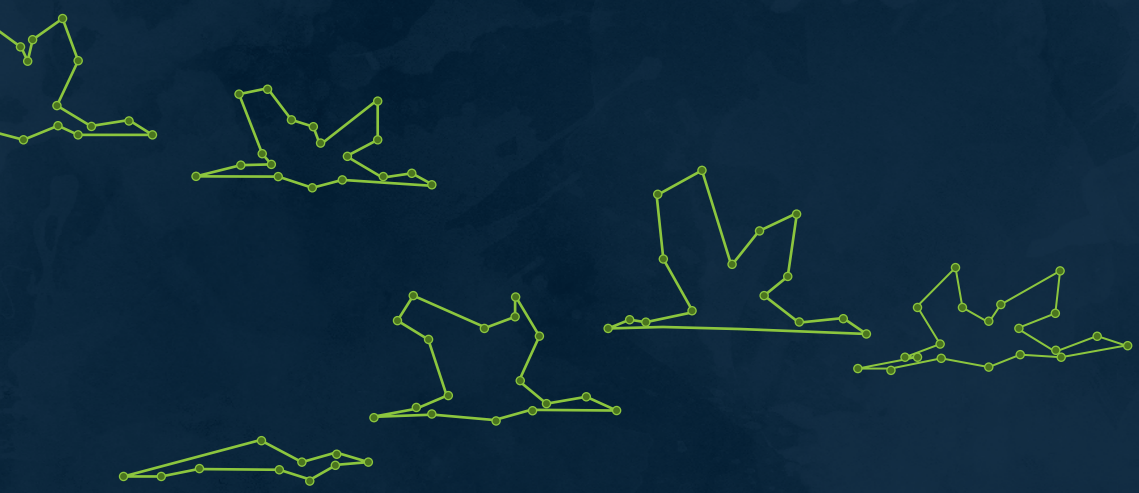
4D MEASURES OF MIGRATION AS A SAFETY PREDICTION OF HIP AND KNEE IMPLANTS

Advances in evaluating implant fixation



PAUL VAN DER VOORT

4D measures of migration as a safety prediction of hip and knee implants

Advances in evaluating implant fixation

Paul van der Voort

Colofon

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CONTENTS

Chapter 1	General introduction and outline of this thesis	7
Chapter 2	Long-term migration of a cementless stem with different bioactive coatings. Data from a "prime" RSA study: lessons learned.	19
Chapter 3	Migration behavior of two clinically excellent performing cementless stems with different design rationale: 5-year follow-up of a randomized RSA study.	47
Chapter 4	Comparison of femoral component migration between Refobacin bone cement R and Palacos R + G in cemented THA: a randomized controlled clinical and RSA study.	67
Chapter 5	Early subsidence of shape-closed THA stems is associated with late revision: a systematic review and meta-analysis of 24 RSA studies and 56 survival studies.	89
Chapter 6	Fixation of high-flexion TKAs: 5-year follow-up results of a 4-arm randomized controlled clinical and RSA study.	113
Chapter 7	A systematic review and meta-regression of mobile-bearing versus fixed-bearing TKA in 41 studies.	137
Chapter 8	Inducible displacement to predict tibial component loosening in TKA: an in vitro study.	155
Chapter 9	Summary and general discussion	179
Chapter 10	Summary in Dutch (Nederlands samenvatting)	189
Appendices	List of publications	199
	Curriculum vitae	203
	Dankwoord	205

General introduction and outline of this thesis

Joint replacement surgery by total hip and total knee arthroplasty (THA and TKA) are among the most performed interventions worldwide (1, 2). The Dutch Arthroplasty Register (LROI) reported a total of 33,248 THAs and a total of 25,859 TKAs performed in 2019 (3). A further increase in these numbers is expected in the future due to aging of the population and a growing number of people with obesity (3). The trend projection suggests an estimated increase in the Netherlands of 140% by 2030 (4, 5). Both THA and TKA are generally considered successful treatments, however 'treatment success' can be interpreted in different ways. Traditionally, outcome is evaluated by objective measurements such as implant survival and revision rates (6). However, in the last decade a shift has occurred towards subjective patient-perceived outcome measures addressing what is most relevant for patients (7).

Subjective outcome measures

Although joint replacement surgery is highly effective in improving health-related quality-of-life at group level, this is not the case on an individual level (8). Up to 30% of joint replacement patients are dissatisfied with the results after surgery and persistent pain is reported in 9% of THA patients and in 20% of TKA patients at long-term follow-up (9-11). Patient-reported outcome measures (PROMs) is the general term used for a variety of self-reported questionnaires which allow researchers to quantify a wide selection of outcome variables like pain, satisfaction, quality of life, and function. Although these PROMs are considered by some to give a good representation of patients' satisfaction and functional gain, one should be aware that they only present the perceived outcome of the pre-, intra-, and postoperative complexity of joint replacement surgery (12). Hence, objective measurements next to PROMs are imperative to evaluate treatment success.

Objective outcome measures

Objective outcome measures after THA and TKA are regularly based on survival and revision rates. According to the Dutch Arthroplasty Register (LROI) in 2019, a total of 2787 THAs revisions were performed with exchange of both or only the femur or acetabular component. In 2019 the overall revision TKA numbers were 1685 revisions of both or only the femur or tibial component. Aseptic loosening was the major cause of revision; accounting for 37.8% of THA and 28.9% of TKA revisions (3). Looking at other joint registries, on average 5 to 10 percent of the patients require revision surgery within 10 years after implantation. Aseptic loosening accounts for the greatest proportion, approximately 40%, of the revision surgeries and is therefore the main threat for implant longevity (13-15). Quantifying implant fixation to anticipate aseptic loosening is an ongoing challenge in follow-up care of joint replacement. Identifying unstable implants prone to failure also permits innovation of novel interventions to prevent progression to gross loosening thereby possibly averting revision surgery.

Aseptic loosening

The exact underlying mechanism of aseptic loosening is still under debate and yet not fully understood (16). The debate has mostly focused on the hypothesis of particle disease, which is based on retrieval studies of failed implants and histological studies of periprosthetic tissue showing wear particles (polyethylene-, cement- or metal particles) and abundant macrophages and giant cells in this tissue. This theory postulates that wear particles generate a proinflammatory state resulting in periprosthetic osteolysis and ultimately implant loosening (17-19). However, as wear particles slowly accumulate in time it cannot explain early cases of aseptic loosening. Hence, the early loosening theory was proposed (20, 21). While the particle disease states that loosening is induced by wear particles, the early loosening theory postulates that loosening is already initiated shorty after surgery by triggering factors such as a poor bony interlock (between the implant-bone, or bone-cement interface), poor bone quality (due to osteoporosis or rheumatoid arthritis), and resorption of a necrotic bone bed (due to surgical trauma or due to the heat from curing cement). Ultimately, the endpoint of both theories is identical; a proinflammatory state promoting osteoclast activity and inhibiting osteogenic activity of osteoblasts. As a result, bone resorption predominates at the implant-bone or bone-cement interface leading to bone defects and the formation of a fibrous-granulomatous interface tissue (22, 23). This interface tissue has negligible stiffness and does not provide a strong interlock, resulting in motion of the implant in relation to the bone (24, 25). After initial loosening, biomechanical factors such as implant design and magnitude of mechanical stress can lead to progression of loosening, resulting in increasing periprosthetic osteolysis and subsequent gross migration. For example, a femoral component with a long neck in a varus position is exposed to extra high torque loads. Aseptic loosening is a slow, continuous process, gradually causing clinical symptoms such as pain. By the time a fibrous tissue layer is visible on conventional radiographs, presented as a radiolucent line around the implant, the loosening process may already be at an advanced stage (26). However, it is possible to detect this loosening process as early as 1 to 2 years postoperatively by measuring implant migration with roentgen stereophotogrammetric analysis (RSA).

RSA

RSA is a highly accurate stereo X-ray technique for the assessment of 3D movement between two rigid bodies, for example movement of an implant relative to the bone. The use of X-rays to determine the 3D position of an object in space dates back to the time X-rays were discovered (27). Modern utilization of RSA is based on the work of Göran Selvik, a Swedish mathematician and anatomist, who described the technique in his thesis in 1972 (28). Over time this technique improved due to the introduction of digital radiographs and software measurements thereby reducing the time for analysis significantly (29, 30). In order to measure movement of an implant in relation to the bone, small X-ray opaque tantalum markers are attached onto the implant by the manufacturer and during surgery markers are placed into the bone surrounding the implant thereby creating two rigid bodies. A typical modern RSA setup consists of two synchronized X-ray

tubes, a calibration box, which holds markers at accurately known positions, and a radiograph detector. The patient is positioned in between the X-ray tubes and the calibration box, producing two plain, stereo radiographs showing the implant of interest, the bone markers and the calibration box markers. With the help of software, the 3D positions of the X-ray tubes are reconstructed from the projected calibration box markers on the two digital radiographs. Subsequently, the 3D positions of the markers on the implant and in the bone can be reconstructed, producing a 3D RSA scene. By fitting the rigid body of the reference bone markers of all following RSA scenes onto the postoperative RSA scene, the migration overtime of the implant relative to the bone can be calculated (31, 32). Measuring migration over time with RSA has an accuracy between 0.05 and 0.5 mm for translations and between 0.15 and 1.15° for rotations (32). Compared to conventional radiographs, which have an accuracy between 5 and 12 mm for translations, the accuracy of RSA is 10-20 fold better (33). The attachment of markers (i.e. marker-based RSA) onto the implant poses some issues; the marker-based implants are more expensive in comparison to their conventional counterparts and the attached markers may jeopardize its strength and could also act as local stress risers. In order to overcome these problems, a method was developed that does not require any markers on the implant: model-based RSA (MB-RSA) (30, 34). MB-RSA uses CAD models or models from reversed engineering instead of markers on the implant. The 3D virtual surface models are "matched" on the radiographs by minimizing the difference between the virtual projection of the model with the actual projection as it appears in a radiograph.

Clinical implication

Due to its high accuracy, migration as measured with RSA, has shown to be able to predict future long-term (10 years) loosening of THA and TKA based on early follow-up (1-2 years) (24, 25, 35-37). Furthermore, combining early RSA migration data with survival studies using meta-regression analyses revealed that early migration of both acetabular cups in THA and tibial components in TKA is associated with late revision (38, 39). Using meta-regression analyses thresholds values for early migration were established, thereby providing an upper limit of acceptable early migration, above which implants are at risk for future failure. The Dutch Orthopaedic Association (NOV) adopted RSA as an early qualitative tool as part of a phased introduction of newly designed implants. For that matter, RSA exposes only a small number of patients during a relatively short period of time to a potential poor "new" implant design (40). In 2013, the International Organization for Standardization (ISO) published a standard protocol for early clinical studies, providing requirements for the clinical assessment of migration of implants with RSA. By performing and reporting results in a standardized manner, comparison of RSA studies is more straightforward and will enhance its applicability as a qualitative tool in a phased introduction of novel implants (41).

Inducible displacement

The evaluation of implants using RSA has primarily focused on the migration of the implant over a period of time, i.e. comparing the postoperative relative position of the implant in relation to the host bone, versus the position of the implant 1 or 2 years later. However, another approach is to instantly measure migration, i.e. comparing the relative position of the implant in a loaded and an unloaded situation. Thereby inducing a displacement on the implant. Inducible displacement is a tool to evaluate implant fixation on a specific moment in time, instead of assessing fixation by measuring migration longitudinally. The first publications describing inducible displacement dates back to the late 1980s, while most research was published in the 1990s (42). Although inducible is promising in theory, the number of publications addressing inducible displacement declined in the 2000s. The latter was probably related to uncertainty about the underlying mechanism of inducible displacement, inconsistent results and the lack of a distinct loading protocol. In theory, inducible displacement can take place within the implant itself (i.e. implant elasticity), as movement or deformation within the fixation interface (implant-bone, implant-cement, cement-bone), or as an elastic deformation within the bone (43, 44). Research on inducible displacement has focussed on TKA and several loading protocols have been employed to generate a displacement. These so-called stress tests have commonly included weight-bearing on the affected limb (single-leg stance, step-up and step-down, squatting) and weight-bearing with a torque applied at the foot to induce a rotatory stress. A number of studies have found significant, albeit weak correlations between inducible displacement and migration (44-48). However, today it is still unclear which approach of inducing a force onto an implant is effective and foremost how much inducible displacement is acceptable and thus can be used as a threshold value to predict the risk of future loosening of an implant.

Advances in measuring implant migration

Migration analysis of implants as measured with RSA has led to several milestones for implant safety in patient care. The association of early migration with late failure has led to the implantation of migration analysis as part of a phased introduction of implants to the market. Another success is the definition of thresholds values for acceptable early migration, it is important to judge these values in time in relation to each other, meaning is a "plateau phase" reached. The latter can be used as a benchmark in a phased introduction of new implants. Also, evaluation of early migration provided more insight into the loosening process and resulted in the early loosening theory of aseptic loosening. Furthermore, ISO guidelines will enhance conformity of RSA studies performed worldwide thereby enhancing developments. However, there are still some advances to be realized. Thresholds values for acceptable early migration are yet only available for acetabular cups in THA and for tibial components in TKA, however not for femoral stems in THA. Moreover, little is known about the migration patterns of distinct implants designs and characteristics. Additionally, RSA studies addressing long-term migration patterns are scarce. What is more, inducible displacement has great potential but needs resurgence.

AIM AND OUTLINE OF THIS THESIS

The overall aim of this thesis is to examine the influence of implant factors on fixation of both THA and TKA, measured as both migration over time and inducible displacement, and quantified by RSA. Within this aim, areas of focus are examining migration patterns of both cemented and cementless femoral stems in THA, determining the effect of mobile-bearings in TKA on migration and survival, and considering how inducible displacement has potential for clinical applications of evaluating implant fixation.

The first part of this thesis concerns femoral stems in THA. In **Chapter 2** the migration of a cementless femoral stem with a long, conical design (Mallory-Head Porous), with up to 25 years of follow-up, is described and compared among different bioactive coatings (i.e. hydroxyapatite, fluorapatite, uncoated). The same Malloy-Head Porous stem is subsequently compared to the Taperloc stem with a flat wedged design. For this purpose, a randomized controlled trial described in **Chapter 3**, was performed comparing the migration and functional outcome of these two cementless stems with different design rationale. **Chapter 4** presents the results of a randomized controlled trial comparing two different types of bone cement (Palacos R + G and Refobacin bone cement R) in a stem with a shaped-closed design (Stanmore). To establish thresholds for acceptable early migration, a systematic review on the association between early migration and late aseptic revision of stems is included in **Chapter 5**.

The second part of this thesis concerns TKA. In **Chapter 6** the migration and functional outcome of four different TKA designs (high-flexion and conventional, either with a mobile-bearing or fixed-bearing) are compared in a randomized controlled trial. The effect of bearing type on implant survival is elaborated in a systematic review between mobile-bearing and fixed-bearing TKA and described in **Chapter 7**.

The third part of this thesis comprises an experimental study investigating approaches to instantly detect loosening in TKA. In **Chapter 8** an *in vitro* study is presented testing different methods to induce a measurable displacement in an artificially created loose implant.

Finally, **Chapter 9** summarizes the studies described in this thesis with a general discussion and final conclusions.

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2

Long-term migration of a cementless stem with different bioactive coatings

Data from a "prime" RSA study: lessons learned

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ABSTRACT

Introduction

Little is known about the long-term migration pattern of cementless stems in total hip arthroplasty (THA). Furthermore, the role of bioactive coatings in fixation, and thus migration, remains uncertain. Hydroxyapatite (HA) is the most commonly used bioactive coating. However, delamination of the coating might induce loosening. Alternatively, fluorapatite (FA) has proved to be more thermostable than HA, thereby potentially increasing longevity. We assessed the long-term migration of cementless stems with different coatings using roentgen stereophotogrammetric analysis (RSA), thereby establishing a reference for acceptable migration.

Methods

61 THAs in 53 patients were randomized to receive either a HA, FA, or uncoated Mallory-Head Porous stem during the years 1992 to 1994. Primary outcome was stem migration measured using RSA and secondary outcome was the Harris Hip Score (HHS). Evaluation took place preoperatively and postoperatively on the second day, at 6, 12, 25 and 52 weeks, and annually thereafter. At the 25-year follow-up, 12 patients (17 THAs) had died and 1 patient (1 THA) was lost to follow-up. Due to the high number of missing second-day postoperative RSA radiographs, the 1-year postoperative RSA radiograph was used as baseline for the comparative analyses.

Results

Mean follow-up was 17 years (SD 6.6). All stems showed initial rapid migration with median subsidence of 0.2 mm (–0.1 to 0.6) and median retroversion of 0.9° (–3.2 to 2) at 12 months, followed by stable migration reaching a plateau phase. No stem was revised, albeit 1 stem showed continuous subsidence up to 1.5 mm. Comparing the different coatings, we could not find a statistically significant difference in overall 25-year migration (p-values > 0.05). Median subsidence at 15-year follow-up was for HA –0.1 mm (–0.4 to 0.2), for FA 0 mm (–0.1 to 0.2), and for uncoated stems 0.2 mm (–0.1 to 0.5). Median internal rotation at 15-year follow-up was for HA not available, for FA 1.1° (–0.5 to 2.6), and for uncoated stems 0° (–0.5 to 0.4). HHS were also comparable (p-values > 0.05), with at 15-year follow-up for HA 85 points (41–99), for FA 76 points (61–90), and for uncoated stems 79 points (74–90).

Conclusions

The long-term migration pattern of cementless stems using different bioactive coatings has not previously been described. No beneficial effect, or side effect at long-term follow-up of bioactive coatings, was found. The provided migration data can be used in future research to establish thresholds for acceptable migration patterns cementless stem designs.

INTRODUCTION

Long-term migration data on cementless femoral stems in total hip arthroplasty (THA) is scarce, with only a few studies reporting migration measured with roentgen stereophotogrammetric analysis (RSA) with follow-up beyond 10 years (1, 2). In a prior meta-analysis we were unable to establish a threshold for acceptable early subsidence for cementless stems, because of the lack of long-term survival and migration data (3). As the number of THAs being performed is still on the rise, as well as the number of relatively young patients receiving mostly cementless THAs, the burden of future failure and subsequent revision is expected to increase (4). Hence longevity of implants is paramount and should be scrutinized.

Although bioactive coatings for cementless stems are widely employed, their beneficial effect remains questionable (5, 6). Pooled data from randomized and cohort studies showed no clinical benefit of hydroxyapatite (HA)-coated implants (7-10) and large registry studies found no difference in risk of revision surgery (5, 11, 12). A recent registry study found an overall lower risk of revision of HA-coated stems, but this was not consistent among different implant types, suggesting a significant influence of distinct design features on longevity (6).

Bioactive coatings were introduced in the 1980s to enhance fixation by osseointegration, with HA used as the most common coating (13, 14). However, retrieval studies have shown resorption and delamination of the HA coating from the implant, which raised concerns regarding the induction of osteolysis and, ultimately, failure of the implant (15, 16). Fluorapatite (FA) was introduced as an alternative to HA with comparable biocompatibility and osteoconductive properties (17), but with better thermostability (18). Hence, FA might adhere better to the implant during the application process using a plasma-spraying technique, thereby possibly reducing resorption and delamination of the coating (19).

HA-coated implants have shown reduced migration in comparison with their uncoated counterparts (20, 21). To our knowledge, FA has not been investigated in RSA studies, or in clinical trials.

In 1991, we initiated a trial to investigate the influence of different coatings on migration of cementless stems, the first RSA study performed at our facility. Despite teething problems, patient follow-up was continued to provide long-term migration data on cementless stems in general, and bioactive coatings specifically.

METHODS

Study design

This study was initially designed in 1991 as a multi-center, single blinded, randomized controlled trial comparing the influence of different coatings on the migration and clinical outcome of cementless THA. During the pilot phase of this study logistical problems were encountered with regard to obtaining RSA radiographs at the different participating hospitals, as this was (at that

time) possible at only 1 institute (Leiden University Medical Center). Subsequently, it was decided to continue as a single-center study performed at the Leiden University Medical Center. From May 1992 to May 1994, all consecutive patients scheduled to receive a cementless primary THA for osteoarthritis, either primary or secondary to a systematic inflammatory disease and younger than 65 years of age, were approached for participation in a randomized, clinical RSA study.

Included patients were randomized to 2 intervention groups receiving either an HA- or FA-coated implant and the control group received an implant without a bioactive coating. Treatment allocation was randomized with the use of a computer-generated randomization scheme and bilateral cases were allowed. The study design was single-blind; surgeons were aware of the coating used; clinical observers were blinded to the type of coating. The study was performed in compliance with the Helsinki Declaration, approval of the institutional medical ethical board was obtained, and all patients gave written informed consent.

Surgical technique

All THAs were implanted by experienced hip surgeons, or under their direct supervision. Surgeries were performed through a direct lateral approach in the lateral decubital position, except for 2 posterolateral approaches. For RSA measurements, 1-mm tantalum markers were inserted into the proximal femur during surgery. All patients received the same rehabilitation program starting with passive and controlled active movements on the first postoperative day and mobilization with full weight-bearing on the second postoperative day, after the first RSA radiograph was obtained.

All patients received a Mallory-Head Porous stem with a dual tapered design with a round cross-sectional geometry (Biomet, Warsaw, IN, USA). The stem is characterized by an anterior and posterior flange and wide lateral fin. It is made of a titanium alloy (Ti-6A1-4V), with a porous coating on the proximal third, a grit-blasted surface on the middle third, and a smooth satin-textured surface on the distal third (Figure 1). The implants with a bioactive coating received either HA or FA plasma-sprayed onto the proximal porous coated surface. All patients received a 28 mm cobalt-chromium head and a cementless Mallory-Head finned Ringloc acetabular cup (Biomet, Warsaw, IN, USA).

Figure 1. Mallory-Head Porous stem, with a porous coating on the proximal third, a grit-blasted surface on the middle third, and a smooth satin-textured surface on the distal third.

Follow-up

Patients were evaluated preoperatively and postoperatively at 6 weeks, 3 months, 6 months, 1 year, and annually thereafter. At each evaluation, RSA radiographs were obtained and the Harris Hip Score (HSS) was determined. Conventional anteroposterior and lateral radiographs were acquired preoperatively, at 6 weeks, and at 2, 5, 10, 20, 25 years postoperatively, and on indication (e.g. pain or suspected failure). On the 6-week postoperative radiographs the stem orientation (i.e. varus, neutral, or valgus) was determined. Patients unable to attend follow-up moments were contacted to check implant status and whether implant-related problems had arisen.

RSA technique

RSA radiographs were obtained using a uniplanar setup with the patient in supine position and the calibration cage underneath the examination table. During follow-up, in 2002, the initial calibration box (Large Reference Box, Leiden, The Netherlands) was replaced by a new box (Carbon Box, Leiden, The Netherlands). Furthermore, in 2004 digital radiography was introduced. Both changes had no effect on the accuracy of the RSA measurements (22). A marker-based analysis was carried out to calculate migration over time (Model-Based RSA software, version 3.34; RSAcore, The Netherlands), using 4 stem markers: 3 markers attached to the stem (performed by the manufacturer) and the center of the head acted as a fourth marker. Migration was expressed as translations along and rotation about 3 axes (longitudinal, transverse, and sagittal) of a right-handed orthogonal coordinate system. Since the failure mechanism of stems consists of subsidence and retroversion (23), the primary effect variables were translation along and rotation about the longitudinal axis. The accuracy of RSA measurements was determined by obtaining double examinations of 29 stems. Assuming zero migration in the brief time interval between these double examinations, the limits of the 95% prediction interval of accuracy of zero migration were determined (Table 1) (24). For all examinations, the mean error of rigid body fitting of the RSA markers in the femur was below 0.35 mm; the mean condition number of the RSA markers was 37 (SD 22; range, 13–111) in the femur. Bone markers were defined as unstable when they moved more than 0.5 mm with respect to the other bone markers. Unstable markers were excluded from the analyses. These values satisfy the marker stability and distribution criteria of the RSA guidelines and the ISO guideline (ISO 16087:2013) (25, 26).

Stem	Transverse	Longitudinal	Sagittal
	(x-asis)	(y-axis)	(z-axis)
Translation — mm	0.22	0.17	0.54
Rotation — degrees	0.8	1.13	0.31

Table 1. Accuracy of RSA measurements (upper limits of 95% zero motion confidence interval).

Statistics

Measured values of normally distributed data are reported as the mean (SD); measured values of non-normally distributed data are reported as the median (range). Estimates are reported as the mean and the 95% confidence interval (CI). Reported analyses were performed according to the per-protocol principle to reflect the genuine effect of treatment (i.e., HA vs. FA vs. uncoated). To safeguard for attrition bias, all analyses were repeated according to the intention-to-treat principle and compared with the outcomes of the per-protocol analyses. Migration and increase in HHS throughout the follow-up period were analyzed with use of a linear mixed model (LMM) with subject as a random effect. This model deals effectively with repeated measurements, missing values, and variation in duration of follow-up (27). Differences between the stems were assessed by estimating the main treatment effect and the stem type × time interaction, both as an overall effect over the entire follow-up period taking the repeating measurements into account. The assessment of the interaction term allows for the investigation of possible time-varying mean differences. At the 5- and 15-year follow-up point, the mean differences were assessed using ANOVA. As a sensitivity analysis, separate adjusted analyses were carried out with age, gender, BMI, and diagnosis (primary or secondary osteoarthritis) as covariates. A p-value of <0.05 was significant (SPSS version 20.0; IBM Corp, Armonk, NY, USA).

RESULTS

Patients

From May 1992 to May 1994, 75 consecutive THAs in 67 patients were assessed for inclusion and 61 THAs in 53 patients were randomized (Figure 2). In 19 THAs (19 patients) RSA analyses could not be performed due to absence of either bone markers (n = 10) or RSA radiographs (n = 9). These 19 patients were comparable to the analyzed group with respect to gender, BMI, age at surgery, surgeon, stem orientation, and preoperative HHS (post-hoc chi-square test and unpaired Student's t-test; p-values > 0.05). Thus, 34 patients (42 THAs) were analyzed with a mean follow-up of 17 years (SD 6.6). 7 stems were HA-coated, 6 stems were FA-coated, and 11 stems were uncoated (Table 2). 1 patient was randomized for a HA-coated stem, but instead received an uncoated stem. In 18 stems the coating was unknown due to missing implant stickers in 9 cases, missing coating details on the implant sticker in 4 cases, and missing medical (paper) records in 5 cases. 12 patients (17 THAs) died during follow-up and 1 patient (1 THA) emigrated and was subsequently lost after 5 years of follow-up.

Migration

Second-day postoperative RSA radiographs were available in only 10 out of 42 stems, whereas RSA radiographs at 1-year follow-up were available in 38 out of 42 stems (Figure 3). As the number of available second-day postoperative RSA radiographs was not sufficient to make meaningful

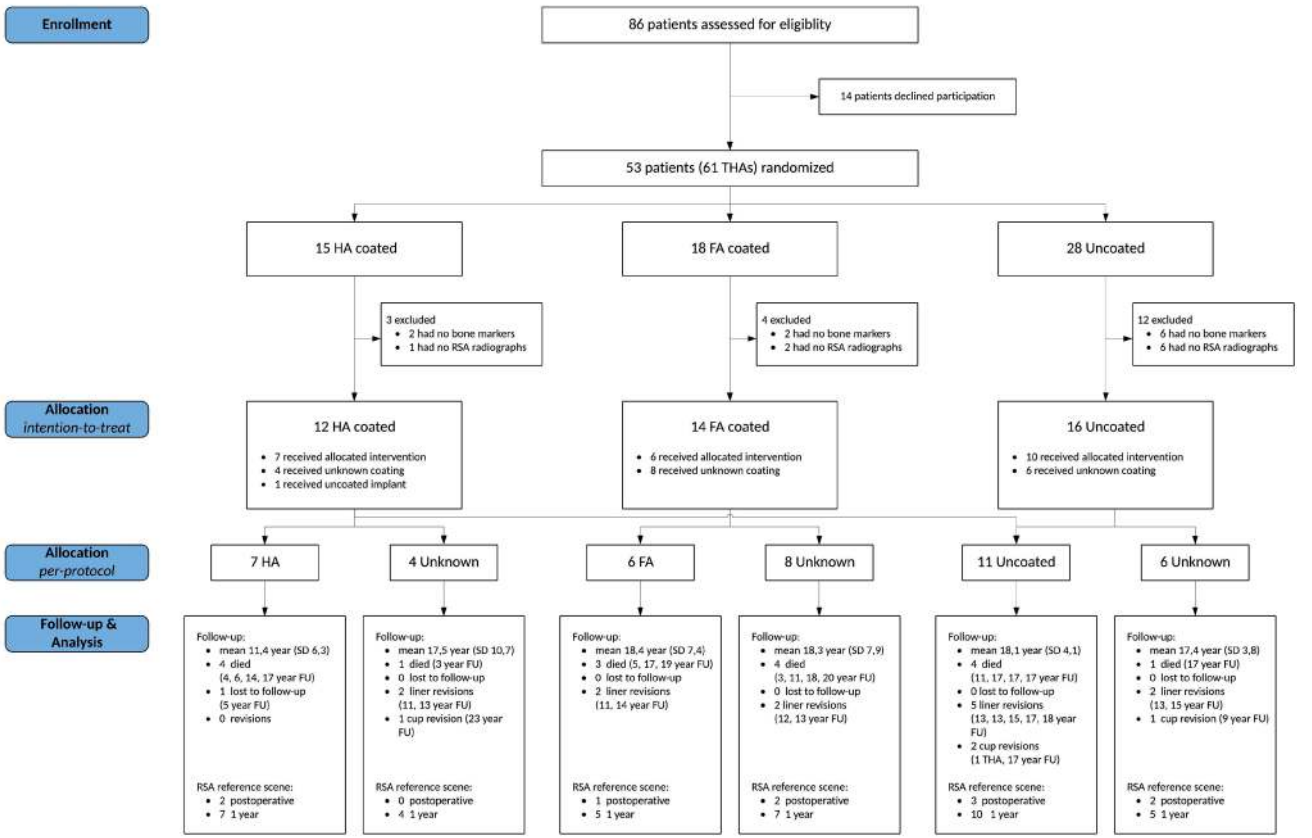

Figure 2. CONSORT flowchart of patient recruitment, allocation and follow-up. THA = total hip arthroplasty; HA = hydroxyapatite; FA = fluorapatite; FU = follow-up; SD = standard deviation.

Characteristic	Hydroxyapatite (n = 7)	Fluorapatite (n = 6)	Uncoated (n = 11)	Unknown (n = 18)
Gender — no. (%)				
Male	3 (42.9%)	1 (16.7%)	5 (45.5%)	7 (38.9%)
Female	4 (57.1%)	5 (83.3%)	6 (54.5%)	11 (61.1%)
BMI* — kg/m²	23.3 ± 5.6	28.1 ± 2.7	23.6 ± 4.5	25.2 ± 3.3
Age at surgery* — yr	57.7 ± 15	56.6 ± 12.5	50.3 ± 14.1	52.6 ± 9
Diagnosis — no. (%)				
Osteoarthritis	5 (71.4%)	2 (33.3%)	4 (36.4%)	6 (33.3%)
Rheumatoid arthritis	1 (14.3%)	2 (33.3%)	4 (36.4%)	9 (50%)
Hip dysplasia	0	1 16.7%)	1 (9.1%)	1 (5.6%)
Ankylosing spondylitis	1 (14.3%)	1 (16.7%)	1 (9.1%)	0
Osteonecrosis	0	0	0	2 (11.1%)
Perthes disease	0	0	1 (9.1%)	0
Side — no. (%)				
Left	4 (57.1%)	5 (83.3%)	5 (45.5%)	6 (33.3%)
Right	3 (42.9%)	1 (16.7%)	6 (54.5%)	12 (66.7%)
Surgeon — no. (%)				
Consultant	7 (100%)	6 (100%)	10 (90.9%)	14 (77.8%)
Resident	0	0	1 (9.1%)	4 (22.2%)
Stem orientation — no. (%)				
Varus	0	1 (16.7%)	0	1 (5.6%)
Neutral (< 3 degrees)	7 (100%)	5 (83.3%)	10 (91%)	16 (88.8%)
Valgus	0	0	1 (9%)	1 (5.6%)
Preoperative HHS* — min 0 - max 100 points	33.2 ± 17.5	34.3 ± 4.5	32.1 ± 13.7	36.8 ± 15

Table 2. Group characteristics at baseline. Values are count unless otherwise specified.

comparative analyses between different coatings, the 10 stems available for direct postoperative migration measurement were analyzed as a single cohort, independent of coating, showing relatively rapid subsidence during the first postoperative year with a median subsidence of 0.2 mm (–0.1 to 0.6) at 12 months, followed by stable subsidence during the remaining follow-up period (Figure 4). During the period of initial subsidence there were also relatively large rotations of these stems in the horizontal plane, which stabilized after 1 year (Figure 5).

The 38 stems available for migration measurement using the 1-year postoperative RSA radiograph as baseline were analyzed both as a single cohort, and in a comparative manner using different coatings. Migration of the overall cohort showed rather stable subsidence and rotation until 14 years of follow-up, after which the migration patterns began to show large variability (Figures 4 and 5). Also, from this time period onward the number of patients attending the RSA outpatient clinic began to decline (Figure 3). For the comparative migration analyses (i.e., HA vs. FA vs. uncoated stems), both intention-to-treat (ITT) and per-protocol (PP) analyses were performed. The ITT analyses reflect the best-case scenario, using allocation as per randomization group of

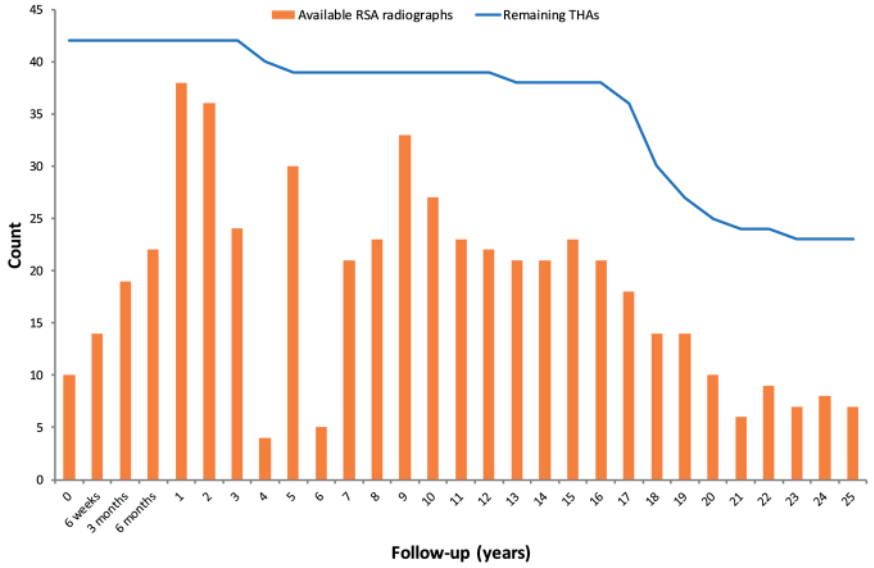

Figure 3. Bar graph showing number of RSA radiographs available for analysis per follow-up point. Line graph showing number of THAs in follow-up (i.e., total minus deceased and lost to follow-up).

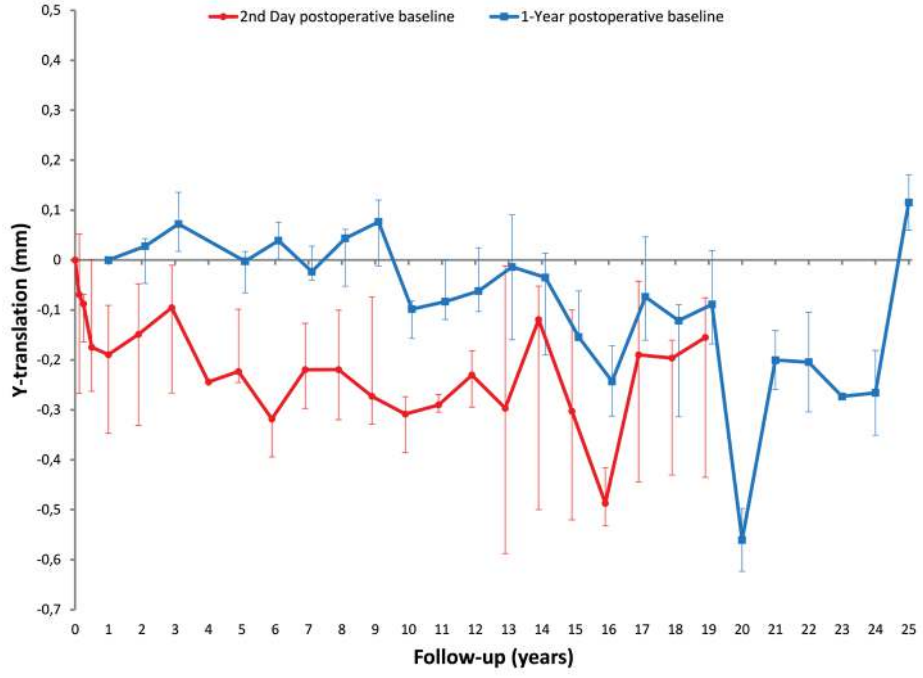

Figure 4. Median Y-translation (i.e., translation along the longitudinal axis) with interquartile ranges of the complete cohort during the 25 years of follow-up, using both the second-day (n = 10) and the 1-year (n = 38) postoperative RSA radiographs as a baseline.

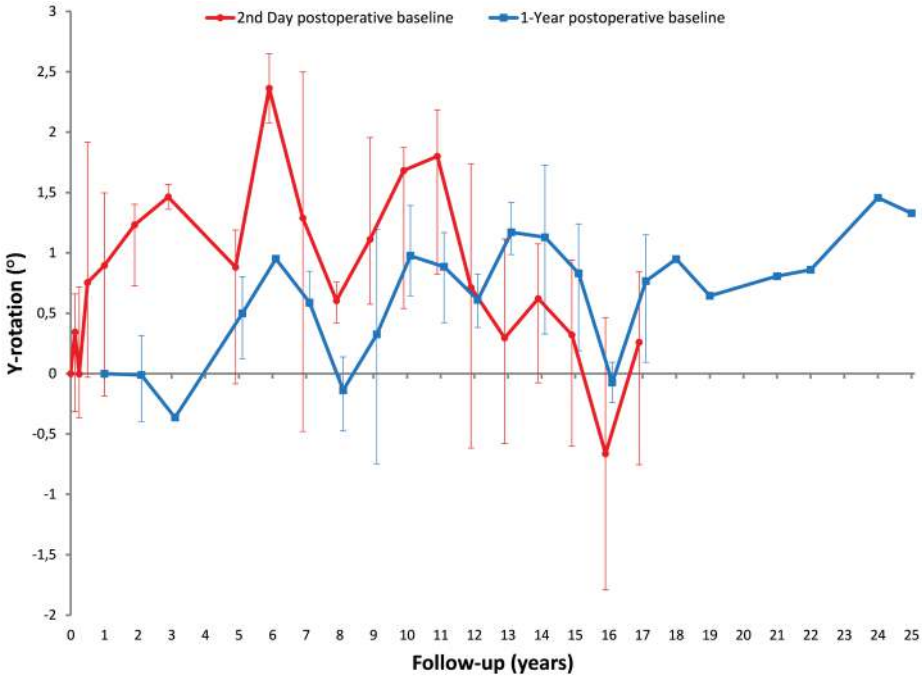

Figure 5. Median Y-rotation (i.e., internal rotation about the longitudinal axis) with interquartile ranges of the complete cohort during the 25 years of follow-up, using the both the second-day (n = 6) and the 1-year (n = 17) postoperative RSA radiograph as a baseline.

42 THAs (including both 24 THAs with verified and 18 THAs with unknown coating) (Figure 6), whereas per-protocol (PP) analyses reflect the genuine effect of the different coatings, including only the 24 THAs with verified coating and excluding the 18 THAs with unknown coating (Figure 7). Post-hoc verification revealed adequate randomization in both ITT and PP analyses as the 3 different coatings coating groups were comparable with respect to gender, BMI, age at surgery, surgeon, stem orientation, and preoperative HHS (post-hoc chi-square test and 1-way ANOVA; p-values > 0.05). Overall, 25-year migration did not reveal a significant difference among the 3 different coatings in both the ITT and PP analyses (LMM; p-values > 0.05; Table 3; Appendix A and B). Furthermore, we could not find a significant difference in time to stabilization and subsequent migration, that is, no evidence of interaction (coating type × time interaction; LMM; p-values > 0.05; Appendix A and B). Migration of the stems was comparable among the 3 coatings at the prespecified time points of 5 years and 15 years postoperatively (1-way ANOVA; p-values > 0.05; Table 3). The results of the adjusted analyses were comparable to the results from the unadjusted analyses and age, gender, diagnosis, and BMI did not significantly influence migration.

Subsidence in 1 stem did not stabilize (Figure 8). This stem was randomized for no coating, but as the implant sticker was missing this could not be verified. At the last available radiograph after 17 years of follow-up there was evidence of subsidence, and around the tip of the stem

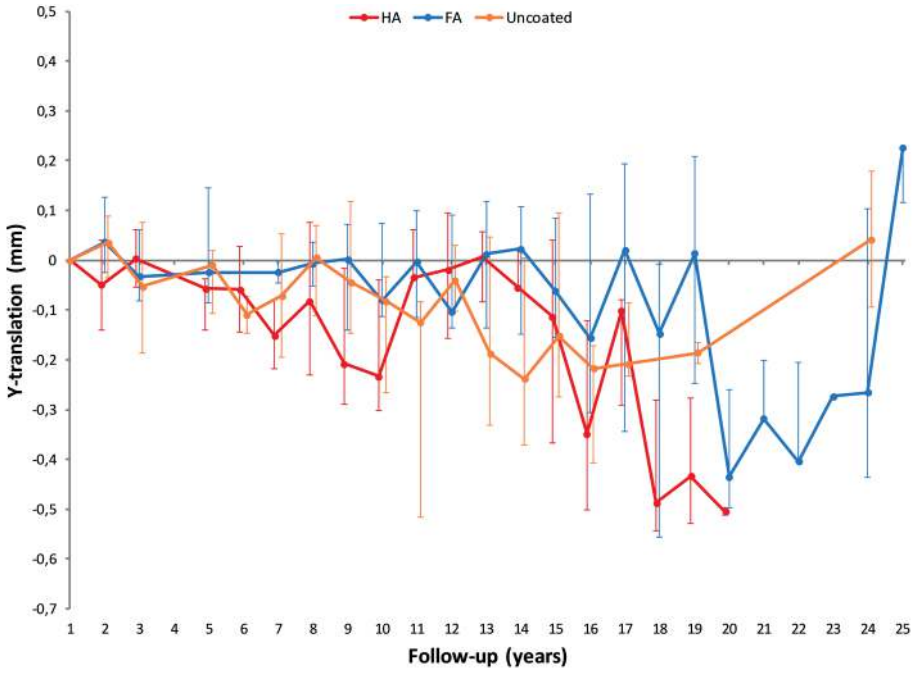

Figure 6. Median Y-translation (i.e., translation along the longitudinal axis) with interquartile ranges during the 25 years of follow-up of the HA, FA, and uncoated stems, using intention-to-treat analysis (i.e., all included stems as per randomization group) and the 1-year postoperative RSA radiograph as a baseline (i.e., unknown initial migration).

radiolucencies and pedestal formation were noticeable. However, the HHS remained higher than 90 points during follow-up.

Clinical outcome

We could not find a significant difference in HHS among the groups during follow-up in both the PP and ITT analyses (LMM; p-values > 0.05; Table 4; Appendix C and D). Between-group differences did not change significantly over time (coating type × time interaction; LMM; p-values > 0.05; Appendix C and D). Adjusted analyses for age, gender, diagnosis, BMI, and postoperative HHS gave similar results. Furthermore, comparing the HHS at the 15-year follow-up point did not yield any statistically significant differences (1-way ANOVA; p-values > 0.05; Table 4).

Survival

None of the stems were revised during follow-up. There were 13 liner revisions in 13 THAs due to wear. In 1 THA (uncoated) with a liner revision 13 years after follow-up, the cup was revised due to aseptic loosening 20 years after follow-up and subsequently re-revised a couple weeks later due to malpositioning. In addition, 2 more cups in 2 THAs (coating unknown) were revised due to aseptic loosening. During follow-up, 12 patients (17 THAs) died due to causes unrelated

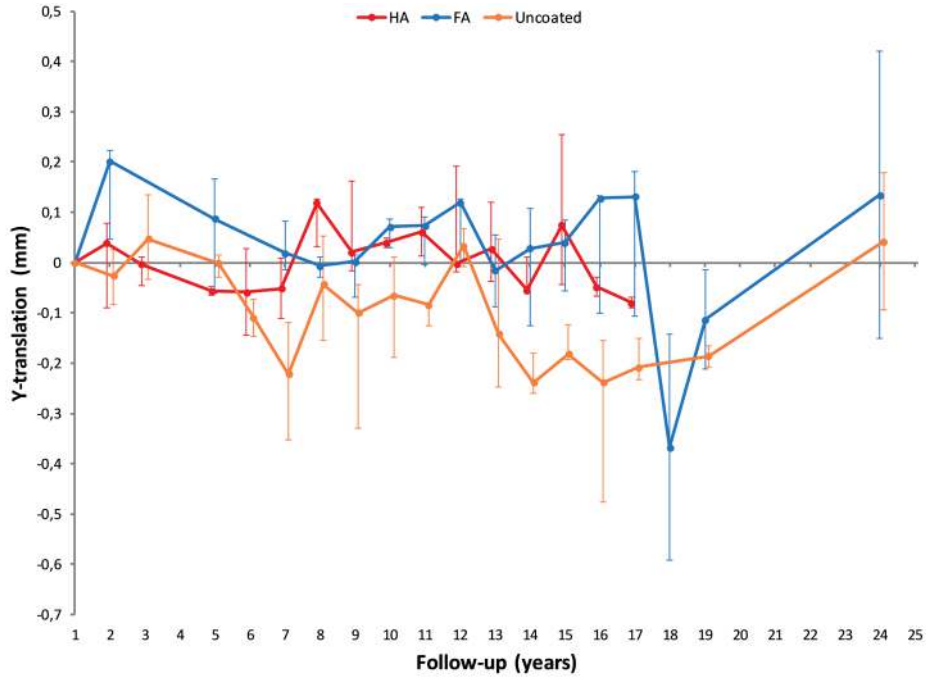

Figure 7. Median Y-translation (i.e., translation along the longitudinal axis) with interquartile ranges during the 25 years of follow-up of the HA, FA, and uncoated stems, using per protocol analysis (i.e., only stems with verified coating) and the 1-year postoperative RSA radiograph as a baseline (i.e., unknown initial migration).

to the THA. 1 patient (1 THA) was lost to follow-up due to emigration, the fate of this THA could not be determined.

DISCUSSION

We found stable migration and thus fixation of the cementless Mallory-Head Porous stem over a period of 25 years. After initial migration, all but 1 out of 42 stems stabilized after 1-year follow-up and there were no stem revisions. 4 cups were revised due to aseptic loosening and 13 liners were revised due to wear. Comparative analyses did not yield a difference in migration and clinical scores among HA, FA, and uncoated cementless stems. Furthermore, there was no difference in time to stabilization between coated and uncoated stems, thus excluding a delamination problem occurring later in follow-up.

