0.3 (0.19–0.38)	0.4 (0.30–0.54)	0.4 (0.24–0.48)	0.2
Longitudinal	0.5 (0.42–0.67)	0.3 (0.18–0.39)	0.5 (0.41–0.66)	0.3 (0.17–0.38)	0.5 (0.41–0.69)	0.3 (0.17–0.41)	< 0.001
Sagittal	0.5 (0.42–0.68)	0.3 (0.17–0.38)	0.7 (0.52–0.80)	0.2 (0.13–0.34)	0.7 (0.55–0.87)	0.3 (0.17–0.42)	< 0.001
Rotations (°)							
Transverse	1.1 (0.79–1.37)	0.6 (0.39–0.83)	1.2 (0.92–1.55)	0.6 (0.35–0.80)	1.3 (0.94–1.64)	0.6 (0.33–0.83)	< 0.001
Longitudinal	0.7 (0.50–0.82)	0.3 (0.17–0.42)	0.8 (0.67–1.04)	0.3 (0.18–0.44)	1.0 (0.78–1.21)	0.3 (0.14–0.43)	< 0.001
Sagittal	0.6 (0.49–0.83)	0.4 (0.30–0.59)	0.8 (0.66–1.04)	0.5 (0.36–0.67)	0.8 (0.57–0.97)	0.5 (0.30–0.65)	0.004
MTPM (mm)	1.5 (1.24–1.88)	0.9 (0.71–1.18)	1.7 (1.35–2.01)	0.9 (0.70–1.17)	1.7 (1.41–2.08)	0.9 (0.72–1.19)	< 0.001

[a] p-values stated in this column indicate testing the between-group mean differences with time over the entire postoperative follow-up period.

Clinical results and adverse events

There were no statistically significant between-group differences with respect to improvement in knee flexion, extension, both KSS scores, and 4 of 5 KOOS subscales. The KOOS subscale quality of life improved equally between groups up to 5-year follow-up ($p = 1.0$), but substantially decreased in the PA-coated group between 5 and 10 years, resulting in a between-group mean difference after 10-year follow-up ($p = 0.02$) (Table IV, see Supplementary data).

Three patients (all with uncoated components) underwent revision surgery; the first due to an early prosthetic joint infection (at 3 months), the second due to a late infection (at 1 year) and the third (at 10 years) due to mechanical failure (complaints of pain and instability, posteromedial wear of the insert, and tibial component loosening was found during revision surgery) (Figure 5, see Supplementary data). One patient (randomized to the uncoated group) received a cemented implant due to an intraoperative fissure of the proximal tibia and was excluded. One patient (randomized to the PA-coated group) was transferred on the day of surgery to another hospital to receive appropriate treatment after a cerebral infarct and was also excluded.

Discussion

Our results show that the short-term effect of Peri-Apatite on uncemented tibial component migration is sustained over time, resulting in less mean migration and absence of components with continuous migration after 10 years. As shown in other long-term RSA studies, stabilization of uncemented tibial components can be achieved despite high initial migration[3, 5]. In the present long-term study, 6 individual components stabilized even after 2 years. Only 2 uncoated components migrated continuously throughout follow-up. Given that most prostheses stabilized within 2 years, the mean migration from 1 year onwards was not statistically significantly different between groups as confirmed in the *post hoc* analysis.

Both "excessive" initial migration in the first year (of more than 0.5 mm for a group of patients) and continuous migration after 1 year (>0.2 mm in the second postoperative year for an individual patient) are associated with, and frequently used as predictors for, aseptic loosening[1, 2]. These studies, however, combined prostheses that rely on primary fixation (cemented and uncemented with screws) and those that rely on secondary biological fixation (uncemented) to evaluate the migration thresholds for prostheses suspected for loosening. Several studies have shown that the typical migration pattern of an uncemented component differs from that of a primary fixated component, especially during the first 2 years [3, 5-7, 22]. We therefore question whether the current migration thresholds are justified for uncemented prostheses, especially for designs without biological mediators (e.g., hydroxyapatite or highly porous metal) to enhance bone ingrowth, and can be used to classify such implants being loose in RSA studies with only 2 years of follow-up.

In our study, 1 TKA was revised at 10-year follow-up due to progressive pain and function impairment due to mechanical failure. Posteromedial polyethylene wear and tibial component loosening was found during revision surgery (Figure 5, see Supplementary data). This patient was not flagged as "loose" through RSA measurements as MTPM values were stable up to 5 years of follow-up but further follow-up measurements were unreliable due to high condition numbers (solid red line in Figure 2). The exact failure mechanism is unknown. Causal factors of posteromedial failure include overloading the medial compartment and malalignment of the femoral component, increasing posteromedial peak contact stresses[23]. Some authors have reported that by cross-linking the polyethylene the fatigue crack propagation resistance is decreased, especially in TKA[24, 25]. However, later reports of fatigue failure are rare and mainly limited to tibial post fractures in posterior-stabilized knees, suggesting this mechanism is unlikely to account for failure in our patient[26, 27].

Although all other subscales of the KOOS score were similar between uncoated and PA-coated components, we did observe a statistically significant difference in the quality of life subscale after 10 years of follow-up. Similar to the occurrence of both the infection cases and the revised case due to mechanical failure (which could all have occurred in either group), the statistical difference in quality of life is most likely a spurious finding and not related to the implant type. Nevertheless, we continue to monitor these patients to observe whether any adverse effect of the given treatment occurs.

Several limitations can be noted. First, a high number of patients were lost to follow-up. Consequently, only 16 patients were available for analysis in the PA-coated group at 10-year follow-up. However, results from the linear mixed-effects model are based on all measurements, not only on remaining patients at final follow-up. Furthermore, as most implants of the lost patients appeared to have stabilized, it is unlikely that the observed results would substantially differ from those presented if patients had continued follow-up. Results of the secondary clinical outcomes should, however, be regarded as exploratory due to the limited sample size and the lower accuracy and precision of these outcome measurements. Second, it remains unknown why 6 components stabilized while 2 did not. Logically, the magnitude of component migration plays a role in preventing the onset of a prosthesis-settling phase. However, other (baseline) factors that may predict high risk patients cannot be found without performing "one-variable-at-a-time" subgroup analyses, which are likely both underpowered and produce false-positive results due to multiple comparisons[28]. We therefore refrained from performing such subgroup analyses. Third, a strict intention-to-treat analysis requires all randomized patients to be analyzed, which was not the case for the 2 excluded patients on the day of surgery. These 2 patients were excluded from further follow-up measurements at the time; hence no data were available for analysis. Furthermore, not receiving the studied intervention can be a legitimate reason for patient exclusion without risking bias, even in an intention-to-treat tria[29].

In summary, the typical biphasic migration pattern of uncemented implants was seen in both the uncoated group and the PA-coated group, but the latter showed statistically significantly less mean migration and absence of components with continuous migration at 10-year follow-up. When evaluating uncemented prostheses, especially those without biological mediators to enhance bone ingrowth, the initial migration phase is longer than in cemented components and can last over 2 years. With such prostheses, short-term RSA cut-off values to determine the risk of failure seem of limited value. Evaluation should thus be based on longer follow-up data and include mean migration results as well as individual component migration results.

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Supplementary data

Table III. Post hoc analysis of between-group mean difference in logMTPM with different time points as baseline: values are mean (standard error) unless otherwise specified

Baseline	LogMTPM Uncoated	LogMTPM PA-coated	Between-group difference mean (95% CI)	p-value
Postoperative–10 years	0.44 (0.04)	0.29 (0.03)	0.15 (0.08 to 0.22)	< 0.001
3 months–10 years	0.12 (0.02)	0.02 (0.02)	0.09 (0.04 to 0.14)	< 0.001
1 year–10 years	0.03 (0.01)	0.00 (0.01)	0.03 (–0.00 to 0.05)	0.1
2 years–10 years	0.01 (0.01)	0.00 (0.01)	0.01 (–0.02 to 0.03)	0.7

Table IV. Clinical scores in degrees or points (95% CI)

	Pre-operatively		5 years		10 years		
	Uncoated	PA-coated	Uncoated	PA-coated	Uncoated	PA-coated	p-value [a]
Knee function (°)							
Flexion	113 (108–118)	118 (112–123)	121 (117–125)	126 (122–130)	123 (120–126)	127 (124–131)	0.9
Extension [b]	-4 (-5 to -2)	-4 (-6 to -3)	-0 (-1 to 1)	0 (-0 to 1)	0 (0 to 0)	0 (0 to 0)	0.5
Knee Society Score (KSS points)							
Knee Score	40 (35–44)	38 (34–43)	97 (92–100)	99 (96–100)	94 (86–100)	97 (94–100)	0.3
Function Score	57 (52–61)	53 (48–58)	88 (81–96)	89 (81–96)	84 (76–91)	86 (78–94)	0.2
Knee injury and Osteoarthritis Outcome Score (KOOS points)							
Symptoms	46 (39–54)	48 (41–55)	91 (85–96)	90 (85–95)	91 (85–96)	90 (85–95)	0.6
Pain	41 (34–48)	41 (34–48)	89 (83–96)	89 (83–96)	91 (86–96)	90 (85–95)	0.7
ADL	44 (36–51)	47 (40–54)	85 (77–93)	87 (80–95)	87 (80–93)	86 (80–93)	0.7
Sports	12 (7–17)	9 (5–14)	45 (33–58)	33 (21–45)	49 (35–63)	54 (39–69)	0.6
Quality of life	23 (18–28)	23 (18–28)	83 (75–92)	84 (75–91)	82 (74–89)	75 (67–83)	0.02

[a] p-values stated in this column indicate testing the between-group mean differences of improvement with time over the entire postoperative follow-up period. Note that not all follow-up measurements are stated, but results from all follow-up measurements were used in the linear mixed-effects model to test for differences. [b] Negative extension means no full extension possible.

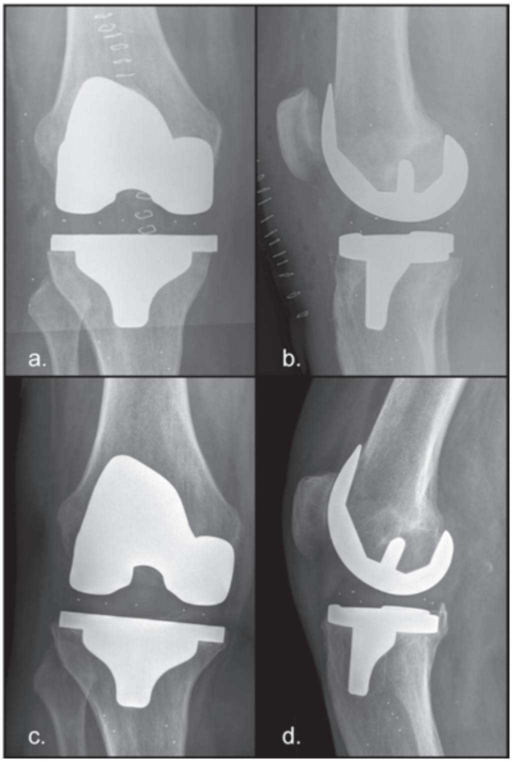

Figure 3. Uncoated TKA in a 65-year-old female (BMI 30) with a preoperatively valgus aligned knee (HKA 186°; postoperative HKA 175°). **a, b** directly postoperative, **c, d** at 10-year follow-up. The tibial component was initially classified as loose and did not stabilize between 2 and 10 years: note the posterior tilt of 9° (with a radiolucent line posterior to the tibial keel and posterior subsidence of the tibial plateau in d) and varus tilt of 6° (with medial subsidence of the tibial plateau in c).

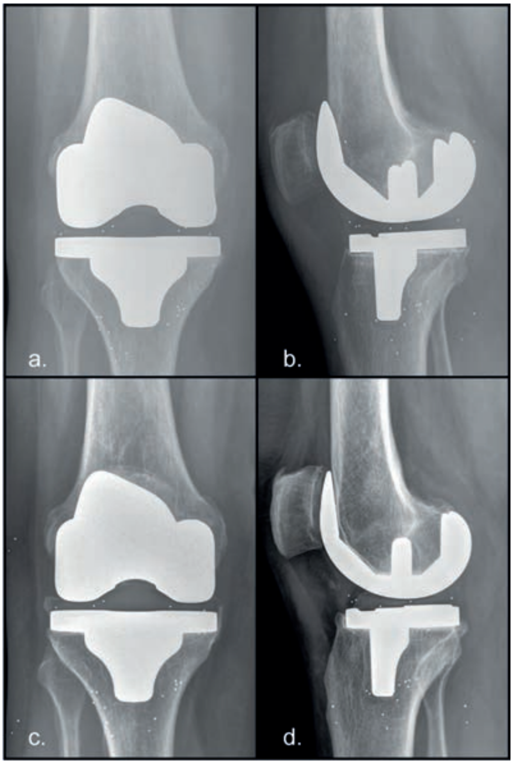

Figure 4. Uncoated TKA in a 56-year-old female (BMI 26) with a preoperatively varus aligned knee (HKA 169°; postoperative HKA 176°). **a, b** at 3-month follow-up, **c, d** at 7-year follow-up. The tibial component was initially classified as loose and did not stabilize between 2 and 7 years: note the anterior tilt of 5° (with a radiolucent line anterior to the tibial keel and anterior subsidence of the tibial plateau in d) and varus tilt of 2° (with medial subsidence of the tibial plateau in c).

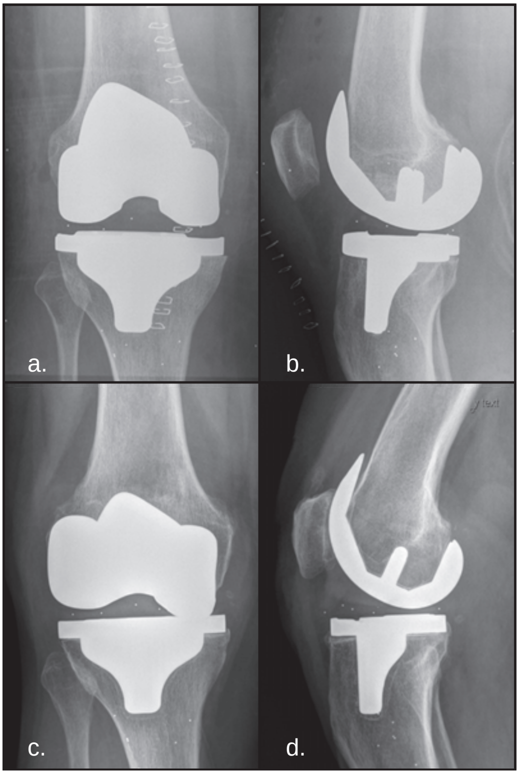

Figure 5. Uncoated TKA in a 60-year-old female (BMI 23) with a pre-operatively varus aligned knee (HKA 176°; postoperative HKA 179°). **a, b** directly postoperative, **c, d** at 10-year follow-up prior to revision surgery. The tibial component was not classified as loose, which might be due to a different failure mechanism of insert wear, instability, and subsequent loosening. RSA measurements were stable up to 5 years, the measurements at 7- and 10-year follow-up were unreliable (as 2 insert markers were over-projected by the femoral component causing high condition numbers). Note the radiolucent lines around the tibial keel (in both c and d) and anteriorly (in d). A possible defect of the insert was confirmed intraoperatively on the posteromedial side. Contrarily to the well-fixed femoral component, the tibial component was easily extracted.

Part II

Surgical and patient risk factors for tibial component migration

6

Marker-based *versus* model-based radiostereometric analysis of total knee arthroplasty migration: a reanalysis with comparable mean outcomes despite distinct types of measurement error

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Abstract

Background and purpose — Pooling data of studies evaluating total knee arthroplasty migration using radiostereometric analysis (RSA) may be compromised when the RSA method used would influence estimated differences between groups. We therefore reanalyzed a marker-based RSA study with model-based RSA to assess possible limitations of each RSA method, including insert micromotions in modular TKA and their effect on estimated group differences.

Patients and methods — All patients had received a cemented Triathlon implant (Stryker, Mahwah, NJ, USA) with either an all-polyethylene (n = 29) or a metal-backed (n = 28) tibial component. The latter group was reanalyzed with model-based RSA. Precision of each RSA method was calculated using double examinations. Bland–Altman plots were constructed to determine the limits of agreement between the 2 RSA methods. Polyethylene insert micromotion was quantified by measuring migration with respect to the metal tray. Finally, analyses of the original study were repeated with the model-based RSA results.

Results — Systematic differences were found in translations between marker-based and model-based RSA as a result of different reference origins being used for migration calculations. Micromotions of the polyethylene insert within the metal tray were negligibly small. Mean migration results were comparable between marker-based and model-based RSA when using the same reference origin, even though conclusions on individual patients may differ between RSA methods due to various types of measurement error (e.g., marker occlusion and model-fit inaccuracies).

Interpretation — At least for the studied TKA design, pooling mean migration data of different RSA methods appears justified. For translations, however, adjustments should be made to correct for differences in reference origin. Migration patterns of individual patients may differ as a result of distinct types of measurement error.

Introduction

Due to the high accuracy and precision of radiostereometric analysis (RSA), late loosening of new implants can already be predicted with 2-year RSA results on small patient numbers[1-3]. RSA requires the bone and prosthesis to be accurately defined in 3 dimensions, usually achieved by inserting tantalum markers in the bone and by attaching or inserting markers (in)to the prosthesis (i.e., marker-based RSA). Prosthesis markers are generally inserted during surgery in the polyethylene of the implant[4]. Alternatively, in model-based RSA the need for prosthesis markers is eliminated by matching a virtual projection of a 3D model with the contours of the radiographic projection of the implant[5]. Results of model-based RSA are suggested to be comparable with conventional marker-based methods on a group level[6], but direct comparisons on individual patient data are scarce[4, 7]. We recently published the 2-year results of a randomized controlled trial (RCT) on implant migration of cemented metal-backed *versus* all-polyethylene tibial components in total knee arthroplasty (TKA) using the Triathlon TKA system (Stryker, Mahwah, NJ, USA)[8]. Higher migration was found after 2 years for the metal-backed components, even though the difference was small. However, as migration measurements were based on markers inserted in the polyethylene, apparent migration of the modular metal-backed components may partly result from micromotion of the polyethylene insert with respect to the metal tray, a phenomenon that has been shown to occur in older fixed-bearing designs[9, 10].

In this study, we reanalyzed the metal-backed components with model-based RSA to eliminate any influence of modularity on migration results and thus investigate whether methodological differences between RSA methods would affect migration results. Second, we quantified movements of the polyethylene insert within the locking mechanism of the metal tray. Finally, we investigated whether the use of model-based RSA would result in different conclusions of the RCT as compared with the marker-based results.

Patients and methods

Full details of the original RCT regarding patients, randomization, follow-up, prosthesis, and surgical techniques have been described previously[8]. Briefly, 2 surgeons implanted cemented, condylar-stabilizing, cruciate-retaining Triathlon total knee prostheses with either all-polyethylene (n = 29) or modular fixed-bearing metal-backed tibial components (n = 30). The metal tray was designed with a full peripheral capture locking mechanism and an anti-rotational central island[11]. Two patients with metal-backed components were analyzed with model-based RSA in the original RCT due to polyethylene marker occlusion, which precluded marker-based measurements. Hence, no marker-based results were available for comparison and these were thus excluded in the present study.

Radiostereometric analysis

The first RSA examination, performed on the first postoperative day, served as the reference for the migration measurements. Subsequent examinations were performed at 3 months, 1 year, and 2 years after surgery. RSA radiographs were performed in supine position with the knee in a biplanar calibration cage (cage 10, RSA Biomedical, Umeå, Sweden) and analyzed using Model-based RSA software version 4.1 (RSAcore, LUMC, Leiden, the Netherlands). For marker-based RSA analysis 5 tantalum markers (0.8 mm in diameter) were inserted during surgery, after drilling appropriate holes, at standardized positions in the polyethylene of both tibia designs. Two markers were placed posteriorly, 2 anteromedially/anterolaterally, and 1 anteriorly. The number of markers available for migration calculations could differ over time due to marker occlusion (Figure 1a). Marker-based results of the metal-backed group were based on all 5 polyethylene markers in only 3 patients. As a result of marker occlusion in 1 or more follow-up moments, marker-based results were based on 4 polyethylene markers in 8 patients and on 3 markers in 17 patients. Model-based reanalysis was performed only in the metal-backed group, as the all-polyethylene components are radiolucent (Figure 1b). In the RSA analysis of the original report, a triangulated surface model (from reversed engineering, reduced to 5,000 triangles) was added for the tibial component and its virtual projections were matched with the contours of the radiographic projection of the implant. All other aspects of the analysis, such as insert markers, bone markers, and calibration markers, remained unchanged. Migration of the 28 metal-backed tibial components, by means of the 3D surface model, was calculated twice: with the reference origin for migration calculations (1) in the geometric center of the model, which is the standard position for model-based RSA analysis, and (2) in the geometric center of

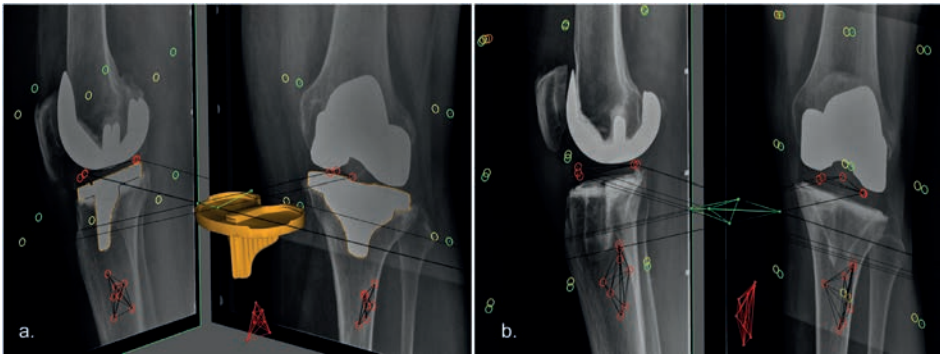

Figure 1. RSA images showing the biplanar (lateral and anteroposterior) views with the polyethylene markers and tibial bone markers encircled in red, the fiducial markers in yellow, and the control markers in green. **(a)** Only 3 of 5 polyethylene markers are visible due to over-projection of 2 markers, in most cases, by the femoral component, which may reduce or invalidate the marker-based accuracy of the RSA measurement. However, migration can also be measured by fitting a model using the contours of the metal-backed tibial component as shown in orange. **(b)** Migration of the radiolucent all-polyethylene tibial component can only be measured with marker-based RSA.

the polyethylene markers, which is the standard position for marker-based RSA analysis (Figure 2). In addition, migration of the polyethylene insert markers was determined to assess whether the insert moved with respect to the metal tray. Lastly, method 2 allowed us to compare model-based metal-backed results with marker-based all-polyethylene results using the same reference origin. The precision of each RSA method was determined by means of double examinations at 1-year follow-up. The precision is expressed as the upper limits of the 95% confidence interval (CI) around zero motion[12]. The primary outcome measure used in the original report is the maximum total point motion (MTPM), which is the length of the translation vector of the marker that moved the most. For model-based RSA, MTPM is the length of the translation vector of the point on the model that moved the most. We also report the number of individual components showing "continuous migration," defined by Ryd *et al.*[2] as an increase in MTPM of ≥ 0.2 mm in the second postoperative year. The limits of marker stability (mean error) and scatter values (condition number) were set at 0.35 mm and 120, respectively, complying with the RSA guidelines[3].

