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Safety of orthopedic implants: implant migration analysis a must

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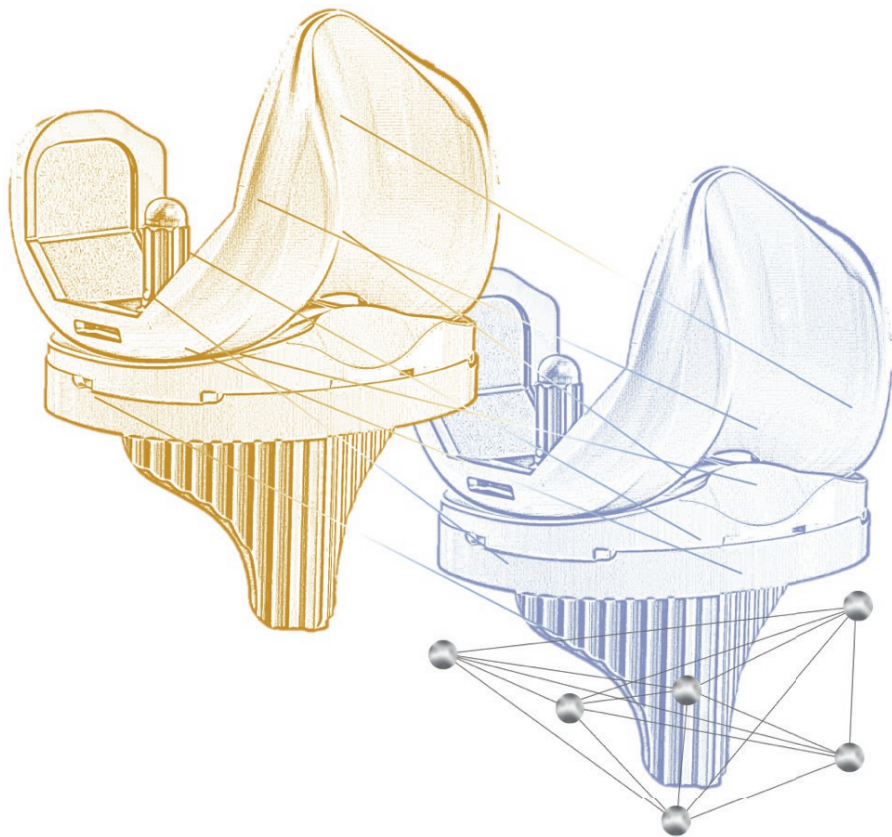
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Safety of Orthopedic Implants

Implant Migration Analysis a Must



Shaho Hasan

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Implant Migration Analysis a must

PhD thesis, Leiden University, The Netherlands

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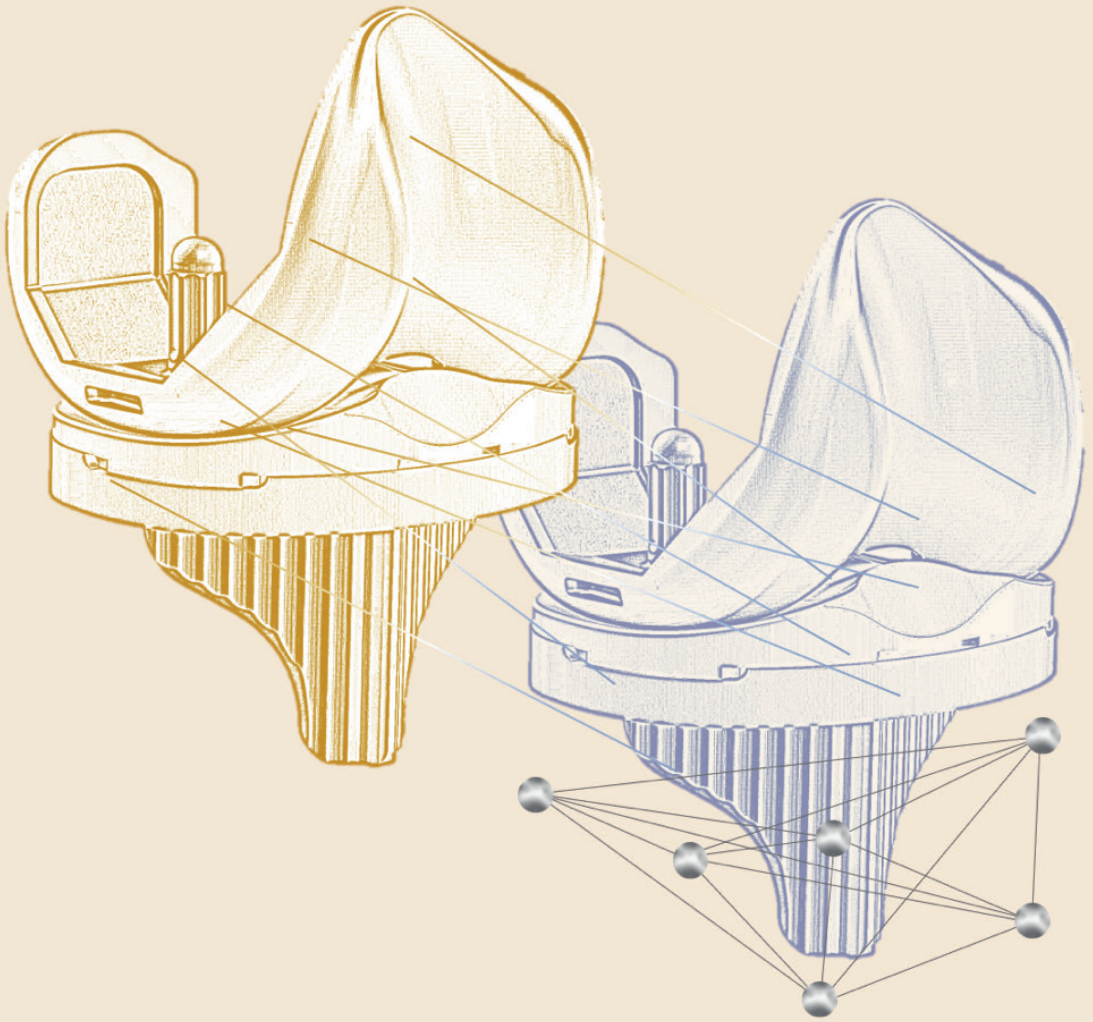
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Chapter I

General introduction

Chapter I General introduction and outline

Total knee arthroplasty

Knee osteoarthritis (OA) is a degenerative disease of the knee joint and often leads to knee pain, limitations in daily functioning and a decrease in quality of life.¹⁻³ Two hundred fifty million people worldwide are suffering from knee OA and the incidence of knee OA has grown dramatically since the 20th century.⁴⁻⁵ First line treatment of knee OA include life style advice, physical therapy and oral or intra-articular analgesics.⁷ If conservative treatment has insufficient effect on patient complaints, end-stage osteoarthritis can be treated with a total knee arthroplasty (TKA). which has excellent long-term results in the population above 65 years of age. TKA is known to alleviate pain and improve knee function.⁸⁻¹⁰ Besides primary OA, other conditions such as inflammatory arthritis, trauma and malignancies can be indications for treatment with TKA.^{11, 12}

TKA is one of the most commonly performed orthopaedic surgeries with 25.885 TKAs registered in the Netherlands during the precovid year 2019, which dropped to 21.444 in the covid year 2021.^{11, 13} This number is expected to rise in the Netherlands and globally due to an aging population, a longer life expectancy, and an increasing body mass index (BMI), but also due to indications in the younger patients, below the age of 55 years.¹⁴⁻²¹ With these rising numbers of TKA performed, the demand and expectations of different patient groups in terms of implant survival and functionality following this procedure is increasing. Therefore, many efforts are put into increasing the longevity in younger age groups but also of functionality following TKA in specific patient groups. Nevertheless, 20% of patients are not satisfied following treatment with TKA, which is in contrast with total hip arthroplasties where less than 5% of patients are not satisfied.^{9, 22-31}

Implant design and surgical technique – principles and improvements

The first modern total condylar TKAs date from the early 1970's among which the Freeman-Swanson the Yamamoto and Insall-Burstein total condylar knee prostheses. In that time, TKAs consisted of a cemented metal femoral component with a cemented all-polyethylene tibial (APT) component.³²⁻³⁸ Following this TKA design, Freeman et al. (1973) formulated 14 basic implant design and surgical principles for TKA which have remained highly relevant up until today. Broadly speaking, these entail that loosening and infection should be avoided, wear debris limited as much as possible, a sufficient range of motion should be possible and the implant should be stable through the entire range of motion [Table I.1].³²

Table I.1 Design and surgical principles as proposed by Freeman et al. (1973)³²

#1	No more bone should be removed as needed for a primary arthrodesis
#2	Loosening should be avoided. This could be minimized by the following principles <ol style="list-style-type: none"> a. The femoral and tibial component should be incompletely constrained to prevent load transfer from the prosthesis to the bone during movement b. Minimalization of friction between both components; Metal-on-polyethylene is therefore preferred over metal-on-metal c. Hyperextension limit should be progressive and not abrupt d. Components should have the largest possible contact area with the bone to spread the load; large bone surfaces on which the prosthesis can sit and the use of cement
#3	The rate of wear debris production should be limited
#4	The produced wear debris should be as harmless as possible
#5	Compact implants with minimal dead spaces should be used to reduce the probability of
#6	The consequence of an infection should be minimized (short stems, avoid intramedullar
#7	A standard procedure protocol should be available
#8	The implant should be able to function from 5° extension to 90° flexion; function above 120
#9	Some freedom in rotation and ad- or abduction should be possible
#10	Soft tissue should resist excessive movements without breaking the bone-prosthesis
#11	It is unwise to depend on the mechanical functioning of the cruciate ligaments for
#12	The prosthesis should permit the removal of intercondylar tissues and should restore
#13	The tibio-femoral replacement should be able to accommodate the patella itself or a
#14	The cost should be minimized by making the smallest practicable number of sizes and versions. This objective is last on the list but should not be forgotten entirely

Due to disappointing survival of APT components, it was thought to improve implant design by adding a modular metal-backed tibial (MBT) component. This

modular component would improve results since MBT components showed promising results in biomechanical studies with favourable load transfers to bone.³⁹⁻⁴³ Furthermore, they provided intraoperative flexibility as the polyethylene thickness could be adjusted after cementation of the metal-backed tibial baseplate.⁴⁴⁻⁴⁶ The latter allows in the preoperative planning for different degrees of constraint of the knee implant such as cruciate-retaining (CR) inserts with less constraint, or posterior-stabilising (PS) inserts with more constraint. In some implants these different design options can be exchanged during surgery, if the femoral component is the same, but usually this is not an option since in the PS design a “box” has to be cut at the femoral side to accommodate the PS femoral component. Nevertheless, a non-modular APT component can never be adjusted for constraint once cemented.⁴⁴⁻⁴⁶

An additional benefit of modularity is that the polyethylene insert can be exchanged without need to revise the whole tibial component. Such an insert exchange could be favourable in case of an infection, wear or instability.⁴⁴⁻⁴⁶ Apart from modularity, another advantage of metal-backed implants is, they can be coated with calcium phosphates to enhance fixation if an uncemented component is used.^{45, 46}

A new manufacturing process introduced high cross-linked polyethylene (HXLPE) to modern TKA. This novel HXLPE lowered the wear rate compared to conventional polyethylene (ultra-high molecular weight polyethylene; UHMWPE).⁴⁷ However, clinical evidence supporting the use of HXLPE is still limited. Several clinical studies did not show a clinical or radiological benefit of HXLPE and no differences in overall survival between HXLPE and UHMWPE was found in several registries.⁴⁸⁻⁵⁶

Although, in the Australian Orthopaedic Association National Joint Replacement Registry a higher survival rate of HXLPE TKA was found for specific TKA designs.⁵⁷ Apart from improvements in material composition, uncemented fixation methods have improved substantially. Ever since the early years of TKA, one of the main reasons for TKA failure was implant loosening.^{11, 12, 36, 58} Therefore, fixation methods of implants have been discussed for several decades. The most common fixation method is cementing of the components using polymethyl methacrylate (PMMA).¹¹

^{12, 58} As a consequence, more complex reconstructions may be needed requiring the use of bone grafts or larger implants for revision surgery.⁵⁹ Other disadvantages are the production of cement debris, the slow degradation of cement with long-term loosening as consequence and the time needed for cement to harden.⁶⁰ Therefore, uncemented fixation has gained interest over the years. Specifically, when using coatings promoting osseointegration. Uncemented fixation allows for a biological fixation of the implant to the bone and preserves bone stock in case of revision surgery.^{60, 61} In the last decades, novel designs and implant coatings have been developed to enhance bone ingrowth into the prosthesis in order to provide a long-lasting fixation.⁶⁰ Additive technology, also known as 3D-printing, was introduced to further optimize osseointegration as it allows the manufacturing of highly porous implants. These highly porous implants could mimic the stiffness and elasticity of bone and could therefore further augment implant fixation.⁶² Uncemented fixation is especially relevant for younger patients as the life-time risk of a TKA revision of these patients is higher compared to the average TKA population.^{60, 61, 63, 64} The major drawback of uncemented TKAs in the past was the increased risk of early failure compared with cemented counterparts. However, recent studies no longer show superiority of cemented TKAs over uncemented TKAs in terms of survival or clinical outcomes.^{61, 65-67} Despite these promising results, uncemented TKAs account for less than 10% of all TKAs registered in arthroplasty registries.^{11, 12, 58}

Evaluation of novel implant designs

Most 50-year-old implant design principles are still valid nowadays. However, minimizing the number of implant designs and sizes is one of the neglected principles while using multiple different implants could be associated with an increased risk of revision [#14, Table I.I].^{24,68} TKAs could differ in several characteristics. First, every manufacturer has his own TKA design or several different TKA designs. Second, the fixation method could either be cemented (i.e., cemented femoral and tibial component), hybrid (i.e., cemented femoral and uncemented

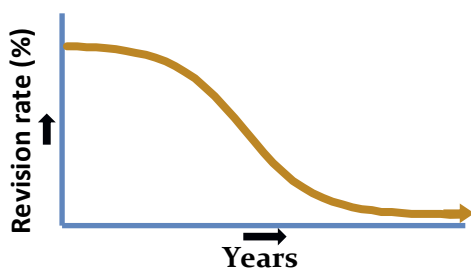
tibial component or vice versa), or uncemented (i.e., uncemented femoral and tibial component). Further, the constraint could differ between designs (e.g., CR or PS). Also, the tibial component could be MBT or APT. Last, MBT components could have fixed- or mobile-bearing inserts. Every different combination of these characteristics could theoretically influence revision rates and functional outcomes even though the differences between these implant characteristics could be small. A study comparing cemented PS designs to cemented CR designs using data from the Dutch Arthroplasty Registry, for example, found that cemented PS designs were 1.5 times more likely to be revised compared to cemented CR designs.⁶⁹

One could question whether further improvements of TKA designs are needed as revision rates have dropped considerably since the introduction of TKA and are relatively low (i.e., ten-year revision rate 4-6%).^{11, 12, 58} While initially a novel design had the potential to significantly reduce the revision rate, the chance of reducing revision rates even further is limited. The evolution of the performance of TKAs in terms of revision rates could be illustrated by a reversed S-curve: an initial slow reduction of revision rate followed by a period of fast reduction [Figure I.I]. After

this period, the curve flattens, and further improvements have minimal or even a detrimental effect on the revision rate [Figure I.I].⁶² However, a reason to continue innovation of TKA designs could be to increase patient satisfaction. Whereas the revision rates have dropped

significantly over the past decades, patient satisfaction trails behind as approximately one in five patient is not satisfied following TKA.²² Many efforts have been put into understanding the reason for this relatively high rate of unsatisfied patients, but unfortunately, the reasons remain unclear. Hence, novel implant designs have been developed aiming to increase patient satisfaction by, for example,

Figure I.I A reversed S-curve illustrating revision rates (y-axis) over time (x-axis).

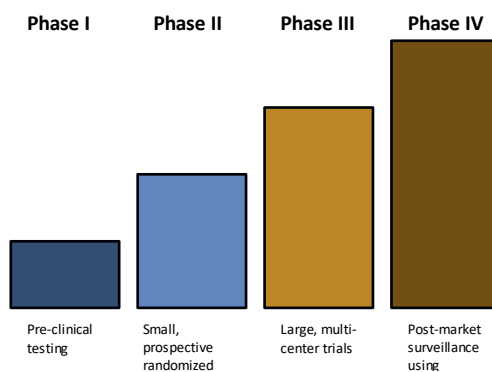


introducing a mobile-bearing insert or an asymmetrical tibial baseplate to allow more natural movement of the knee joint which in turn could theoretically increase patient satisfaction following TKA.

These novel TKA designs are introduced on a regular basis and often without (sufficient) evidence of lower revision rates or better clinical outcomes compared to their predecessor.⁷⁰ An evidence-based approach is needed when introducing novel TKA designs to expose a minimal number of patients to a novel treatment to ensure patient safety. Therefore, several authors suggested the introduction of novel implants in a phased fashion.^{6, 71-76} A phased introduction includes several phases which are considered necessary to safely implement novel TKA designs without compromising patient safety [Figure I.II].^{6, 71-76} The first phase includes pre-clinical testing which is followed by a phase that should include prospective, randomized controlled clinical trials. These clinical trials preferably include a limited number of patients to minimize the risks associated with a novel TKA design. Results from phase II could be used to assess

whether it is beneficial to continue to phase III. In the next clinical phase (i.e., phase III), large, multicentre studies are conducted to assess whether the novel design improves patient outcomes in a more generic population before this novel implant is widely implemented in clinical practice and is then continued to be monitored for any unintended consequences (as part of post-marketing surveillance). A phased introduction is needed to prevent implant failures which have previously been shown to result in severe patient morbidity.^{77, 78}

Figure I.II A phased introduction including four steps: 1) pre-clinical testing, 2) small, prospective randomized clinical trials, 3) large, multicentre trials, and 4) post-market surveillance using registries⁶



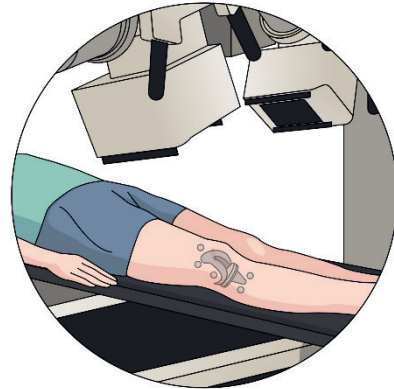
The role of Radiostereometric Analysis in evaluation of implant designs

Radiostereometric analysis (RSA) is suggested to be implemented as an early detection tool in the first clinical step of a phased implant introduction.^{6, 71, 73, 74, 76, 79}

The reason for this is that RSA could provide accurate objective results on the performance of novel implants after one or two years. These studies frequently compare well-performing design with a novel design in a randomised trial and it requires only a limited number of approximately 30 patients per treatment arm. RSA uses two 2D

radiographs taken in a stereo fashion to reconstruct a 3D image to estimate migration of implants [Figure I.III].⁷⁹ RSA calculates the position of the implant by measuring the position of radiopaque tantalum markers, which are inserted in the bone surrounding the implant during surgery, relative to predefined markers positioned on a calibration box.⁷⁹ These radiopaque tantalum beads have a varying diameter (0.5-, 0.8-, or 1.0-mm).⁷⁹⁻⁸³ During follow-up visits, the position of the implant relative to the tantalum markers in the bone is again calculated and any change in relative implant position over time is considered to be migration.⁷⁹ The position of the implant can be determined by attaching tantalum beads to the implant before surgery, by inserting tantalum beads in the polyethylene (marker-based RSA) or by using a model of the implant (model-based RSA), which has the advantage that it does not require markers in or attached to the implant.⁸⁴ The change of implant position is called migration and expressed as translation along or rotation about the transverse, longitudinal, and sagittal axis. Maximum total point motion (MTPM) is used as a summary measure and is an estimate of the length of the translational vector of the point with the greatest

Figure I.III Radiostereometric analysis set-up. Two Rontgen foci are positioned above the knee implant and the knee implant is positioned above a calibration box. Several tantalum beads have been inserted in the tibial bone and/or femoral bone during surgery, and are used to measure migration of the implant.



migration.⁸⁵ MTPM is frequently used to assess the stability of an implant and the risk of tibial loosening as an increased MTPM is associated with tibial loosening.⁸⁶⁻⁸⁸ To assess the risk of tibial failure, certain thresholds have been proposed. First, Ryd et al. (1995) analysed 155 TKAs and unicondylar knee arthroplasties (UKAs), and suggested that implants migrating >0.2 mm were at risk of failure due to aseptic loosening.⁸⁶ Approximately 20 years later, Pijls et al. (2012) conducted a meta-analysis of all TKA RSA studies and associated migration found in these RSA studies to five- and ten-year revision rates of the same implants reported in clinical studies and arthroplasty registries.⁸⁷ They suggested a classification into three categories according to the extent of migration at one year. The thresholds for these categories were <0.54 mm MTPM (i.e., acceptable), 0.54 - 1.60 mm MTPM (i.e., at risk), and >1.60 mm MTPM (i.e., unacceptable). TKA designs with a mean migration <0.54 mm migration was considered safe to use and the use of implants with more than 1.60 mm migration should be avoided. Implants with a migration between these two thresholds should be carefully monitored in future studies and clinical practice. Both studies suggested that tibial migration and the risk of failure due to loosening were associated. This makes RSA a very suitable tool to detect any problems early and explains why it is frequently used to compare different TKA designs.