To our knowledge, this is the first long-term RSA study with over 20 years of follow-up, and the first RSA study comparing migration of HA, FA, and uncoated stems. Only a few RSA studies describe migration beyond 10-year follow-up. Sesselman et al. (2018) reported migration of 26 cementless Cerafit stems with a follow-up of 10 years. They found a median subsidence of 0.01 mm

Migration	Hydroxyapatite		Fluorapatite		Uncoated		PER PROTOCOL Main effect	PER PROTOCOL Prespecified time point
	N	Median (range)	N	Median (range)	N	Median (range)	*p*-value	*p*-value
SUBSIDENCE — mm*								
year 2	7	0.04 (-0.19 to 0.32)	5	0.20 (-0.02 to 0.27)	8	-0.03 (-0.16 to 0.12)	0.14	
year 5	2	-0.06 (-0.07 to -0.04)	5	0.09 (-0.16 to 0.44)	6	0.00 (-0.12 to 0.12)		0.6
year 10	2	0.04 (0.02 to 0.06)	4	0.07 (-0.08 to 0.12)	7	-0.07 (-0.41 to 0.37)		
year 15	3	0.07 (-0.16 to 0.44)	3	0.04 (-0.15 to 0.13)	5	-0.18 (-0.52 to 0.12)		0.51
year 20	0	-	1	-	1	-		
year 25	0	-	1	-	1	-		
INTERNAL ROTATION — degrees								
year 2	3	-0.21 (-1.35 to 0.24)	2	-1.02 (-1.23 to -0.81)	3	-0.50 (-0.76 to 0.25)	0.49	
year 5	1	-	2	-0.53 (-0.74 to -0.32)	2	-0.10 (-0.48 to 0.28)		-
year 10	1	-	2	-0.14 (-0.22 to -0.05)	2	-0.33 (-0.52 to -0.13)		
year 15	0	-	2	1.08 (-0.46 to 2.62)	2	-0.02 (-0.45 to 0.42)		-
year 20	0	-	0	-	0	-		
year 25	0	-	0	-	0	-		

Table 3. Stem migration during 25 years of follow-up: per-protocol analysis (i.e., only stems with verified coating), using the 1-year postoperative RSA radiograph as a baseline (i.e., unknown initial migration). Values are count, median (range).

Clinical scores	Hydroxyapatite		Fluorapatite		Uncoated		PER PROTOCOL Main effect	PER PROTOCOL Prespecified time point
	N	Median (range)	N	Median (range)	N	Median (range)	*p*-value	*p*-value
HHS — min 0 - max 100 points								
preoperative	5	35 (8 to 57)	3	34 (30 to 39)	9	37 (8 to 54)	0.56	
year 2	2	80.5 (65 to 96)	2	90 (89 to 91)	4	95 (85 to 100)		
year 5	2	99.5 (99 to 100)	3	76 (69 to 84)	5	85 (66 to 100)		
year 10	4	86 (72 to 94)	5	73 (62 to 90)	7	86 (61 to 98)		
year 15	4	84.5 (41 to 99)	5	76 (61 to 90)	6	79 (74 to 90)		0.9
year 20	0	-	2	63 (57 to 69)	2	82.5 (82 to 83)		
year 25	0	-	1	-	1	-		

Table 4. Harris Hip Score (min 0 – max 100 points) during 25 years of follow-up: per-protocol analysis (i.e., only stems with verified coating). Values are count, median (range).

at 2-year and 0.09 mm at 10-year follow-up, with most of the subsidence occurring during the first 6 postoperative weeks. Critchley et al. reported migration of 30 cementless Corail stems with a follow-up of 14 years (2). They found a mean subsidence of 0.62 mm at 2-year and 0.7 mm at 14-year follow-up, with initial rapid subsidence over 6 weeks and subsequent stabilization. In our study subsidence was 0.15 mm at 2-year, 0.3 mm at 10-year, and 0.1 mm at 14-year follow-up, with

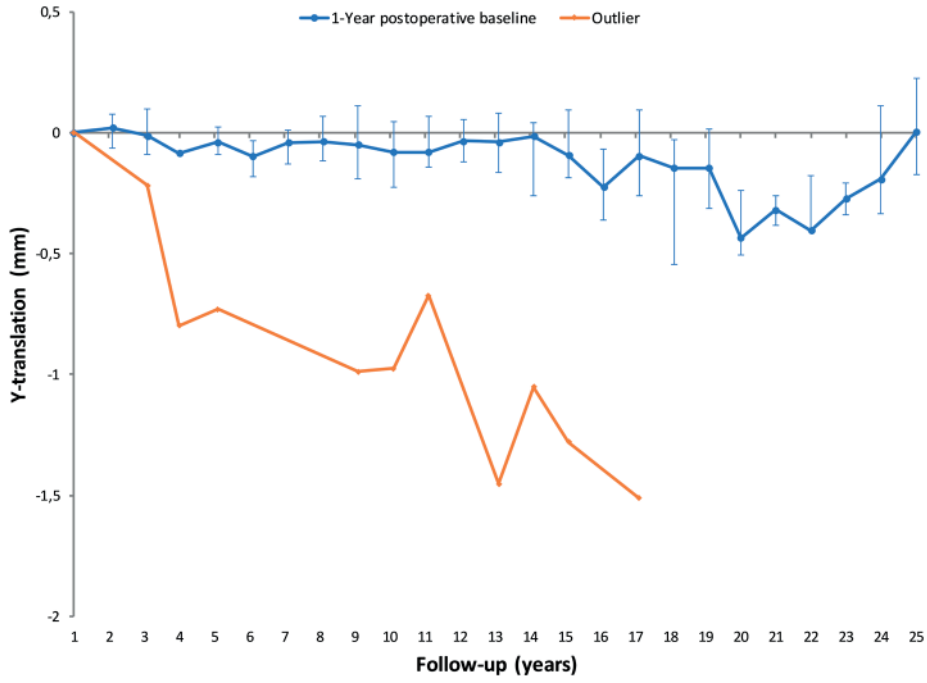

Figure 8. Median Y-translation (i.e., translation along the longitudinal axis) with interquartile ranges of the complete cohort during the 25 years of follow-up with the influential outlier excluded and shown separately.

most of the subsidence occurring during the first 2 postoperative years. These studies, using different cementless stem designs, all show initial migration of different magnitude with subsequent stabilization, emphasizing the influence of design features on migration, and thus fixation.

Søballe et al. and Kärrholm et al. performed RSA studies comparing the migration of HA-coated stems with stems without bioactive coating (20, 21). Søballe et al. found more migration (MTPM) of uncoated titanium stems compared with HA-coated stems, although subsidence was comparable after 1-year follow-up with a mean of 0.09 mm for the HA-coated stems (20). Kärrholm et al. compared migration of HA-coated stems with cemented and cementless stems over a 2-year period (21). They found a median of 0.05 mm proximal migration of HA-coated stems compared with 0.12 mm subsidence of cemented and 0.1 mm of cementless stems. As these differences were statistically significant both authors concluded that HA seems to enhance early fixation. In our study we could not find a benefit of HA on long-term fixation. There might be a benefit of HA during the first postoperative year. However, due to insufficient data we were unable to find such a difference. Our study shows that once a stem has stabilized there is no difference in migration among the different coatings.

Several reviews have been published comparing HA-coated implants with uncoated implants. Gandhi et al. reported no difference in aseptic loosening, or in HHS (7). Goosen et al. reported no difference in HHS, endosteal bone ingrowth, and radiolucent lines (8). Li et al. could not find

a difference in HHS, or radioactive lines (9), and Chen et al. reported no benefit of HA in terms of survivorship, but HA-coated implants showed better postoperative HHS and less femoral osteolysis during follow-up (10).

A recent registry study found an overall lower risk of stem revision for any reason for HA-coated stems compared with a non-HA coated stem; however, the rate for stem revision for HA-coated Mallory-Head stems was higher compared with the non-HA-coated counterpart (0.11% vs. 0.02%) (6). This study suggests that longevity of implants might be related more to specific implant design than to type of coating.

There are no other RSA studies available evaluating the migration of the Mallory-Head Porous stem, except for 1 study described in chapter 3. The Mallory-Head Porous stem described in chapter 3 showed median subsidence of 0.2 mm (range 0.4–4.8) at 5 years' follow-up of uncoated stems. In the current study we found the same median subsidence at 5 years' follow-up but the range in this study was considerably smaller, with the largest subsidence being only 0.4 mm. Insufficient data on initial migration during the first postoperative year in this study might explain this difference.

The cementless Mallory-Head Porous stem has an excellent 10-year survival record with 48 stem revisions of 5,932 primary THAs in the Dutch Arthroplasty Register (28) and 27 stem revisions of 3,303 primary THAs in the Australian Orthopaedic Association National Joint Replacement Registry (29).

All stems in our study showed stable subsidence, except for 1. This stem, with an untraceable coating, was inserted because of severe osteoarthritis at the age of 61 years. There was no preoperative template available, but the postoperative radiograph showed a varus position of the stem with insufficient contact with the lateral cortex at the metaphysis, suggesting undersizing. Albeit that initial subsidence was unknown, the stem showed progressive subsidence from the 1-year follow-up onwards. On the 17-year follow-up radiograph there was obvious subsidence visible, next to radiolucencies and pedestal formation. Remarkably, this patient never scored less than 90 points on the HHS scale and at the 17-year follow-up moment the patient was asymptomatic, although, aged 78 years, she walked only about 200 meters.

Overall, there was rather stable migration up to 14 years reaching a plateau phase, but thereafter migration patterns began to show greater variability, which especially holds for subsidence. From then onwards, patient attendance for regular follow-up also decreased dramatically, resulting in only 5 stems being available for analysis at 20-year follow-up. This low number of available, analog RSA radiographs in combination with relative low accuracy compared with the modern RSA technique are the most probable reasons for the great variability in stem migration patterns (30). Furthermore, as most stems available for analyses beyond 20 years were FA coated, it could be reasoned that in this selected group of patients either overall subsidence increased or the FA coating broke down after more than a decade, leading to increased subsidence. However, the latter cannot be substantiated as no data on the non-coated control group was available. Additionally, the increasing retroversion, together with to increasing subsidence, might be related to a more

sedentary lifestyle of these slightly older patients. For that matter, standing up from a chair creates a retroversion force at the neck of the femoral stem.

This was the first RSA study performed at our institution, therefore it gave some insights into initial study set-up logistics. There was experience neither with inserting markers in periprosthetic bone, nor with the validity of the instrument used at that time to insert markers, which turned out to skip 1 out of 4 markers. This was noticed only after RSA radiographs were evaluated in too late a postoperative period. For that reason, a novel tantalum marker inserter was developed. Additionally, there was a lack of the expertise needed for optimal logistics concerning RSA radiographs. Initially, a single researcher (RN) took care of study logistics and RSA radiograph analyses without secretarial assistance. Hence, patients missing a follow-up moment were noticed only weeks later. These technical and logistical shortcomings resulted in the exclusion of 19 THAs. Furthermore, stem allocation to the randomization groups was not adequately documented and implant stickers of the manufacturer were missing or lacking essential information. The latter might have been related to the distinctive manufacturing process for stems in the current study; the attachment of 3 RSA markers and applying 3 different coatings might have interfered with regular application of implant stickers.

This study has several limitations. First, there were too few migration measurements available during the first postoperative year to make meaningful analyses using the second-day postoperative radiograph as baseline, which is the conventional manner to calculate migration over time. However, as stems susceptible to failure will typically show progressive migration, using the 1-year postoperative RSA radiograph will also detect stems prone to failure. Second, the given coating could not be verified in 18 stems due to due to missing or insufficient implant stickers. To overcome this problem of unknown coatings, both per-protocol and intention-to-treat analyses were performed. The latter reflects the base case scenario, assuming all stems received the coating as per randomization. This is a plausible assumption as only 1 of 24 known coatings received a different coating as per randomization. Third, the Mallory-Head Porous stem is nowadays seldom used, limiting the clinical applicability of this study.

In conclusion, this study could not establish a beneficial effect at long-term follow-up of bioactive coatings on migration, and thus fixation, in this type of stem. Neither could delamination of the less thermostable HA coating be proven. This study provides value migration data that can be used to establish an acceptable migration pattern of cementless stems with which new stem designs can be compared.

APPENDIX

Migration	Hydroxyapatite			Fluorapatite			Uncoated			PER PROTOCOL		
										Main effect	Group × Time Interaction	Prespecified time point
	N	Mean (SD)	Median (range)	N	Mean (SD)	Median (range)	N	Mean (SD)	Median (range)	*p*-value	*p*-value	*p*-value
TRANSLATION — mm												
x-asis (medial-lateral)												
year 2	7	-0.07 (0.29)	-0.16 (-0.49 to 0.45)	5	-0.09 (0.17)	0.00 (-0.37 to 0.05)	8	0.01 (0.22)	-0.08 (-0.16 to 0.50)			
year 5	2	-0.39 (0.40)	-0.39 (-0.67 to -0.10)	5	-0.17 (0.35)	-0.06 (-0.78 to 0.13)	6	0.01 (0.12)	0.02 (-0.13 to 0.15)			0.21
year 10	2	-0.25 (0.17)	-0.25 (-0.37 to -0.13)	4	0.00 (0.11)	-0.03 (-0.10 to 0.17)	7	0.09 (0.22)	0.07 (-0.19 to 0.49)	0.49	0.98	
year 15	3	-0.20 (0.09)	-0.22 (-0.28 to -0.09)	3	0.02 (0.10)	-0.01 (-0.06 to 0.13)	5	-0.01 (0.13)	-0.02 (-0.17 to 0.13)			0.50
year 20	0	-	-	1	-	-	1	-	-			
year 25	0	-	-	1	-	-	1	-	-			
y-axis (cranial-caudal)[1]												
year 2	7	0.02 (0.17)	0.04 (-0.19 to 0.32)	5	0.14 (0.13)	0.20 (-0.02 to 0.27)	8	-0.03 (0.09)	-0.03 (-0.16 to 0.12)			
year 5	2	-0.06 (0.02)	-0.06 (-0.07 to -0.04)	5	0.09 (0.23)	0.09 (-0.16 to 0.44)	6	0.00 (0.08)	0.00 (-0.12 to 0.12)			0.60
year 10	2	0.04 (0.03)	0.04 (0.02 to 0.06)	4	0.05 (0.09)	0.07 (-0.08 to 0.12)	7	-0.07 (0.25)	-0.07 (-0.41 to 0.37)	0.14	0.98	
year 15	3	0.12 (0.30)	0.07 (-0.16 to 0.44)	3	0.00 (0.14)	0.04 (-0.15 to 0.13)	5	-0.18 (0.23)	-0.18 (-0.52 to 0.12)			0.51
year 20	0	-	-	1	-	-	1	-	-			
year 25	0	-	-	1	-	-	1	-	-			

Appendix A. Stem migration during 25 years of follow-up. Per protocol analysis (i.e. only stems with verified coating), using the 1-year postoperative RSA radiograph as a baseline (i.e. unknown initial migration).

[1] Negative values correspond to subsidence

[2] Positive values correspond to internal rotation

Migration	PER PROTOCOL											
	Hydroxyapatite			Fluorapatite			Uncoated			Main effect	Group × Time Interaction	Prespecified time point
	N	Mean (SD)	Median (range)	N	Mean (SD)	Median (range)	N	Mean (SD)	Median (range)	*p*-value	*p*-value	*p*-value
z-axis (anterior-posterior)												
year 2	7	0.20 (0.76)	-0.09 (-0.61 to 1.56)	5	0.51 (0.45)	0.42 (0.06 to 1.21)	8	0.04 (0.15)	0.09 (-0.29 to 0.15)			
year 5	2	-0.12 (0.19)	-0.12 (-0.26 to 0.01)	5	0.71 (0.63)	0.66 (-0.04 to 1.63)	6	0.29 (0.36)	0.28 (-0.19 to 0.89)			0.05
year 10	2	0.10 (0.21)	0.10 (-0.05 to 0.25)	4	0.14 (0.26)	0.13 (-0.16 to 0.46)	7	0.07 (0.47)	0.18 (-0.74 to 0.59)	0.08	0.53	
year 15	3	0.34 (0.45)	0.19 (-0.01 to 0.85)	3	0.49 (0.17)	0.57 (0.29 to 0.60)	5	-0.17 (0.38)	-0.06 (-0.81 to 0.16)			0.27
year 20	0	-	-	1	-	-	1	-	-			
year 25	0	-	-	1	-	-	1	-	-			
ROTATION — degrees												
x-asis (transverse)												
year 2	3	0.13 (0.62)	0.00 (-0.42 to 0.80)	2	-0.04 (0.28)	-0.04 (-0.24 to 0.16)	3	0.18 (0.36)	0.15 (-0.17 to 0.54)			
year 5	1	-	-	2	-0.32 (0.28)	-0.32 (-0.52 to -0.12)	2	0.20 (0.03)	0.20 (0.18 to 0.21)			-
year 10	1	-	-	2	0.12 (0.28)	0.12 (-0.07 to 0.32)	2	0.62 (0.89)	0.62 (-0.01 to 1.25)	0.48	0.91	
year 15	0	-	-	2	-0.57 (0.42)	-0.57 (-0.86 to -0.27)	2	0.27 (0.43)	0.27 (-0.03 to 0.58)			-
year 20	0	-	-	0	-	-	0	-	-			
year 25	0	-	-	0	-	-	0	-	-			

Appendix A (continued). Stem migration during 25 years of follow-up. Per protocol analysis (i.e. only stems with verified coating), using the 1-year postoperative RSA radiograph as a baseline (i.e. unknown initial migration).

[1] Negative values correspond to subsidence

[2] Positive values correspond to internal rotation

Migration	Hydroxyapatite			Fluorapatite			Uncoated			PER PROTOCOL		
										Main effect	Group × Time Interaction	Prespecified time point
	N	Mean (SD)	Median (range)	N	Mean (SD)	Median (range)	N	Mean (SD)	Median (range)	*p*-value	*p*-value	*p*-value
y-axis (longitudinal)[2]												
year 2	3	-0.44 (0.82)	-0.21 (-1.35 to 0.24)	2	-1.02 (0.30)	-1.02 (-1.23 to -0.81)	3	-0.34 (0.53)	-0.50 (-0.76 to 0.25)			
year 5	1	-	-	2	-0.53 (0.30)	-0.53 (-0.74 to -0.32)	2	-0.10 (0.53)	-0.10 (-0.48 to 0.28)			-
year 10	1	-	-	2	-0.14 (0.12)	-0.14 (-0.22 to -0.05)	2	-0.33 (0.28)	-0.33 (-0.52 to -0.13)	0.49	0.16	
year 15	0	-	-	2	1.08 (2.18)	1.08 (-0.46 to 2.62)	2	-0.02 (0.62)	-0.02 (-0.45 to 0.42)			-
year 20	0	-	-	0	-	-	0	-	-			
year 25	0	-	-	0	-	-	0	-	-			
z-axis (sagittal)												
year 2	3	-0.07 (0.46)	0.15 (-0.60 to 0.23)	2	0.18 (0.11)	0.18 (0.11 to 0.26)	3	0.09 (0.17)	0.18 (-0.11 to 0.19)			
year 5	1	-	-	2	0.12 (0.06)	0.12 (0.07 to 0.16)	2	0.01 (0.19)	0.01 (-0.13 to 0.15)			-
year 10	1	-	-	2	0.09 (0.04)	0.09 (0.06 to 0.12)	2	-0.06 (0.09)	-0.06 (-0.12 to 0.00)	0.27	1.00	
year 15	0	-	-	2	0.05 (0.34)	0.05 (-0.19 to 0.29)	2	0.03 (0.01)	0.03 (0.02 to 0.04)			-
year 20	0	-	-	0	-	-	0	-	-			
year 25	0	-	-	0	-	-	0	-	-			

Appendix A (continued). Stem migration during 25 years of follow-up. Per protocol analysis (i.e. only stems with verified coating), using the 1-year postoperative RSA radiograph as a baseline (i.e. unknown initial migration).

[1] Negative values correspond to subsidence

[2] Positive values correspond to internal rotation

Migration	Hydroxyapatite			Fluorapatite			Uncoated			INTENTION TO TREAT		
										Main effect	Group × Time Interaction	Prespecified time point
	N	Mean (SD)	Median (range)	N	Mean (SD)	Median (range)	N	Mean (SD)	Median (range)	*p*-value	*p*-value	*p*-value
TRANSLATION — mm												
x-asis (medial-lateral)												
year 2	12	-0.01 (0.28)	-0.03 (-0.49 to 0.50)	12	-0.05 (0.13)	-0.01 (-0.37 to 0.15)	11	0.04 (0.17)	0.06 (-0.16 to 0.30)	0.83	0.99	
year 5	6	-0.15 (0.29)	-0.11 (-0.67 to 0.13)	10	-0.08 (0.27)	-0.05 (-0.78 to 0.17)	10	0.07 (0.34)	0.09 (-0.63 to 0.70)			0.32
year 10	6	-0.01 (0.22)	0.01 (-0.37 to 0.20)	9	-0.09 (0.25)	-0.03 (-0.62 to 0.17)	10	0.15 (0.64)	0.11 (-1.08 to 1.48)			
year 15	6	-0.17 (0.09)	-0.17 (-0.28 to -0.05)	7	-0.09 (0.27)	-0.03 (-0.70 to 0.13)	8	-0.17 (0.49)	-0.05 (-1.34 to 0.13)			0.89
year 20	2	-0.11 (0.00)	0.00 (-0.11 to -0.11)	4	-0.32 (0.38)	-0.32 (-0.72 to 0.10)	1	-	-			
year 25	1	-	-	3	0.01 (0.10)	0.02 (-0.10 to 0.10)	1	-	-			
y-axis (cranial-caudal)[1]												
year 2	12	-0.03 (0.15)	-0.05 (-0.19 to 0.32)	12	0.06 (0.12)	0.04 (-0.15 to 0.27)	11	0.02 (0.11)	0.04 (-0.16 to 0.21)	0.45	0.85	
year 5	6	-0.09 (0.08)	-0.06 (-0.23 to -0.02)	10	0.06 (0.23)	-0.02 (-0.17 to 0.44)	10	-0.06 (0.28)	-0.01 (-0.73 to 0.36)			0.36
year 10	6	-0.19 (0.19)	-0.23 (-0.41 to 0.06)	9	-0.06 (0.19)	-0.08 (-0.50 to 0.12)	10	-0.21 (0.40)	-0.08 (-0.98 to 0.37)			
year 15	6	-0.12 (0.37)	-0.11 (-0.59 to 0.44)	7	-0.03 (0.21)	-0.06 (-0.32 to 0.33)	8	-0.23 (0.48)	-0.15 (-1.28 to 0.24)			0.59
year 20	2	-0.50 (0.02)	0.00 (-0.52 to -0.49)	4	-0.32 (0.41)	-0.43 (-0.69 to 0.26)	1	-	-			
year 25	1	-	-	3	0.15 (0.13)	0.23 (0.00 to 0.23)	1	-	-			

Appendix B. Stem migration during 25 years of follow-up. Intention to treat analysis (i.e. all included stems as per randomization group), using the 1-year postoperative RSA radiograph as a baseline (i.e. unknown initial migration).

[1] Negative values correspond to subsidence (i.e. distal migration)

[2] Positive values correspond to internal rotation

Migration	Hydroxyapatite			Fluorapatite			Uncoated			INTENTION TO TREAT		
										Main effect	Group × Time Interaction	Prespecified time point
	N	Mean (SD)	Median (range)	N	Mean (SD)	Median (range)	N	Mean (SD)	Median (range)	*p*-value	*p*-value	*p*-value
z-axis (anterior-posterior)												
year 2	12	0.25 (0.61)	0.13 (-0.61 to 1.56)	12	0.19 (0.58)	0.18 (-1.17 to 1.21)	11	0.11 (0.22)	0.13 (-0.29 to 0.60)			
year 5	6	0.24 (0.52)	0.12 (-0.26 to 1.18)	10	0.22 (0.79)	0.18 (-1.34 to 1.63)	10	0.02 (0.43)	0.03 (-0.67 to 0.89)			0.70
year 10	6	0.10 (0.23)	0.01 (-0.13 to 0.50)	9	0.03 (0.32)	0.08 (-0.55 to 0.46)	10	-0.07 (0.49)	-0.07 (-0.74 to 0.60)	0.33	0.91	
year 15	6	0.38 (0.46)	0.18 (-0.01 to 1.05)	7	0.15 (0.52)	0.29 (-0.78 to 0.60)	8	-0.23 (0.46)	-0.10 (-0.93 to 0.36)			0.84
year 20	2	-0.13 (0.31)	0.00 (-0.35 to 0.09)	4	0.17 (0.98)	-0.10 (-0.69 to 1.58)	1	-	-			
year 25	1	-	-	3	0.32 (0.38)	0.54 (-0.12 to 0.54)	1	-	-			
ROTATION — degrees												
x-asis (transverse)												
year 2	5	-0.31 (0.86)	-0.36 (-1.57 to 0.80)	5	-0.57 (1.04)	-0.24 (-2.41 to 0.16)	5	-0.10 (0.46)	-0.17 (-0.59 to 0.54)			
year 5	3	-0.63 (1.64)	0.07 (-2.49 to 0.55)	4	-0.08 (0.36)	-0.07 (-0.52 to 0.34)	5	-0.20 (0.68)	0.18 (-1.30 to 0.33)			0.73
year 10	3	0.45 (0.27)	0.35 (0.23 to 0.75)	5	-0.38 (0.96)	-0.07 (-2.08 to 0.32)	4	0.44 (0.69)	0.37 (-0.23 to 1.25)	0.79	0.47	
year 15	2	-0.81 (1.69)	-0.81 (-2.01 to 0.39)	4	-0.05 (0.70)	-0.07 (-0.86 to 0.81)	4	-0.08 (0.70)	0.08 (-1.07 to 0.58)			0.61
year 20	1	-	-	0	-	-	0	-	-			
year 25	1	-	-	1	-	-	0	-	-			

Appendix B (continued). Stem migration during 25 years of follow-up. Intention to treat analysis (i.e. all included stems as per randomization group), using the 1-year postoperative RSA radiograph as a baseline (i.e. unknown initial migration).

[1] Negative values correspond to subsidence (i.e. distal migration)

[2] Positive values correspond to internal rotation

Migration	Hydroxyapatite			Fluorapatite			Uncoated			INTENTION TO TREAT		
										Main effect	Group × Time Interaction	Prespecified time point
	N	Mean (SD)	Median (range)	N	Mean (SD)	Median (range)	N	Mean (SD)	Median (range)	*p*-value	*p*-value	*p*-value
y-axis (longitudinal)[2]												
year 2	5	0.08 (0.93)	0.24 (-1.35 to 1.11)	5	-0.37 (0.77)	-0.37 (-1.23 to 0.82)	5	-0.18 (0.54)	-0.41 (-0.76 to 0.50)			
year 5	3	0.59 (1.13)	0.57 (-0.53 to 1.74)	4	0.14 (0.85)	0.07 (-0.74 to 1.18)	5	0.26 (0.44)	0.32 (-0.48 to 0.68)			0.75
year 10	3	-0.02 (0.89)	-0.47 (-0.59 to 1.01)	5	0.03 (0.73)	-0.05 (-0.94 to 1.05)	4	0.67 (1.31)	0.39 (-0.52 to 2.42)	0.35	0.55	
year 15	2	1.17 (0.24)	1.17 (1.00 to 1.34)	4	0.52 (1.59)	0.19 (-0.92 to 2.62)	4	0.51 (0.86)	0.42 (-0.45 to 1.65)			0.79
year 20	1	-	-	0	-	-	0	-	-			
year 25	1	-	-	1	-	-	0	-	-			
z-axis (sagittal)												
year 2	5	-0.24 (0.58)	0.09 (-1.09 to 0.23)	5	-0.03 (0.38)	0.11 (-0.69 to 0.26)	5	0.00 (0.18)	-0.08 (-0.20 to 0.19)			
year 5	3	-0.33 (0.88)	0.14 (-1.34 to 0.23)	4	-0.02 (0.19)	0.02 (-0.28 to 0.16)	5	-0.07 (0.25)	0.03 (-0.48 to 0.15)			0.67
year 10	3	0.16 (0.05)	0.16 (0.11 to 0.20)	5	-0.18 (0.33)	-0.01 (-0.56 to 0.12)	4	-0.03 (0.07)	-0.02 (-0.12 to 0.05)	0.71	0.49	
year 15	2	-0.57 (1.07)	-0.57 (-1.32 to 0.18)	4	0.08 (0.23)	0.10 (-0.19 to 0.29)	4	-0.24 (0.37)	-0.11 (-0.76 to 0.04)			0.36
year 20	1	-	-	0	-	-	0	-	-			
year 25	1	-	-	1	-	-	0	-	-			

Appendix B (continued). Stem migration during 25 years of follow-up. Intention to treat analysis (i.e. all included stems as per randomization group), using the 1-year postoperative RSA radiograph as a baseline (i.e. unknown initial migration).

[1] Negative values correspond to subsidence (i.e. distal migration)

[2] Positive values correspond to internal rotation

Clinical scores	Hydroxyapatite			Fluorapatite			Uncoated			PER PROTOCOL		
										Main effect	Group × Time Interaction	Prespecified time point
	N	Mean (SD)	Median (range)	N	Mean (SD)	Median (range)	N	Mean (SD)	Median (range)	*p*-value	*p*-value	*p*-value
HHS — min 0 - max 100 points												
preoperative	5	33.20 (17.48)	35 (8 to 57)	3	34.33 (4.51)	34 (30 to 39)	9	32.11 (13.68)	37 (8 to 54)			
year 2	2	80.50 (21.92)	80.5 (65 to 96)	2	90.00 (1.41)	90 (89 to 91)	4	93.75 (6.34)	95 (85 to 100)			
year 5	2	99.50 (0.71)	99.5 (99 to 100)	3	76.33 (7.51)	76 (69 to 84)	5	84.40 (12.50)	85 (66 to 100)			
year 10	4	84.50 (9.71)	86 (72 to 94)	5	75.00 (12.65)	73 (62 to 90)	7	80.57 (14.46)	86 (61 to 98)	0.56	0.31	
year 15	4	77.25 (25.38)	84.5 (41 to 99)	5	76.20 (12.48)	76 (61 to 90)	6	80.17 (5.85)	79 (74 to 90)			0.90
year 20	0	-	-	2	63.00 (8.49)	63 (57 to 69)	2	82.50 (0.71)	82.5 (82 to 83)			
year 25	0	-	-	1	-	-	1	-	-			

Appendix C. Harris Hip score during 25 years of follow-up. Per protocol analysis (i.e. only stems with verified coating).

Clinical scores	Hydroxyapatite			Fluorapatite			Uncoated			INTENTION TO TREAT		
										Main effect	Group × Time Interaction	Prespecified time point
	N	Mean (SD)	Median (range)	N	Mean (SD)	Median (range)	N	Mean (SD)	Median (range)	*p*-value	*p*-value	*p*-value
HHS — min 0 - max 100 points												
preoperative	7	31.86 (14.53)	31 (8 to 57)	4	31.00 (7.62)	32 (21 to 39)	11	35.91 (14.77)	37 (8 to 61)			
year 2	4	83.75 (15.11)	87 (65 to 96)	4	80.50 (12.40)	83.5 (64 to 91)	6	91.67 (10.25)	96 (74 to 100)			
year 5	4	97.25 (4.86)	99.5 (90 to 100)	9	83.78 (9.71)	84 (69 to 96)	8	82.63 (13.52)	83 (66 to 100)			
year 10	8	90.38 (9.29)	92.5 (72 to 100)	10	83.40 (14.58)	88 (62 to 100)	11	79.45 (16.63)	86 (54 to 98)	0.95	0.26	
year 15	7	77.43 (23.94)	89 (41 to 99)	8	82.13 (12.56)	88.5 (61 to 95)	10	79.20 (8.84)	79 (60 to 91)			0.84
year 20	1	-	-	5	71.00 (11.05)	69 (57 to 87)	3	84.00 (2.65)	83 (82 to 87)			
year 25	1	-	-	4	86.25 (5.85)	86.5 (79 to 93)	2	77.50 (2.12)	77.5 (76 to 79)			

Appendix D. Harris Hip score during 25 years of follow-up, Intention to treat analysis (i.e. all included stems as per randomization group).

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3

Migration behavior of two clinically excellent cementless stems with different design rationales: 5-year follow-up of a randomized RSA study

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ABSTRACT

Introduction

Excellent long-term survival has been reported for both the Taperloc and the Mallory-Head cementless stems. However, little is known about the migration behavior of these stems which have different design rationales. The purpose of this randomized clinical trial was to compare the migration and clinical outcomes of these stems during 5 years of follow-up.

Methods

42 consecutive hips in 38 patients scheduled to receive cementless THA were randomized to either a Taperloc or a Mallory-Head Porous stem. Evaluation took place preoperatively and postoperatively on the second day, at 6, 12, 26, and 52 weeks, and annually thereafter. Primary outcome was stem migration measured using roentgen stereophotogrammetric analysis and secondary outcomes were the Harris Hip Score (HHS) and 36-Item Short-Form Health Survey (SF-36). No patients were lost to follow-up; in 1 patient the THA was removed due to deep infection 3 months postoperatively. In 6 hips migration measurements were not possible due to insufficient marker configuration.

Results

Throughout the follow-up period of 5 years, 3D migration was comparable between the Taperloc and the Mallory-Head Porous stems (p-values > 0.05). However, at the 5-year follow-up point the retroversion of the Mallory-Head Porous stem was 0.9° more than the Taperloc stem ($p = 0.04$). Initial subsidence and retroversion were respectively as large as 6.8 mm and 3.6° for the Taperloc stem and 5 mm and 3.6° for the Mallory-Head Porous stem. After the first postoperative year, both implants had stabilized. The mean increment of HHS, as well as the SF-36 scores during the 5-year follow-up, were comparable between the 2 stems.

Conclusions

The excellent long-term survival of both designs was confirmed in this study showing comparable initial migration with subsequent stabilization. However, the Taperloc design with a flat, wedged geometry showed better rotational stability.

INTRODUCTION

The stems of the Taperloc and Mallory-Head Porous total hip arthroplasty (THA) are straight and tapered designs, achieving metaphyseal fixation through a porous coating. The Taperloc stem has a rectangular, flat and thin transverse geometry, while the Mallory-Head Porous stem has a circular transverse geometry (Figure 1)(1).

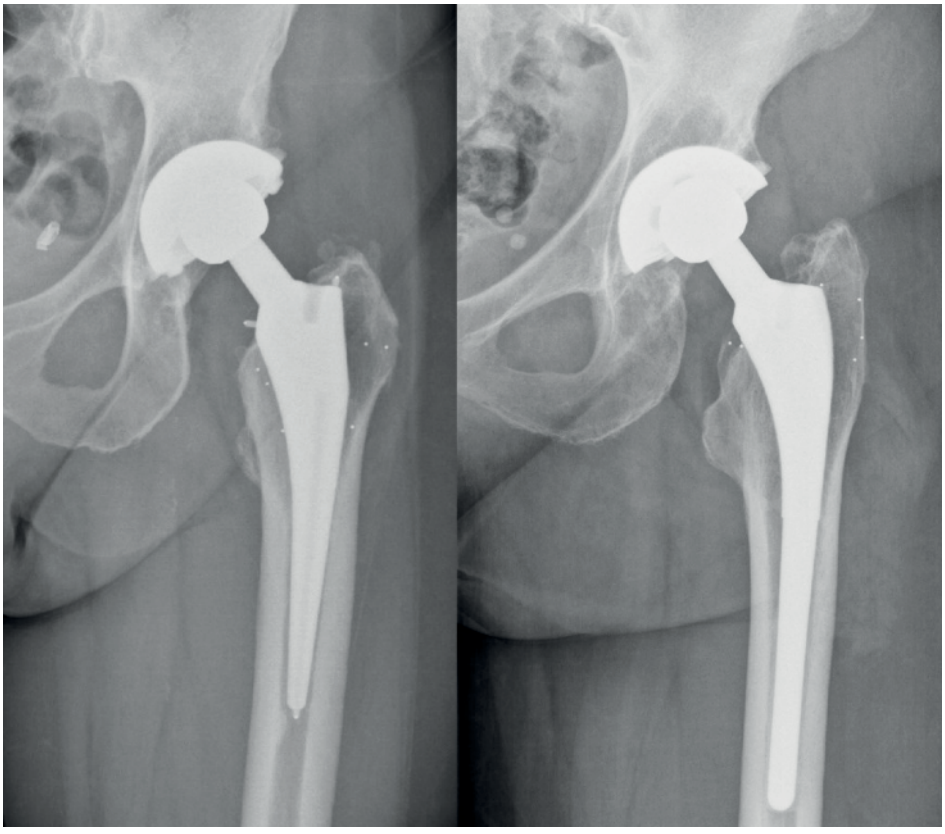

Figure 1. Radiographs of the Taperloc femoral stem on the left and the Mallory-Head Porous femoral stem on the right.

These 2 stems with different design rationales have proven to be safe choices in THA, showing excellent survival in long-term studies (2, 3). However, studies evaluating the migration behavior, as measured with roentgen stereophotogrammetric analysis (RSA), of these clinically well performing stems are scarce and non-existent for the Mallory-Head Porous stem (4-7). The association between short-term RSA results and future loosening of THA has been described for different cemented THA designs (8, 9). However, the influence of particular design features on the migration behavior of cementless stems is rarely described.

In this study, we report the 5-year results of a randomized trial in which we compare the migration, measured with RSA, and clinical outcome of the 2 differently designed cementless stems, thereby analyzing the influence of particular design features on migration behavior. We hypothesized that the migration and clinical outcome of the Taperloc stem would be comparable with that of the Mallory-Head Porous stem.

METHODS

Study design

After the approval of the institutional medical ethical board was obtained (reference code P00.167), all consecutive patients scheduled to receive a cementless primary THA for symptomatic osteoarthritis, either primary or secondary to a systematic inflammatory disease, were approached for participation in a randomized, clinical RSA study. Included patients gave their written informed consent and were randomized to receive either a cementless Taperloc (Biomet, Warsaw, IN, USA) or a cementless Mallory-Head Porous (Biomet, Warsaw, IN) stem. Treatment allocation was randomized with use of a computer-generated randomization scheme and bilateral cases were allowed. The study design was single-blinded; patients were unaware of the allocated stem, but surgeons who implanted the stem and clinical observers evaluating the radiographs could not be blinded. The study was performed in compliance with the Helsinki Declaration. Reporting of the trial was in accordance with the Consolidated Standards of Reporting Trials (CONSORT) and the ISO standard [Implants for surgery - Roentgen stereophotogrammetric analysis for the assessment of migration of orthopaedic implants (16087:2013)] (10, 11).

Surgical technique

All THAs were implanted by experienced specialist hip surgeons, or under their direct supervision, through a lateral approach in the lateral decubitus position. For RSA measurements, 1-mm tantalum markers were inserted into the proximal femur during surgery. All patients received the same rehabilitation program commencing with passive and controlled active movement on the first postoperative day and mobilization with full weight bearing was started on the second postoperative day.

The Taperloc stem has a rectangular cross-sectional geometry with a single taper wedge design. The stem is made of a titanium alloy (Ti-6A1-4V), with a porous plasma-sprayed coating on the proximal third, and a smooth surface on the middle and distal third. The Mallory-Head Porous stem has a round cross-sectional geometry with a dual-tapered design. The stem is characterized by an anterior and posterior flange and wide lateral fin. The stem is made of a titanium alloy (Ti-6A1-4V), with a porous plasma-sprayed coating on the proximal third, a grit-blasted surface on the middle third, and a smooth satin-textured surface on the distal third. The porous surface of both stems used in this trial was not augmented with a coating. All patients received a 28-mm cobalt-chrome head and a cementless Mallory-Head finned Ringloc acetabular cup (Biomet, Warsaw, IN).

Follow-up

Patients were evaluated preoperatively and postoperatively at 6 weeks, 3 months, 6 months, 1 year, and annually thereafter, until 5 years of follow-up. At each evaluation, RSA radiographs were obtained and the Harris Hip Score (HSS) and 36-Item Short-Form Health Survey (SF-36) were determined (12, 13). Conventional anteroposterior and lateral radiographs were acquired preoperatively, at 6 weeks, 2 years, 5 years and on indication (e.g. pain or suspected failure). On the preoperative radiographs the metaphyseal canal shape was classified by the canal flare index (CFI), defined as ratio of the intra-cortical width of the femur at a point 20 mm proximal to the lesser trochanter and at the diaphyseal canal isthmus (14). A CFI of <3.0 described a stovepipe shape, 3.0–4.7 was normal, and 4.7–6.5 described a champagne-flute shape (15). On the 6-week postoperative radiographs the stem orientation (i.e. varus, neutral or valgus) was determined. The 2- and 5-year postoperative radiographs were evaluated for presence of radiolucent lines (16), bone resorption, cortical thickening and pedestal formation.

RSA technique

RSA radiographs were obtained using a uniplanar setup with the patient in supine position and the calibration cage (Carbon box, Leiden, The Netherlands) underneath the examination table. The first RSA examination was made before weight-bearing on the second postoperative day and the relative position of the stem to the bone at that time served as the baseline for all further examinations. A marker-based analysis was carried out to calculate migration over time (Model-Based RSA software, version 3.34; RSAcore, The Netherlands), using 4 stem markers: 3 markers were attached to the stem by the implant manufacturer, and the center of the head acted as a fourth marker. Migration was expressed as translations along and rotation about 3 axes (longitudinal, transverse, and sagittal) of a right-handed orthogonal coordinate system. Since the failure mechanism of stems consists of subsidence and retroversion (8), the primary effect variables were translation along and rotation about the longitudinal axis. The accuracy of RSA measurements was determined by obtaining double examinations of 19 stems 1 year postoperatively. Assuming zero migration in the brief time interval between these double examinations, the limits of the 95% prediction interval of accuracy of zero migration were determined (Table 1) (17). For all examinations, the mean error of rigid body fitting of the RSA markers in the femur was below 0.35 mm; the mean condition number of the RSA markers was 29 (SD 16; range 11–90) in the femur. Bone markers were defined as unstable when they moved more than 0.5 mm with respect to the other bone markers. Unstable markers were excluded from the analyses. These values satisfy the marker stability and distribution criteria of the ISO guideline; (ISO 16087:2013) (11).

Stem	Transverse	Longitudinal	Sagittal
	(x-asis)	(y-axis)	(z-axis)
Translation — mm	0.11	0.14	0.49
Rotation — degrees	0.59	0.75	0.29

Table 1. Accuracy of RSA measurements (upper limits of 95% zero motion confidence interval).

Statistics

Based on earlier RSA studies and owing to the high degree of accuracy of RSA, 20 stems were required for each trial arm, as was standard at our institution at the time this study was designed (8, 18-20). The distribution of the acquired data was tested for normality using the Shapiro-Wilk test. Normality was assumed if the test statistic W was >0.90. Measured values of normally distributed data are reported as the mean and the SD; measured values of non-normally distributed data are reported as the median and the range. Estimates are reported as the mean and the 95% confidence interval (CI). Reported analyses were performed according to the per-protocol principle to reflect the genuine effect of treatment (i.e. Taperloc or Mallory-Head Porous). To safeguard for attrition bias, all analyses were repeated according to the intention-to-treat principle and compared with the outcomes of the per-protocol analyses.

Migration and increase in HHS throughout the follow-up period were analyzed with use of a linear mixed model (LMM) with subject as a random effect. This model deals effectively with repeated measurements, missing values and variation in duration of follow-up (21). Differences between the stems were assessed by estimating the main treatment effect and the 'stem type' × 'time interaction', both as an overall effect over the entire follow-up period taking the repeating measurements into account. The assessment of the interaction term allows for the investigation of possible time-varying mean differences. At the 2- and 5-year follow-up, the mean differences were assessed with the use of an unpaired Student's t-test as specified in the study protocol. As a sensitivity analysis, separate adjusted analyses were carried out with age, gender, body mass index (BMI), and diagnosis (primary or secondary osteoarthritis) as covariates. SF-36 scores were compared with the use of an unpaired Student's t-test (normally distributed data) or Mann-Whitney U-test (MWU, non-normally distributed data). A p-value of <0.05 was significant (SPSS version 20.0; SPSS, Chicago, IL).

RESULTS

Patients

A total of 88 consecutive THAs in 78 patients were assessed for inclusion and 42 THAs in 38 patients were randomized (Figure 2). 19 patients (20 THAs) received a Taperloc stem and 20 patients (22 THAs) received a Mallory-Head Porous stem (Table 2). No patients died during the 5-year follow-up and no patients were lost to follow-up. Patients excluded from the RSA analysis remained in the study and received routine clinical and radiographic follow-up.

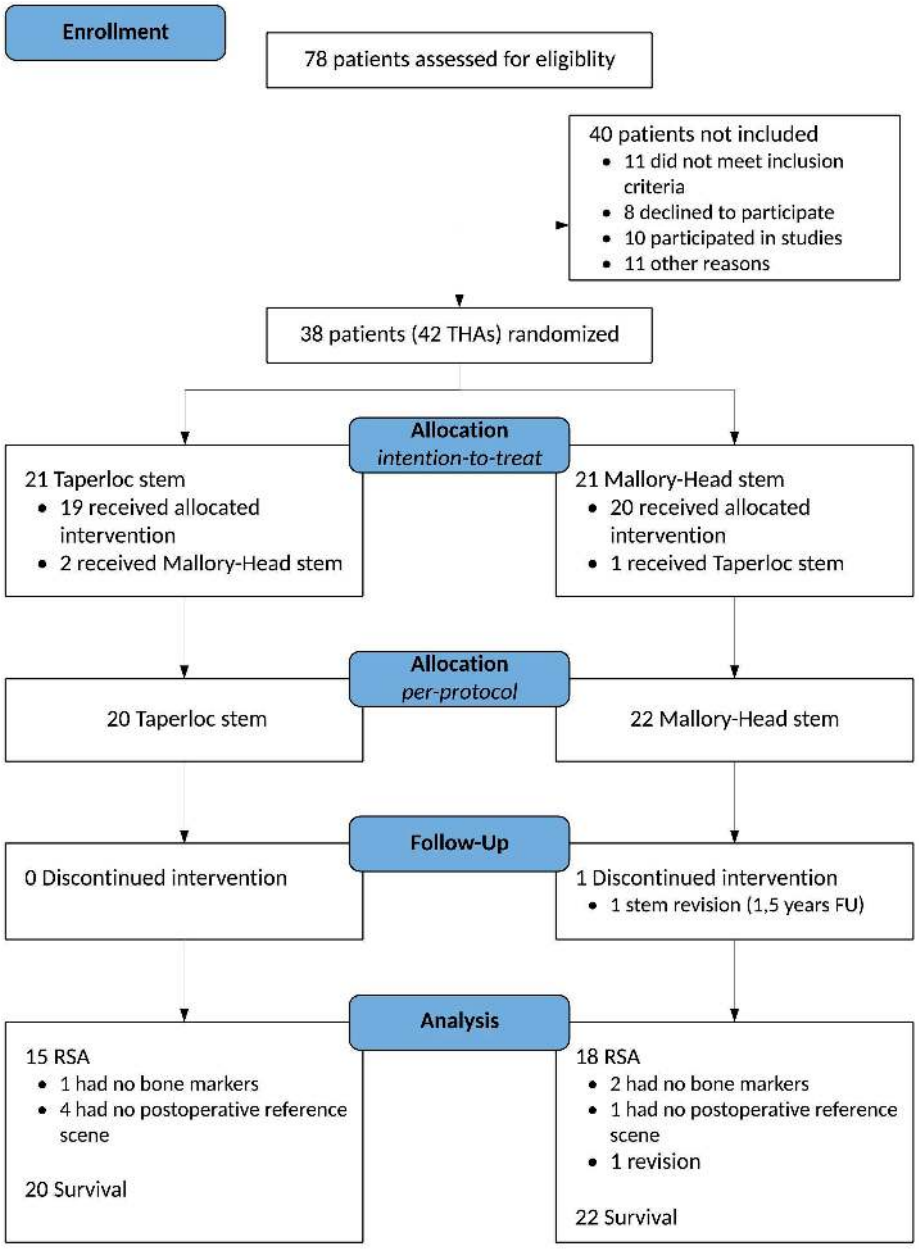

Figure 2. CONSORT flowchart of patient recruitment, allocation and follow-up. THA = total hip arthroplasty; FU = follow-up.

Characteristic	*Taperloc stem*	*Mallory-Head stem*
	(n = 20)	(n = 22)
Gender — no. (%)		
Male	5 (25%)	9 (37.5%)
Female	15 (75%)	13 (62.5%)
BMI* — kg/m²	28.6 ± 4.6	26.6 ± 5.0
Age at surgery* — yr	54.7 ± 7.4	56.4 ± 7.9
Diagnosis — no. (%)		
Osteoarthritis	7 (35%)	10 (45.5%)
Rheumatoid arthritis	2 (10%)	4 (18.2%)
Osteonecrosis	5 (25%)	3 (13.6%)
Hip dysplasia	2 (10%)	3 (13.6%)
Other	4 (20%)	2 (9%)
Side — no. (%)		
Left	8 (40%)	10 (45.5%)
Right	12 (60%)	12 (54.5%)
Surgeon — no. (%)		
Consultant	16 (80%)	19 (86.4%)
Resident	4 (20%)	3 (13.6%)
Stem orientation — no. (%)		
Varus	0	0
Neutral (< 3 degrees)	19 (95%)	19 (86.4%)
Valgus	1 (5%)	3 (13.6%)
Canal Flair Index†	3.7 ± 0.6	3.6 ± 0.7
Dorr classfication — no. (%)		
A	3 (15%)	5 (22.7%)
B	15 (75%)	17 (77.3%)
C	2 (10%)	0
Preoperative HHS* — min 0 - max 100 points	41.9 ± 16.3	44.8 ± 14.6

Table 2. Group characteristics at baseline. Values are count unless otherwise specified.