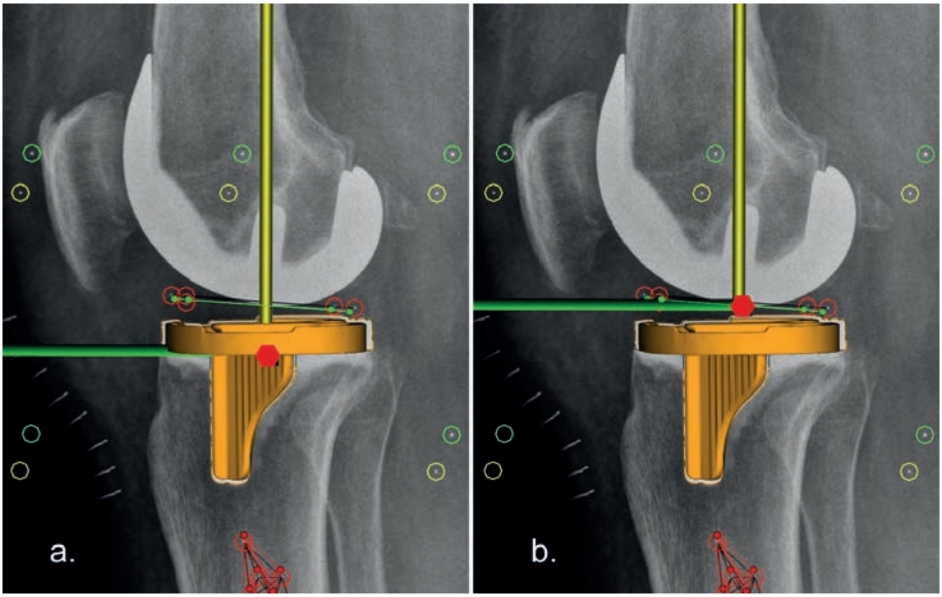

Figure 2. Lateral views showing the different reference origins (center of migrating model at reference time point T0) in **(a)** model-based and **(b)** marker-based RSA. The longitudinal axis is represented by the yellow line, the sagittal axis by the green line, and the red hexagon represents the origin. To fully compare model-based and marker-based RSA data using the same reference origin, a second model-based analysis was performed with the reference origin fixed in the center of the polyethylene markers as shown in b.

Statistics

We first estimated differences in model-based analyses with 2 different reference origins, i.e., the reference origin in the geometric center of the model *versus* the geometric center of the polyethylene markers, using regression analysis. Bland–Altman plots were constructed to determine the limits of agreement between the two RSA methods[13]. The limits of agreement, defined as the mean ± 1.96×SD, should be within ± 0.5 mm of translation or ± 0.8° of rotation for the measures to be considered equivalent. These thresholds were chosen as these are considered the smallest values of clinically relevant early migration when used as a predictor of aseptic loosening[6, 7, 14]. Boxplots were constructed to investigate micromotion of the polyethylene markers with respect to the metal tray along and about each orthogonal axis. Finally, an identical linear mixed-effects model as described in the original report[8] was used to analyze differences in migration between (model-based) metal-backed and (marker-based) all-polyethylene components while using the same reference origin (center of the polyethylene markers). As in the original report, log-transformation of outcome measures was applied wn necessary to obtain normal distributions, and the same sensitivity analysis was performed given the unevenly distributed baseline characteristics sex and surgeon as possible confounders by adding these variables to the linear mixed-effects model[8]. Significance was set at $p < 0.05$ (IBM SPSS Statistics 24.0; IBM Corp, Armonk, NY, USA).

Ethics, registration, funding, and potential conflicts of interest

The original study was approved by the Regional Ethical Review Board in Lund (entry no. 2013/434) and registered at isrctn.com (ID: ISRCTN04081530). All patients gave informed consent. The costs of the RSA radiographs made for the original study were supported by Stryker. The sponsor did not take part in the design, conduct, analysis, or interpretations stated in both the previous and current manuscript. The authors declare no competing interests.

Results

Double examinations were performed in 21 metal-backed components at 1-year follow-up to determine the precision of the RSA measurements. Model-based results were less precise in rotations, especially about the longitudinal axis (Table I).

Table I. Precision of RSA measurements (upper limits of the 95% CI around zero motion unless otherwise stated)

Group	Translations (*mm*)			Rotations (*degrees*)			MTPM	
RSA method	Trans-verse	Longi-tudinal	Sagittal	Trans-verse	Longi-tudinal	Sagittal	Mean	Upper limitof CI
All-polyethylene (n = 26 double examinations)								
Marker-based	0.11	0.15	0.09	0.17	0.11	0.11	0.14	0.14
Metal-backed (n = 21 double examinations)								
Marker-based	0.07	0.11	0.13	0.08	0.14	0.11	0.12	0.11
Model-based	0.08	0.11	0.13	0.19	0.64	0.15	0.25	0.32
Polyethylene micromotion	0.06	0.06	0.11	0.14	0.68	0.16	0.19	0.30

Marker-based versus model-based RSA

Regression analysis revealed that with (1) routine model-based RSA *versus* (2) model-based RSA with the reference origin in the geometric center of the polyethylene markers, the transverse, longitudinal, and sagittal translations were overestimated by 29% (CI 25–32), 7% (CI 0–13) and 26% (CI 24–28), respectively (illustrated for transverse translations in Figures 3a and 3b). As expected (for mathematical reasons, see Appendix), rotations and MTPM values were not influenced by the position of the reference origin and therefore identical between both model-based analyses. For fair comparison of marker-based and model-based translations, the reference origin for the model-based analysis was thus fixed at the geometric center of the polyethylene markers for the remaining analyses described below. This resolved the proportional bias (shown in Figure 3b and absent in Figure 3d)[15].

Comparing marker-based with model-based RSA, translations showed small limits of agreement indicating that both methods can be used interchangeably (Table II). The limits of agreement for the rotations and MTPM were larger, especially for rotations about the longitudinal axis (Table II).

Table II. Differences between marker-based and model-based translations and rotations with the reference origin fixed at the geometric center of the polyethylene markers

	Translations (*mm*)			Rotations (*degrees*)			
Factor	Trans-verse	Longi-tudinal	Sagittal	Trans-verse	Longi-tudinal	Sagittal	MTPM (*mm*)
Mean (SD)	-0.01 (0.05)	-0.03 (0.05)	-0.05 (0.10)	-0.02 (0.13)	0.09 (0.29)	-0.06 (0.18)	-0.03 (0.21)
95% CI [a]	-0.11 to 0.09	-0.12 to 0.07	-0.25 to 0.16	-0.28 to 0.24	-0.48 to 0.66	-0.41 to 0.29	-0.45 to 0.39

[a] The values represent the limits of agreement (interchangeability) between the 2 methods (Bland and Altman) and are based on all (n = 28) patients.

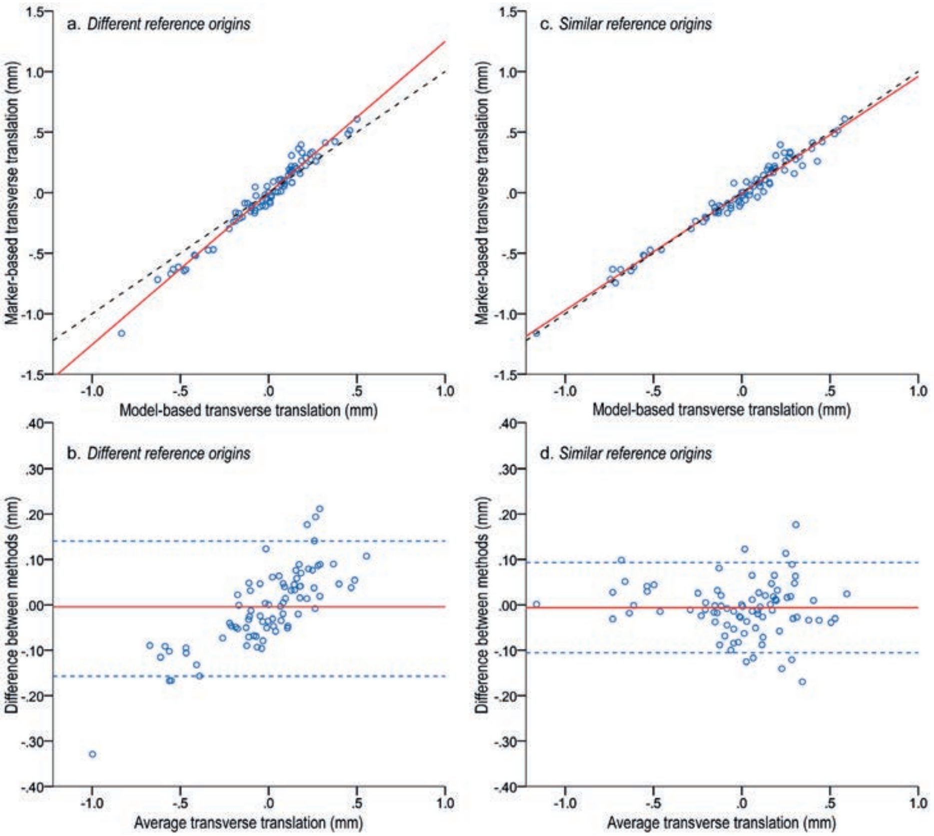

Figure 3. Scatter-plots showing **(a)** that marker-based transverse translation values are generally larger than model-based values due to the difference in position of the geometric center (which is either in the geometric center of the markers inserted in the polyethylene or in the geometric center of the model), also indicated **(in b)** by the proportional bias observed in the Bland–Altman plot (i.e., the difference between methods is proportional to the level of the measured variable)[15]). **(c)** If model-based analysis is performed with the reference origin fixed at the geometric center of the polyethylene markers, results are nearly identical between methods, as also indicated **(in d)** by the absence of proportional bias and the small limits of agreement in the Bland–Altman plot. Solid red lines in a and c: regression line. Dashed lines in a and c: line of equality. Solid red lines in b and d: mean of differences. Dashed horizontal lines in b and d: 95% limits of agreement.

Micromotion of the polyethylene insert with respect to the metal tray

Boxplots were constructed to investigate micromotion of the polyethylene insert with respect to the metal tray along and about each orthogonal axis at 3, 12, and 24 months' follow-up (Figure 4). The majority of the measurements were within the 95% confidence interval of zero motion (i.e., the precision of the RSA method, indicated by the shaded areas in Figure 4) and group median values did not appear to increase over time. A few outliers depicted in Figure 4 were evaluated to determine the nature of the extreme values, all of which were found to be due to measurement error as a result of instability or occlusion of the polyethylene markers. The error of patient 6 was due to one polyethylene marker

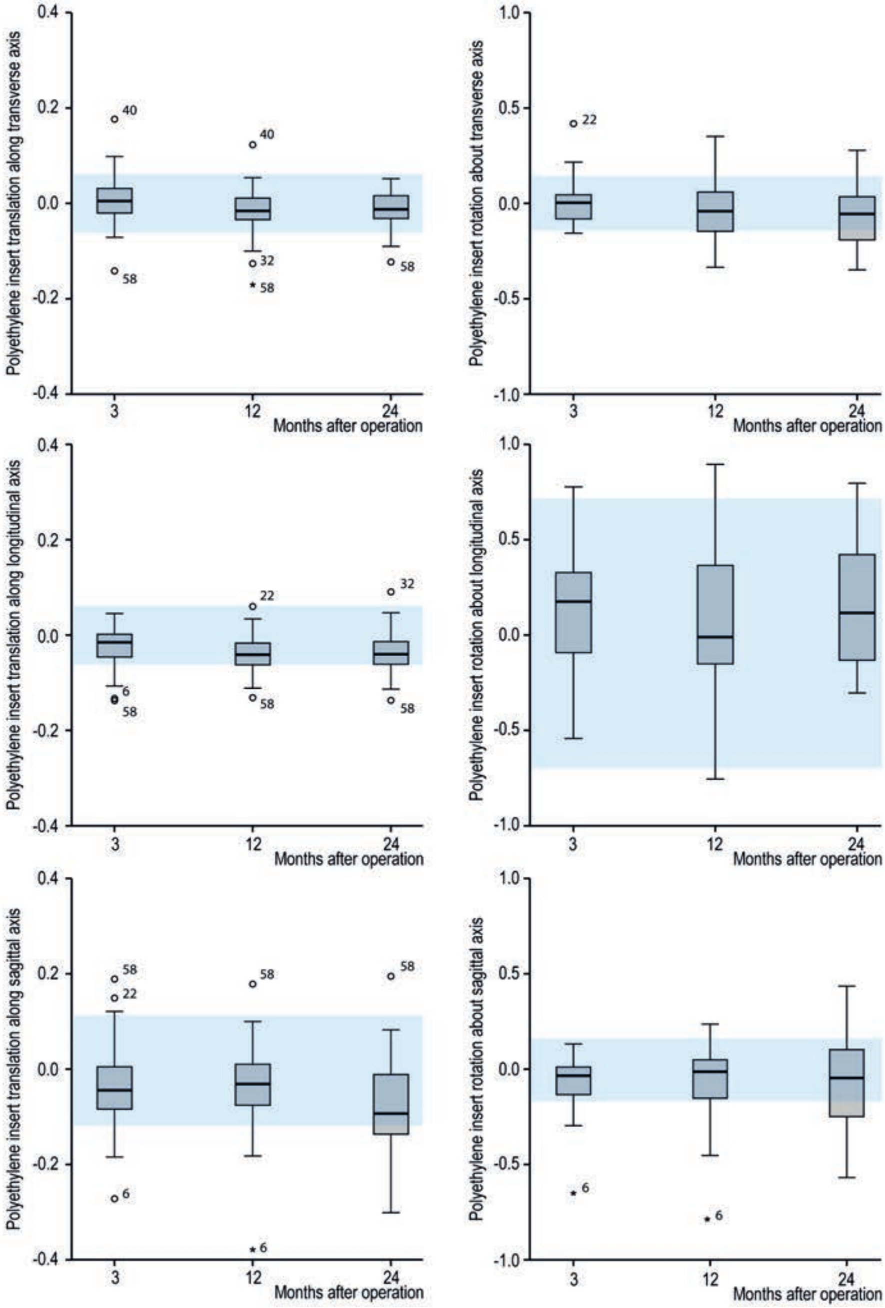

Figure 4. Box-and-whisker plots showing the polyethylene insert translations and rotations with respect to the metal tray at each follow-up (n = 28). The line in boxes indicate group median, the box the interquartile range (IQR); the whiskers the maximum values and outliers are depicted as circles (> 1.5×IQR) and stars (> 3×IQR). Shaded blue areas represent the 95% confidence intervals of zero motion (i.e., RSA precision, determined with double examinations), numbers of the outliers are patient study numbers.

moving posteriorly close to the periphery of the drilled hole where it was inserted (resulting in a mean error between 0.31 and 0.33 at 3, 12, and 24 months, close to the limit of 0.35). This marker stabilized within 3 months, as the polyethylene micromotion values were close to zero when 3 months' follow-up was taken as the reference (mean error between 0.02 and 0.03 at 12 and 24 months). A similar cause was found in the analysis of patient 58, but in this case 2 anterior markers moved anteriorly; results were also close to zero when 3 months' follow-up was taken as the reference. In the analysis of patient 22, patient 32, and patient 40, only 3 polyethylene markers were available of which 1 was partly occluded in 1 or more follow-up moments by either the tibial component or by another marker; slightly adjusting the position of these markers resulted in values close to zero in all directions.

Change in results of original trial

When repeating the analysis of the primary outcome (MTPM after 2 years of follow-up) of the original report[8] with the model-based migration values, comparable group differences were found: the all-polyethylene group had a MTPM (CI) of 0.61 (0.49–0.74) *versus* 0.81 (0.68–0.95) for the marker-based metal-backed group; and *versus* 0.82 (0.68–0.96) for the model-based metal-backed group (Figure 5).

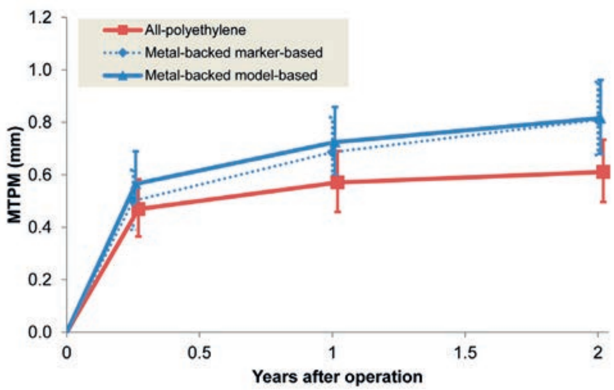

Figure 5. RSA analysis results of maximum total point motion (MTPM). The mean and 95% confidence interval for the metal-backed group is shown for both the marker-based (dashed blue line) as well as the model-based (solid blue line) analysis.

In the original paper, continuous migration of ≥ 0.2 mm in MTPM in the second post-operative year was seen in 4 components in both groups. These 4 individual components of the metal-backed group showed similar migration patterns using model-based analysis (i.e., continuous migration in the second postoperative year). However, 2 additional metal-backed components showed continuous migration based on the model-based analysis. In both cases, the increase in MTPM in the second postoperative year was likely the result of a sudden increase in rotation about the longitudinal axis due to model-fit inaccuracies, as all other parameters remained stable (data not shown).

The other RSA parameters showed comparable between-group results when repeating the analysis with model-based migration values, except for translations along and rotations about the longitudinal (y-)axis, again, due to model-fit inaccuracies (Table III, see Supplementary data).

In this trial, 2 surgeons performed the surgeries. When stratifying the results by surgeon as performed in the post hoc sensitivity analysis of the original report, the observed difference in MTPM in favor of the all-polyethylene design was smaller and not statistically significant. Repeating this sensitivity analysis with the model-based measurements resulted in similar conclusions (Table IV, see Supplementary data).

Discussion

We investigated whether model-based RSA, utilizing a different reference origin as compared with marker-based RSA, would affect migration outcomes. By doing so, we were also able to quantify movements of the polyethylene insert within the locking mechanism of the Triathlon metal tray and explore the disadvantages of each RSA method. If the results differed systematically, pooling and comparing RSA data from studies using different RSA techniques would be impaired unless adjusted for the methods being used. However, if the insert moves with respect to the metal tray in modular TKA, then marker-based migration values of the tibial component in the transverse plane are unreliable[10], and likely produce random error that cannot be corrected for when comparing with model-based RSA studies. Now that an increasing number of RSA studies are available with long-term follow-up, meta-analysis becomes possible—but one must ascertain pooling of data is justified when different RSA methods have been used.

Our study demonstrated systematic differences in translations but not rotations between model-based RSA and marker-based RSA. These differences are caused by the difference in reference origin that is used for migration calculation[7]. As compared with the tibia 3D surface model, the origin in the center of the polyethylene markers overestimated the model-based transverse, longitudinal, and sagittal translations of the tibial component by 29%, 7%, and 26%, respectively. Correcting for this proportional bias, by using a factor or by using the same reference coordinate system in both analysis methods, resulted in nearly identical translations between model-based and marker-based analysis. For the rotations and MTPM values, the limits of agreement between marker-based and model-based RSA were larger because of the reduced precision of model-based rotations, particularly about the longitudinal axis. This is known and due to the relatively round, symmetrical shape of the tibial component in the transverse plane[4]. Still, the limits of agreement between methods were within ± 0.5 mm and ± 0.8° and conclusions on the primary outcome of the RCT regarding group differences in MTPM remained unchanged. Furthermore, we found no evidence for the presence of insert micromotion and excluded this as a cause of unreliable marker-based migration measurements for the modular Triathlon TKA system. For the individual patient, however, use of a different method may result in substantial differences due to various types of measurement error (e.g., marker occlusion and model-fit inaccuracies). Therefore, one must not put too much weight on strict migration thresholds in individual patients (e.g., 0.2 mm of MTPM migration in the second postoperative year).

Our findings are in line with an earlier comparison between marker-based and model-based RSA[7]. However, in that study, among other methodological differences, a uniplanar RSA setup was used resulting in marked differences in accuracy between "in-plane" and "out-of-plane" translations and rotations. In the present study we used a biplanar technique, and we did not find such a dichotomy in accuracy. Nevertheless, our findings further support their conclusion that model-based RSA can be used interchangeably with marker-based RSA, at least for the Triathlon TKA, provided that the same reference origin is used or corrected for using a factor when analyzing translations.

Previous studies evaluating insert micromotion relative to the metal tray in modular TKAs found small movements in Nuffield fixed-bearing TKAs (Corin Medical Ltd., UK)[9] and NexGen fixed-bearing TKAs (Zimmer, USA)[16]. In the latter study, these movements were closely examined and found to be greater in the transverse plane, which corresponds to the polyethylene–metal tray interface[17]. This contrasts with our results and may be explained by the different designs of the locking mechanisms that were used. In a recent retrieval study of Łapaj *et al.*[11], backside damage as a result of abrasion following micromotion of the polyethylene was found in designs with dovetail locking mechanisms, especially in the NexGen trays. Contrarily, they found no evidence for abrasion in the Triathlon knees owing to the full peripheral capture locking mechanism. Furthermore, the anti-rotational central island of the Triathlon design has been shown to effectively reduce micromotion to a minimum for a given reacted torque as compared with other TKA designs, including NexGen[18], although this mechanical study was performed by the research and development department of Stryker. It should be noted, however, that random error as a result of the reduced precision of model-based RSA limits firm conclusions on the presence of (longitudinal) rotations of the polyethylene within the locking mechanism. Nevertheless, the found translations were minimal and all outliers were found to be caused by polyethylene marker instability or occlusion, thus unlikely to be the result of micromotion in the polyethylene–metal tray interface.

A limitation of this study is that we compared the results of only one tibial component design. As the precision of model-based RSA depends on the shape and accuracy of the fitted model[5], differences between marker-based and model-based RSA results may be smaller or larger depending on the TKA design and also depending on the location of the prosthesis markers, either in the insert, or attached to the metal tibial component.

In summary, systematic differences in translations between marker-based and model-based RSA analysis disappeared when adjusted for the different reference origins being used for migration calculations. Micromotions of the polyethylene insert within the Triathlon metal tray were at most negligibly small. Mean migration results of model-based and marker-based measurements were comparable between groups when using the same reference origin, even though migration patterns of individual patients may differ between RSA methods due to various types of measurement error.

Note: the authors are grateful to Håkan Leijon for providing the marker-based RSA measurements and for his valuable help in performing the additional model-based RSA measurements.

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Supplementary data

Table III. RSA migration analysis of mean absolute translation and rotation along and about each orthogonal axis (log-values are back-transformed in the original scale)

	All-polyethylene mean (95% CI) (n = 29)	Metal-backed marker-based mean (95% CI) (n = 28)	Metal-backed model-based mean (95% CI) (n = 28)
Translation along transverse axis (mm)			
3 months	0.14 (0.09 to 0.20)	0.21 (0.15 to 0.27)	0.20 (0.15 to 0.27)
1 year	0.14 (0.09 to 0.20)	0.21 (0.16 to 0.27)	0.21 (0.16 to 0.27)
2 years	0.19 (0.14 to 0.25)	0.26 (0.20 to 0.32)	0.26 (0.20 to 0.32)
Translation along longitudinal axis (mm)			
3 months	0.12 (0.08 to 0.15)	0.11 (0.08 to 0.15)	0.12 (0.08 to 0.15)
1 year	0.13 (0.09 to 0.16)	0.13 (0.09 to 0.16)	0.15 (0.12 to 0.19)
2 years	0.10 (0.07 to 0.14)	0.15 (0.11 to 0.18)	0.17 (0.14 to 0.21)
Translation along sagittal axis (mm)			
3 months	0.19 (0.11 to 0.27)	0.22 (0.14 to 0.31)	0.24 (0.16 to 0.33)
1 year	0.24 (0.16 to 0.33)	0.38 (0.29 to 0.47)	0.38 (0.29 to 0.48)
2 years	0.25 (0.17 to 0.34)	0.44 (0.35 to 0.55)	0.43 (0.34 to 0.53)
Rotation about transverse axis (degrees)			
3 months	0.38 (0.27 to 0.49)	0.23 (0.14 to 0.34)	0.25 (0.15 to 0.35)
1 year	0.48 (0.37 to 0.61)	0.38 (0.27 to 0.49)	0.40 (0.30 to 0.52)
2 years	0.47 (0.36 to 0.59)	0.47 (0.35 to 0.59)	0.45 (0.33 to 0.57)
Rotation about longitudinal axis (degrees)			
3 months	0.18 (0.11 to 0.25)	0.19 (0.13 to 0.27)	0.29 (0.22 to 0.38)
1 year	0.20 (0.13 to 0.28)	0.24 (0.17 to 0.31)	0.38 (0.30 to 0.47)
2 years	0.20 (0.13 to 0.27)	0.28 (0.20 to 0.35)	0.41 (0.32 to 0.50)
Rotation about sagittal axis (degrees)			
3 months	0.26 (0.18 to 0.33)	0.24 (0.16 to 0.32)	0.21 (0.14 to 0.28)
1 year	0.32 (0.25 to 0.40)	0.28 (0.20 to 0.36)	0.24 (0.16 to 0.31)
2 years	0.34 (0.26 to 0.42)	0.33 (0.25 to 0.41)	0.25 (0.18 to 0.33)

Table IV. Adjusted RSA migration analysis of log-transformed maximum total point motion (logMTPM)

	Mean difference in logMTPM between groups (95% CI)	
	Marker-based [a]	**Model-based [b]**
Treatment effect (reference: all-polyethylene)		
3 months	-0.007 (-0.049 to 0.036)	0.013 (-0.031 to 0.057)
1 year	0.014 (-0.029 to 0.057)	0.025 (-0.019 to 0.069)
2 years	0.030 (-0.013 to 0.074)	0.038 (-0.007 to 0.083)
Sex effect (reference: male)		
3 months	0.008 (-0.043 to 0.045)	0.002 (-0.044 to 0.047)
1 year	0.017 (-0.027 to 0.062)	0.011 (-0.034 to 0.057)
2 years	0.026 (-0.020 to 0.068)	0.031 (-0.015 to 0.077)
Surgeon effect (reference: surgeon 1)		
3 months	0.083 (0.040 to 0.126)	0.077 (0.033 to 0.121)
1 year	0.113 (0.071 to 0.156)	0.099 (0.055 to 0.143)
2 years	0.132 (0.089 to 0.174)	0.114 (0.070 to 0.158)

[a] All-polyethylene (n = 29) *versus* marker-based metal-backed (n = 28).
[b] All-polyethylene (n = 29) *versus* model-based metal-backed (n = 28).