Outline of this thesis

The aim of the present thesis was to contribute to better understand the influence of differences in implant design and surgical techniques on migration of TKA, and more broadly on the effect of using RSA and other markers to detect loosening early.

The association between migration measured with RSA and aseptic loosening is well studied in clinical studies. However, whether TKA designs studies in RSA studies have lower revision rates in arthroplasty registries is unclear. Therefore, **Chapter II** compared the five- and ten-year revision rates of RSA-tested with non-RSA-tested TKAs reported in arthroplasty registries.

Although RSA is an objective method to assess clinical outcome following TKA, a disadvantage of RSA as a diagnostic tool for implant loosening is that it can only be used if RSA markers are inserted during surgery. A few other non-operative markers to identify loosened implants have been described. Having pre-emptive markers of implant loosening could potentially open strategies to not only prevent more severe implant loosening, but also has the potential to monitor disease progression.

Chapter III aimed to identify the most frequently studied markers which can discriminate between loosened and stable THAs and TKAs, and therefore have the most promising results in differentiating between these groups.

Any change in implant design or surgical technique could potentially have a major impact on revision rates or functional outcomes after TKA. Therefore, **Chapter IV**, **Chapter V**, and **Chapter VI** assessed the effect of two different design changes on migration in a randomized controlled trial using RSA. First, a MBT and APT TKA were compared up to two years in **Chapter IV**. Second, a cemented TKA was compared to a 3D-printed, uncemented TKA in terms of migration in **Chapter V**. Although two-year migration is a commonly used follow-up duration for RSA studies, longer follow-up is needed to determine whether implants showing continuous migration in the second postoperative year continue to migrate or stabilize. The aim of **Chapter VI** was therefore to compare migration up to five years

of metal-backed (MBT) and all-polyethylene tibial (APT) components in total knee arthroplasty using a cruciate-stabilising (CS) design in one study and a posterior-stabilising (PS) design in another study. In addition, migration profiles of continuously migrating implants in the second postoperative year were evaluated.

As noted earlier, thresholds in migration have been defined to identify which implants are at risk for loosening. These thresholds have been determined for TKA, while migration patterns of unicondylar knee arthroplasties (UKAs) could be different. Therefore, we evaluated migration patterns of tibial components of UKAs in a meta-analysis (**Chapter VII**).

Beside these implant design characteristics, the surgical technique itself, such as coronal alignment of TKAs, could also have effect on implant migration. Malaligned TKAs have a higher risk of revision, but recent studies have shown ambiguous results regarding the importance of alignment on implant survival and patient satisfaction. Even more, some advocate TKA placement according to the preoperative constitutional aligned limb.⁸⁹ For that matter, the effect of alignment on TKA migration was studied, comparing tibial component migration up to two years between ‘malaligned’ TKAs (i.e. varus or valgus alignment) with aligned TKAs, taking into account the preoperative varus or valgus aligned native knee (**Chapter VIII**).

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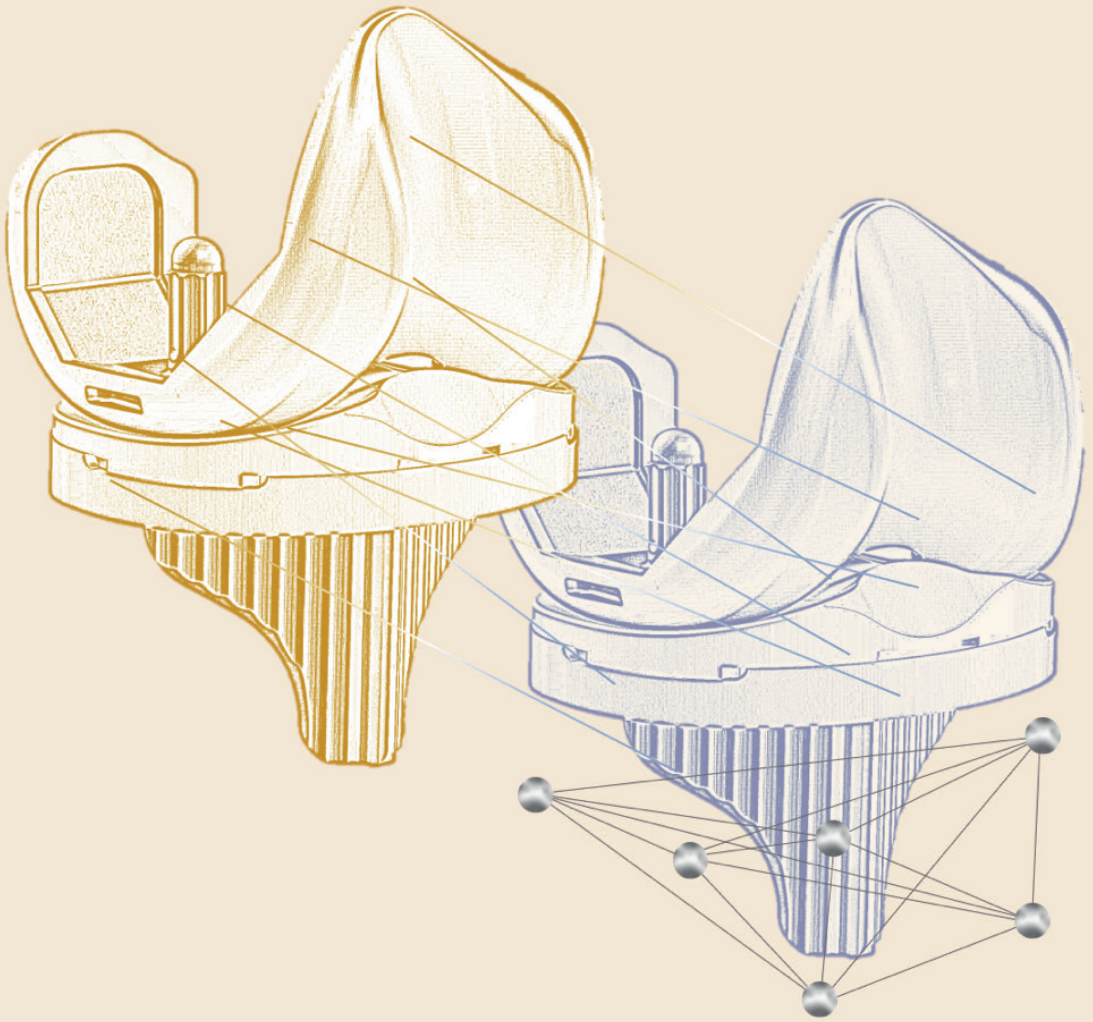
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Chapter II

TKA implants on average have
lower mean 10-year revision rates than
non-RSA-tested designs

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Abstract

Background

The number of revisions after TKA is expected to rise because of aging populations in many countries and because patients are undergoing TKA at younger ages. Aseptic loosening is a major reason for late revision, which can be predicted by radiostereometric analysis (RSA) of small groups of patients at 2 years of follow-up. RSA is therefore an ideal tool to assess new TKA designs before they are introduced to the market, although not every TKA design has been studied with RSA. If RSA-tested TKA designs have lower 10-year revision rates in national registries than non-RSA-tested TKA designs, RSA testing of all new designs could be advocated.

Questions/purposes

In this study, we asked: Is there a difference in the all-cause revision rate between non-RSA-tested and RSA-tested TKA designs registered in national knee arthroplasty registries at 5 and 10 years of follow-up?

Methods

Knee arthroplasty registries were identified through the European Federation of National Associations of Orthopaedics and Traumatology webpage and through a manual internet search. Inclusion criteria were a minimum follow-up duration of 10 years and available revision or survival data per TKA design. Twenty-six registries were identified; seven were included comprising 339 TKA designs, of which 236 designs were classified as RSA-tested and 103 as non-RSA-tested. Six registries were excluded because no report was published. One registry was excluded because no fixation method was mentioned (79 TKA designs). Another registry was excluded because there was no 10-year data available (22 non-RSA-tested designs; 10 RSA-tested designs). Eleven registries were excluded because these registries did not provide revision rates per design and had not reached 10 years follow-up. The revision rates with their standard errors were extracted per design. We used the data

from a recent meta-analysis to identify whether a TKA design was previously tested with RSA. This meta-analysis found 53 RSA studies comprising 70 different TKA designs. The prosthesis model, fixation method and insert type were extracted from these RSA-studies. The design characteristics of the TKA reported in the knee arthroplasty registries were also extracted, and if possible, matched to the TKA designs reported in the RSA-studies. At 5 years of follow-up, 191 TKA designs were identified as non-RSA-tested and 92 were identified as RSA-tested. At 10 years of follow-up, 154 TKA designs and 74 TKA designs were classified as non-RSA-tested and RSA-tested, respectively. A random-effects model using the Metafor Package in R statistics was used to estimate the pooled revision rate at 5 and 10 years of follow-up for both groups. The difference in revision rates between groups at 5 and 10 years of follow-up was estimated by including RSA as a factor in the random-effects model.

Results

Mean all-cause revision rates at 5 years for non-RSA-tested and RSA-tested implants were 3.6% (95% CI 3.4 to 3.8) and 2.9% (95% CI 2.7 to 3.0), with a mean difference of 0.6% favoring RSA-tested implants (95% CI 0.4 to 0.8; $p < 0.001$). Mean all-cause revision rates at 10 years for non-RSA-tested and RSA-tested implants were 5.5% (95% CI 5.2 to 5.9) and 4.4% (95% CI 4.1 to 4.7), with a mean difference of 0.9% favoring RSA-tested implants (95% CI 0.4 to 1.3; $p < 0.001$).

Conclusions

Although there are exceptions, across registries, TKA designs that have been tested in an RSA setting have a slightly lower (about 1%) mean all-cause revision rate at 5-year and 10-year follow-up than those tested in a non-RSA setting do.

Acknowledging the inherent limitations of this observational study, a risk difference of 1% could potentially translate into an approximate 20% decrease in revision burden up to 10 years, which may have a profound impact on patient morbidity and health-related costs.

Level of Evidence

Level III, therapeutic study.

Introduction

The number of revisions after TKA is expected to rise because of aging populations in many countries, and because of increased usage of this procedure in younger patients.^{1, 2} Unfortunately, the introduction of newer TKA designs has not always resulted in fewer revisions.^{3, 4} A major reason for long-term revision of a TKA implant is aseptic loosening, which can be predicted using the 2-year postoperative prosthesis migration profile, measured using radiostereometric analysis (RSA).^{5, 6} RSA was first described in 1974, has been improved for use with digital radiographs, and has been used with various TKA designs.⁷⁻¹³ Given the high precision of RSA, RSA studies generally need only approximately 50 patients per group to detect a difference in prosthesis migration between TKA designs, making RSA an ideal tool to evaluate new TKA designs in early clinical trials.¹⁴ The importance of RSA studies before widespread market introduction of new designs has been noted in numerous reports that correlate early (1 to 2 years) migration patterns of knee implants with 10-year survival of these implants.^{5, 6, 14, 15} Phased introduction of new TKA designs, including those evaluated in early clinical RSA trials, has been proposed to improve patient safety.^{14, 16-19}

However, not every TKA design has been studied with RSA before market introduction. In the AOANJR registry for instance, nearly 194 different TKA design combinations have been registered, with reported 10-year survival rates ranging from 86.5% to 98.1%, and most designs were not evaluated in an RSA study.²⁰ RSA could be used to warn clinicians about implants that are more likely to have an increased risk of aseptic loosening, thus safeguarding against the widespread use of such implants. Such a warning might result in withdrawal of designs from the market, thereby leaving only the better-performing implants and preventing many early revisions.¹⁴ Following this mechanism, TKA designs tested with RSA may be expected to have a lower revision rate during long-term follow-up than non-RSA-tested TKA designs. In an earlier report with shorter follow-up, Nelissen et al. (2011) found that RSA-tested TKA designs had a lower revision rate in three national knee

arthroplasty registries with up to 5 years of follow-up.¹⁴

Here, we used six national registries and one regional registry to answer the question: Is there a difference in the all-cause revision rate between non-RSA-tested and RSA-tested TKA designs registered in national knee arthroplasty registries at 5 and 10 years of follow-up?

Materials and Methods

Study Search

Through the Network Orthopaedic Registries of Europe—European Federation of National Associations of Orthopaedics and Traumatology webpage (EFORT), national and regional knee arthroplasty registries were identified.²¹ A manual world-wide-web search was then conducted to identify any knee arthroplasty registry not listed on the EFORT webpage. Published reports were extracted from these registries. Inclusion criteria were a minimum follow-up duration of 10 years and available revision or survival data for each TKA design. Knee arthroplasty registries were excluded if no information regarding the fixation method was provided. However, if a study or report stated that more than 90% of the TKA designs were cemented, the entire registry was included and all TKA designs were assumed to be cemented (but tested in a sensitivity analysis – see below). No language restriction was used.

The search yielded 26 annual reports of knee arthroplasty registries, of which six national registries (from Australia, Finland, New Zealand, Norway, Sweden, and the United Kingdom) and one regional registry (Emilia-Romagna, Italy) were included (Fig. II.1).^{20, 22-27} TKA designs of one registry were excluded due to unknown fixation method. TKA designs from another registry were excluded as only 7-year data was available. All other excluded registries did not have 10-year follow-up and did not report revision rates per TKA design (Fig. II.1). From the seven registries, 339 TKA designs were extracted. The maximum follow-up duration ranged between 13 and 41 years, and all registries had a completeness of $\geq 95\%$ for primary TKA. The definition

of completeness was not clarified in all registries but was defined as the percentage of patients receiving a primary TKA included in the registry in most registries. The mean age at the time of surgery ranged from 68 years to 71 years [Table II.I]. The Finnish registry did not report a mean age but divided patients into four age groups (younger than 55 years, 55 to 64 years, 65 to 74 years, and 75 years and older), with most patients (39%) in the 65 to 74 years age group. The proportion of female patients in the registries ranged from 47% in the Sweden registry to 71% in the Emilia-Romagna, Italy registry [Table II.I].

Table II.I Characteristics of included registries

	Australia	Finland	Emilia-Romagna (Italy)	New Zealand	Norway	Sweden	United Kingdom
TKAs (n)	547,407	194,787	39,782	93,497	29,834	109,393	975,739
Follow-up (years)	16	25	16	17	23	41	13
TKA designs (n)	143	356	39	34	19	13	56
Publication year	2017	2018	2017	2017	2018	2017	2017
Completeness (%)	98%	96%	98%	> 95% ^a	97%	97%	96%
Age (mean, years)	68.5	65-74	70.6	68	68.5	69	70
Sex (female, %)	56%	68%	71%	52%	63%	47%	57%
The three most-used TKA designs							
1	Triathlon ^b	Triathlon ^b	Attune ^d	Triathlon ^b	NexGen ^c	NexGen ^c	
2	NexGen Flex CR ^c	NexGen ^c	NexGen ^c	Attune ^d	LCS Complete ^d	PFC ^d	
3	NexGen Flex LPS ^c	PFC Sigma ^d	Legion ^e	Genesis II ^e	PFC Sigma ^d	Triathlon ^b	
Revision due to loosening of all TKA in registry (%)	26%	9%		19%		26%	26%
TKAs (n)	547,407	194,787	39,782	93,497	29,834	109,393	975,739

^aIn 95% of public hospitals.