Migration

Throughout the follow-up period of 5 years, the migration of the 2 femoral stem designs along and about any of the 3 orthogonal axes was not significantly different (main effect; LMM; p-values ≥ 0.05; Figure 3) (Table 3). However, difference in retroversion between the 2 stems was nearly significant (main effect; LMM; p-value = 0.05; Figure 4) (Table 3), with the Mallory-Head Porous stem showing more retroversion. At the pre-specified time point of 5 years postoperatively the Mallory-Head Porous stem showed 0.9° (unpaired Student's t-test; 95% CI, 0–1.8°; p = 0.04; Table 3) more retroversion than the Taperloc stem. There was no difference in time to stabilization and subsequent migration; that is, no evidence of interaction. The results from the adjusted analyses were comparable with the results from the unadjusted analyses and neither age, gender, BMI, diagnosis nor CFI significantly influenced migration (LMM; p-values > 0.05).

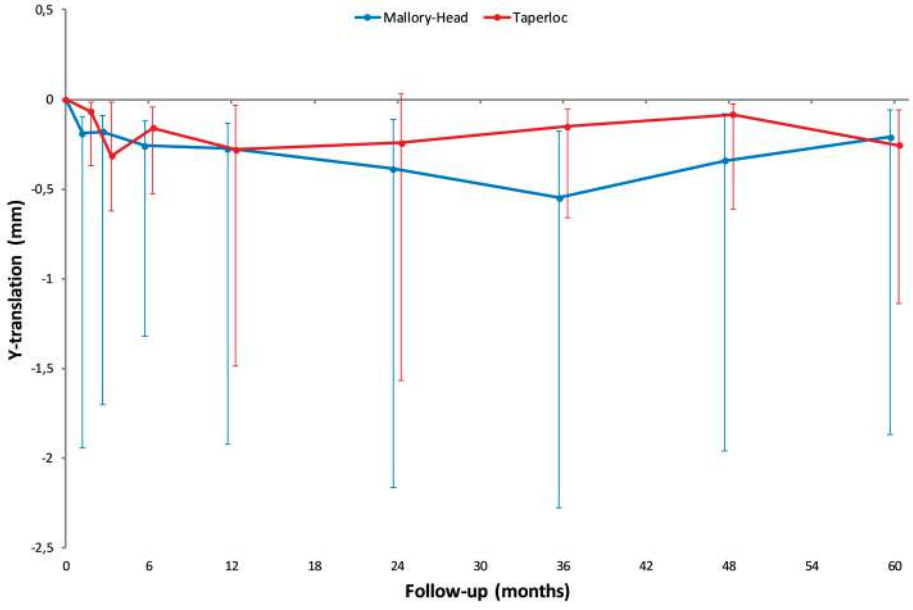

Figure 3. Line graphs showing the median Y-translation (i.e. translation along the longitudinal axis) with interquartile range during the 5 years of follow-up for the Taperloc and Mallory-Head Porous stems.

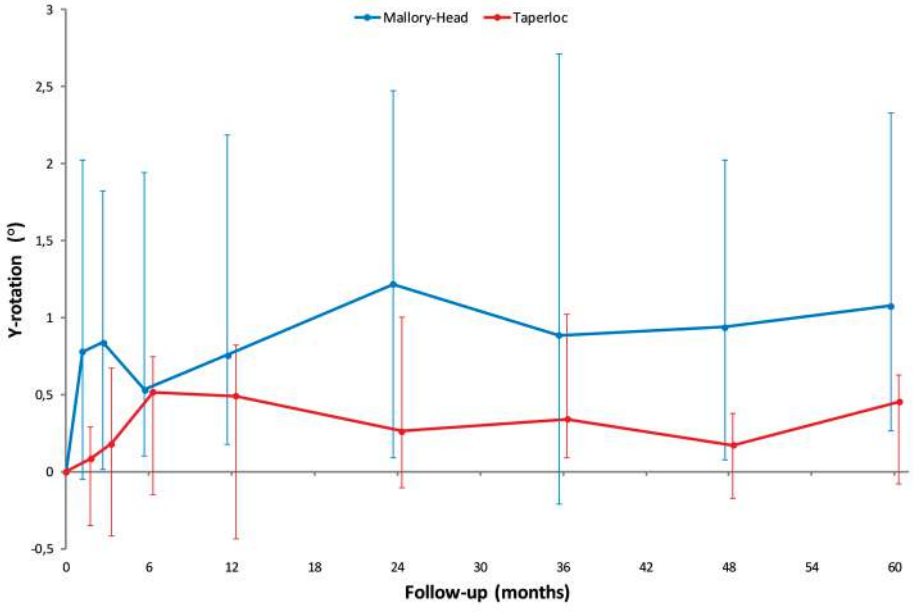

Figure 4. Line graphs showing the median Y-rotation (i.e. internal rotation about the longitudinal axis) with interquartile range during the 5 years of follow-up for the Taperloc and Mallory-Head Porous stems.

Migration	*Taperloc stem*			*Mallory-Head stem*			PER PROTOCOL		
							Main effect	Group × Time Interaction	Prespecified time point
	N	Mean (SD)	Median (range)	N	Mean (SD)	Median (range)	*p*-value	*p*-value	*p*-value
TRANSLATION — mm									
x-asis (medial-lateral)									
week 6	13	-0.05 (0.39)	0.01 (-1.2 to 0.47)	15	0.09 (0.36)	0.14 (-0.8 to 0.71)			
month 3	13	-0.02 (0.43)	0.07 (-1.2 to 0.69)	18	0.09 (0.35)	0.08 (-0.73 to 0.82)			
month 6	14	-0.01 (0.36)	0.05 (-1.15 to 0.31)	16	0.04 (0.34)	0.08 (-0.95 to 0.66)			
year 1	13	0.05 (0.44)	0.11 (-1.15 to 0.81)	18	0.09 (0.42)	0.13 (-1.05 to 0.94)	0.53	0.88	
year 2	13	0.04 (0.49)	0.13 (-1.26 to 0.8)	16	0.11 (0.51)	0.12 (-1.07 to 1.06)			0.44
year 3	13	-0.04 (0.42)	0.09 (-1.2 to 0.45)	15	0.08 (0.45)	0.07 (-1.05 to 0.84)			
year 4	12	0.08 (0.22)	0.12 (-0.41 to 0.48)	14	0.09 (0.38)	0.12 (-0.94 to 0.84)			
year 5	15	0.02 (0.48)	0.11 (-1.23 to 0.89)	18	0.11 (0.38)	0.1 (-0.78 to 0.83)			0.55
y-axis (cranial-caudal)									
week 6	13	-0.76 (1.62)	-0.07 (-4.73 to 0.28)	15	-1.27 (1.72)	-0.19 (-4.83 to 0.14)			
month 3	13	-0.98 (1.74)	-0.32 (-5.47 to 0.22)	18	-1.14 (1.65)	-0.18 (-4.86 to 0.08)			
month 6	14	-0.61 (1.12)	-0.16 (-4.11 to 0.01)	16	-1.08 (1.61)	-0.26 (-4.96 to 0.11)			
year 1	13	-1.18 (2.07)	-0.28 (-6.84 to 0.23)	18	-1.25 (1.73)	-0.28 (-4.81 to 0.09)	0.75	0.23	
year 2	13	-1.21 (2.12)	-0.24 (-7.03 to 0.32)	16	-1.34 (1.83)	-0.39 (-4.89 to 0.22)			0.80
year 3	13	-0.72 (1.21)	-0.15 (-4.13 to 0.2)	15	-1.46 (1.85)	-0.55 (-4.88 to 0.23)			
year 4	12	-0.41 (0.69)	-0.08 (-1.96 to 0.3)	14	-1.25 (1.78)	-0.34 (-4.93 to 0.19)			
year 5	15	-1.13 (2)	-0.26 (-7.11 to 0.08)	18	-1.2 (1.77)	-0.21 (-4.98 to 0.21)			0.91
z-axis (anterior-posterior)									
week 6	13	-0.14 (0.44)	-0.09 (-1.04 to 0.61)	15	-0.15 (0.47)	-0.12 (-1.05 to 0.78)			
month 3	13	-0.15 (0.62)	-0.05 (-1.84 to 0.77)	18	-0.13 (0.44)	-0.04 (-1.06 to 0.49)			
month 6	14	-0.09 (0.31)	-0.19 (-0.61 to 0.47)	16	-0.12 (0.45)	-0.08 (-1.13 to 0.62)			
year 1	13	-0.28 (0.63)	-0.3 (-1.94 to 0.8)	18	-0.16 (0.47)	-0.19 (-1.1 to 0.69)	0.87	0.85	
year 2	13	-0.2 (0.72)	-0.1 (-2.16 to 0.84)	16	-0.21 (0.57)	-0.19 (-0.96 to 0.82)			0.91
year 3	13	-0.04 (0.42)	-0.17 (-0.64 to 1.03)	15	-0.19 (0.5)	-0.15 (-1 to 0.71)			
year 4	12	0.01 (0.35)	-0.07 (-0.49 to 0.76)	14	-0.15 (0.38)	-0.08 (-1 to 0.67)			
year 5	15	-0.2 (0.83)	-0.17 (-2.98 to 0.57)	18	-0.13 (0.42)	-0.19 (-0.92 to 0.8)			0.75

Table 3. Analysis of femoral component migration during 5 years of follow-up.

Migration	*Taperloc stem*			*Mallory-Head stem*			PER PROTOCOL		
							Main effect	Group × Time Interaction	Prespecified time point
	N	Mean (SD)	Median (range)	N	Mean (SD)	Median (range)	*p*-value	*p*-value	*p*-value
ROTATION — degrees									
x-asis (transverse)									
week 6	13	0.04 (0.47)	0.15 (-0.93 to 0.72)	12	-0.15 (0.47)	-0.1 (-1 to 0.54)			
month 3	12	-0.06 (0.38)	-0.03 (-0.55 to 0.62)	14	-0.15 (0.4)	-0.22 (-0.68 to 0.56)			
month 6	13	0.02 (0.3)	0.05 (-0.49 to 0.44)	13	-0.07 (0.5)	0.09 (-0.8 to 0.69)			
year 1	12	-0.05 (0.47)	-0.07 (-0.79 to 0.64)	14	-0.01 (0.44)	0.05 (-0.6 to 0.73)			
year 2	12	-0.11 (0.46)	-0.05 (-0.95 to 0.5)	12	-0.04 (0.34)	-0.05 (-0.65 to 0.48)	0.75	0.63	0.56
year 3	12	0.11 (0.45)	0.16 (-0.59 to 0.67)	12	0.05 (0.49)	0.01 (-0.7 to 0.88)			
year 4	11	0.07 (0.48)	-0.02 (-0.66 to 0.82)	12	0.03 (0.49)	-0.15 (-0.7 to 0.79)			
year 5	14	-0.06 (0.5)	-0.04 (-1.02 to 0.65)	14	-0.06 (0.45)	-0.03 (-0.65 to 0.75)			0.99
y-axis (longitudinal)									
week 6	13	0 (1.09)	0.08 (-1.59 to 2.68)	12	1.09 (1.37)	0.78 (-0.5 to 3.67)			
month 3	12	0.23 (1.27)	0.18 (-1.89 to 3.29)	14	1.1 (1.33)	0.84 (-0.42 to 4.15)			
month 6	13	0.38 (1.09)	0.52 (-1.45 to 3.15)	13	1.05 (1.22)	0.53 (-0.63 to 3.46)			
year 1	12	0.29 (1.51)	0.49 (-2.54 to 3.64)	14	1.16 (1.26)	0.76 (-0.38 to 3.57)			
year 2	12	0.33 (1.36)	0.26 (-2.94 to 2.53)	12	1.39 (1.47)	1.22 (-0.29 to 3.63)	0.06	0.97	0.10
year 3	12	0.3 (1.16)	0.34 (-2.82 to 1.83)	12	1.23 (1.53)	0.89 (-0.51 to 3.77)			
year 4	11	0.03 (0.98)	0.17 (-2.43 to 1.56)	12	1.16 (1.29)	0.94 (-0.33 to 3.6)			
year 5	14	0.33 (0.96)	0.46 (-1.96 to 2.27)	14	1.26 (1.28)	1.08 (-0.49 to 3.64)			0.04
z-axis (sagittal)									
week 6	13	0.03 (0.31)	0.02 (-0.32 to 0.66)	12	-0.05 (0.52)	-0.12 (-0.57 to 1.43)			
month 3	12	-0.01 (0.35)	-0.02 (-0.63 to 0.58)	14	-0.13 (0.46)	-0.15 (-0.65 to 1.26)			
month 6	13	-0.03 (0.25)	-0.02 (-0.52 to 0.45)	13	-0.12 (0.4)	-0.07 (-0.77 to 0.76)			
year 1	12	0.04 (0.47)	-0.02 (-0.5 to 1.01)	14	-0.18 (0.36)	-0.14 (-0.75 to 0.47)			
year 2	12	0.07 (0.58)	-0.05 (-0.63 to 1.32)	12	-0.1 (0.44)	0.01 (-0.71 to 0.81)	0.31	0.62	0.49
year 3	12	0.05 (0.53)	0.04 (-0.75 to 1.22)	12	-0.1 (0.41)	-0.16 (-0.57 to 0.8)			
year 4	11	0.04 (0.52)	0.09 (-0.84 to 1.22)	12	-0.07 (0.41)	-0.1 (-0.62 to 0.79)			
year 5	14	0.03 (0.52)	0.06 (-0.98 to 0.99)	14	-0.11 (0.41)	-0.18 (-0.62 to 0.95)			0.43

Table 3 (continued). Analysis of femoral component migration during 5 years of follow-up.

Migration	*Taperloc stem*			*Mallory-Head stem*			PER PROTOCOL		
							Main effect	Group × Time Interaction	Prespecified time point
	N	Mean (SD)	Median (range)	N	Mean (SD)	Median (range)	*p*-value	*p*-value	*p*-value
MEAN TOTAL POINT MOTION — mm									
week 6	13	1.58 (1.57)	0.99 (0.41 to 5.57)	12	2.61 (1.81)	1.78 (0.69 to 5.84)			
month 3	12	1.71 (1.87)	1.06 (0.34 to 6.35)	14	2.39 (1.71)	1.72 (0.64 to 5.99)			
month 6	13	1.21 (1.08)	1.04 (0.28 to 4.6)	13	2.32 (1.67)	1.74 (0.46 to 5.87)			
year 1	12	2.15 (2.13)	1.49 (0.56 to 7.79)	14	2.44 (1.79)	2 (0.51 to 5.91)			
year 2	12	2.15 (2.18)	1.29 (0.47 to 8.09)	12	2.67 (1.9)	1.84 (0.93 to 6.01)	0.18	0.15	0.13
year 3	12	1.7 (1.12)	1.69 (0.42 to 4.39)	12	2.83 (1.76)	2.31 (0.8 to 5.93)			
year 4	11	1.34 (0.67)	1.48 (0.58 to 2.32)	12	2.44 (1.7)	1.9 (0.73 to 5.75)			
year 5	14	2.1 (2.09)	1.34 (0.37 to 8.22)	14	2.49 (1.77)	1.84 (0.42 to 6.02)			0.42

Table 3 (continued). Analysis of femoral component migration during 5 years of follow-up.

On an individual level evaluation of stem migration revealed stabilization of all stems within the first postoperative year. However, initial subsidence and retroversion varied widely. The highest subsidence for the Taperloc stems was 6.8 mm and for the Mallory-Head Porous stems 5 mm (Figure 5). The highest retroversion was 3.6° for both stems (Figure 6).

Intention-to-treat

After randomization and during surgery, 3 patients did not receive the allocated stem due to unfamiliarity of the surgeon with the ongoing study (Figure 1). 1 patient incorrectly received a Taperloc stem and 2 patients incorrectly received a Mallory-Head Porous stem. Analyses of the results according to the intention-to-treat principle did not alter previous results.

Clinical outcome

The postoperative HHS after 5 years of follow-up had significantly increased with an estimated mean of 44.7 points (unpaired Student's t-test; 95% CI, 35.9–53.5 points; $p < 0.001$) compared to preoperative. The HHS score was not significantly different between the 2 stems throughout follow-up (LMM; $p > 0.05$) (Table 4). Between-group differences of HHS did not change significantly over time (stem type × time interaction; LMM; $p > 0.05$). As for SF-36, there were no significant differences between the 2 stems at the 2- and 5-year follow-up point ($p > 0.05$) (Table 4).

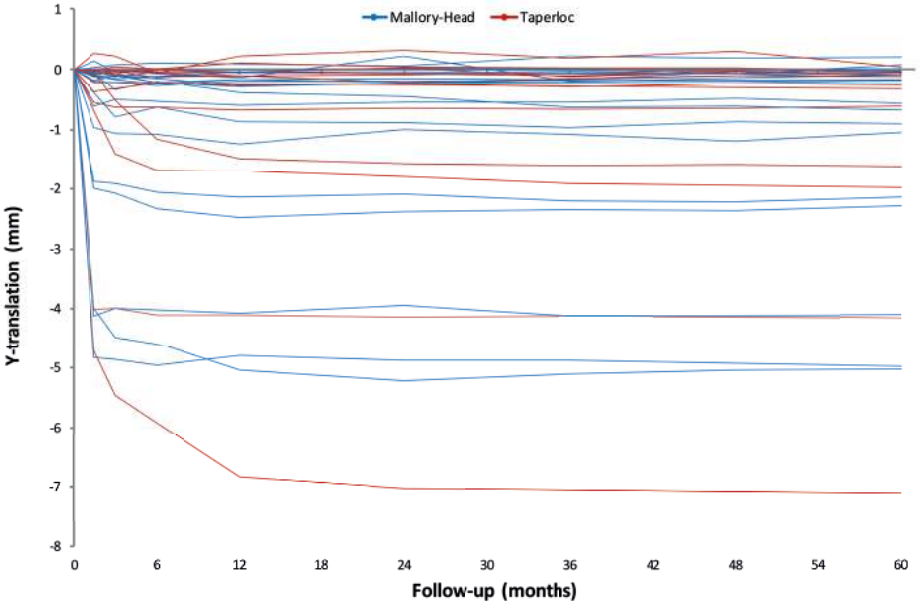

Figure 5. Line graphs showing the Y-translation (i.e. distal translation along the longitudinal axis) of all stems during the 5 years of follow-up.

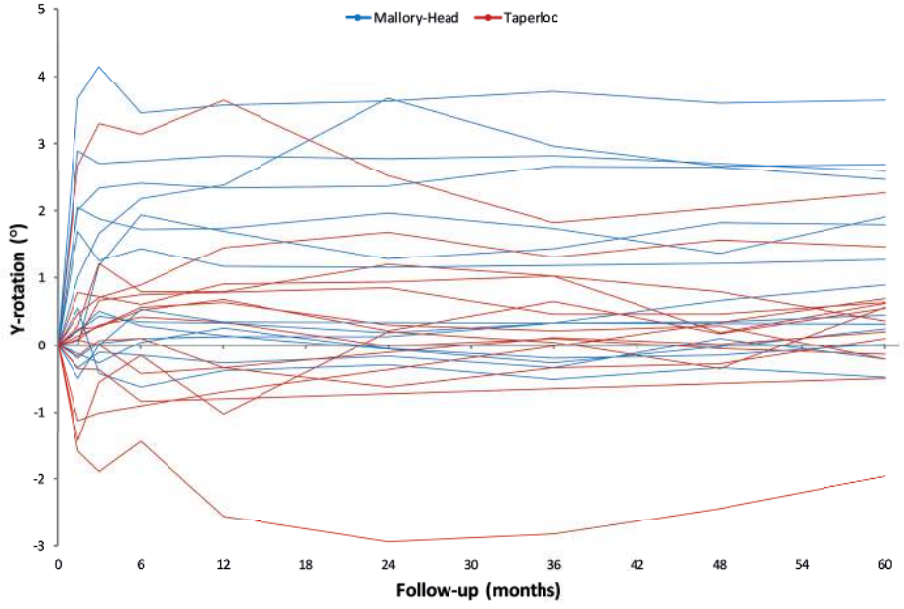

Figure 6. Line graphs showing the Y-rotation (i.e. internal rotation about the longitudinal axis) of all stems during the 5 years of follow-up.

Outcome	*Taperloc stem*		*Mallory-Head stem*		PER PROTOCOL		
					Main effect	Group × Time Interaction	Prespecified time point
	N Mean (SD)	Median (range)	N Mean (SD)	Median (range)	*p*-value	*p*-value	*p*-value
HHS — min 0 - max 100 points							
preoperative	15 42.27 (15.76)	41 (13 to 83)	17 44.65 (14.98)	44 (16 to 69)			
week 6	16 71.19 (18.01)	77 (29 to 88)	16 71.63 (11.04)	75 (51 to 84)			
month 3	18 79.67 (14.37)	86.5 (57 to 96)	17 82.29 (11.21)	84 (66 to 99)			
month 6	19 82.21 (10.56)	82 (64 to 97)	18 90.39 (9.78)	93 (68 to 100)			
year 1	18 86.39 (14.61)	91.5 (45 to 100)	19 91.53 (10.97)	95 (60 to 100)			
year 2	19 90.63 (8.98)	94 (70 to 100)	16 90 (8.63)	92.5 (73 to 100)	0.67	0.35	0.57
year 3	16 90.56 (8.4)	93 (69 to 100)	16 94.25 (3.28)	94 (89 to 100)			
year 4	16 89.63 (8.87)	92 (70 to 99)	12 92 (7.91)	93 (73 to 100)			
year 5	18 87.11 (12.87)	90 (54 to 100)	12 93.75 (5.71)	94 (81 to 100)			0.49
SF-36 — min 0 - max 100 points							
Physical component							
preoperative	5 41.75 (14.14)	41.04 (21.68 to 62.84)	7 45.87 (10.44)	44.99 (28.82 to 59.66)			
week 6	6 50.38 (13.1)	53.06 (24.93 to 57.41)	6 41.26 (9.86)	43.05 (29.45 to 52.83)			
month 3	6 46.51 (9.41)	48.75 (33.59 to 53.12)	5 42.25 (13.8)	50.5 (19.94 to 52.14)			
month 6	6 43.44 (10.53)	45.61 (24.02 to 51.92)	6 45.95 (9.22)	46.42 (33.82 to 59.19)			
year 1	9 36.87 (13.78)	38.23 (17.98 to 56.6)	5 51.94 (8.07)	51.51 (39.54 to 59.66)			
year 2	8 43.62 (13.75)	49.8 (20.58 to 52.59)	4 45.38 (5.39)	43.52 (41.21 to 53.27)			0.73
year 3	9 34.69 (11.68)	33.27 (19.6 to 52.59)	5 39.42 (6.49)	40.45 (30 to 47.98)			
year 4	7 44.95 (9.27)	50.02 (31.53 to 53.78)	6 43.31 (6.81)	40.15 (37.88 to 53.29)			
year 5	4 37.55 (13.29)	36.95 (25.92 to 50.39)	6 40.71 (10.23)	38.89 (27.31 to 53.79)			0.62
Mental component							
preoperative	5 48.83 (9.79)	53.53 (34.47 to 58.05)	7 50.53 (9.87)	49.18 (39.21 to 64.89)			
week 6	6 55.21 (3.37)	56.25 (48.82 to 60.76)	6 50.99 (10.96)	49.25 (33.83 to 63.76)			
month 3	6 55.81 (4.73)	57.34 (49.87 to 59.14)	5 50.03 (12.5)	50.54 (33.25 to 64.32)			
month 6	6 53.01 (5.13)	52.93 (47.2 to 69.72)	6 49.12 (11.44)	52.15 (32.74 to 61.3)			
year 1	9 53.43 (8.18)	50.69 (40.23 to 66.75)	5 47.83 (10.36)	49.07 (34.65 to 56.06)			
year 2	8 54.32 (5.85)	53.5 (47.59 to 65.94)	4 47.29 (7.11)	46.94 (39.21 to 52.88)			0.13
year 3	9 53.82 (8.53)	56.23 (36.95 to 56.9)	5 44.68 (13.59)	38.99 (33.83 to 47.2)			
year 4	7 49.08 (7.95)	52.37 (39.54 to 59.24)	6 46.94 (10.39)	44.89 (34.34 to 50.48)			
year 5	4 54.18 (4.17)	54.21 (49.07 to 53.65)	6 43.32 (9.69)	42.3 (38.5 to 62.35)			0.14

Table 4. Analysis of clinical outcome during 5 years of follow-up.

Radiographic outcome

2 stems (1 Taperloc and 1 Mallory-Head Porous) showed non-progressive, 2-mm radiolucent lines between the stem and bone in Gruen zones 1 and 8. Interestingly, both of these stems showed high initial subsidence, 6.8 mm and 5 mm respectively. After initial subsidence, both stems stabilized and were considered not to be at risk for aseptic loosening after 5 years of follow-up.

Survival

In 1 patient with a Mallory-Head Porous stem, both the femoral and acetabular components were removed and a Girdlestone procedure was subsequently performed due to a deep infection of the implant 3 months postoperatively. In another patient with a Taperloc stem, the liner and head were revised due to liner wear shortly after the 5-year follow-up point.

DISCUSSION

In this randomized, clinical RSA study, hip stem migration, HHS and SF-36 were comparable between the Taperloc and Mallory-Head Porous femoral components during 5 years of follow-up. There were no revisions for aseptic loosening and no stems were considered to be at risk for aseptic loosening. No stems showed continuous migration; that is, all stems stabilized after initial migration.

In this study, there was no significant difference in 3D migration between the 2 stems. However, the Mallory-Head Porous stem showed more retroversion in comparison with the Taperloc stem and the variance in retroversion was larger in the Mallory-Head Porous group. This suggests better rotational stability of the flat, wedge shaped Taperloc stem. However, rotational stability does not seem to affect subsidence; the subsidence during 5 years of follow-up as well as the subsidence rate during the first postoperative year was comparable between the 2 stems.

This is the first study comparing the migration of the Taperloc and Mallory-Head Porous femoral components, and the first study to evaluate the migration of the Mallory Head stem. In our study the mean subsidence of the non-HA coated Taperloc stem was 1.2 mm after 2 years and this is more than the values of 0.44 mm (non-HA coated) and 0.25 mm (HA coated) subsidence at 2 year follow-up reported by Wykman et al. and Bøe et al. (4, 5). The relatively high subsidence in our study can be explained by 2 outliers showing high initial subsidence of 4 mm and 7 mm. Furthermore, the reported subsidence in these studies might be an underestimation since the reference RSA scene was made 1 week postoperatively. Mean retroversion of 0.33° at 2-year follow-up in our study is comparable to reported values of 0.17° (HA-coated) and 0.46° (BM-coated) (5). Flatøy et al. reported the 5-year results of the same study published earlier by Bøe et al., showing initial subsidence up to 10.4 mm with subsequent stabilization of all stems (5, 6). Nebergall et al. reported comparable results to our study with a similar non-HA coated Taperloc stem, showing

initial migration up to 9.3 mm with subsequent stabilization of all stems and a median subsidence of 0.03 mm after 5 years of follow-up (7).

There was a high variation in initial migration for both the Taperloc and the Mallory-Head Porous stem. The Taperloc stem showed up to 7 mm of subsidence and the Mallory-Head Porous stem showed up to 5 mm of subsidence. Both stems showed initial retroversion of about 3°. For all stems, initial migration occurred during the first 3 postoperative months. Stems showing little initial migration quickly stabilized, while stems showing large initial migration took up to 2 years to stabilize. After the second postoperative year, all stems had stabilized. This suggests that high initial migration is acceptable as long as the stem does not continue to migrate and ultimately stabilizes. All implants showing high initial subsidence also showed high initial rotation into retroversion. 2 of the stems showing high initial migration, showed non-progressive radiolucencies of 2 mm. In the other stems, there were no radiolucencies present.

This study shows that it can take up to 2 years before the stem stabilizes. Several studies with cemented stems have shown that high initial migration is predictive of late aseptic loosening (8, 9). Some of these studies have shown that high initial migration during the first postoperative year is already predictive of late aseptic loosening (22). This study, however, demonstrates that it can take up to 2 years before a cementless implant stabilizes without being at risk of aseptic loosening after 4 years of follow-up. The failure mechanism of cementless stems might therefore be different from cemented stems (23).

We should also consider some limitations. Firstly, this was one of the first RSA studies performed at our institution; hence there was little experience with the procedure of placing tantalum markers in the periprosthetic bone. Therefore, 8 patients had to be excluded due to marker problems. However, no patients were lost to follow-up. Secondly, there was no difference in stem morphology in terms of Canal Flair Index or Dorr classification. Different stem morphologies might favor one femoral stem design over another. Unfortunately, this study was not powered to make such recommendations. Thirdly, this trial was not prospectively registered in an ICMJE approved registry. At the time this study was designed, registration of trials had not yet been established.

In conclusion, this study confirms the excellent clinical and survival results of the Taperloc and Mallory-Head Porous stems provided by survival studies. Both stems are safe choices in total hip arthroplasty. The Taperloc provides better initial rotational stability but the clinical benefit of this has not been proven.

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4

Comparison of femoral component migration between Refobacin bone cement R and Palacos R + G in cemented THA: a randomized controlled clinical and RSA study

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ABSTRACT

Introduction

The widely used and well-proven Palacos R (a.k.a. Refobacin Palacos R) bone cement is no longer commercially available and was superseded by Refobacin bone cement R and Palacos R + G in 2005. However, the performance of these newly introduced bone cements have not been tested in a phased evidence-based manner, including roentgen stereophotogrammetric analysis (RSA).

Methods

In this blinded, randomized, clinical RSA study, the migration of the Stanmore femoral component was compared between Refobacin bone cement R and Palacos R + G in 62 consecutive total hip arthroplasties. The primary outcome measure was femoral component migration measured using RSA and secondary outcomes were Harris hip score (HHS), Hip disability and Osteoarthritis Outcome Score (HOOS), EuroQol 5D (EQ-5D) and Short Form 36 (SF-36).

Results

Femoral component migration was comparable between Refobacin bone cement R and Palacos R + G during the 2-year follow-up period with an estimated mean difference of 0.06 mm of subsidence ($p = 0.56$) and 0.08° of retroversion ($p = 0.82$). 5 hips (3 Refobacin bone cement R and 2 Palacos R + G) showed non-stabilizing, continuous migration; the femoral cement mantle in these hips, was mean 0.7 mm thicker ($p = 0.02$) and there were more radiolucencies at the bone-cement interface ($p = 0.004$) in comparison to hips showing stabilizing migration. Postoperative HHS was comparable throughout the follow-up period ($p = 0.62$). HOOS, EQ5D, and SF-36 scores were also comparable (p-values > 0.05) at the 2-year follow-up point.

Conclusions

Refobacin bone cement R and Palacos R + G show comparable component migration and clinical outcome during the first 2 postoperative years. Hips showing continuous migration are at risk for early failure. However, this seems to be unrelated to cement type, but rather to cementing technique.

INTRODUCTION

For several decades, high-viscosity gentamycin loaded bone cement manufactured by Heraus Kluzer GmbH, branded as either Palacos R (distributed by Schering Plough) or Refobacin Palacos R (distributed by E. Merck/Biomet), was considered the benchmark for fixation of cemented orthopaedic implants. Its production ceased in 2005 due to a re-organization of the company. Heraeus Medical and Biomet responded by introducing Refobacin bone cement R (produced by AAP Biomaterials GmbH & Co; distributed by Biomet, Warsaw, Indiana) and Palacos R + G (produced by Heraeus Kulzer GmbH; distributed by Heraeus Medical GmbH, Hanau, Germany) (1). These new cements were promoted as having the same characteristics as the original Palacos R/Refobacin Palacos R cement (2-4).

However, both Dall et al. and Kock et al. showed that the newly introduced cements did not appear to have similar handling properties, curing characteristics or viscoelastic properties as the original cement (3, 4). Moreover, the introduction of the new cements did not follow a phased evidence-based market introduction, including roentgen stereophotogrammetric analysis (RSA), as proposed by Malchau and Nelissen et al. (5, 6). Early migration which is associated with poor long-term survival can be measured by RSA (7-12).

We have undertaken a blinded, randomized, clinical and RSA study, comparing the migration and clinical outcome of femoral components in primary total hip arthroplasty (THA), cemented with either Refobacin bone cement R or Palacos R + G over a 2-year period. We hypothesized that the migration of the femoral components and the clinical outcome of the hips cemented with Refobacin cement R would be comparable with hips cemented with Palacos R + G.

METHODS

Study design

Between November 2007 and November 2010, 99 consecutive patients at our tertiary referral center, in need of THA for osteoarthritis, either primary or secondary to an inflammatory disease, were invited to participate in this study. Exclusion criteria were patients needing THA for reasons other than osteoarthritis and those requiring revision THA. Patients were randomized to receive either Refobacin bone cement R (produced by AAP Biomaterials GmbH & Co; distributed by Biomet) or Palacos R + G (produced by Heraeus Kulzer GmbH; distributed by Heraeus Medical GmbH). Allocation involved a computer-generated randomization program. Patients and the independent examiners performing the RSA and clinical assessments, were blinded to the type of cement which was used; the surgeons were not blinded. The study had ethical approval (reference code P07.008), and all patients gave written consent.

Surgical technique

All operations were performed by 5 experienced specialist hip surgeons or under their direct supervision, using a direct lateral approach with the patient in the lateral decubitus position. All patients received a collared femoral component with a smooth surface (Stanmore, Biomet), and a 28 mm cobalt-chrome head and a cemented ArCom (Biomet) polyethylene acetabular component. For RSA measurements, at least 5; 1-mm tantalum markers were inserted into the proximal femur during surgery. No markers were inserted into the acetabulum. A third generation cementing technique using pulsatile lavage, vacuum mixing, retrograde injection, and pressurization, was used in all cases. Both Refobacin cement R and Palacos R + G are polymethyl methacrylate (PMMA) based cements and consist of 2 primary components: a PMMA powder and a liquid monomer (methylmethacrylate, or MMA). The chemical composition of both cements differs slightly (Table 1).

Components	*Palacos R / Refobacin Palacos R*	*Refobacin bone cement R*	*Palacos R + G*
POWDER			
Gentamcin sulphate (antibiotics)	0.8 g	0.8 g	0.8 g
Methylmethacrylate (polymer)	33.6 g	33.6 g	33.8 g
Benzoylperoxide (polymerization initiator)	0.3 g	0.3 g	0.3 g
Zirconiumdioxide (radiopacifier)	6.1 g	6.1 g	6 g
Chlorophyl (colouring agent)	+	-	+
LIQUID			
Methylmethacrylate (monomer)	18.4 g	18.4 g	18.4 g
N,N-dimethyl-p-toluidine (polymerization initiator)	0.4 g	0.4 g	0.4 g
Chlorophyl (colouring agent)	+	+	+
Hydroquinone (stabiliser)	+	+	+

Table 1. Chemical composition of the original Palacos R / Refobacin Palacos R in comparison to its successor Refobacin bone cement R and Palacos R + G.

Follow-up

Patients were evaluated preopertively and on the second day and at 6 weeks, 3 months, 6 months, 1 year and 2 years postopertively. At each evaluation, RSA radiographs were undertaken and the Harris hip score (HHS) (13), the Hip disability and Osteoarthritis Outcome Score (HOOS) (14, 15), EuroQol 5D (EQ-5D) (16, 17) and Short Form 36 (SF-36)(18) scores were obtained. Conventional anteroposterior and lateral radiographs were performed preoperatively and at 6 weeks and 2 years postoperatively or if there was a clinical indication. The following assessments were made from the 6-week postoperative radiographs: the orientation of the femoral component (varus, neutral or valgus), cement grading according to Barrack et al. (19), and the mean thickness of the cement mantle in all 14 Gruen zones (20). The 2-year postoperative radiographs were evaluated for the presence of cement fractures and radiolucent lines at the cement-bone interface.

RSA technique

RSA radiographs were obtained using a uniplanar setup with the patient supine and the calibration cage (Carbon box, Leiden, The Netherlands) underneath the examination table. The first examination was made before weight-bearing on the second postoperative day and the relative position of the stem to the bone, at that time, served as the baseline for all further examinations. If the configuration of the markers was inadequate or too few (< 5) markers had been used, the patient was excluded from the RSA analyses, however, remained in the study. As the femoral component was not equipped with tantalum markers, elementary geometrical shapes (EGS) of the head, cone and tip of the stem were used to represent the femoral component (Figure 1) (21, 22). A model-based analysis using EGS models were carried out to calculate the migration (Model-Based RSA software, version 3.34; RSAcore, Leiden, The Netherlands). The accuracy of RSA measurements was determined by obtaining double examinations of 40 femoral components 1-year postoperatively. Assuming zero migration in the brief time interval between these double examinations, the limits of the 95% prediction interval of accuracy of zero migration were determined (Table 2) (23). For all examinations, the mean rigid body error of the RSA markers in the femur was 0.12 mm (SD 0.06); the mean condition number of the RSA markers was 23.1 (SD 7.3; 7.4 to 59.8) in the femur. Bone markers were considered to be unstable if they moved by > 0.5 mm with respect to other markers. Unstable markers were excluded from the analyses. These values satisfy the marker stability and distribution criteria of the ISO standard; (ISO 16087:2013) (24).

Statistics

Based on earlier RSA studies with collared femoral components, the smallest effect of interest was set at 0.3 mm at 2 years with a SD of 0.4 mm (25, 26). A power analysis indicated that a minimum of 23 femoral components in each group were required to have an 80% chance of detecting a difference in means of 0.3 mm (SD 0.4) at the 5% level of significance, using an unpaired t-test. In total 62 hips, in 59 patients, were randomized to allow for loss to follow-up. The distribution of the acquired data was tested for normality using the Shapiro-Wilk test. Normality was assumed if the test statistic W was > 0.90. Measured values of normally distributed data are reported as the mean and the SD; measured values of non-normally distributed data are reported as the median and the range. Estimates are reported as the mean and the 95% confidence interval (CI). Reported analyses were performed according to the per-protocol principle, to reflect the genuine effect of treatment (i.e. Refobacin cement R or Palacos R + G). In order to safeguard for attrition bias, all analyses were repeated according to the intention-to-treat principle and compared with the outcomes of the per-protocol analyses. Migration and HHS throughout the follow-up period were analyzed using a linear mixed model (LMM) with the patient as random intercept. This model deals with repeated measurements, missing values and variation in the duration of follow-up (27). As a sensitivity analysis, separate adjusted analyses were carried out with age, gender, body mass index (BMI), and diagnosis (primary or secondary osteoarthritis) as covariates. HHS was additionally corrected for preoperative HHS. The rate of migration and the mean HOOS, EQ5D, SF-36 scores

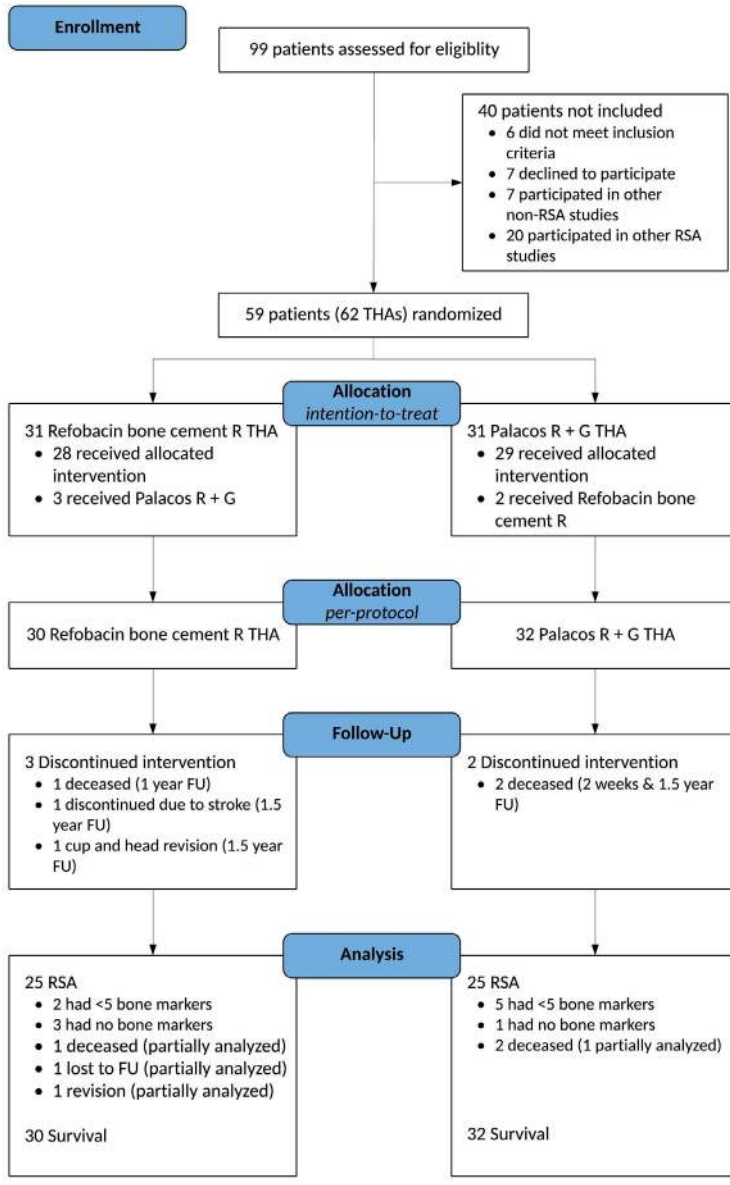

Figure 1. CONSORT flowchart of patient recruitment, allocation and follow-up. THA = total hip arthroplasty; FU = follow-up.

Stem	Transverse	Longitudinal	Sagittal
	(x-axis)	(y-axis)	(z-axis)
Translation — mm	0.07	0.08	0.24
Rotation — degrees	0.27	0.64	0.13

Table 2. Accuracy of RSA measurements (upper limits of 95% zero motion confidence interval).

2 years postoperatively were compared using an unpaired t-test for normally distributed data and a Mann-Whitney U-test (MWU) for non-normally distributed data. Post hoc, multiple hypotheses testing on the same dataset was corrected for by applying a Bonferroni correction. A post hoc nested case-control study was performed to study factors related to non-stabilizing migration. For this purpose, the groups of patients were divided into 2 subgroups, 1 involving femoral components with non-stabilizing, continuous migration (i.e. outliers; defined as migration rate above third quartile (Q3) + 1.5 × IQR), and controls defined as femoral components showing stabilizing migration. The unpaired t-test was used to compare continuous data between these groups, and the Fisher's exact test (FET) was used to compare categorical data. A p-value of < 0.05 was (SPSS version 20.0; SPSS, Chicago, Illinois).

RESULTS

Patients

A total of 138 consecutive THAs in 99 patients were assessed for inclusion during the study period and 62 THAs in 59 patients were randomized; 28 patients (30 THAs) received Refobacin cement R and 31 (32 THAs) received Palacos R + G. (Figure 2; Table 3).

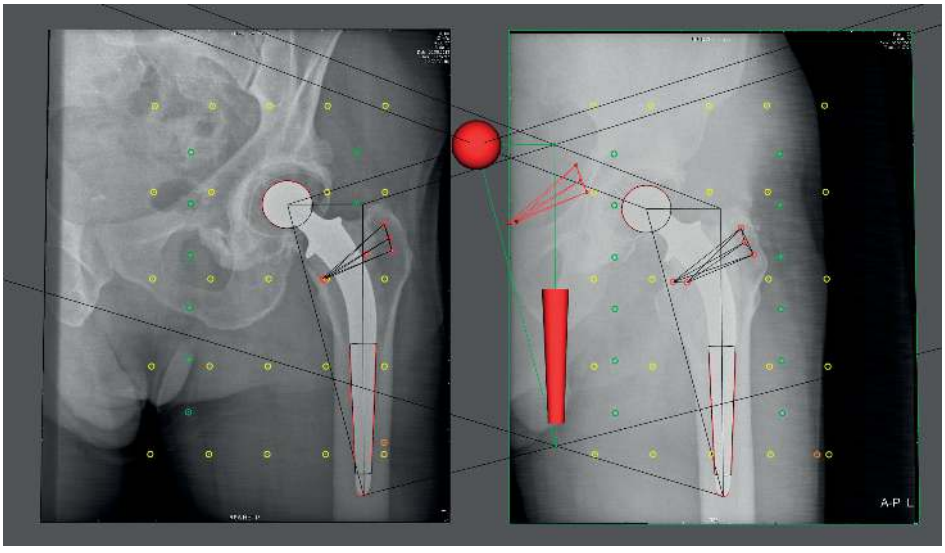

Figure 2. Screen output from Model-Based RSA software showing the elementary geometrical shapes (EGS) of the head, cone and tip of the stem which were used to represent the femoral component.

Characteristic	*Refobacin bone cement R* (n = 30)	*Palacos R + G* (n = 32)
Gender — no. (%)		
Male	4 (13.3%)	12 (37.5%)
Female	26 (86.7%)	20 (62.5%)
BMI* — kg/m²	26.9 (SD 5.1)	26.4 (SD 4.2)
Age at surgery* — yr	75.7 (SD 6.5)	73.4 (SD 5.6)
Diagnosis — no. (%)		
Osteoarthritis	26 (86.7%)	28 (87.5%)
Rheumatoid arthritis	1 (3.3%)	1 (3.1%)
Osteonecrosis	2 (6.7%)	2 (6.3%)
Posttraumatic	1 (3.3%)	1 (3.1%)
Side — no. (%)		
Left	13 (43.3%)	10 (31.3%)
Right	17 (56.7%)	22 (68.7%)
Surgeon — no. (%)		
Consultant	16 (53.3%)	13 (40.6%)
Resident	14 (46.7%)	19 (59.4%)
Stem size — no. (%)		
Size 1	1 (3.3%)	0 (0%)
Size 2	9 (30%)	8 (25%)
Size 3	13 (43.4%)	18 (56.2%)
Size 4	7 (23.3%)	6 (18.8%)
Stem orientation — no. (%)		
Varus	1 (3.3%)	1 (3.1%)
Neutral (< 3 degrees)	26 (86.7)	30 (93.8%)
Valgus	3 (10%)	1 (3.1%)
Cement mantle thickness† — mm	4.0 ± 0.7	3.9 ± 0.6
Cementing grade — no. (%)		
A	22 (73.3%)	29 (90.6%)
B	8 (26.7%)	3 (9.4%)
Preoperative HHS* — min 0 - max 100 points	44.6 ± 16.8	48.3 ± 16.4

Table 3. The characteristics of the patients at baseline.
* The values (mm) are given as the mean and the standard deviation.
† Thickness of the cement mantle in all 14 Gruen zones, given as the mean and standard deviation.

Migration

Throughout the 2-year follow-up period, the migration of the femoral component along and about any of the 3 orthogonal axes, was not significantly different in these 2 groups (LMM; p-values > 0.025 (Bonferroni correction); Appendix A). The main pattern of migration was one of subsidence and retroversion (i.e. distal translation along and internal rotation about the longitudinal axis). Femoral components cemented with Refobacin cement R had a mean of 0.06 mm more

subsidence (difference between intercepts; LMM; 95% CI -0.15 to 0.28; p = 0.56), and 0.08° more retroversion (difference between intercepts; LMM; 95% CI, -0.63° to 0.79°; p = 0.82) than those cemented with Palacos R + G. The subsidence of the femoral components was slightly greater in men than women (LMM; 0.24 mm; 95% CI 0.35 to 0.45; p = 0.02) and greater in patients with secondary osteoarthritis than in those with primary osteoarthritis (LMM; 0.36 mm; 95% CI 0.11 to 0.62; p = 0.01). Migration other than subsidence was not significantly associated with age, gender, BMI, or diagnosis (LMM; p-values > 0.05). The median rate of subsidence between the first and second postoperative year was the same for both groups at 0.1 mm/year (0 to 1) (MWU; p = 0.41). The median rate of retroversion between the first and second postoperative year was 0.5 mm/year (0 to 3.8) for the Refobacin group and 0.4 mm/year (0.1 to 2.2) for the Palacos R + G group (MWU; p = 0.25). The evaluation of migration of the femoral components at an individual level showed stabilization within the first postoperative year of all but 3 components cemented with Refobacin bone cement R (R1-3, Figs 3 and 4) and 2 cemented with Palacos R + G (P1-2, Figs 3 and 4). These 5 outliers showed continuous migration after the first postoperative year of > 0.2 mm subsidence per year or > 1° of retroversion per year, or both (i.e. rate of migration > Q3 + 1.5 × IQR).