Appendix

Prosthesis migration

RSA is generally used to calculate prosthesis migration, defined as the change in position and orientation of a prosthesis with respect to the bone[1, 2]. Tantalum markers inserted into the bone and added to the prosthesis define landmarks that are used for accurate calculations. In Model-based RSA, the prosthesis itself is used as a marker, making prosthesis markers obsolete. By matching the virtual projections of a 3D surface model of the prosthesis with the detected roentgen projections of the prosthesis, the position and orientation of the prosthesis is calculated[3]. First step in migration calculation is the landmark transform that aligns the bone markers in the follow-up moment (t1) with the bone markers in the reference moment (t0)[2]. This removes the "patient movement" between the different RSA acquisition moments (Figure A1).

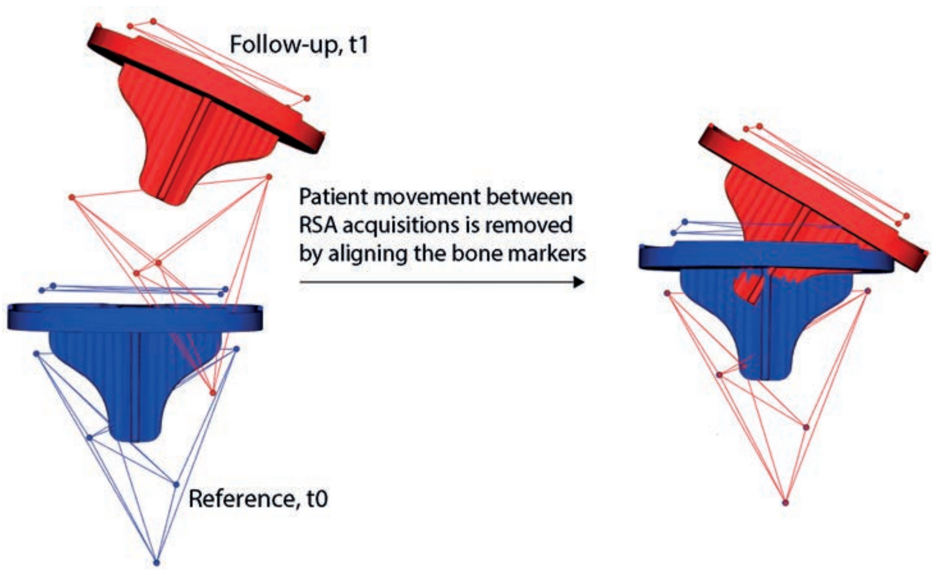

Figure A1. Transformation of the follow-up bone markers in the follow-up moment (t1) to the bone markers in the reference moment (t0) is performed (note that, in this example, the prosthesis migration is exaggerated).

The second step is the calculation of the change in position and orientation of the prosthesis between the reference moment and the follow-up moment. This change in position and orientation is thus relative to the bone markers.

In routine RSA calculations migration is expressed in a coordinate system that has its origin in the geometric center of either the prosthesis 3D surface model, or the prosthesis markers, in the reference follow-up moment, and is aligned with the global coordinate system as defined by the calibration cage of the reference RSA examination[1, 2, 4]. We call this coordinate system the reference coordinate system. In RSA calculations, the translation is calculated for the reference origin (Figure A2).

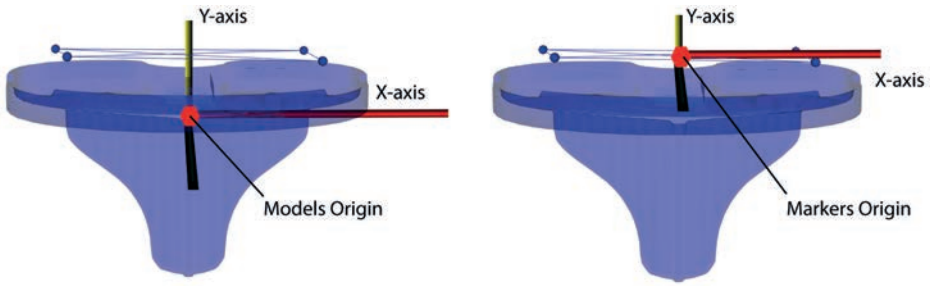

Figure A2. The **left side** of the figure shows the position of the reference origin of the 3D surface model (Model Origin) used for model-based RSA migration calculation and the **right side** of the figure shows the reference origin in the geometric center of the polyethylene markers (Markers Origin) used for marker-based RSA migration calculation. The X-axis is the transverse axis, the Y-axis is the longitudinal axis, and the Z-axis is the sagittal axis.

The calculated migration describes a transformation of the prosthesis from the reference moment to the follow-up moment and is expressed as a series of rotations about the 3 orthogonal axes and translations along these axes. The mathematics of RSA calculations are extensively described in Selvik[4] and Söderkvist and Wedin[5] and we will visually demonstrate the effect of changing the reference origin, without changing the orientation of the reference coordinate system, on the calculated migration (Figure A3).

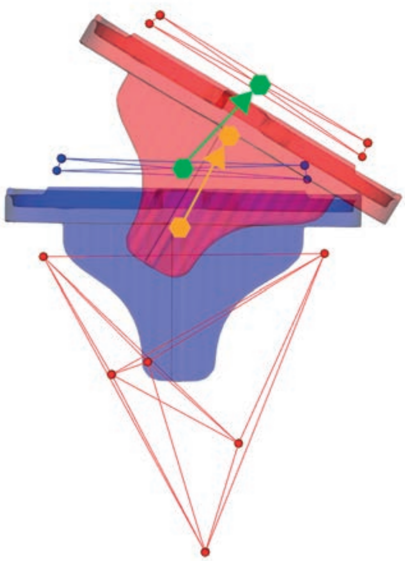

Figure A3. The prosthesis model migrated from t0 (blue) to t1 (red). The orange vector indicates the translation of the Model Origin in Model-based RSA. For the Markers Origin, translation is different (green vector).

Because the prosthesis in itself is a rigid structure (rigid body), the entire prosthesis rotates exactly the same from t0 to t1. Changing the reference origin position from "Model Origin" to "Markers Origin" and maintaining the orientation of the coordinate system does not affect the rotation of the prosthesis from t0 to t1. In Figure A3 the orange vector indicates the migration of the "Model Origin" in model-based RSA migration calculation and the green vector indicates the migration of the "Markers Origin" for marker-based RSA using polyethylene markers. The calculated translations along the orthogonal axes, for the Model and Markers reference origins, are different:

Calculated translations for the 2 reference origin positions (in simplified example):

Model Origin translation (x, y, z):	*10.00*	*20.00*	*0.00*
Markers Origin translation (x, y, z):	*16.50*	*18.25*	*0.00*

In Figure A3 these differences are reflected by different direction and length of the orange and green vectors.

In Figure A4 the effect of the position of the reference origin is shown in steps for the migration of the tibia prosthesis from t0 to t1. The position of the blue model after the Z-axis rotation differs slightly due to the difference of the reference origins: the upper row is for the Models Origin reference and the lower row is for the Markers Origin reference.

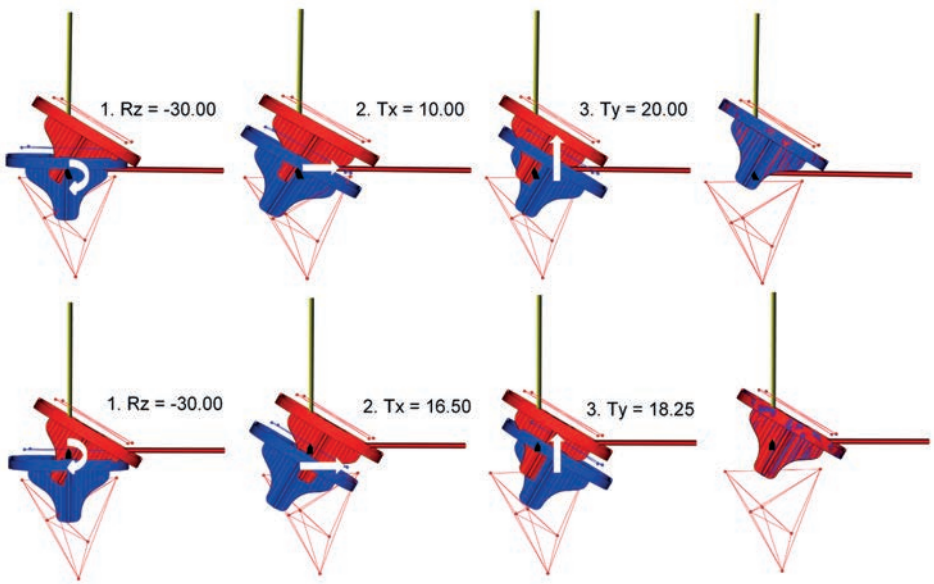

Figure A4. The **upper row** illustrates RSA migration of the tibia prosthesis from t0 (blue) to t1 (red) using the Model Origin: the model is rotated about the Z-axis (–30°), and translated along the X-axis (10 mm) and Y-axis (20 mm). The **lower row** illustrates RSA migration of the tibia prosthesis from t0 (blue) to t1 (red) using the Markers Origin: the model is rotated about the Z-axis (–30°), and translated along the X-axis (16.5 mm) and Y-axis (18.25 mm).

Point motion, maximum total point motion

For individual points on the prosthesis (e.g., markers attached to the prosthesis, virtual markers or 3D surface model points) the translation along each axis can be calculated from the x-, y-, and z-coordinates of these points at t1 and t0. The point motion can be calculated based on Pythagoras' theorem:

point motion = $\sqrt{(Tx2 + Ty2 + Tz2)}$

In Figure A5 the point motion of 4 virtual markers on the tibia prosthesis is shown.

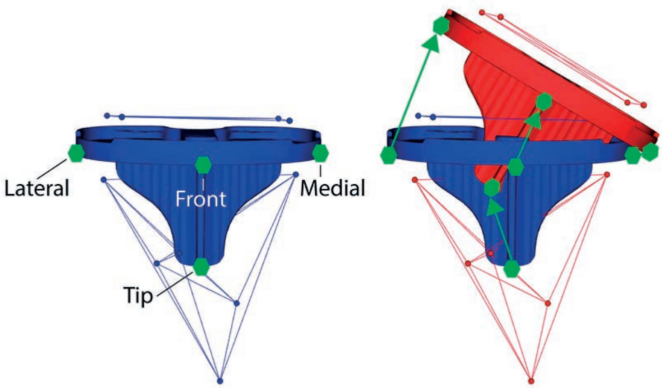

Figure A5. The change in position of 4 virtual markers on the tibia prosthesis model from t0 (blue) to t1 (red)

The point motion of the virtual markers from Figure A5 is:

	x	y	z	Point motion (mm)
Front	10.41	19.89	0	22.45
Lateral	15.56	39.12	0	42.10
Medial	5.26	0.67	0	5.30
Tip	−6.15	24.33	0	25.09

The virtual marker with the largest point motion is the "Lateral" marker. The virtual marker with the smallest point motion is the "Medial" marker. In the example migration shown in this Appendix, the tibia model rotates approximately around the medial edge of the prosthesis. Virtual markers close to this "true" rotation point have small point motions, and virtual markers at larger distances from this true rotation point have larger point motions. Maximum total point motion (MTPM), which is frequently used to summarize the migration of a prosthesis, is the length of the translation vector of the marker or virtual marker in a rigid body that has the greatest migration. For model-based RSA, MTPM is the length of the translation vector of the point on the model that moved the most.

The difference between the x-, y-, and z-coordinates at t0 and t1 used to calculate point motion is independent of the selected reference origin. As a consequence, point motion, including MTPM, will not differ between migration calculations with different reference origins.

In summary

- The position of the reference coordinate system, used to describe prosthesis migration, has an effect on the calculated prosthesis translations but not on the prosthesis rotations.
- The translation of individual markers, virtual markers, or points on the 3D surface model are not affected by the position of the reference origin. Hence, MTPM is not affected by changing the reference origin.
- In general, it can be stated that the further away from the true point of rotation a (virtual) marker lies, the larger the calculated translations are. This also applies to the reference origin, as this is also a "point."
- Changing the orientation of the reference coordinate system (not demonstrated in this Appendix) does have an effect on the calculated translations and rotations of the prosthesis.
- Changing the orientation of the reference coordinate system does not affect the magnitude of individual point motion, but it does affect the direction of the point motion.

Appendix references

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7 The effect of coronal alignment on tibial component migration following total knee arthroplasty: a cohort study with long-term radiostereometric analysis results

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Abstract

Background — Recent short-term studies of total knee arthroplasty (TKA) have claimed improved clinical outcomes and implant survival when aiming to restore constitutional joint kinematics, as compared with neutral mechanical axis alignment. However, implant durability may be compromised when aligned in varus or valgus. With use of data pooled from 3 long-term radiostereometric analysis (RSA) studies, the aim of the present study was to assess the effects of coronal alignment on tibial component migration.

Methods — Coronal alignment parameters from full-leg radiographs were measured and the constitutional leg alignment was determined for each patient. We evaluated the effect of the postoperative hip-knee-ankle angle, relative to both the mechanical axis and the constitutional alignment, on tibial component migration. In-range knees were defined as within ± 3° of either the neutral mechanical axis or constitutional alignment of the patient. Analysis was performed with a linear mixed-effects model, corrected for study, age, sex, preoperative alignment, diagnosis, and body mass index.

Results — A total of 85 cemented TKAs were included, of which 3 were revised for aseptic loosening and another 4 were considered loose. The median follow-up was 11 years. No loose tibial components were observed in mechanically in-range knees, whereas all loose tibial components were out of range. Mechanically varus knees showed the highest mean migration (maximum total point motion) of 1.55 mm (95% confidence interval [CI], 1.16 to 2.01 mm) after 5 years, compared with 1.07 mm (95% CI, 0.63 to 1.64 mm) and 0.77 mm (95% CI, 0.53 to 1.06 mm) for valgus and in-range knees, respectively ($p < 0.001$). In contrast, looking at constitutional alignment, loose tibial components were found among both constitutionally in-range and out-of-range knees. Mixed-model analysis showed comparable migration among constitutionally in-range, more-in-varus, and more-in-valgus aligned knees.

Conclusions — Mechanically out-of-range alignment, especially mechanical varus, led to higher tibial component migration. However, matching the constitutional alignment of the patient did not preclude high implant migration. RSA trials randomizing different alignment techniques are needed to confirm the results of the present study.

Introduction

Achieving neutral coronal alignment of the lower limb during total knee arthroplasty (TKA) has historically been considered essential for optimal implant durability and functional outcomes. Surgeons therefore traditionally aim to align within a "safe zone" of ± 3° from the neutral mechanical axis. It has been shown, however, that within the general population, 32% of men and 17% of women have so-called constitutional varus alignment at the end of skeletal growth[1]. Forcing neutral alignment during TKA in those patients would be undesirable and would necessitate soft-tissue releases[2], which might partly explain the large percentage (18% to 54%) of patients who are not fully satisfied following TKA[3-5]. Several studies found that leaving residual varus alignment in those knees results in better clinical scores without compromising implant survivorship[6-8]. Some authors have therefore advocated the use of an alternative alignment technique called kinematic alignment, the aim of which is to restore the knee to the pre-arthritic state rather than aiming for a standard neutral position[9-12].

If surgeons are not aiming for neutral alignment and instead aim to align to the pre-arthritic state of the knee, many prostheses will be placed in a varus or valgus position, given the alignment distribution in the general population[1]. However, concerns have been raised regarding the effect of intentionally aligning in varus or valgus on long-term implant survival, as the implants are designed for neutral mechanical alignment[13]. Several studies have shown increased contact stresses on the medial side in knees aligned in varus and increased ligament forces in knees aligned in valgus, resulting in varus knees failing more often as a result of medial tibial collapse and valgus knees failing more often as a result of ligamentous instability[14-18]. Recent studies, however, did not demonstrate superior 15 to 20-year survivorship of neutrally aligned knees compared with knees aligned in >3° of varus or valgus[19, 20], which, together with high dissatisfaction rates after TKA and the popularity surrounding kinematic alignment, challenges the previously held beliefs about the optimal coronal alignment strategy[21].

Numerous biomechanical, finite-element, and clinical studies have evaluated the effect of coronal alignment on contact forces, bone strains, clinical outcomes, and survivorship[22-26]. Until recently, none of those studies have included radiostereometric analysis (RSA) as an outcome measure. Because RSA is a highly accurate method to quantify implant motion in vivo, it is generally used to evaluate implant migration and predict the risk of loosening while exposing only small numbers of patients to experimental prosthesis designs or surgical techniques[27, 28]. The aim of the present study was to specifically evaluate the effect of postoperative coronal alignment, relative to both the mechanical axis and the constitutional alignment, on tibial component migration with use of pooled long-term RSA data. We hypothesized that TKAs aligned in-range with the mechanical axis would display the lowest migration as compared with varus or valgus-aligned TKAs, whereas knees aligned in-range relative to the constitutional alignment of the patient would not display less migration because of the increased stress and strain experienced by knees placed in mechanical varus or valgus.

Materials and methods

Study design

Data for the patients in this study were pooled from 3 individual studies, including 1 that is currently unpublished, conducted at a single academic center from 2002 to 2010 to evaluate the implant migration of new, cemented TKA designs with use of RSA[29, 30]. All patients continued to undergo follow-up, including RSA measurements, to assess long-term migration. Each of the 3 studies has been approved by the local ethics committee, and approval for pooling of long-term follow-up data was waived by the same committee for the present study. Because of the poor ability to assess limb alignment from short views of the knee[31], patients were only included if both preoperative and postoperative full-leg radiographs were available.

The full-leg radiographs were made according to a standardized protocol, as described by Moreland *et al.*[32], with the patient in a standing position with the patellae facing forward and the x-ray beam centered on the knee. After 2006, digital radiographs were made utilizing similar positioning (centered on the knee) and distance to the tube (350 cm) as compared with the analogue radiographs made prior to 2006. The full-leg radiographs were not made at fixed time points across studies; the median time of assessment was 1 month preoperatively and 6 months postoperatively. Coronal alignment parameters, including the hip-knee-ankle angle (HKA), the mechanical medial proximal tibial angle, and the mechanical lateral distal femoral angle, were digitally measured twice (in a blinded fashion with a 2-week interval) for all subjects by a single observer according to a strict protocol to define the center of the femoral head, femoral notch, tibial spines, and the talus[32]. A second observer measured a randomized set of 40 radiographs according to the same protocol. Previous studies have demonstrated excellent intraobserver and interobserver reliability using this methodology, with intraclass correlation coefficients (ICCs) of >0.90[33, 34]. In the present study, the intraobserver ICCs for HKA, mechanical medial proximal tibial angle, and mechanical lateral distal femoral angle were 0.98, 0.97, and 0.97, respectively, and the interobserver ICCs were 0.97, 0.98, and 0.92, respectively. To determine the constitutional alignment of the patient, ideally, a full-leg radiograph is made directly after the end of skeletal growth[1]. Because such radiographs were not available for obvious reasons, the constitutional HKA was estimated with use of the mechanical medial proximal tibial angle and the mechanical lateral distal femoral angle; that is, ignoring the degenerative changes within the joint. However, severe degenerative changes might influence the validity of this method, as osteoarthritis is characterized by loss of cartilage, joint space narrowing, and bone attrition in varying degrees. Thus, to test if increasing deformity compromised estimation of the constitutional HKA, the estimated constitutional HKA of 21 patients who had full-leg radiographs available at both "early-stage" osteoarthritis (with an Ahlbäck grade of I or II)[35] and "end-stage" osteoarthritis (Ahlbäck grade III to V) was compared by a single assessor in a blinded fashion with a 2-week interval between measurements. Despite progressive degeneration resulting in more varus or valgus alignment (with a mean time between radiographs of 34 months and a mean absolute difference ± standard deviation [SD] in HKA of 2.6° ± 2.3°), the estimated constitutional HKA was comparable between measurements, with a mean difference of 0.6° ± 1.0°, resulting in an ICC of 0.94.

RSA measurements were made with use of reverse-engineered models in Model-based RSA[36] (version 4; RSAcore; Leiden University Medical Center). The first postoperative RSA examination served as the reference for the migration measurements; subsequent examinations were conducted at 3 months, 6 months, and 1 year postoperatively, and annually thereafter. Analysis was in accordance with the RSA guidelines[37].

Statistical analysis

Mean values and SDs are presented for measured variables; point estimates are provided including the 95% confidence interval (CI). In-range knees were defined as within 3° of either the mechanical axis or preoperative constitutional HKA alignment. The effect of the postoperative HKA, with respect to both the mechanical axis and constitutional alignment, on tibial component migration was evaluated with use of linear mixed-effects model analysis. This method ensured that the correlation of measurements performed on the same subject were taken into account and enabled inclusion of all patients in the analysis, while effectively dealing with missing data[38, 39]. Fixed factors were HKA group (in-range, valgus, and varus), position of the tibial and femoral components, time, and the interaction of HKA group with time; participants were included as a random factor, and adjustments were made for study, age, sex, preoperative alignment, diagnosis, and body mass index (BMI) by including these variables as covariates. A compound symmetry covariance structure was assumed. The interaction term was included to investigate time-varying mean differences. Differences between groups were evaluated as an overall effect over 5 years of follow-up to safeguard against multiple testing at each follow-up; 5 years was chosen to avoid the observed loss to follow-up of patients beyond 5 years affecting model fit and statistical power. The primary outcome of tibial component migration was the maximum total point motion, which is the length of the translation vector of the point on the tibial component that has moved most[37]. Translations along and rotations about the 3 orthogonal axes were also analyzed (with use of absolute values) to assess differences in the magnitude of migration in each direction. RSA parameters were log-transformed during statistical modeling to obtain normally distributed variables, computed as $\log_{10}$(variable + 1). As a sensitivity analysis, the primary outcome analysis was repeated with stratification by preoperative alignment to assess whether conclusions would alter depending on the preoperative alignment category (neutral, valgus [HKA > 183°], or varus [HKA < 177°]). Then, subgroups were made to analyze primary outcome results of the constitutional alignment groups within each mechanical alignment category and vice versa to investigate whether mechanical or constitutional alignment was the decisive factor for migration. SPSS Statistics (version 24.0; IBM) was used for all analyses; significance was set at $p < 0.05$.