^bStryker Inc, Mahwah, NJ, USA

^cZimmer Inc, Warsaw, IN, USA

^dDeputy Synthes, Warsaw, IN, USA

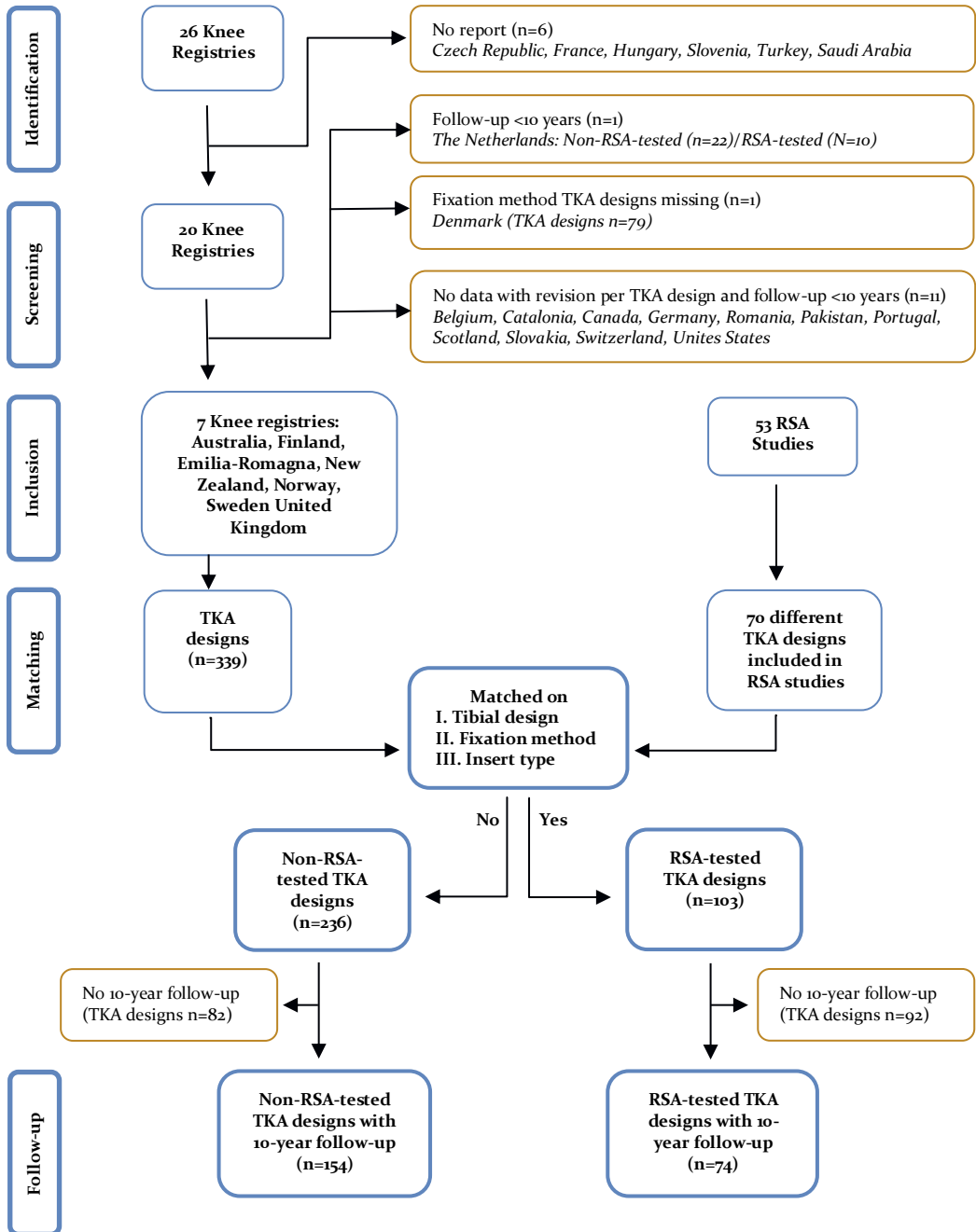
^eSmith&Nephew, Memphis, TN, USA

reconstruction prostheses were excluded. The number of designs ranged between 13 and 143 per annual report.

To identify whether a TKA design was previously tested with RSA, we used the data from a recent meta-analysis.¹⁵ In short, this meta-analysis searched PubMed, EMBASE, Web of Science, and the Cochrane Library for studies using RSA and primary TKA before July 2016. Data on all designs were extracted from the 53 included studies, which included 70 different RSA-tested TKA designs [Fig. II.I]. Design characteristics of the TKA reported in the knee arthroplasty registries were extracted and, if possible, matched to the TKA designs reported in the RSA-studies. Every TKA design reported in the included knee arthroplasty registries was classified as non-RSA-tested or RSA-tested, resulting in two groups in every registry. For a design to be classified as RSA-tested, the design in the registry had to be identical to the design reported in an RSA study. If the insert was not specified in the registry, but the design and fixation matched the TKA design, the design was classified as RSA-tested [Fig. II.I].

Seven registries with 339 TKA designs were included of which 236 were classified as non-RSA-tested and 103 as RSA-tested. Fixation was uncemented for 54 designs and cemented for 285 designs. Cruciate-retaining inserts were used in 110 designs and posterior-stabilizing in 72 designs or not explicitly mentioned. Mobile bearings were used in 49 designs. The Norwegian registry only reported 3-year and 10-year revision rates and could therefore not be included at 5 years. At 5 years, 191 TKA designs were identified as non-RSA-tested [Supplemental data II.I]. In addition, 92 TKA designs were identified as RSA-tested [Supplemental data II.II]. At 10 years, 154 TKA designs were classified as non-RSA-tested [Supplemental data II.III] and 74 designs were identified as RSA-tested [Supplemental data II.IV]. Between baseline and 10 years, 82 non-RSA-tested and 29 RSA-tested designs could not be included as these had not reached 10 years of follow-up.

Figure II.I Inclusion Flowchart



Data Analysis

First, a random-effects model was used to calculate the pooled all-cause revision percentages and their standard errors at 5 and 10 years of follow-up for the non-RSA-tested and RSA-tested TKA designs, including a DerSimonian-Lard estimator to take into account the heterogeneity between the designs.²⁹ RSA-tested (yes or no) was included as a factor to test for a difference between groups at 5 and 10 years of follow-up. Moreover, pooled all-cause revision percentages and their standard errors were calculated separately for each registry for non-RSA-tested and RSA-tested TKA designs.

In all random-effects models, a DerSimonian-Lard estimator was used to estimate heterogeneity.²⁹ In a sensitivity analysis, the more conservative empirical Bayes estimator was used to test whether the heterogeneity estimator would affect the results.³⁰ The I^2 was used to estimate the extent of heterogeneity. The heterogeneity is the variation between the designs in both groups, which is considered low, moderate, or high if I^2 is 25%, 50% or 75%, respectively.^{31, 32} Outcomes are given in percentages with 95% CIs. The Metafor Package in R Statistics (version 3.6.1; R Foundation for Statistical Computing, Vienna, Austria) was used for all analyses.³³

Post-hoc sensitivity analyses

We performed three post-hoc sensitivity analyses to test the impact of various assumptions on the primary outcome. The first analysis excluded data from registries for which the fixation method was missing (Sweden and Emilia-Romagna, Italy), and data from the registry that did not report the insert of the design (New Zealand). The second analysis included the four RSA studies from the meta-analysis that were excluded from the primary analysis because of not reporting migration data or other reasons. This resulted in reclassification of six non-RSA-tested TKA designs as RSA-tested. The third analysis included data from the Danish and Dutch knee arthroplasty registries that fulfilled all but one of the inclusion criteria.^{34, 35} The Danish TKA designs lacked information on fixation and were assumed to be

cemented in this sensitivity analysis, and the Dutch registry published 10 years follow-up data in November 2019 (after initial manuscript submission) and could only be included recently.

Results

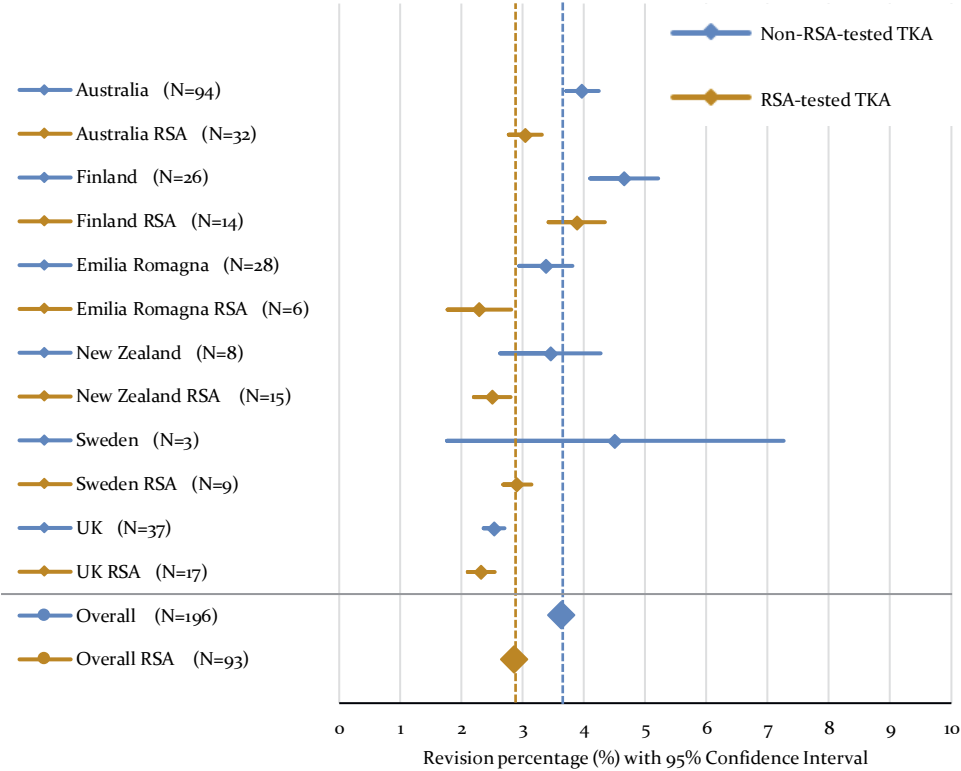
Revision Rates of Non-RSA-tested and RSA-tested TKA Designs at 5 Years of Follow-up

All-cause revision at 5 years was slightly less for the RSA-tested designs than for the non-RSA-tested designs [Fig. II.II]. Mean all-cause revision rates at 5 years for non-RSA-tested and RSA-tested implants were 3.6% (95% CI 3.4 to 3.8) and 2.9% (95% CI 2.7 to 3.0), with a mean difference of 0.6% (95% CI 0.4 to 0.8; $p < 0.001$) favoring RSA-tested implants. Using the more conservative Empirical Bayes estimator, the mean difference was 0.7% (95% CI 0.3 to 1.0; $p < 0.001$) in favor of RSA-tested implants.

The revision rates of the RSA-tested TKA designs in the registries ranged between 2.3% and 3.9%, whereas revision rates of the non-RSA-tested TKA designs ranged from 2.5% to 4.7%. In all registries, the point estimate of RSA-tested TKA designs was lower than that of non-RSA-tested designs, but the absolute difference between groups was smallest in the United Kingdom (0.2% at 5 years of follow-up). The highest revision rate of RSA-tested implants was reported in Finland (3.9% at 5 years of follow-up). New Zealand and Sweden used more RSA-tested TKA designs than non-RSA-tested TKA designs, in contrast to other countries. Australia had the greatest number of TKA designs registered ($n = 126$). Within the RSA-tested and non-RSA-tested groups, high variation was found between the TKA designs, expressed by the high heterogeneity (I^2 96% in the non-RSA-tested group and 98% in the RSA-tested group). Including fixation or insert in the model did not reduce the heterogeneity, suggesting that there is large variation in revision rates between designs. In addition, it is important to note that although a slightly lower mean all-cause revision rate was found for RSA-tested TKA, some non-RSA-tested TKA

performed well, whereas some RSA-tested TKA performed poorly.

Fig. II.II This forest plot shows revision rates of the non-RSA-tested and RSA-tested TKA designs with 95% CIs at 5 years of follow-up per registry and the pooled revision rate per group with 95% CI. In addition, the sensitivity analysis including designs from the Dutch and Danish knee arthroplasty registry.

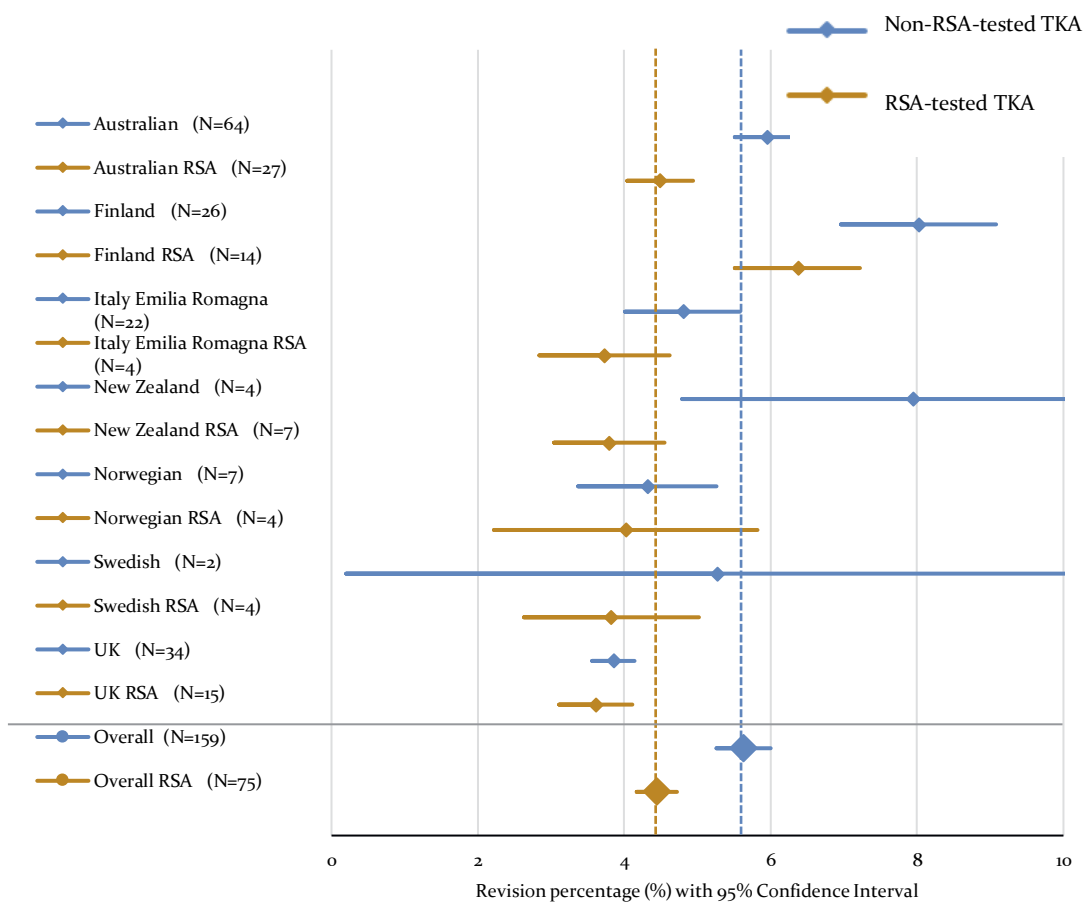


Revision Rates of Non-RSA-tested and RSA-tested TKA Designs at 10 Years of Follow-up

Similarly, all-cause revision at 10 years was slightly less common among RSA-tested designs than it was in non-RSA-tested designs [Fig II.III]. Mean all-cause revision rates at 10 years for non-RSA-tested and RSA-tested implants were 5.5% (95% CI 5.2 to 5.9) and 4.4% (95% CI 4.1 to 4.7), with a mean difference of 0.9% (95% CI 0.4 to

1.3; $p < 0.001$) favoring RSA-tested implants. Using the more conservative Empirical Bayes estimator, the mean difference was 0.9% (95% CI 0.2 to 1.6; $p = 0.01$) favoring RSA-tested implants. The revision rates in the registries ranged between 3.9% and 8.0% for non-RSA-tested and between 3.6% and 6.4% for RSA-tested TKA designs with large heterogeneity in both groups (I^2 97%).

Fig. II.III This forest plot shows revision rates of the non-RSA-tested and RSA-tested TKA designs with 95% CIs at 10 years of follow-up per registry and the pooled revision rate per group with 95% CI. In addition, the sensitivity analysis including designs from the Dutch and Danish knee arthroplasty registry.



Post-hoc Sensitivity Analyses

First, excluding the data from registries with assumed fixation method or inserts (Sweden, New Zealand and Emilia-Romagna, Italy) resulted in a slightly smaller mean difference in all-cause revision rate between groups of 0.5% (95% CI 0.2 to 0.8; $p < 0.001$) at 5 years and 0.7% (95% CI 0.2 to 1.2; $p = 0.003$) at 10 years. Second, reclassifying the TKA-designs from the excluded studies did not influence the mean revision rates in both groups nor on the difference between groups (data not shown). Third, including both the Danish and Dutch registries, the mean difference of all-cause revision rate between RSA-tested and non-RSA-tested designs was 0.6% (95% CI 0.4 to 0.8; $p < 0.001$) in favor of RSA-tested designs at 5-year follow-up. At 10-year follow-up, the mean difference in all-cause revision was 0.9% (CI 95% 0.4 to 1.3; $p < 0.001$) favoring RSA-tested implants.

Discussion

Regulations regarding the introduction of new orthopaedic devices should have a healthy balance between innovation and patient safety.¹⁸ To improve patient safety, new medical device regulations were established in Europe; they require clinical evidence before new implants are introduced to the European Union market.³⁶ RSA may be an important part of such clinical testing, and its use as an early-warning system for implants likely to fail as a result of aseptic loosening has often been proposed.^{14, 16, 18, 37, 38} However, it is unknown whether RSA-tested TKA designs are associated with a lower revision rate during long-term follow-up in registries, though this may seem likely if problematic RSA tested designs are withdrawn from the market. By pooling data from several national registries and a regional registry, we found that implants that had undergone RSA testing, overall had a slightly (about 1%) lower all-cause revision rate at 5 and 10 years compared with implants that had not undergone RSA testing.

We should consider the following limitations. First, our study was an observational study and cannot imply causation between RSA and a lower TKA revision rate, but

rather showed an association between these two factors. Second, the classification of TKA designs as RSA-tested or non-RSA-tested came from another meta-analysis.¹⁵ However, a post-hoc sensitivity analysis showed similar results after reanalyzing the data from the meta-analysis and reclassifying the six TKA-designs that were excluded in the meta-analysis from non-RSA-tested to RSA-tested. Third, we should consider the possibility that differential loss to follow-up may have influenced the results, although here the loss to follow-up was comparable between both groups. Fourth, revision rates as reported from the registries were used as the outcome measure, which is relatively crude. Such rates are influenced not only by the performance of a particular TKA design, but also by patients' complaints (for example, pain) and the surgical decision-making process, which is affected by factors such as patients' comorbidities, cultural differences between patients (such as pain acceptance), and waiting lists.³⁹ Nevertheless, many implants were included in the study, and we assume that both groups were similarly affected by these factors influencing revision. Fifth, mechanical loosening of the tibia is not the only reason for revision. Other common reasons are instability and infection, which are not assessed by RSA.³⁵ A phased introduction should therefore include clinical trials to assess these contributing factors for revision. In addition, the absolute difference was small at both 5 and 10 years (less than 1%), raising the question of the relevance of this effect. However, this effect should be interpreted considering the total revision rate, which is also low (about 5% at 10 years), meaning an absolute difference of 0.5% to 1% results in a decrease of approximately 10% to 20% for all-cause revision at 5 and 10 years. Considering the enormous number of TKA procedures performed globally, a 1% decrease in TKA revision could have a tremendous impact on the burden for patients needing a TKA revision and result in considerable reduction of health-related costs. Another limitation that should be noted is that there was high heterogeneity in all analyses, which could not be explained by the fixation method or the different inserts (data not shown). Heterogeneity is thus likely attributed to the many different designs included in the study with varying performance between the different designs. It should thus be emphasized that not all non-RSA-tested TKA

designs performed poorly and, vice versa, not all RSA-tested TKA designs performed well. Finally, we had to assume the fixation method for two registries and the insert type for one registry, which might have results in misclassification of some TKA designs although our sensitivity analysis showed this was not likely to change the results or conclusions.