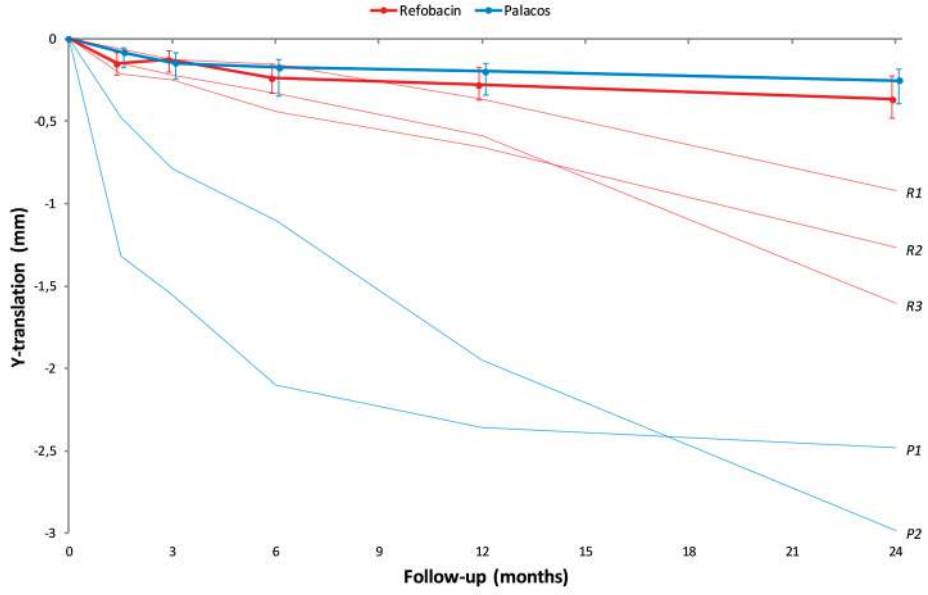

Figure 3. Line graphs showing the subsidence (i.e. distal translation along the longitudinal axis) during the 2 years of follow-up for femoral components cemented with Refobacin bone cement R and Palacos R + G (median and interquartile range, thick blue and red lines). The individual femoral components showing continuous subsidence are represented by thin lines (R1-3 (Refobacin bone cement R) and P1-2 (Palacos R + G)).

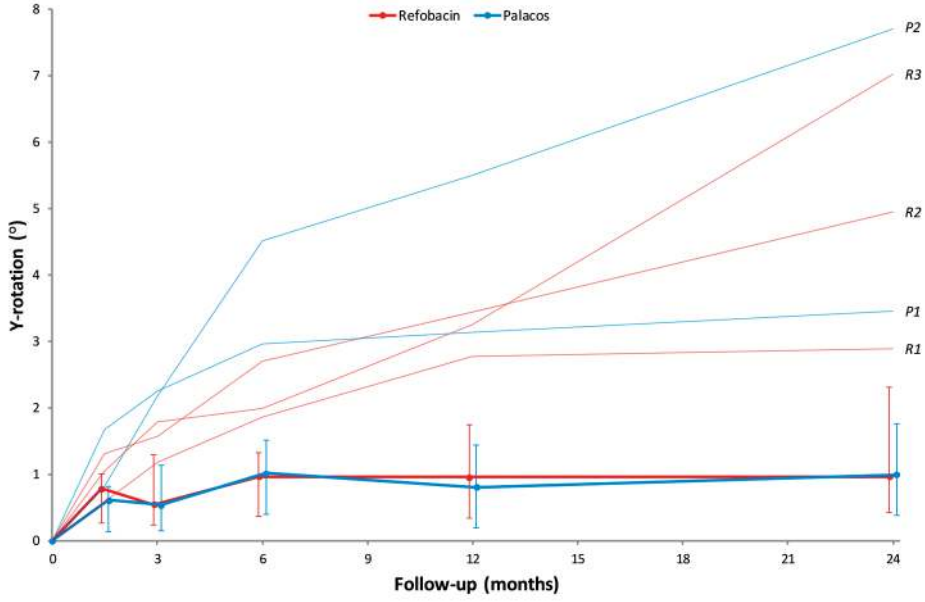

Figure 4. Line graphs showing the retroversion (i.e. internal rotation about the longitudinal axis) during the 2 years of follow-up for femoral components cemented with Refobacin bone cement R and Palacos R + G (median and interquartile range, thick blue and red lines).

Intention-to-treat

After randomization and during surgery, 5 patients did not receive the allocated bone cement due to the surgeon's lack of familiarity with the study (Figure 1). 2 patients incorrectly received Refobacin cement R and 3 incorrectly received Palacos R + G. Analysis of the results according to the intention-to-treat principle did not alter former results (Appendix A).

Clinical outcome

The mean HHS score did not differ significantly between the 2 groups throughout the follow-up period of 2 years (LMM; p = 0.62; Appendix B). Hips cemented with Palacos R + G showed an estimated mean of 2.1 points more improvement than those cemented with Refobacin cement R (difference between intercepts; LMM; 95% CI -6.3 to 10.6; p = 0.62). Postoperative HHS was higher with a higher preoperative HHS (difference in slope; LMM; 0.34 per preoperative point; 95% CI 0.18 to 0.51; p < 0.001). Age, gender, BMI, and diagnosis were not significantly associated with postoperative HHS (LMM; p-values > 0.05). The mean HOOS-QOL, HOOS-PS, EQ5D and SF-36 scores were not significantly different in the 2 groups at 2 years follow-up (p-values > 0.05; Appendix B).

Radiographic outcome

In 1 femoral component, cemented with Refobacin cement R, a small non-circumferential cement fracture appeared on the 2-year lateral radiograph in Gruen zone 10. On the same radiograph, small (< 2 mm) radiolucent lines around the proximal part of the stem (Gruen zones 8, 9, 13 and 14) were visible. This component also showed continuous subsidence and retroversion (R3, Figs 3 and 4). This patient had a contralateral THA cemented with Palacos R + G with neither radiolucencies, nor continuous migration at 2 years. No other THA had signs of a cement fracture on the 2-year conventional radiographs and there were no progressive radiolucent lines or radiolucent lines > 1 mm.

Nested case-control study

A total of 50 hips (5 cases and 45 controls) were available for the nested case-control study in a post hoc analysis. 5 hips (cases, 5 patients) showed non-stabilizing, continuous migration and 45 hips (controls, 44 patients) showed stabilizing migration (Table 4). No significant differences were found between the non-stabilizing and stabilizing femoral components with respect to patient demographics or clinical scores. However, in the non-stabilizing components, the mean thickness of the cement mantle of all 14 Gruen zones was greater (t-test; mean difference 0.7 mm; 95% CI 0.1 to 1.2 mm), and cementing grade B was more prevalent (FET; 80% in cases versus 13.3% in controls; p = 0.004).

DISCUSSION

In this blinded, randomized, clinical RSA study, the migration of the femoral component and mean HHS scores were comparable between those cemented with Refobacin cement R and those cemented with Palacos R + G during the first 2 postoperative years. The preoperative HHS scores mainly determined the postoperative HHS scores. Patient reported outcome measures (HOOS, EQ5D and SF-36 scores) also showed no difference. Migration stabilized in all except 5 hips (3 with Refobacin cement R and 2 with Palacos R + G). 5 components showed continuous subsidence and retroversion during the second postoperative year and are considered to be at risk for early aseptic loosening. The mean thickness of the cement mantle of these non-stabilizing components was larger than in the stabilizing components. Radiolucencies at the bone-cement interface were more frequent in non-stabilizing components.

This is the first randomized study comparing the migration of femoral components cemented with Refobacin cement R and Palacos R + G and shows how RSA can be used to evaluate newly designed bone cements before their introduction to the market. Evaluating innovations with RSA, as part of a phased evidence-based introduction, is relatively fast and inexpensive, and few patients are exposed to a potentially unsafe novelty. For example, RSA studies evaluating Boneloc cement, the Interax total knee arthroplasty and the Proxilock THA showed excessive migration compared

Characteristic	Cases	Controls	Mean difference	95% CI	*p* value
	n = 5	n = 45	cases vs. controls		
Bone cement — no. (%)					
Refobacin bone cement R	3 (60%)	22 (48.9%)			
Palacos R + G	2 (40%)	23 (51.1%)			1.00
Migration rate* — mm/year					
Subsidence	0.6 (0.1 to 1)	0 (0 to 0.2)			<0.001
Retroversion	1.5 (0.1 to 3.8)	0.4 (0.1 to 1.2)			0.17
Gender — no. (%)					
Male	2 (40%)	12 (26.7%)			
Female	3 (60%)	33 (73.3%)			0.61
BMI* — kg/m²	26.8 (21.9 to 29.1)	25.9 (19.7 to 40.6)			0.78
Age at surgery† — yr	69.8 ± 5.7	74.8 ± 5.6	5.00	-0.3 to 10.3	0.06
Diagnosis — no. (%)					
Osteoarthritis	3 (60%)	40 (88.9%)			
Rheumatoid arthritis	1 (20%)	1 (2.2%)			
Osteonecrosis	1 (20%)	2 (4.4%)			
Posttraumatic	0 (0%)	2 (4.4%)			0.25
Surgeon — no. (%)					
Consultant	3 (60%)	23 (51.1%)			
Resident	2 (40%)	22 (48.9%)			1.00
Stem size — no. (%)					
Size 1	0 (0%)	1 (2.2%)			
Size 2	1 (20%)	14 (31.1%)			
Size 3	2 (40%)	21 (46.7%)			
Size 4	2 (40%)	9 (20%)			0.33
Offset†	44.1 ± 4.7	45.8 ± 3.8	1.70	-2.0 to 5.4	0.36
Stem orientation — no. (%)					
varus	1 (20%)	1 (2.2%)			
neutral (< 3 degrees)	4 (80%)	41 (91.1%)			
valgus	0 (0%)	3 (6.7%)			0.25
Cement mantle thickness‡ — mm	4.5 ± 0.7	3.8 ± 0.6	-0.66	-1.2 to -0.1	0.02
Cementing grade — no. (%)					
A	1 (20%)	39 (86.7%)			
B	4 (80%)	6 (13.3%)			0.004
HHS† — min 0 - max 100 points					
preoperative	45.2 ± 17.5	47.5 ± 17.6	2.28	-14.6 to 19.1	0.79
2 year improvement	43.2 ± 30.6	35.5 ± 20.7	-7.43	-28.2 to 13.4	0.47

Table 4. Results of the nested case-controlled study.

Cases: components showing a migration rate higher or lower than the interquartile range

Controls: components showing a migration rate within the interquartile range

* The values are given as the mean and the range

† The values are given as the mean and the standard deviation

‡ Cement mantle thickness of all 14 Gruen zones, given as the mean and standard deviation

CI: confidence interval

with a control group within 2 years of follow-up (7, 28-30). Moreover, 3 meta-analyses have shown that RSA can be used to predict late aseptic loosening (31-33). Hence, RSA analyses of medical innovations as part of a phased evidence-based introduction, is conducive to patient safety (5, 6, 34, 35).

Recently, Olerud et al. performed a case-control study comparing Refobacin cement R with its predecessor Palacos R/Refobacin Palacos R (36). The median subsidence which they reported 2 years postoperatively (1.28 mm) was considerably more than the median subsidence which we found (0.37 mm). The median retroversion at this time (1°) was comparable to our findings. A possible explanation for the difference in subsidence is the design of the femoral component. Olerud et al. used a collarless, highly polished femoral component (MS-30; Zimmer) (36), which is designed to subside within the cement mantle as a consequence of cement creep (37). This type of stem is a 'force-closed' design; the gradually subsiding, tapered design achieves stability by the closing forces of the cement mantle (38). The Stanmore femoral component, in contrast, is a 'shape-closed' design theoretically not allowing it to subside. It also has a collar preventing subsidence (39). Continuous subsidence of a collared, 'shape-closed' design, might therefore be at risk for early loosening and failure.

In the current study, 5 components showed continuous migration during the second post-operative year. These components were compared with stabilizing components in a case-control manner. We found a thicker mean cement mantle and more hips classified as Barack cementing grade B in the non-stabilizing hips. This suggests that the technique of cementing is paramount for achieving stable fixation. This technique was also thought to be the reason for the discrepancy between early migration of the Scientific Hip Prosthesis (Biomet) reported by Nivbrant et al. (40), and fair mid-term clinical results of the same design reported by Broeke et al (41). In the former study, 58% of the 20 femoral components were classified as well cemented (Barrack grade A) in comparison to 76% of the 38 well cemented components in the latter study (40, 41).

This study had some limitations. In 11 THAs the migration could not be evaluated due to poor configuration of the markers caused by the surgeon's lack of familiarity with the study. This occurred in the early stages of the study. For the same reason, 5 patients did not receive the allocated bone cement. However, comparing the per-protocol analysis and the intention-to-treat analysis did not yield any differences.

In conclusion, THAs cemented with Refobacin cement R and Palacos R + G show comparable migration of the femoral component and clinical outcome 2 years postoperatively. However, outliers in both groups, comprising 5 out of 59 THAs, show non-stabilizing, continuous migration. The technique of cementing in these hips appeared to be less optimal.

Take home message: Regardless of the type of cement used, application of the proper cementing technique is paramount.

APPENDIX

							PER PROTOCOL	INTENTION TO TREAT
	Refobacin bone cement R			*Palacos R + G*			Main effect	Main effect
Migration	N	Mean (SD)	Median (range)	N	Mean (SD)	Median (range)	*p*-value	*p*-value
TRANSLATION — mm								
x-asis (medial-lateral)								
week 6	11	0.05 (0.12)	0.02 (-0.14 to 0.26)	16	0.09 (0.09)	0.06 (-0.03 to 0.25)		
month 3	22	0.04 (0.15)	0.02 (-0.27 to 0.35)	23	0.11 (0.14)	0.06 (-0.07 to 0.51)		
month 6	25	0.05 (0.17)	0.01 (-0.28 to 0.46)	25	0.12 (0.2)	0.06 (-0.08 to 0.88)	0.82	0.69
year 1	24	0.1 (0.2)	0.02 (-0.12 to 0.6)	24	0.11 (0.24)	0.06 (-0.11 to 1.12)		
year 2	22	0.11 (0.37)	0.03 (-0.6 to 1.2)	24	0.14 (0.28)	0.11 (-0.14 to 1.32)		
y-axis (cranial-caudal)								
week 6	11	-0.14 (0.03)	-0.15 (-0.27 to 0.02)	16	-0.18 (0.34)	-0.08 (-1.32 to 0.16)		
month 3	22	-0.12 (0.03)	-0.13 (-0.33 to 0.28)	23	-0.23 (0.34)	-0.15 (-1.55 to 0.15)		
month 6	25	-0.22 (0.03)	-0.24 (-0.44 to 0.13)	25	-0.3 (0.44)	-0.17 (-2.1 to 0.14)	0.56	0.95
year 1	24	-0.28 (0.04)	-0.28 (-0.66 to 0.17)	24	-0.38 (0.57)	-0.2 (-2.36 to 0.1)		
year 2	22	-0.43 (0.08)	-0.37 (-1.6 to 0.08)	24	-0.46 (0.72)	-0.25 (-2.98 to 0.08)		
z-axis (anterior-posterior)								
week 6	11	-0.1 (0.23)	-0.06 (-0.51 to 0.31)	16	-0.08 (0.14)	-0.12 (-0.29 to 0.15)		
month 3	22	-0.11 (0.24)	-0.11 (-0.77 to 0.21)	23	-0.11 (0.16)	-0.13 (-0.42 to 0.14)		
month 6	25	-0.2 (0.28)	-0.11 (-0.92 to 0.12)	25	-0.16 (0.28)	-0.14 (-1.1 to 0.21)	0.51	0.77
year 1	24	-0.26 (0.27)	-0.16 (-0.97 to 0.09)	24	-0.14 (0.27)	-0.11 (-0.91 to 0.23)		
year 2	22	-0.24 (0.41)	-0.1 (-1.32 to 0.68)	24	-0.19 (0.29)	-0.18 (-1.1 to 0.2)		
ROTATION — degrees								
x-asis (transverse)								
week 6	11	-0.2 (0.72)	-0.11 (-2.11 to 0.48)	16	-0.06 (0.21)	-0.06 (-0.38 to 0.48)		
month 3	22	-0.02 (0.53)	0 (-1.51 to 1.38)	23	-0.07 (0.27)	-0.04 (-0.72 to 0.57)		
month 6	25	0.05 (0.56)	0.01 (-1.28 to 1.51)	25	0 (0.43)	-0.04 (-0.77 to 1.54)	0.99	0.29
year 1	24	0 (0.49)	-0.04 (-0.76 to 1.71)	24	-0.09 (0.3)	-0.08 (-0.76 to 0.33)		
year 2	22	0.06 (0.58)	-0.05 (-1.07 to 1.93)	24	-0.06 (0.34)	-0.07 (-0.94 to 0.41)		

Appendix A. Analysis of femoral component migration during 2 years of follow-up.

		Refobacin bone cement R			*Palacos R + G*		PER PROTOCOL	INTENTION TO TREAT
							Main effect	Main effect
Migration	N	Mean (SD)	Median (range)	N	Mean (SD)	Median (range)	*p*-value	*p*-value
y-axis (longitudinal)								
week 6	11	0.58 (0.59)	0.78 (-0.57 to 1.31)	16	0.62 (0.61)	0.61 (-0.23 to 2.12)		
month 3	22	0.61 (0.82)	0.54 (-1.37 to 1.78)	23	0.76 (0.81)	0.54 (-0.38 to 2.5)		
month 6	25	0.91 (0.78)	0.96 (-0.56 to 2.7)	25	1.05 (1.11)	1.01 (-1.09 to 4.51)	0.82	0.84
year 1	24	1.14 (1.02)	0.96 (-0.16 to 3.44)	24	1.06 (1.32)	0.8 (-0.62 to 5.49)		
year 2	22	1.45 (1.84)	0.96 (-1.68 to 7.02)	24	1.4 (1.63)	0.99 (-0.2 to 7.7)		
z-axis (sagittal)								
week 6	11	-0.2 (0.37)	-0.1 (-1.05 to 0.16)	16	-0.05 (0.2)	-0.05 (-0.44 to 0.45)		
month 3	22	-0.12 (0.36)	-0.07 (-0.86 to 0.53)	23	-0.06 (0.24)	-0.07 (-0.55 to 0.58)		
month 6	25	-0.19 (0.35)	-0.16 (-0.88 to 0.45)	25	-0.08 (0.32)	-0.06 (-1.05 to 0.68)	0.06	0.41
year 1	24	-0.22 (0.38)	-0.16 (-1.07 to 0.45)	24	-0.09 (0.33)	-0.07 (-1.1 to 0.65)		
year 2	22	-0.28 (0.58)	-0.17 (-1.74 to 0.72)	24	-0.13 (0.4)	-0.1 (-1.43 to 0.85)		
MEAN TOTAL POINT MOTION — mm								
week 6	11	1.19 (1.21)	0.84 (0.4 to 4.66)	16	0.76 (0.47)	0.55 (0.33 to 2.07)		
month 3	22	1.09 (0.89)	0.77 (0.25 to 3.6)	23	0.89 (0.59)	0.73 (0.12 to 2.54)		
month 6	25	1.28 (0.89)	1.01 (0.31 to 4)	25	1.19 (1.06)	0.72 (0.23 to 4.38)	0.22	0.34
year 1	24	1.36 (0.99)	1.08 (0.41 to 4.43)	24	1.21 (0.96)	0.82 (0.39 to 4.49)		
year 2	22	1.78 (1.5)	1.2 (0.26 to 5.42)	24	1.41 (1.19)	0.91 (0.44 to 5.8)		

Appendix A (continued). Analysis of femoral component migration during 2 years of follow-up.

Outcome	*Refobacin bone cement R*			*Palacos R + G*			PER PROTOCOL		INTENTION TO TREAT	
							Main effect	Specific time point effect	Main effect	Specific time point effect
	N	Mean (SD)	Median (range)	N	Mean (SD)	Median (range)	*p*-value	*p*-value	*p*-value	*p*-value
HHS — min 0 - max 100 points										
preoperative	27	44.59 (16.75)	44 (11 to 77)	27	48.26 (16.38)	48 (22 to 83)				
week 6	14	76.5 (16.77)	81.5 (36 to 95)	20	79.95 (10.47)	80 (61 to 100)				
month 3	20	75.2 (10.23)	74.5 (56 to 97)	26	83.12 (12.89)	86 (48 to 100)				
month 6	25	80.32 (15.27)	84 (42 to 100)	25	86.96 (13)	90 (55 to 100)	0.62		0.41	
year 1	24	79.67 (16.21)	81 (35 to 100)	24	86.33 (15.9)	91.5 (37 to 100)				
year 2	21	79.95 (17.48)	85 (39 to 100)	25	83.72 (21.57)	91 (22 to 100)				
HOOS-QOL — min 0 - max 100 points										
preoperative	0	N/A	N/A	0	N/A	N/A				
week 6	6	36.46 (9.2)	34.38 (25 to 50)	7	49.11 (14.63)	50 (31.25 to 68.75)				
month 3	1	N/A	N/A	9	54.17 (19.01)	50 (37.5 to 100)				
month 6	10	61.25 (13.44)	62.5 (37.5 to 81.25)	10	62.5 (23.2)	62.5 (31.25 to 100)				
year 1	14	60.27 (22.28)	62.5 (25 to 100)	17	70.96 (22.96)	68.75 (6.25 to 100)				
year 2	12	64.58 (24.91)	59.38 (31.25 to 100)	19	74.34 (27.07)	75 (6.25 to 100)		0.16		0.38

Appendix B. Analysis of clinical outcome during 2 years of follow-up.
N/A: not available

Outcome							PER PROTOCOL		INTENTION TO TREAT	
	Refobacin bone cement R			*Palacos R + G*			Main effect	Specific time point effect	Main effect	Specific time point effect
	N	Mean (SD)	Median (range)	N	Mean (SD)	Median (range)	*p*-value	*p*-value	*p*-value	*p*-value
HOOS-PS — min 100 - max 0 points										
preoperative	0	N/A	N/A	0	N/A	N/A				
week 6	6	49.65 (20.48)	55,9 (16,4 to 67,9)	8	45.95 (6.05)	48,8 (20 to 67,9)				
month 3	3	33.3 (11.62)	30,4 (23,4 to 46,1)	7	35.99 (9.96)	33,9 (8,8 to 90,8)				
month 6	7	40.41 (19.68)	37,7 (12,7 to 74,8)	9	39.41 (9.52)	30,4 (0 to 90,8)				
year 1	13	31.1 (17.23)	33,9 (0 to 55,9)	13	27.02 (4.98)	20 (12,7 to 61,6)				
year 2	11	29.54 (24.53)	23,4 (0 to 74,8)	18	26.83 (5.91)	20 (0 to 90,8)		0.67		0.74
EQ5D — min -0.33 - max 1 points										
preoperative	0	N/A	N/A	0	N/A	N/A				
week 6	8	0.73 (0.09)	0.74 (0.57 to 0.86)	6	0.73 (0.15)	0.78 (0.52 to 0.89)				
month 3	5	0.7 (0.12)	0.69 (0.57 to 0.9)	11	0.73 (0.26)	0.78 (0.22 to 1)				
month 6	10	0.59 (0.25)	0.69 (0.07 to 0.78)	8	0.74 (0.23)	0.78 (0.22 to 1)				
year 1	19	0.66 (0.24)	0.69 (0.17 to 1)	15	0.7 (0.32)	0.81 (-0.3 to 1)				
year 2	15	0.68 (0.25)	0.78 (0.12 to 1)	21	0.72 (0.29)	0.81 (0 to 1)		0.35		0.51

Appendix B (continued). Analysis of clinical outcome during 2 years of follow-up.
N/A: not available

Outcome							PER PROTOCOL		INTENTION TO TREAT	
	Refobacin bone cement R			*Palacos R + G*			Main effect	Specific time point effect	Main effect	Specific time point effect
	N	Mean (SD)	Median (range)	N	Mean (SD)	Median (range)	*p*-value	*p*-value	*p*-value	*p*-value
SF-36 — min 0 - max 100 points										
Physical component										
preoperative	6	42.76 (5.93)	42.89 (33.58 to 50.24)	2	42.17 (2.97)	42.17 (40.07 to 44.27)				
week 6	9	42.47 (9.6)	41.37 (30.73 to 56.96)	9	44.07 (8.7)	44.86 (28.49 to 59.7)				
month 3	7	44.78 (5.34)	45.4 (34.1 to 50.24)	11	47.97 (13.77)	44.74 (22.74 to 71.21)				
month 6	9	44.3 (9.53)	40.7 (30.24 to 59.36)	7	45.64 (10.83)	44.78 (28.62 to 62.03)				
year 1	16	52.3 (10.58)	49.53 (36.91 to 69.74)	14	53.37 (12.49)	55.39 (33.51 to 68.92)				
year 2	13	49.58 (16.57)	47.16 (27.42 to 71.85)	20	54.19 (13.52)	54.37 (25.57 to 71.33)		0.48		0.38
Mental component										
preoperative	6	58.16 (15.19)	56.45 (41.53 to 81)	2	59.96 (6.83)	59.96 (55.13 to 64.79)				
week 6	9	58.35 (15.31)	61.99 (40.9 to 80.53)	9	55.67 (11.08)	54.11 (44 to 72.65)				
month 3	7	55.06 (15.82)	56.75 (28.78 to 72.19)	11	64.49 (8.25)	64.37 (51.73 to 80.13)				
month 6	9	55.16 (17.06)	55.78 (26.01 to 76.82)	7	66.45 (8.53)	66.63 (53.83 to 75.48)				
year 1	16	58.64 (14.33)	59.9 (33.95 to 76.67)	14	61.84 (15.17)	65.32 (29.58 to 79.86)				
year 2	13	60.32 (17.96)	65.6 (31.12 to 84.82)	20	63.51 (11.96)	64.89 (37.42 to 80.75)		0.83		0.91

Appendix B (continued). Analysis of clinical outcome during 2 years of follow-up.
N/A: not available

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5

Early subsidence of shape-closed THA stems is associated with late revision: a systematic review and meta-analysis of 24 RSA studies and 56 survival studies

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ABSTRACT

Introduction

Few studies have addressed the association between early migration of femoral stems and late aseptic revision in total hip arthroplasty. We performed a meta-regression analysis on 2 parallel systematic reviews and meta-analyses to determine the association between early migration and late aseptic revision of femoral stems.

Methods

Of the 2 reviews, one covered early migration data obtained from roentgen stereophotogrammetry (RSA) studies and the other covered long-term aseptic revision rates obtained from survival studies with endpoint revision for aseptic loosening. Stems were stratified according to the design concept: cemented shape-closed, cemented force-closed, and cementless. A weighted regression model was used to assess the association between early migration and late aseptic revision, and to correct for confounders. Thresholds for acceptable and unacceptable migration were determined in accordance with the national joint registries (≤ 5% revision at 10 years) and the NICE criteria (≤ 10% revision at 10 years).

Results

24 studies (731 stems) were included in the RSA review and 56 studies (20,599 stems) were included in the survival analysis review. Combining both reviews for the 3 design concepts showed that for every 0.1-mm increase in 2-year subsidence, as measured with RSA, there was a 4% increase in revision rate for the shape-closed stem designs. This association remained after correction for age, gender, diagnosis, hospital type, continent, and study quality. The threshold for acceptable migration of shape-closed designs was defined at 0.15 mm; stems subsiding less than 0.15 mm in 2 years had revision rates of less than 5% at 10 years, while stems exceeding 0.15 mm subsidence had revision rates of more than 5%.

Conclusion

There was a clinically relevant association between early subsidence of shape-closed femoral stems and late revision for aseptic loosening. This association can be used to assess the safety of shape-closed stem designs. The published research is not sufficient to allow us to make any conclusions regarding such an association for the force-closed and cementless stems.

INTRODUCTION

Over 1 million total hip arthroplasties (THAs) are performed every year worldwide, and this number is expected to double within the next 2 decades (1). The design and method of fixation of a THA determines the stability of the implant, and these are therefore crucial factors for achievement of long-term survival. However, most of the new THA designs have been introduced onto the market without demonstrating good performance (2). This has led to several THAs having high failure rates, such as the Charnley Elite Plus (3). To prevent future disasters with orthopaedic implants, several countries have developed guidelines to guarantee patient safety, e.g. the NICE guidelines (NHS). Furthermore, it has become increasingly evident that a phased evidence-based introduction, as is common with pharmaceuticals, is necessary to regulate the introduction of new THA designs to the market (4-6). This should include systematic assessment and early detection of aseptic loosening in small groups of patients.

Although it may take as long as 10 years for aseptic loosening of implants to become manifest, it is possible to detect the loosening process as early as 1–2 years postoperatively, using roentgen stereophotogrammetry (RSA). Since RSA allows in vivo, 3D measurement of the migration of THAs with an accuracy of 0.2 mm for translations and 0.5° for rotations, only a small number of patients is needed to compare a new innovative design to a gold-standard design (3, 7-11). Thus, only a few patients will have been exposed if that design turns out to be a poor one. RSA could therefore play an important role in phased evidence-based market introduction of new THA designs (12-15).

Following on from our 2 earlier studies on the association between early migration and late aseptic revision of tibial components and acetabular cups, this systematic review and meta-analysis focused on the femoral stem (16, 17). We hypothesized that early migration, as measured with RSA, is associated with late revision for aseptic loosening. We systematically reviewed the association between early migration and late revision for aseptic loosening of the femoral stem in primary THA. This could eventually lead to clinical guidelines, to be used in a phased introduction of new THA designs.

METHODS

Study design

We performed a meta-regression analysis (international registration number NTR3129; www.trialregister.nl) combining RSA migration data with survival analysis data for each stem design, to assess the association between early migration and late aseptic revision. To this end, 2 parallel systematic reviews (Figure 1) and meta-analyses were performed on studies of patients treated with THA for primary osteoarthritis (OA), secondary osteoarthritis (SA), and fractures of the proximal femur (FF). One review covered early migration data on femoral stems, obtained from RSA studies. The other review covered long-term aseptic revision rates obtained from survival

studies, with revision for aseptic loosening of femoral stems as the endpoint. The data were stratified according to the design concept of the femoral stem (i.e. cemented shape-closed, cemented force-closed, and cementless)(18). During all phases of the review process, author RN with over 20 years of experience of both RSA and THA, was available for consultation.

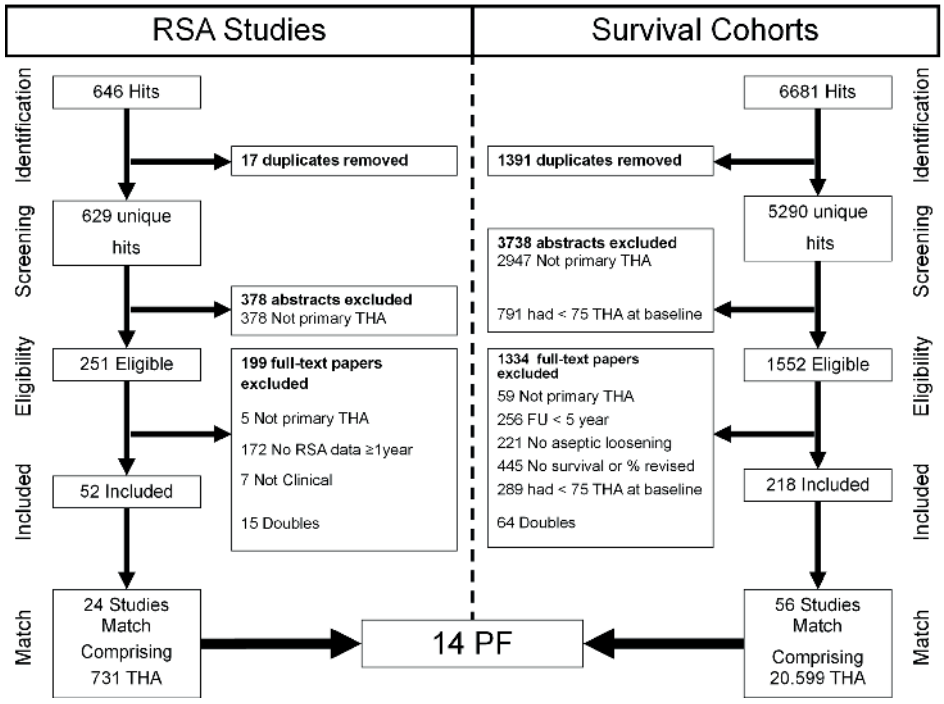

Figure 1. PRISMA flow chart of both reviews. Details of the 14 PF combinations can be found in Table 1.

Systematic review of RSA studies

Literature search

A literature search was performed in cooperation with a medical librarian (JP), to minimize publication bias (19). The search strategy and bibliographies used were the same as in the systematic review and meta-analysis on early migration of acetabular cups in relation to late aseptic revision (16). Relevant articles were screened for additional references. Then a separate search was conducted in 9 leading orthopaedic and biomechanical journals (Acta Orthop, Bone Joint J, Clin Orthop Relat Res, J Arthroplasty, J Bone Joint Surg Am, Knee Surg Sports Traumatol Arthrosc, J Orthop Res, J Biomech, and Clin Biomech). Finally, was used to search for additional relevant studies. Articles in English, French, Italian, Spanish, Dutch, and German were considered. The search strategy consisted of the following components—each defined by a combination of controlled vocabulary and free text terms: (1) RSA, and (2) joint replacement. More details of the strategy and glossary terms used can be found in the Appendix.

Inclusion and exclusion analysis

Initial screening based on the title and abstract of RSA studies was performed by BP to identify studies on patients treated with THA for osteoarthritis, spondyloarthritis, or femoral fracture. In cases where the information in the abstract did not suffice or where there was any doubt, studies remained eligible. The full text of eligible studies was independently evaluated in duplicate by 2 reviewers (BP and MN). The inclusion criteria for RSA studies were (1) primary THA, and (2) a minimum RSA follow-up of 1 year, measuring femoral stem migration.

Data extraction

Migration data from RSA studies was independently extracted in duplicate by PV and MN. Since the failure mechanism of femoral stems involves subsidence and retroversion, the data extraction of RSA studies focused on subsidence and retroversion of the femoral stem in the first 2 postoperative years (8). Data concerning patient demographics and regional influences were extracted to allow for confounder correction (20). The design concept of different femoral stems (i.e. cemented shape-closed, cemented force-closed, or cementless) was determined by RN.

Quality assessment

The quality of the RSA studies was independently appraised in duplicate by PV and JJ at the level of outcome using the AQUILA methodological score (20). For the RSA studies, we modified the AQUILA score by removing items that were not considered relevant for appraisal of early migration: long-term follow-up and revision assessment.

Systematic review of survival studies

Literature search

The search strategy and bibliographies were comparable to those used in the RSA review, with the exception of the components of the search strategy. The search strategy for the survival studies consisted of the following components, each defined by a combination of controlled vocabulary and free text terms: (1) joint replacement, (2) implant failure, and (3) survival analysis. More details of the strategy and glossary terms used can be found in the Appendix.

Inclusion and exclusion analysis

The procedure for screening of the survival studies for eligibility and subsequent inclusion and exclusion analysis was identical to the procedures for the RSA studies with the exception of the inclusion and exclusion criteria. The inclusion criteria for survival studies were (1) primary THA; (2) follow-up time of 5, 10, 15, 20, or 25 years (in the final analysis, only 10 years of follow-up was used); (3) endpoint being revision surgery for aseptic loosening of the femoral stem, or indication for revision surgery when there was poor general health or patient decline; and (4) survival or percentage revised being available for a specific follow-up period (see point 2). Studies with less than 75 THAs at baseline were excluded.

Data extraction

Revision rates for aseptic loosening of the femoral stem at 5-year intervals from survival studies were independently extracted in duplicate by PV and JJ. Data concerning patient demographics and regional influences were also extracted to allow for confounder correction. The design concept of different femoral stems was determined by RN.

Quality assessment

The quality of the survival studies was independently appraised in duplicate by PV and JJ at the level of outcome using the AQUILA methodological score (20).

Analysis

The data were analysed according to the same methodology as previously used in the systematic review and meta-analysis on early migration of acetabular cups in relation to late aseptic revision (16). A detailed description of the analysis, methodology, and a worked example are available in the online Appendix. The association between early migration and late revision was determined by matching the results from the RSA review to the results of the survival analysis review according to the type of prosthesis and fixation method (e.g. cemented or cementless), here abbreviated to PF combination. Matching according to PF combination prevents confounding by PF combination, since PF combination is determined by technical factors known to be associated with both migration and a high likelihood of revision for aseptic loosening (AJR 2013, NJR 2012, SHAR 2011). PF combinations were subsequently stratified according to design concept (i.e. cemented shape-closed, cemented force-closed, or cementless). Depending on the studies available, it is possible that there would be more than 1 combination of matching of RSA and survival studies for a particular PF combination. For instance, if there are 3 RSA studies and 2 survival studies of the same PF combination, then there would be 6 possible combinations (3 × 2). All combinations were considered in the analysis. A meta-analysis for the revision rates at 10 years was performed. A model for the censoring mechanism was employed to reconstruct the data, and then a generalized linear mixed model with study as a random effect was applied to estimate the survival at 10 years and its confidence interval (21-24). Regarding the RSA studies, pooling of migration results at the level of PF combinations was based on weights according to study size (N).

The 10-year results of THA with high revision rates are not likely to be published once 5-year published results show high revision rates. Since 10-year revision rates in the registries are on average 1.7 times higher than 5-year revision rates, any missing 10-year results were estimated from 5-year results by applying the factor 1.7. This method was validated by comparing the estimated 10-year results with the known 10-year results for the complete cases (25-27).

Adjustment for confounding

Since RSA migration data and survival analysis data were extracted from different studies, it may be possible that differences between study populations might confound the observed as-

sociation. In order to address this issue, we determined the degree of similarity of the study population between the RSA data and survival analysis data for the same stem design, expressed by a match score, for age, gender, diagnosis, hospital type, and continent. The match score has been constructed according to the results of a Delphi survey among an international group of 37 independent experts and can vary between 0 (poor) and 5 (excellent) (20). This RSA study and the survival study combination scored 1 point for each of the following criteria (up to a maximum of 5 points): (1) the difference in mean age between patients from the RSA study and those from the survival study was 5 years or less; (2) the difference in percentage of females between the RSA study and the survival study was 10% or less; (3) the difference in percentage of patients diagnosed with primary osteoarthritis between the RSA study and the survival study was 10% or less; (4) the RSA study and the survival study were performed in a similar type of hospital (e.g. both in university medical centers); and (5) the RSA study and the survival study were performed on the same continent. All other cases scored zero points. We used a weighted regression model to assess the association between early migration and late aseptic revision, corrected for the influence of match score, quality of RSA study, quality of survival study, number of THAs in the RSA studies, and number of THAs in the survival studies.

Migration thresholds

According to the principle of "primum non nocere", new implant designs should perform at least as well as the revision standard of national registries with high validity: ≤ 3% revision at 5 years and ≤ 5% revision at 10 years according to the Swedish Hip Arthroplasty Register and the Australian National Joint Replacement Registry (25, 27). To have a safe margin, these more conservative criteria were chosen over the NICE criteria thresholds (i.e. 5% revision at 5 years and 10% revision at 10 years) (28). Based on the revision standard of the national registries, the following 3 categories were constructed for the phased introduction of new THA: "acceptable", "at risk", and "unacceptable". The category "acceptable" was defined as the level of migration up to which all survival studies have lower revision rates than the standard. The category "unacceptable" was defined as the level of migration from which all revision rates are higher than the standard. The category "at risk" was defined as the migration interval between the "acceptable" and "unacceptable" thresholds, in which studies with revision rates lower and higher than the standard were observed.

Appraisal of publication bias

We assessed the potential effect of publication bias by comparing the results from the meta-analysis to the results from national joint registries, since they do not suffer from publication bias (25-27). Accordingly, the PF combinations that perform better than average in the meta-analysis should also perform better than average in the national joint registries. The same principle also applies to PF combinations that perform worse than average. For this purpose, the pooled migration per specific combination of prosthesis type and fixation method was sorted according to revision rate and visualized in a dot chart.

RESULTS

RSA studies

The literature search yielded 629 hits for the RSA review, and 24 studies were included comprising 731 femoral stems (Figure 1) (3, 10, 18, 29-52). The mean AQUILA methodological quality score of the RSA studies on a 7-point scale was 5.2 (SD 1.2). Subsidence of the femoral stem was the most frequently reported migration value: 1-year and 2-year subsidence was reported in 22 and 20 out of 27 RSA studies, respectively. Retroversion at 1 year and 2 years was reported in 10 and 13 RSA studies, respectively. Posterior head migration (translation along the z-axis) was reported infrequently and inconsistently, and did not allow a meaningful analysis.

Survival studies

The literature search generated 5,290 hits for the survival analysis review and 56 studies were included with a total of 20,599 femoral stems (Figure 1) (53-118). The mean AQUILA methodological quality score of the survival studies on an 11-point scale was 7.0 (SD 2.1).

Early migration and late revision

The matching procedure resulted in 14 different PF combinations (i.e. type of prosthesis and fixation method) and 100 combinations of RSA and survival studies (Table 1). In the entire heterogeneous group of different PF combinations, there was no statistically significant ($p > 0.05$) association between migration, either subsidence or retroversion, and prosthesis survival (Figure 2). Then we divided the PF combinations into more homogenous groups according to design concept: cemented shape-closed, cemented force-closed, and cementless (18). For the shape-closed femoral stems, there was an association between subsidence of shape-closed femoral stems and implant survival (Figure 3). For every 0.1-mm increase in 2-year subsidence in shape-closed designs, there was a 4.2% (95% CI: 1.3–7.1; $p < 0.05$) increase in the aseptic revision rate at 10 years. This association remained significant after correction for RSA study quality, survival study quality, number of femoral stems in the RSA study, number of femoral stems in the survival study, and match score (all p-values < 0.05) (Table 2). The force-closed stems, consisting exclusively of the polished Exeter stem in the current meta-analysis, showed excellent long-term survival with no stems exceeding the revision threshold of 5% at 10 years (Figure 2). Further analysis for the force-closed stems was considered inappropriate given the small number of PF combinations and the lack of contrast in revision rates (i.e. no high revision rates (> 5%)) (Figure 2). For the same reason, no meaningful analyses could be carried out for the cementless stems since only 1 PF combination (Ribbed uncoated stem) showed a revision rate of more than 5% at 10 years. None of the design concepts showed an association between retroversion or continuous migration (i.e. 2-year migration minus 1-year migration) and implant survival.

PFI	Prosthesis (stems)	Fixation	RSA studies (N)	Survival studies (N)	Combinations (N)
1	ABG I	HA coated	1	8	8
2	Bicontact	Porous-coated	1	4	4
3	Charnely Elite Plus (SC)	Cement (high viscosity)	2	2	4
4	Charnely Elite Plus (SC)	Cement (low viscosity)	1	1	1
5	Cementless Spotorno	Uncoated	1	7	7
6	Exeter (FC)	Cement (high viscosity)	4	8	32
7	Exeter (FC)	Cement (low viscosity)	3	1	3
8	Honnart Partel-Garches	Uncoated	1	1	1
9	Lubinus SP II (SC)	Cement (high viscosity)	3	5	15
10	Omnifit	HA coated	1	5	5
11	Ribbed	Uncoated	1	1	1
12	Scanhip (SC)	Cement (high viscosity)	1	2	2
13	Spectron EF (SC)	Cement (high viscosity)	3	4	12
14	Taperloc	Porous-coated	1	5	5
Total			*24*	*54*	*100*

Table 1. Details of prosthesis and fixation (PF) combinations.
SC = shape-closed; FC = force-closed; HA = Hydroxyapatitie; ABG = Anatomique Benoist Giraud

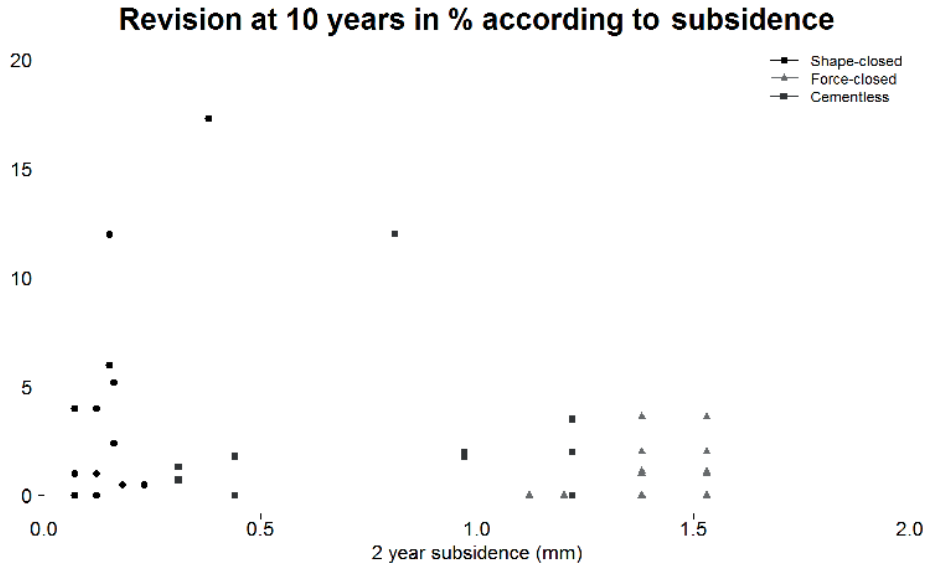

Figure 2. Scatter plot showing the subsidence at 2 years (in mm) and revision rate for aseptic loosening of the femoral stem at 10 years (percentage), categorized according to design concept (i.e. shape-closed, force-closed, cementless).

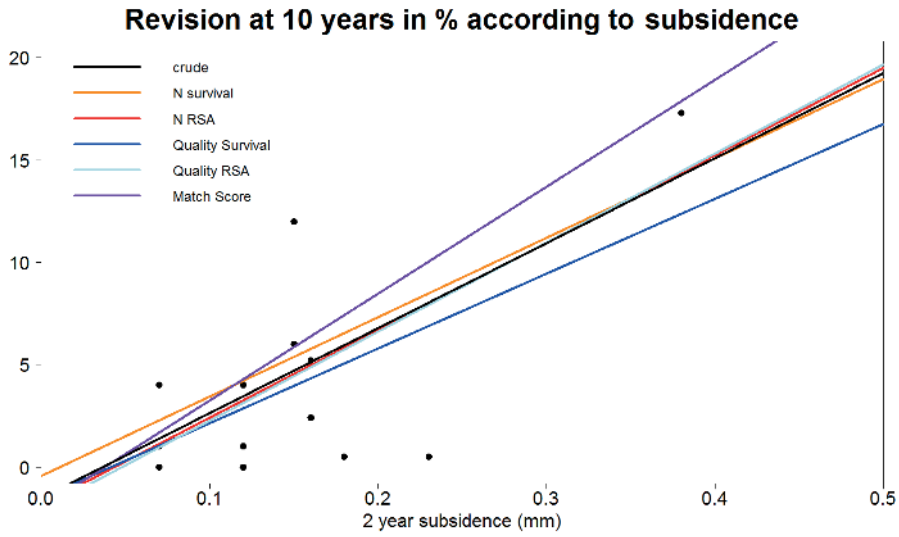

Figure 3. Scatter plot showing the association between 2-year subsidence (in mm) and revision rate for aseptic loosening of the shape-closed femoral stem at 10 years (percentage). The coloured lines are derived from weighted regression according to match quality, survival study quality, and RSA quality (the coefficients and 95% CIs are presented in Table 2).

	Increase in revision (%) / mm in subsidence	95% CI
Crude	4.2	1.3 - 7.1
Adjusted for*:		
N survival**	3.9	6 - 7.2
N RSA**	4.3	1.2 - 7.4
Survival study quality	3.7	6 - 6.7
RSA study quality	4.4	1.8 - 7
Total Match Score	5.2	2.7 - 7.7
Range of values	3.7 - 5.2	6 - 7.7

Table 2. Association between 2-year subsidence of shape-closed femoral stems and revision rate for aseptic loosening at 10 years. Increase in 10-year revision rate (%) for each 0.1-mm increase in subsidence at 2 years. In the crude analysis (unadjusted), 4.2% (95% CI: 1.3–7.1; $p < 0.05$) was added to the 10-year revision rate for every 0.1-mm increase in subsidence at 2 years.