Results

Preoperative and postoperative full-leg radiographs were available for 88 of the 135 TKAs included in the 3 RSA studies. Three were excluded from analysis: 2 because the patients underwent a valgus-producing high tibial osteotomy prior to radiographic examination and 1 because there were too few matching RSA markers to perform migration measurements. Thus, a total of 85 cemented TKAs in 81 patients were available for analysis (Figure 1). Baseline demographic characteristics are described in Table I.

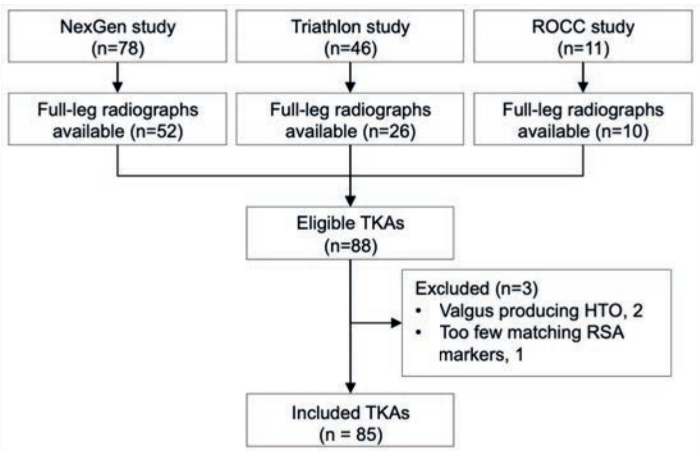

Figure 1. Flowchart illustrating the patient inclusion and exclusion of the 3 studies that comprised the present study. HTO = high tibial osteotomy.

During follow-up, 7 tibial components were considered loose on the basis of clinical evaluation and radiographic findings, of which 3 were revised for aseptic loosening and 4 were not yet revised at the request of the patient (Table II). One other revision procedure was performed for instability and malposition of components. The median follow-up was 11 years (95% CI, 10.2 to 11.8 years). The median number of valid RSA measurements per TKA was 9 (range, 2 to 15). For the 85 TKAs included in the analysis, the distribution of the preoperative HKA, the estimated constitutional HKA, and the postoperative HKA are shown in Figure 2.

Table I. Baseline demographic characteristics

	Stable (N = 78 TKAs)	Loose (N = 7 TKAs)	P Value*
Age† *(yr)*	68.7 ± 10.5	67.1 ± 10.7	0.706
BMI† *(kg/m²)*	28.3 ± 5.4	28.8 ± 5.8	0.841
Female sex‡	63 (81)	6 (86)	1.0
Diagnosis‡			0.274
Osteoarthritis	48 (62)	3 (43)	
Rheumatoid arthritis	27 (35)	3 (43)	
Posttraumatic OA	3 (4)	1 (14)	
Ahlbäck grade‡			0.326
I	1 (1)	1 (14)	
II	33 (42)	3 (43)	
III	37 (47)	3 (43)	
IV	7 (9)	0 (0)	
ASA classification‡			1.0
I	9 (12)	1 (14)	
II	52 (67)	5 (71)	
III	17 (22)	1 (14)	
Prosthesis type‡			0.141
NexGen (Zimmer)	49 (63)	2 (29)	
ROCC (Biomet)	8 (10)	1 (14)	
Triathlon (Stryker)	21(27)	4 (57)	
Bearing type‡			0.698
Fixed-bearing	43 (55)	3 (43)	
Mobile-bearing	35 (45)	4 (57)	

*P values were calculated with the Fisher exact test for qualitative variables and ANOVA for continuous variables. †The values are given as the mean ± SD. ‡The values are given as the number of TKAs, with the percentage of TKAs in that column in parentheses. ASA = American Society of Anesthesiologists, OA = osteoarthritis.

During follow-up, 7 tibial components were considered loose on the basis of clinical evaluation and radiographic findings, of which 3 were revised for aseptic loosening and 4 were not yet revised at the request of the patient (Table II). One other revision procedure was performed for instability and malposition of components. The median follow-up was 11 years (95% CI, 10.2 to 11.8 years). The median number of valid RSA measurements per TKA was 9 (range, 2 to 15). For the 85 TKAs included in the analysis, the distribution of the preoperative HKA, the estimated constitutional HKA, and the postoperative HKA are shown in Figure 2.

Mechanical alignment migration results

A total of 47 knees were mechanically aligned in-range (i.e., HKA of 177° to 183°), 29 in varus (HKA <177°), and 9 in valgus (HKA >183°) (Figure 2). No loose tibial components were observed in knees aligned in-range, whereas loose components were identified in 6 varus-aligned knees and 1 valgus-aligned knee (Figure 3). Mixed-model analysis showed significant differences in mean migration over 5 years of follow-up among alignment groups ($p < 0.001$), with the highest tibial component migration observed in varus-aligned TKAs (mean maximum total point motion, 1.55 mm; 95% CI, 116 to 2.01 mm) compared with

Table II. Details of revised and loose cases*

	Preoperative Alignment (°)				Postoperative Alignment (°)				
Case	**mMPTA**	**mLDFA**	**HKA**	**Estimated Constitutional HKA**	**mMPTA**	**mLDFA**	**HKA**	**Latest Follow-up** *(mo)*	**Tibial Component Migration at Latest Follow-up** *(MTPM in mm)*
Revised 1 (NexGen FB)	88.6	86.5	181.2	182.1	85.7	89.4	176.1	24	7.4
Revised 2 (ROCC MB)	87.8	90.9	171.0	176.9	90.1	93.7	176.2	48	4.4
Revised 3 (Triathlon FB)	82.7	88.2	168.3	174.5	84.3	95.0	168.2	72	7.6
Loose 1 (Triathlon FB)	84.9	88.2	166.0	176.7	84.6	91.4	173.3	12	8.2
Loose 2 (Triathlon MB)	89.8	86.6	187.7	183.2	87.8	92.0	176.6	72	12.1
Loose 3 (NexGen MB)	88.9	81.8	184.9	187.1	89.8	85.9	183.4	48	6.4
Loose 4 (Triathlon MB)	85.1	90.3	172.8	174.8	90.7	93.3	176.1	84	2.9

*mMPTA = mechanical medial proximal tibial angle, mLDFA = mechanical lateral distal femoral angle, MTPM = maximum total point motion, FB = fixed-bearing, MB = mobile-bearing.

Table III. Analysis of RSA migration during 5 years of follow-up*

	Mechanical Alignment				Constitutional Alignment			
	In-Range (N = 47)	**Valgus (N = 9)**	**Varus (N = 29)**	**P Value†**	**In-Range (N = 36)**	**More-in-valgus (N = 11)**	**More-in-varus (N = 38)**	**P Value†**
Translations *(mm)*								
Transverse	0.14 (0.08 to 0.20)	0.16 (0.06 to 0.26)	0.23 (0.16 to 0.31)	0.156	0.17 (0.11 to 0.24)	0.16 (0.07 to 0.27)	0.19 (0.12 to 0.26)	0.991
Longitudinal	0.21 (0.10 to 0.32)	0.23 (0.06 to 0.43)	0.52 (0.37 to 0.68)	0.013	0.27 (0.16 to 0.40)	0.15 (−0.02 to 0.35)	0.43 (0.29 to 0.58)	0.886
Sagittal	0.23 (0.11 to 0.37)	0.35 (0.13 to 0.61)	0.45 (0.28 to 0.63)	0.026	0.35 (0.21 to 0.51)	0.13 (−0.06 to 0.36)	0.40 (0.24 to 0.58)	0.837
Rotations (°)								
Transverse	0.43 (0.24 to 0.66)	0.76 (0.38 to 1.24)	0.57 (0.32 to 0.85)	0.056	0.56 (0.34 to 0.82)	0.32 (0.02 to 0.70)	0.66 (0.41 to 0.95)	0.946
Longitudinal	0.33 (0.20 to 0.47)	0.39 (0.17 to 0.66)	0.79 (0.58 to 1.02)	0.001	0.51 (0.36 to 0.69)	0.27 (0.06 to 0.54)	0.52 (0.36 to 0.71)	0.908
Sagittal	0.28 (0.16 to 0.42)	0.36 (0.15 to 0.60)	0.63 (0.46 to 0.83)	<0.001	0.40 (0.26 to 0.56)	0.37 (0.15 to 0.64)	0.47 (0.31 to 0.65)	0.997
MTPM *(mm)*	0.77 (0.53 to 1.06)	1.07 (0.63 to 1.64)	1.55 (1.16 to 2.01)	<0.001	1.11 (0.81 to 1.46)	0.67 (0.29 to 1.15)	1.23 (0.89 to 1.63)	0.990

*The values are given as the mean after 5 years of follow-up, with the 95% CI in parentheses; values are back-transformed in the original scale in millimeters or degrees. MTPM = maximum total point motion. †The p values indicate testing for overall changing effects with time over 5 years of follow-up.

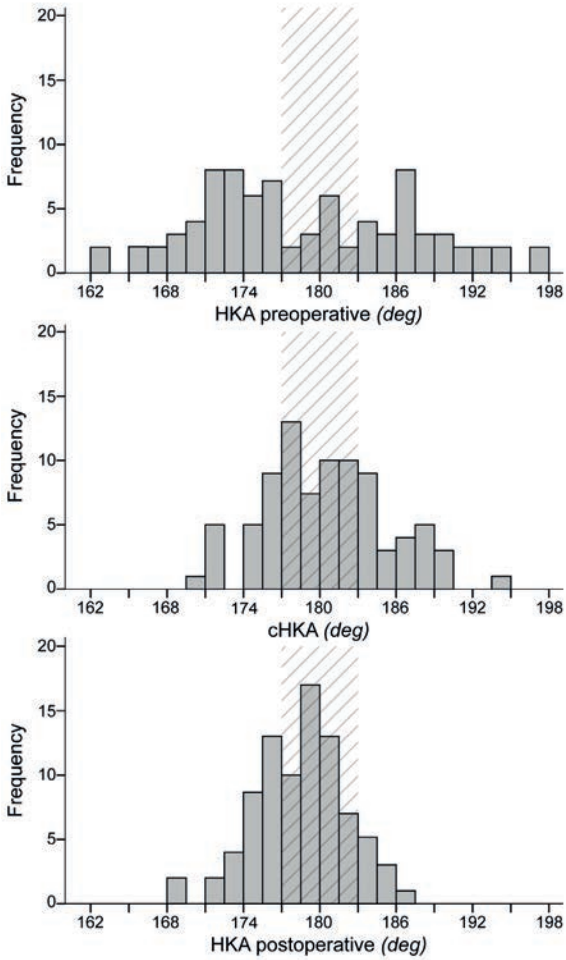

Figure 2. Histograms showing **(top)** measured preoperative HKA, **(middle)** estimated constitutional HKA (cHKA), and **(bottom)** measured postoperative HKA. Shaded area is within ±3° of the neutral mechanical axis, and values larger than 180° indicate valgus alignment.

valgus-aligned (1.07 mm; 95% CI, 0.63 to 1.64 mm) and in-range knees (0.77 mm; 95% CI, 0.53 to 1.06 mm) (Figure 4-A and Table III). In contrast to overall limb alignment, the individual orientations of the tibial and femoral components did not have a significant effect on migration. Significant differences were observed in longitudinal translation (i.e., subsidence; $p = 0.013$), sagittal translation (i.e., anterior/posterior translation; $p = 0.026$), longitudinal rotation (i.e., internal/external rotation; $p = 0.001$), and sagittal rotation (i.e., varus/valgus rotation; $p < 0.001$) (Table III). Repeating the primary outcome analysis within separate strata of preoperative alignment produced similar results, with the highest migration values in varus-aligned TKAs in each stratum, although the differences observed in the group of preoperatively neutral TKAs failed to reach significance (Table IV).

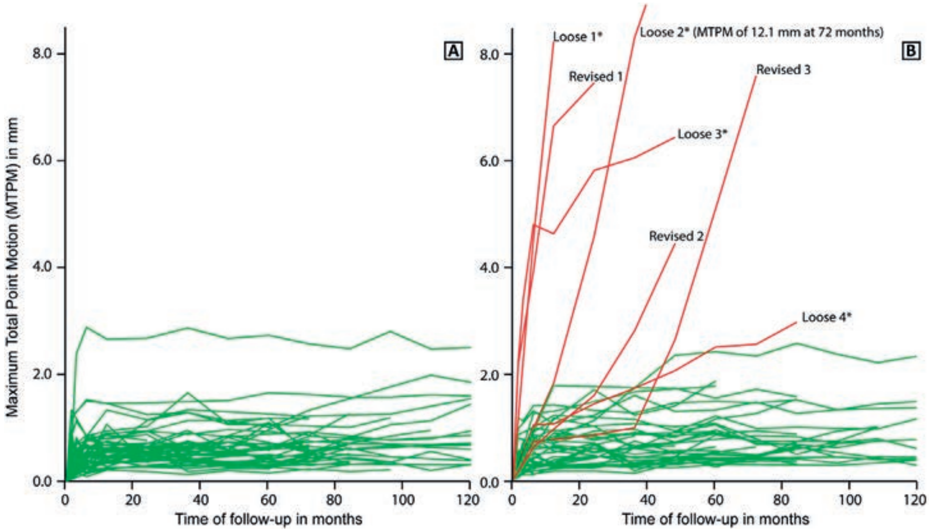

Figure 3. RSA data showing the maximum total point motion of individual patients over 10 years of follow-up, divided into 2 groups by postoperative alignment relative to the mechanical axis. **Figure 3-A** Components with a postoperative alignment in-range with the mechanical axis (HKA of 177° to 183°). **Figure 3-B** Components with out-of-range alignment (HKA of >183° [valgus] or <177° [varus]). *Implant loose but not (yet) revised.

Constitutional alignment migration results

Thirty-six knees were aligned within ±3° of the constitutional alignment of the patient (i.e., in-range), 38 in >3° of varus, and 11 in >3° of valgus. Loose components were observed among both constitutionally in-range and out-of-range knees (Figure 5). Mixed-model analysis showed comparable tibial component migration (in all directions) among constitutionally in-range, "more-in-valgus," and "more-in-varus" knees during the first 5 years of follow-up (Figure 4-B and Table III). Repeating the analysis within separate strata of preoperative alignment produced similar results (Table IV).

In subgroup analysis, mechanical alignment appeared to be the major determinant for migration, with the highest migration values observed in mechanically varus-aligned TKAs within each constitutional alignment category, whereas no significant differences were observed among any constitutional alignment subgroup across mechanical alignment categories (Table V).

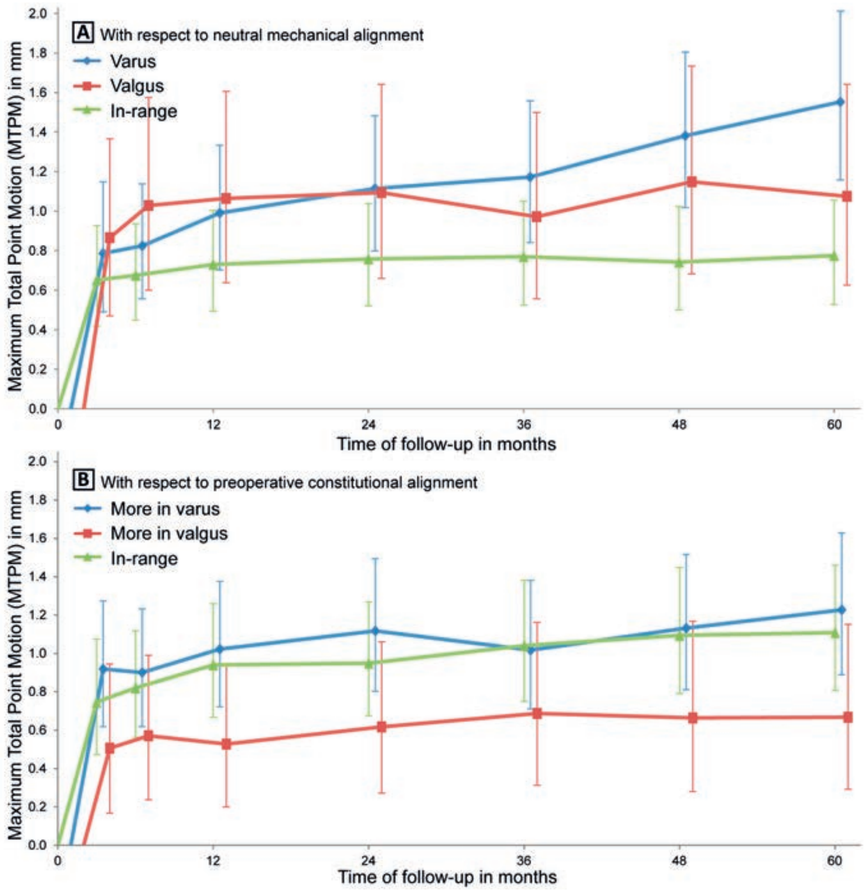

Figure 4. RSA data analyzed by alignment group during the first 5 years of follow-up. Values are back-transformed in the original scale in mm. **Figure 4-A** The mean maximum total point motion and 95% CI across alignment groups according to the postoperative mechanical alignment (in-range HKA, 177° to 183°; varus, <177°; and valgus, >183°). **Figure 4-B** The mean maximum total point motion and 95% CI across alignment groups according to the constitutional alignment of the patient (in-range HKA, within ±3°; and out of range, >3° varus or valgus deviation).

Table IV. Effect of postoperative coronal alignment on tibial component migration stratified by preoperative alignment*

	Mechanical Alignment				Constitutional Alignment			
	In-range	**Valgus**	**Varus**	**P Value†**	**In-range**	**More-in-valgus**	**More-in-varus**	**P Value†**
Preoperative Alignment								
Neutral (177° to 183°)	0.81 (0.44 to 1.28); n = 8	0.93 (0.03 to 2.60); n = 1	1.48 (0.79 to 2.44); n = 4	0.107	0.91 (0.52 to 1.38); n = 9	0.93 (0.01 to 2.66); n = 1	1.35 (0.58 to 2.48); n = 3	0.246
Valgus (>183°)	0.57 (0.34 to 0.85); n = 19	1.13 (0.60 to 1.83); n = 6	1.43 (0.77 to 2.34); n = 5	<0.001	0.68 (0.27 to 1.22); n = 7	No estimate; n = 0	0.84 (0.56 to 1.16); n = 23	0.978
Varus (<177°)	0.66 (0.45 to 0.91); n = 20	0.77 (0.08 to 1.90); n = 2	1.35 (1.03 to 1.72); n = 20	0.013	1.00 (0.73 to 1.30); n = 20	0.73 (0.40 to 1.14); n = 10	1.09 (0.72 to 1.55); n = 12	0.736

*The values are given as the mean maximum total point motion (MTPM) after 5 years of follow-up, with the 95% CI in parentheses; n values indicate the number of knees. Values are back-transformed in the original scale in millimeters. †The p values indicate testing for overall changing effects with time over 5 years of follow-up.

Table V. Subgroup analysis of the effect of postoperative alignment on tibial component migration

	Constitutional Alignment			
	In-range	More-in-valgus	More-in-varus	P Value[†]
Mechanical alignment*				
In-range	0.71 (0.56 to 0.88); n = 25	0.68 (0.46 to 0.94); n = 6	0.54 (0.24 to 0.91); n = 16	0.716
Valgus	0.97 (0.44 to 1.70); n = 2	0.82 (0.49 to 1.22); n = 3	1.20 (0.42 to 2.40); n = 4	0.624
Varus	1.44 (1.09 to 1.84); n = 9	0.97 (0.52 to 1.56); n = 2	1.40 (0.93 to 1.97); n = 18	0.983
P value[‡]	<0.001	0.244	0.001	

*The values are given as the mean maximum total point motion after 5 years of follow-up, with the 95% CI in parentheses; n values indicate the number of knees. Values are back-transformed in the original scale in millimeters. [†]The p values in this column indicate testing for overall changing effects with time over 5 years of follow-up stratified by mechanical alignment. [‡]The p values in this row indicate testing for the overall changing effects with time over 5 years of follow-up stratified by constitutional alignment.

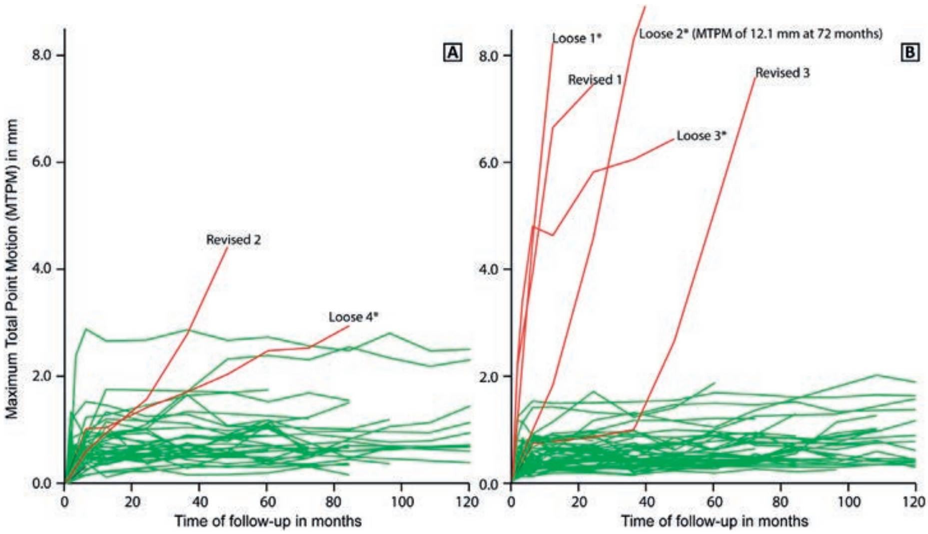

Figure 5. RSA data showing the maximum total point motion of individual patients over 10 years of follow-up, divided into 2 groups by postoperative alignment relative to constitutional alignment. **Figure 5-A** Components with a postoperative in-range alignment (HKA within ±3° of the constitutional alignment of the patient). **Figure 5-B** Components with out-of-range alignment (>3° varus or valgus deviation). *Implant loose but not (yet) revised.

Discussion

The results of the present study showed that mechanical varus and valgus alignment of the lower limb following cemented TKA leads to higher tibial component migration, especially in knees aligned in mechanical varus. Furthermore, loose tibial components were only observed in mechanically out-of-range TKAs, whereas loose components were observed in both constitutionally in-range and out-of-range TKAs, and no significant differences in migration were observed among TKAs aligned in-range, "more in valgus," and "more in varus" relative to the constitutional alignment of the patient. Notably, subgroup analysis revealed that within each constitutional alignment category, mean migration values were higher in components that were placed in mechanical varus compared with mechanically in-range TKAs. As hypothesized, matching the constitutional alignment of the patient did not preclude high migration, especially in mechanically varus-aligned TKAs.

Excessive early tibial component migration, as measured with RSA, has been shown to be predictive for late aseptic loosening[40, 41]. Consequently, patients at a high risk for late aseptic loosening can be identified with use of RSA even before symptoms occur. Because RSA is a highly accurate and an objective continuous outcome measure, we were able to study the effect of coronal alignment on late failure with use of migration as the outcome measure. This outcome measure, as opposed to revision data, is less subjective to competing risk factors such as death or the willingness of the patient or surgeon to revise, which both lead to an underestimation of the number of failed prostheses. On the other hand, as migration is only a proxy for clinical failure, some components with excessive migration may remain asymptomatic. In addition, only failure mechanisms associated with micromotion are predicted by RSA. These limitations notwithstanding, we were able to demonstrate marked differences between mechanically in-range and out-of-range TKAs in a relatively small cohort of patients, whereas larger-cohort studies that used revision data could not demonstrate improved survivorship of neutrally aligned knees[19, 20].

Recently, Teeter *et al.*[42] conducted another study using RSA to evaluate the effect of coronal alignment on tibial component migration. Although the authors found that greater tibial varus alignment was associated with greater tibial component migration, they did not find significant differences in migration between neutral and varus overall limb alignment; however, only 7 neutrally aligned and 6 varus-aligned knees were available for analysis. The results of the present study include a much larger group of patients and demonstrate that overall limb alignment significantly affected tibial component migration, supporting the findings of recent finite-element studies that showed adverse stresses and strains in varus aligned knees[17, 18]. Results of the finite-element studies and the present study conflict with those reported by Bonner *et al.*[19] and Abdel *et al.*[20], which challenged the need for neutral mechanical alignment, and highlight that methods to resist the stress and strain associated with mechanically out-of-range TKAs must be further investigated before alternative alignment techniques become widely adopted. Oussedik *et al.*[13] suggested that uncemented biological fixation may be more durable in less favorable mechanical bone and ligament conditions because of the greater capacity to adapt and remodel over time compared with cement fixation. Future studies with long-term migration data for uncemented TKAs may indicate whether a biological fixation is able to adapt to asymmetric loading conditions.