We found that RSA-tested TKA designs had a slightly (about 1%) lower mean all-cause revision rate at 5 and 10 years than non-RSA-tested designs. These results are in line with a previously published study comparing non-RSA-tested and RSA-tested TKA designs in three knee arthroplasty registries up to 5-year follow-up.¹⁴ Our findings might be explained by the fact that RSA could provide an early warning about inferior TKA designs that fail because of aseptic loosening of the tibia. This early warning function could theoretically lower revision rates if poorly performing implants were withdrawn from the market or no longer used, and well-studied and excellent-performing TKA designs continuing to be used. Given our observational study we were unable to test this hypothesis in the present study or determine whether this is the case. Possible alternative explanations could be that RSA testing is a proxy for a rigorous clinical testing program by the manufacturer, or that more prudent surgeons are more likely to use RSA tested implants.

Before introduction of the new European medical device regulations, a phased introduction of new implants was proposed by several authors and the Idea, Development, Exploration, Assessment, Long-term Study—Devices (IDEAL) consortium to guide the introduction of novel devices.^{14, 16, 18, 37, 38, 40} The best clinical introduction of a new TKA implant, in our opinion, would be to clinically evaluate implant fixation (that is, micromotion) as well as the surgical procedure. Thus, RSA studies and larger prospective studies could be nested in national or regional registries. Beyond Compliance, an initiative originating from the United Kingdom supporting the safe introduction of implants by bringing clinicians, implant manufacturers and an independent expert panel together to assess outcomes of joint replacements, could be performed parallel to RSA studies.^{18, 41} RSA studies or implant

migration studies (Einzel-Bild-Röntgen-Analyse, CT-RSA) could play an important role in such a phased, stepwise introduction of new implants.⁴² Because of the accuracy of the RSA technique, there is no need to expose large groups of patients to new implant designs that could potentially be inferior to the current state-of-the-art designs. In addition to exposing fewer patients, shorter follow-up is needed, as migration results of implants after 2 years are often able to show differences in migration, in contrast to the long-term follow-up needed for classic observational studies, with survival of the implant as endpoint.^{14, 16}

Reducing the revision rate of TKA is particularly of interest because this procedure is estimated to increase by approximately 600% between 2005 and 2030, resulting in 268,200 revisions in 2030 in the United States alone.¹ Considering that the mean cost of revision TKA in the United States is USD 49,360, using only selected well-performing TKA designs might save billions of dollars annually.⁴³

Conclusions

The number of different TKA designs is enormous, with new designs being introduced almost annually, and surgeons should remain skeptical about novel designs without proper evidence.^{4, 20} Several well-studied and excellent-performing TKA designs are currently available, and new designs should prove that they outperform these legacy products before replacing them. RSA testing is one method of testing new prosthesis introductions. Although there are exceptions, we found that TKA designs tested in an RSA setting were associated with a slightly lower (about 1%) mean all-cause revision rate at 5-year and 10-year follow-up than those tested in a non-RSA setting. The relevance of this small effect should be interpreted in the context of this being a relative decrease of approximately 20% for all-cause revision at 5 and 10 years while also considering the enormous number of TKA procedures performed globally. Future studies should address the possible explanations for the association found between RSA-testing and a lower mean all-cause revision.

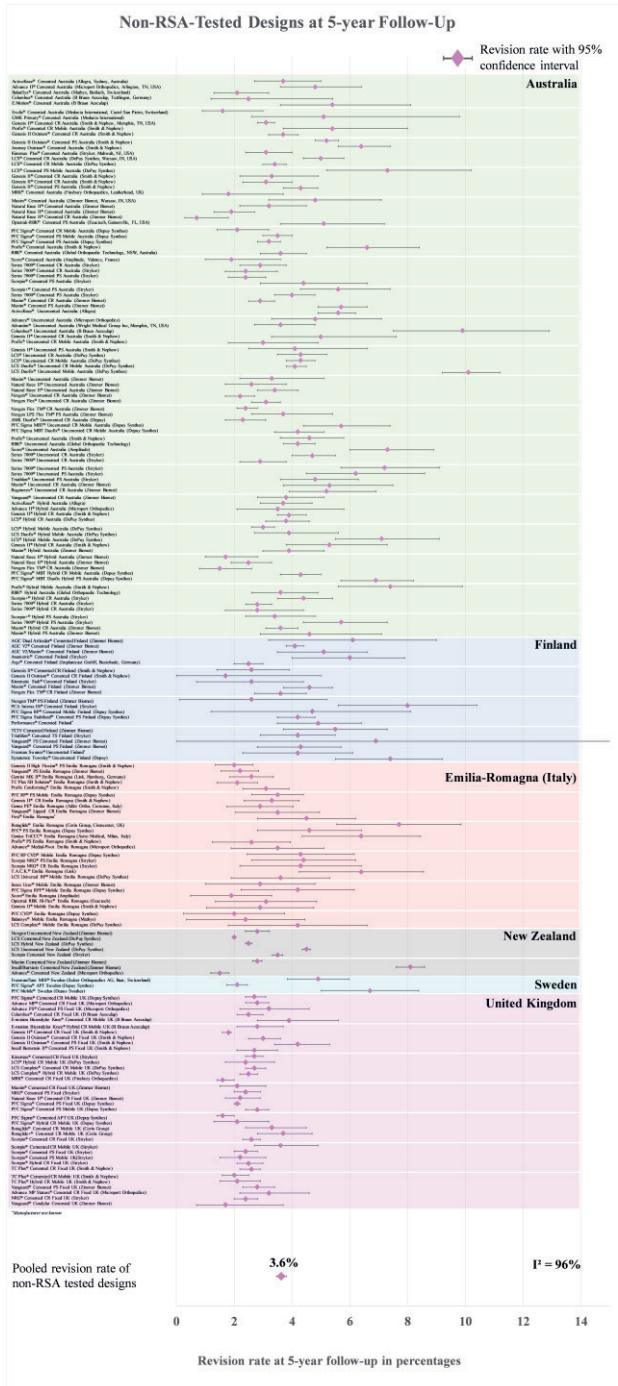
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Supplemental data



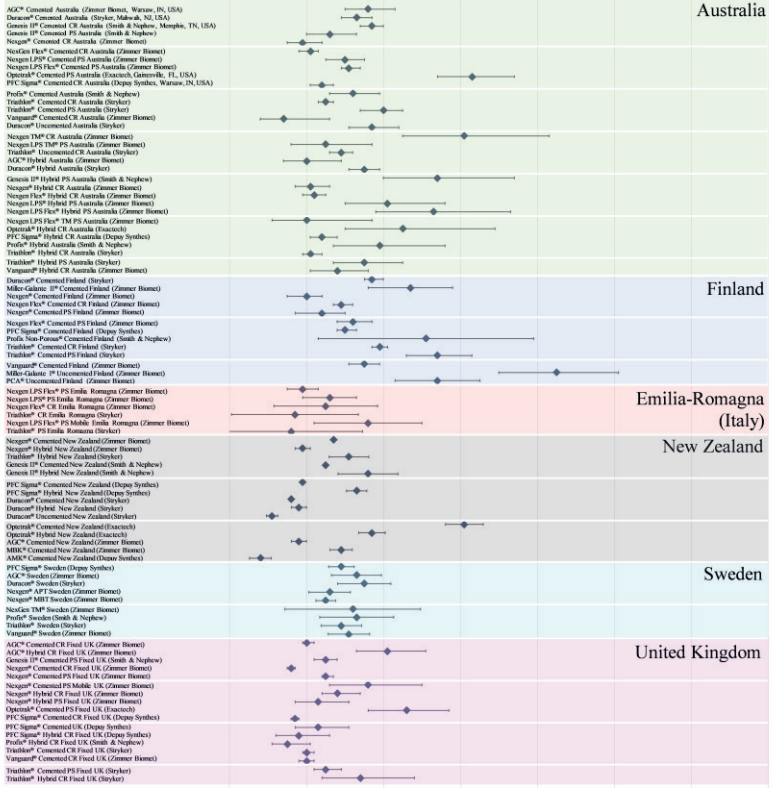
Supplemental II.I

This forest plot shows revision rates with 95% CIs at 5 years of follow-up of the non-RSA-tested TKA designs, subdivided per registry, and the pooled revision rate at 5 years of follow-up with 95% CI. The heterogeneity between TKA designs stands out, with an I^2 of 96%.

High-quality image available online

RSA-Tested Designs at 5-year follow-up

Revision rate with 95% confidence interval



Pooled mean revision rate of RSA-Tested

2.9%

I² = 98%

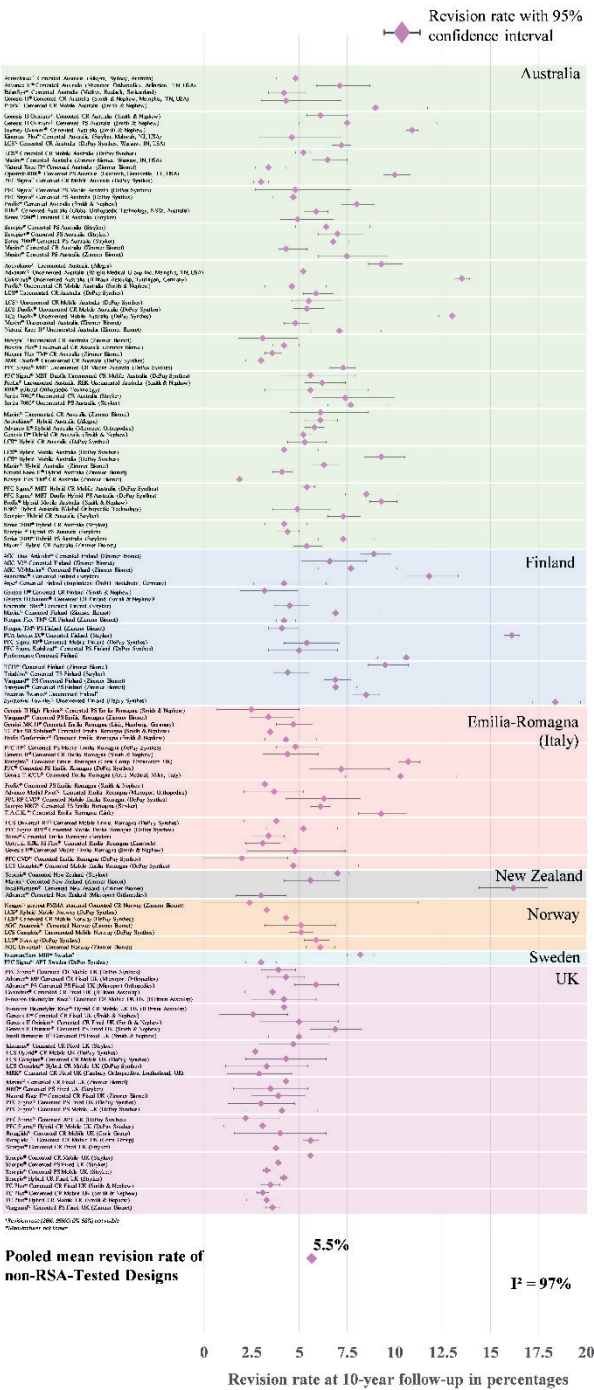
Revision rate at 5-year follow-up in percentages

Supplemental II.II

Forest plot showing the revision rates with 95% confidence intervals at 5-year follow-up of the RSA-tested TKP designs subdivided per registry, and the pooled revision rate at 5-year follow-up with 95% confidence interval. The heterogeneity between the TKP designs stands out with a I² of 98%.

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Non-RSA-Tested Designs at 10-year Follow-Up

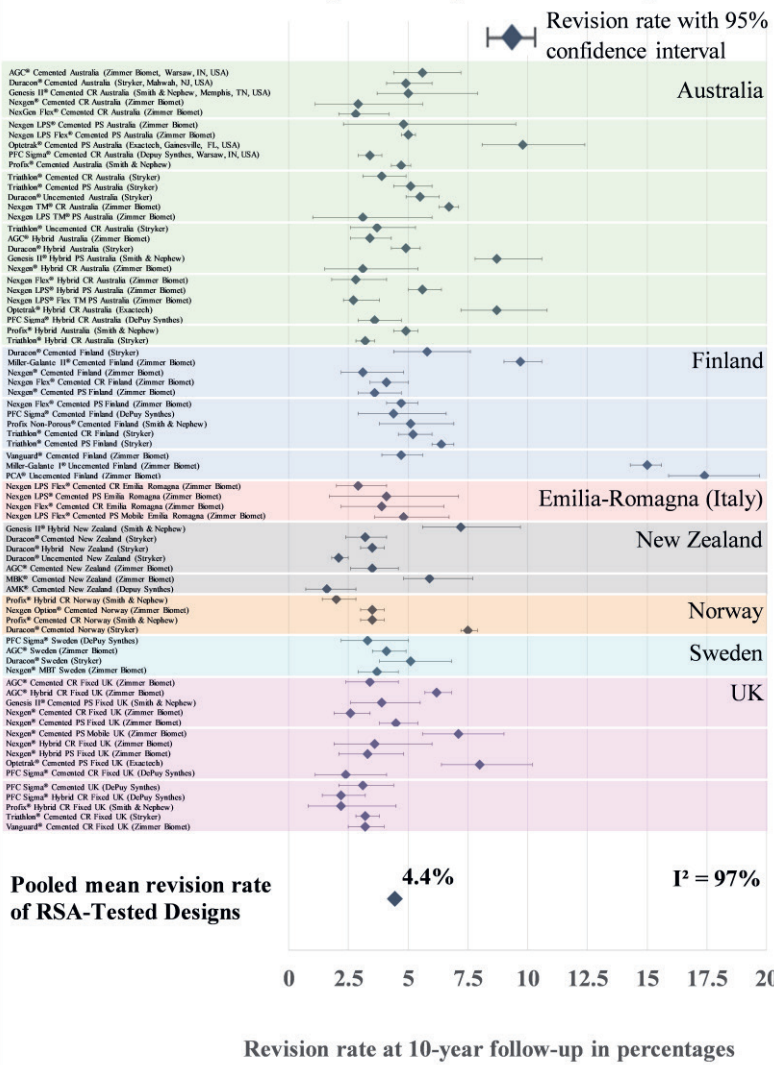


Supplement II.III

Forest plot showing the revision rates with 95% confidence intervals at 10-year follow-up of the non-RSA-tested TKP designs subdivided per registry, and the pooled revision rate at 10-year follow-up with 95% confidence interval. The heterogeneity between TKP designs stands out with a I^2 of 97%

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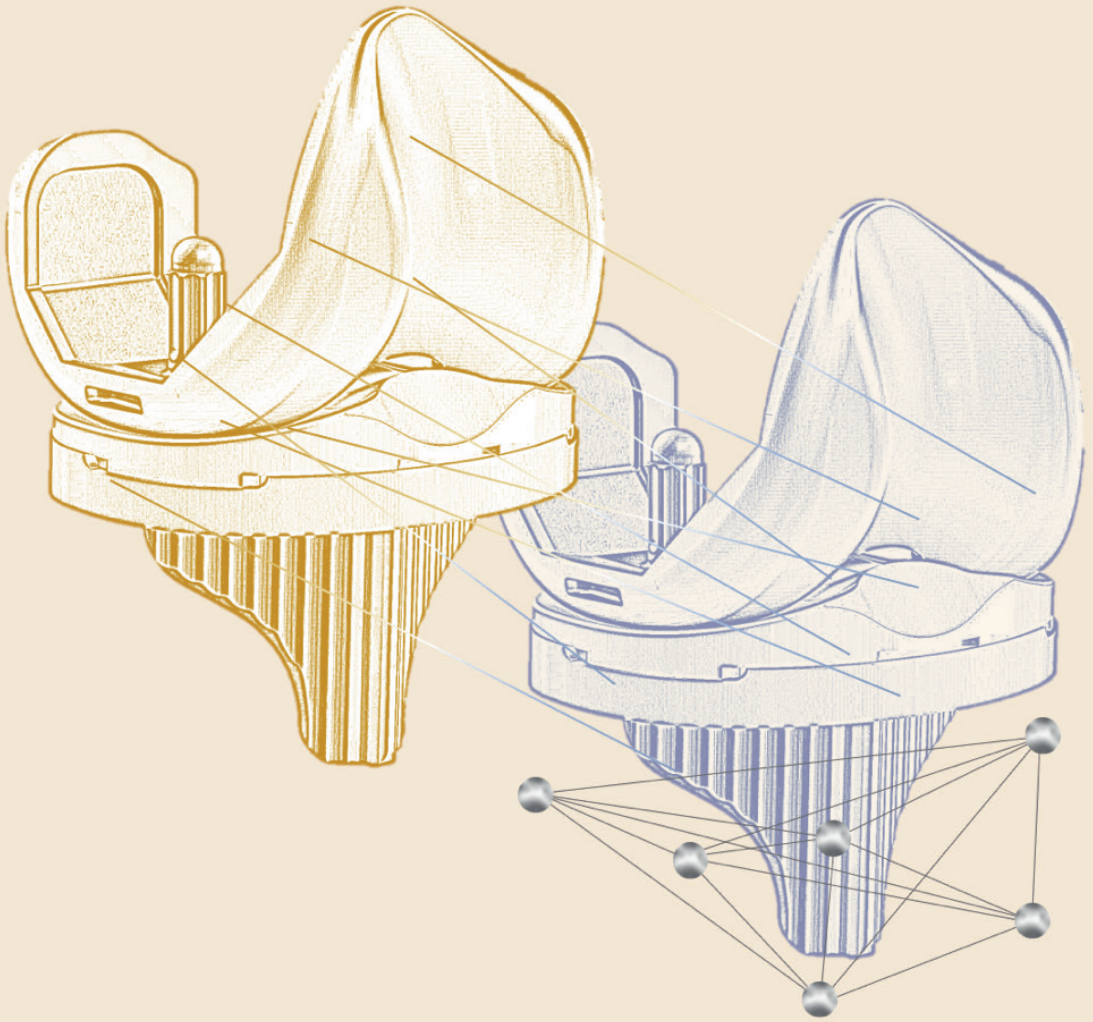
RSA-Tested Designs at 10-year Follow-Up



Supplemental II.IV

Forest plot showing the revision rates with 95% confidence intervals at 10-year follow-up of the RSA-tested TKP designs subdivided per registry, and the pooled revision rate at 10-year follow-up with 95% confidence interval. The heterogeneity between the TKP designs stands out with a I^2 of 97%.

High-quality image available online



Chapter III

Bio-markers to discriminate between aseptic loosened and stable total hip or knee implants

A systematic review

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Abstract

Loosening is the major cause for failure of total hip and total knee replacements (THRs/TKRs). Pre-emptive diagnostics of asymptomatic loosening could open strategies to prevent gross loosening. A multitude of biological markers may discriminate between loosened and stable implants, but it is unknown which have the best performance. The present systematic review aims to assess which markers have shown the most promising results in differentiating between stable and aseptic loosened THRs and TKRs. PubMed, Embase, Web of Science, Cochrane library and Academic Search Premier were systematically searched up to January 2020 for studies including THR/TKR and markers to assess loosening. Two reviewers independently screened records, extracted data and assessed the risk of bias using the ICROMS-tool to classify the quality of the studies. Thirty-five (five high-quality) studies were included, reporting on a median of 50 patients (range 18–527). Serum, urine, and radiological markers were studied in 22, ten and seven studies, respectively. Tumour necrosis factor α , interleukinb and osteocalcin were significantly higher in loosened compared to stable implants. Urinary N-terminal telopeptide had significantly elevated levels in loosened prostheses. Radiologically measured migration and radiolucent lines were increased in loosened implants. In conclusion, several serum, urine, and radiological markers were promising in discriminating between loosened and stable implants. We recommend future studies to study these markers in a longitudinal fashion to assess whether progression of loosening is associated with an increase or decrease of these markers. In particular, high-quality studies assessing the usability of these markers are needed.