Early migration

The force-closed stems showed the largest amount of early subsidence, with a pooled mean subsidence of 1.0 mm (SE 0.05) and 1.3 mm (SE 0.01) at 1 and 2 years, respectively (Figure 4). The pooled subsidence of the cementless stems was in-between that of cemented force-closed and shape-closed stems. The cementless stems showed a pooled mean subsidence of 0.6 mm (SE 0.08) at 1 year and 0.7 mm (SE 0.07) at 2 years. The shape-closed stems showed a pooled mean subsidence of 0.11 mm (SE 0.01) and 0.14 mm (SE 0.01) at 1 and 2 years, respectively.

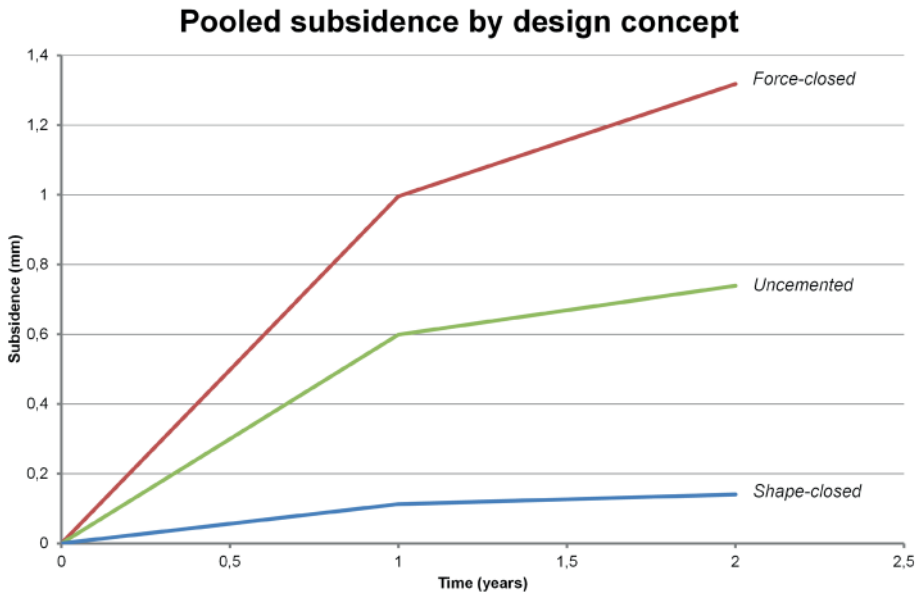

Figure 4. Line chart of the pooled subsidence (in mm) up to 2 years, according to design concept (i.e. shape-closed, force-closed, cementless). The standard errors were 0.05 mm and 1 mm (force-closed), 0.08 mm and 0.07 mm (cementless), and 0.01 mm and 0.01 mm (shape-closed) at 1 and 2 years, respectively.

Migration thresholds

Figure 5 shows the 3 categories of the stems. Subsidence at 2 years was between 0 and 0.15 mm; there was no stem with more than 5% revision for aseptic loosening at 10 years. In the case of 2-year subsidence of more than 0.23 mm, there was no stem with less than 5% revision for aseptic loosening at 10 years. This indicates that accepting 5% revision at 10 years resulted in a threshold of 0.15 mm for acceptable subsidence at 2 years. The threshold for unacceptable subsidence is less distinct, given the lack of data points with an excessive revision rate. However, stems with a subsidence of more than 0.15 mm are at risk of early revision. Adoption of the NICE criteria (10% revision at 10 years) does not alter the threshold of acceptable subsidence of 0.15 mm at 10 years.

Publication bias

The pooled 2-year migration, ranked by the pooled 10-year revision rate for each PF combination, is presented in Figure 6. The PF combinations that migrate less than the acceptable threshold (i.e. Lubinus SP and Spectron EF) have been—according to the Swedish Register—the most and the fourth most commonly used femoral components during the past 10 years, with survival rates of 98% and 97% at 10 years (SHAR). Conversely, the PF combinations that are classified as unacceptable on the basis of their pooled migration (i.e. Charnely Elite Plus) have been abandoned, and are no longer used (3). These examples show that the possible influence of publication bias on the results is small.

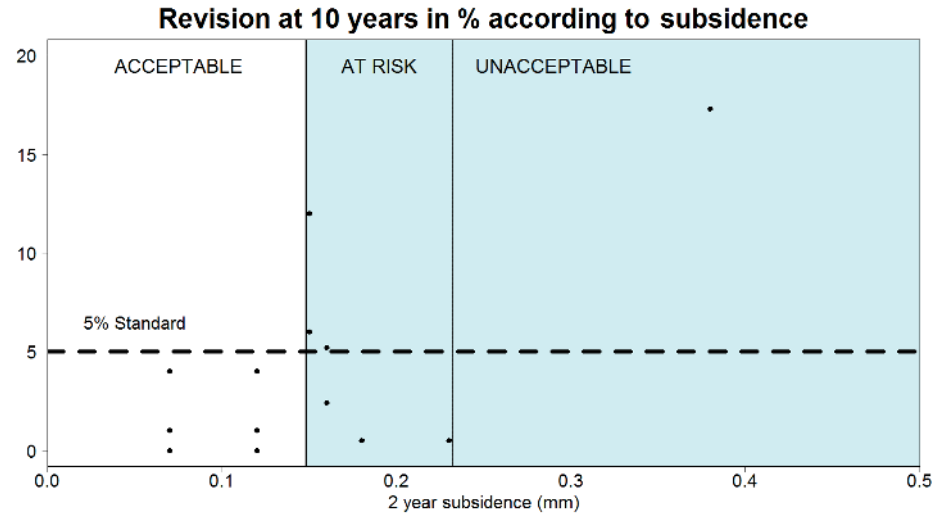

Figure 5. Scatter plot showing the 2-year subsidence and revision rate of shape-closed femoral stems for aseptic loosening at 10 years. The threshold of 0.15 mm for acceptable subsidence is shown. The threshold of 0.23 mm for unacceptable subsidence could be defined less precisely and is also shown. Adoption of the NICE criteria (10% revision at 10 years) did not alter these thresholds.

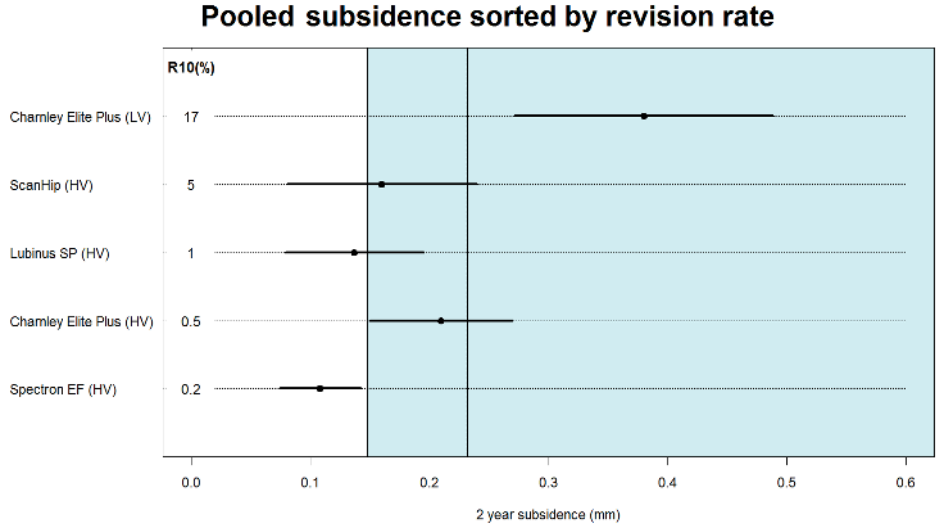

Figure 6. Dot chart showing the pooled 2-year subsidence of shape-closed femoral stems ranked by the pooled 10-year revision rate for each PF combination. The threshold of 0.15 mm for acceptable subsidence is shown and the less precisely definable threshold for unacceptable subsidence (0.23) is also shown.

DISCUSSION

The results of this meta-regression analysis, combining data from RSA studies and survival studies, show a clinically relevant association between early subsidence of shape-closed femoral stem designs, as measured with RSA, and clinical failure (i.e. aseptic revision surgery) at 10-year follow-up, corrected for age, gender, diagnosis, type of hospital, region, size of study, and quality of study. For every 0.1-mm increase in subsidence, the 10-year revision rate increases by mean 4% (95% CI: 1.3–7.1). The force-closed stem designs, which in the current meta-analysis consisted of only polished Exeter stems, showed the greatest amount of early subsidence and had excellent long-term survival with none of the stems exceeding the revision threshold of 5% at 10 years. This suggests that subsidence is beneficial for force-closed stems. However, more research with different force-closed stems is necessary to confirm this idea. The subsidence of the cementless stems varied between that of cemented shape-closed stems and force-closed stems, and there was only 1 PF combination with a revision rate of more than 5% (Ribbed uncoated stem). The available data did not provide a clear pattern for identification of unsafe cementless designs. Perhaps stabilization of migration is more suitable than the absolute value of migration for identification of unsafe cementless femoral stems.

The results of our systematic review demonstrate that RSA studies can identify unsafe shape-closed femoral stems as early as 2 years postoperatively. Next to tibial components and acetabular components, our finding is another example of the potential of RSA for early identification of prostheses that perform less optimally (16, 17). Compared to the present policy of introduction of new prostheses, RSA has the potential to prevent widespread use of unsafe prostheses and save numerous patients from revision surgery.

The strengths of our systematic review have been the large number of studies included (78) and the large number of patients (> 20,000), which resulted in 14 different PF combinations. Although no association could be found between early migration and long-term aseptic revision for all PF combinations, the large variation in PF combinations gives us insight in the migration patterns of femoral stems. Since the migration and revision rates were from different studies, the RSA data could not have been used (incorporated) in the decision to perform a revision, so there was no incorporation bias. We considered that the influence of publication bias for the shape-closed femoral stems was small, since the results from the meta-analysis were similar to those from the national joint registries. Confounders only had a small influence on the association between early migration and long-term aseptic revision.

We should also consider some limitations. We were unable to find an association for the complete group of PF combinations and only found an association for the subgroup of shape-closed designs. This was due to the high variation in migration patterns of different PF combinations. The design concept (i.e. shape-closed, force-closed, or cementless) of a THA determines its migration pattern, and every design concept should therefore be analysed separately (18). More research on

each design concept is necessary to give a better understanding of acceptable and unacceptable migration for each of the concepts.

Furthermore, the quality of the survival studies and RSA studies showed a large degree of variation. A high methodological quality of all the studies included would have been desirable. Nevertheless, the quality of the survival studies and of the RSA studies showed only small effects on the association between migration and revision rate.

We should also take into account the fact that RSA only evaluates aseptic loosening. Although aseptic loosening is the foremost reason for failure, there are other failure mechanisms (e.g. infection, pain, and instability or pseudotumors in metal-on-metal total hip arthroplasty) which are not evaluated by RSA. RSA studies are therefore only the first step, after preclinical testing, in the phased introduction as proposed by both Faro and Huiskes and Malchau (4, 12, 14). Several authors have pleaded for a phased evidence-based market introduction of new prostheses comparable to the introduction of new drugs to the consumer market (4, 119-121). During phase A, multiple single-center RSA studies should be performed to determine the safety of the THA regarding the risk of revision for aseptic loosening and wear. Thresholds for acceptable and unacceptable initial migration can be used for assessment of the new prosthesis (4, 14). Thus, the observed association in our study between early migration and long-term revision on shape-closed designed femoral stems can be adopted in phased evidence-based market introduction of new THAs. Given that the THA is safe, phase B studies must be conducted to evaluate the clinical performance of the THA regarding pain relief and functioning (clinical scores and patient-reported outcome measures (PROMS)) and to determine the rate of complications within a limited period that is feasible (e.g. severe adverse effects of the implant). Successful completion of phase B would allow introduction to the market and would herald phase C, where the performance of the THA must be monitored by post-marketing surveillance in national joint registries (6). This includes both the revision rate and patient evaluations using PROMS.

The Charnley Elite Plus stem is of special interest. This THA was introduced as successor to the well-established Charnley THA. It was assumed that small alterations in the design would enhance survival and patient outcome. However, early clinical studies gave conflicting findings, with some suggesting a similar outcome to that of the conventional Charnley stem, while others suggested a worse outcome (80, 85). Hauptfleisch et al. found survival of 83% at 10 years, which was in accordance with their earlier predictions of high failure rates based on early RSA evaluation (3). These authors blamed the design of the Charnley Elite Plus for the poor survival. However, the cement used in that study was low-viscosity cement, and Derbyshire et al. pointed out that the low-viscosity cement might also have been the reason for the poor survival (122). Our results suggest a similar reason: the pooled survival of the Charnley Elite Plus cemented with low-viscosity cement was far worse than the acceptable threshold. The same stem cemented with high-viscosity cement showed better survival, approaching the acceptable threshold. If the threshold of acceptable migration of the prosthesis had been known at the time the Charnley Elite Plus was introduced, it would have been classified as unacceptable after only 2 years of RSA

follow-up. This example illustrates the clinical value of migration thresholds for early identification of THAs that have a high likelihood of failure at long-term follow-up. Moreover, this example highlights that not only design but also type of fixation should be taken into account when evaluating femoral stem survival. For the Charnley Elite Plus femoral stem, it was not only the design but also the fixation (low-viscosity or high-viscosity cement) that influenced both early migration and long-term survival. Labelling of femoral stems according to the PF (prosthesis and fixation) combination principle is therefore imperative.

Various authors and regulatory agencies recognize the potential of RSA (3, 4, 8, 9). The NICE guidelines of 2003 require adequate long-term clinical data for hip prostheses and regard RSA as a promising technique that may be an early-warning indicator of expected poor long-term revision rates (28). Recently, the International Organization for Standardization (ISO) and the European Standards Working Group on Joint Replacement Implants published a standard protocol for early clinical studies that provides requirements for the clinical assessment of migration of orthopaedic implants with RSA (123). The Dutch Orthopaedic Society (NOV) now requires a phased introduction with mandatory RSA studies before any new THA is considered for introduction to the Dutch market (124). In addition, new initiatives for increasing patient safety such as the Beyond Compliance Service not only support the stepwise introduction of new implants to the market, but also acknowledge the importance of training established surgeons how to use a new innovative design (125).

In conclusion, 2-year early migration of shape-closed design femoral stems is associated with 10-year revision for aseptic stem loosening. The proposed migration thresholds provide insight into the failure mechanism of shape-closed femoral stems. Too few RSA study and survival study combinations for force-closed and cementless stem designs were found to give meaningful recommendations on the predictive value of early migration for aseptic revision of these designs. If more RSA migration studies are performed, the value of early migration profiles of these designs will be possible.

APPENDIX

Details of the literature search strategy

RSA studies

PubMed: ("Photogrammetry"[Mesh] OR "roentgen stereophotogrammetric analysis" OR rsa OR radiostereometr* OR stereophotogrammetr* OR "roentgen fluoroscopic")
AND
("Joint Prosthesis"[Mesh] OR hip prosthesis OR knee prosthesis OR TKA OR THA OR THR OR TKR OR "joint replacement" OR Arthroplasty, Replacement[mesh] OR "total knee replacement" OR "total hip replacement")

Survival cohort studies

PubMed: ("Joint Prosthesis"[Mesh] OR hip prosthesis OR knee prosthesis OR TKA OR THA OR THR OR TKR OR "joint replacement" OR Arthroplasty, Replacement[mesh] OR "total knee replacement" OR "total hip replacement")
AND
("Prosthesis Failure"[Mesh] OR "prosthetic loosening" OR "aseptic loosening" OR "implant loosening" OR "implant failure")
AND
("survival analysis"[MeSH Terms] OR ("survival"[All Fields] AND "analysis"[All Fields]) OR "survival
analysis"[All Fields] OR cohort studies[mesh] OR "follow up" OR "follow-up" OR experience OR outcome)
These strings were adapted to fit the vocabulary of the other databases mentioned above.
The results were limited to humans.

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Fixation of high-flexion TKAs: 5-year follow-up results of a 4-arm randomized controlled clinical and RSA study

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ABSTRACT

Introduction

High-flexion total knee arthroplasty (TKA) was introduced to meet the demands of daily activity requiring increased knee flexion. However, concerns have been raised regarding the fixation of high-flexion TKA components and increased rates of loosening have been reported. To date, migration, and thus fixation, of high-flexion TKA components has not been analyzed and the preferential bearing type (mobile or fixed) is unknown.

Methods

Of 86 consecutive eligible patients, 74 patients (78 knees) scheduled for TKA were randomized to 1 of 4 Legacy Posterior Stabilized (LPS) TKA designs: (1) LPS-Flex mobile, (2) LPS-Flex fixed, (3) LPS mobile, and (4) LPS fixed. The primary outcome was component migration measured with use of roentgen stereophotogrammetric analysis, and secondary outcomes were postoperative knee flexion and extension and Knee Society Score. Patients were evaluated postoperatively at 6, 12, 26, and 52 weeks, and annually thereafter. At the 5-year follow-up, 8 patients had died, and 2 patients were lost to follow-up. 77 tibial and 42 femoral components were suitable for migration measurements.

Results

The overall 5-year migration of the 77 tibial components was not significantly different among the 4 TKA designs (compared with the LPS fixed design, the range of overall mean differences for the other 3 designs was 0.02 to 0.25 mm) and migration was comparable at the 2 and 5-year follow-up. Migration stabilized in all but 3 components (2 LPS-Flex mobile and 1 LPS fixed); 1 of these components has already been revised and was aseptically loose. The overall 5-year migration of the 42 femoral components was comparable among the 4 designs (compared with the LPS fixed design, the range of overall mean differences for the other 3 designs was 0.01 to 0.18 mm) and was similar at 2 and 5 years postoperatively. 1 femoral component (LPS-Flex mobile) migrated excessively. In patients who had a mean postoperative flexion of ≥125° or a maximum flexion of ≥135° during the 1 to 5-year follow-up period, migration of high-flexion components was comparable with that of conventional components and indicative of appropriate fixation. Postoperative flexion, extension, Knee Society Score, and Knee Society Score function were comparable during the 5-year follow-up period and at the 2 and 5-year follow-up.

Conclusions

The LPS-Flex TKA with either a mobile or a fixed bearing had migration comparable that of with its conventional counterpart and is expected to have similar (excellent) long-term survival in these patients.

INTRODUCTION

Total knee arthroplasty (TKA) is a common and successful procedure (1). However, not all patients are satisfied with the result (2, 3). The postoperative range of motion may not meet all patient expectations and demands after TKA (4-6). Recently, new TKA designs have been introduced that allow flexion up to 155° (high-flexion or "high-flex" designs) to meet the demands of increased flexion required during deep kneeling, squatting, cross-legged sitting, or praying (7-9). Both mobile and fixed-bearing variants are available to offer their specific advantages, if any (10-12), for high-flexion TKAs.

It is unclear whether these designs result in improved functional outcome and whether this high-flexion potential is actually used (13-18). Moreover, concerns have been expressed regarding the fixation of high-flexion designs because of possibly inferior implant stability secondary to potentially higher stresses at the implant-cement interface, increased edge-loading, higher insert wear, and larger femoral bone resection (19-23). Indeed, reported short-term results have not been unanimously good; 1 study showed aseptic loosening in 38% of 72 NexGen Legacy (Zimmer, Warsaw, Indiana) posterior stabilized high-flexion implants after 32 months of follow-up (24), another study found progressive radiolucent lines in 14% of 218 implants of this same design and a 3.2% revision rate after 49 months (25), and a third study showed a 3.6% revision rate after 11 months for 197 Columbus (B. Braun Aesculap, Tuttlingen, Germany) posterior stabilized high-flexion implants (26).

Early implant migration, as measured with use of roentgen stereophotogrammetric analysis (RSA), is associated with long-term implant survival for loosening (27-30). To date, migration and fixation of high-flexion implants have not been analyzed. In this study, we report the 5-year results of a 4-arm randomized controlled trial in which we compare the migration and clinical outcome of high-flexion TKA with either a fixed or a mobile bearing with that of its conventional, well-established counterpart with either a fixed or a mobile bearing. We hypothesized that the fixation of the high-flexion design was comparable with that of the conventional design, but that higher postoperative flexion could be achieved.

METHODS

Study design

From September 2002 to April 2005, all consecutive patients scheduled to undergo primary TKA at our tertiary referral center for symptomatic end-stage osteoarthritis, either primary or secondary to a systemic inflammatory disease, were approached for participation in a 4-arm randomized clinical and RSA study. Patients were randomized to receive either a high-flexion or a conventional NexGen Legacy Posterior Stabilized (LPS) TKA (Zimmer) with either a mobile or a fixed bearing. Thus, there were 4 treatment arms: (1) LPS-Flex mobile TKA, (2) LPS-Flex fixed TKA,

(3) LPS mobile TKA, and (4) LPS fixed TKA. Patients were randomized for treatment allocation with use of a computer-generated randomization scheme and could have only 1 knee enrolled in the study. With bilateral TKA, patients received the same design in both knees and only 1 TKA was included in the study. Patients were blinded to the allocated TKA. Clinical follow-up assessments were performed by independent examiners unaware of the TKA implanted. Assessments and treatment decisions were blinded from migration measurements. The study was performed in compliance with the Helsinki Declaration, approval of the institutional medical ethical board was obtained, and patients gave informed consent. The trial was registered at the Dutch Trial Registry (TC3287). Reporting of the trial was in accordance with the Consolidated Standards of Reporting Trials (CONSORT)(31) and the RSA guidelines (32).

Surgical technique

All TKAs were performed by 2 experienced specialist knee surgeons (H.M.J.vDL.-vDZ. and R.G.H.H.N.) or under their direct supervision with use of the same operative technique. Exposure was through a standard midline incision and medial parapatellar arthrotomy under tourniquet control. For the femoral component of the high-flexion component, an additional 2-mm bone resection of the posterior condyles was required. Pulsatile lavage of the osseous surface was undertaken before the cementing of the components (Palacos; Heraeus-Kulzer, Hanau, Germany). The patella was resurfaced in all but 6 TKAs. Appropriate soft-tissue procedures were performed to realign the knee and to create a stable prosthesis. For RSA measurements, 1-mm tantalum balls were inserted into the distal part of the femur and proximal part of the tibia during surgery. The rehabilitation program was the same for all patients: physiotherapy with passive and controlled active movement was started on the first postoperative day and mobilization with full weight-bearing was started on the second postoperative day.

Follow-up

Patients were evaluated preoperatively and postoperatively at 6, 12, 26, and 52 weeks, and annually thereafter. At each evaluation, RSA radiographs were made and flexion, extension, and the Knee Society Score (KSS) (33) were determined. Standing anteroposterior and lateral radiographs were made at 6 weeks, 2 years, and 5 years postoperatively and if symptoms were present. Femoral-tibial alignment was measured and follow-up radiographs were evaluated for the presence of radiolucent lines and abnormalities (34).

RSA technique

RSA radiographs were made with use of a uniplanar setup with the patient in a supine position and the calibration cage (Carbon box, Leiden, The Netherlands) under the examination table. Migration was analyzed with use of Model-Based RSA (Medis specials, Leiden, The Netherlands), which has been validated on this implant design (35). The first RSA examination was made before weight-bearing on the second postoperative day and served as the reference for all further

examinations. All evaluations are related to the relative position of the implant to the bone at that time. Migration is expressed along or around the 3 orthogonal axes: longitudinal, transverse, and sagittal. In addition, the maximum total point motion, the migration vector length of the point on the implant that has moved the most, was calculated (32). The accuracy of individual RSA measurements was specified as the limits of the 95% prediction interval of the accuracy of zero motion and was calculated at the 1-year follow-up for the tibial component with use of 50 double examinations and for the femoral component with use of 25 double examinations (see Appendix) (36). For all examinations, the mean error of rigid body fitting of the RSA markers in the tibia and femur was below 0.35 mm; the mean condition number (and standard deviation) of the RSA markers was 28 ± 14 (range, 14 to 75) in the tibia and 51 ± 31 (range, 16 to 145) in the femur. These values satisfy the marker stability and distribution criteria of the RSA guidelines (32).

Statistics

Eighteen TKAs per design were required to detect a mean difference (and standard deviation) of 0.3 ± 0.4 mm at the 2-year follow-up in the primary outcome measure (tibial component migration) with a power of 0.80 at the significance level of $p = 0.05$ using an analysis of variance (ANOVA). Seventy-8 knees were randomized to account for possible dropouts. The measured values are reported as the mean and the standard deviation, and the estimates are reported as the mean and the 95% confidence interval (95% CI). Analysis was performed according to the intention-to-treat principle. Postoperative outcome measures were analyzed with use of a linear mixed model. This technique is recommended for analysis of repeated measurements; it takes the correlation of values within subjects into account and deals effectively with missing values and loss to follow-up. Consequently, statistical inference can be based on the data of more TKAs than only those of patients who completed the 5-year follow-up (37, 38). Differences among the groups were assessed by estimating the main treatment effect and the treatment × time interaction, both as an overall effect over the entire follow-up period to safeguard against multiple testing for all individual follow-up moments. The assessment of the interaction term allows for the investigation of possible time-varying mean differences. A Bonferroni correction was applied to post hoc tests among groups. The maximum total point motion served as the primary migration outcome and was log-transformed to obtain a normally distributed variable. At the 2- and 5-year follow-ups, the mean differences were assessed with use of ANOVA as specified in the study protocol. As a sensitivity analysis, separate analyses without influential outliers and adjusted analyses were carried out. In the adjusted analysis, the following variables were added: patient age and gender, diagnosis (primary or secondary osteoarthritis), body mass index (BMI), and femoral-tibial angle. Analysis of functional outcome was also adjusted for baseline values. Because the design alterations of high-flexion TKAs are specifically intended to improve flexion in the high-flexion segment of the allowable knee motion, the effect on fixation of high-flexion components actually acting in this high-flexion segment was further investigated with use of a formal subgroup analysis (39, 40). Under the hypothesis of improved stabilization of high-flexion designs, the significance of the

interaction term high-flexion segment × high-flexion TKA design was assessed on the maximum total point motion. A p value of <0.05 was considered to be significant (SPSS version 18.0; SPSS, Chicago, Illinois).

RESULTS

Patients

From September 2002 to April 2005, 86 consecutive patients were assessed for inclusion and 74 patients (78 TKAs) were randomized (Figure 1). At admission for a contralateral TKA, 4 patients were inadvertently included in the study and did receive a randomly allocated TKA. These patients remained in the study. 19 patients received an LPS-Flex mobile TKA, 20 patients received an LPS-Flex fixed TKA, 18 received an LPS mobile TKA, and 21 received an LPS fixed TKA (Table 1). 2 patients were lost to follow-up: 1 because of emigration and 1 who could not be traced. 4 patients were unable or refused to attend the clinic for follow-up radiographs, but the prosthesis status was verified at the 5-year follow-up.

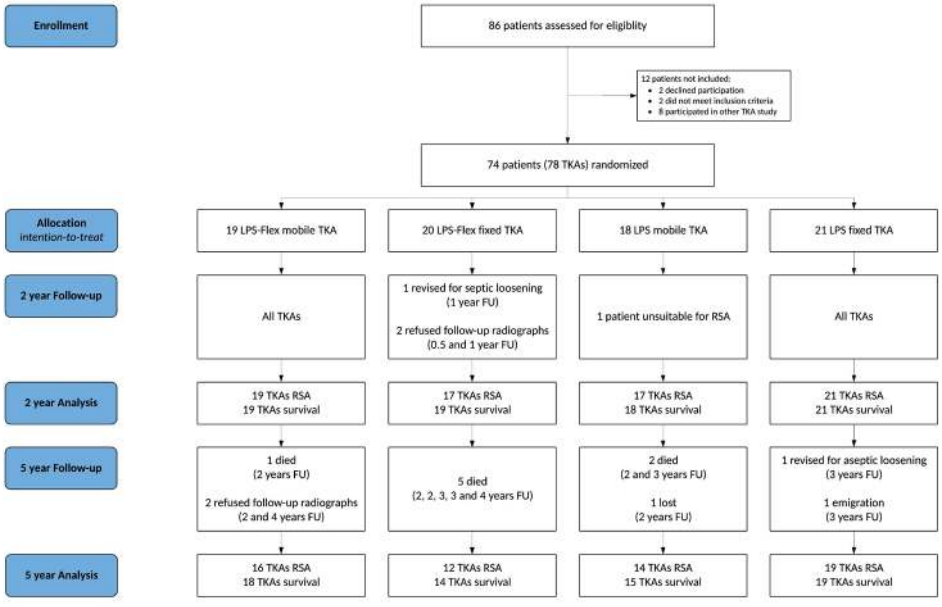

Figure 1. CONSORT flowchart of patient recruitment, allocation, and follow-up. TKA = TKA and FU = follow-up.

Tibial component migration could not be determined in 1 patient because of insufficient tibial RSA markers. Because of marker migration (that is, unstable markers) in the distal part of the

Characteristic	*LPS-Flex mobile* (n = 19)	*LPS-Flex fixed* (n = 20)	*LPS mobile* (n = 18)	*LPS fixed* (n = 21)
Gender — no. (%)				
Male	4 (21.1%)	6 (30%)	0	5 (23.8%)
Female	15 (78.9%)	14 (70%)	18 (100%)	16 (76.2%)
BMI* — kg/m²	25.9 ± 4.5	26.5 ± 4.2	29.0 ± 3.9	27.6 ± 4.8
Age at surgery* — yr	66.8 ± 14.2	72.2 ± 8.4	68.7 ± 8.8	68.5 ± 11.8
Diagnosis — no. (%)				
Osteoarthritis	8 (42.1%)	5 (25%)	7 (38.9%)	10 (47.6%)
Rheumatoid arthritis	11 (57.9%)	15 (75%)	11 (61.1%)	10 (47.6%)
Ankylosing spondylitis	0	0	0	1 (4.8%)
Femoral-tibial angle*				
Preoperative — degrees	174.3 ± 7.0	174.1 ± 9.9	176.0 ± 9.6	173.5 ± 9.5
Postoperative — degrees	174.8 ± 3.9	176.5 ± 2.2	175.5 ± 4.5	175.0 ± 2.6
Preoperative function*				
Flexion — degrees	110.8 ± 9.6	105.3 ± 18.0	103.1 ± 14.4	108.6 ± 15.7
Extension — degrees	-7.1 ± 8.4	-5.5 ± 7.1	-6.7 ± 9.6	-7.1 ± 8.9
KSS — points	34.8 ± 11.7	38.4 ± 18.9	33.7 ± 10.0	32.4 ± 12.8
KSS function — points	23.2 ± 17.7	35.8 ± 24.7	27.5 ± 25.5	33.8 ± 20.7

Table 1. Group characteristics at baseline. Values are count unless otherwise specified.

femur and insufficient or incorrectly positioned markers, the assessment of femoral component migration was possible in only 42 of the 78 components (9 LPS-Flex mobile, 13 LPS-Flex fixed, 10 LPS mobile, and 10 LPS fixed). Included patients unsuitable for RSA measurements remained in the study and received routine clinical and radiographic follow-up.

Migration of the tibial component

The overall 5-year migration of the tibial components was not significantly different among the 4 TKA designs (p = 0.373) (see Appendix). Compared with the LPS fixed design, the estimated between-group mean differences for the maximum total point motion were 0.08 mm (95% CI, –0.15 to 0.42 mm) for the LPS-Flex mobile, 0.02 mm (95% CI, –0.19 to 0.33 mm) for the LPS-Flex fixed, and 0.25 mm (95% CI, –0.04 to 0.69 mm) for the LPS mobile (see Figure 2 and Appendix for translations and rotations). Also, there was no difference in time to stabilization and subsequent migration, that is, no evidence of interaction (p = 0.672). Migration was comparable among the 4 designs at the prespecified time points of 2 years (p = 0.565) and 5 years (p = 0.604) postoperatively (see Appendix). Post hoc, between-group comparisons yielded no significant differences among groups (p > 0.0125).

The evaluation of the migration of individual tibial components revealed stabilization of all but 3 tibial components. These 3 components (2 LPS-Flex mobile and 1 LPS fixed) showed high initial migration without subsequent stabilization (Figure 2). 1 of these components has been revised and

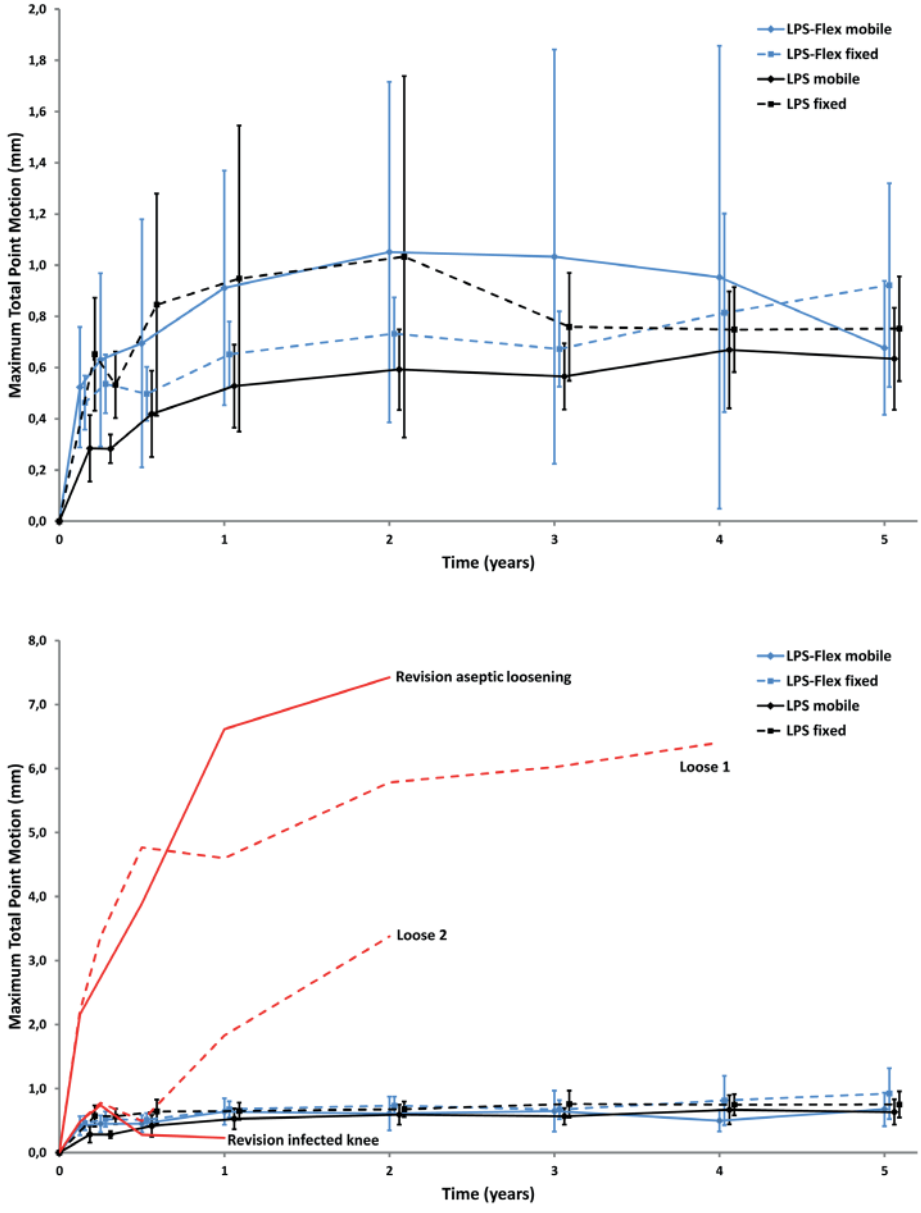

Figure 2. Line graphs showing the tibial component maximum total point motion during 5 years of follow-up for the 4 different groups: (top) the mean and the 95% CI for the groups and (bottom) the mean and the 95% CI for the same groups with the influential outliers excluded from the groups and shown separately. In the bottom part of the figure, the solid red lines indicate the migration of the revised component and the dashed red lines indicate a component with excessive migration suspected for component loosening.

was confirmed to be loose; the other 2 components had not been revised but were considered to be loose. 1 of these patients was unable to attend the clinic for follow-up radiographs because of a stroke and the other patient had severe dementia and refused clinic attendance. The high magnitude of the migration in these 3 components may have a large effect on the mean group migration; however, evaluation excluding these influential outliers did not alter the former conclusions. In these stable components, no significant overall effect of a high-flexion design was found on tibial component migration; the overall maximum total point motion mean difference was 0.03 mm (95% CI, –0.08 to 0.17 mm; p = 0.594). However, fixed-bearing designs showed significantly higher initial migration than mobile-bearing designs; the overall maximum total point motion mean difference was 0.14 mm (95% CI, 0.02 to 0.29 mm; p = 0.024). The results from the adjusted analyses were comparable with the results from the unadjusted analyses and age, gender, diagnosis, BMI, and postoperative femoral-tibial alignment did not significantly influence migration (p > 0.05).

Migration of the femoral component

The overall 5-year migration of the femoral components was not significantly different among the 4 TKA designs (p = 0.949). Compared with the LPS fixed design, the estimated between-group mean differences for the maximum total point motion were 0.03 mm (95% CI, –0.44 to 0.99 mm) for LPS-Flex mobile, 0.01 mm (95% CI, –0.43 to 0.86 mm) for LPS-Flex fixed, and 0.18 mm (95% CI, –0.36 to 1.24 mm) for LPS mobile (see Figure 3 and Appendix for translations and rotations). There was also no evidence of time dependence for this difference (p = 0.672). Migration was comparable among the four designs at 2 years (p = 0.971) and 5 years (p = 0.443) postoperatively (see Appendix). Post hoc, between-group comparisons yielded no significant differences between groups (p > 0.0125).

1 femoral component (LPS-Flex mobile) showed very high initial migration incompatible with stabilization (Figure 3). For this TKA, the tibial component was also considered to be loose: for the TKA with a loose tibial component and for the TKA with a revised tibial component, RSA of the femoral component was not possible. Analysis excluding this influential outlier did not change the former conclusions. No significant overall effect of a high-flexion design was found on femoral component migration; the overall maximum total point motion mean difference was –0.06 mm (95% CI, –0.32 to 0.32 mm; p = 0.703). Femoral component migration of the fixed-bearing designs was not significantly higher than migration of mobile-bearing designs; the overall maximum total point motion mean difference was 0.21 mm (95% CI, –0.15 to 0.44 mm; p = 0.213). Results from the adjusted analyses were comparable with results from the unadjusted analyses and age, gender, diagnosis, BMI, and postoperative femoral-tibial alignment did not significantly influence migration (p > 0.05).

Subgroup analysis in patients with high postoperative flexion

In the 23 patients (14 LPS-Flex and 9 LPS TKAs) who achieved a mean postoperative flexion of ≥125° during the 1 to 5-year follow-up period or in the 18 patients (11 LPS-Flex and 7 LPS TKAs) who

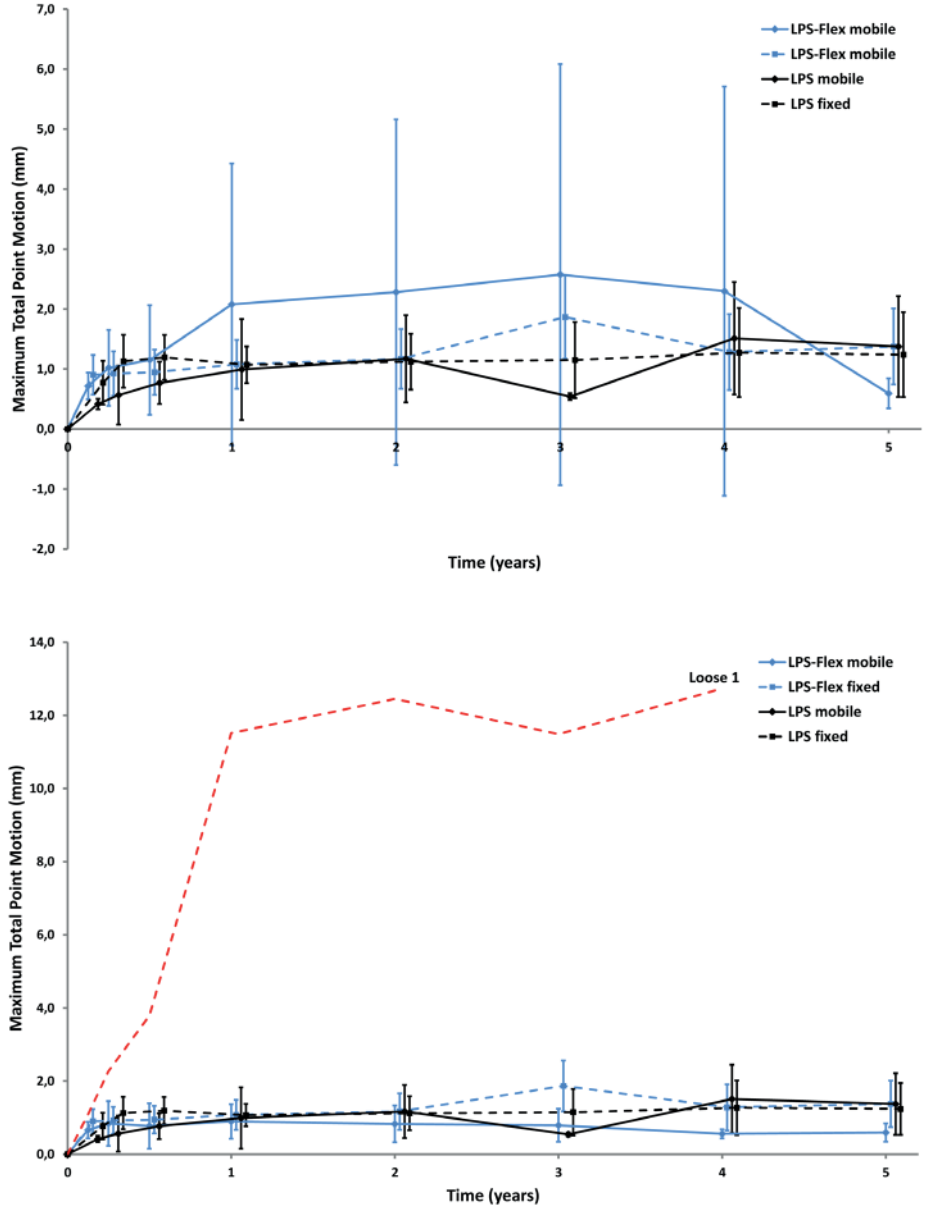

Figure 3. Line graphs showing the femoral component maximum total point motion during 5 years of follow-up for the 4 different groups: (top) the mean and the 95% CI for the groups and (bottom) the mean and the 95% CI for the same groups with the influential outliers excluded from the groups and shown separately. In the bottom part of the figure, the dashed red line indicates a component with excessive migration suspected for component loosening.

had a maximum flexion of ≥135° during the 1 to 5-year follow-up period, the migration of tibial and femoral components was not significantly different from conventional TKAs and from those TKAs not acting in the high-flexion, range-of-motion segment. The estimated adjusted mean difference in maximum total point motion of high-flexion TKA components in patients with a mean postoperative flexion of ≥125° was 0.30 mm (95% CI, –0.45 to 1.61 mm; p = 0.503) for tibial components and 0.22 mm (95% CI, –0.48 to 1.49 mm; p = 0.612) for femoral components (Figure 4). The estimated adjusted mean difference in maximum total point motion of high-flexion TKA components in patients with a mean postoperative flexion of ≥135° was 0.01 mm (95% CI, –0.93 to 2.54; p = 0.998) for tibial components and –0.27 mm (95% CI, –1.06 to 2.31 mm; p = 0.718) for femoral components.

Clinical outcome

Flexion, extension, KSS, and KSS function significantly improved (p < 0.001) after TKA. No significant differences were found among the groups during the 5-year follow-up period and in the scores at the 2 and 5-year follow-ups (see Appendix). Between-group differences did not change significantly over time. Postoperative flexion was higher with higher preoperative flexion (0.36° per preoperative degree [95% CI, 0.20° to 0.52°]; p < 0.001) and lower BMI (–0.76° per unit BMI [95% CI, –1.33° to –0.20°]; p = 0.009), whereas postoperative extension was slightly lower in male patients compared with female patients (–1.82° [95% CI, –3.53° to –0.11°]; p = 0.037). The postoperative KSS score was higher with higher preoperative KSS score (0.17 per preoperative unit [95% CI, 0.03 to 0.31]; p = 0.020) and lower in males (–6.29 [95% CI, –11.2 to –1.32]; p = 0.014). Postoperative KSS function was higher with higher preoperative KSS function (0.48 per preoperative unit [95% CI, 0.21 to 0.76]; p = 0.001) and lower age (–0.96 per year of age [95% CI, –1.58 to –0.35]; p = 0.003).

Radiographic outcome

1 tibial component (LPS fixed) showed progressive radiolucent zones of >2 mm around the entire tibial component and was revised for aseptic loosening. The femoral component showed no progressive radiolucent lines or radiolucent lines of >1 mm. 1 other tibial component (LPS-Flex fixed) showed non-progressive radiolucent lines of 2 mm underneath the lateral plateau of the tibial component.

Survival

The 5-year survival rate for all-cause revision was 97.4% (95% CI, 93.8% to 100%). 1 TKA was revised for septic loosening 1 year after implantation and 1 TKA was revised for aseptic loosening of the tibial component 2.7 years postoperatively (the femoral component was firmly fixed during revision surgery).

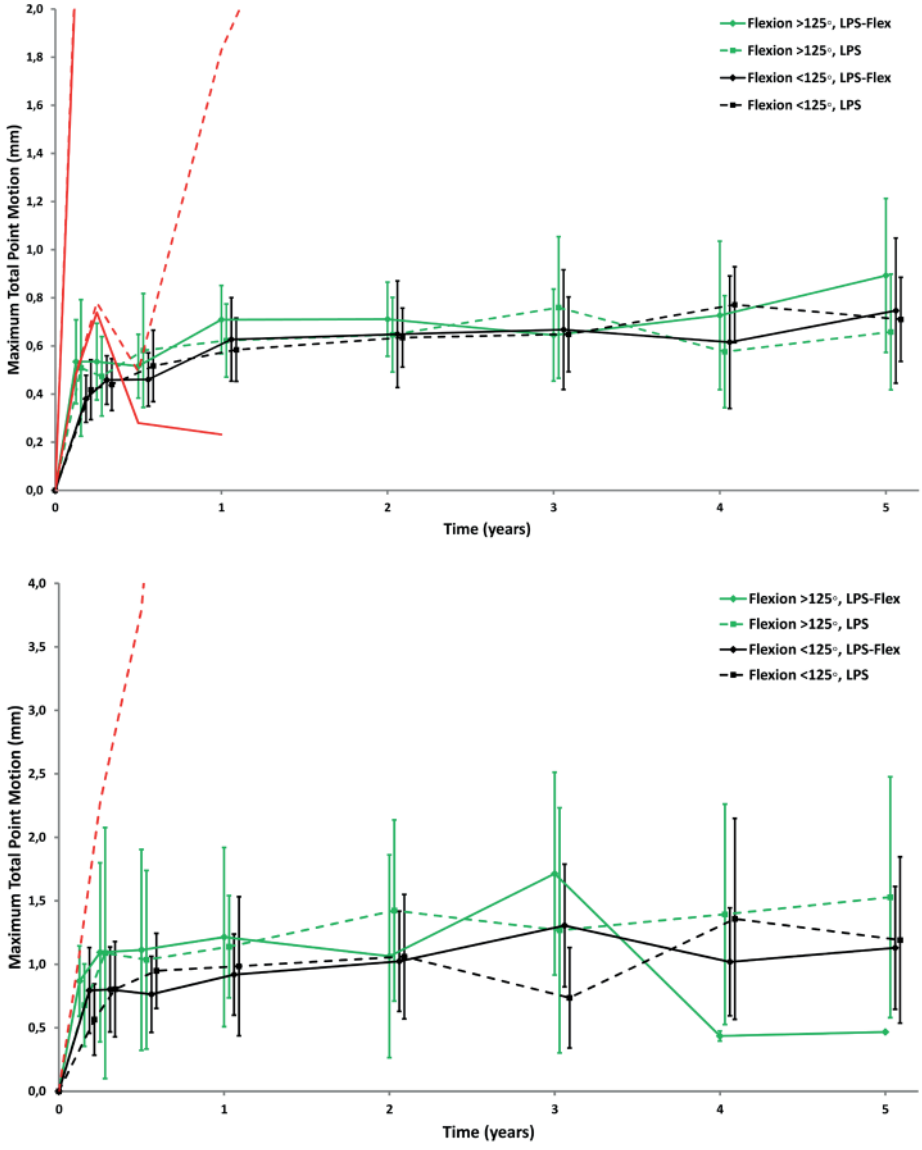

Figure 4. Line graphs showing (top part) tibial component and (bottom part) femoral component maximum total point motion during five years of follow-up for high-flexion and conventional TKA designs with mean postoperative flexion of ≥125°and <125°. The values are given as the mean and the 95% CI, and influential outliers are shown separately. In the top part of the figure, the solid red lines indicate the migration of the revised component. In both parts of the figure, the dashed red line indicates a component with excessive migration suspected for component loosening.