The present study had several limitations. First, we only assessed static coronal alignment. Several studies have shown inconsistencies between static alignment and dynamic kinematics, which may partly explain why some varus or valgus aligned TKAs show excellent long-term outcomes[2]. Second, we estimated constitutional alignment with use of full-leg radiographs made while varying degrees of degenerative changes were present, which may induce measurement error compared with a pre-morbid assessment; the latter, however, is often unavailable. Although comparable estimates were made in 21 patients assessed when they had early and end-stage osteoarthritis, the approach used in this study to assess constitutional alignment requires validation, preferably also in non-arthritic knees and patients with early-stage osteoarthritis. The use of the contralateral knee may be considered as an alternative method if one assumes constitutional alignment to be symmetrical and only if osteoarthritis is unilaterally present[42], which was not the case for the majority of patients in this study. Third, given the small number of TKAs available in the subgroup analyses, results should be interpreted with caution because of the risk of inadequate statistical power. Fourth, all included patients were managed with the intent to achieve neutral mechanical alignment, and thus the constitutional alignment analysis should not be interpreted as being the result of kinematically aligned TKAs—which may produce different outcomes because tibial varus in kinematically aligned TKA is often compensated for by valgus positioning of the femoral component, resulting in neutral overall limb alignment in the majority of patients[13, 43].

To conclude, tibial component migration significantly differed between the mechanical alignment groups, with the highest level of migration observed in mechanically varus TKAs. In contrast, matching the constitutional alignment of the patient did not preclude high implant migration, especially in mechanically varus knees. RSA trials randomizing different alignment techniques are needed to confirm the results of this study.

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8

Risk factors for tibial component loosening: a meta-analysis of long-term follow-up RSA data

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Abstract

Background — Radiostereometric analysis (RSA) is a highly accurate tool to detect implant migration and predict loosening following total knee arthroplasty (TKA). However, little is known about the predisposing risk factors for implant migration, nor which migration profile should be considered physiological (i.e., merely part of an implant-settling phase) and which should be considered pathological (i.e., having a high probability for implant loosening). By pooling individual participant data from long-term follow-up RSA studies, we aimed to identify predisposing risk factors for tibial component loosening.

Methods — Individual data were collected for 630 patients from 11 RSA studies. The repeated measurements were analyzed with use of a linear mixed-effects model, determining the effect of age, sex, body mass index, diagnosis, preoperative and postoperative limb alignment, and prosthesis characteristics on tibial component migration over time, taking into account the clustering of patients within studies.

Results — High initial migration was found to result in early mechanical loosening in 18 cases (2.9%) and septic loosening in 2 cases (0.3%), whereas stabilization of high initial migration occurred in 17 cases (2.7%). Late loosening occurred in 13 cases (2.1%). All other 580 cases (92.1%) showed early stabilization and remained stable over time. Mixed-effects model analyses showed that for cemented prostheses, sex, diagnosis, and posterior cruciate ligament type had an effect on migration, but these differences were nonsignificant when analyzing migration from 3 months onwards. Uncemented prostheses aligned in varus showed more migration than neutrally and valgus-aligned TKAs ($p = 0.031$), and this difference increased over time ($p < 0.001$). Significantly higher migration was observed following uncemented TKA without an osseointegration-promoting surface ($p < 0.001$).

Conclusions — For cemented prostheses, increased migration during the first 3 postoperative months was observed for female patients, patients with rheumatoid arthritis, and patients who underwent a posterior-stabilized TKA. For uncemented prostheses, both postoperative varus alignment of the lower limb and the absence of an osseointegration-promoting surface significantly increased postoperative tibial component migration.

Introduction

Radiostereometric analysis (RSA) is a highly accurate tool to detect implant migration[1]. Early migration following total knee arthroplasty (TKA) is predictive for late loosening[2, 3]. Clinical RSA studies can play an important role in the stepwise introduction of new implants[4] and may lower the revision burden, as RSA-tested implants on average have had a lower 10-year rate of revision than implants that have not been tested with RSA[5]. Furthermore, RSA studies have given insight into differences in migration pattern between TKA designs and modes of fixation. For example, it is well known that on a group level, uncemented implants typically display a biphasic migration pattern with high initial migration before stabilization, as opposed to cemented implants showing only marginal initial migration[2, 6].

For the individual patient, however, little is known about predisposing risk factors for tibial component migration and which migration profile can be considered physiological (i.e.,merely part of an implant-settling phase) and which migration profile should be considered pathological (i.e., having a high probability for implant loosening). Some RSA studies have tested the effect of baseline characteristics such as sex and body mass index on migration[7-9]. However, most of the RSA studies of which we are aware were designed to analyze differences in implant migration between 2 groups of patients receiving a different type of implant. Attempts to find the effect of baseline characteristics on migration by performing additional "1-variable-at-a-time" subgroup analyses are therefore often underpowered[10]. By pooling individual participant data on total knee implant migration from multiple RSA studies, the statistical power is increased, thus enabling more valid subgroup analyses[11]. As such, we aimed to find distinct migration profiles and predisposing patient and implant-based risk factors for tibial component loosening.

Materials and Methods

Study Design

Individual data were collected from 11 long-term follow-up RSA studies, with a total of 668 patients identified who underwent TKA at 4 different surgical centers between 1994 and 2010. All studies were randomized controlled trials (RCTs) that compared implants of the same manufacturer within each study with either different fixation methods, different insert designs, or slight alterations in tibial component design (Table I). One study (by Henricson and Nilsson) was changed in design from an RCT to a comparison of 2 consecutive cohorts for logistical reasons[12]. All primary studies were approved by local ethics committees, and approval for the pooling of data was waived for the present study (entry no. P15.198).

Details of the RSA methods used were described in each of the individual studies (Table I). It is known that translations are systematically overestimated in marker-based RSA using polyethylene insert markers, as compared with model-based RSA, because of the different reference origin used for migration calculations[13]; thus, pooling translation data from studies using different RSA methods may not be justifiable. In contrast, maximum total point motion, which is the length of the translation vector of either the point on the tibial component (for model-based RSA) or the marker that moved the most, is not overestimated by 1 method compared with the other. Therefore, maximum total point motion was used as the outcome of interest in the present study. The radiographic examinations required for RSA were made within the first postoperative days and at 3 months, 6 months, 1 year, 2 years, 5 years, and 10 years postoperatively. Examinations were excluded if not adhering to the RSA guidelines[1].

Table I. Study characteristics*

	Implants	**Years of Inclusion**	**RSA Type**
Nieuwenhuijse (2013)[31]	Zimmer NexGen PS cemented (1) High Flex MB; (2) High Flex FB; (3) standard MB; (4) standard FB	2002-2006	Model-based
Pijls (2012)[26]	Howmedica Interax CR (1) cemented; (2) HA; (3) uncoated mesh-wire surface only	1994-1998	Marker-based (tibial component markers)
Pijls (2012)[32]	Howmedica Interax cemented (1) ISA CR MB; (2) PS FB	1998-2000	Marker-based (tibial component markers)
van Hamersveld (2017)[33]	Stryker Triathlon CR (1) cemented; (2) PA	2009-2010	Marker-based (insert markers)
van Hamersveld (2018)[34]	Stryker Triathlon PS cemented (1) FB; (2) MB	2008-2010	Model-based
van Hamersveld (2018)[14]	Stryker Triathlon CR uncemented (1) porous-coated only; (2) PA	2007-2008	Marker-based (insert markers)
Molt (2014)[35]	Stryker Triathlon cemented (1) CR; (2) PS	2007	Marker-based (insert markers)
Molt (2012)[36]	Stryker (1) Duracon CR cemented; (2) Triathlon CR cemented	2006	Marker-based (insert markers)
Molt (2014)[37]	Stryker Triathlon CR cemented (1) normal stem; (2) short stem	2008	Marker-based
Henricson (2016)[12]	Zimmer NexGen CR (1) cemented (2) uncemented monoblock Trabecular Metal (HP)	2003-2005	Marker-based (tibial component markers)
Nilsson (2006)[28]	Smith & Nephew Profix CR (1) HA; (2) HA with screws; (3) cemented	1997-2003	Marker-based (insert markers)

*PS = posterior-stabilized, MB = mobile-bearing, FB = fixed-bearing, HA = hydroxyapatite coating, CR = cruciate-retaining, PA = hydroxyapatite coating via peri-apatite technique, and HP = highly porous metal.

The repeated measurements of each patient were plotted in an attempt to find distinct migration profiles. Components were considered loose according to the RSA thresholds of continuous migration defined by Ryd et al. [3]. Under this definition, loose components could be divided into 2 groups, (1) high second-year migration (i.e., ≥0.2 mm of migration between 1 and 2 years postoperatively) followed by progressive migration (i.e., ≥0.1 mm of migration/year after the second year), and (2) stable at first (i.e., <0.2 mm of second-year migration) but with progressive migration after 2 years of follow-up. For the stable components, a cutoff value of 2.5 mm of translation (including the maximum total point motion) or 2.5° of rotation was set to differentiate between stable components with low migration values and components with high initial migration followed by stabilization. This cutoff value was based on findings in earlier studies that showed that uncemented implants without a biological mediator such as hydroxyapatite have an average of 2.1mmof migration without signs of loosening at 10 years postoperatively, whereas outliers with signs of loosening had >2.5 mm of migration[14].

Statistical Analysis

Linear mixed-effects models were used to determine the effect of implant and patient characteristics on implant migration, analyzed across all patients (irrespective of migration profile) but separately for cemented and uncemented components. Mixed-effects models were used because they deal effectively with missing values, ensure that the correlation of measurements performed on the same subject is taken into account, and lastly, to enable inclusion of all available patients in the analysis[15, 16]. Only variables that were measured in all of the individual studies were included in the mixed-effects model. Patients were included as a random factor. The baseline characteristics were added to the model as a fixed factor, as was the interaction between baseline characteristics and time. This interaction term was included to assess time-varying differences. For all analyses, the study itself was included as a covariate to account for clustering of patients. For the analyses of the uncemented components, implant surface type (i.e., uncemented implants with an osseointegration-promoting surface such as a hydroxyapatite coating or highly porous metal and uncemented implants with porous coating only) was added to the model as a covariate given the prolonged initial migration of implants without such a surface promoting osseointegration. The following fixed factors were also added to the model for all analyses: sex, diagnosis (i.e., osteoarthritis, secondary osteoarthritis, and rheumatoid arthritis), bearing type (i.e., fixed-bearing and mobile-bearing), posterior cruciate ligament status (i.e., cruciate-retaining and cruciate-sacrificing), body mass index (i.e., <25, 25 to 30, and >30 kg/m2), age (i.e., <60, 60 to 70, and >70 years), and preoperative and postoperative alignment (as measured in a standardized way with use of full-leg radiographs, with neutral defined as a hip-knee-ankle angle of 177° to 183°, varus as <177°, and valgus as >183°[17]). A compound symmetry covariance structure was assumed. The influence of the covariates on migration was analyzed as an overall effect over 5 years of follow-up because testing at multiple time points would have increased the risk of identifying spurious effects. Five years was chosen because there was loss to follow-up affecting model fit and statistical power after this time point. As maximum total point motion is a vector, it was log-transformed during statistical modeling to obtain a normally distributed variable. The postoperative RSA examination served as the reference for migration calculations. Uncemented tibial components have a so-called biphasic migration pattern that consists of the initial migration (i.e., settling phase) and the subsequent stabilization[14]. Stabilization generally occurs within the first few months. We therefore also assessed the influence of potential predisposing risk factors for migration after 3 months postoperatively. SPSS Statistics (version 24.0; IBM) was used for all analyses. Significance was set at $p < 0.05$.

Results

A total of 668 patients were included in the studies, of whom 38 were excluded because the available RSA data were based on <3 markers or were not available at all (Figure 1). Over the course of follow-up, a total of 26 tibial components were revised (6 for aseptic loosening, 12 for infection, and 8 for ligamentous instability, pain, or fracture). Another 25 showed continuous migration during long-term follow-up and thus were considered loose. Univariate analysis showed that patients with loose components more often had rheumatoid arthritis, which was significant for the cemented components. Furthermore, patients with loose uncemented components had a lower body mass index, and loosening occurred more often in uncemented implants without a hydroxyapatite coating or highly porous metal; in particular, the uncoated Interax (Howmedica) prosthesis showed a high percentage of loosening. None of the other recorded baseline characteristics were significantly different between stable and loose components in either cemented or uncemented TKAs (Table II).

Migration Patterns

Evaluation of migration patterns using the aforementioned cutoff values showed that there were 580 components (92.1%; 393 cemented, 187 uncemented) with low initial migration and no signs of progression over time. A total of 17 components (2.7%; 5 cemented, 12 uncemented) showed high initial migration followed by stabilization. Of those that were loose, 18 components (2.9%; 9 cemented, 9 uncemented) showed early loosening within 2 years, and 13 components (2.1%; 8 cemented, 5 uncemented) were stable in the first 2 postoperative years followed by late loosening. Another 2 components (0.3%; 1 cemented, 1 uncemented) had microbiologically confirmed septic loosening (Figure 2).

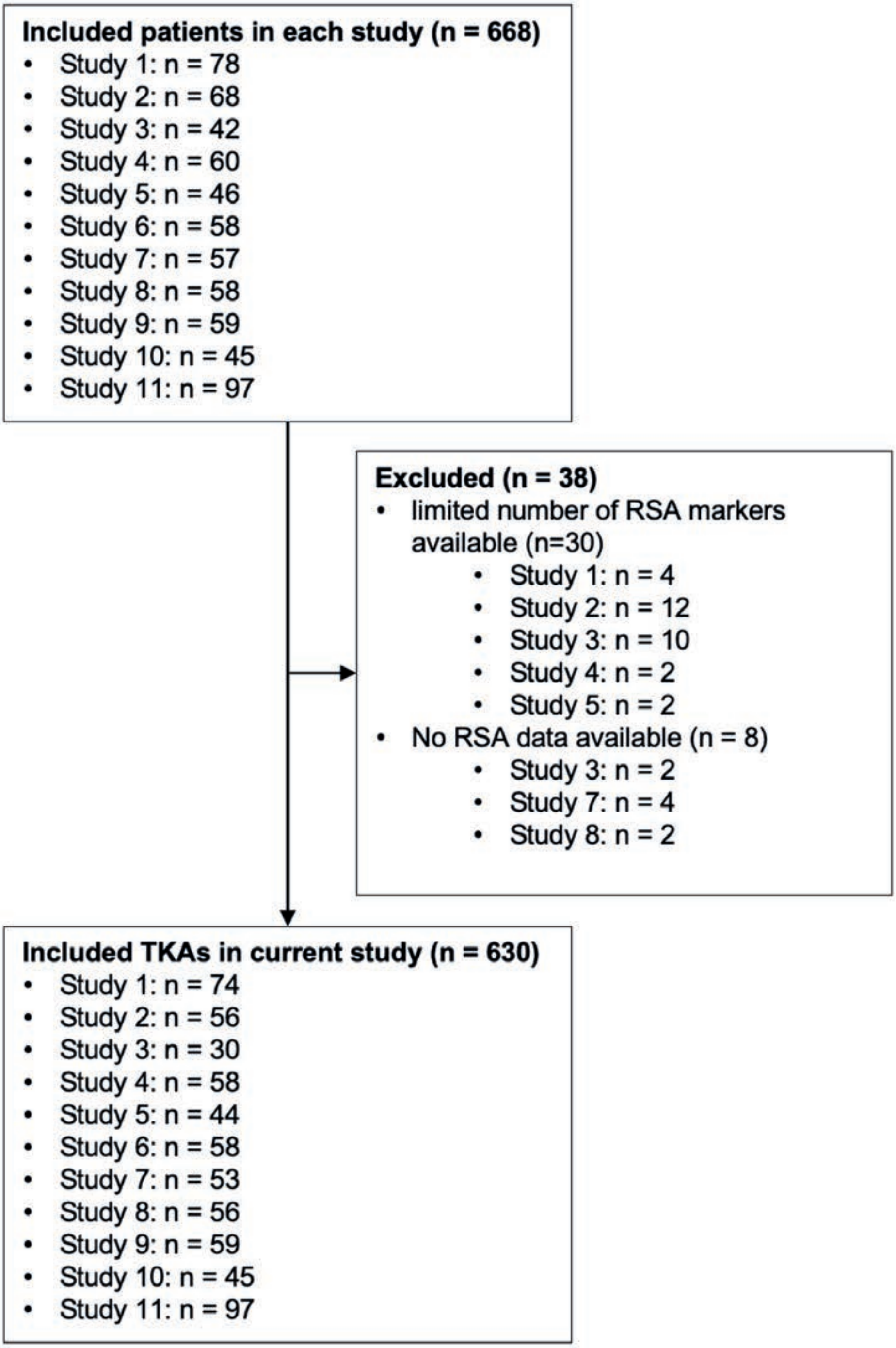


Figure 1. Flowchart showing patient inclusion and exclusion for each individual RCT included in the present study.

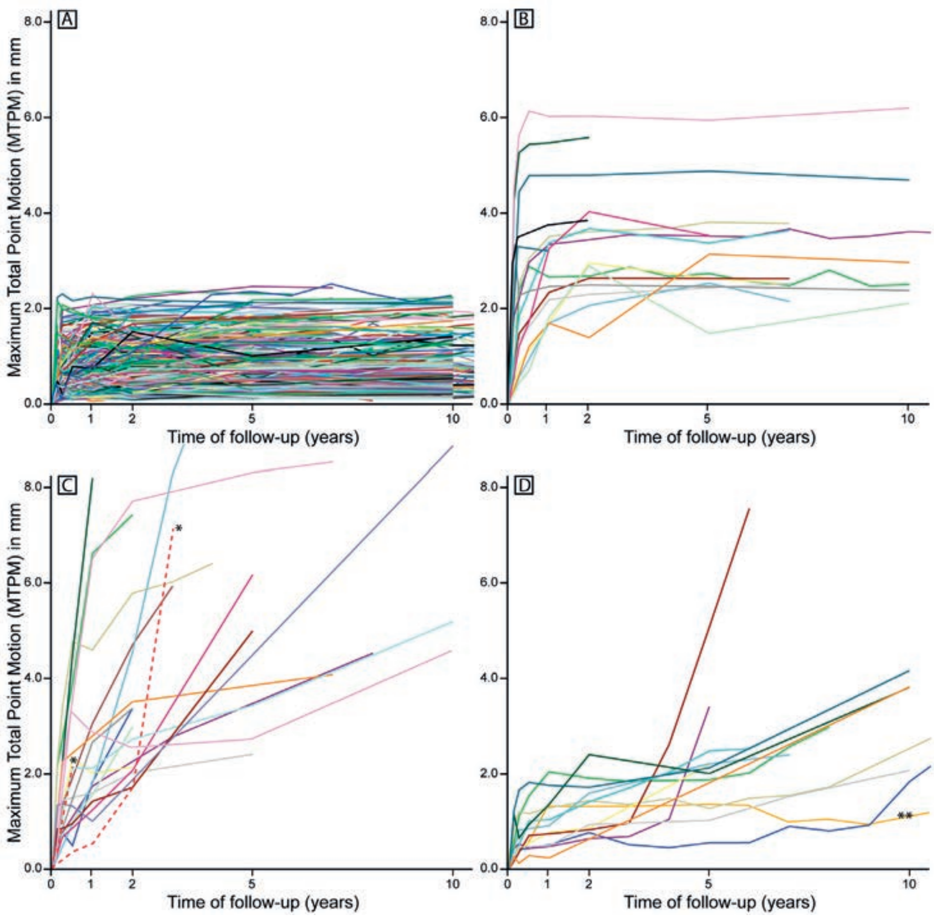
Table II. Baseline demographic characteristics*

	Cemented TKA			Uncemented TKA		
	Stable (N = 398)	Loose (N = 18)	P Value†	Stable (N = 199)	Loose (N = 15)	P Value†
Age‡ *(yr)*	65.6 ± 10.0	67.8 ± 9.1	0.355	61.2 ± 10.3	62.3 ± 10.4	0.691
BMI‡ *(kg/m²)*	28.5 ± 4.5	28.1 ± 4.8	0.705	28.6 ± 4.4	26.2 ± 4.2	0.046
Female sex	260 (65.3%)	13 (72.2%)	0.621	123 (61.8%)	10 (66.7%)	0.789
Diagnosis			0.034			0.081
OA	307 (77.1%)	10 (55.6%)		140 (70.4%)	7 (46.7%)	
Rheumatoid arthritis	73 (18.3%)	8 (44.4%)		41 (20.6%)	7 (46.7%)	
Posttraumatic OA	18 (4.5%)	0 (0.0%)		18 (9.0%)	1 (6.7%)	
Prosthesis type			0.941			0.020
Interax (Howmedica)	46 (11.6%)	1 (5.6%)		32 (16.1%)	7 (46.7%)	
NexGen (Zimmer)	90 (22.6%)	4 (22.2%)		25 (12.6%)	0 (0.0%)	
Duracon (Stryker)	26 (6.5%)	1 (5.6%)		—	—	
Triathlon (Stryker)	204 (51.3%)	10 (55.6%)		84 (42.2%)	3 (20.0%)	
Profix (Smith & Nephew)	32 (8.0%)	2 (11.1%)		58 (29.1%)	5 (33.3%)	
Bearing type			0.376			NA
Fixed-bearing	337 (84.7%)	13 (72.2%)		199 (100%)	15 (100%)	
Mobile-bearing	61 (15.3%)	5 (27.8%)		—	—	
PCL type			0.082			NA
Posterior-stabilized	153 (38.4%)	11 (61.1%)		199 (100%)	15 (100%)	
Cruciate-retaining	245 (61.6%)	7 (38.9%)		—	—	
Implant surface			NA			0.001
HA/HP	—	—		160 (80.4%)	6 (40.0%)	
Porous coating only	—	—		39 (19.6%)	9 (60.0%)	

*Values are given as the mean ± standard deviation or as the count with the percentage in parentheses. BMI = body mass index, OA = osteoarthritis, PCL = posterior cruciate ligament, NA = not applicable, HA = hydroxyapatite coating, and HP = highly porous metal. †P values were calculated with use of the Fisher exact test for qualitative variables and analysis of variance for continuous variables.

Effect of Patient and Implant-Based Characteristics on Implant Migration

For the cemented components, linear mixed-effects model analyses showed that 3 factors had a significant effect on migration over 5 years of follow-up, with increased migration following TKA observed in female patients (p = 0.029), in patients with rheumatoid arthritis (p = 0.047), and when a posterior-stabilized implant was utilized (p < 0.001) (Table III and Appendix Figure E-1). No other covariates showed a statistically significant or clinically relevant effect on migration. When analyzing migration from 3 months onwards, differences were smaller for all covariates and did not reach significance (Table IV).



Figures 2-A through 2-D. Spaghetti plots showing the 4 possible implant-migration profiles. **Figure 2-A** A total of 580 components showed low initial migration and were stable over time. **Figure 2-B** A total of 17 components showed high initial migration (>2.5 mm translation or 2.5° rotation in the first 2 years) but were stable thereafter. **Figure 2-C** A total of 18 components showed early signs of loosening with progressive migration. **Figure 2-D** A total of 13 components were stable at first but showed progressive migration thereafter. *Another 2 components (depicted in Figure 2-C) had microbiologically confirmed septic loosening. **Increased migration apparent after 12 years.

For the uncemented components, the postoperative alignment category had a significant effect on migration over 5 years of follow-up (Table III and Appendix Figure E-2). TKAs aligned in varus showed 1.71 mm of migration (95% confidence interval [CI], 1.41 to 2.05 mm), significantly more than valgus (1.21 mm; 95% CI, 0.97 to 1.48 mm) and neutrally aligned TKAs (1.24 mm; 95% CI, 1.08 to 1.41 mm) ($p = 0.031$). When analyzing migration from 3 months onwards, the effect of postoperative alignment was more evident ($p < 0.001$) (Figure 3, Table IV). There was also a marked difference in migration between uncemented components with and without an osseointegration-promoting surface (Figure 4-A, Table III).