Keywords: Arthroplasty, Loosening, Markers

Background

Aseptic loosening is the leading cause for revision of total hip and total knee replacements (THRs/TKRs) reported in national arthroplasty registries.^{1, 2} Aseptic loosening may have a multitude of causes among which factors related to implant design, surgical technique, and genetic predisposition.³⁻⁵ For the implant related causes, the polymer, bone cement, and metal wear particles released due to repetitive motion of the joint can induce inflammation and osteolysis.⁶⁻⁸ The latter may differ between individuals due to reaction of the foreign body inflammatory response.^{4, 5} Other mechanisms influencing aseptic loosening such as stress-shielding, micromotion, high fluid pressure and endotoxins have been proposed as well.⁹⁻¹²

Ultimately, aseptic loosening can be confirmed intraoperatively, but any diagnostic before extensive surgery helps in the decision to perform surgery in patients with complaints of their implant. Even more since the presence of pain of THRs or TKRs is not always associated with a loosened implant. Except implant migration diagnostics, few other markers are available to diagnose aseptic loosening at an early stage in asymptomatic patients.^{12, 13} Earlier identification of loosened implants is important to prevent complications as radiological signs only become visible after several years and patients could be asymptomatic up to the point that major revision surgery is required.^{14, 15} Furthermore, late diagnosis of loosening could increase the incidence of complications such as fractures with an increased mortality risk after revision surgery as consequence.¹⁶ Although currently no other treatment besides revision surgery is available for aseptic loosened implants, novel treatments such as minimal invasive refixation using cement injection or drugs such as bisphosphonates to prevent bone loss could be viable options in the future.¹⁷⁻²¹ Pre-emptive diagnostics of implant loosening in asymptomatic patients could potentially open strategies to not only prevent more severe implant loosening by acting as a therapeutic target, but also has the potential to monitor disease progression.²²

Implant loosening is a complex mechanism which is controlled by an intricate balance of biomechanical forces and a balance between osteoblasts and osteoclasts. The latter can be quantified by several markers such as serum and urine markers.^{7, 23-25} Several studies assessed these markers to discriminate between aseptic loosened and stable implants.^{26, 27} However, the number of patients included in these studies was mostly too small to draw any conclusions about the validity of the marker to differentiate between aseptic loosened and stable implants. Moreover, a wide variety of markers in THRs and TKRs have been studied, making it difficult to ascertain the most promising test to discriminate between aseptic loosened and stable implants. Two systematic reviews have previously been conducted, in 2011 and 2014, to assess the feasibility of several markers to differentiate between aseptic loosened and stable implants. However, these reviews did not assess the quality of the included studies and need updating to determine the most promising marker.^{26, 27} Therefore, the present systematic review aims to identify the most frequently studied markers which are able to discriminate between aseptic loosened and stable THRs and TKRs, and therefore have the most promising results in differentiating between these groups.

Methods

This systematic review was performed in concordance with the PRISMA 2020 statement and was registered with Prospero (CRD42019133137) prior to the screening of studies.^{28, 29} No funding was acquired for the present review. Level of evidence: 3a.

Search strategy and selection

A search strategy was constructed by an experienced librarian (JS). PubMed, Embase, Web of Science, Cochrane library, and Academic Search Premier were searched for publications up to the 30th of January 2020 without restriction of publication date. Based on the previous systematic reviews, the current search was composed of three

components: THR or TKR (e.g. “Arthroplasty, replacement, hip”[Mesh], “Arthroplasty, replacement, knee”[Mesh]); aseptic loosening, osteolysis or wear (e.g. “Osteolysis”[Mesh], “Prosthesis failure”[Mesh]); and determinants for aseptic loosening (e.g. “Biomarkers”[Mesh], “Risk factors”[Mesh]; see Appendix A for the complete search strategies). Wear was included to prevent missing relevant studies, but studies reporting only wear were excluded during screening.

Two reviewers (SH and PvS) screened all titles and abstracts independently. Any discrepancy was resolved through discussion. A third reviewer was available if consensus could not be reached. Inclusion criteria were studies comprising primary THRs and/or TKRs having both a study group with aseptic loosening (i.e. confirmed during revision surgery) or osteolysis (i.e. confirmed radiologically) as well as a control group with stable implants. Studies were excluded that did not use a marker, defined as a non-operative test used to differentiate between aseptic loosened and stable implants. Moreover, studies without aseptic loosening as outcome as well as studies among patients with an infection, tumour reconstructions or metal-on-metal implants were excluded. In addition, animal studies and in vitro studies were excluded. Studies in English, Dutch, German, and French were eligible for inclusion and were translated by both reviewers (SH and PvS). Authors were contacted if a full-text could not be found.

Data extraction

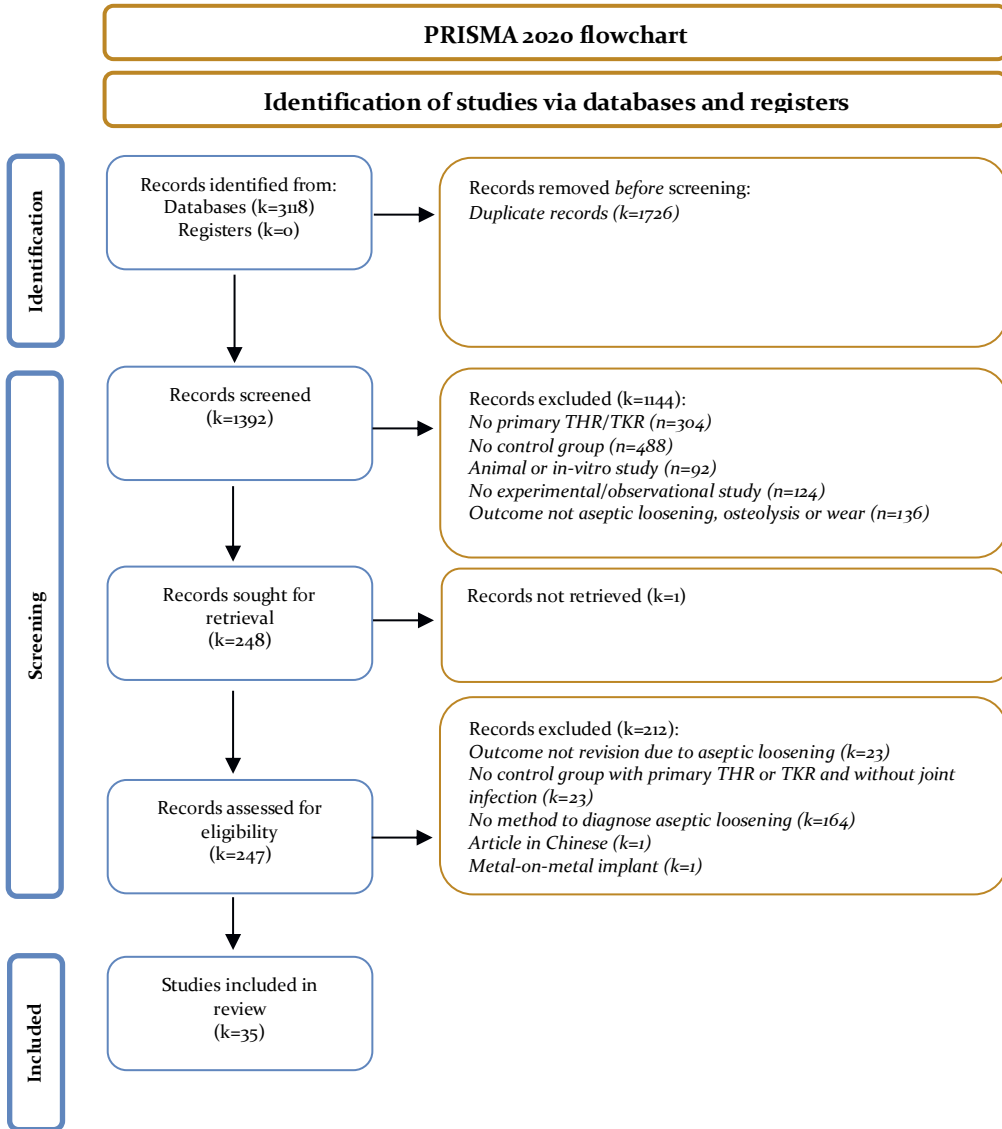
Data were extracted by both reviewers independently using a prespecified SPSS file (IBM SPSS Statistics 26.0; IBM Corp, Armonk, NY, USA). Data extracted were author, title, year of publication, country of the first author, study design, specific joint (i.e. THR and/or TKR) and the marker used to differentiate between loosened and stable implants. The number of patients in the aseptic loosened and the control group were collected as well as the percentage of female patients, the mean age of both groups and the primary diagnosis of the patients. Fixation method and hip bearing was collected only in THR studies. Outcomes of studies were collected in the original

unit including confidence intervals, standard errors (se) or standard deviations (SD), if available. If absolute values were not reported in the text but only in a graph, the values were estimated from the graph. If the same marker was reported by three or more studies, results were plotted in a forest plot. Differences between loosened and stable implants were assessed at diagnosis or before surgery. In case of longitudinal data collection, the final measurement before revision surgery was used and plotted. Data were not pooled because patients, the method of data reporting (e.g. median or mean) and the units of outcomes differed significantly between studies. If the se was not reported, it was calculated by dividing the SD by the square root of the number of patients included.³⁰

Assessment of risk of bias

The risk of bias (RoB) was assessed independently by both reviewers (SH, PvS) using the Innovative Tools for Quality Assessment: Integrated Quality Criteria for Review of Multiple Study Designs (ICROMS).³¹ The ICROMS comprises seven dimensions with three to six specific criteria per dimension. Every study design must meet a minimum score and mandatory criteria to be included in a review. However, the present review included all studies independent of the ICROMS score and reported the RoB for every study with the rationale that the RoB could be taken into account when weighting study results while excluding studies with high or medium RoB would result in the loss of possibly valuable information. All included studies in the present review were cohort studies for which the specific ICROMS criteria are outlined in appendix B. Studies scoring at least 18 points and fulfilling the mandatory criteria were classified as high quality (HQ) studies. Studies scoring at least 18 points but failing to fulfil the mandatory criteria were classified as moderate quality (MQ) studies. Studies scoring less than 18 points were classified as a low quality (LQ) study. There were no studies that fulfilled all the mandatory criteria but failed to score at least 18 points.

Figure III.I inclusion flowchart. THR = Total hip replacements; TKR = Total knee replacements



Results

Study selection

The search yielded 3118 records. After removing duplicates, 1392 records remained. A total of 1144 records were excluded as 304 did not involve primary THR or TKR, 488 did not have a control group, 92 involved animal or in-vitro studies, 124 did not have an experimental or observational design, and 136 did not use aseptic loosening, osteolysis or wear as outcome, resulting in 248 reports to be assessed for eligibility. One report could not be retrieved. Of the 247 reports, 212 were excluded as 23 did not involve aseptic loosening, 23 did not have a control group with a stable primary THR/TKR without a joint infection, 164 did not involve a marker for aseptic loosening, one comprised metal-on-metal hip implants, and one article was in Chinese, leaving 35 studies to be included [Fig. III.I].

Risk of bias within studies

Five studies scored at least 18 points on the ICROMS quality assessment score, fulfilled the mandatory criteria, and were classified as HQ studies. Fifteen studies scored at least 18 points but did not fulfil the mandatory criteria and were classified as MQ studies. Fifteen studies scored less than 18 points and were classified as LQ studies [Table III.I]. The mean ICROMS score was 18 points (SD 3.1). Most studies failed to fulfil the mandatory criteria due to not addressing incomplete data. In addition, only a few studies performed a blinded assessment of the outcomes [Table III.I].

Study characteristics

Thirty studies included only THR, four studies included both THR and TKR, and one study included only TKR. Markers used in these studies were serum markers (n = 22), urine markers (n = 10), radiological markers (n = 7) or skin markers (n = 1). The

Table III.I

Author	Year	1A*	2E*	3E	3F	3G*	4C*	5B	6C	7A	7B	7C	7D	7E	ICROMS score
Chaganti ³²	2013	2	2	2	2	2	2	2	2	2	2	2	2	2	26
Trehan ⁴⁵	2017	2	2	0	2	2	2	2	2	2	2	2	2	2	24
Streit ⁵⁸	2016	2	2	0	2	2	2	2	2	2	2	2	1	2	23
Morakis ⁶³	2011	2	2	0	2	2	2	2	2	2	0	2	2	2	22
Kobayashi ⁶⁰	1997	2	2	2	1	2	2	2	2	2	0	2	2	0	21
Hundric-Haspl ³³	2006	2	2	0	2	2	0	2	2	2	2	2	2	2	22
Ovrenovits ⁴⁷	2015	2	2	0	2	2	0	2	2	2	2	2	1	2	21
Savarino ⁶⁸	2010	2	0	2	2	1	2	2	2	2	0	2	2	2	21
Ross ²²	2018	2	2	0	2	0	2	1	2	2	2	2	1	2	20
Lawrence ⁴⁸	2015	2	2	0	2	2	0	2	2	2	0	2	2	2	20
Streich ⁴⁰	2003	2	2	0	2	2	0	2	2	2	0	2	2	2	20
Antoniou ⁵⁵	2000	2	1	0	2	2	0	2	2	2	1	2	2	2	20
Friedrich ³⁸	2017	2	2	0	2	2	0	2	0	2	2	2	1	2	19
He ³⁵	2013	2	2	0	2	2	0	1	2	2	0	2	2	2	19
Streich ³³	2009	2	2	0	2	2	0	2	2	1	0	2	2	2	19
Wilkinson ⁴²	2003	2	2	0	2	2	0	2	2	1	0	2	2	2	19
Witzleb ⁵⁶	2001	2	1	0	2	1	0	2	2	2	1	2	2	2	19
Granchi ³⁷	2006	2	0	0	2	2	0	2	2	2	0	2	2	2	18
Moreschini ³⁹	1997	2	2	0	2	2	0	2	2	2	0	2	2	0	18
Kreibich ⁶⁹	1996	2	2	0	2	2	0	2	2	2	0	2	2	0	18

Table III.I continued

Author	Year	1A*	2E*	3E	3F	3G*	4C*	5B	6C	7A	7B	7C	7D	7E	ICROMS score
Roato ⁴⁶	2010	2	1	0	0	2	0	2	2	2	0	2	2	2	17
von Schewelov ⁵⁴	2006	2	1	0	2	2	0	2	1	1	2	2	0	2	17
Schneider ⁴¹	1998	2	2	0	2	2	0	1	2	2	0	2	2	0	17
Stromberg ⁶¹	1996	2	1	0	2	1	2	1	2	2	0	2	2	0	17
Mont ⁷⁰	1995	2	2	0	1	2	2	0	2	2	0	2	2	0	17
Tang ⁴⁴	2016	2	1	0	2	2	0	2	2	2	0	2	2	0	17
Wu ³⁴	2009	2	0	0	2	1	0	2	2	2	0	2	2	2	17
Cenni ⁵¹	2003	2	0	0	2	2	0	2	0	2	0	2	2	2	16
Granchi ⁵²	2000	2	0	0	2	2	0	2	2	2	0	2	2	0	16
Gil-Albarova ⁶²	1992	2	1	0	1	2	0	2	2	2	0	2	2	0	16
Fiorito ³⁶	2003	2	0	0	2	2	0	1	2	2	0	2	2	0	15
Krimer ⁵⁹	1996	2	1	0	2	1	2	1	0	2	0	2	2	0	15
Schneider ⁴⁹	1997	2	1	0	2	1	0	1	2	1	0	2	2	0	14
Steinbeck ⁷¹	2014	0	0	0	2	0	0	2	0	2	2	2	2	0	12
Pellengahr ⁵⁷	2001	2	1	0	2	1	0	2	0	2	0	0	2	0	12

Table III.I Risk of bias (RoB) table. A score of 0 (i.e. did not fulfil the criteria), 1 (i.e. unclear if criteria is fulfilled), or 2 (i.e. did fulfil the criteria) points could be given to every criterion. * indicates the mandatory criteria and these criteria are dark coloured. The green highlighted studies have an ICROMS score ≥ 8 , and fulfil the mandatory criteria, and were therefore classified as low RoB/high quality. The grey highlighted studies have an ICROMS ≥ 8 points, but do not fulfil the mandatory criteria, and were therefore classified as moderate RoB/moderate quality. The red highlighted studies have an ICROMS < 8 points, and do not fulfil the mandatory criteria, and were therefore classified as high RoB/low quality. ICROMS = Integrated Quality Criteria for Review of Multiple Study Designs.