DISCUSSION

Migration, and thus fixation, of the tibial and femoral components of the high-flexion and conventional designs of the LPS TKA was comparable and independent of the bearing type during the first 5 years after implantation. Also, in the subgroup of TKAs that operated in the high-flexion range-of-motion segment (with a mean 1 to 5-year flexion of ≥125° or a maximum 1 to 5-year flexion of ≥135°), no difference in migration was found and the implants had a stable fixation. With the numbers available, however, no differences in clinical outcome were detected either.

To our knowledge, this is the first trial evaluating the migration of high-flexion TKAs, including both mobile and fixed-bearing designs, and one of the first to show intermediate-term clinical results. On the basis of the results of our migration analysis, the fixation of the LPS-Flex TKA was comparable with that of the conventional LPS TKA. Consequently, irrespective of the bearing type, the expected long-term survival regarding aseptic loosening of the LPS-Flex is similarly excellent to that of the LPS. The 10-year survival rate of 98.3% has recently been shown by the first published long-term follow-up study (41). In contrast, several short-term studies have shown inferior survival (24-26) and several national registries show lower survival of high-flexion TKAs (42, 43). This discrepancy cannot be clarified because of the non-comparative study design or the non-randomized TKA allocation, and long-term results of randomized studies are necessary for a definitive answer to this question.

Concomitantly, however, we were unable to find a significant clinical benefit of high-flexion designs over conventional designs. Although this may be due to the fact that our study was not powered to detect small differences in this outcome measure, this is in accordance with the results from large randomized trials powered to detect small differences in postoperative flexion (13-15). Thus, on average, there may be no clinically relevant benefit of high-flexion TKA designs over conventional TKA designs. However, specific individual patients may benefit from the high-flexion potential of these designs, especially those with a good preoperative function (16-18).

This study had several limitations. First, the migration of many femoral components could not be evaluated because of an insufficient number of markers in the femur that were suitable for analysis. Tibial components have traditionally been the component responsible for the majority of TKA revisions for aseptic loosening and therefore this study was designed and was powered to evaluate the stability of tibial components. However, studies showing high incidences of femoral component loosening in high-flexion TKAs led us to investigate the migration of the femoral components as well (24-26). Insertion and positioning of femoral markers were difficult because they need to be placed in or near the femoral cortical bone for appropriate marker stability without being obscured by the femoral TKA component in both RSA images. Because there was no selection in the way that bone markers were inserted or were positioned in the femur and because 42 TKAs (22 high-flexion and 20 conventional) were still available for evaluation, we believe that our results regarding femoral component migration are valid and of importance. Second, the fact that our study took place in a tertiary referral center and included a high propor-

tion of patients with osteoarthritis secondary to an inflammatory disease may compromise the generalizability of our findings.

In conclusion, migration, and thus fixation, of the LPS high-flexion TKA was comparable with those of the LPS conventional TKA and independent of the bearing type used. Even in the high-flexion segment, no difference in migration was found and a stable fixation was achieved. However, the high-flexion potential was, on average, not utilized more by patients with high-flexion TKAs and the major determinant for postoperative flexion was the preoperative flexion. Nevertheless, for this TKA, the high-flexion design is expected to have (excellent) long-term survival in these patients similar to that of its conventional counterpart and may represent a suitable treatment option in selected patients expected to benefit from the high-flexion potential.

APPENDIX

Component	Translation — mm			Rotation — degrees			Maximum total point motion (mm)
	Transverse (x-axis)	Longitudinal (y-axis)	Sagittal (z-axis)	Transverse (x-axis)	Longitudinal (y-axis)	Sagittal (z-axis)	
Tibial (n = 50)	0.06	0.07	0.18	0.27	0.40	0.12	0.45
Femoral (n = 25)	0.16	0.08	0.17	0.23	0.35	0.14	0.50

Appendix A. Accuracy of RSA measurements (upper limits of 95% zero motion confidence interval).

Migration	TKA*				INTENTION TO TREAT		
	LPS-Flex mobile	*LPS-Flex fixed*	*LPS mobile*	*LPS fixed*	Main effect†	Group × Time Interaction‡	Prespecified time point
	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	*p*-value	*p*-value	*p*-value
TIBIAL COMPONENT — logMTPM§							
week 6	-1.08 (0.26)	-0.92 (0.13)	-1.48 (0.15)	-0.68 (0.17)			
month 3	-0.80 (0.18)	-0.75 (0.13)	-1.32 (0.10)	-0.67 (0.11)			
month 6	-0.81 (0.20)	-0.79 (0.10)	-1.11 (0.18)	-0.50 (0.20)			
year 1	-0.49 (0.20)	-0.54 (0.12)	-0.81 (0.15)	-0.41 (0.16)			
year 2	-0.53 (0.24)	-0.40 (0.11)	-0.65 (0.13)	-0.33 (0.16)	0.37	0.67	0.57
year 3	-0.61 (0.29)	-0.50 (0.15)	-0.68 (0.16)	-0.45 (0.15)			
year 4	-0.68 (0.28)	-0.45 (0.21)	-0.53 (0.17)	-0.39 (0.12)			
year 5	-0.65 (0.22)	-0.31 (0.22)	-0.58 (0.15)	-0.44 (0.16)			0.6
FEMORAL COMPONENT — logMTPM§							
week 6	-0.52 (0.21)	-0.32 (0.20)	-0.92 (0.11)	-0.49 (0.24)			
month 3	-0.52 (0.33)	-0.31 (0.21)	-0.89 (0.32)	-0.03 (0.25)			
month 6	-0.64 (0.34)	-0.26 (0.20)	-0.45 (0.21)	0.08 (0.17)			
year 1	-0.29 (0.22)	-0.14 (0.20)	-0.37 (0.31)	-0.05 (0.17)			
year 2	-0.45 (0.30)	-0.10 (0.23)	-0.15 (0.29)	-0.10 (0.25)	0.95	0.14	0.97
year 3	-0.37 (0.25)	0.48 (0.28)	-0.62 (0.06)	-0.09 (0.28)			
year 4	-0.61 (0.11)	0.06 (0.29)	0.22 (0.31)	-0.03 (0.30)			
year 5	-0.59 (0.22)	0.14 (0.28)	0.06 (0.30)	-0.06 (0.28)			0.44

Appendix B. Analysis of maximum total point motion (MTPM) of the tibial and femoral components during 5 years of follow-up.

*The values are given as the mean and the standard error in log(millimeters).

†This category assumes no interaction with time and indicates testing for the overall, between-group mean difference over the entire postoperative follow-up period.

‡This category indicates testing for overall changing treatment effects with time over the entire postoperative follow-up period.

§logMTPM = log-transformed maximum total point motion.

Clinical outcome	TKA*				INTENTION TO TREAT		
	LPS-Flex mobile	*LPS-Flex fixed*	*LPS mobile*	*LPS fixed*	Main effect†	Group × Time Interaction‡	Prespecified time point
	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	*p*-value	*p*-value	*p*-value
FLEXION — degrees							
week 6	110.0 (4.0)	99.4 (4.7)	102.5 (4.3)	102.9 (3.2)			
month 3	115.0 (2.7)	108.8 (3.2)	103.2 (3.2)	112.1 (2.3)			
month 6	117.5 (2.8)	116.9 (4.0)	106.9 (3.9)	112.7 (3.3)			
year 1	120.8 (2.7)	114.4 (2.8)	109.4 (4.0)	113.8 (2.8)			
year 2	119.7 (2.6)	115.8 (4.0)	110.4 (4.2)	114.3 (2.9)	0.92	0.68	0.32
year 3	122.9 (2.3)	121.3 (4.9)	115.8 (2.7)	118.2 (2.8)			
year 4	123.9 (2.7)	117.5 (4.7)	110.4 (4.1)	119.3 (3.2)			
year 5	118.9 (3.4)	118.1 (3.4)	113.7 (4.5)	118.3 (3.6)			0.76
EXTENSION — degrees							
week 6	-3.0 (1.5)	-5.6 (1.6)	-3.3 (1.3)	-2.8 (1.7)			
month 3	-3.4 (1.4)	-3.9 (1.5)	-1.1 (1.1)	-5.6 (1.7)			
month 6	-1.9 (1.1)	-2.8 (1.4)	0.9 (0.9)	-3.4 (1.5)			
year 1	0.8 (0.6)	-0.3 (1.5)	-1.3 (1.0)	-1.2 (1.5)			
year 2	-0.8 (0.6)	-0.3 (1.6)	-1.4 (0.8)	-0.7 (1.0)	0.89	0.82	0.91
year 3	0.5 (0.9)	0.0 (1.5)	0.8 (2.0)	-0.3 (1.4)			
year 4	0.0 (0.5)	- 0.5 (1.1)	-2.3 (1.6)	1.0 (0.7)			
year 5	-0.7 (0.5)	-1.1 (1.1)	0.0 (0.6)	0.7 (0.7)			0.48
KSS — min 0 - max 100 points							
week 6	75.9 (3.2)	69.6 (3.5)	74.2 (3.0)	75.5 (3.0)			
month 3	80.5 (2.5)	78.3 (2.5)	74.9 (3.3)	79.6 (1.6)			
month 6	79.6 (2.8)	82.3 (2.2)	75.9 (3.6)	79.3 (3.2)			
year 1	82.9 (2.3)	82.9 (2.1)	77.7 (3.5)	81.8 (1.9)			
year 2	81.2 (3.2)	82.9 (2.0)	77.7 (3.5)	79.9 (2.7)	0.74	0.78	0.65
year 3	80.7 (3.9)	79.1 (3.5)	77.7 (3.3)	80.2 (3.2)			
year 4	84.5 (2.9)	77.6 (4.4)	77.8 (3.3)	83.7 (1.4)			
year 5	81.9 (3.4)	82.8 (3.2)	84.1 (1.4)	83.6 (1.6)			0.93
KSS FUNCTION — min 0 - max 100 points							
week 6	75.9 (3.2)	69.6 (3.5)	74.2 (3.0)	75.5 (3.0)			
month 3	80.5 (2.5)	78.3 (2.5)	74.9 (3.3)	79.6 (1.6)			
month 6	79.6 (2.8)	82.3 (2.2)	75.9 (3.6)	79.3 (3.2)			
year 1	82.9 (2.3)	82.9 (2.1)	77.7 (3.5)	81.8 (1.9)			
year 2	81.2 (3.2)	82.9 (2.0)	77.7 (3.5)	79.9 (2.7)	0.32	0.73	0.53
year 3	80.7 (3.9)	79.1 (3.5)	77.7 (3.3)	80.2 (3.2)			
year 4	84.5 (2.9)	77.6 (4.4)	77.8 (3.3)	83.7 (1.4)			
year 5	81.9 (3.4)	82.8 (3.2)	84.1 (1.4)	83.6 (1.6)			0.34

Appendix C. Analysis of functional outcome during 5 years of follow-up.

*The values are given as the mean and the standard error.

†This category assumes no interaction with time and indicates testing for the overall, between-group mean difference over the entire postoperative follow-up period.

‡This category indicates testing for overall changing treatment effects with time over the entire postoperative follow-up period.

Migration Tibial component	TKA*				INTENTION TO TREAT		
	LPS-Flex mobile	*LPS-Flex fixed*	*LPS mobile*	*LPS fixed*	Main effect†	Group × Time Interaction‡	Prespecified time point
	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	*p*-value	*p*-value	*p*-value
TRANSLATION — mm							
x-asis (medial-lateral)							
week 6	-0.01 (0.04)	0.02 (0.03)	-0.02 (0.02)	0.02 (0.03)			
month 3	-0.00 (0.04)	0.02 (0.03)	-0.01 (0.02)	0.02 (0.03)			
month 6	0.01 (0.05)	0.05 (0.03)	-0.03 (0.02)	0.09 (0.04)			
year 1	0.04 (0.05)	0.07 (0.04)	-0.02 (0.03)	0.11 (0.05)	0.3	0.41	
year 2	0.07 (0.05)	0.07 (0.04)	-0.00 (0.04)	0.09 (0.06)			0.55
year 3	0.09 (0.07)	0.08 (0.05)	-0.03 (0.04)	0.10 (0.04)			
year 4	0.05 (0.06)	0.09 (0.05)	-0.08 (0.06)	0.12 (0.04)			
year 5	0.00 (0.03)	0.07 (0.05)	-0.06 (0.05)	0.07 (0.04)			0.1
y-axis (cranial-caudal)							
week 6	0.06 (0.03)	0.06 (0.02)	0.03 (0.02)	0.03 (0.03)			
month 3	0.06 (0.04)	0.08 (0.02)	0.05 (0.02)	0.05 (0.02)			
month 6	0.02 (0.05)	0.07 (0.03)	0.11 (0.03)	-0.00 (0.05)			
year 1	0.02 (0.06)	0.13 (0.03)	0.12 (0.04)	0.04 (0.05)	0.88	0.13	
year 2	-0.07 (0.10)	0.13 (0.04)	0.14 (0.04)	0.05 (0.04)			0.08
year 3	0.04 (0.09)	0.16 (0.04)	0.15 (0.05)	0.10 (0.04)			
year 4	0.02 (0.09)	0.05 (0.09)	0.14 (0.05)	0.09 (0.04)			
year 5	0.03 (0.09)	0.03 (0.09)	0.11 (0.04)	0.08 (0.04)			0.56
z-axis (anterior-posterior)							
week 6	0.10 (0.07)	-0.05 (0.04)	0.03 (0.04)	-0.11 (0.07)			
month 3	0.11 (0.10)	-0.07 (0.04)	0.04 (0.03)	-0.01 (0.05)			
month 6	0.14 (0.14)	-0.06 (0.05)	0.09 (0.05)	0.10 (0.13)			
year 1	0.11 (0.14)	-0.12 (0.07)	0.08 (0.06)	0.13 (0.18)	0.39	0.67	
year 2	0.25 (0.17)	-0.16 (0.07)	0.13 (0.05)	0.18 (0.22)			0.25
year 3	0.26 (0.22)	-0.07 (0.07)	0.11 (0.04)	-0.04 (0.07)			
year 4	0.32 (0.26)	-0.13 (0.11)	0.15 (0.08)	0.00 (0.07)			
year 5	0.09 (0.07)	-0.22 (0.12)	0.13 (0.07)	0.02 (0.08)			0.04

Appendix D. Analysis of tibial component migration during 5 years of follow-up.

*The values are given as the mean and the standard error.

†This category assumes no interaction with time and indicates testing for the overall between-group mean difference over the entire postoperative follow-up period.

‡This category indicates testing for overall changing treatment effects with time over the entire postoperative follow-up period.

Migration Tibial component	TKA*				INTENTION TO TREAT		
	LPS-Flex mobile	*LPS-Flex fixed*	*LPS mobile*	*LPS fixed*	Main effect†	Group × Time Interaction‡	Prespecified time point
	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	*p*-value	*p*-value	*p*-value
ROTATION — degrees							
x-asis (transverse)							
week 6	0.09 (0.16)	-0.09 (0.05)	0.05 (0.12)	-0.08 (0.11)	0.66	0.13	
month 3	0.18 (0.24)	-0.18 (0.10)	-0.08 (0.07)	0.02 (0.11)			
month 6	0.28 (0.30)	-0.00 (0.11)	0.10 (0.15)	0.10 (0.23)			
year 1	0.19 (0.32)	0.04 (0.13)	0.14 (0.16)	0.38 (0.26)			
year 2	0.40 (0.40)	-0.04 (0.16)	0.17 (0.15)	0.24 (0.33)			0.78
year 3	0.60 (0.45)	-0.14 (0.18)	0.08 (0.11)	-0.05 (0.14)			
year 4	0.57 (0.55)	-0.26 (0.27)	0.27 (0.21)	-0.20 (0.16)			
year 5	0.15 (0.12)	-0.50 (0.27)	0.25 (0.17)	-0.13 (0.16)			0.03
y-axis (longitudinal)							
week 6	-0.04 (0.10)	-0.10 (0.11)	-0.08 (0.05)	-0.01 (0.15)	0.71	0.14	
month 3	-0.06 (0.09)	0.05 (0.14)	-0.09 (0.05)	0.11 (0.13)			
month 6	-0.09 (0.14)	-0.02 (0.09)	0.00 (0.07)	-0.15 (0.20)			
year 1	-0.02 (0.15)	-0.19 (0.12)	0.05 (0.07)	-0.18 (0.20)			
year 2	-0.05 (0.16)	-0.20 (0.13)	0.08 (0.06)	-0.22 (0.22)			0.55
year 3	-0.21 (0.25)	-0.17 (0.13)	-0.05 (0.11)	0.18 (0.17)			
year 4	-0.09 (0.25)	-0.07 (0.28)	0.05 (0.10)	-0.07 (0.13)			
year 5	0.09 (0.15)	-0.14 (0.25)	0.10 (0.10)	0.15 (0.15)			0.62
z-axis (sagittal)							
week 6	-0.03 (0.08)	-0.05 (0.03)	0.04 (0.05)	-0.03 (0.05)	0.31	0.15	
month 3	-0.04 (0.11)	-0.04 (0.04)	-0.01 (0.03)	-0.06 (0.06)			
month 6	-0.15 (0.13)	-0.03 (0.04)	0.07 (0.07)	-0.12 (0.08)			
year 1	-0.25 (0.15)	-0.07 (0.05)	0.07 (0.09)	-0.14 (0.09)			
year 2	-0.48 (0.21)	-0.15 (0.06)	0.03 (0.10)	-0.15 (0.10)			0.07
year 3	-0.43 (0.24)	-0.14 (0.07)	-0.00 (0.12)	-0.21 (0.10)			
year 4	-0.17 (0.19)	-0.23 (0.16)	0.19 (0.16)	-0.23 (0.11)			
year 5	-0.11 (0.12)	-0.24 (0.13)	0.15 (0.12)	-0.19 (0.12)			0.14

Appendix D (continued). Analysis of tibial component migration during 5 years of follow-up.

*The values are given as the mean and the standard error.

†This category assumes no interaction with time and indicates testing for the overall between-group mean difference over the entire postoperative follow-up period.

‡This category indicates testing for overall changing treatment effects with time over the entire postoperative follow-up period.

Migration Femoral component	TKA*				INTENTION TO TREAT		
	LPS-Flex mobile	*LPS-Flex fixed*	*LPS mobile*	*LPS fixed*	Main effect†	Group × Time Interaction‡	Prespecified time point
	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	*p*-value	*p*-value	*p*-value
TRANSLATION — mm							
x-asis (medial-lateral)							
week 6	-0.01 (0.05)	-0.01 (0.12)	-0.02 (0.05)	0.07 (0.09)			
month 3	0.15 (0.07)	-0.04 (0.12)	0.04 (0.04)	0.07 (0.09)			
month 6	0.10 (0.09)	0.08 (0.11)	0.05 (0.03)	0.09 (0.05)			
year 1	0.21 (0.12)	-0.02 (0.15)	0.01 (0.08)	0.04 (0.05)			
year 2	0.26 (0.14)	-0.07 (0.17)	0.01 (0.06)	0.10 (0.06)	0.80	0.11	0.32
year 3	0.21 (0.15)	-0.12 (0.32)	-0.17 (0.02)	0.06 (0.05)			
year 4	0.21 (0.13)	0.03 (0.29)	0.12 (0.14)	0.14 (0.08)			
year 5	0.02 (0.12)	-0.18 (0.23)	0.01 (0.12)	0.13 (0.08)			0.48
y-axis (cranial-caudal)							
week 6	0.12 (0.05)	0.14 (0.07)	0.05 (0.03)	0.12 (0.05)			
month 3	0.10 (0.08)	0.18 (0.07)	0.07 (0.03)	0.28 (0.13)			
month 6	0.08 (0.10)	0.03 (0.04)	0.03 (0.05)	0.31 (0.14)			
year 1	-0.13 (0.19)	0.18 (0.08)	-0.05 (0.14)	0.29 (0.12)			
year 2	-0.10 (0.22)	0.20 (0.08)	-0.02 (0.14)	0.32 (0.15)	0.23	0.07 (0.34 §)	0.19
year 3	-0.14 (0.30)	0.28 (0.16)	0.10 (0.05)	0.32 (0.19)			
year 4	-0.19 (0.26)	0.41 (0.13)	-0.05 (0.19)	0.35 (0.19)			
year 5	0.09 (0.03)	0.37 (0.16)	-0.05 (0.15)	0.34 (0.18)			0.22
z-axis (anterior-posterior)							
week 6	-0.11 (0.11)	0.03 (0.15)	0.07 (0.06)	0.08 (0.11)			
month 3	0.04 (0.24)	0.03 (0.16)	0.16 (0.10)	0.28 (0.20)			
month 6	0.10 (0.28)	0.15 (0.17)	0.30 (0.10)	0.10 (0.23)			
year 1	0.64 (0.60)	0.18 (0.16)	0.46 (0.30)	0.11 (0.16)			
year 2	0.65 (0.70)	0.12 (0.20)	0.37 (0.26)	0.14 (0.17)	0.84	0.30	0.72
year 3	0.95 (0.89)	0.31 (0.39)	0.18 (0.10)	0.12 (0.16)			
year 4	1.00 (0.80)	0.18 (0.22)	0.48 (0.37)	-0.12 (0.20)			
year 5	0.19 (0.11)	0.03 (0.33)	0.50 (0.31)	-0.21 (0.15)			0.22

Appendix E. Analysis of femoral component migration during 5 years of follow-up.

*The values are given as the mean and the standard error.

†This category assumes no interaction with time and indicates testing for the overall between-group mean difference over the entire postoperative follow-up period.

‡This category indicates testing for overall changing treatment effects with time over the entire postoperative follow-up period.

§ This is the p-value from the analysis without the influential outliers and was tested because of the borderline significance of the primary analysis.

Migration Femoral component	TKA*				INTENTION TO TREAT		
	LPS-Flex mobile	*LPS-Flex fixed*	*LPS mobile*	*LPS fixed*	Main effect†	Group × Time Interaction‡	Prespecified time point
	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	*p*-value	*p*-value	*p*-value
ROTATION — degrees							
x-asis (transverse)							
week 6	0.30 (0.16)	0.18 (0.15)	-0.05 (0.14)	0.16 (0.21)			
month 3	0.12 (0.39)	0.22 (0.16)	-0.02 (0.07)	0.17 (0.33)			
month 6	0.22 (0.45)	-0.05 (0.16)	-0.10 (0.17)	0.41 (0.28)			
year 1	-0.66 (0.89)	0.13 (0.15)	-0.52 (0.47)	0.48 (0.14)			
year 2	-0.58 (1.07)	0.20 (0.20)	-0.22 (0.41)	0.49 (0.22)	0.41	0.15	0.48
year 3	-0.87 (1.18)	0.25 (0.41)	0.10 (0.24)	0.59 (0.30)			
year 4	-1.17 (1.17)	0.43 (0.21)	-0.26 (0.50)	0.89 (0.39)			
year 5	0.06 (0.01)	0.36 (0.29)	-0.34 (0.41)	1.00 (0.35)			0.09
y-axis (longitudinal)							
week 6	0.06 (0.17)	-0.13 (0.13)	-0.05 (0.05)	-0.00 (0.19)			
month 3	-0.35 (0.17)	0.05 (0.18)	-0.41 (0.32)	0.02 (0.27)			
month 6	-0.29 (0.33)	0.09 (0.19)	-0.40 (0.25)	0.10 (0.19)			
year 1	-0.79 (0.86)	0.11 (0.20)	-0.22 (0.15)	0.05 (0.10)			
year 2	-1.17 (1.13)	0.20 (0.22)	-0.58 (0.23)	-0.03 (0.16)	0.51	0.58	0.23
year 3	-1.12 (1.15)	0.22 (0.45)	-0.30 (0.33)	-0.00 (0.15)			
year 4	-1.62 (1.24)	-0.35 (0.09)	-0.82 (0.29)	-0.28 (0.19)			
year 5	-0.46 (0.02)	-0.06 (0.22)	-0.56 (0.14)	-0.14 (0.19)			0.20
z-axis (sagittal)							
week 6	-0.02 (0.13)	0.05 (0.10)	-0.12 (0.09)	0.12 (0.13)			
month 3	0.03 (0.17)	0.09 (0.04)	-0.18 (0.15)	0.06 (0.20)			
month 6	0.02 (0.14)	0.20 (0.12)	-0.13 (0.12)	0.14 (0.20)			
year 1	0.07 (0.21)	0.22 (0.11)	-0.00 (0.12)	0.07 (0.23)			
year 2	0.05 (0.28)	0.24 (0.14)	-0.19 (0.15)	0.05 (0.27)	0.35	0.93	0.56
year 3	-0.1 (0.25)	0.44 (0.27)	-0.22 (0.02)	-0.20 (0.31)			
year 4	-0.24 (0.28)	0.57 (0.35)	-0.32 (0.23)	0.26 (0.19)			
year 5	-0.09 (0.34)	0.47 (0.41)	-0.28 (0.18)	0.24 (0.16)			0.15

Appendix E (continued). Analysis of femoral component migration during 5 years of follow-up.

*The values are given as the mean and the standard error.

†This category assumes no interaction with time and indicates testing for the overall between-group mean difference over the entire postoperative follow-up period.

‡This category indicates testing for overall changing treatment effects with time over the entire postoperative follow-up period.

§ This is the p-value from the analysis without the influential outliers and was tested because of the borderline significance of the primary analysis.

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7

A systematic review and meta-regression of mobile-bearing versus fixed-bearing TKA in 41 studies

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ABSTRACT

Introduction

Mobile-bearing (MB) total knee arthroplasty (TKA) was introduced to reduce the risk of aseptic loosening and wear of polyethylene inserts. However, no consistent clinical advantages of mobile- over fixed-bearing (FB) TKA have been found. In this study we evaluated whether mobile bearings have an advantage over fixed bearings with regard to revision rates and clinical outcome scores. Furthermore, we determined which modifying variables affected the outcome.

Methods

A systematic search of the literature was conducted to collect clinical trials comparing MB and FB in primary TKA. The primary outcomes were revision rates for any reason, aseptic loosening and wear. Secondary outcomes included range of movement, Knee Society score (KSS), Oxford knee score (OKS), Short-Form 12 (SF-12) score and radiological parameters. Meta-regression techniques were used to explore factors modifying the observed effect.

Results

Our search yielded 1827 publications, of which 41 studies met our inclusion criteria, comprising over 6000 TKAs. Meta-analyses showed no clinically relevant differences in terms of revision rates, clinical outcome scores or patient-reported outcome measures between MB and FB TKAs.

Conclusion

It appears that theoretical assumptions of superiority of MB over FB TKA are not borne out in clinical practice.

INTRODUCTION

Mobile-bearing (MB) total knee arthroplasty (TKA) was introduced to reduce the risk of aseptic loosening and wear of the polyethylene insert by increasing implant conformity and minimising the stresses transmitted to the implant–bone interface (1, 2). Whether these properties of MB TKA lead to superior clinical performance over fixed-bearing (FB) TKA is unclear. Several randomised clinical trials have reported conflicting results, and meta-analyses have reported no difference in clinical outcome between MB and FB TKA (3-5). These meta-analyses were inconclusive with regard to implant longevity, and all had restricted inclusion criteria, leaving only a limited number of studies to be examined. Therefore, this systematic review and meta-analysis addressed implant longevity and included controlled trials without restrictions, thereby providing a comprehensive overview and minimising bias. The primary objective of this study was to determine the clinical outcome of MB TKA in comparison to the conventional FB TKA in primary TKA, with regard to revision rates, range of movement, Knee Society score (KSS) (6), Oxford knee score (OKS) (7), Short-Form 12 (SF-12) score (8), Western Ontario and McMaster Universities osteoarthritis index (WOMAC) (9) and radiological parameters. The second objective was to search for modifying variables affecting the outcome, using meta-regression analysis.

METHODS

Systematic review

The aim of the search was to identify randomised controlled clinical trials comparing the outcomes of MB and FB primary TKA. The search strategy was composed in collaboration with an experienced medical librarian in order to minimise publication bias (10). The following databases were searched up to 2012: Medline, EMBASE (OVID version), Web of Science, Cochrane Library and CINAHL (EbscoHost version). The search strategy consisted of the following components, each defined by a combination of controlled vocabulary and free text terms: 1) osteoarthritis or rheumatoid arthritis; 2) total knee arthroplasty; and 3) randomised controlled trial or controlled clinical trial. There were no restrictions on language or date, and relevant articles were screened for additional references.

2 reviewers (KAN, BGP) independently selected the trials to be included in the review. Initial screening based on title and abstract was performed to identify studies that met the following inclusion criteria: 1) the study had to be a (randomised) controlled clinical trial; 2) the interventions evaluated in the trials had to be MB and FB primary TKA; 3) the indication for the patient to undergo TKA had to be osteoarthritis or rheumatoid arthritis; 4) outcome measurement(s) in the studies had to include rate of revision (for any reason, aseptic loosening or wear) with a minimum follow-up of 5 years, functional outcome score, or patient-reported outcome measurement. Subsequently, the full texts of eligible studies were evaluated and studies were excluded when: 1)

the study did not meet the initial inclusion criteria for title and abstract; and 2) the population had already been reported in another included study (the most informative version was included). Abstracts without full text were given full consideration when sufficient clinical outcome data for further analysis were available.

Outcome measures

Primary outcomes were revision rate for any reason, aseptic loosening and wear. Secondary outcomes included functional outcome scores (range of movement and KSS), patient-reported outcome measurements, (SF-12, OKS and WOMAC), radiological evaluation (radiolucent lines and osteolysis around the implant) and implant migration (maximum total point motion (MTPM)) as measured by radio stereophotogrammetric analysis (RSA). A clinically relevant difference between the designs was a difference of 10° in range of movement or 10 points on clinical scores (e.g. OKS, SF-12), based on an expert Delphi consensus study (11).

Data extraction

2 reviewers (PvdV, KAN) independently extracted data concerning participants (age, gender, body mass index, aetiology); methods (study design, number of TKAs, start inclusion, mean follow-up, number lost to follow-up, date of publication, funding, country); interventions (type of arthroplasty, type of MB, management of the posterior cruciate ligament, use of cement, treatment of the patella); outcomes (revision rates, range of movement, KSS, HSS, OKS, WOMAC, SF-12, radiolucent lines and osteolysis around the implant, MTPM).

Quality assessment

Critical appraisal was conducted independently by 2 reviewers (PvdV, KAN) using the Jadad scale (12). This is a 5-item scale designed to assess randomisation, blinding, withdrawals and dropouts, and the score for each article ranges from 0 (lowest quality) to 5 (highest quality). As blinding of the surgeon is not feasible, studies were regarded as 'double-blind' when blinding of both patient and assessor was reported. Disagreements about study selection, data extraction and clinical appraisal were resolved by consensus with a third reviewer (RGHHN), who acted as a referee.

Analysis

All data were combined for random-effects meta-analysis (RMA) according to the pooled Mantel–Haenszel test for risk differences (RDs) with 95% confidence intervals (CI), and the pooled standard error for mean differences (MDs) also with 95% CI. Heterogeneity between studies was tested with the I^2 statistic (13). This test describes the proportion of total variation in outcome measures across studies that is due to heterogeneity rather than chance. Outcome measures showing heterogeneity among different studies were explored with meta-regression analysis (MRA). This model searches for modifying variables that affect the outcome between studies, and can therefore help resolve contradictory outcomes of different studies. Potentially associated

variables, such as mean follow-up time, patellar resurfacing and type of MB design, served as covariates to the regression model. In order to assess for publication bias we constructed a funnel plot for studies reporting the primary outcome. A 'trim and fill' method was used when there was asymmetry in the funnel plot to adjust for publication bias owing to missing studies and estimate the overall effect size (14). All analyses were performed with the metaphor package for R v2.13 (R Development Core Team, Vienna, Austria) (15).

RESULTS

Study characteristics

The literature search yielded 1827 possible papers for analysis, of which 41 studies met the inclusion criteria: one publication described two studies (16) (Figure 1). Those 41 studies comprised 3024 MB and 3155 FB primary TKAs (Table 1). A total of 40 were randomised controlled trials (2, 4, 16-52) and 1 was a controlled clinical trial (53). 1 included study was an abstract describing an unpublished randomised controlled trial (21). The mean follow-up ranged from 0.5 to 13.2 years. In 19 studies (63%) funding had been received from industry. In all, 39 articles were written in English and 1 article in German (42).

Arthroplasty characteristics

With regard to the type of MB, the majority of the studies (26 of 40 reporting on bearing type, 65%) used a rotating platform MB, 3 (7%) a meniscal bearing, 9 (23%) an anteroposterior gliding and rotating platform, and 2 (5%) a floating platform. In the MB group, 16 studies reported the use of a posterior stabilised implant versus 18 in the FB group. In 24 studies the patella was resurfaced. All tibial components were cemented, except in 1 study (23).

Study quality

All but 1 study described the randomisation process, with 29 studies reporting an adequate generation of allocation sequences. Blinding was reported in 8 studies, but only 1 study reported blinding of both patient and assessor. The mean total Jadad score was 2.7 (SD 0.8). Meta-regression analysis showed no effect of the study quality, expressed as the total Jadad score, on the range of movement (0.2°/Jadad unit (95% CI -1.2 to 1.6); p = 0.8, MRA), KSS clinical score (-0.5/Jadad unit (95% CI -1.8 to 0.8); p = 0.4, MRA) and KSS functional score (0.4/Jadad unit (95% CI -1.2 to 1.9); p = 0.6, MRA). There was no evidence of publication bias in studies reporting revision rates confirmed by the lack of asymmetry of the funnel plots.

Revision rates

Meta-analyses for the primary outcomes in studies with a minimum follow-up of 5 years and studies with a minimum follow-up of 10 years revealed no differences in revision rates for any

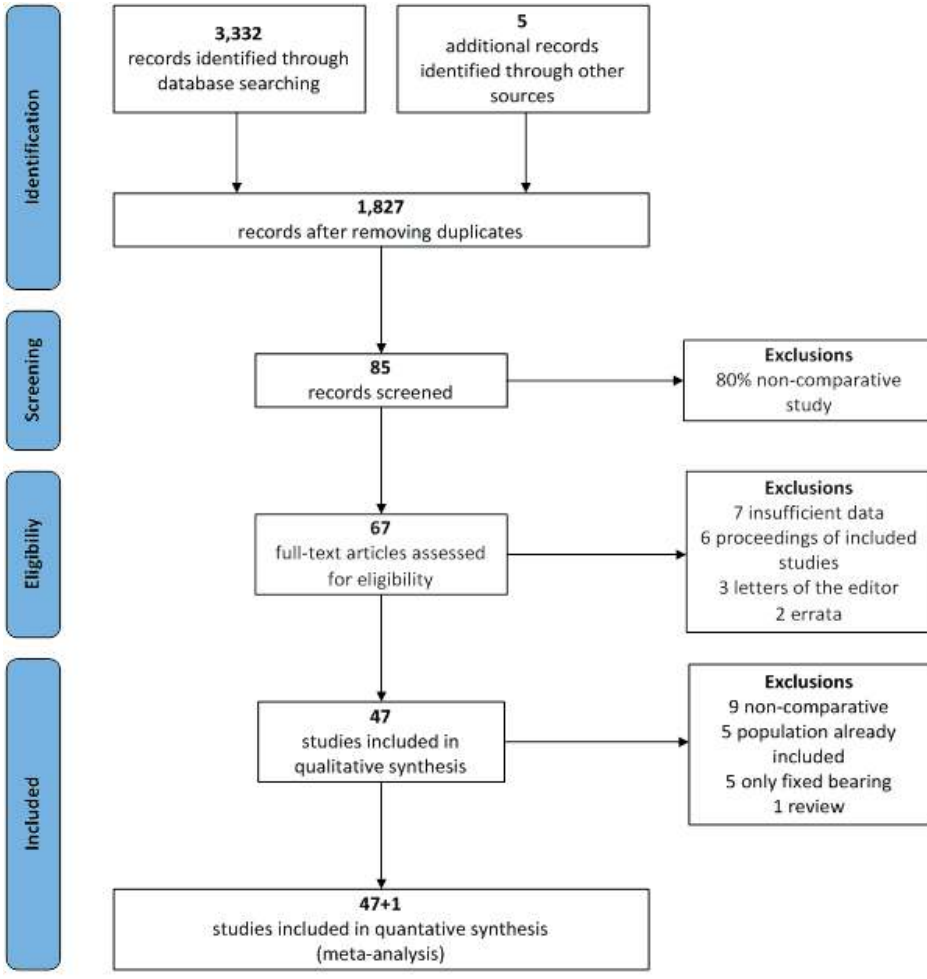

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram depicting the number of records identified, included or excluded, and reasons for exclusion.

Study	Year of publication	IMPLANT				Mean FU (years)	Mean age (years)	Female (%)	OA (%)
		Design	N	Type	Mobile bearing design				
Aglietti et al.	2005	MB	103	MBK - Zimmer	RP + AP gliding	3	70	84	100
		FB	107	NexGen LPS - Zimmer					
Ball et al.	2010	MB	51	Scorpio - Stryker	RP	4	65	56	n/a
		FB	49	Scorpio - Stryker					
Beard et al.	2007	MB	40	TMK - Biomet	RP + AP gliding	3.7	73	60	100
		FB	40	AGC - Biomet					
Bhan et al.	2005	MB	34	LCS - DePuy	RP	6	63	69	50
		FB	34	Columbus - Zimmer					
Breugem et al.	2008	MB	48	NexGen LPS - Zimmer	RP	1	70	64	100
		FB	55	NexGen LPS - Zimmer					
Chatterji et. al.	2005	MB	70	NexGen - Zimmer	RP	1	67	n/a	93
		FB	69	NexGen - Zimmer					
Garling et al.	2005	MB	21	Interax - Stryker	RP + AP gliding	2	66	64	31
		FB	21	Interax - Stryker					
Gasparini et al.	2004	MB	50	n/a	n/a	1.3	n/a	n/a	n/a
		FB	50	n/a					
Gioe et al.	2009	MB	n/a	PFC Sigma - DePuy	RP	3.5	72	3	97
		FB	n/a	PFC Sigma - DePuy					
Grodzki et al.	2001	MB	26	LCS - DePuy	RP	1	73	n/a	100
		FB	12	PFC Sigma - DePuy					
Hansson et al.	2004	MB	25	Rotaglide - Corin	RP + AP gliding	2	75	50	100
		FB	27	Nuffield - Corin					
Hanusch et al.	2010	MB	n/a	PFC Sigma - DePuy	RP	1.1	70	50	100
		FB	n/a	PFC Sigma - DePuy					
Harrington et al.	2009	MB	68	PFC Sigma - DePuy	RP	2	64	64	86
		FB	72	PFC Sigma - DePuy					
Hasegawa et al.	2009	MB	25	PFC Sigma - DePuy	RP	3.3	73	88	100
		FB	25	PFC Sigma - DePuy					
Henricson et al.	2006	MB	26	MBK - Zimmer	RP + AP gliding	2	72	63	100
		FB	26	NexGen LPS - Zimmer					
Higuchi et al.	2009	MB	31	PFC Sigma - DePuy	RP	4	68	72	100
		FB	45	PFC Sigma - DePuy					
Jacobs et al.	2011	MB	50	BalanSys - Mathys medical	RP + AP gliding	n/a	67	71	100
		FB	48	BalanSys - Mathys medical					

Table 1. Details of the included studies of mobile-bearing (MB) and fixed-bearing (FB) total knee arthroplasties.

RP: rotating platform

AP: anteroposterior gliding platform

Study	Year of publication	IMPLANT				Mean FU (years)	Mean age (years)	Female (%)	OA (%)
		Design	N	Type	Mobile bearing design				
Jolles et al.	2006	MB	12	NexGen LPS - Zimmer	RP	0.5	n/a	n/a	n/a
		FB	19	NexGen LPS - Zimmer					
KAT Trial Group	2009	MB	230	TMK - Biomet	RP + AP gliding	2	69	60	93
		FB	244	AGC - Biomet					
Kim D et al. (1717)	2011	MB	40	PFC Sigma - DePuy	RP	2.5	67	96	100
		FB	40	NexGen LPS - Zimmer					
Kim TK et al. (95A)	2010	MB	38	e.motion FP - Braun-Aesculap	FP	2	69	97	100
		FB	38	Genesis II - Smith & Nephew					
Kim TK et al. (95B)	2010	MB	38	e.motion FP - Braun-Aesculap	FP	2	69	97	100
		FB	38	Genesis II - Smith & Nephew					
Kim YH et al. (647)	2001	MB	120	LCS - DePuy	MeBe	7.4	65	69	95
		FB	120	AMK - DePuy					
Kim YH et al. (318)	2007	MB	160	LCS - DePuy	RP	13.2	70	95	94
		FB	160	AMK - DePuy					
Kim YH et al. (343)	2007	MB	194	PFC Sigma - DePuy	RP	5.6	67	64	99
		FB	194	PFC Sigma - DePuy					
Kim YH et al. (210)	2009	MB	69	LCS - DePuy	MeBe	10.8	48	74	95
		FB	69	AMK - DePuy					
Kim YH et al. (272)	2009	MB	92	PFC Sigma - DePuy	RP	2.6	70	92	100
		FB	92	Advance medial pivot - Wrigth medical					
Ladermann et al.	2008	MB	52	PFC Sigma - DePuy	RP	7.1	71	69	90
		FB	52	PFC Sigma - DePuy					
Lampe et al.	2011	MB	48	Columbus - B.Braun-Aesculap	RP	1	70	73	89
		FB	52	Columbus - B.Braun-Aesculap					
Lizaur-Utrilla et al.	2011	MB	61	Trekking - Samo	RP	2.5	74	79	100
		FB	58	Multigen Plus - Lima					
MacDonald et al.	2005	MB	n/a	SAL - Sulzer orthopaedics	RP + AP gliding	3.4	n/a	n/a	n/a
		FB	n/a	AMK - DePuy					
Mahoney et al.	2011	MB	252	Scorpio - Stryker	RP	5.9	66	64	100
		FB	255	Scorpio - Stryker					
Matsuda et al.	2010	MB	30	NexGen LPS-Flex - Zimmer	RP	5.7	75	77	96
		FB	31	NexGen LPS-Flex - Zimmer					
Mockel et al.	2004	MB	23	PFC Sigma - DePuy	RP	0.5	69	71	79
		FB	40	Natural knee II - Centerpulse					

Table 1 (continued). Details of the included studies of mobile-bearing (MB) and fixed-bearing (FB) total knee arthroplasties.
RP: rotating platform
AP: anteroposterior gliding platform

Study	Year of publication	IMPLANT				Mean FU (years)	Mean age (years)	Female (%)	OA (%)
		Design	N	Type	Mobile bearing design				
Munro et al.	2010	MB	n/a	PFC Sigma - DePuy	RP	2	67	44	100
		FB	n/a	PFC Sigma - DePuy					
Pagnano et al.	2004	MB	80	PFC Sigma - DePuy	RP	5	67	70	100
		FB	160	PFC Sigma - DePuy					
Rahman et al.	2010	MB	27	PFC Sigma - DePuy	RP	3.5	62	63	92
		FB	27	PFC Sigma - DePuy					
Rees et al.	2005	MB	40	TMK - Biomet	RP + AP gliding	n/a	71	n/a	100
		FB	40	AGC - Biomet					
Saari et al.	2003	MB	7	Freeman-Samuelson - Finsbury orthopaedics	RP	1	69	77	100
		FB	15	Freeman-Samuelson - Finsbury orthopaedics					
Scuderi et al.	2011	MB	201	NexGen LPS-Flex - Zimmer	RP	2.5	64	58	97
		FB	187	NexGen LPS-Flex - Zimmer					
Silvestre et al.	2008	MB	69	Ceragyr - Ceraver-Osteal	RP + AP gliding	4.7	69	72	n/a
		FB	71	Hermes - Ceraver-Osteal					
Tibesku et al.	2011	MB	16	Genesis II - Smith & Nephew	RP + AP gliding	2	66	64	100
		FB	17	Genesis II - Smith & Nephew					
Uvehammer et al.	2007	MB	16	Freeman-Samuelson - Finsbury orthopaedics	RP	2	69	80	100
		FB	19	Freeman-Samuelson - Finsbury orthopaedics					
Vasdev et al.	2009	MB	60	LCS - DePuy	RP	3.5	63	58	100
		FB	60	NexGen LPS - Zimmer					
Watanabe et al.	2005	MB	22	Rotaglide - Corin	RP + AP gliding	8.1	60	96	18
		FB	22	NexGen LPS - Zimmer					
Wohlrab et al.	2009	MB	30	NexGen LPS-Flex - Zimmer	RP	5.5	66	56	100
		FB	30	NexGen LPS - Zimmer					
Woolson et al.	2011	MB	60	LCS - DePuy	RP	11.4	78	n/a	80
		FB	47	NexGen LPS - Zimmer					
Wylde et al.	2008	MB	118	Kinemax Plus - Stryker	n/a	2	68	55	90
		FB	132	Kinemax Plus - Stryker					

Table 1 (continued). Details of the included studies of mobile-bearing (MB) and fixed-bearing (FB) total knee arthroplasties.
RP: rotating platform
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reason, or for aseptic loosening or wear. In studies with a minimum follow-up of 5 years (n = 13) there were 40 revisions for any reason in 1172 MB TKAs, and 28 revisions for any reason in 1245 FB TKAs (RD -0.01 (95% CI -0.02 to 0.0); p = 0.3, RMA) (Figure 2). 3 MB TKAs and 1 FB TKA were revised for aseptic loosening (RD 0.0 (95% CI 0.0 to 0.0); p = 0.7, RMA); 4 MB TKAs and 8 FB TKAs were revised for wear (RD 0.0 (95% CI 0.0 to 0.0); p = 0.7, RMA). In studies with a minimum follow-up of 10 years (n = 3) there were 13 revisions for any reason in 289 MB TKAs, and 11 revisions for any reason in 276 FB TKAs (RD 0.0 (95% CI -0.01 to 0.0); p = 0.8, RMA). 1 MB TKA and 1 FB TKA were revised for aseptic loosening (RD 0.0 (95% CI 0.0 to 0.0); p = 0.7, RMA). 3 MB TKAs and 6 FB TKAs were revised for wear (RD 0.0 (95% CI 0.0 to 0.0); p = 0.2, RMA). There was no evidence of heterogeneity across studies (I^2 = 0.00) for all 3 outcomes (i.e. revision rate for any reason, aseptic loosening and wear). Therefore, it was not necessary to explore sources of heterogeneity using meta-regression analysis.

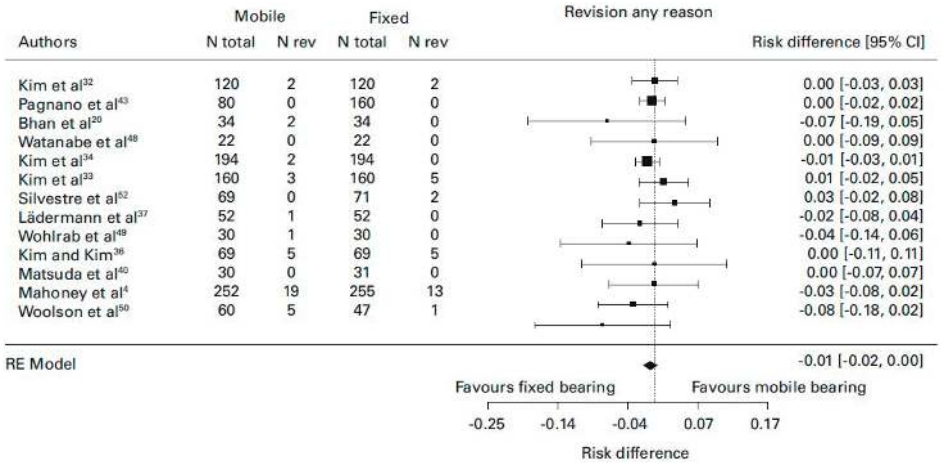

Figure 2. Forest plot showing the risk difference in revision rate for any reason between mobile- (MB) and fixed-bearing (FB) total knee arthroplasty (TKA) for studies with a minimum follow-up of 5 years. There is no difference in revision rate for any reason between MB and FB TKA (rev, revised; RE, random effects; CI, confidence interval).