Table III. Migration analysis from immediately postoperatively to 5 years postoperatively

	Cemented TKA (N = 416)		Uncemented TKA (N = 214)	
	Mean MTPM† (95% CI)	**P Value‡**	**Mean MTPM† (95% CI)**	**P Value‡**
Sex		0.029		0.456
Male	0.63 (0.56 to 0.70)		1.27 (1.09 to 1.47)	
Female	0.75 (0.69 to 0.80)		1.26 (1.11 to 1.42)	
Diagnosis		0.047		0.306
OA	0.69 (0.64 to 0.75)		1.36 (1.19 to 1.56)	
Rheumatoid arthritis	0.79 (0.68 to 0.90)		1.04 (0.82 to 1.30)	
Posttraumatic OA	0.59 (0.41 to 0.79)		1.24 (0.92 to 1.61)	
Bearing type		0.795		NA
Fixed-bearing	0.71 (0.67 to 0.76)		1.26 (1.13 to 1.40)	
Mobile-bearing	0.67 (0.56 to 0.79)		No data	
PCL type		<0.001		NA
Posterior-stabilized	0.75 (0.64 to 0.87)		No data	
Cruciate-retaining	0.69 (0.62 to 0.75)		1.26 (1.13 to 1.40)	
BMI		0.843		0.915
<25 kg/m^2	0.71 (0.63 to 0.81)		1.25 (1.04 to 1.48)	
25-30 kg/m^2	0.71 (0.65 to 0.78)		1.30 (1.12 to 1.48)	
>30 kg/m^2	0.69 (0.63 to 0.77)		1.24 (1.04 to 1.45)	
Age		0.147		0.735
<60 yr	0.69 (0.61 to 0.77)		1.20 (1.03 to 1.39)	
60-70 yr	0.73 (0.66 to 0.81)		1.32 (1.10 to 1.55)	
>70 yr	0.69 (0.62 to 0.77)		1.32 (1.08 to 1.59)	
Preoperative alignment		0.565		0.571
Neutral	0.73 (0.64 to 0.82)		1.25 (1.02 to 1.51)	
Valgus	0.64 (0.56 to 0.73)		1.39 (1.15 to 1.65)	
Varus	0.73 (0.67 to 0.79)		1.22 (1.07 to 1.39)	
Postoperative alignment		0.824		0.031
Neutral	0.71 (0.66 to 0.77)		1.24 (1.08 to 1.41)	
Valgus	0.67 (0.58 to 0.77)		1.21 (0.97 to 1.48)	
Varus	0.70 (0.60 to 0.81)		1.71 (1.41 to 2.05)	
Implant surface	NA	NA		<0.001
HA/HP			0.96 (0.87 to 1.07)	
Porous coating only			1.61 (1.34 to 1.92)	

MTPM = maximum total point motion, OA = osteoarthritis, NA = not applicable, PCL = posterior cruciate ligament, BMI = body mass index, HA = hydroxyapatite coating, and HP = highly porous metal. †MTPM values were calculated at 5 years postoperatively and back-transformed in the original scale in millimeters. ‡P values indicate testing the overall changing effects over 5 years of follow-up.

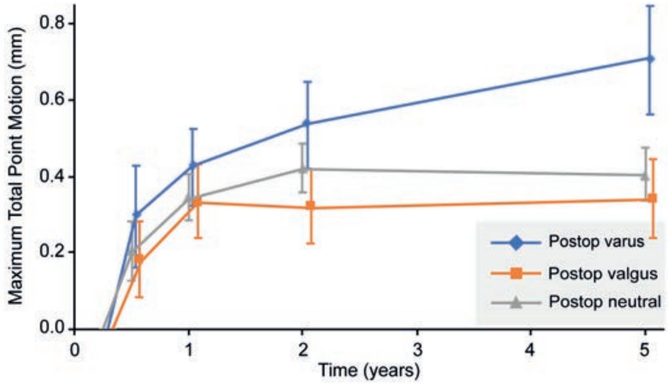


Figure 3. The mean maximum total point motion and 95% CI from 3 months to 5 years of follow-up for the uncemented components, analyzed by postoperative alignment category (neutral, hip-knee-ankle angle of 177° to 183°; varus, <177°; and valgus, >183°).

The uncemented components with such a surface showed comparable migration from 3 months onwards (0.26 mm; 95% CI, 0.22 to 0.31 mm) compared with cemented components (0.32 mm; 95% CI, 0.29 to 0.35 mm), whereas uncemented components without an osseointegration-promoting surface showed significantly more migration (0.58 mm; 95% CI, 0.46 to 0.71 mm) ($p < 0.001$) (Figure 4-B, Table IV).

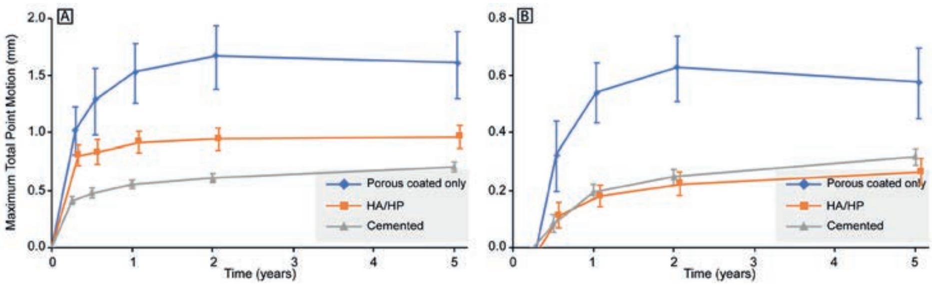


Figure 4. The mean maximum total point motion and 95% CI from immediately postoperatively to 5 years of follow-up (Figure 4-A) and from 3 months to 5 years of follow-up (Figure 4-B) for both the cemented components and the uncemented components. Uncemented components were further divided into groups: those with an osseointegration-promoting surface (HA/HP [hydroxyapatite coating or highly porous metal]) and without (porous-coated only).

Table IV. Migration analysis from 3 months to 5 years postoperatively

	Cemented TKA (N = 416)		Uncemented TKA (N = 214)	
	Mean MTPM† (95% CI)	**P Value‡**	**Mean MTPM† (95% CI)**	**P Value‡**
Sex		0.141		0.208
Male	0.27 (0.22 to 0.32)		0.37 (0.29 to 0.45)	
Female	0.34 (0.31 to 0.38)		0.44 (0.37 to 0.51)	
Diagnosis		0.769		0.604
OA	0.32 (0.29 to 0.36)		0.46 (0.39 to 0.53)	
Rheumatoid arthritis	0.33 (0.26 to 0.40)		0.32 (0.22 to 0.42)	
Posttraumatic OA	0.25 (0.12 to 0.38)		0.36 (0.23 to 0.51)	
Bearing type		0.963		NA
Fixed-bearing	0.32 (0.29 to 0.35)		0.41 (0.36 to 0.47)	
Mobile-bearing	0.31 (0.23 to 0.39)		No data	
PCL type		0.903		NA
Posterior-stabilized	0.33 (0.26 to 0.41)		No data	
Cruciate-retaining	0.31 (0.27 to 0.35)		0.41 (0.36 to 0.47)	
BMI		0.548		0.677
<25 kg/m^2	0.31 (0.26 to 0.37)		0.35 (0.26 to 0.44)	
25-30 kg/m^2	0.30 (0.26 to 0.35)		0.45 (0.37 to 0.53)	
>30 kg/m^2	0.34 (0.29 to 0.38)		0.43 (0.34 to 0.52)	
Age		0.517		0.175
<60 yr	0.29 (0.24 to 0.34)		0.40 (0.32 to 0.48)	
60-70 yr	0.35 (0.30 to 0.40)		0.51 (0.42 to 0.61)	
>70 yr	0.32 (0.26 to 0.37)		0.32 (0.22 to 0.43)	
Preoperative alignment		0.695		0.696
Neutral	0.33 (0.27 to 0.39)		0.40 (0.30 to 0.51)	
Valgus	0.25 (0.20 to 0.31)		0.47 (0.36 to 0.57)	
Varus	0.34 (0.30 to 0.38)		0.39 (0.33 to 0.47)	
Postoperative alignment		0.128		<0.001
Neutral	0.31 (0.27 to 0.35)		0.40 (0.34 to 0.48)	
Valgus	0.30 (0.24 to 0.36)		0.34 (0.24 to 0.45)	
Varus	0.31 (0.24 to 0.38)		0.71 (0.57 to 0.86)	
Implant surface	NA	NA		<0.001
HA/HP			0.26 (0.22 to 0.31)	
Porous coating only			0.58 (0.46 to 0.71)	

MTPM = maximum total point motion, OA = osteoarthritis, NA = not applicable, PCL = posterior cruciate ligament, BMI = body mass index, HA = hydroxyapatite coating, and HP = highly porous metal. †MTPM values were calculated at 5 years postoperatively and back-transformed in the original scale in millimeters. ‡P values indicate testing the overall changing effects from 3 months to 5 years postoperatively.

Discussion

Continuous implant migration measured with RSA has been shown to be predictive of late loosening, long before symptoms occur[2, 3]. The previous RSA studies of which we are aware were not sufficiently powered to assess the effect of patient and implant-based characteristics on tibial component migration following TKA. By pooling long-term follow-up RSA data of individual participants, we were able to find predisposing risk factors for loosening in both cemented and uncemented prostheses.

For cemented prostheses, increased migration—particularly in the first 3 months—was observed following TKA in female patients, in patients with rheumatoid arthritis, and when a posterior-stabilized implant was utilized. As for the adverse effect of female sex, the present findings are in line with registry data that show revisions for aseptic loosening to be more common in female patients[18, 19]. Although it seems tempting to explain this sex difference as being related to suboptimal bone mineral density in postmenopausal women, the underlying cause of revision was not studied in these registries. One RSA study has shown a relationship between preoperative bone mineral density and tibial component migration, albeit following uncemented TKA[20]. Likewise, the effect of rheumatoid arthritis on initial migration found in the present study may also be related to low preoperative bone mineral density in these patients. Lastly, contact stresses on the post-cam mechanism of the more constrained posterior-stabilized prostheses may explain the increased initial migration observed in the first 3 months in the present study[21], a finding that was also consistent with the increased revision rates of posterior-stabilized prostheses found in registry data[19, 22]. In contrast with our smaller previously published study with pooled individual participant data[23], we did not find an effect of postoperative coronal alignment on migration following cemented TKA.

For the uncemented prostheses, postoperative varus alignment of the lower limb significantly increased migration. It appeared, therefore, that biological fixation following contemporary uncemented TKA may not be sufficiently able to adapt and remodel over time in less favorable mechanical conditions (i.e., continued postoperative asymmetric loading conditions of the implant due to varus alignment of the lower limb) [24]. This finding should dissuade surgeons from aligning the overall limb in excessive varus when using new TKA alignment strategies that aim to restore constitutional alignment of the limb. Furthermore, we found that uncemented implants with a hydroxyapatite coating or highly porous metal showed quicker stabilization of migration than those with only a porous coating, and even less migration than cemented components when analyzing migration from 3 months onwards (while still including all cases). New biological mediators are continually being marketed in an attempt to minimize initial migration and promote durable biological fixation of uncemented implants; however, it is vitally important to carefully evaluate the effect of these mediators on migration. For example, Nivbrant et al. [25] recently showed that the

Advanced Coated System (Implantcast) with a ceramic coating of titaniumnitride showed both high initial and ongoing migration. This particular implant thus appears to behave more like the porous-coated prostheses in the current study.

The 4 possible implant migration profiles included components with (1) early stabilization of migration that remained stable over time, (2) high initial migration followed by stabilization, (3) high initial migration and progressive loosening, and (4) an initially stable pattern followed by late loosening (Figure 2). The underlying causes of high initial migration are different from those that result in late loosening; thus, each migration profile reflects different failure mechanisms and consequently may require different radiographic surveillance regimens. In uncemented components, high initial migration may also be physiological and merely part of a biphasic migration pattern with high initial migration (i.e., a settling phase) before stabilizing[2, 6]. Previous long-term follow-up RSA studies have shown that long-lasting biological fixation can be achieved despite high initial migration in both uncemented components with a hydroxyapatite coating and uncemented components made of highly porous metal[12, 14, 26]. Uncemented components without an osseointegration-promoting surface, however, more often show a prolonged settling phase (possibly >2 years) or may not stabilize at all[14, 27]. These implants should thus be monitored for a longer period of time. In the present study, we also found 5 cemented knee prostheses with high initial migration before stabilization. These 5 prostheses (1 NexGen PS [Zimmer Biomet], 1 Triathlon CR [Stryker], and 3 Profix CR [Smith & Nephew]) all showed initial medial or lateral subsidence of the tibial component, which could possibly be a result of poor bone quality of the proximal-medial or proximal-lateral aspect of the tibia, respectively. However, it remains unclear why the cement did not provide a rigid initial fixation. We also found 13 prostheses (8 cemented and 5 uncemented) with late loosening, which reflects the occurrence of bone resorption at the cement-bone or prosthesis-bone interface[28]. Three of the uncemented prostheses that showed late loosening were uncoated Interax prostheses, which were withdrawn from the market after an RSA trial showed poor stabilization of migration[27]. The other 2 prostheses were uncemented hydroxyapatite-coated Profix CR prostheses (including 1 with additional screws), which have been shown to induce osteolysis and subsequent loosening[28-30].

One strength of the present study was the large number of patients with individual RSA data available, enabling subgroup analyses with sufficient power to find predisposing risk factors for tibial component loosening. Limitations included the relatively small number of baseline characteristics that were evaluated, as we could only analyze variables that were measured in all of the studies. For example, it would be of interest to analyze the effect of certain biomarkers and bone mineral density on migration in such a large group of patients with long-term migration data. Another limitation was that different RSA methods were used across studies, which might result in patients from 1 study being more susceptible to certain types of measurement errors than others[13]. However, we did statistically correct for clustering of patients within each study.

In conclusion, for cemented prostheses, we found increased migration in the first 3 postoperative months in female patients, in patients with rheumatoid arthritis, and when a posterior-stabilized cemented implant was utilized. For uncemented prostheses, both postoperative varus limb alignment and the absence of an osseointegration-promoting surface were also found to be predictors of increased migration, putting patients at risk for subsequent loosening.

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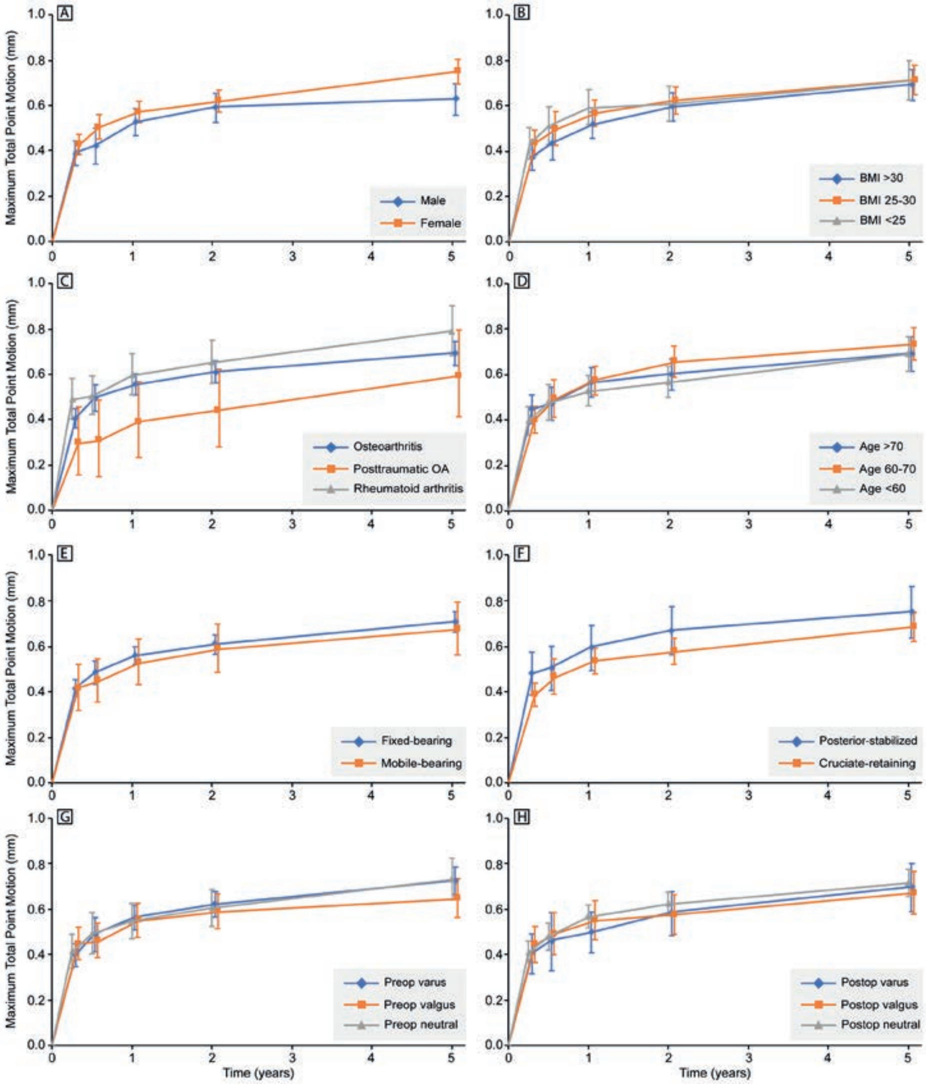
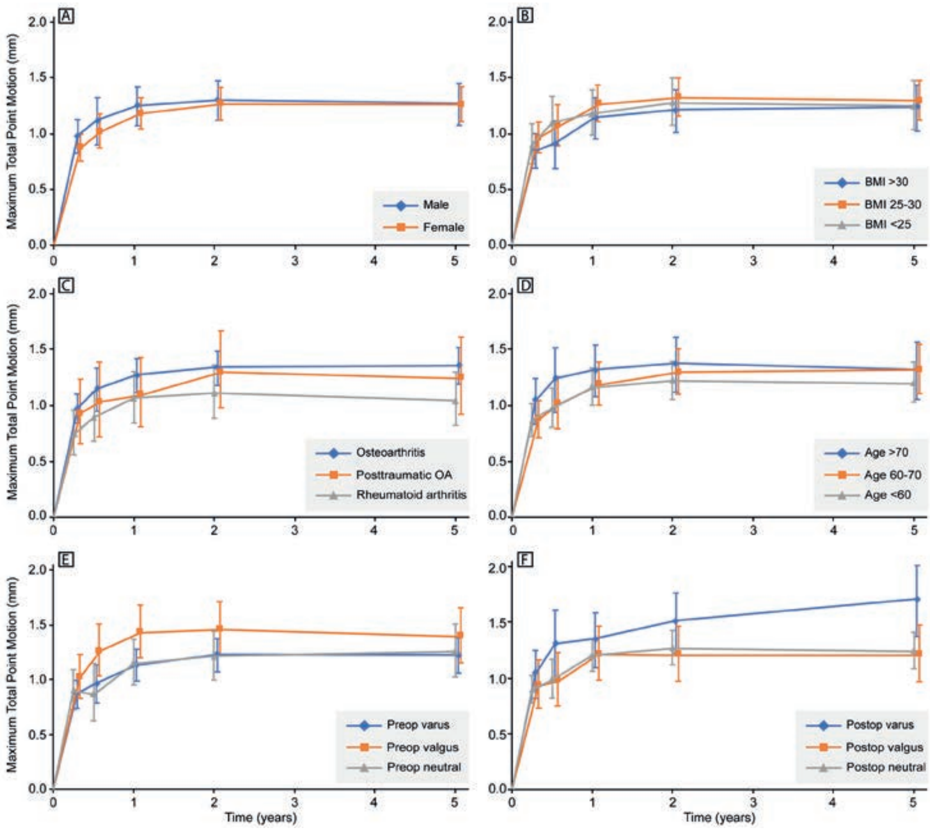
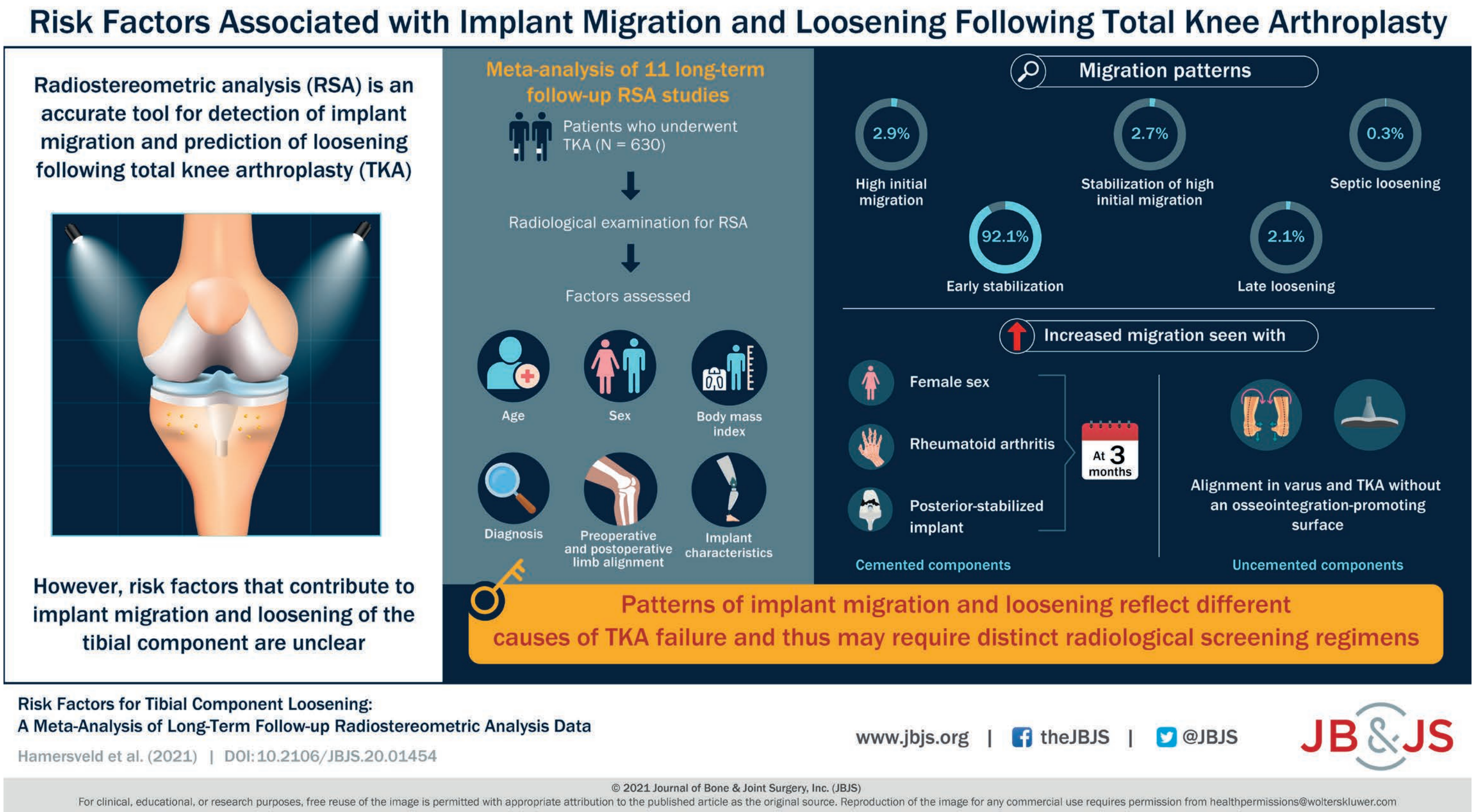
Appendix



Appendix Figure E-1. Cemented TKA RSA analysis result of the mean maximum total point motion (MTPM) and 95% CI from immediate postoperative to 5 years of follow-up, analyzed by (A) gender, (B) BMI category, (C) diagnosis, (D) age category, (E) bearing type, (F) PCL type, (G) preoperative alignment, and (H) postoperative alignment (neutral HKA of 177-183°; varus <177°; and valgus >183°). Values are back-transformed in the original scale in mm.