Table III.II

Author	Year	Joint	Fixation method	Assessment method	Study group with aseptic loosening or osteolysis	Number of patients (female) in loose group	Number of patients (female) in control group	Age loose group, mean in years	Age control group, mean in years
Chaganti ²	2013	Hip	Mixed fixation methods	Serum markers	Aseptic loosening	15 (5)	13 (4)	70	71
Trehan ⁵	2018	Hip	Mixed fixation methods	Serum markers	Aseptic loosening	20 (9)	10 (6)	68	63
Streit ⁸	2016	Hip	Mixed fixation methods	Radiography	Aseptic loosening	9 (3)	73 (40)	53	56
Morakis ⁴³	2011	Hip	Cemented	Serum markers Radiography	Osteolysis	12 (12)	12 (12)	72	73
Kobayashi ⁶⁰	1997	Hip	Mixed fixation methods	Radiography	Aseptic loosening	41 (24)	486 (332)	50	60
Hundric-Haspl ³³	2006	Hip & Knee	NR	Serum markers	Osteolysis	50 (40)	50 (43)	65	62
Ovrenovits ⁴⁷	2015	Hip	Uncemented	Serum markers	Aseptic loosening	10 (NR)	10 (6)	NR	60
Savarino ⁶⁸	2010	Hip	NR	Serum markers	Aseptic loosening	27 (33)	19 (15)	69	62
Ross ²	2018	Hip	Mixed fixation methods	Urine markers	Osteolysis	16 (7)	11 (4)	56	61
Lawrence ⁴⁸	2015	Hip	Cemented	Serum markers Urine markers	Osteolysis	26 (7)	24 (8)	73	74
Streich ⁴⁰	2003	Hip	Mixed fixation methods	Serum markers	Aseptic loosening	23 (10)	23 (12)	65 ^{median}	67 ^{median}
Antoniou ³⁵	2000	Hip	NR	Urine markers	Osteolysis	21 (3)	8 (0)	54	67
Friedrich ⁸	2017	Hip & Knee	NR	Serum markers	Aseptic loosening	51 (33)	21 (13)	68	64
He ³⁵	2013	Hip	Mixed fixation methods	Serum markers	Aseptic loosening	31 (8)	19 (10)	66	61
Streich ⁵³	2009	Hip	Uncemented	Urine markers	Aseptic loosening	52 (26)	52 (26)	65 ^{median}	63 ^{median}
Wilkinson ⁴²	2003	Hip	Cemented	Serum markers Urine markers Radiography	Osteolysis	23 (6)	26 (8)	73	75
Witzleb ⁵⁶	2001	Hip & Knee	Mixed fixation methods	Urine markers	Aseptic loosening	58 (42)	67 (48)	68	68
Granchi ³⁷	2006	Hip	Mixed fixation methods	Serum markers	Osteolysis	36 (23)	33 (20)	65	58
Moreschini ³⁹	1997	Hip	Mixed fixation methods	Serum markers	Osteolysis	9 (7)	13 (8)	63	62
Kreibich ⁶⁹	1996	Hip	Uncemented	Serum markers	Aseptic loosening	14 (5)	14 (7)	51	54

Roato ⁶	2010	Hip	Mixed fixation methods	Serum markers	Aseptic loosening	15 (NR)	15 (NR)	76	75
von Schewelov ⁵⁴	2006	Hip	Mixed fixation methods	Urine markers	Aseptic loosening	33 (19)	127 (76)	50	61
Schneider ⁴¹	1998	Hip	Mixed fixation methods	Serum markers Urine markers	Aseptic loosening	50 (27)	50 (29)	70	68
Stromberg ⁶¹	1996	Hip	Cemented	Radiography	Aseptic loosening	NR (NR)	42 (34)	NR	63
Mont ⁷⁰	1995	Knee	Uncemented	Radiography	Aseptic loosening	30 (21)	30 (21)	55	55
Tang ⁴⁴	2016	Hip	NR	Serum markers	NR	26 (12)	26 (10)	59	59
Wu ³⁴	2009	Hip	Mixed fixation methods	Serum markers	Aseptic loosening	43 (24)	16 (12)	67	61
Cenni ⁵⁸	2003	Hip	Mixed fixation methods	Serum markers	NR	23 (15)	15 (9)	69	58
Granchi ⁵³	2000	Hip	NR	Serum markers	NR	13 (9)	11 (5)	64 ^{median}	4.4 ^{median}
Gil-Albarova ⁶³	1992	Hip	Cemented	Skin test	Aseptic loosening	26 (15)	8 (5)	60	58
Fiorito ³⁶	2003	Hip	Uncemented	Serum markers	Osteolysis	8 (4)	10 (2)	62	66
Krismer ⁵⁹	1996	Hip	NR	Radiography	Aseptic loosening	NR (NR)	NR (NR)	NR	NR
Schneider ⁴⁹	1997	Hip	Mixed fixation methods	Serum markers Urine markers	Aseptic loosening	37 (22)	30 (17)	70	64
Steinbeck ⁷¹	2014	Hip	Uncemented	Tissue	Aseptic loosening	16 (5)	2 (2)	64	67
Pellengahr ⁵⁷	2001	Hip & Knee	NR	Urine markers	Aseptic loosening	35 (24)	34 (20)	68	67

Table III.11 Study characteristics. A study group had aseptic loosening if this was confirmed radiographically. The green highlighted studies have an ICROMS score ≥ 8 , and fulfil the mandatory criteria. The grey highlighted studies have an ICROMS ≥ 8 points, but do not fulfil the mandatory criteria. The red highlighted studies have an ICROMS < 8 points, and do not fulfil the mandatory criteria. NR = Not reported. ICROMS = Integrated Quality Criteria for Review of Multiple Study Designs. References are cited using superscript.

number of patients included ranged from 18 to 527 with a median of 50 (Interquartile range (IQR) 28 - 75). In the aseptic loosened group, the median number of patients was 26 (IQR 15 - 37; range 8 - 58), and the median number of patients in the control group was 20 (IQR 12 - 36; range 2 - 486). The number of women in each study varied between 10%-100%. The mean age in the aseptic loosened and control group was 64 years (SD 7.5), and 64 years (SD 5.8), respectively [Table III.II].

Serum markers

Twenty-two out of 35 (63%) included studies used serum markers of which three were HQ, 11 were MQ and eight were LQ studies [Table III.III].

Five studies assessed tumour necrosis factor α [TNF α ; Table III.III]. A statistically significant increased TNF α was found in loosened implants in one HQ, one MQ, and one LQ study,³²⁻³⁴ while no difference between groups was found in one MQ and one LQ study [Fig. III.II].^{35, 36} Aseptic loosened implants thus seemed to have higher TNF α compared to stable implants.

Four studies assessed receptor activator kappa-B ligand (RANKL) and osteoprotegerin (OPG) [Table III.III]. A statistically significant lower RANKL in loosened implants was found in one MQ study, and no difference was found in one HQ and two MQ studies [Fig. III.III]. A statistically significant higher OPG concentration in the aseptic loosened group was found in one MQ study, while the three other studies (one HQ and two MQ) found no difference between both groups [Fig. III.IV].^{32, 35, 37, 38} RANKL and OPG therefore did not seem to be different for aseptic loosened and stable implants.

Three MQ and two LQ studies assessed interleukin-1b (IL-1b) [Table III.III]. A statistically significant higher IL-1b concentration was found in the loosened group in one MQ and one LQ study,^{33, 34} while no difference between groups was found in another MQ and LQ study.^{35, 36} In one MQ study, IL-1b was detectable in four out of nine patients with aseptic loosened implants, and detectable in one out of thirteen

patients with stable implants [Fig. III.V].³⁹ Interleukin-1 (IL-1) was used in one HQ study which found comparable levels between loosened and stable implants.³²

Table III.III

Serum markers	Aseptic loosened group				Stable group			Quality
	Mean	Unit	SD		Mean	Unit	SD	
TNF α	7.1 ^{median}	pg/mL	11.6	>	1.5 ^{median}	pg/mL	1.3	HQ ³²
	32.7	pg/mL	32.4	>	22.9	pg/mL	18.7	MQ ³³
	32.2	pg/mL	50.6	=	15.9	pg/mL	7.4	MQ ³⁵
	37	pg/mL	18.1	>	8.1	pg/mL	5.5	LQ ³⁴
	4.32	pg/mL	5.2	=	3.84	pg/mL	1.13	LQ ³⁶
TNF mRNA	No difference			=	No difference			LQ ⁴⁴
TNFBeta	23175	pg/mL	8873	=	21120	pg/mL	13657	LQ ³⁶
IL-1	0.4	pg/mL	0.37	=	0.29	pg/mL	0.34	HQ ³²
IL-1b	3.7	pg/mL	5.5	>	1.5	pg/mL	2	MQ ³³
	1.75		1.44	=	0.97		0.29	MQ ³⁵
	Detectable in 4/9 patients			=	Detectable in 1/13 patient			MQ ³⁹
	9.1	pg/mL	3.9	>	6.4	pg/mL	4.1	LQ ³⁴
	2.15	pg	1.37	=	2.26	pg	0.89	LQ ³⁶
IL-2r	469	μ /mL	155	=	515	μ /mL	160	MQ ⁴⁰
IL-6	8.9	pg/mL	13.2	=	3.5	pg/mL	0.7	HQ ³²
	4.0	pg/mL	5.3	=	4.1	pg/mL	6.1	MQ ⁴⁰
	2.86	pg/mL	1.95	=	4.58	pg/mL	4.02	LQ ³⁶
IL-8	14.7	pg/mL	9	>	8.1	pg/mL	4.7	MQ ³³
IL-11	0	pg/mL		=	1.22	pg/mL	2.57	LQ ³⁶
OPG	7.9	pmol/L	3	=	7.5	pmol/L	2.2	HQ ³²
	No difference			=	No difference			MQ ³⁸
	26.7		19.9	=	24.1		5.2	MQ ³⁵
	4198	pg/mL	286	>	2397	pg/mL	1632	MQ ³⁷
RANKL	19.1	pmol/L	23.9	=	44.8	pmol/L	55	HQ ³²
	No difference			=	No difference			MQ ³⁸
	109.3		212.7	=	189		86.1	MQ ³⁵
	1483.0	pg/mL	1179	<	3312	pg/mL	2211	MQ ³⁷
RANKL mRNA	7.4 times higher in AL group			=	7.4 times higher in AL group			LQ ⁴⁴
hsCRP	1.86	mg/dL	4.76	=	0.24	mg/dL	0.19	HQ ³²
GM-CSF	3.97	pg/mL	5.33	=	Not detectable	pg/mL		MQ ⁴⁰
Elastase	58.91	ng/mL	46.78	=	56.56	ng/mL	44.95	MQ ⁴⁰
NTX	25.671		27.528	=	20.192		4.962	MQ ³⁵
	27.22	nMBCE	5.15	>	19.53	nMBCE	6.32	HQ ⁴³
PICP	-1251.864		308.54	=	-1444.529		169.25	MQ ³⁵
	107.5	ng/mL	70.4	=	82.2	ng/mL	32.8	LQ ^{41/49}
PINP	No difference			=	No difference			MQ ⁴²
PIINP	No difference			=	No difference			MQ ³⁹
CCL18	66	nM		=	78	nM		HQ ⁴⁵
CHIT1	98	nM		>	39	nM		HQ ⁴⁵
CTX	0.56	ng/mL	0.2	>	0.27	ng/mL	0.14	HQ ⁴³
β CTX								
Femoral loosening	0.43 ^{median}	ng/mL	31-0.56 ^e	=	0.33 ^{median}	ng/mL	22-0.48 ^f	MQ ⁴²
Acetabular loosening	0.45 ^{median}	ng/mL	23-0.57 ^e	=	0.33 ^{median}	ng/mL	29-0.45 ^f	MQ ⁴²
OC	28.9	ng/mL	10.38	>	18.66	ng/mL	5.05	HQ ⁴³
	No difference			=	No difference			MQ ⁴²
	Higher			>	Lower			LQ ^{41/49}
Osteoclastogenesis	134		64	>	22		21	LQ ⁴⁶
Osteoclasts rate, day 7	23.4	%	5.3	>	3.4	%	0.5	LQ ⁴⁴
Osteoclasts rate, day 14	82.5	%	14.7	>	17.7	%	5.6	LQ ⁴⁴
Osteoclasts rate, day 21	92.8	%	20.6	>	32.1	%	9.3	LQ ⁴⁴
Bone erosion rate day 14	43.40	%		>	12.90	%		LQ ⁴⁴
Bone erosion rate day 21	88.40	%		>	31.60	%		LQ ⁴⁴
CD4+ (%)	Higher			>	Lower			LQ ⁴⁶
CD8+ (%)	Higher			>	Lower			LQ ⁴⁶
CD11a								MQ ⁴⁷
Lymphocytes	1140.9		885.4	=	1086.4		456	
Monocytes	1901.5		1269	=	2637.4		3064.7	
Granulocytes	1344.2		1259.9	=	812.3		318.4	

Figure III.II Mean serum TNF α in the aseptic loosened and control group. Differences were assessed at diagnosis of loosening or before revision surgery. The blue, round shaped point estimates represent the AL groups and the yellow, diamond shaped point estimates represent the control groups. Error bars represent 95% confidence intervals. TNF α = tumour necrosis factor α ; AL = aseptic loosening; HQ = High quality; MQ = Moderate quality; LQ = Low quality.

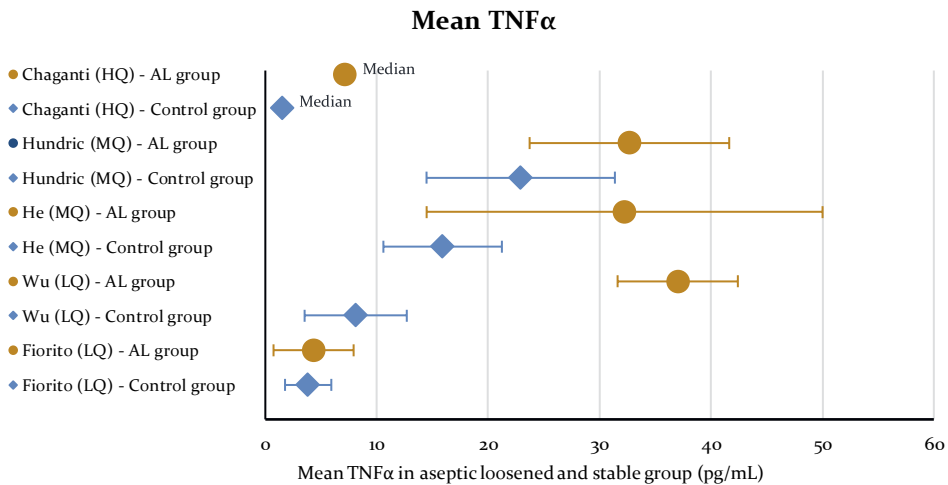


Figure III.III Mean serum RANKL in the aseptic loosened and control group. Differences were assessed at diagnosis of loosening or before revision surgery. The blue, round shaped point estimates represent the AL groups and the yellow, diamond shaped point estimates represent the control groups. Error bars represent 95% confidence intervals. *value displayed is the true value divided by 10. RANKL = receptor activator factor kappa-B ligand; AL = aseptic loosening; HQ = High quality; MQ = Moderate quality.

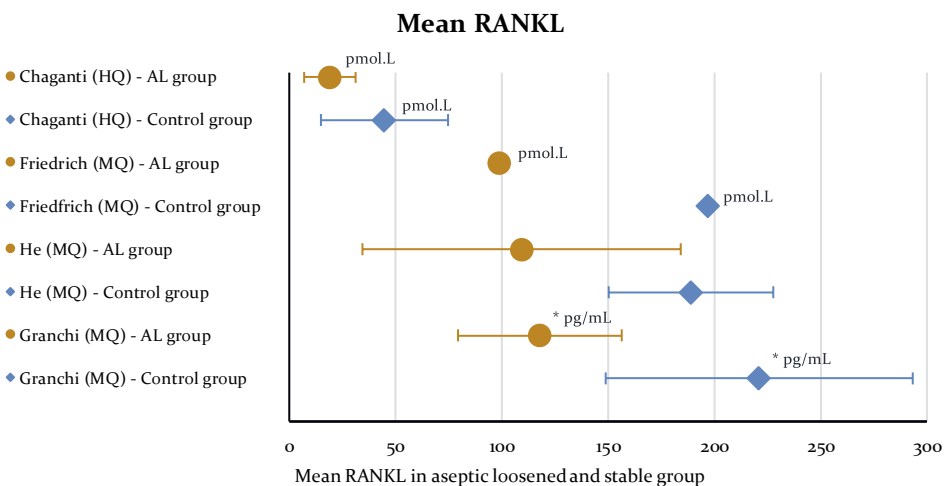


Figure III.IV Mean serum OPG in the aseptic loosened and control group. Differences were assessed at diagnosis of loosening or before revision surgery. The blue, round shaped point estimates represent the AL groups and the yellow, diamond shaped point estimates represent the control groups. Error bars represent 95% confidence intervals. *value displayed is the true value divided by 100. OPG = osteoprotegerin; AL = aseptic loosening; HQ = High quality; MQ = Moderate quality.

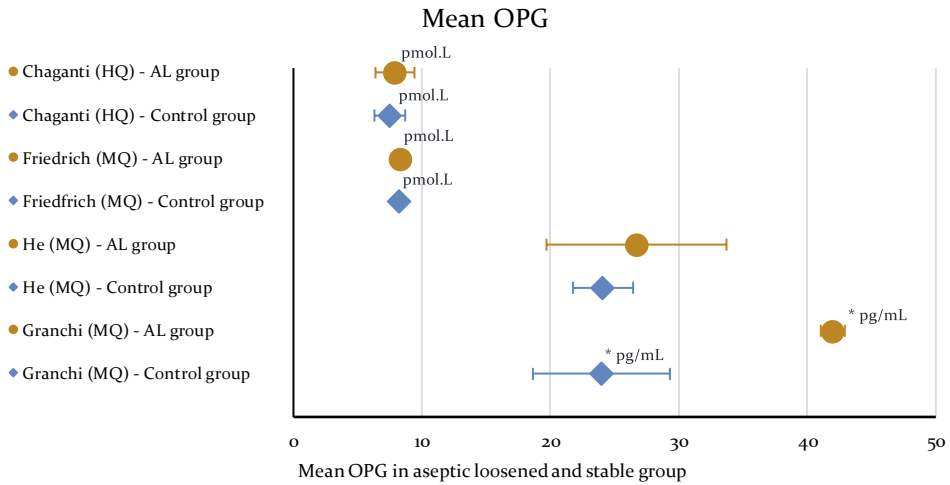


Figure III.V Mean serum IL-1b in the aseptic loosened and control group. Differences were assessed at diagnosis of loosening or before revision surgery. The blue, round shaped point estimates represent the AL groups and the yellow, diamond shaped point estimates represent the control groups. Error bars represent 95% confidence intervals. IL-1b = interleukin-1b; AL = aseptic loosening; MQ = Moderate quality; LQ = Low quality.

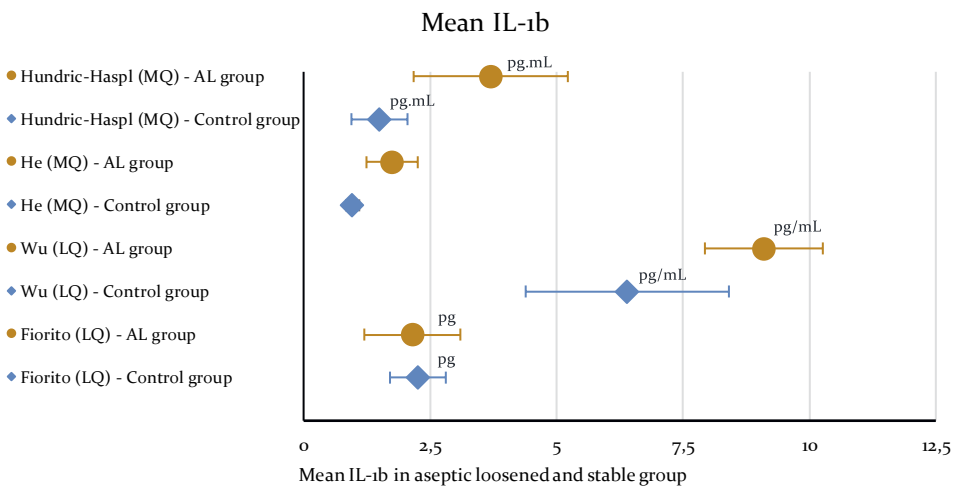
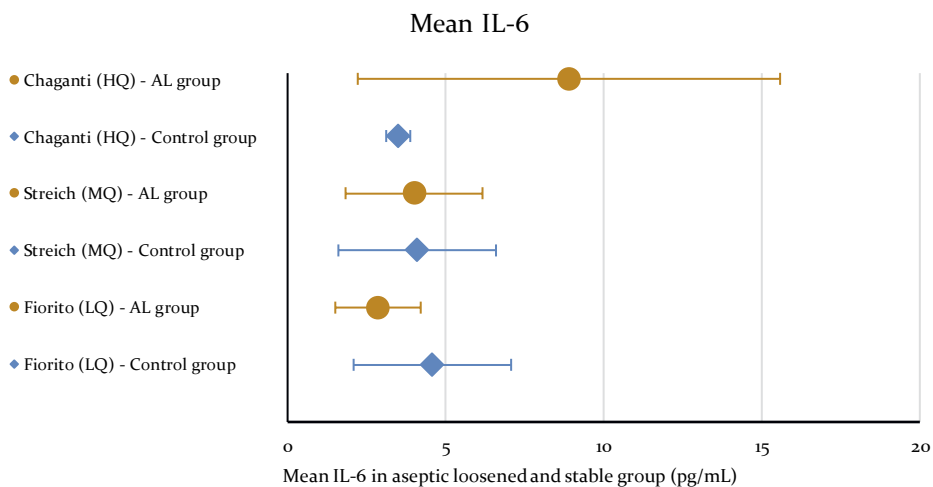


Figure III.VI Mean serum IL-6 in the aseptic loosened and control group. Differences were assessed at diagnosis of loosening or before revision surgery. The blue, round shaped point estimates represent the AL groups and the yellow, diamond shaped point estimates represent the control groups. Error bars represent 95% confidence intervals. IL-6 = interleukin-6; AL = aseptic loosening; MQ = Moderate quality; LQ = Low quality.