Functional scores

Meta-analyses for the secondary outcomes showed an MD in the range of movement of 0.5° (95% CI -0.8 to 1.7); p = 0.6, RMA) in favour of MB TKA (Figure 3). However, there was considerable heterogeneity (I^2 = 0.75) across studies reporting range of movement, which could be explained by stratifying for the type of MB using meta-regression analysis. In comparison with FB TKA, rotating platforms showed a significantly better range of movement (MD +1.4°, 95% CI 0.2 to 2.7; p = 0.02, MRA) (Table 2). The anteroposterior gliding and rotating platform showed a significantly worse range of movement (MD -3.1°, 95% CI -5.5 to -0.8) compared with FB TKA (p = 0.01, MRA). The meniscal bearing and floating platform TKA showed a respectively better (MD +0.4°, 95% CI -3.6

to 4.5) and worse (MD -0.3°, 95% CI -4.8 to 4.3) range of movement in comparison with FB TKA, albeit not significant (respectively, p = 0.8 and p = 0.9, MRA). There were no significant differences in KSS clinical (MD +0.3, 95% CI -0.7 to 1.2; p = 0.4, RMA) and functional scores (MD +0.8, 95% CI -0.4 to 2; p = 0.1, RMA) between MB TKA and FB TKA. Heterogeneity across studies reporting KSS clinical and functional scores were moderate (I^2 = 0.67 and I^2 = 0.39, respectively). This heterogeneity could not be explained by stratifying for type of MB or any other distinct factor. The Hospital for Special Surgery knee score (54) and other clinical knee scores were not analysed because they were inconsistently and infrequently reported.

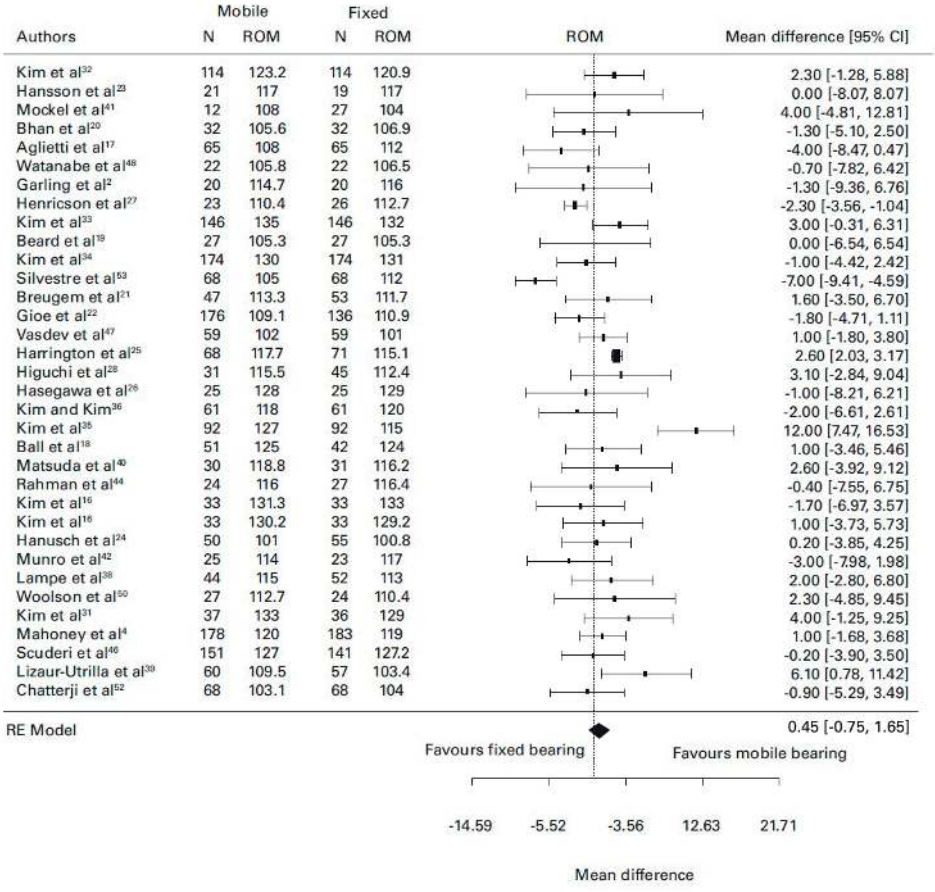

Figure 3. Forest plot showing the mean difference in postoperative range of movement (ROM) between mobile- (MB) and fixed-bearing (FB) total knee arthroplasty (TKA). There is no difference in range of movement between MB and FB TKA. However, a wide variation in data is clearly visible, indicating heterogeneity across different studies (RE, random effects; CI, confidence interval).

	Rotating platform		*Meniscal bearing*		*AP gliding & rotating platform*		*Floating platform*	
	Mean difference (95% CI)	*p*-value	Mean difference (95% CI)	*p*-value	Mean difference (95% CI)	*p*-value	Mean difference (95% CI)	*p*-value
Range of motion	1.44 (0.20 to 2.69)	0.02	0.42 (-3.63 to 4.48)	0.84	-3.14 (-5.47 to -0.81)	0.01	-0.26 (-4.81 to 4.28)	0.9
Knee Society score								
Clinical	0.35 (-0.79 to 1.49)	0.6	0.12 (-3.6 to 2.85)	0.95	-0.02 (-2,42 to 2,38)	1	0.23 (-3.49 to 3.95)	0.9
Function	1.35 (-0.15 to 2.86)	0.1	1 (-6.13 to 8.14)	0.78	-0.92 (-4.23 to 2.38)	0.6	-0.57 (-4.5 to 3.35)	0.8

Table 2. The influence of outcome measures on type of mobile-bearing (MB) design. The different MB designs are compared with fixed-bearing (FB) total knee arthroplasty (TKA). A positive coefficient favours MB TKA, a negative coefficient favours FB TKA. Range of movement is significantly different between the rotating platform and the anteroposterior gliding and rotating platform, with the rotating platform having the best range of movement compared with FB TKA (MD, mean difference; CI, confidence interval).

Patient-reported outcome measurements

The SF-12 physical score was significantly better for the MB TKA (MD +1.3 (95% CI 0.1 to 2.5); p = 0.01, RMA). There were no differences in SF-12 mental score (MD +0.02 (95% CI -1.5 to 1.6); p = 0.9, RMA), OKS (MD +0.6 (95% CI -0.5 to 1.7); p = 0.4, RMA) or WOMAC score (MD -0.1 (95% CI -1.5 to 1.4); p = 0.8, RMA).

Radiological evaluation

Radiological evaluation revealed no differences for the presence of radiolucencies (RD 0.0 (95% CI 0.0 to 0.0); p = 0.2, RMA) or of osteolysis (RD 0.0 (95% CI 0.0 to 0.0); p = 0.9, RMA) around the implant. As only a limited number of studies reported MTPM and because of the considerable heterogeneity (I^2 = 0.44) across those studies, the MTPM could not be used for analysis.

DISCUSSION

The results of the meta-analyses indicated that there were no clinically relevant differences in terms of revision rates, range of movement, KSS, OKS, SF-12 or radiological parameters. Considering the large number of trials included (41 studies comprising over 6000 TKAs), this study provides strong evidence against any clinical advantages of MB over FB TKA.

Previous meta-analyses have investigated the difference between MB and FB TKA (3, 5). By including clinical trials without restrictions, our comprehensive overview maximised the number of observations and strengthens the outcomes. The possibility of introducing heterogeneity by including a wider range of implant types was analysed with meta-regression analysis.

The primary outcome of this study, revision rate, is inextricably linked to follow-up time. The anticipated benefit of MB TKA of fewer revisions is expected to manifest itself after longer follow-up. In order to account for the potential late appearance of revisions, only studies with a minimum follow-up of five years were included in the meta-analyses for revision rates. We found no difference in revision rates between MB and FB TKA. The results of this meta-analysis could therefore not support the theoretical benefits of MB TKA.

There were no differences between MB and FB TKA in terms of incidence of radiolucencies and osteolysis around the implant. Studies reporting MTPM measured with RSA have showed no difference at 2 years of follow-up, suggesting good long-term survival for both designs (23, 27). Garling et al. also found no difference between MB and FB TKA implant migration measured with RSA at 2 years of follow-up (2). However, low variability in the data from the MB group was suggestive of a more predictable and forgiving design with respect to these small degrees of implant migration compared with the FB design. RSA is a feasible method to assess implant migration, and short-term RSA results have proved to be predictive of implant longevity (55). Therefore, more long-term RSA studies would enhance our understanding of the predictive value of RSA on future implant failure due to aseptic loosening in MB and FB TKA.

We found no clinically relevant difference in the range of movement between MB and FB TKA. However, there was considerable heterogeneity across the studies, indicating that any differences in the range of movement between MB and FB TKA may depend on other factors. Indeed, the variation in design of the mobile bearing produces differences in range of movement between MB and FB TKA. Several MB designs are available, each accommodating different types of mobility, ranging from pure rotation to pure translation to combined rotation and translation. Most designs consist of a single piece of polyethylene, whereas the meniscal bearing type has individual medial and lateral inserts. Although we found a significant difference in the rotating platform and the anteroposterior and rotating platform compared with FB TKA, this difference was small (< 10°) and may lack clinical relevance (11). Previous meta-analyses by Carothers et al. and Wen et al. also reported an influence of the design of MB platform on postoperative range of movement (3, 5). Carothers et al. compared different MB designs in 14 studies and found a significant difference in the rotating platform over platforms with a combined anteroposterior and rotation movement (3). The mean improvement in range of movement was 5.8° better in the rotating platform group. However, they did not use a FB control group, so their results may be subject to confounding factors. Wen et al5 performed subgroup analyses comparing rotating platforms and anteroposterior gliding and rotating platforms to FB TKAs in 6 studies (5). They found a trend towards a better range of movement of 1° for the FB TKA than with the rotating platform MB TKA, which was considered to be clinically irrelevant.

It should be recognised that the preoperative range of movement has an important influence on postoperative range of movement (56). In order to give an accurate comparison between MB and FB TKA in terms of range of movement, the improvement in range of movement should be examined. Although many studies report the preopeartive range of movement, few studies report

the improvement. Using the pre- and postoperative ranges to calculate the improvement is not feasible, as these values might not represent the same patients.

We found no difference in clinical outcome scores between MB and FB TKA. The KSS was the most frequently reported clinical outcome score, especially in studies emanating from North America. However, the KSS is not validated and may not be sensitive enough to detect a difference. Therefore, we also evaluated the OKS, a validated clinical outcome score (7). Meta-analysis of the OKS confirms the meta-analysis of the KSS in that no significant difference between MB and FB TKA could be established. With regard to other patient-reported outcome measures, we could find no clinically relevant difference between MB and FB TKA. There was a significant difference in SF-12 score, which in the most favourable case would be 2 points in favour of MB TKA, but this difference is not clinically relevant.

The strengths of our study are the large number of patients and revisions and the lack of restrictions in the literature search. Our results therefore represent a comprehensive overview of experience with MB and FB TKA. The meta-regression analysis provided the possibility to show, within a large population, which factors influence the outcome measures and to correct for factors that might modify the results. The influence of publication bias was negligible as determined by funnel plots.

We acknowledge some limitations. It was not possible to meta-analyse some important outcomes, such as implant migration measured by RSA, because they were reported infrequently and inconsistently. The methodological quality of the included studies varied. Although high quality is preferable, there was no influence of study quality, expressed by the Jadad score, on the outcomes.

In conclusion, this systematic review and meta-analysis comprising over 6000 TKAs did not show any clinically relevant differences in revision rates, clinical outcome scores or patient-reported outcome measures between MB and FB TKA. The rotating platform designs performed slightly better than the anteroposterior gliding and rotating platform types in terms of range of movement, but this difference was small and unlikely be clinically relevant. Theoretical assumptions of less aseptic loosening and wear for MB TKA could not be proven, at this point in time, as revision rates between the 2 designs were comparable.

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8

Inducible displacement to predict tibial component loosening in total knee arthroplasty: an in vitro study

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Submitted

ABSTRACT

Introduction

Inducible displacement (ID) is a promising technique to instantly detect loosening, in contrast to detection of loosening over a period of time, by applying an external force to the implant causing motion of the implant in relation to the bone. However, it is still unclear how an external force should be applied onto the implant inducing a valid implant displacement. Therefore, we performed an in vitro sensitivity study, aimed to establish the optimal direction and magnitude of force necessary to induce the largest possible implant displacement using the minimal possible force.

Methods

8 cadaveric tibiae were prepared with tibial knee component (i.e. tibial tray), surrounded by a silicone elastomer lining mimicking a fibrous tissue layer, thereby simulating a loose implant. Subsequently, a maximum force of 800 N was applied parallel to the anatomical axis of the tibia, next to a force perpendicular to the anatomical axis of the tibia with an increasing magnitude of 50-100-150-200 N.

Results

We observed large implant displacement in combination with high reproducibility by a loading force parallel to the anatomical axis in the centerline of the tibial tray and perpendicular to the anatomical axis on the medial and lateral part of the tibial tray. We found that with increasing fibrous tissue layer thickness the displacement also increased, suggesting that the fibrous tissue is primarily responsible for the measured displacement.

Conclusions

These findings affirm that ID has the potential to be used as an instant biomarker to detect loose implants.

INTRODUCTION

Total knee arthroplasty (TKA) is a successful procedure with nearly 30,000 procedures in 2018 in the Netherlands and shows a continuous increase over the years (1). This increasing demand for TKA's will affect the number of failures and ensuing revision procedures, which can increase up to 10% at 10 years (2).

Aseptic loosening is in about a third of the cases the reason for revision surgery (1, 3-5). Aseptic loosening is a multifactorial process leading to bone resorption around the implant and the subsequent formation of fibrous tissue between bone and implant (6-9). This interface tissue has inferior mechanical properties as compared to bone, resulting in mechanical instability and subsequent displacement over time of the implant relative to the bone (10, 11).

Accurate measurement of implant displacement can be determined with roentgen stereophotogrammetric analysis (RSA) and displacement measured over a minimum period of 2 years is a predictor for future loosening, defined as progressive displacement over time resulting in revision surgery (12-14). Hence, RSA is used as one of the first steps in the stepwise introduction of newly developed implants (15). Moreover, RSA can be used to measure inducible displacement (ID), defined as instantaneous, reversible (i.e. elastic) displacement of an implant due to the application of an external force (16). It was determined that ID is associated with progressive implant displacement over time and therefore has the potential to predict loosening based on a single measurement, providing an instant diagnosis or biomarker of loosening (17-19).

Over the past decades, several RSA studies investigated the feasibility of ID in clinical practice. Different approaches for inducing a displacement on a TKA have been performed: single-leg stance (18-28), step-up and step-down motion (29), lunging (19, 22, 28), or by applying a torque about the longitudinal axis of the tibia (18-23, 25, 27, 28). Despite of its strong potential, these studies did not result in a distinctive approach for ID. Hence, the diagnostic value of ID for aseptic loosening still has to be proven.

The current study aims to evaluate inducible displacement of a tibial knee component (i.e. tibial tray) in an *in vitro* simulation set-up. The goal of this sensitivity analysis is to identify the direction and the magnitude of force necessary to induce the largest displacement with the least possible force at the implant. To the best of our knowledge, this is the first study to perform *in vitro* experiments on cadaveric tibia bones implanted with a tibial tray surrounded by a surrogate fibrous tissue to mimic a loose implant. Forces of different magnitudes and in different directions were applied to the tibial tray and subsequent displacement of the tibial tray relative to the bone was measured, thereby anticipating the *in vivo* feasibility of ID.

METHODS

Phantom setup

For the test-objects, 8 (4 left and 4 right) tibiae were selected out of 18 formalin embalmed dissected human cadaveric tibiae. This selection was based on corresponding sizes of the tibia plateau suitable to accommodate the same implant size. The tibiae were obtained from 4 donors (1 female, 3 males) with a mean age of 81.5 years (SD 15.2). CT and DEXA scans were performed to respectively, exclude focal bone pathology and to determine bone mineral density (BMD). An experienced knee surgeon dissected soft tissue of the tibiae and subsequently implanted a tibial tray using standard surgical procedures including a tibial broach as prescribed by the manufacturer. In anticipation of the forthcoming surrogate fibrous tissue the tibial tray was not cemented. The NexGen Legacy Posterior Stabilized tibial tray size 6 (Zimmer Inc., Warsaw, IN, USA) was used. Subsequently, the tibiae were cut at the proximal diaphysis 11 cm distal from the tibia plateau and mounted in a standardized vertical position in a polyvinyl-chloride cylinder using epoxy (Figure 1). An adapter was constructed consisting of a stable base panel with a central canister to hold the different test-objects (Figure 2).

Figure 1. Front-top view of the test-object (polyvinyl-chloride cylinder filled with epoxy resin fixating a right-sided cadaveric tibiae including the tibial tray).

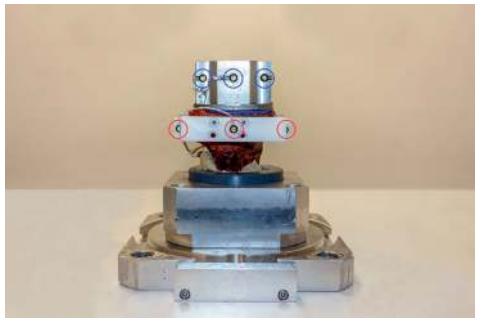


Figure 2. Front view of the adapter (base-panel and cannister) holding the test-object (polyvinyl-chloride cylinder with a right-sided cadaveric tibiae and tibial tray) and metal holder with infrared markers (blue circles) on top of the tibial tray and plastic holder with infrared markers (red circles) attached to the cadaveric tibia.

Measuring device

An Optotrak Certus (Northern Digital Inc., Waterloo, Canada) motion capture system was used to assess the induced displacements of the tibial tray relative to the bone with a resolution of 0.01 mm and an accuracy of 0.1 mm. 3 active infrared markers were placed on a metal holder which was rigidly attached to the upper surface of the tibial tray. 3 other markers were fixed in a plastic holder which was attached to the anterior surface of the cadaveric tibia using 2 screws (Figure 2). Both sets of markers formed a triangle-shaped rigid body around the tibial tray and the cadaveric tibia. While the load was held constant, the spatial position of all 6 markers was registered with a frequency of 100 Hz for 3 seconds.

Surrogate fibrous tissue layer

To mimic a loose implant, metal 3D printed replicas of the standard tibial broach, albeit 1 and 2 mm larger in every direction, were used to create space in between the keel of the tibial tray and the bone. This space was filled with silicone elastomers to resemble fibrous tissue. To find a silicone elastomer that has similar elasticity as human fibrous tissue, the mechanical properties of human fibrous tissue reported by Kraaij et al. were used as a guideline (11). A composite consisting of 90% relatively flexible silicone (*Dragon Skin FX-Pro, Smooth-On, Inc,* Mancungie, PA, USA) and 10% relatively stiff silicone (*Dragon Skin 20, Smooth-On, Inc,* Mancungie, PA, USA) was chosen as the most appropriate surrogate fibrous tissue (detailed description in Appendix A). This composite was cured in 3D printed molds based on the contours of the tibial base plate with an additional 1- and 2-mm interposition (Figure 3).

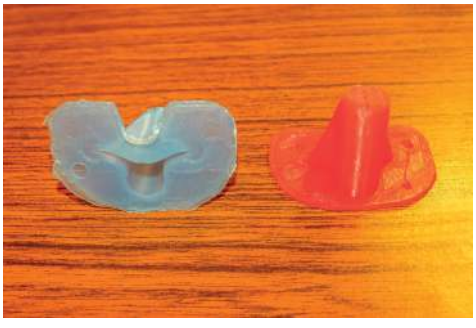


Figure 3. Surrogate fibrous tissue 1 mm (left) and 2 mm (right).

Loading experiments

The tibial tray was loaded in 2 configurations; vertical-loading and horizontal-loading. Vertical-loading was performed parallel to the anatomical axis using a tensile testing machine (LR5K Plus, Lloyd Instruments, Fareham Hants, UK) with a 5 kN S-type load cell (Sentronik, Miami, FL, USA). The tibial tray was loaded at a central and 2 eccentric positions (Figure 4). The sequence of vertical-loading positions was randomized and each load was gently built up to 800 N, representing a single leg stance of an approximately 80 kg weighting individual. Each loading cycle was

performed twice; the first cycle was a test run to make sure the implant and fibrous tissue were properly seated, and the second cycle was used to measure displacement. Horizontal-loading was performed perpendicular to the anatomical tibial axis and applied at the upper rim of the tibial tray at 7 different positions, representing a shear stress along the tibial tray (Figure 5). Direct anterior loading was not feasible as the markers were blocked in this position. To apply the horizontal-load, a circular track was milled into the base panel of the adapter in which a bar could freely rotate around the canister holding the test-object. In the bar a threaded loading pin was installed, which via a 1 kN S-type load cell (Sentronik, Miami, FL, USA) was connected to a handle. By manually turning the handle, the loading stick was driven forward on to the edge of the tibial tray, thereby applying a load in a horizontal direction. To make sure the horizontal-load was applied at identical angles among the test-objects, the tibial tray was pre-drilled with 7 conical dents in the desired angles to accommodate the sharp tip of the loading pin. The sequence of horizontal-loading positions was randomized and at each position sequential loads of 50, 100, 150 and 200 N were applied, and displacement was measured at each step. The measuring sequence was identical for all test-objects and began with vertical-loading and horizontal-loading with the 1-mm surrogate fibrous tissue and were subsequently repeated with the 2-mm surrogate fibrous tissue. After finishing the experiments with the surrogate fibrous tissue, for 2 of the test-objects, the implant was cemented using a vacuum mixed High-Fatigue bone cement (Zimmer Inc., Warsaw, IN, USA) and the vertical- and horizontal-loading cycles were repeated.

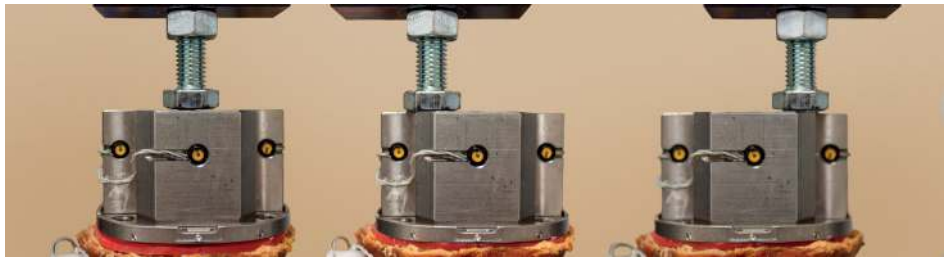


Figure 4. Front view of top-loading on a tensile testing machine via a central and 2 eccentric (medial/lateral) positions (bone/implant perspective).

Data processing

Both the tibial tray and the cadaveric tibia were equipped with 3 optical markers each describing a rigid body in space. 2 Cartesian coordinate systems were created, one for each rigid body, to describe the positions of the optical markers in space. The origin of both coordinate systems were the markers located on the lateral side of a left tibia and on the medial side of a right tibia (Figure 6). To describe the displacement between bone and implant, the coordinate system of the tibial tray was used as a reference as the positions of these markers were more consistent among the different test-objects compared to the markers on the bone. ID was described as orthogonal translations an rotations, relative to the unloaded baseline measurement performed at the start of

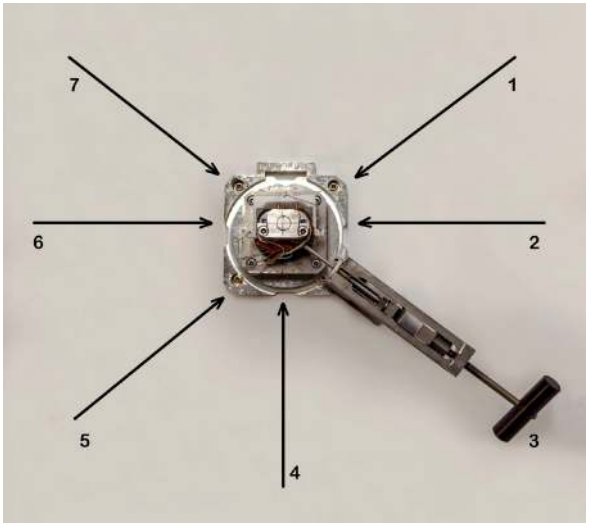


Figure 5. Top view of the side-loading set-up. The 7 loading directions are indicated by arrows (bone/implant perspective). Anterior loading was not feasible as the infrared markers were blocked.
Loading position 1 (45°): Anteromedial (left tibia) – Anterolateral (right tibia)
Loading position 2 (90°): Medial (left tibia) – Lateral (right tibia)
Loading position 3 (135°): Posteromedial (left tibia) - Posterolateral (right tibia)
Loading position 4 (180°): Posterior (left tibia) – Posterior (right tibia)
Loading position 5 (225°): Posterolateral (left tibia) – Posteromedial (right tibia)
Loading position 6 (270°): Lateral (left tibia) – Medial (right tibia)
Loading position 7 (315°): Anterolateral (left tibia) - Anteromedial (right tibia)

every loading cycle and were calculated according to the method of Söderkvist et al. (30). As for translations, a central point C_T was virtually created on the tibial tray to correct for the location of the implant's markers 27 mm above the tibial tray (Figure 6). Rotations were described as Euler angles derived from the rotation matrix in the order of x-rotation first, then y'-rotation and finally z'-rotation. The norm of the translation and rotation vectors were subsequently calculated using the Pythagorean theorem. The application of this theorem is valid for any 3D translations, but only for rotations of small magnitude, which is the case in this study (14).

Data analysis

ID for each test-object was described as 3D-translations (mm) and rotations (°). Subsequently, the mean and standard deviation of all test-objects was calculated for each loading position and magnitude of force applied at the implant, as well as for each surrogate fibrous tissue later thickness. The most optimal loading position was defined as the combination of large displacement (i.e. high mean) in combination with high reproducibility (i.e. small SD). To find the optimal loading position each loading position with magnitude were given a rank; rank 1 was given to highest displacement and to the smallest SD. Subsequently, the optimal loading position and magnitude was determined, based on the highest ranks (detailed calculation in Appendix B).

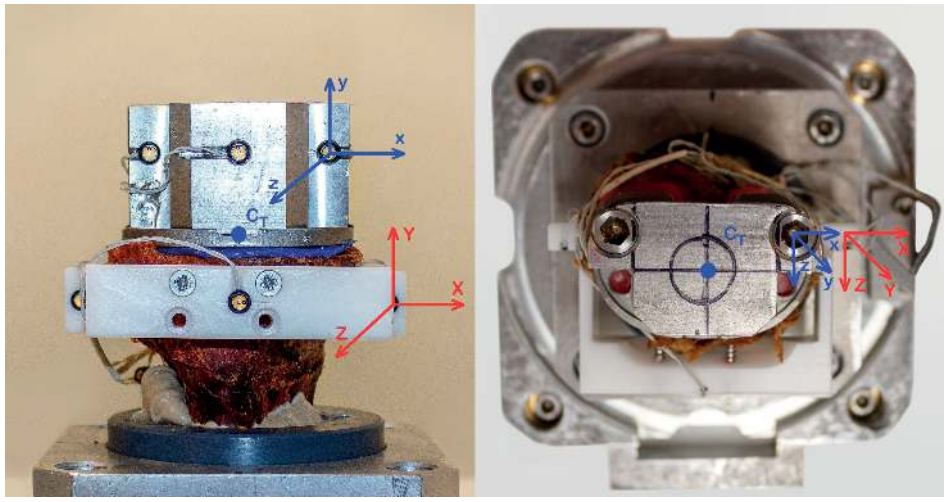


Figure 6. Coordinate systems for the implant (blue) and for the bone (red) and position of the central point (C_T).

RESULTS

Vertical-loading

Translation ranged from 0.8 to 1 mm for the 1-mm fibrous tissue layer and from 1.4 to 1.6 mm for the 2-mm fibrous tissue layer, showing the largest translation in the central position, and the smallest SD in the central and lateral position (Figure 7). Rotation ranged from 0.4 to 1.1° for the 1-mm fibrous tissue layer and from 0.6 to 1.8° for the 2-mm fibrous tissue layer, showing the largest rotation in the lateral position, and the smallest SD in the central and medial position (Figure 7). Translation and rotation for the cemented implants was almost zero, with equally low standard deviations (Figure 7). The central loading position shows the best (i.e. highest) rank for combined fibrous tissue layer thickness and displacement, hence is the preferred position for loading a clinical situation (Table 1).

Position	1-mm Fibrous tissue layer				2-mm Fibrous tissue layer				Combined	
	TRANSLATION — mm		ROTATION — degrees		TRANSLATION — mm		ROTATION — degrees			
	Mean (SD)	Rank*	Mean (SD)	Rank*	Mean (SD)	Rank*	Mean (SD)	Rank*	Rank**	Place
Central	1.0 (0.1)	1 + 1 = 2	0.8 (0.3)	2 + 1 = 3	1.6 (0.4)	1 + 3 = 4	1.1 (0.3)	2 + 1 = 3	12	1
Medial	1.0 (0.6)	1 + 3 = 4	0.4 (0.4)	3 + 2 = 5	1.5 (0.3)	2 + 2 = 4	0.6 (0.3)	3 + 1 = 4	17	3
Lateral	0.8 (0.4)	2 + 2 = 4	1.1 (0.6)	1 + 3 = 4	1.4 (0.2)	3 + 1 = 4	1.8 (0.6)	1 + 3 = 4	16	2

Table 1. Top-loading displacement and ranking with a load of 800 N.

* Rank is calculated by summing the mean rank and standard deviation (SD) rank.

** Rank is calculated by summing the 4 ranks of the translations and rotations of the two fibrous tissue layers. A high mean (i.e. large displacement) and a small SD (i.e. high reproducibility) leads to a high rank.

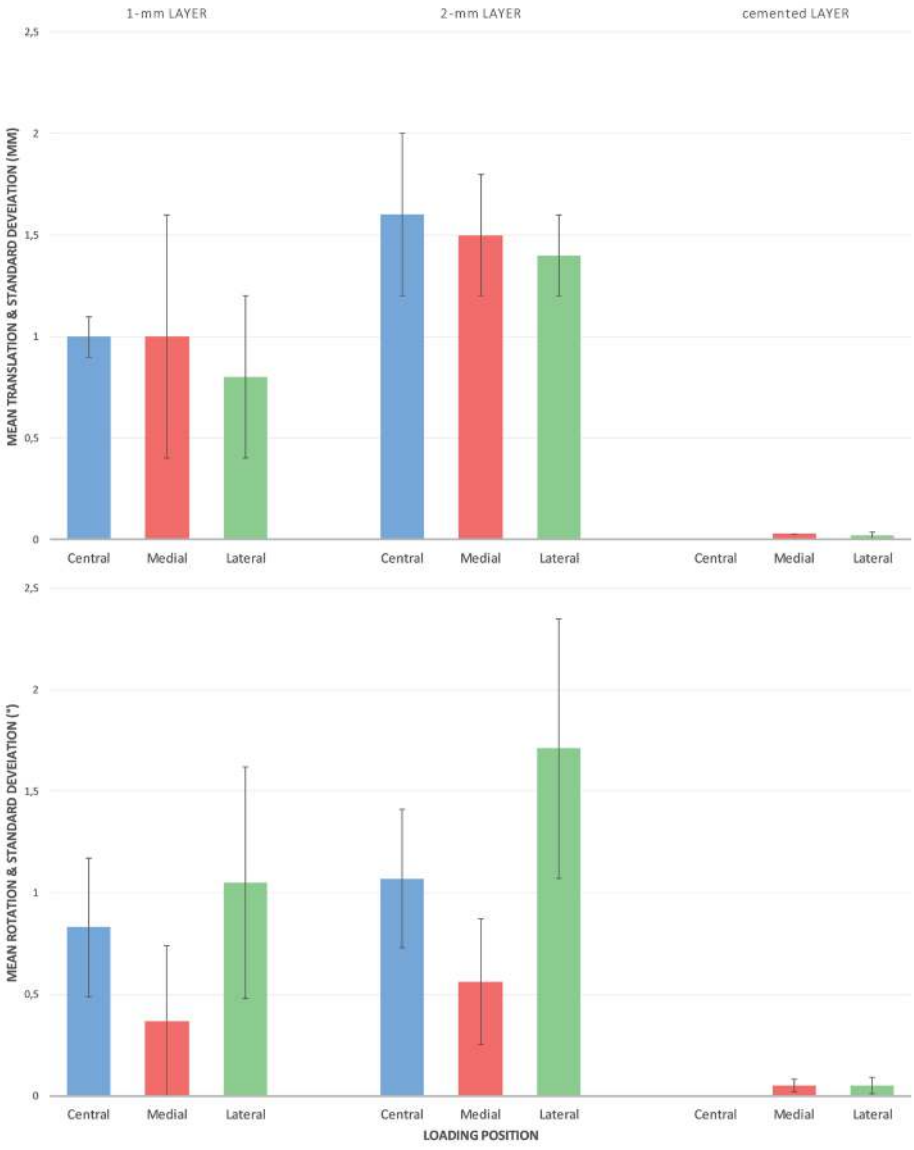


Figure 7. Bar charts showing top-loading mean translation [UPPER FIGURE] and mean rotation [LOWER FIGURE], including standard deviation (SD) per loading position (central, medial and lateral) and per fixation method (1- & 2-mm fibrous tissue and cement).

Horizontal-loading

Translation ranged from 1.4 to 3.7 mm for the 1-mm fibrous tissue layer and from 1.4 to 4.4 mm for the 2-mm fibrous tissue layer, showing the largest translation in the medial and lateral position, and the smallest SD in the posteromedial position (Figure 8). Rotation ranged from 0.7 to 1.9° for the 1-mm fibrous tissue layer and from 0.9 to 2.1° for the 2-mm fibrous tissue layer, showing the

largest rotation in the medial and the posterolateral position, and the smallest SD in the lateral position (Figure 9). To some extent, in all positions, the implant was pushed out of the tibia with higher loads. This was most noticeable in the posterior position above 100N and therefore these measurements were omitted. Translation and rotation for the cemented implants was almost zero, with equally low standard deviations. The lateral and medial positions at 200 N show the best (i.e. highest) rank for combined fibrous tissue layer thickness and displacement, hence is the preferred position for loading a clinical situation (Table 2).

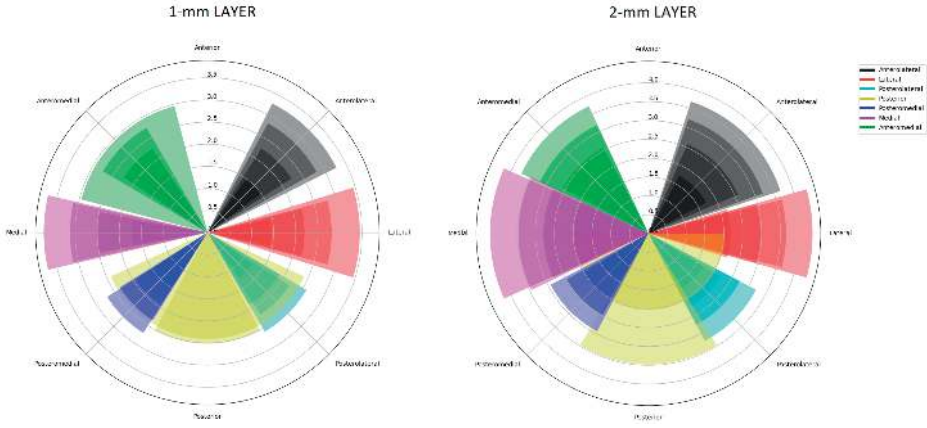


Figure 8. Polar bar charts showing the mean translation and standard deviation per loading position (spokes) for the 1-mm [LEFT FIGURE] and 2-mm [RIGHT FIGURE] fibrous tissue. Each spoke consists of bars representing increasing loads with decreasing color saturation (i.e. 50-100-150-200N). Length of each bar represents the translation (mm) and width the standard deviation per load (i.e. 50-100-150-200N).

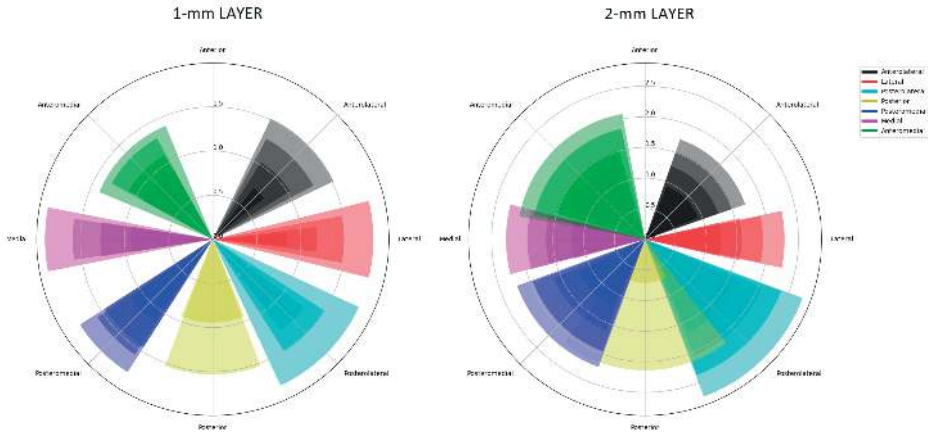


Figure 9. Polar bar charts showing the mean rotation and standard deviation per loading position (spokes) for the 1-mm [LEFT FIGURE] and 2-mm [RIGHT FIGURE] fibrous tissue. Each spoke consists of bars representing increasing loads with decreasing color saturation (i.e. 50-100-150-200N). Length of each bar represents the rotation (°) and width the standard deviation per load (i.e. 50-100-150-200N).

Position	FORCE — N	1-mm Fibrous tissue layer				2-mm Fibrous tissue layer				Combined	
		TRANSLATION — mm		ROTATION — degrees		TRANSLATION — mm		ROTATION — degrees			
		Mean (SD)	Rank*	Mean (SD)	Rank*	Mean (SD)	Rank*	Mean (SD)	Rank*	Rank**	Place
Anterolateral	50	1.5 (0.3)	24 + 2 = 26	0.7 (0.2)	26 + 2 = 28	1.7 (0.6)	24 + 10 = 34	0.9 (0.8)	25 + 13 = 38	126	19
	100	2.3 (0.4)	16 + 11 = 27	1.0 (0.5)	20 + 16 = 36	2.6 (0.8)	15 + 18 = 33	1.3 (0.9)	21 + 19 = 40	136	24
	150	2.8 (0.6)	6 + 21 = 27	1.3 (0.6)	14 + 21 = 35	3.2 (0.9)	9 + 22 = 31	1.5 (0.9)	19 + 21 = 40	133	23
	200	3.3 (0.6)	3 + 23 = 26	1.5 (0.7)	8 + 22 = 30	3.7 (0.9)	4 + 24 = 28	1.7 (0.9)	13 + 20 = 33	117	16
Lateral	50	1.4 (0.4)	25 + 8 = 33	0.8 (0.2)	25 + 1 = 26	2.2 (0.6)	19 + 11 = 30	1.2 (0.4)	22 + 4 = 26	115	14
	100	2.2 (0.5)	18 + 16 = 34	1.2 (0.2)	17 + 3 = 20	3.0 (0.5)	11 + 6 = 17	1.6 (0.4)	17 + 3 = 20	91	6
	150	2.8 (0.5)	7 + 18 = 25	1.5 (0.4)	10 + 10 = 20	3.6 (0.5)	5 + 5 = 10	1.9 (0.4)	10 + 1 = 11	66	3
	200	3.5 (0.6)	2 + 22 = 24	1.8 (0.5)	3 + 17 = 20	4.4 (0.5)	1 + 7 = 8	2.3 (0.4)	3 + 2 = 5	57	1
Posterolateral	50	1.3 (0.3)	26 + 3 = 29	1.0 (0.3)	21 + 4 = 25	1.7 (0.5)	25 + 2 = 27	1.7 (0.7)	14 + 10 = 24	105	13
	100	1.9 (0.5)	20 + 20 = 40	1.3 (0.3)	15 + 5 = 20	2.2 (0.5)	18 + 4 = 22	2.1 (0.8)	8 + 12 = 20	102	12
	150	2.2 (0.4)	17 + 10 = 27	1.5 (0.4)	9 + 15 = 24	2.7 (0.6)	14 + 15 = 29	2.4 (0.8)	2 + 15 = 17	97	10
	200	2.6 (0.5)	10 + 19 = 29	1.8 (0.7)	2 + 23 = 25	3.2 (0.6)	8 + 13 = 21	2.7 (0.9)	1 + 17 = 18	93	7
Posterior	50	2.5 (1.0)	11 + 24 = 35	1.5 (0.7)	7 + 24 = 31	3.5 (1.1)	6 + 25 = 31	2.1 (1.3)	6 + 26 = 32	129	22
	100	2.4 (2.3)	13 + 26 = 39	0.9 (0.8)	22 + 25 = 47	2.0 (3.1)	20 + 26 = 46	0.7 (1.0)	26 + 23 = 49	181	26
Posteromedial	50	1.5 (0.4)	23 + 5 = 28	1.1 (0.3)	18 + 9 = 27	1.4 (0.5)	26 + 3 = 29	1.2 (0.6)	23 + 9 = 32	116	15
	100	1.9 (0.4)	19 + 9 = 28	1.5 (0.4)	11 + 14 = 25	2.0 (0.5)	21 + 1 = 22	1.6 (0.8)	15 + 11 = 26	101	11
	150	2.3 (0.5)	14 + 14 = 28	1.6 (0.4)	6 + 11 = 17	2.5 (0.5)	17 + 8 = 25	2.0 (0.8)	9 + 16 = 25	95	9
	200	2.7 (0.4)	9 + 12 = 21	1.8 (0.4)	4 + 13 = 17	2.9 (0.6)	12 + 14 = 26	2.2 (0.9)	5 + 18 = 23	87	5

Table 2. Side-loading displacement and ranking with an increasing load of 50-100-150-200 N.

* Rank is calculated by summing the mean rank and standard deviation (SD) rank.

** Rank is calculated by summing the 4 ranks of the translations and rotations of the 2 fibrous tissue layers.

A high mean (i.e. large displacement) and a small SD (i.e. high reproducibility) leads to a high rank.

Position	FORCE — N	1-mm Fibrous tissue layer				2-mm Fibrous tissue layer				Combined	
		TRANSLATION — mm		ROTATION — degrees		TRANSLATION — mm		ROTATION — degrees			
		Mean (SD)	Rank*	Mean (SD)	Rank*	Mean (SD)	Rank*	Mean (SD)	Rank*	Rank**	Place
Medial	50	1.7 (0.3)	21 + 1 = 22	0.9 (0.3)	23 + 8 = 31	2.0 (0.9)	22 + 21 = 43	1.2 (0.5)	24 + 8 = 32	128	21
	100	2.5 (0.4)	12 + 4 = 16	1.3 (0.3)	16 + 7 = 23	2.8 (0.9)	13 + 20 = 33	1.6 (0.5)	16 + 5 = 21	93	7
	150	3.1 (0.4)	4 + 13 = 17	1.6 (0.3)	5 + 6 = 11	3.5 (0.9)	7 + 23 = 30	1.9 (0.5)	11 + 7 = 18	76	4
	200	3.7 (0.5)	1 + 15 = 16	1.9 (0.4)	1 + 12 = 13	4.2 (0.8)	2 + 19 = 21	2.3 (0.5)	4 + 6 = 10	60	2
Anteromedial	50	1.6 (0.4)	22 + 6 = 28	0.9 (0.5)	24 + 19 = 43	1.8 (0.6)	23 + 9 = 32	1.3 (0.8)	20 + 14 = 34	137	25
	100	2.3 (0.4)	15 + 7 = 22	1.1 (0.5)	19 + 18 = 37	2.6 (0.6)	16 + 12 = 28	1.5 (1.0)	18 + 22 = 40	127	20
	150	2.7 (0.5)	8 + 17 = 25	1.3 (0.6)	13 + 20 = 33	3.2 (0.7)	10 + 16 = 26	1.8 (1.1)	12 + 24 = 36	120	17
	200	3.0 (1.1)	5 + 25 = 30	1.4 (0.8)	12 + 26 = 38	3.7 (0.7)	3 + 17 = 20	2.1 (1.2)	7 + 25 = 32	120	17

Table 2 (continued). Side-loading displacement and ranking with an increasing load of 50-100-150-200 N.

* Rank is calculated by summing the mean rank and standard deviation (SD) rank.

** Rank is calculated by summing the 4 ranks of the translations and rotations of the 2 fibrous tissue layers.

A high mean (i.e. large displacement) and a small SD (i.e. high reproducibility) leads to a high rank.

DISCUSSION

This *in vitro* work aimed at identifying the optimal direction and magnitude of load transfer to a tibial tray of a TKA to induce a detectable and reproducible displacement. We conducted extensive experiments using 8 cadaveric tibiae implanted with a tibial tray and with a surrogate fibrous tissue to simulate loosening. A silicone elastomer was composed with comparable loading characteristics as human fibrous tissue. All specimens were loaded parallel to the anatomical axis of the tibia (vertical-loading) at 800 N, and perpendicular to the anatomical axis (horizontal-loading) at 4 magnitudes (50-100-150-200 N). To the best of our knowledge, this is the first study to perform an *in vitro* study on ID.

Vertical-loading in the centerline of the anatomical axis of the tibia and horizontal-loading on the medial and lateral side of the tibial tray produced the largest displacements with the highest reproducibility. *In vivo,* the former corresponds to a single leg stance or a step-up/step-down movement, and the latter to a shear stress along the tibial tray. Torsion loading about the anatomical axis of the tibia was not analyzed in our study.

In theory, ID can take place within the implant itself (i.e. implant elasticity), as movement between or deformation within the fixation interface (implant-bone, implant-cement, cement-bone), or as an elastic deformation within the bone (31). In our study, ID increased with increasing layer thickness hence supporting the assumption that the fibrous tissue was dominantly responsible for the observed displacement. This finding is supported by several other studies also suggesting ID mainly occurs in the fixation interface (20, 25, 29, 32) and contradicts the findings of Ryd et al. and Toksvig-Larsen et al. suggesting that ID is related to elasticity of the implant and the surrounding bone (19, 33).

Furthermore, there was a clear difference in ID between a cemented tibial tray (i.e. fixed implant) and a tibial tray surrounded by fibrous tissue (i.e. loose implant) in our study. The displacement of the cemented tibial trays did not exceed 0.1 mm with vertical loading at 800 N, indicating that ID greater than 0.1 mm is suggestive of loosening in our test set-up. *In vivo* studies of ID in stable (i.e. non progressive migration over time) TKA components ranged from 0 to 0.9 mm. (18-25, 27-29, 34). However, several studies have reported ID in TKAs regarded as stable implants, that were higher than 0.9 mm. Ryd et al. reported displacement in a case up to 1.7 mm (33), Albrektsson et al. reported cases up to 2.1 and 5 mm displacement, with the latter value regarded as being nonrepresentative by the authors (27) and, Lam Tin Cheung et al. reported a case with 1.84 mm displacement, albeit with radiolucencies visible on conventional radiographs, but without continuous migration over time (25).

Unfortunately, there are no studies available reporting ID of implants proven to be loose. However, there are several studies available measuring ID in implants showing signs of imminent loosening (e.g. progressive migration and radiolucent lines around the implant). Implants showing relatively larger migration during follow-up, showed higher ID in comparison to implants showing less migration over time (20, 23, 34, 35). Lam Tin Cheung et al. performed ID after 10-years of

follow-up and found a higher mean MTPM (1.35 mm, SD 0.38) in implants showing radiolucent lines compared to implants without radiolucent lines (0.68 mm, SD 0.36).

In our study we found the largest displacement with shear loading conditions (horizontal-loading). However, this is partially related to the experimental setup in which the tibial tray was pushed out of the tibia with increasing force. In comparison to a clinical setting, a shear force is often accompanied by an axial (inward directed) pressure (e.g. femur condyles, ligaments), which were not replicated in our study. Therefore, the absolute values of displacement in our study cannot be compared to clinical studies of ID, moreover, it is difficult to translate a direct horizontal load onto the implant to a clinically applicable load. However, shear stress as induced in our experiments might to some extent be generated through external torsion loading. *In vivo* studies typically show the largest displacement with torsion loading (18-23, 27). As such, torsion loading might be the most promising field of research for ID.