Appendix Figure E-2. Uncemented TKA RSA analysis result of the mean maximum total point motion (MTPM) and 95% CI from immediate postoperative to 5 years of follow-up, analyzed by (A) gender, (B) BMI category, (C) diagnosis, (D) age category, (E) preoperative alignment, and (F) postoperative alignment (neutral HKA of 177-183°; varus <177°; and valgus >183°). Values are back-transformed in the original scale in mm



Appendix Infographic.

9 Summary and general discussion

Summary

The aims of this thesis were to evaluate the effect of different implant design aspects on tibial component migration on a group level as measured with radiostereometric analysis (RSA). Furthermore, after exploring whether it is justified to pool outcomes from studies using different RSA techniques, we determined risk factors for loosening in such pooled data sets including implant design aspects, surgical alignment and patient characteristics.

The effect of implant design on tibial component migration

The first design aspect that was studied is the tibial component material. In **chapter 2**, we present the two-year results of a randomized controlled trial comparing cemented condylar-stabilizing total knee prostheses with either monoblock all-polyethylene tibial components (n = 29) or modular metal-backed tibial components (n = 30). The surgeries were performed by two experienced surgeons using a standardized technique. Tantalum markers were placed into the proximal tibial metaphysis and within the polyethylene to facilitate marker-based RSA measurements. Besides RSA, clinical scores including the Knee Society Score, the Forgotten Joint Score and the Knee Osteoarthritis and Injury Outcome Score were also evaluated throughout follow-up. After two years, a small but statistically significantly difference was found in favor of the all-polyethylene design, with a mean maximum total point motion (MTPM) of 0.61 mm (95% CI 0.49 to 0.74) for the all-polyethylene group *versus* 0.81 mm (95% CI 0.68 to 0.96) for the metal-backed group (p = 0.03). This difference was smaller and not statistically significant when adjusting for the operating surgeon in a *post hoc* analysis. Comparable improvements on all clinical outcome scores were found between groups. We concluded that the risk of aseptic loosening of all-polyethylene tibial components of this design is at least comparable with, if not less than, that of its metal-backed counterpart.

The second design aspect that was studied is the bearing concept. We performed a randomized clinical trial comparing migration and clinical outcomes of an otherwise similarly designed cemented fixed-bearing and (rotating-platform) mobile-bearing total knee arthroplasty (TKA) design, for which the results are presented in **chapter 3**. Although migration and clinical outcomes were similar between designs, several complications occurred which were inherent to the mobile-bearing design. In five cases, the surgeon experienced difficulties with gap balancing during mobile-bearing surgery, which led to the decision to deviate from the randomized treatment allocation and implant fixed-bearing components instead. Especially in patients with compromised (peri-)articular tissue (e.g., due to rheumatoid arthritis or previous surgery such as high tibial osteotomy), bone resections and soft-tissue releases are performed conservatively which may result in difficulties to place the mobile bearing onto the central post of the baseplate without forcing and thus potentially damaging the locking mechanism. In one procedure, damage of the locking mechanism instigated an insert dislocation, for which the revision surgery was sadly the onset of many adverse sequalae. Patient inclusion was prematurely terminated for patient safety reasons, awaiting investigation of the insert dislocation. After analyzing the final results of this study, we concluded that there was no clear benefit of this mobile-bearing design with respect to implant migration and clinical outcome scores, whilst this design posed a more challenging procedure to some surgeons with risks to patients.

The third design aspect that was studied is the mode of fixation. In **chapter 4**, we randomized 60 patients to either a cemented TKA or an uncemented TKA coated with hydroxyapatite via a solution deposition technique called peri-apatite (PA). After five years of follow-up, we found higher initial migration for the uncemented PA coated TKAs, resulting in statistically significantly more overall migration of 0.97 mm (95% CI 0.81 to 1.11) as compared with 0.62 mm (95% CI 0.49 to 0.76) for the cemented group ($p = 0.003$). However, we also performed a *post hoc* analysis to compare migration after the initial settling phase by assessing the between-group differences in migration with three months as a baseline. Between three months and five years of follow-up, we found statistically significantly less migration in favor of the uncemented PA group, showing 0.13 mm (95% CI 0.01 to 0.25) of migration *versus* 0.27 mm (95% CI 0.19 to 0.36) for the cemented group ($p = 0.02$). Continuous migration between two and five years was seen in one implant in each group, with the cemented implant showing a more ominous migration pattern as compared with the uncemented implant.

In **chapter 5**, we evaluated whether the observed beneficial effect of PA-coating on uncemented total knee implants is sustained over time and, more importantly, whether continuous migration (i.e., >0.2 mm of migration) in the second postoperative year proves predictive for mechanical loosening after uncemented TKA. Sixty patients were randomized to either a PA-coated or uncoated (porous only) implant. In the short-term report of this study, continuous migration in the second postoperative year was observed in one PA-coated and seven uncoated implants. After ten years of follow-up, the PA-coated implants had a statistically significantly lower mean migration of 0.94 mm (95% CI 0.72 to 1.2) as compared with 1.72 mm (95% CI 1.4 to 1.2) for the uncoated group ($p < 0.001$). There was also a significant difference in migration between groups when analyzing migration with three months as baseline, but not with one year as baseline as both groups showed hardly any mean migration from that point onwards. Stabilization of continuous migration of the uncoated implants occurred between three months and one year of follow-up, whereas this was within the first three postoperative months for the PA-coated group. The individual implants showing continuous migration in the second postoperative year all stabilized between two years and final follow-up, except for two implants in the uncoated group. Both tibial components showed radiolucent lines and subsidence of the tibial component on conventional radiographs at final follow-up. Given the late stabilization, beyond the two years mark, observed in six implants, short-term RSA cut-off values to determine the risk of failure seem might be of limited value in these uncemented implants. The latter seems to be more prominent for knee implants without a biological mediator to enhance bone ingrowth. In these uncemented implants, three- to five-year follow-up is probably needed to predict its bone-fixation properties at the long-term.

Surgical and patient risk factors for tibial component migration

In the second part of this thesis, we pooled individual participant data of multiple RSA studies in order to increase statistical power and be able to find risk factors for loosening for the individual patient. However, we first had to confirm whether it is justified to pool data from studies using different RSA methods. As marker-based and model-based RSA both introduce different types of measurement error and may even introduce systematic bias due to methodological differences, we reanalyzed a marker-based RSA study with model-based RSA as described in **chapter 6**. The original study was a comparison between cemented all-polyethylene and cemented modular metal-backed tibial components. By reanalyzing the latter group with model-based RSA, we were able to find systematic differences in translations but not rotations and MTPM between both methods. These differences were caused by a difference in reference origin that is being used for migration calculation by each method. As a result, the marker-based method overestimated the transverse, longitudinal, and sagittal translations by 29%, 7% and 26%, respectively. When correcting for this proportional bias by using the same reference coordinate system, nearly identical translations were found. We also found slightly larger limits of agreement for the rotations and MTPM values between both RSA methods, which is caused by some imprecision of the model-based measurements due to relatively round, symmetrical shape of the tibial component in the transverse plane[1]. However, the limits of agreement were still considered precise enough. We were also able to demonstrate that there was no insert micromotion with respect to the metal tray affecting the migration results, a phenomenon that was found in older fixed-bearing designs[2, 3]. However, results of some individual patients differed substantially at some follow-up examinations due to different types of measurement error (e.g., marker occlusion in marker-based RSA and model-fit inaccuracies in model-based RSA). We therefore concluded that although both methods produced comparable results on a group level, one must not put too much weight on strict migration thresholds in individual patients as a sudden increase in migration may also be the result of measurement error.

Orthopaedic surgeons traditionally aim for a neutral coronal alignment of the lower limb during total knee arthroplasty, regardless of the patients' anatomy. Several short- to midterm studies have claimed improved clinical outcomes when constitutional (i.e., pre-morbid) joint kinematics are restored[4-10], e.g., with use of kinematic alignment techniques in which the lower limb is aligned according to its pre-arthritic varus or valgus state. However, such novel alignment techniques may impair the long-term survival of the implants as asymmetric loading in varus or valgus may result in mechanical loosening. We therefore specifically analyzed the effect of coronal alignment on tibial component migration with use of pooled long-term RSA data (**chapter 7**). Coronal alignment parameters were measured on pre- and postoperative full-leg radiographs in 85 patients that underwent cemented TKA. The patients' constitutional leg alignment was determined with use of the preoperative full-leg radiographs. The effect of the postoperative hip-knee-ankle angle on migration was determined relative to both the mechanical axis and the patients' constitutional alignment. After 5 years of follow-up, knees aligned in mechanical varus showed the highest mean migration of 1.55 mm (95% CI, 1.16 to 2.01 mm), compared with 1.07 mm (95% CI, 0.63 to 1.64 mm) and 0.77 mm (95% CI, 0.53 to 1.06 mm) for valgus and in-range knees, respectively ($p < 0.001$). In contrast, no significant differences in migration were seen across constitutional alignment categories. Furthermore, matching the patients' constitutional alignment did not preclude high migration, especially in mechanically varus-aligned TKAs. Given these results, the (adverse) effects of component alignment should be further investigated before alternative alignment techniques become widely adopted.

Chapter 8 describes the results of a large meta-analysis of 630 patients collected from 11 RSA studies with long-term data available. By doing so, we were able to determine the effect of patient, implant and alignment characteristics on tibial component migration over time. By pooling such a large group of patients, statistical power increases as compared with the individual studies in which subgroup analyses on patient characteristics are underpowered and may produce false positive results due to multiple comparisons[11]. We found early mechanical loosening to occur in 2.9% of the implants, late loosening in 2.1%, septic loosening in 0.3% and stabilization of high initial migration in 2.7%. All other implants showed a stable migration pattern over time. In cemented prostheses, increased migration was found in females, in patients with rheumatoid arthritis and when a posterior-stabilized design was implanted. These differences were smaller and not significant when analyzing migration from three months onwards. We hypothesized that the initial increase in migration may be due to a lower bone mineral density in females and in patients with rheumatoid arthritis, and due to increased contact stresses on the post-cam mechanism in cases where a more constrained posterior-stabilized design was implanted. As a result, subsidence of the prosthesis is likely to occur within the first three months upon weight bearing. In uncemented prostheses, postoperative varus limb alignment increased migration and this became more evident with time. Furthermore, uncemented implants without an osseointegration promoting surface (i.e., porous coating only without additional hydroxyapatite coatings, nor made of highly porous metal) showed delayed stabilization and increased risk for failed ingrowth as compared with uncemented implants with a surface promoting osseointegration. The use of these biological mediators thus minimizes both initial and continuous migration. The found migration profiles reflect different failure mechanisms with early, progressive loosening being the result of subsidence of the tibial tray into the tibial plateau due to failed ingrowth or tibial collapse. Late loosening may be the result of progressive bone resorption at the cement-bone or prosthesis-bone interface[12]. Lastly, high initial migration may also be merely physiological, especially in uncemented prostheses without an osseointegration promoting surface. These implants may thus require longer follow-up with radiographic surveillance to ensure stabilization of migration.

General discussion

In the past five decades, total knee arthroplasty (TKA), and particularly its surgical procedure, has changed in many aspects. The first designs were reserved for highly disabled patients with extensive degeneration and deformities[13]. With improvements in design, functional results and implant longevity, the indication for arthroplasty changed and broadened to high demand patients. Some of the changes in implant design were minor, others fundamentally altered the design rationale, fixation techniques and implant materials in continuous attempts to improve function while minimizing the risk of loosening, the leading cause of revision[14, 15]. Registry data show that the majority of surgeons performing TKA today use a modular metal-backed, fixed-bearing design with cement fixation. Through three randomized controlled trials (RCTs), we contribute to the evidence base by examining whether changes in different design aspects improve migration patterns in comparison with a modern modular metal-backed fixed-bearing cemented TKA design (Triathlon, Stryker). A fourth RCT was conducted to determine the long-term effect on migration of an additional surface coating after an uncemented modular metal-backed fixed-bearing TKA.

All-polyethylene tibial components

Before the introduction of metal-backed tibial components in TKA in the late 1970s, almost all designs had an all-polyethylene tibial component[16]. As the metal-backed designs proved superior in several aspects including the risk of aseptic loosening, first-generation all-polyethylene designs were abandoned. However, there is a growing body of evidence that modern all-polyethylene designs perform at least equally well[17-19]. In **chapter 2**, we confirmed our hypothesis that the studied condylar stabilizing (CS) all-polyethylene components showed comparable (in the *post hoc* sensitivity analysis) or even less migration (in the primary analysis) after two years of follow-up than its metal-backed counterpart. The results of our study are in line with other RSA studies showing comparable implant migration[20-27]. Hyldahl *et al.*[24] hypothesized that the all-polyethylene components may partly absorb eccentric forces as they are more elastic than the rigid metal-backed components. The all-polyethylene tibial component designs may thus be slightly more resistant to adverse tensile forces upon peripheral compressive loading. Despite the comparable outcomes between all-polyethylene and metal-backed designs described in the abovementioned studies, all-polyethylene components are still rarely used. Given the reduced costs of manufacturing these implants, surgeons should consider using them more often now that the demand for TKA is growing substantially[16, 28].

An interesting finding in **chapter 2** was the surgeon effect in the *post hoc* sensitivity analysis, showing a statistically significant difference in migration between the implants operated by surgeon 1 and surgeon 2. This may indicate that meticulous performance of each surgical step can improve the outcome, at least on a subclinical level. A later study evaluating a posterior-stabilized (PS) all-polyethylene design with a PS metal-backed design, again performed by the same two surgeons, found no surgeon effect on migration[27]. Given that the same two surgeons performed the surgeries, it seems likely that it is not the surgeon experience per se, but rather the combination with the CS design which may be less forgiving. This stresses the importance for future new designs or changes in designs, to not only investigate their performance in ideal circumstances by very experienced surgeons, but also in routine practice.

Mobile-bearing insert

Mobile-bearing TKA designs were introduced to deal with two major problems affecting implant longevity: loosening and wear. The mobile-bearing design has an additional flat non-constrained articulation with the tibial component, thereby allowing a more congruent articulation with the femoral component which theoretically reduces both contact stresses at the implant-bone interface and polyethylene wear[29, 30]. However, previous RSA trials found no superiority of either design on tibial component migration[2, 31-33], and even questioned whether mobility is present in vivo due to (among other reasons) formation of fibrous tissue and a mismatch in pivot point of the rotating platform and the actual tibiofemoral rotation point[34]. Furthermore, mobile-bearing arthroplasty is technically more challenging with additional risks including insert dislocations[35-37]. In our study (**chapter 3**), no differences were found in migration between the single-radius mobile-bearing and fixed-bearing TKA design after six years of follow-up. We did experience a great number of adverse events in the mobile-bearing group which could likely be attributed to difficulty of intra-operative assembly of the mobile bearing insert of this design. In line with the conclusions of an earlier report on a subset of our study population[38], we believe that there is no clear benefit of this type of mobile-bearing design. For that matter, the manufacturer of this prosthesis decided to discontinue the mobile-bearing variant because of the observed complications. Moreover, the fixed-bearing single-radius design allows for some axial rotation during deep flexion with minimal constraint forces, which effectively eliminates the theoretical advantages of the mobile-bearing design.

Cementless fixation

The optimal fixation method of TKA is an ongoing debate. Cement has historically been considered the gold standard, producing reliable results. In contrast, early uncemented prostheses often failed miserably due to experimentation in design[39]. The high failure rates resulted in near abandonment of uncemented components, but the desire to achieve a more durable, biologic fixation in younger, heavier and more active patients undergoing TKA has caused a resurgence of interest in cementless fixation techniques[12, 40-42]. With the introduction of new implant materials and coating techniques, innovations in porous ingrowth technology may further improve osseointegration and thus the fixation of uncemented implants. We evaluated the effect of one of those new coatings called peri-apatite (PA), which is a solution deposition technique to increase the coverage of hydroxyapatite onto the 3D implant surface (**chapter 4**)[43]. We found higher initial migration in the first three months for the uncemented PA-coated tibial components as compared with cemented components. However, a stable migration pattern was found between three months and five years of follow-up while the cemented components showed slightly more migration from three months onwards. As found in previous long-term RSA studies[44, 45], the initial migration found after uncemented TKA is often benign and merely part of a typical biphasic migration pattern. After three months, full stabilization of migration of the PA-coated components suggests a durable biological fixation has been achieved which, in contrast with cement fixation, may not be subjected to loss of cement-bone interlock due to continuous trabecular resorption as well as deformation and degradation of the cement mantle over the years[46-48]. In **chapter 5**, the long-term results of an additional study showed that the early stabilization of the PA-coated tibial components is sustained over time, resulting in low mean migration values and the absence of components with continuous migration after ten years of follow-up as compared with 'uncoated' uncemented components (i.e., porous coated only with cobalt-chromium sintered beads without the additional PA-coating). In this study, the mean initial migration of the PA-coated components was comparable with the migration values found in **chapter 4**, with a mean MTPM of 0.9 mm. In contrast, the uncoated components had a much higher mean MTPM of 1.5 mm, time to stabilization was observed to take longer and several individual components with continuous migration did not stabilize over time resulting in radiolucent lines and subsidence of the tibial components visible on conventional radiographs at final follow-up.

Especially in young patients, uncemented fixation techniques may be preferred due to the long-lasting biological fixation of the implant. Uncemented implants relying on ingrowth are well suited to hip arthroplasty as the forces acting on the interface are largely compressive, the knee differs however[39]. In the knee, compression alternates with adverse tensile forces. Therefore, bone ingrowth needs to occur fast after an initial rigid (press-fit) stability. Peri-apatite proves to be a valuable mediator for such a long-term biological fixation of tibial components, although migration in the first weeks after implantation is still larger than after cemented TKA. New component designs and biomaterials may be able to further improve the fixation of cementless implants. These must be carefully evaluated however, as some new designs clearly do not suffice. For example, Nivbrant *et al.* (2020)[49] recently published the two-year results of an RCT evaluating the ACS knee (Implantcast), which has an additional ceramic coating of titanium nitride. The uncemented tibial components in this study displayed high initial migration which did not stabilize in a large number of patients. The authors raised their concerns about the risk of loosening given the observed late ongoing subsidence and high MTPM values, and advised to only use the cemented version of this TKA design. This particular implant has also been identified to have a much higher than anticipated revision rate in the Australian registry[14]. On the other hand, more promising are the 3D printed highly porous metal implants matching the pore size and elasticity of the surrounding trabecular bone, which may further improve osseointegration and should prevent a mismatch in stiffness and shear forces at the implant-bone interface[50]. Hasan *et al.* (2020)[51] recently showed that the initial migration of such a 3D printed implant is indeed slightly less than that of the PA-coated implants studied in this thesis. Hence, it appears that this design and biomaterial may further improve the fixation of cementless implants.

The value of short-term RSA outcomes in randomized controlled trials

The introduction of new orthopaedic implants and surgical techniques has been disastrous at times. For example, hip prostheses that were fixed with a new type of cement called Boneloc showed a remarkable increase in revision risk for aseptic loosening of up to fourteen times[52, 53]. This is just one example of many other introductions that have failed miserably. New implants should therefore have been rigorously tested in a stepwise manner, including preclinical studies and small, randomized clinical trials prior to market introduction[54, 55]. Clinical RSA studies play an important role. If the manufacturer of Boneloc cement, for example, performed such a study, widespread introduction into the international market would have been prevented. The results of a randomized RSA study including only 30 patients, performed after market introduction by an independent research group, were unambiguous; a substantially higher initial migration within six months and no signs of stabilization at one year follow-up was found for the patients that received Boneloc cement as compared with conventional cement[56]. The authors therefore did not recommend the use of this new type of cement. A later study showed similar results with increased migration and clinical failure after TKA with Boneloc cement[57].

Earlier evaluation of prostheses using RSA could play an important role in lowering the total revision burden. A recent study showed that RSA-tested knee implants on average have a lower 10-year revision rate than implants that have not been tested with RSA[58]. Possible explanations for this difference are (1) the early warning function of poor performance (i.e., high migration values) leading to subsequent discontinuation of the given implant and continued use of well-fixed implants; (2) RSA testing may be a proxy for rigorous clinical testing by the manufacturer; and (3) prudent surgeons may choose to only use thoroughly tested implants[58]. However, although excessive implant migration may correctly predict a high failure rate[59], the short-term cut-off values that have been proposed in earlier studies may not be applicable to all implants or fixation techniques. The cut-off values reported by Ryd *et al.*[60] and Pijls *et al.*[61] suggest that one only needs two-year data to determine whether an increased risk of loosening at ten years is likely or not. Many RSA studies therefore terminate after two years. Indeed, when analyzing the migration of a certain prosthesis in a randomized setting, two-year data can be sufficient if both prostheses are comparable in many aspects, especially if the same cement is used for fixation. We performed such randomized controlled trials (RCTs) in **chapters 2 and 3**. The results of these trials show no major differences in terms of early migration, which allows for subsequent clinical and registry studies to evaluate other outcomes in larger groups of patients. In c**hapter 4**, we compared the migration of a cemented implant with an uncemented implant. As the uncemented implants showed clear stabilization of migration, here too the short-term migration values are sufficient to conclude that there are no major concerns regarding the expected long-term survival of the investigated implants. Conversely, the uncoated implants in **chapter 5** showed much higher initial migration and several individual implants showed continuous migration in the second postoperative year. Given the known biphasic migration pattern of uncemented components, two-year data were too short to make any succinct statements on whether delayed stabilization will occur or that a high incidence of aseptic loosening is likely. Hence, the known and much used cut-off values at one to two years are too short to be applied for uncemented knee implants, whilst three- to five-year data might suffice. Although the long-term outcomes presented in **chapter 5** showed delayed stabilization of the majority of the uncoated implants, we advise against the widespread use of the uncoated version of this specific implant given the magnitude of the mean migration and the number of implants showing progressive migration with subsequent radiographic signs of loosening on conventional radiographs.

Longer follow-up is also needed to assess whether continuous migration observed in the second postoperative year is the result of marker instability or model-fit inaccuracies in the marker-based or model-based RSA examinations, respectively. Even though we demonstrated in **chapter 6** that mean migration values are comparable between marker-based and model-based measurements, measurement errors related to the used RSA method may produce falsely high migration measurements for individual patients (as confirmed by the results of the alternative RSA method not subjected to this type of measurement error). We thus advise to avoid making strong statements regarding the occurrence of continuous migration based on the final available RSA examination.

Predisposing factors for loosening

National arthroplasty registries provide important analyses on patient- and implant-related factors for revision arthroplasty. Likewise, large cohort studies evaluating risk factors for revision often rely on implant revision as the main outcome measure. When analyzing the effect of certain factors on the risk of loosening, however, revision data have its limitations. The decision to revise is subjective to major competing risk factors such as death and the willingness of the patient or surgeon to revise. As loosening of an implant is asymptomatic at first, the onset of symptoms that gradually progress years after implantation are often present in a patient that is now at a higher age with increasing comorbidities and lower functional demands. Even if the diagnosis of loosening is made, the orthopaedic surgeon may be in doubt of when to offer a revision arthroplasty. How many complaints should the patient have? The experience of the surgeon in revision arthroplasty may result in hesitance given the uncertainties whether the, often complex, procedure will have a beneficial effect on the patients' complaints or make it worse. As revisions are publicly marked as failure of the center in which they are performed in some national arthroplasty registries, it may even promote reluctance to revise, subsequently denying patients with inferior results an opportunity to gain improved outcomes of a well performed revision arthroplasty.

Patients with excessive early tibial component migration measured with RSA can be identified long before symptoms occur. As RSA is a highly accurate and objective outcome measure, the data presented in this thesis are less subjective to competing risk factors than revision as an outcome measure in registry data and cohort studies. The downside of RSA is that it is only a proxy for clinical failure associated with micromotion of the implant. Some patients remain asymptomatic despite excessive migration measured with RSA, which may be partly due to lower functional demands of the given patient. These limitations notwithstanding, pooling long-term RSA data as performed in **chapter 7** and **chapter 8** have given insight into factors associated with increased migration and thus the risk of loosening of the implant. Knowing these risk factors can aid the surgeon in choosing the optimal implant design and surgical technique for each patient, as well as to decide on the timing and duration of postoperative radiographic surveillance.