Interleukin-6 was studied in one HQ, one MQ and one LQ study, and none of these studies found a difference between both groups [Fig. III.VI].^{32, 36, 40} Other interleukins studied were interleukin-2r, interleukin-8, and interleukin-11 [Table III.III]. Evidence showing whether interleukin levels can discriminate between loosened and stable implants is thus limited.

Procollagen type I C-terminal peptide (PICP), procollagen type I N-terminal peptide (PINP), and procollagen type III N-terminal peptide (PIIINP) were examined in two studies (one MQ, one LQ), one MQ study, and one MQ study, respectively [Table III.III]. No difference in any of these markers was found between patients with loosened versus stable implants, indicating poor usability of these markers to identify patients with aseptic loosening.^{35, 39, 41, 42}

Osteocalcin was compared between aseptic loosened and stable implants in one HQ, one MQ and one LQ study [Table III.III]. The osteocalcin was statistically significantly higher in the aseptic loosened group in the HQ and LQ study^{41, 43} while no difference was found in the MQ study.⁴² Osteocalcin might thus have the potential to discriminate between loosened and stable implants.

In addition to these more frequently studied serum markers, over 40 other serum markers were studied by only one study [Table III.III].^{32-34, 36, 39, 40, 44-52}

Urine markers

Ten out of 35 studies (29%) included urine markers of which six were of MQ and four were of LQ [Table III.IV].

N terminal telopeptide (NTX) was assessed in six studies. NTX was assessed in a longitudinal fashion in one MQ study and this MQ study did not find a difference at any time point between the loosened and stable group, nor did two other MQ studies.^{22, 53, 54} One MQ study compared aseptic loosened acetabular cups to stable cups, and aseptic loosened femoral stems to stable stems, and found that the

Table III.IV Urine markers results table. Some studies did not report the unit of the outcome. If the outcome was significantly higher in the aseptic loosened group, the study was marked with **> in green**. If the outcome was significantly lower, the study was marked with **< in red**. If no difference between both groups was found, the study was marked with **= in yellow**. Numbers in superscript refer to the reference list.

95%CI = 95% Confidence Interval; SD = Standard deviation; IQR = interquartile range; RoB = risk of bias; HQ = High quality study; MQ = Moderate quality study; LQ = Low quality study.

Urine markers	Aseptic loosened group				Stable group			Quality
	Mean	Unit	95%CI		Mean	Unit	95%CI	
NTX	No difference			=	No difference			MQ ²²
Femoral loosening Acetabular loosening	73 ^{median}	nmol/mmol creatinine		>	25 ^{median}	nmol/mmol creatinine		MQ ⁵⁵
	51.4	nmol/mmol creatinine		=	53	nmol/mmol creatinine		MQ ⁵³
	61	nm BCE/mM creatinine	40.9-72.1	>	39.9	nm BCE/mM creatinine	27.0-52.7	MQ ⁴²
	62.3	nm BCE/mM creatinine	32.0-72.1	=	42.8	nm BCE/mM creatinine	28.1-53.2	MQ ⁴²
	34	nM BCE/nM	12 ^{SD}	=	29	nm BCE/nM	15 ^{SD}	LQ ⁵⁴
	96	nmol/mmol creatinine		>	40	nmol/mmol creatinine		LQ ⁴¹
αCTX	Higher			>	Lower			MQ ²²
	0.61 ^{median}	ng/mL		=	0.63 ^{median}	ng/mL		MQ ⁴⁸
βCTX	No difference			=	No difference			MQ ²²
CTX (NS)	94.3 ^{median}	nmol/mmol creatinine		=	67.0 ^{median}	nmol/mmol creatinine		MQ ⁵³
DPD	Lower			<	Higher			MQ ²²
Femoral loosening Acetabular loosening	9.17 ^{median}	nmol/mmol creatinine		>	5.72 ^{median}	nmol/mmol creatinine		MQ ⁵³
	8.2	nmol/mmol creatinine		=	8.2	nmol/mmol creatinine		MQ ⁵⁶
	61.0	nmol/mM creatinine	40.9-72.1	=	39.9	nmol/mM creatinine	27.0-52.7	MQ ⁴²
Male	62.3	nmol/mM creatinine	32.0-72.1	=	42.8	nmol/mM creatinine	28.1-53.2	MQ ⁴²
Female	7.8	nmol/mmol creatinine		=	5.8	nmol/mmol creatinine		LQ ⁵⁷
	8.6	nmol/mmol creatinine		=	10.1	nmol/mmol creatinine		LQ ⁵⁷
IL-6	Higher			>	Lower			MQ ²²
IL-8	No difference			=	No difference			MQ ²²
OPG	No difference			=	No difference			MQ ²²
PYR	No difference			=	No difference			MQ ²²
PYD	Higher			>	Lower			LQ ⁴¹
DPYD	Higher			>	Lower			LQ ⁴¹

NTX was higher in the aseptic loosened groups, but this difference only reached statistical significance in the femoral group.⁴² Higher NTX levels of loosened implants was found in one MQ and one LQ study.^{41, 55} Overall, NTX thus tended to be higher in aseptic loosened implants [Fig. III.VII].

Urinary C terminal telopeptide (CTX) was assessed in three MQ studies (Table III.IV). αCTX was statistically higher in loosened implants in one MQ study,²² while no difference between groups was found in another MQ study.⁴⁸ One study did not specify whether α- or β-crosslaps were assessed but found no difference in CTX between groups.⁵³ Evidence supporting the use of urinary CTX to assess aseptic loosening was thus limited.

Urinary deoxypyridinoline (DPD) was compared between aseptic loosened and stable implants in four MQ studies and one LQ study [Table III.IV]. A lower DPD concentration of loosened implants compared to stable implants was found in one MQ study,²² no difference between groups was found in two MQ studies,^{42, 56} and a higher DPD concentration of loosened implants was found in one MQ study.⁵³ One LQ study separated male and female patients and found a higher DPD in male patients with aseptic loosened implants, but a lower DPD in female patients with aseptic loosened implants compared to male and female patients with stable implants, respectively.⁵⁷ These results suggest poor usability of DPD as a marker to assess aseptic loosening [Fig. III.VIII].

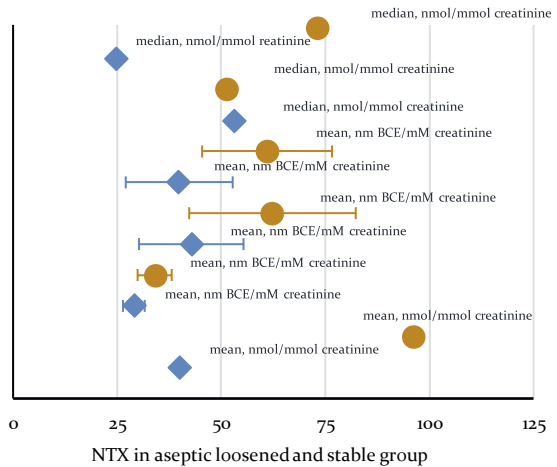
Radiological markers

Seven out of 35 studies (20%) used radiological markers to compare aseptic loosened and stable implants of which three were HQ, one was MQ, and three were LQ studies. Migration was assessed in two HQ studies and one LQ study using EBRA-FCA (one HQ and one LQ study)^{58, 59} or conventional radiographs (one HQ study).⁶⁰ Migration was higher in the loosened group compared to the stable group in all three studies and could thus be used a marker to discriminate between loosened and stable implants.

Figure III.VII and III.VIII. Mean urinary NTX and DPD in the aseptic loosened and control group. Differences were assessed at diagnosis of loosening or before revision surgery. The blue, round shaped point estimates represent the AL groups and the yellow, diamond shaped point estimates represent the control groups. Error bars represent 95% confidence intervals. NTX = N-terminal telopeptide; DPD = deoxypyridinoline; AL = aseptic loosening; MQ = Moderate quality; LQ = Low quality.

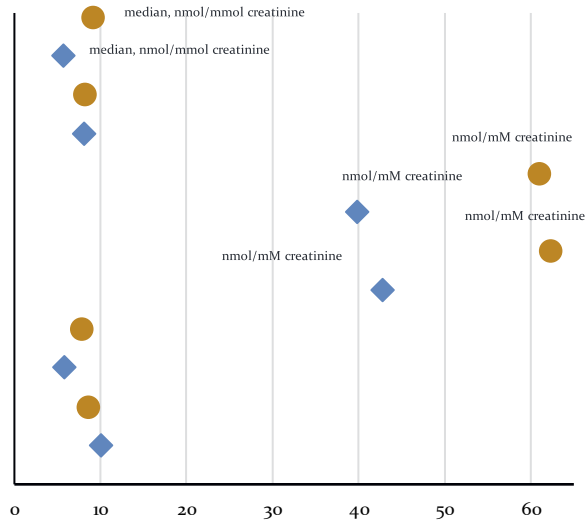
Urinary NTX

- Antoniou (MQ) - AL group
- ◆ Antoniou (MQ) - Control group
- Streich (MQ) - AL group
- ◆ Streich (MQ) - Control group
- Wilkinson (MQ) - femur AL group
- ◆ Wilkinson (MQ) - femur Control group
- Wilkinson (MQ) - acetabulum AL group
- ◆ Wilkinson (MQ) - acetabulum Control group
- von Schewelov (LQ) - AL group
- ◆ von Schewelov (LQ) - Control group
- Schneider (LQ) - AL group
- ◆ Schneider (LQ) - Control group



Urinary DPD

- Streich (MQ) - AL group
- ◆ Streich (MQ) - Control group
- Witzleb (MQ) - AL group
- ◆ Witzleb (MQ) - control group
- Wilkinson (MQ) - femur AL group"
- ◆ Wilkinson (MQ) - femur Control group
- Wilkinson (MQ) - acetabulum AL group
- ◆ Wilkinson (MQ) - acetabulum Control group"
- Pellengahr (LQ) - male AL group
- ◆ Pellengahr (LQ) - male Control group
- Pellengahr (LQ) - female AL group
- ◆ Pellengahr (LQ) - female Control group



Urinary DPD in aseptic loosened and stable group, mean (nmol/mmol creatinine)

Bone Mineral Density (BMD) was compared in one HQ and one MQ study. The BMD was measured at the lumbar spine,⁴³ around the cup,⁴² around the femoral component,⁴² and at different locations of the tibia.⁴³ The BMD did not differ at the lumbar spine (HQ study) and did not differ around the cup (MQ study) between groups. The BMD around the femoral components was significantly lower in the aseptic loosened group (MQ study). The BMD at 4%, 14%, and 38% of the tibial length measured from the distal tibial end was assessed in one HQ study.⁴³ This study found that the BMD was lower at 14% of the tibial length and at 38% of the tibial length, only the cortical BMD was significantly lower in the aseptic loosened group. The usability of BMD as a marker to discriminate between aseptic loosened and stable implants was thus limited.

Lytic lesions and radiolucent lines were compared between both groups in a HQ study which found a significant increase in lytic lesions and radiolucent lines in the aseptic loosened group.⁶⁰ Demarcation of bone-cement and progressive radiolucency at the tip of the cement was analysed in a LQ study using conventional anteroposterior and lateral radiographs at one year follow-up, and found that loosened stems showed significantly more demarcation of bone-cement and progressive radiolucency at the tip of the cement compared to stable stems.⁶¹ Lytic lesions, radiolucent lines and demarcation of bone-cement were suggestive for aseptic loosening.

Skin markers

Skin markers were assessed in one LQ study in patients with loosened and stable cemented THRs, and a higher reaction to polymethylmethacrylate bone cement was found in patients with loosened implants, indicating that a lymphocyte-mediated immune response was induced in loosened cemented implants.⁶² Skin markers might be able to discriminate between loosened and stable implants but only one study using this marker was included in the present review.

Discussion

Serological, urine and radiological markers for aseptic implant loosening of total hip and total knee implants were evaluated for their ability to discriminate between well fixed and loosened implants. Both serological and urine markers are used as a proxy for implant-bone stability. Serum markers were most frequently studied. For that matter, TNF α , IL-1 β , and osteocalcin were elevated in patients with aseptic loosening of a primary THR or TKR in most studies. Urinary NTX was the only urine marker found in our review to discriminate between aseptic loosened and stable implants. In radiological studies, migration was most frequently studied and aseptic loosened implants migrated more in all studies compared to stable implants. Beside migration, radiolucent lines surrounding the stem or to a lesser extent the socket were suggestive for aseptic loosening.

A higher concentration of the serum markers TNF α , IL-1 β , and osteocalcin in aseptic loosened implants was found in several studies but a few other studies did not detect a difference. Other fundamental research may help to understand the role of these markers in the mechanism resulting in aseptic loosening and osteolysis. TNF α and IL-1 β play an important role in the inflammation and especially TNF α has shown to induce osteolysis *in vivo*.⁶³ Schwarz et al. compared mice that overproduce TNF α with mice that had a defective TNF α signalling pathway and found that the mice that were overexpressed to TNF α showed an increased osteolysis, whereas the defective mice showed little osteolysis.⁶³ Osteocalcin on the other hand is secreted by osteoblasts and plays an important role in the bone formation.⁶⁴ A recent murine study assessed osteocalcin and implant loosening in a longitudinal fashion and found a correlation between serum osteocalcin and implant fixation.⁶⁵ The present review suggests that an increased serum TNF α , IL-1 β , and osteocalcin level could be indicative for aseptic loosening.

In contrast to the many serum markers studied, only a few urine markers were studied of which NTX, CTX and DPD were most popular. Urinary NTX showed the

most promising results in discriminating between aseptic loosened and stable implants [Fig. III.VIII], whereas urinary DPD showed conflicting results and seemed to have the least discriminative ability [Fig. III.IX]. This finding was supported by a canine study which assessed urinary CTX, NTX and DPD.⁶⁶ This canine study concluded that urinary NTX was the most discriminatory resorption bone marker in focal malignant osteolysis.⁶⁶ In the first 6 months, urinary NTX appears to be elevated in all patients following THR or TKR, but levels return to normal hereafter making these markers potentially usable to identify loosening after 6 months.⁵⁰ Interestingly, Ross et al. found that preoperative α CTX had the highest accuracy in identifying patients at risk for aseptic loosening, suggesting that at risk patients could be identified prior to the primary joint replacement surgery.²² However, none of the other included studies found a difference in CTX between groups. Future studies should further investigate whether NTX and CTX urine markers can discriminate between aseptic loosened and stable implants.

Currently, radiological assessment of an implant is the most used in clinical practice to identify for aseptic loosening. Radiolucent lines, cysts and migration are suggestive for loosening. However, most of these characteristics become only visible at an advanced stage of osteolysis. The present review found three studies using migration of which two used EBRA-FCA and one study used measurements on conventional radiographs. Other tests such as radiostereometric analysis (RSA) can measure micromotion, and high initial migration or continuous migration measured with RSA is suggestive for early aseptic loosening of an implant.^{12, 13, 67} Although RSA has the ability to identify patients at risk for aseptic loosening as early as one or two years after the primary surgery, this technique is costly. Secondly, RSA needs tantalum markers to be inserted in the periprosthetic bone. Therefore, other more accessible serological and urine markers could be valuable to identify patients at risk for aseptic loosening as these are readily available and have the potential to track disease progression or to function as a target for future treatment.

Several limitations of this review should be noted. First, only a limited number of the included studies were of good methodological quality (HQ). The lack of HQ studies emphasises the need for well-designed studies to assess the ability of these markers to discriminate between loosened and stable implants. Three specific RoB scoring criteria were frequently lacking in the included studies which were a blinded assessment of primary outcome, the assessment of incomplete data, and the reporting of limitations. Although blinding may not always be possible, future studies should clearly assess missing data, eligible patients, excluded patients, and the limitations of their study. Second, there was significant variability between studies in the methods used to measure serum and urine markers, and in the reporting of the outcomes which limited the ability to pool data. This was mostly due to a difference in the units of measurement and due to succinct reporting of outcomes with some studies only reporting whether there was a difference accompanied with p-value but without absolute numbers or a figure. We recommend future studies to report their results uniformly to allow between study comparisons and to report absolute numbers of their outcome. Third, the present systematic review included studies which used markers to assess loosened and stable implants following the search strategy from two previously conducted systematic reviews.^{26, 27} Studies that did not use the term marker (or a related term) were thus not included, which may explain that only one study on skin markers was found, but searching for every individual marker or test was unfeasible considering the large number available. Last, several markers were assessed by only a single study. As some of these markers were significantly different between aseptic loosened and stable implants, we recommend future studies to assess these possible markers of aseptic loosening.

The present review examined several markers in their ability to identify implants with osteolysis and aseptic loosening in THRs and TKRs. Especially serum TNF α , IL-1b and osteocalcin showed a promising role in discriminating between loosened and stable implants and urinary NTX as one of the few urine markers. Moreover,

migration was the most frequent radiological marker, which was increased in loosened implants in all studies with an increased incidence of radiolucent lines being another marker. We therefore recommend future studies to study these serum, urine, and radiological markers in a longitudinal fashion to assess whether progression of loosening is associated with an increase or decrease of these markers. In particular, high-quality studies assessing the usability of these markers are needed.