This study has several limitations. Firstly, the *in vitro* character of this studies does not resemble the interplay of forces in an *in vivo* knee. Hence, our experiments are a simplification of actual biomechanics and should be regarded as such. Secondly, *in vivo* it is unlikely that fibrous tissue will homogenously cover the implant as was the case in our study. Hence, our magnitudes of displacement might be an overestimation, as *in vivo* there will be anytime areas of solid fixation next to areas of fibrous tissue. Thirdly, we only accounted for elastic deformation of the fibrous tissue whereas actual fibrous tissue likely will show also plastic deformation, which might alter the reproducibility of ID.

In conclusion, ID has the potential to assess implant stability. However, more research is necessary to investigate the nature of measured displacement when applying a load, determine the best clinical application to induce a displacement on an implant and, ultimately define a threshold for acceptable ID. The next step in this research would be the design of a loading device for clinical use, as we would like to use ID for early diagnosis of loosening.

APPENDIX A: SURROGATE FIBROUS TISSUE

The material serving as a surrogate fibrous tissue had to fulfil requirements regarding the mechanical properties, i.e. being similar to human fibrous tissue. Silicone elastomers were chosen as the material of choice due to the easy handling and molding characteristics. Furthermore, Waide et al. identified a silicone elastomer resembling the mechanical properties of canine fibrous tissue (36). The experiments conducted by Kraaij et al. served as a guideline for finding a silicone elastomer with comparable mechanical properties as human fibrous tissue (11). Silicone elastomers were obtained from 2 manufactures and were tested in the same manner as Kraaij's tests on human tissue (Appendix Table 1).

Name	MANUFACTURER	STRETCH	VISCOSITY	HARDNESS	TEAR STRENGTH
		%	Centipoise (CPS)	Shore A	Pounds per sq. inch (PSI)
Dragon Skin 10	A	1	23000	10	475
Dragon Skin 20	A	620	20000	20	550
Dragon Skin 30	A	364	30000	30	500
Dragon Skin FX-Pro	A	763	18000	2	288
Ecoflex 5	A	1	13000	5	350
Mold Max 20	A	512	20000	20	555
Mold Max 30	A	300	25000	30	577
Mold Max 40	A	250	45000	40	550
Sylgard® 184	B	n.s.	3500	43	980
Sylgard® 186	B	225	66700	24	305
Silastic® MDX4-4210	B	470	110000	30	730
Smooth-Sil 950	A	320	35000	50	725
SORTA-Clear 40	A	400	35000	40	800

Appendix Table 1. Characteristics of tested silicone elastomers.
A = *Smooth-On Inc.,* Mancungie, PA, USA
B = *Dow Corning Corp.*, Midland, MI, USA

A tensile test machine, type *LR5K*, and the data analysis software *NEXYGENPlus* (both: *Lloyd Instruments*, Fareham Hants, UK) were used to perform the compression tests. The load cell used was a 1 kN S-type (Sentronik, Miami, FL, USA). The compression tests were performed with a speed of 0.1mm/min until a load of 10 N was reached. By exporting the experimental data of load and corresponding extension over time, $F(t)$ and $E(t)$, stress-strain curves were generated. First, the sample thickness h was determined, using the starting height of the anvil, h_a, and E at a threshold load of F_{th}. F_{th} was chosen to be 0.1 N, based on Kraaij's assumption that at this load, the anvil touches the sample. Thus, the sample's thickness is:

$h = h_a - E\ (F_{th})$

To determine the strain over time, $\varepsilon(t)$, first the change of the sample thickness has to be computed:

$\Delta h = E(t) - h$

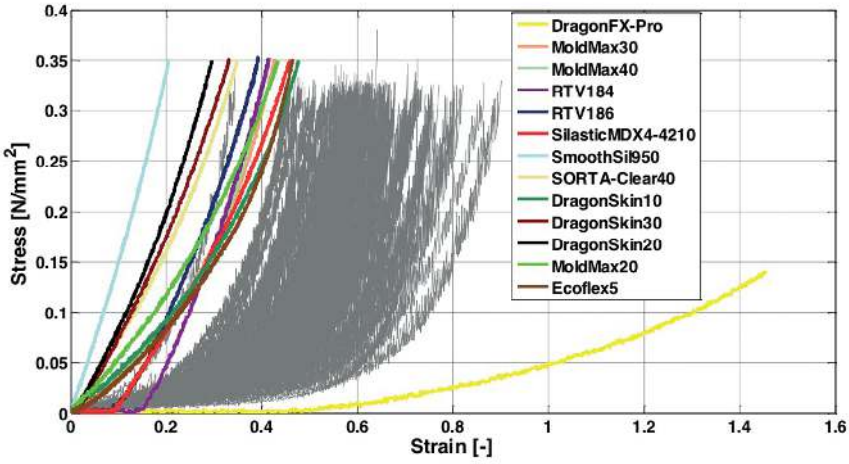
$\varepsilon(t) = \frac{\Delta h}{h}$

To find the corresponding stress, $\sigma(t)$, the sample's surface was calculated using the sample's radius:

$A = \varpi \cdot r^2$

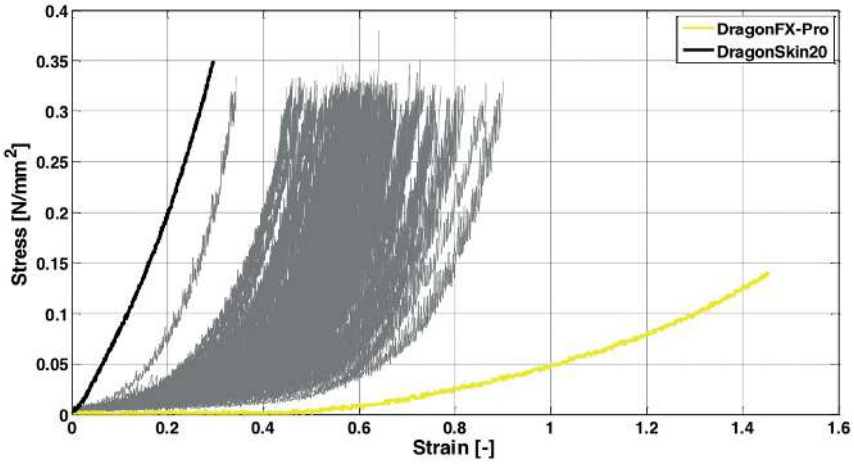
$\sigma(t) = \frac{F(t)}{A}$

Subsequently, the stress-strain curves were generated by plotting $\sigma(t)$ against $\varepsilon(t)$ (Appendix Figure 1).



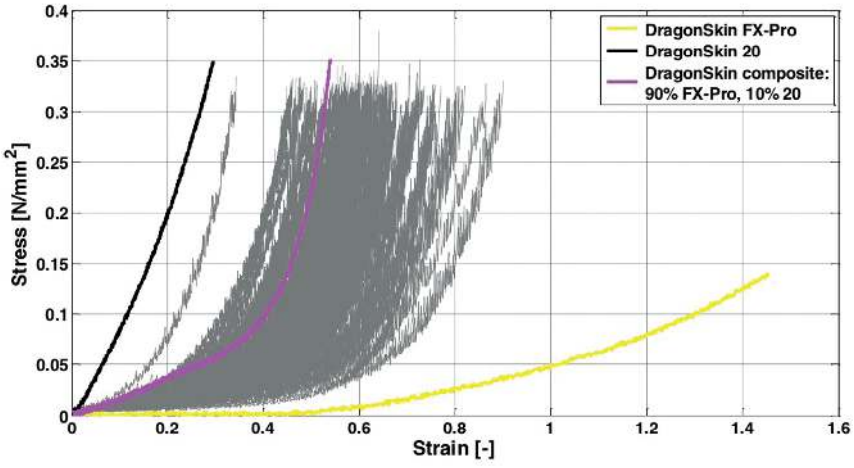
Appendix Figure 1. Line graph showing stress-strain curves of human fibrous tissue (grey) and for 13 silicone elastomers listed in Appendix A Table 1.

Human tissue's behavior is bifold: flexible below a stress of 0.01 N/mm^2 and stiff with higher stress. As the tested silicone elastomers behavior is more or less linear, none of tested silicone elastomers approximated the human tissue's curves sufficiently. Therefore, 2 materials had to be combined in order to achieve a better approximation of the human tissue's mechanical behavior. To choose the most promising combination, the E-modules of the different samples were analyzed. For that, 2 linear fittings were created for each samples' curve: one for the area of a stress below 0.01 N/mm^2 and one for the area above that threshold. The same was done for the human tissue using the average of all curves. *Dragon Skin FX-Pro (Smooth-On, Inc,* Mancungie, PA, USA*)* showed the best fit for stress below 0.01 N/mm^2 and for higher stress all other samples showed equal fit. Hence, the second material was chosen based on its working time in order to ensure a successful mixing procedure. *Dragon Skin 20 (Smooth-On, Inc,* Mancungie, PA, USA*)* with a curing time of 25 minutes was the most compatible option in comparison with a curing time of 12 minutes of *Dragon Skin FX* (Appendix Figure 2).



Appendix Figure 2. Line graph showing stress-strain curves of human fibrous tissue (grey) and the 2 silicone elastomers chosen to be combined in order to find a proper surrogate fibrous tissue.

The 2 chosen materials were mixed in following proportions (*Dragon Skin FX-Pro* : *Dragon Skin 20*): 10% : 90%, 20% : 80%, 40% : 60%, 50% : 50%, 60% : 40%, 80% : 20%, and 90% : 10%. Both materials were prepared according to the manufacturer's instructions, mixed in corresponding proportion – measured by weight – and filled into a mold holding up to twelve probes of a diameter of 40 mm. After complete curing, all the probes were tested and the probe consisting of 90 % *Dragon Skin FX-Pro* and 10 % *Dragon Skin 20* provided the most satisfactory result (Appendix Figure 3).



Appendix Figure 3. Line graph showing stress-strain curves of human fibrous tissue (grey) and the 2 silicone elastomers chosen to be combined (yellow & black) to create the proper surrogate fibrous tissue (purple).

APPENDIX B: DATA ANALYSIS

Displacement was described as orthogonal translations and rotations, relative to the unloaded baseline measurement performed at the start of every loading cycle. For an example of displacement in horizontal-loading of one test-object with a 1-mm fibrous tissue layer see Appendix Table 2.

Position	FORCE — N	TRANSLATION — mm			ROTATION — degrees		
		x	y	z	α	β	γ
Anterolateral	50	0.8	0.1	0.9	-1	-0.9	0.1
	100	1.2	0.1	1.3	-1.4	-1.3	0.1
	150	1.4	0.2	1.6	-1.6	-1.6	0.2
	200	1.6	0.2	1.9	-1.8	-1.7	0.2
Lateral	50	0.7	-0.2	0.1	-0.6	-0.6	-0.1
	100	1.6	-0.3	0.1	-0.8	-1.1	-0.1
	150	2.2	-0.3	0	-0.9	-1.5	0
	200	2.7	-0.2	-0.1	-1	-1.8	0.1
Posterolateral	50	0.2	-0.1	-1.1	-0.8	-0.7	-0.8
	100	0.4	-0.3	-1.6	-0.9	-0.9	-1
	150	0.6	-0.4	-1.9	-1	-1.1	-1.2
	200	0.7	-0.6	-2.3	-1.2	-1.3	-1.4
Posterior	50	0.4	0.1	-1.4	0.6	0.2	-0.1
	100	-0.5	0.8	-3.5	-0.4	-0.7	-1.4
Posteromedial	50	-1.4	0	-0.9	0.9	1	-0.2
	100	-1.6	-0.1	-1.2	1	1.1	-0.3
	150	-1.7	-0.1	-1.5	1	1.1	-0.5
	200	-1.9	-0.2	-1.7	1	1.1	-0.6
Medial	50	-2	-0.1	0.1	-0.2	0.5	-0.5
	100	-2.5	-0.1	0.1	-0.3	0.5	-0.7
	150	-3	0	0.1	-0.4	0.6	-0.8
	200	-3.4	0.1	0.1	-0.4	0.7	-0.9
Anteromedial	50	-1.1	0	0.6	0.3	0.6	0.1
	100	-1.3	-0.1	0.9	0.2	0.6	0
	150	-1.7	-0.1	1.1	0.3	0.8	0
	200	-2	-0.1	1.4	0.1	0.7	0

Appendix Table 2. Example of displacement of the tibial tray of one test-object (left tibia) with translation described in 3 axes, and rotation described in 3 Euler angles.

For each test-object combined with either a 1-mm of 2-mm surrogate fibrous tissue layer the loading cycles resulted for vertical-loading in 3 displacements (3 loading positions * 1 load), and for horizontal-loading in 28 displacements (7 loading positions * 4 loads [i.e. 50-100-150-200N]). For each displacement the mean and corresponding standard deviation (SD) of the test-objects

combined were calculated. The 28 displacements generated via horizontal-loading were reduced to 26 feasible displacements as during the horizontal-loading via position 1 the tibial tray was pushed out of the tibia with higher loads. Thus, resulting in 3 displacements for vertical-loading and 26 displacements for horizontal-loading, with each displacement expressed as a translation and rotation. The most optimal loading positions was defined as creating the largest displacement (i.e. highest mean) with the highest reproducibility (i.e. smallest SD). Therefore, the 3 displacements for vertical-loading and the 26 displacements for horizontal-loading where ranked per surrogate fibrous tissue layer. For an example of ranking of rotation during horizontal-loading see Appendix Table 3.

Position	FORCE — N	1-mm Fibrous tissue layer				2-mm Fibrous tissue layer			
		Mean	Rank*	SD	Rank*	Mean	Rank*	SD	Rank*
Anterolateral	50	1.3	14	1	22	1.1	18	0,6	18
	100	1.8	9	1.2	24	1.5	10	1	23
	150	2.1	6	1.2	26	1.9	7	1,2	24
	200	2.4	5	1.2	25	2.3	4	1,4	26
Lateral	50	1.4	13	0.7	13	1.3	14	0,3	1
	100	1.7	10	0.7	15	1.9	8	0.3	2
	150	2.1	7	0.7	16	2.4	3	0.3	3
	200	2.4	4	0.8	17	3	1	0.4	6
Posterolateral	50	2	8	0.8	18	1.4	12	0.5	11
	100	2.5	3	0.9	19	1.9	9	0.6	13
	150	2.9	2	0.9	21	2.2	6	0.7	20
	200	3.3	1	1	23	2.6	2	0.9	22
Posterior	50	1.4	11	0.7	14	2.2	5	1.2	25
	100	1	19	0.9	20	0.6	26	0.9	21
Posteromedial	50	0.8	26	0.4	8	0.8	22	0.5	9
	100	0.9	22	0.5	10	1.1	17	0.6	12
	150	1	18	0.5	11	1.3	15	0.6	16
	200	1.1	16	0.5	12	1.5	11	0.6	19
Medial	50	0.9	23	0.3	1	0.7	25	0.4	5
	100	1.1	17	0.3	2	1	20	0.4	4
	150	1.2	15	0.3	3	1.2	16	0.4	7
	200	1.4	12	0.4	4	1.4	13	0.4	8
Anteromedial	50	0.8	25	0.4	9	0.7	24	0.6	17
	100	0.8	24	0.4	7	0.8	23	0.6	15
	150	1	21	0.4	5	0.9	21	0.5	10
	200	1	20	0.4	6	1	19	0.6	14

Appendix Table 3. Mean displacement (rotation in degrees) and standard deviation (SD) during horizontal-loading with corresponding rank in a (left tibia).

* A high mean (i.e. large displacement) and a small SD (i.e. high reproducibility) leads to a high rank.

To find the most optimal loading position independent of surrogate fibrous tissue layer thickness, mean and SD where combined in the following equation:

$$R_t = \frac{Rt_1(s) + Rt_1(sd) + Rr_1(s) + Rr_1(sd) + Rt_2(s) + Rt_2(sd) + Rr_2(s) + Rr_2(st)}{8}$$

R_t = Total rank per loading and magnitude combination
Rt_1 = Translation rank for 1-mm fibrous tissue layer
Rr_1 = Rotation rank for 1-mm fibrous tissue layer
Rt_2= Translation rank for 2-mm fibrous tissue layer
Rr_2= Translation rank for 2-mm fibrous tissue layer
S = mean
SD = standard deviation
With mean and standard deviation same weight factor (i.e. equally important)

The loading position resulting in the lowest R corresponds to the most optimal loading position. If 2 loading positions are equivalent in their results in this regard, the one with the lower force magnitude is to be preferred, based on means of clinical feasibility.

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9

Summary and general discussion

Improving implant longevity is an eminent challenge in joint replacement surgery with aseptic loosening as the major reason for early failure necessitating revision surgery in both total hip and total knee arthroplasty (THA and TKA) (1-4). Analysis of implant fixation by measuring migration with roentgen stereophotogrammetric analysis (RSA) has shown that the loosening process starts at very early onset after implantation (5, 6). Implants showing relative high migration during the first post-operative year are prone to failure and subsequent revision later on (7-13). However, it is still not crystallized how specific implant characteristics, the surgical procedure, or even medication affect the implant migration pattern and what degree of initial migration is acceptable without jeopardizing longevity of implant fixation at 10-20 years.

In this thesis the migration pattern in relation to longevity of both cemented and cementless stems in THA, the influence of mobile-bearings in TKA on migration and survival, and methods to instantly evaluate implant fixation by inducible displacement have been studied.

OVERVIEW MAIN FINDINGS

Migration of cementless femoral stems in total hip arthroplasty

The long-term migration pattern of a cementless femoral stem in THA with different bioactive coatings is described in chapter 2. A tapered, conical stem (Mallory-Head Porous) was evaluated with on the porous-coated proximal third of the stem either a hydroxyapatite, fluorapatite, or no additional coating plasma-sprayed. The stem is designed to achieve fixation at the metaphyseal-diaphyseal junction via its canal filling round cross-sectional geometry and additional flanges. All stems showed rapid initial migration with up to 0.6 mm (median 0.2 mm) subsidence and rotated up to 3.2° (median 0.9° retroversion) in the first postoperative year. After the first postoperative year, the migration rate stabilized reaching a plateau phase that endured for a maximum of 25 years follow-up. However, there was 1 stem showing progressive subsidence up to 1.5 mm during follow-up resulting in radiolucencies and pedestal formation on the conventional radiograph, but without debilitating symptoms in a sedentary patient. This stem was not revised and the postoperative radiograph showed undersizing as possible explanation of the gross migration. Overall, the addition of a bioactive coating did not result in better fixation (i.e. less migration). Furthermore, the rate of initial migration was not related to radiolucencies appearing later on.

The migration of the same stem (Mallory-Head Porous) was compared to a shorter, flat wedged stem (Taperloc) in chapter 3. The Taperloc stem has a rectangular cross-sectional geometry designed to engage medial to lateral in the metaphysis (14). This is in contrast to the longer, conical Mallory-Head Porous stem providing canal-filling fixation at the metaphyseal-diaphyseal junction (14). After 12 months the Taperloc stem had subsided up to 6.8 mm (median 0.3 mm), compared to a maximum of 4.8 mm (median 0.3 mm) subsidence for the Mallory-Head Porous stem. The Taperloc stem rotated up to 3.6° (median 0.5° retroversion), compared to a maximum of 3.6° (median 0.8° retroversion) rotation for the Mallory-Head Porous stem. After this high

initial migration during the first postoperative year both stems reached a plateau phase without outliers showing progressive migration. No stem was revised for aseptic loosening. However, 1 Taperloc and 1 Mallory-Head Porous stem developed radiolucent lines as shown on conventional radiographs. These stems did reach a plateau phase of migration, but both stems showed high initial migration. Although statistically comparable over a period of 5 years, the Taperloc stem subsided more during the first year and the Mallory-Head Porous stem had rotated more after 5 years of follow-up. This observation is in agreement with the design rationale of both stems; the Taperloc stem provides better rotational stability in comparison to the Mallory-Head Porous stem.

The adage of early migration leading to late aseptic loosening could not be confirmed for the cementless stems described in chapter 2 and 3 (8, 9). However, reaching a plateau phase of stable migration seems to be paramount for stem longevity. The level at which the plateau phase is reached corresponds to the degree of early migration and seems unrelated to stem survival. Nonetheless, stems showing high initial migration, and thus a high-level plateau phase, showed more frequently signs of loosening on conventional radiographs, albeit without clinical signs of loosening.

Due to high variation in the initial migration of cementless stems without failures, no threshold values could be established for acceptable early migration (chapter 2 and 3). A threshold value for acceptable early migration was sought in a systematic review and meta-analysis described in chapter 5. By matching RSA data of specific stems to survival data from separate studies, only a threshold for acceptable migration of cemented shaped-closed stems could be defined. For cementless stems, there was too little data available to establish a meaningful benchmark.

Migration of cemented femoral stems in total hip arthroplasty

Migration of a cemented shape-closed (i.e. composite-beam) femoral stem is described in chapter 4. A collared stem with a smooth surface finish (Stanmore) was compared between two types of bone cement; established Palacos R + G and novel Refobacin bone cement R. Migration was comparable between the two bone cements during follow-up. Except for 5 outliers, all stems showed initial subsidence (median 0.2 mm for Palacos R + G and 0.3 mm for Refobacin bone cement R) and retroversion (median 0.8° for Palacos R + G and 1° for Refobacin bone cement R) with subsequent stabilization during the first postoperative year. The 5 outliers (2 Palacos R + G and 3 Refobacin bone cement R stems) showed continuous migration, with subsidence up to 2.4 mm and retroversion up to 5.5°, 1 year after implantation. These outliers were compared to identical stems showing non-continuous, stabile migration. The outliers had on average a thicker cement mantle (mean 0.7 mm thicker) and displayed more radiolucencies at the bone-cement interface. The outliers are at risk for future loosening.

The smooth surface finish of the Stanmore stem might accommodate some degree of initial migration to settle the stem within the cement mantle. However, gross initial and continuous migration of the stem within the cement mantle is theoretically not possible in a shaped-closed

design due to a collar at the femoral neck. Hence, continuous migration as shown by the outliers is more likely between the bone-cement interface suggesting failure of anchoring of the cement-mantle by interdigitation.

Chapter 5 describes the relation between early migration of shape-closed stems and subsequent late revision. By matching RSA studies with survival studies describing identical shape-closed designs, analyses yielded that for every 0.1 mm increase in 2-year subsidence, there was a 4% increase in revision rate for shape-closed stems. Consequently, the threshold for acceptable migration of shape-closed stems was defined at 0.15 mm; stems subsiding less than 0.15 mm in 2 years had revision rates of less than 5% at 10 years, while stems exceeding 0.15 mm subsidence had revision rates of more than 5%. Such relation and corresponding threshold could not be established for cemented force-closed designs. Force-closed (i.e. taper-slip) stems are the counterpart of shape-closed stems and typically have a smooth, polished surface finish without a proximal collar allowing settling (i.e. subsidence) of the stem within the cement mantle. The difference in design rationale between these two stems can be demonstrated by the pooled subsidence calculated in chapter 5; shape-closed design showed mean subsidence of 0.1 mm in the first post-operative year versus 1 mm for force-closed designs. Moreover, force-closed stem designs such as the Exeter stem show continuous subsidence without absolute stability up to 12 years after implantation (15).

Migration of total knee arthroplasty

In chapter 6 the migration of 4 different TKA designs are compared; a novel femoral component allowing more flexion (NexGen Legacy Posterior Stabilized Flex) is compared to its conventional counterpart (NexGen Legacy Posterior Stabilized) and a mobile-bearing is compared to a fixed-bearing. The overall 5-year migration was not significantly different among the four TKA designs. However, tibial components with a fixed-bearing showed higher initial migration compared to tibial components with a mobile-bearing. This finding could not be duplicated in the femoral components. Except for 4 components, all TKA showed stabilization after initial migration during the first post-operative year. A TKA with a high-flexion femoral component and a mobile-bearing showed continuous migration of both the tibial and femoral component and was considered to be loose. 2 other tibial components were also loose: 1 high-flexion mobile-bearing and 1 conventional fixed-bearing TKA, both showing continuous migration. The migration of the femoral component in these TKAs was unknown.

The design philosophy of the mobile-bearing was to increase conformity between the tibial and femoral components thereby minimizing stresses transmitted to the bone-implant-cement interface. This theory seems to be valid as fixed-bearing TKA showed higher initial migration. However, not resulting in better fixation in the long-term.

The same conclusion can be drawn in chapter 7 which describes a systematic review and meta-analysis comparing mobile-bearing with fixed-bearing TKA. Pooling of both studies reporting a minimum 5-year follow-up and studies reporting a minimum of 10-year follow-up, did not yield any

difference in terms of revision rates for any reason, for aseptic loosening, or for wear. There were 3 revisions in 1172 mobile-bearing TKAs and 1 revision in 1245 fixed-bearing TKA for aseptic loosening in studies with a minimum of 5 years follow-up. Except for two studies, migration was not consistently reported and meta-analyses could not be performed. It appears that theoretical assumptions of the superiority of mobile-bearing over fixed-bearing TKA in terms of enhanced survival are not borne out in clinical practice.

Feasibility of inducible displacement in total knee arthroplasty

Instead of measuring migration over time, the principle of inducible displacement is to instantly measure displacement by subjecting an implant to an external force thereby inducing a movement. To revive this technique, chapter 8 describes an *in-vitro* sensitivity study aimed to establish the optimal direction and magnitude of force necessary to induce the largest possible implant displacement using the minimal possible force. To that cause, tibial base plates (tibial component of a TKA) were embedded in surrogate fibrous tissue made out of polymers and were subsequently implanted in cadaveric tibiae. With increasing fibrous tissue layer thickness, the displacement also increased, independent of the direction of force, hence suggesting that the fibrous tissue layer thickness is primarily responsible for the measured displacement. Large implant displacement in combination with high reproducibility was observed by a loading force parallel to the anatomical axis, in the centreline of the tibial tray and also perpendicular to the anatomical axis on the medial and lateral part of the tibial tray. These findings affirm that inducible displacement has the potential to be used as an instant biomarker to detect loose implants. However, more research is needed to investigate its clinical feasibility.

CONCLUSIONS, IMPLICATIONS AND FUTURE PERSPECTIVES

The migration pattern of femoral stems in THA is dependent on implant design and cannot be appreciated as a single homogenous group (chapter 5). Stem design dictates its migration behavior. Cemented shape-closed designs are not designed to allow high subsidence and therefore are at risk for failure if they do (chapters 4 and 5). On the contrary, cemented force-closed stems tolerate high initial subsidence without leading to subsequent early revision (chapter 5). Furthermore, it seems that the magnitude of initial stem migration during the first postoperative year is not a reliable prognostic factor for failure later on (chapter 2). However, progressive migration, beyond the initial early postoperative period is. Cementless stems can show rapid initial migration with subsequent flattening of the migration curve thereby reaching a stable plateau phase without being at risk for future loosening (chapter 3). Hence, migration patterns of femoral stems should be categorized by implant design, instead of evaluated as 1 uniform group, thereby defining thresholds for acceptable initial migration more readily.

The theoretical advantages of novelties such as mobile-bearing and high-flexion TKA do not result in clinical improvements in terms of better functionality, less migration and thus better survival (chapters 6 and 7). The balance between innovation and patient safety is delicate; novel features designed to be beneficial can turn out to be disastrous (16, 17). Hence, testing of innovations before introduction to the market is paramount (18). Migration measurement with RSA is to that end a valuable tool; exposing only a relatively small number of patients to a potentially unsafe design within 1-2 years. The application of RSA in this manner as part of a phased introduction has already been adopted by the Dutch Orthopaedic Association (NOV) in their guidelines.

We have shown that inducible displacement is feasible in an *in-vivo* experiment; an external force provoked a motion at the bone-implant interface of a loose implant (chapter 8). However, there are some hurdles on the way to clinical application. Thus, future research should focus on testing clinical set-ups to find its most suitable clinical purpose. Potentially, inducible displacement could be beneficial in the phased introduction of new implants by reducing the migration measurement period of 1-2 years significantly. Furthermore, on an individual level, inducible displacement can be advantageous as a clinical tool for assessing implant stability in symptomatic patients with joint replacements.

In the end, the goal of innovation should be improved patient care with an advantageous benefit/risk ratio for patients based on clinical evidence as is requested by the new European Medical Device Regulation (MDR 2017/745) (19); no medical device innovation without clinical evaluation.

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10

Summary in Dutch (Nederlands samenvatting)

NEDERLANDSE SAMENVATTING (SUMMARY IN DUTCH)

Achtergrond

Gewrichtsvervangende chirurgie van het heup- en kniegewricht middels het plaatsten van respectievelijk een totale heupprothese (THP) en een totale knieprothese (TKP), behoren tot de meest succesvolle en meest uitgevoerde operaties ter wereld. Het doel van gewrichtsvervangende chirurgie is een langdurig pijnvrij en functioneel gewricht realiseren. Het kan echter voorkomen dat een gewrichtsprothese vroegtijdig 'faalt' waarbij er pijnklachten en functiebeperkingen ontstaan. De meest voorkomende oorzaak van falen is loslating van de prothese zonder dat er sprake is van een infectie (aseptische loslating). Loslating van een prothese is doorgaans alleen te herstellen door middel van een complexe en langdurige operatie (revisieoperatie) waarbij de kans op complicaties groot is.

Niet alleen vormt de behandeling van loslating een uitdaging: dat geldt ook voor de diagnostiek van loslating. Tot op heden is hier nog geen gouden standaard voor gedefinieerd. In een gevorderd stadium van loslating zijn op röntgenopnames weliswaar radiolucente lijnen rondom de prothese zichtbaar maar bij beginnende loslating is dit niet of nauwelijks het geval. Een experimentele techniek om loslating op te sporen is middels röntgen stereophotogrammetrische analyse (RSA), waarbij met hoge precisie de positie van een prothese ten opzichte van het bot kan worden bepaald. Door meerdere metingen uit te voeren over een bepaalde periode kan de verplaatsing (migratie) van een prothese ten opzichte van het bot worden gemeten en zodoende een maat geven voor de fixatie van een prothese in het bot. Migratie wordt uitgedrukt als translatie en rotatie in 3 vlakken waarbij de meeste verplaatsing doorgaans plaats vindt in de lengterichting van de prothese: de prothese zakt in het bot (inzakking) en draait om haar lengteas heen (rotatie). Middels RSA-onderzoek is reeds aangetoond dat het loslatingsproces al snel na plaatsing van de prothese begint en dat de migratie in het eerste postoperatieve jaar (vroege migratie) geassocieerd is met aseptische loslating op de lange termijn. Het is echter nog onduidelijk welke mate van vroege migratie acceptabel is zonder de levensduur te beïnvloeden en welke factoren (bv. protheseontwerp, chirurgietechniek, medicatie) daarnaast van invloed zijn op het migratiepatroon.

In dit proefschrift wordt onderzocht of er een relatie is tussen het migratiepatroon en de levensduur van THPs, wat de invloed van mobile-bearing TKP is op de migratie en de levensduur, en wat de nieuwe methodes zijn om loslating te diagnosticeren.

OVERZICHT VAN DE BELANGRIJKSTE RESULTATEN VAN DIT PROEFSCHRIFT

Migratie van ongecementeerde stelen in totale heupprothesiologie

Het lange termijn migratiepatroon van een ongecementeerde steel met verschillende coatings wordt beschreven in hoofdstuk 2. Een taps toelopende, conische steel (Mallory-Head Porous)

is geëvalueerd met een hydroxyapatiet, fluorapatiet, en zonder extra coating. De Mallory-Head Porous steel fixeert perspassend met haar gehele circumferentie op de meta-diafyse overgang. Alle stelen laten gedurende het eerste postoperatieve jaar een snelle migratie zien van maximaal 0,6 mm inzakking (mediaan 0,2 mm) en maximaal 3,2° rotatie (mediaan 0,9° retroversie). Na het eerste postoperatieve jaar vertraagt de migratie en wordt een plateaufase bereikt. Een steel vertoont echter progressieve inzakking met een maximum van 1,5 mm waarbij op röntgenopnames radiolucente lijnen zichtbaar zijn, maar er klinisch geen tekenen van loslating zijn. Deze steel is niet gereviseerd en een mogelijke verklaring is dat deze steel relatief klein is ten opzichte van het bot. Op basis van deze studie kan gesteld worden dat het toevoegen van een hydroxyapatiet of een fluorapatiet coating niet tot een verbetering van fixatie leidt. Daarnaast kan geconcludeerd worden dat de snelheid van initiële inzakking geen relatie heeft op het ontstaan van radiolucente lijnen.

In hoofdstuk 3 wordt dezelfde steel (Mallory-Head Porous) vergeleken met een kleinere, slankere en wigvormige steel (Taperloc). De Taperloc steel heeft, in tegenstelling tot de Mallory-Head Porous steel, een rechthoekige dwarsdoorsnede waardoor de steel mediaal en lateraal in de metafyse fixeert. 12 maanden na plaatsing is de Taperloc steel maximaal 6,8 mm (mediaan 0,3 mm) ingezakt, en de Mallory-Head Porous steel maximaal 4,8 mm (mediaan 0,3 mm). De Taperloc steel roteert maximaal 3,6° (mediaan 0,5° retroversie) in 12 maanden en de Mallory-Head Porous steel roteert maximaal 3,6° (mediaan 0,8° retroversie). Na snelle migratie in de eerste 12 maanden postoperatief, vertraagt de migratie van beide stelen en volgde een plateaufase zonder uitschieters. Gedurende de onderzoeksperiode zijn er geen stelen gereviseerd. Op röntgenopnames vertoont 1 Taperloc en 1 Mallory-Head Porous steel radiolucente lijnen. Beide stelen laten stabilisatie van migratie zien maar vertonen beide wel relatief veel migratie gedurende de eerste 12 maanden postoperatief. Alhoewel er geen significante verschillen in migratie tussen de Taperloc en de Mallory-Head Porous steel zijn aangetoond, vertoont de Taperloc steel meer inzakking gedurende het eerste postoperatieve jaar en is de Mallory-Head Porous steel meer geroteerd na 5 jaar. Deze bevindingen komen overeen met de ontwerp filosofie van beide stelen: de Taperloc steel geeft meer rotatie stabiliteit dan de Mallory-Head Porous steel.

Het adagium dat vroege migratie leidt tot aseptische loslating op de lange termijn kan voor deze stelen niet bevestigd worden. Daarentegen lijkt het bereiken van een plateaufase met stabiele migratie relevanter te zijn voor de levensduur van stelen. Op welk niveau de plateaufase wordt bereikt is gerelateerd aan de mate van vroege migratie en is niet gerelateerd aan de levensduur. Desalniettemin, laten stelen met veel vroege migratie gevolgd door een hoge plateaufase wel vaker tekenen van loslating zien op röntgenopnames.

Door de hoge variatie van vroege migratie van ongecementeerde stelen zonder falers, en zonder revisieoperaties, kan er geen afkapwaarde voor acceptabele vroege migratie worden vastgesteld (hoofdstuk 2 en 3). Aldus is middels een systematische literatuuronderzoek en meta-analyse getracht een afkapwaarde voor acceptabele vroege migratie te definiëren (hoofdstuk 5). Migratiedata en levensduurdata van identieke stelen uit verschillende studies zijn aan elkaar gekoppeld en

levert voor gecementeerde stelen een afkapwaarde voor acceptabele vroege migratie op. Voor ongecementeerde stelen is er te weinig data beschikbaar om een afkapwaarde te definiëren.

Migratie van gecementeerde stelen in totale heupprothesiologie

Migratie van gecementeerde stelen wordt beschreven in hoofdstuk 4. Gecementeerde stelen kunnen grofweg worden ingedeeld in twee types: stelen met een kraag (shape-closed) en stelen zonder een kraag (force-closed). De kraag van een shape-closed steel zorgt ervoor dat de steel kan afsteunen op het bot en voorkomt daarmee inzakking. Een force-closed steel klemt zich door de taps toelopende vorm vast in de cementmantel.

De migratie van een shape-closed steel (Stanmore) is vergeleken tussen twee types botcement: gevestigd Palacos R + G en nieuw Refobacin bone cement R. Gedurende de onderzoeksperiode van 2 jaar is er geen verschil in migratie tussen de twee types botcement aangetoond. Met uitzondering van 5 stelen, laten alle vroege inzakking zien (mediaan 0,2 mm voor Palacos R + G en mediaan 0,3 mm voor Refobacin bone cement R) met rotatie in retroversie (mediaan 0,8° voor Palacos R + G en mediaan 1° voor Refobacin bone cement R) gevolgd door stabilisatie in het eerst postoperatieve jaar. 5 stelen (2 Palacos R + G en 3 Refobacin bone cement R) laten progressieve migratie zien met inzakking tot 2,4 mm en rotatie tot 5,5° in het eerste postoperatieve jaar. Deze uitschieters zijn vervolgens vergeleken met stelen die wel stabiele migratie vertonen. De uitschieters hebben gemiddeld een dikkere cementmantel (gemiddeld 0,7 mm dikker) en vertonen meer radiolucente lijnen op de bot-cement overgang. Deze uitschieters kunnen worden beschouwd als hoog risico op toekomstige loslating.

Het gladde oppervlak van de Stanmore steel laat mogelijk enige vroege migratie toe zodat de steel zich kan vastzetten in de cementmantel. Veel inzakking is theoretisch niet mogelijk vanwege blokkering door de kraag; inzakking van de uitschieters heeft daarom waarschijnlijk plaatsgevonden op de cement-bot overgang in plaats van op de prothese-cement overgang. Dit duidt op loslating van de verankering van de cementmantel.

Hoofdstuk 5 beschrijft de relatie tussen vroege migratie van shape-closed stelen en aseptische loslating van de steel gevolgd door revisie chirurgie. Door het koppelen van RSA-data aan levensduur data voor identieke stelen uit verschillende studies, is aangetoond dat voor elke 0,1 mm meer inzakking (2 jaar na plaatsing) er een 4% verhoogd risico is op een revisie (10 jaar na plaatsing). Vervolgens is de afkapwaarde voor shape-closed stelen vastgesteld op 0,15 mm: stelen die minder dan 0,15 mm inzakken binnen 2 jaar na plaatsing hebben een kans van kleiner dan 5% op revisie binnen 10 jaar. Daarentegen hebben stelen die meer dan 0,15 mm inzakken een kans op revisie van meer dan 5% binnen 10 jaar. Een dergelijke relatie en afkapwaarde kan niet worden vastgesteld voor force-closed stelen. Force-closed stelen zijn de tegenhanger van shape-closed stelen en hebben doorgaans een glad, gepolijst oppervlak zonder kraag waardoor de steel zich in de cementmantel kan vastzetten. Het verschil in ontwerpfilosofie kan worden geïllustreerd door de mate van inzakking samen te voegen uit verschillende studies. Shape-closed stelen tonen gemiddeld een inzakking van 0,1 mm in het eerste postoperatieve jaar tegenover 1 mm voor

force-closed stelen. Bovendien laten force-closed stelen zoals de Exeter steel een continue inzakking zien zonder absolute stabiliteit tot 12 jaar na plaatsing.

Migratie van totale knieprotheses

Hoofdstuk 6 beschrijft het migratiepatroon van 4 verschillende TKP ontwerpen. Een TKP ontworpen om meer flexie te bieden, een zogenaamd "high-flexion" ontwerp (NexGen Legacy Posterior Stabilized Flex), is vergeleken met haar conventionele tegenhanger (NexGen Legacy Posterior Stabilized). Daarnaast zijn beide types TKPs vergeleken met zowel een mobile-bearing als een fixed-bearing. Mobile-bearing TKP is ontworpen om de conformiteit tussen het femur- en het tibiacomponent te vergroten om zodoende stress op de overgang van de prothese naar het bot te verminderen en daarmee de levensduur van de prothese te verlengen.

Gedurende de 5-jarige onderzoeksperiode is er geen significant verschil in migratie tussen de 4 verschillende ontwerpen aangetoond. Echter laten tibiacomponenten met een fixed-bearing meer vroege migratie zien in vergelijking met tibiacomponenten met een mobile-bearing. De femurcomponenten laten geen verschil zien in migratie tussen de fixed- en de mobile-bearing. Na initiële vroege migratie stabiliseert de migratie van vrijwel alle TKPs, behalve 1 femurcomponent en 3 tibiacomponenten. Van een TKP met een high-flexion femurcomponent en een mobile-bearing laten zowel het femur- als het tibiacomponent progressieve migratie zien. Daarnaast laten 2 andere tibiacomponenten: 1 high-flexion mobile-bearing en 1 conventionele fixed-bearing, progressieve migratie zonder stabilisatie zien. Van deze 2 tibiacomponenten is de migratie van het femurcomponent niet bekend.

De fixed-bearing TKPs laten meer vroege migratie zien in vergelijking met mobile-bearing TKPs en daarmee lijkt de ontwerpfilosofie van minder stress op de prothese-bot overgang valide. Echter kan er geen verschil op de lange termijn worden aangetoond.

Dezelfde conclusie kan getrokken worden uit de studie beschreven in hoofdstuk 7. Door middel van een systematisch literatuuronderzoek en meta-analyse worden mobile-bearing met fixed-bearing TKPs vergeleken. 41 studies die oftewel de 5-jarige of de 10-jarige levensduur beschrijven, zijn samengevoegd. Met betrekking tot de 5-jarige levensduur zijn er 3 revisies voor aseptische loslating in 1172 mobile-bearing TKPs, tegenover 1 revisie voor aseptische loslating in 1245 fixed-bearing TKPs. Helaas beschrijven slechts 2 studies de migratie en zodoende is het niet mogelijk om een meta-analyse voor migratie uit te voeren. De theoretische aanname van een betere levensduur van mobile-bearing TKPs lijkt in de praktijk derhalve niet op te treden.

Mogelijkheden van "inducible displacement" in totale knieprothesiologie

Voor RSA-studies is doorgaans een onderzoeksperiode van minimaal 1 jaar nodig om de migratie en dus fixatie van een prothese te beoordelen. Een manier om direct een maat voor fixatie te krijgen is middels een techniek genaamd 'inducible displacement'. Het principe van inducible displacement is om een beweging te induceren door een externe kracht op de prothese aan te brengen. De verplaatsing van de prothese van een ongeladen naar een geladen toestand wordt

hierbij gemeten en geeft zodoende een maat voor fixatie. De haalbaarheid van deze techniek is uitvoerig onderzocht maar er is nog geen eenduidige toepassing gedefinieerd. In hoofdstuk 8 wordt een basale studie beschreven om te onderzoeken hoe met een zo klein mogelijke kracht een zo groot mogelijk verplaatsing van een prothese kan worden bewerkstelligd. Hiervoor zijn tibiacomponenten van een totale knieprothese in kadaverbotten geïmplanteerd. Aangezien in losse protheses een fibreus weefsel rondom de prothese in de loop van de tijd ontstaat, is een surrogaat fibreus weefsel ontworpen met siliconen om zo een losse tibiacomponent na te bootsen. Uit de metingen blijkt dat met toenemende dikte van het surrogaat fibreus weefsel de geïnduceerde verplaatsing ook toeneemt, ongeacht op wat voor manier kracht wordt aangebracht op de tibiacomponent. Derhalve kan gesteld worden dat de dikte van het fibreus weefsel primair verantwoordelijk is voor de gemeten verplaatsing. Grote verplaatsing in combinatie met een hoge reproduceerbaarheid wordt gezien door een kracht aan te brengen parallel aan de anatomische as en daarnaast loodrecht op de anatomische as: mediaal en lateraal op de tibiacomponent. Geconcludeerd kan worden dat inducible displacement potentie heeft om losse protheses op te sporen. Echter is meer onderzoek nodig naar de klinische toepasbaarheid.

CONCLUSIE, IMPLICATIES EN TOEKOMSTPERSPECTIEVEN

Het migratiepatroon van THP stelen is afhankelijk van het ontwerp en zodoende dienen stelen niet als een homogene groep beschouwd te worden (hoofdstuk 5). Het ontwerp van de steel dicteert het migratiepatroon. Zo zijn gecementeerde shape-closed stelen niet ontworpen om in het femur te zakken en indien dat wel gebeurt is er een risico op vroegtijdig falen (hoofdstuk 4 en 5). Daarentegen zijn gecementeerde forced-closed stelen juist wel ontworpen om in het femur zakken zonder het risico op vroegtijdig falen (hoofdstuk 5). Het lijkt erop dat de mate van inzakking van stelen in het femur gedurende het eerste jaar na plaatsing geen betrouwbare prognostische factor voor falen is (hoofdstuk 2). Toenemende inzakking zonder afvlakking en stabilisatie lijkt daarentegen wel gerelateerd aan uiteindelijk falen. Gecementeerde stelen kunnen postoperatief snel inzakken om vervolgens te stabiliseren en de migratiecurve een plateaufase bereikt zonder dat de stelen het risico lopen op toekomstig falen (hoofdstuk 3). Het migratiepatroon dient daarom gecategoriseerd te worden op basis van protheseontwerp en niet beschouwd te worden als een enkele homogene groep. Zodoende kunnen afkapwaardes voor acceptabele vroege inzakking nauwkeuriger gedefinieerd worden.

De theoretische meerwaarde van nieuwe ontwikkelingen zoals mobile-bearing en high-flexion TKP resulteert niet in klinische verbetering uitgedrukt in functionaliteit, minder migratie of een langere levensduur (hoofdstuk 6 en 7). De balans tussen innovatie en patiëntveiligheid is delicaat: nieuwe ontwikkelingen ter verbetering van de levensduur kunnen juist het omgekeerde effect hebben en schadelijk zijn. Uitgebreid testen van innovaties voordat ze op de markt komen is daarom van groot belang. In dat licht is migratie gemeten met RSA een waardevolle techniek: slecht een

beperkt aantal patiënten wordt blootgesteld aan een potentieel schadelijke prothese. Zodoende is het gebruik van RSA als onderdeel van een gefaseerde introductie van nieuwe protheses reeds opgenomen in de richtlijnen ven de Nederlandse Orthopedische Vereniging.

We hebben aangetoond dat inducible displacement haalbaar is in *in-vivo* experimenten: een externe kracht veroorzaakte een meetbare verplaatsing van een losse prothese op de prothese-bot overgang (hoofdstuk 8). Echter zijn er een aantal obstakels op de weg naar klinische toepassing, toekomstig onderzoek dient daarom hierop gericht te zijn. Mogelijk kan inducible displacement gebruikt worden in de gefaseerde introductie van nieuwe protheses en zo de onderzoeksperiode van 1-2 jaar significant reduceren. Daarnaast kan op individueel niveau inducible displacement gebruikt worden als diagnosticum om losse prothese op te sporen in symptomatische patiënten.

Tenslotte, innovaties dienen de patiëntenzorg te verbeteren waarbij de voordelen ruim moeten opwegen tegen de nadelen: geen innovatie zonder klinische evaluatie.

A

List of publications

Curriculum vitae

Dankwoord

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CURRICULUM VITAE

Paul van der Voort was born on the 27th of March 1985 in Delft, the Netherlands. He grew up and attended secondary school in Valkenswaard. After graduating in 2003, he spent a year studying in Delft before commencing medical school at Leiden University. During his medical studies, he worked as a teaching assistant at the department of anatomy and adventured to Malawi and Australia for clinical rotations.

After obtaining his medical degree in 2010 he worked as a general surgery resident (not in training) at Haaglanden Medical Center in the Hague. From 2011 onwards he worked as a researcher at the orthopaedic department of the Leiden University Medical Center under the supervision of Prof. Dr. R.G.H.H. Nelissen and Prof. Dr. Ir. E.R. Valstar. The results of this research are described in this thesis and were presented at multiple national and international scientific conferences.

In 2014 Paul commenced his orthopaedic residency at the general surgery department of the Tergooi Hospital in Hilversum (Dr. A.A.W. van Geloven). In 2016 he continued his training at the orthopaedic department of the Leiden University Medical Center (Prof. Dr. R.G.H.H. Nelissen), Haaglanden Medical Center in the Hague (Dr. E.R.A. van Arkel) and Sint Maartenskliniek in Nijmegen (Dr. V.J.J.F Busch).

After finishing his orthopaedic training in June 2021, Paul commenced a trauma and arthroplasty fellowship in Adelaide, Australia (Prof. Dr. R.L. Jaarsma). Paul is currently living in Adelaide with Anne and their newborn son Ben.

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