A remarkable difference with revision data is that we did not find age to be associated with increased migration. In national arthroplasty registries, younger patients have a much higher revision rate than older patients[42, 62]. Possible explanations include a higher physical activity, a "higher expectancy of pain relief" and "a health condition that better allows for revision surgery"[63]. Thus, the willingness of the patient and surgeon to revise plays an important role in the effect of age in revision data. The higher physical activity at younger age on the other hand, appears to play a minor role in the onset of loosening when migration is analyzed as a proxy for failure (**chapter 8**). In our study, the mean migration of both cemented and uncemented components did not differ between three different age groups. However, it is possible that the occurrence of late loosening in 13 prostheses is the result of cement debonding and osteolysis in physically active patients, which could not be further evaluated due to the small number of events.

There is conflicting evidence on the effect of body mass index (BMI) on revision for loosening of the implant. Ritter *et al.*[64] found increasing BMI to be associated with an increasing risk for failure (other than infection), although patients with a BMI below 23 kg/m^2 also had an increased risk of failure as compared with the 23-26 kg/m^2 group. They concluded to "intuitively believe that poor implant alignment combined with a high BMI represents a much greater risk to implant survival than either risk factor alone"[64]. Abdel *et al.*[65] also found BMI to be inversely related to 20-year implant survivorship (excluding infection). Other authors did not find such an association[66]. National arthroplasty registry data primarily show BMI to be associated with an increased risk of infection and not aseptic loosening[14]. In **chapter 8**, BMI was not found to be associated with an increase in migration despite what is often intuitively thought. The association of BMI and migration may be very small and therefore clinically irrelevant after TKA with a neutral mechanical alignment. Future studies analyzing specific cohorts of patients with a varus or valgus implant alignment may show more relevant associations, as indeed one expects implant survival to be especially impaired by asymmetric loading conditions in the presence of a high BMI.

Coronal alignment of the lower limb has attracted much attention as new alignment techniques are being popularized in search of improving the patients' satisfaction after TKA. The goal of these new techniques, such as kinematic alignment, are to restore the patients' native anatomy rather than aligning the limb in standard neutral position as in mechanical alignment. By doing so, the three kinematic axes of the knee are respected and all bone resections, corrected for wear, are equal in thickness to the implanted components[67]. By resurfacing the knee in this manner, the components will be intentionally placed in varus or valgus in a large proportion of patients given the normal distribution of native lower limb alignment[68, 69]. The upside of this method is that the tension of the soft-tissue envelope is restored, hence releases of the collateral, posterior cruciate and retinacular ligaments are rarely needed[8, 69]. However, there are concerns about the risk of aseptic loosening in components subjected to asymmetric loading conditions when a neutral mechanical alignment has not been achieved. Short-term outcomes of kinematically aligned knees have not shown 'catastrophic' failure in knees aligned in varus or valgus, but these outcomes cannot be extrapolated to the long-term[8, 70]. The ten-year results of one study are promising with only 3 revisions for aseptic loosening (1.5% in 198 kinematically aligned TKAs), but these single-surgeon outcomes have yet to be reproduced by other authors[71]. For mechanically aligned TKA, conflicting evidence has been reported on surgical imprecision potentially leading to malalignment and its impact on long-term outcomes. Some authors have found increased failure rates[64, 72-75], while others did not find such an association[65, 76]. RSA may contribute to this discussion by its ability to measure migration long before a prosthesis will fail, and less dependent on surgeon and patient factors influencing a decision for revision surgery. In **chapter 7**, we found mechanical varus alignment to have the highest tibial component migration after cemented TKA. Furthermore, mean migration values were higher in mechanical varus as compared with neutral and valgus even in patients that were aligned in range with their constitutional alignment. Therefore, we advise to further investigate the effect of alternative alignment techniques on implant survival before implementing new alignment techniques on a large scale that do not aim for neutral mechanical alignment. It must be stressed however that the patients in this study were all treated with the intent to achieve a neutral mechanical alignment, but in some cases ended up with an unintended varus or valgus alignment, rather than with such a new technique actually intending to achieve the patients' constitutional alignment which is often in varus or valgus. In **chapter 8**, a similar effect of coronal alignment on migration was only found after uncemented TKA. The absence of an effect of alignment on migration after cemented TKA may be related to the fact that a much larger group of patients (> 400) was included in the analysis, resulting in relatively fewer cases with high migration. Furthermore, the aetiology of loosening is complex. High migration seems to occur more often in a group of patients with the lower limb aligned in varus, but varus alignment is tolerated for in the majority of these cases suggesting other factors play a crucial part in the onset of loosening such as the patient activity level, BMI, bone mineral density, ligament balancing, quality of the fixation technique, other alignment parameters such as the posterior slope of the tibial component, the magnitude of alignment correction and the presence of residual fixed flexion deformity[77-79].

We found three factors to be associated with higher initial migration after cemented TKA in **chapter 8**: female gender, rheumatoid arthritis and a posterior stabilized design. From three months onwards, no association was found for these factors. We hypothesized that slight tibial collapse upon weightbearing as a result of either decreased bone mineral density (in postmenopausal women and patients with rheumatoid arthritis) or increased contact stresses in the more constrained posterior-stabilized design occurs in the first weeks after implantation, after which a stable situation is achieved. Two other RSA studies have shown a relationship between migration and a lower bone mineral density, which besides patient-related factors is affected by the prosthesis design that can induce periprosthetic stress shielding (bone loss) and subsequent migration[77, 80].

Future perspectives

The studies presented in this thesis highlight the need for more research on risk factors for implant loosening and have pointed to some avenues that may be particularly relevant. It would be helpful to further expand the pooled RSA database to be able to perform subgroup analyses within various alignment categories and enable some of the questions raised above to be answered. Also, the addition of other relevant factors such as bone mineral density measurements, sagittal alignment parameters (posterior slope) and magnitude of alignment correction could give more insight into the mechanisms leading to aseptic loosening. Perhaps the most interesting field to further explore is the effect of different alignment strategies on implant migration. Until recently, not a single study evaluating kinematically aligned TKA has used RSA as an outcome measure. Laende *et al.*[81] have published the first randomized controlled trial analyzing migration with RSA, randomizing between kinematically aligned versus mechanically aligned TKA. After two years of follow-up, they found similar migration patterns between groups and no significant relationship between postoperative limb alignment and migration. They concluded that their findings support continued investigation of alternative alignment techniques. This is indeed what should be done; continued investigation of the effect of alternative alignment strategies with different implants and fixation techniques, monitored with RSA to enable early detection of any problem in a continuous cycle of improvements, to be able to provide patients the best possible short- and long-term clinical outcomes.

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10 In memoriam Edward Valstar (1970–2017)

In memoriam

Professor Edward Valstar died at the age of only 47 years on May 17, 2017. As stated in a touching tribute by his close colleagues and long-time friends, he had to battle an unfair fight against a "bunch of deteriorated pancreatic cells" (Rob Nelissen, Bart Kaptein, DirkJan Veeger, *Acta Orthopaedica* 2017, 88, 701-702).

Edward inspired many young academics at both the Leiden University Medical Center and the Delft University of Technology. His combined expertise in technology and health care led to his appointment as one of the first Medical Delta professors (i.e., being part of a select group of professors with a dual appointment at Leiden University Medical Center and Delft University of Technology). While working as an engineer within the field of medicine, he was able to connect clinic, technology and biology together. Given his quality in doing so, he successfully collaborated with many clinicians and scientists all around the world. One of the examples of yet another fruitful collaboration is his paper on RSA standardization (2005), which was written with Swedish orthopaedic surgeons who initially had opposing ideas on his scientific output. Only a few years later, he was one of the founding members of the International Radiostereometry Society and initiator of biennial RSA meetings, which further strengthened the RSA community and elevated RSA research to a next level.

Besides research, Edward was always interested in the personal lives of his peers and students. For that matter, he was one of the few professors that showed work can be done during working hours, while life can (and should) be lived with family and friends during evenings, weekends and holidays. During the first years of my PhD, Edward gave me the freedom to set my own path as I started my scientific career. Meanwhile, he pushed me to collaborate and build a successful bridge between Leiden and the research group of Sören, who was later gratefully added as a co-promotor. While finishing this dissertation, I realize that many more collaborations have been established within the RSA community; Edward is greatly missed, though his values and philosophy have evidently continued to live on.

Edward Valstar at TedX Delft: Joined at the Hip (a must see on YouTube).

A

Appendices

Nederlandse samenvatting

De levensduur van totale knieprotheses (TKP) is gemiddeld helaas nog altijd korter dan men zou verwachten, iets wat met name veroorzaakt wordt doordat er bij een deel van de patiënten als complicatie loslating van de metalen componenten in het bot optreedt. Sinds de jaren '70 zijn er veel aanpassingen geweest aan het ontwerp van de prothese, de materialen en de fixatiemethoden om het risico op loslating te verkleinen. Echter, zeker voor patiënten die voor hun 55ste levensjaar een knieprothese krijgen is de kans dat zij één of meerdere revisie-operaties nodig zullen hebben aanzienlijk, tot wel 20% voor vrouwen en 35% voor mannen. Op het moment dat de prothese eenmaal los zit, is een grote revisie-operatie de enige oplossing om voor patiënten een betere functie te krijgen en van de pijn af te komen. Helaas leidt een dergelijke revisie-operatie tot minder gunstige resultaten dan na de eerste operatie, in termen van functie en kwaliteit van leven. Daarnaast is de revisie zelf een lange ingreep met een verhoogd perioperatief risico op complicaties. Bij kwetsbare ouderen wordt een dergelijke revisie-operatie soms niet meer gedaan, gezien de nadelen zwaarder kunnen wegen dan de mogelijk winst voor deze patiëntencategorie. Om het risico op falen van de prothese te minimaliseren, is onderzoek nodig naar het waarom een prothese loslaat. Dit is des te belangrijker gezien de verwachting dat het aantal mensen dat per jaar een knieprothese nodig zal hebben de komende jaren exponentieel zal toenemen.

De studies in dit proefschrift maken gebruik van radiostereometrische analyse (RSA), de nauwkeurigste röntgentechniek voor het bepalen van microbewegingen van orthopaedische implantaten zoals knie- en heupprotheses. Eerder is aangetoond dat vroege postoperatieve **migratie** (i.e. detectie van microbewegingen) van de geïmplanteerde componenten ten opzichte van het bot voorspellend is voor de kans op loslating op de lange termijn. Doordat de RSA-methode zo nauwkeurig is, hoeft slechts een klein aantal patiënten onderzocht te worden om aan te tonen of het implantaat een veilig migratiepatroon laat zien. Bovendien kan het risico op loslating na 10 jaar al binnen 1 tot 2 jaar na de operatie worden ingeschat, lang voordat de patiënten daadwerkelijk klachten krijgen die passen bij loslating. Het doel van dit proefschrift is om het effect van specifieke aanpassingen in het ontwerp van de knieprothese op de zojuist beschreven migratie en daarmee het risico op loslating grondig te onderzoeken middels gerandomiseerde, gecontroleerde klinische studies. Hiernaast hebben we, door een veelvoud van dit soort studies te combineren, kunnen onderzoeken welke eigenschappen van de knieprothese, de patiënt en de chirurgische technieken een verhoogd risico op loslating met zich meebrengen.

Deel 1 – Het effect van aanpassingen in prothese-ontwerp op migratie

In **hoofdstuk 2** presenteren we de resultaten van een gerandomiseerde, gecontroleerde klinische studie waarin we gecementeerde protheses vergelijken die nagenoeg gelijk zijn in ontwerp, behoudens het materiaal van de 'tibia component' (het deel dat in het scheenbeen zit). Van de 59 patiënten die geïncludeerd werden, kregen er 30 de gebruikelijke metalen componenten met een dunne lager van plastic (polyethyleen), de overige 29 kregen een component die in zijn geheel van polyethyleen is gemaakt. Dit laatste ontwerp is goedkoper om te produceren maar heeft in het verleden bij oudere ontwerpen minder gunstige resultaten laten zien, waarna dit type prothese 'uit de mode' is geraakt. Nu er steeds meer patiënten in aanmerking komen voor dergelijke operaties, komen ook dit soort protheses weer op de markt om de kosten van de procedure te verlagen. In de studie laten we zien dat dergelijke protheses tegenwoordig op zijn minst even gunstige resultaten behalen twee jaar na de operatie ten opzichte van de metalen componenten met polyethyleen lager, zowel qua hoeveelheid gemeten migratie door middel van RSA als ook in klinische scorelijsten waarbij gekeken wordt naar functie en patiënt tevredenheid.

Daarnaast werd gezien dat de uitvoerend chirurg van enige invloed was op de uitkomst, waarbij de protheses die door chirurg 1 geïmplanteerd werden minder migratie lieten zien dan de protheses door chirurg 2. Dit gevonden effect laat zien dat een technisch optimaal uitgevoerde operatie het verschil kan maken op de lange termijn, in ieder geval op subklinisch niveau (en wél meetbaar met RSA).

In **Hoofdstuk 3** worden de resultaten beschreven van een gerandomiseerde RSA-studie waarbij een gecementeerde prothese met de gebruikelijke vast polyethyleen lager vergeleken wordt met een gecementeerde prothese met een mobiel lager, welke kan roteren ten opzichte van de metalen tibia component. Het mobiel lager biedt theoretische voordelen omdat de beweeglijkheid gedurende kniebuigingen zorgt voor minder druk op het metalen onderdeel en het kunststof lager en daarmee voor minder slijtage en kans op loslating. De studieresultaten laten zien dat alhoewel de onderzoeksuitkomsten zes jaar na de operatie vergelijkbaar zijn tussen de protheses met vaste en mobiele lagers, er veel meer complicaties optraden in de laatste groep. Dit komt doordat de operatie technisch lastiger is. Gedurende de operaties waarbij gerandomiseerd was voor een mobiel lager werd bij vijf patiënten alsnog een vast lager geïmplanteerd. In een zesde operatie had dit, achteraf gezien, ook moeten gebeuren want hierbij werd het mechanisme van het mobiel lager waarschijnlijk tijdens de operatie beschadigd, waardoor na de operatie het lager kon luxeren, met complicaties als gevolg. De studie werd na een analyse van deze complicatie stopgezet. We concludeerden dan ook dat de theoretische voordelen bij dit type mobiel lager niet gezien werden.

Het derde aspect dat we hebben onderzocht is de methode van fixatie. In **hoofdstuk 4** werd op basis van randomisatie gekozen voor ofwel een gecementeerde prothese of een ongecementeerde prothese met een 'peri-apatite' coating die de mate van botingroei zou kunnen bevorderen. Vijf jaar na de operatie werd meer migratie gezien van de ongecementeerde prothese. Dit was een uitkomst die we al verwachtten omdat botcement zorgt voor een directe prothese-bot fixatie terwijl ongecementeerde protheses enkele weken tot maanden de tijd nodig hebben om volledig in te groeien. In een tweede analyse waarin we de ingroeifase niet meenamen in de metingen, dus alleen met data vanaf 3 maanden, zien we juist minder migratie bij de ongecementeerde protheses ten opzichte van de gecementeerde protheses. De resultaten van de twee analyses laten zien dat de ongecementeerde prothese ondanks de iets hogere initiële migratie wel degelijk een stabiele biologische fixatie verkrijgt, die naar alle waarschijnlijkheid stabieler is op de lange termijn dan cement doordat de laatstgenoemde fixatie onderhevig kan zijn aan degradatie van het cement, met achteruitgang van de prothese-cement-bot verankering als gevolg.

In **hoofdstuk 5** bekijken we de lange termijn resultaten van een vierde studie waarin gerandomiseerd is tussen ongecementeerde protheses mét en zonder de peri-apatite coating. Niet alleen liet de groep met de coating veel minder migratie zien, ook waren deze allemaal stabiel op de lange termijn terwijl er in de groep zonder de coating enkele protheses dusdanig los gingen zitten dat dit proces ook op conventionele röntgenfoto's duidelijk zichtbaar werd. Ongecementeerde protheses van dit type knieprothese moeten dus een extra coating hebben om de ingroei van bot te stimuleren, ondanks dat deze coating vaak extra kosten met zich meebrengt.

Deel 2 – Chirurgische en patiënt gerelateerde risicofactoren voor migratie

Door de hoge nauwkeurigheid van RSA zijn er zoals eerder genoemd maar weinig patiënten nodig per studie om tot een duidelijke uitspraak te komen over de fixatie van een implantaat in het bot. Het nadeel van de kleine aantallen is dat het lastig is om over ándere risicofactoren voor migratie (en daarmee het risico op loslating van de prothese) uitspraken te doen dan de factor die primair is onderzocht. De groepen zijn simpelweg niet groot genoeg om subgroep analyses van enige waarde te kunnen toepassen.

Daarom beschrijven we in het tweede deel van dit proefschrift hoe we de ruwe data van een aantal eerdere RSA-studies combineren, om zo andere risicofactoren voor migratie van de prothese te analyseren.

Om dit betrouwbaar te kunnen doen, evalueren we eerst in **hoofdstuk 6** of het valide is om de data van RSA-studies die gebruik maken van verschillende soorten RSA-technieken te bundelen (i.e. marker-based en model-based) nadat we in de analyse corrigeren voor het verschil in referentiepunt.

De eerste studie (beschreven in **hoofdstuk 7**) waarin we drie RSA-studies combineren beschrijft het effect van de operatietechniek op gemeten migratie van de prothese. Hierbij wordt gekeken op welke manier de orthopeed tijdens de operatie de beenas van het aangedane been corrigeert, van varus ('O-been') naar neutraal of valgus ('X-been') of vice versa. De reden om dit te onderzoeken is dat recent steeds vaker gekozen wordt voor een techniek waarbij niet langer het aangedane been naar neutraal wordt gecorrigeerd maar steeds vaker in enige varus of valgus wordt gelaten. Van oudsher is de gedachte dat protheses langer meegaan als de belasting hierop evenredig wordt verdeeld, dus met een neutrale beenas. De laatste jaren waren er studies gepubliceerd die lieten zien dat een neutrale beenas voor veel mensen niet fysiologisch is. Hieruit ontstond de mening dat correctie van de natuurlijke beenas naar een neutrale beenas ten tijde van een gewrichtsvervangende operatie voor minder gunstige resultaten zou zorgen wat betreft functie en patiënttevredenheid. Er was echter geen bewijs dat het implanteren van een knieprothese in een natuurlijke beenas stand (varus of valgus) niet een gevaar was voor de levensduur van de prothese. Onze studieresultaten laten zien dat protheses die niet naar neutraal gecorrigeerd waren meer migratie laten zien, in het bijzonder bij de knieën die na de operatie nog in varus stonden. Dit was ook zo voor protheses die na de operatie in de varus stand stonden die overeen kwam met de voor die patiënt fysiologische varus stand. Op basis van onze resultaten blijkt derhalve dat het waarschijnlijk is dat de knieprotheses die niet gecorrigeerd worden tot een neutrale beenas een verhoogd risico hebben op loslating.

Tot slot wordt in **hoofdstuk 8** beschreven hoe, in samenwerking met twee Zweedse ziekenhuizen, de ruwe data van 11 RSA-studies werd gecombineerd om gegevens van 630 patiënten te kunnen analyseren met betrekking tot mogelijke risicofactoren voor migratie van de knieprothese. We hebben zowel gecementeerde als ongecementeerde protheses kunnen analyseren. Hierbij werd gekeken naar patiëntfactoren zoals geslacht, leeftijd, body mass index (BMI), diagnose (artrose, posttraumatische artrose en reuma) en de beenas voorafgaande aan de operatie. Daarnaast werden kenmerken van de gebruikte prothese (vast of mobiel lager, mét of zonder behoud van de achterste kruisband, mét of zonder coating om botingroei te stimuleren) en de beenas na de operatie als mogelijke factoren onderzocht. Het blijkt dat binnen de groep patiënten met een gecementeerde prothese en een verminderde botkwaliteit (zoals postmenopauzale vrouwen of patiënten met reuma) of waarbij meer kracht op de prothese komt (doordat de achterste kruisband chirurgisch is verwijderd) iets meer migratie wordt gezien, met name in de eerste drie maanden. Na het plaatsen van een ongecementeerde prothese zien we dat de implantaten zonder extra coating beduidend meer migratie laten zien. Ook was er meer migratie als de beenas na de operatie in varus staat. Andere factoren lijken geen overtuigend effect te hebben op migratie.

Conclusies en toekomstvisie

De studies beschreven in dit proefschrift laten zien dat kleine aanpassingen in het ontwerp van de knieprothese voor andere uitkomsten kunnen zorgen dan gewenst. Het is dus raadzaam om ten alle tijden kritisch te blijven op nieuwe, innovatief bedoelde ontwerpen. Elke aanpassing moet goed onderzocht worden door middel van (pre-)klinische studies, waarbij implantaat migratie metingen (zoals RSA) essentieel zijn.

We hebben geconcludeerd dat gecementeerde knieprotheses met een tibia component volledig van polyethyleen vergelijkbare resultaten laat zien als de (duurdere) modulaire protheses van polyethyleen en metaal. Daarnaast blijken de theoretische voordelen van een mobiel lager in het onderzochte type knieprothese niet aanwezig te zijn en de operatie eerder gecompliceerder te maken.

Wat betreft het type fixatie, laten de resultaten van de ongecementeerde protheses zien dat de uitkomsten hiervan zich tegenwoordig beter laten voorspellen. Indien het poreuze oppervlak van dergelijke protheses een extra coating krijgt (of geprint is met een zeer poreuze structuur) om de botingroei te bevorderen, lijkt de biologische fixatie op de lange termijn gunstiger dan na een gecementeerde prothese.

In de studies met gecombineerde ruwe data zien we dat een aantal theoretische risicofactoren ook daadwerkelijk een risico voor migratie van de prothese vormden, waaronder een varus beenas na de operatie. De asymmetrische belasting waaraan de prothese dan onderworpen wordt, is met de huidige typen knieprotheses dusdanig ongunstig dat het wenselijk blijft om tijdens de operatie een neutrale beenas na te streven. Desondanks zijn er steeds meer orthopeden die opteren om de fysiologische beenas van de patiënt na te streven, terwijl dit voor ongunstige lange termijn effecten zou kunnen zorgen. Er zullen dus nog meer studies moeten volgen die primair kijken naar het effect van de beenas correctie op migratie van de prothese.

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Curriculum vitae

Koen van Hamersveld was born on the 15th of June, 1989 in Amstelveen, The Netherlands. In 2007, he graduated from secondary school (Het Baken Park Lyceum, Almere) after which he started to study medicine at the Vrije Universiteit Amsterdam. During medical school and several years hereafter, he continued to play field hockey resulting in multiple championships with his club Almeerse, including winning the play-offs in 2015/16 to gain promotion to the men's highest national league.

Playing sports may have instigated his professional interest in orthopaedic surgery and traumatology, which started with elective internships at the VU University Medical Center during the final year of his medical training. After graduating from medical school in 2013, he started to work as an orthopaedic resident (not in training) at The Maartenskliniek, Woerden until January 2015. He then started to work on the research projects described in this thesis, as part of a PhD trajectory at the Department of Orthopaedics at the Leiden University Medical Center under supervision of prof. dr. R.G.H.H. Nelissen, prof. dr. ir. E.R. Valstar and dr. P.J. Marang-van de Mheen. During his PhD, he established international research collaborations and presented his work at multiple international scientific meetings. Following a (still ongoing) fruitful collaboration between the departments of orthopaedics of Leiden and the group of dr. S. Toksvig-Larsen in Hässleholm/Lund, Sweden, dr. S. Toksvig-Larsen was later added as a copromotor of his PhD.

In July 2018, he started his training to become an orthopaedic surgeon at the Department of General Surgery in Westfriesgasthuis, Hoorn, followed by residencies at the Department of Orthopaedics in Haga Hospital in The Hague & Reinier Haga Orthopedic Center in Zoetermeer (2020-2021) and Leiden University Medical Center (2021).