Acknowledgements

None

Appendix A and B accessible digitally

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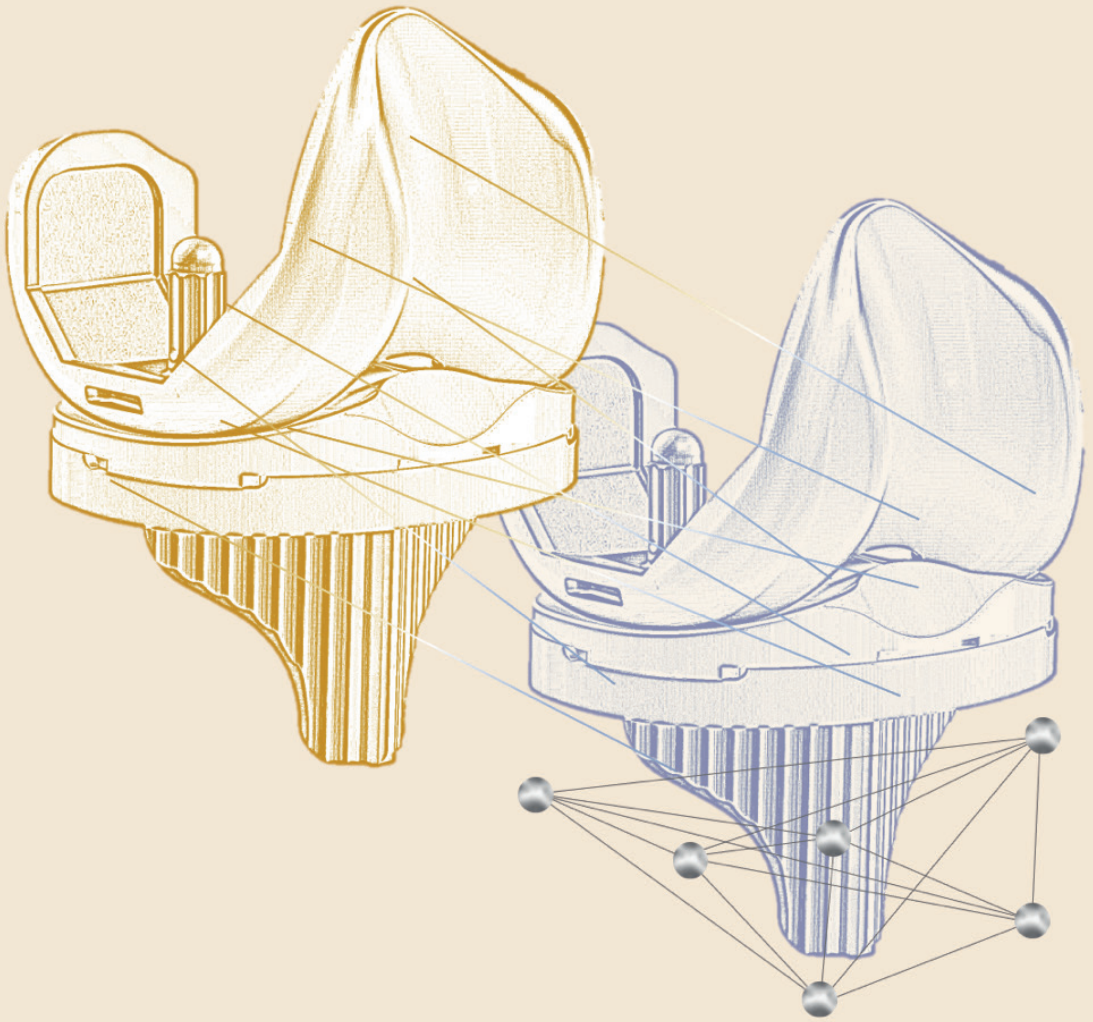
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Chapter IV

All-polyethylene versus metal-backed posterior stabilized total knee arthroplasty

Similar 2-year results of a randomized radiostereometric analysis study

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Abstract

Background and purpose

The all-polyethylene tibial (APT) component introduced in the early 1970's, was surpassed by the metal-backed tibial (MBT) trays as the first choice for total knee arthroplasty (TKA). With improved polyethylene, the modern APT components can reduce costs, and have shown equivalent results in survivorship and early migration of the cruciate retaining and cruciate stabilizing designs. This study compares the 2-year migration of a similarly designed APT-posterior stabilized (PS) and a MBT-PS TKA, using radiostereometric analysis (RSA).

Patients and methods

60 patients were randomized to receive either an APT Triathlon PS or a MBT Triathlon PS TKA (Stryker, NJ, USA). Migration measured by RSA and clinical scores were evaluated at baseline and at 3, 12, and 24 months postoperatively. Repeated measurements were analyzed with a linear mixed model and generalized estimating equations.

Results

The mean maximum total point movement (MTPM) at 3, 12, and 24 months was 0.41mm (95%CI 0.33-0.50), 0.57mm (CI 0.44-0.70) and 0.56mm (CI 0.42-0.69) respectively in the MBT group and 0.46mm (CI 0.36-0.57), 0.61mm (CI 0.49-0.73) and 0.64mm (CI 0.50-0.77) in the APT group. 2 MBT and 1 APT implant were considered unstable at 2-year follow-up. The KSS-Knee score and KSS-Function across 3, 12 and 24 months were comparable in both groups.

Interpretation

For an APT-PS designed component, MTPM measured with RSA is comparable to the MBT-PS component after 2-year of follow-up. No differences in complications or clinical outcomes were found.

Introduction

Despite many advantages of the all-polyethylene tibial (APT) component, like avoiding backside wear, preserving tibial bone and lower costs, it accounts for only 0.1-13% of the total knee arthroplasties (TKA) registered.^{1, 2} When TKA was introduced in the early 1970s, implants included APT components, but this design was soon replaced by a metal-backed tibial (MBT) component due to disappointing survival rates of the APT.^{3, 4} However, the APT is now regaining interest due to the higher costs of the MBT.^{5, 6} Furthermore, APT has comparable results to MBT.⁵ The advantage of the APT is that it preserves tibial bone as less resection is needed for the same polyethylene thickness, and that it avoids backside wear.^{4, 5, 7, 8}

Several studies have compared the outcomes of more recent APT designs with MBT in terms of survival, revision, and complications. Although reporting contradicting results, most studies found comparable survival rates of the APT and MBT.^{4, 7, 9-11} Radiostereometric analysis (RSA) objectively measures migration of a prosthesis and can predict revision for aseptic loosening after 2-year.^{12, 13} Few RSA studies comparing the APT and MBT have been conducted, showing less migration for the APT design in 1 study¹⁴, whilst others found no difference¹⁵⁻¹⁸, but these studies only included Cruciate Retaining (CR) or Condylar Stabilizing (CS) TKA and not Posterior Stabilizing (PS) TKAs. The use of PS designed TKAs varies and is particularly popular in the United States and the Netherlands where it comprises 49% and 56% of all TKAs used, respectively.^{19, 20} The cam-post design of a PS insert could cause additional stress on the tibial component compared to a CR design.^{21, 22} So apart from mixed results in studies with CR and CS designs, outcomes of these studies cannot be extrapolated to PS implants because of this cam-post design. A study comparing PS designed APT and MBT components is therefore needed.

Hence, we compared the migration of an APT- versus a MBT-PS designed prosthesis with up to 2-year follow-up using RSA.

Patients and methods

This study was a prospective, randomized RSA trial comparing the APT-PS Triathlon Total Knee System to the MBT-PS Triathlon (Stryker, Warsaw, USA). Between November 2014 and June 2015, 60 consecutive patients were included and randomized to either an APT-PS or a MBT-PS component at the Hässeholm Hospital (Sweden). A blocked, computer-generated randomization scheme with a 1:1 ratio was used for randomization with a block size of 20. Patients were blinded to the treatment allocation and remained blinded throughout the study. Surgery was performed by 2 orthopedic surgeons who opened sealed opaque envelopes on the day of surgery. Clinical scores were assessed by blinded physical therapists. Inclusion criteria were patients with a painful knee resulting from osteoarthritis who were scheduled to undergo primary total knee surgery and were willing to sign an Informed Patient Consent Form. Main exclusion criteria were BMI > 40, a flexion or varus/valgus contracture >15°, pre-operative knee score >70 and patients who could not make the follow-up visits because of living far away from the hospital.

Prosthesis and surgical procedure

The Triathlon APT is made from conventional polyethylene, sterilized with gamma radiation in vacuum and is packaged in Nitrogen gas (N₂Vac). The modular MBT component uses a highly cross-linked polyethylene insert (X₃, Stryker Orthopaedics, Mahwah, USA). Patients were operated in concordance with the surgical protocol using a midline incision and a medial parapatellar approach. No tourniquet was used. Smartset GHV bone cement (DePuy CMW, Blackpool, UK) was only applied to the tibial baseplate. Perioperatively, 8 well-scattered tantalum beads (ø 0.8 mm; RSA Biomedical, Umeå, Sweden) were inserted into the tibial bone as reference markers. 5 beads were inserted into the polyethylene insert of the MBT and on a similar position in the polyethylene of the APT. Patellae were reshaped. Postoperative regime included immediate full weight-bearing and there were no differences in postoperative treatment between both groups.

Outcome measures

Primary outcome measure was prosthetic migration after 2-year measured by RSA defined as the Maximum Total Point Movement (MTPM), which is the length of the translational vector of the marker with the greatest migration in translation or rotation along the transverse, longitudinal or sagittal axis. In concordance with the ISO 16087 Standard, migration of a left-sided patient will be transformed to match the data of a right-sided patient to enable comparison between patients.

Translations and rotations are expressed according to the right-hand screw rule.²³ RSA radiographs were taken with the patient in supine position and the knee in a calibration cage using a biplanar technique in a 90-degree angle (Cage 10, RSA Biomedical, Umeå, Sweden). Radiographs were taken within 1-2 days postoperatively and at 3, 12, and 24 months. The first postoperative examination was taken as reference for subsequent examinations. At 12 months, double measurements were made to determine the precision of the examination. As no migration is expected between these 2 examinations performed at the same point in time, any migration measured will be the measurement error. The precision is expressed as the standard deviation of these measurements. Marker-based analysis using the software Model-based RSA version 4.11 (RSAcore, Leiden, the Netherlands) was used. A mean error of rigid body fitting below 0.35 mm and a condition number below 120 were set as cut-off points. A marker configuration model was used if not enough markers were visible at any follow-up moment.²⁴ Individual prostheses were considered stable if the increase in MTPM between 1-and 2-year postoperative was ≤ 0.2 mm, and consequently any prosthesis with a MTPM increase of >0.2 mm was considered as at risk for loosening.¹²

Secondary outcome measures were the Knee Society Score (KSS), the Knee Osteoarthritis Outcome Score (KOOS) and the Forgotten Joint Score (FJS). The KSS and KOOS were measured pre-operatively and at 3, 12 and 24 months. The FJS was measured at 3, 12, and 24 months. All scores ranged from 0 to 100 with higher scores indicating better scores.

Sample size

Sample size was calculated assuming that a difference of 0.3 mm for translation and 0.25° for rotation would be clinically relevant. 17 patients were needed in each group with an alpha of 0.05 and a power of 0.80. Taking into account that patients with inappropriate marking of the prosthesis or tibial bone will be excluded as well as possible patients lost to follow up, 30 patients in each group were included.

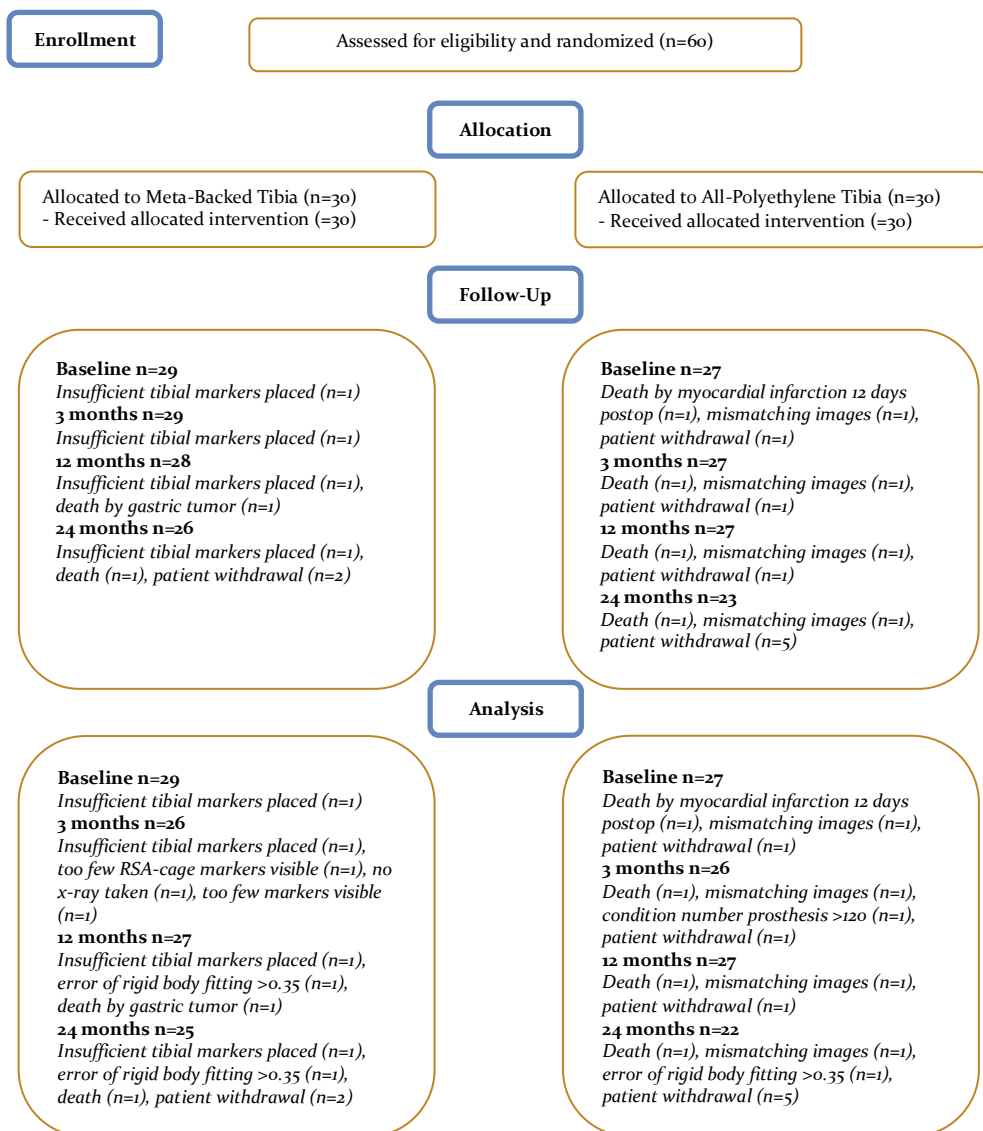
Statistics

Analyses were performed according to the intention-to-treat principle. MTPM, translations, rotations, and clinical outcome scores were analysed with a linear mixed model if normally distributed. This model is recommended to analyse repeated measurements as it takes the within-subject correlation as well as the missing values into account.²⁵ The model consisted of a group variable (APT versus MBT), a time variable (baseline, 3 months, 12 months, and 24 months) and an interaction term (fixed effects). An Auto-Regressive Order-1 covariance matrix was used to model remaining variability. The Generalised Estimating Equations (GEE) approach was used if a normal distribution could not be obtained through transformation. This approach was needed for the analysis of MTPM, the KSS-Knee score and the KOOS-Sports subscore. Mean translations and rotations are reported per group at 3, 12, and 24 months. Mean scores of the KSS-Knee, KSS-Function and the 5 subscales of the KOOS are reported per group preoperatively, and at 3, 12, and 24 months postoperatively. The mean FJS is reported at 3, 12, and 24 months postoperatively. P-values <0.05 were considered statistically significant. Means are reported with 95% confidence intervals (CI). Analyses were performed with SPSS version 23 (IBM SPSS Statistics 23.0; IBM Corp, Armonk, NY, USA).

Ethics, registration, funding, and potential conflicts of interest

Approval of the Regional Ethical Review Board in Lund was obtained before recruitment (entry no. 2014/513). This study was registered at the ISRCTN Registry (ISRCTN10744502) and was conducted in concordance with the CONSORT statement. All patients provided informed consent. Stryker funded this study but did not take any part in the design, conduct, analysis, and interpretations stated in this paper.

Figure IV.I CONSORT Flow Chart



Results

60 patients were included and randomized to either the APT-PS or the MBT-PS Total Knee Prosthesis. After randomization, 4 patients were excluded. 56 patients were thus included in the analysis [Figure IV.I]. During follow-up, 9 patients withdrew or had radiographs which could not be analyzed, leaving 47 patients for analysis at 2 years [Figure IV.I]. Age, BMI, sex, ASA score and Ahlbäck classification were similar at baseline. Each surgeon operated approximately half of the patients in both groups. Postoperatively, the MBT implants seemed to be more in varus compared to the APT [Table IV.I].

Table IV.I Baseline demographic characteristics

	Metal-Backed PS	All-Polyethylene	Total
Patients, n	29	27	56
Age, mean years (SD)	68 (4)	68 (4)	68 (4)
BMI, mean kg/m² (SD)	28 (4)	29 (3)	28 (3)
Sex, n			
Female	17	13	30
Male	12	14	26
ASA classification, n			
I	4	7	11
II	18	17	35
III	7	3	10
Surgeon, n			
#1	14	14	28
#2	15	13	28
Ahlbäck classification, n			
II	5	4	9
III	23	23	46
IV	1	0	1
HKA postoperative, n			
Varus (<177°)	7	3	10
Neutral (177-183°)	15	17	32
Valgus (>183°)	2	4	6
Missing*	5	3	8

SD = Standard Deviation, HKA = Hip-knee-ankle angle. * Some patients had no postoperative long-leg radiographs taken and HKA could not be assessed.

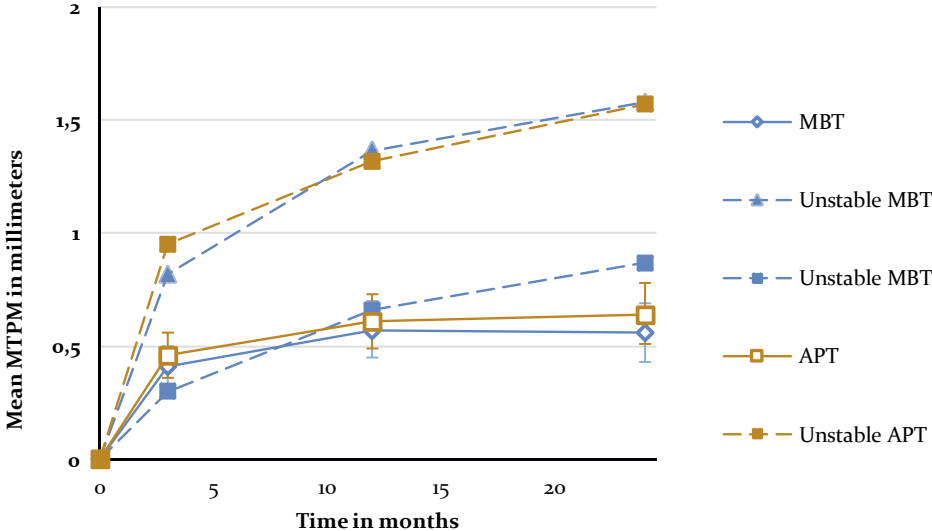
The mean MTPM across 3, 12, and 24 months was similar in both groups. The mean MTPM change from 12 to 24 months was -0.01 mm (CI -0.19; 0.17) in the MBT group and 0.03 (CI -0.14; 0.21) in APT group [Table IV.II; Figure IV.II]. Two implants in the MBT and 1 in the APT group displayed >0.2 mm MTPM between 1-and 2-year follow-up and were considered unstable [Figure IV.II]. The MBT group showed lift-off (positive), while the APT group showed tibial subsidence (negative) [Figure IV.III C]. A different migration pattern between the groups was also visible in the rotation along the longitudinal axis, being external (negative) in the MBT and internal (positive) in the APT group [Figure IV.III E]. Other translations and rotations were

Table IV.II Mean maximum total point motion of the metal-backed and all-polyethylene group with 95% confidence intervals (95%CI)

Time (months)	Metal-backed mean (95%CI)	All-polyethylene mean (95%CI)
3	0.41 (0.33-0.50)	0.46 (0.36-0.57)
12	0.57 (0.44-0.70)	0.61 (0.49-0.73)
24	0.56 (0.42-0.69)	0.64 (0.50-0.77)

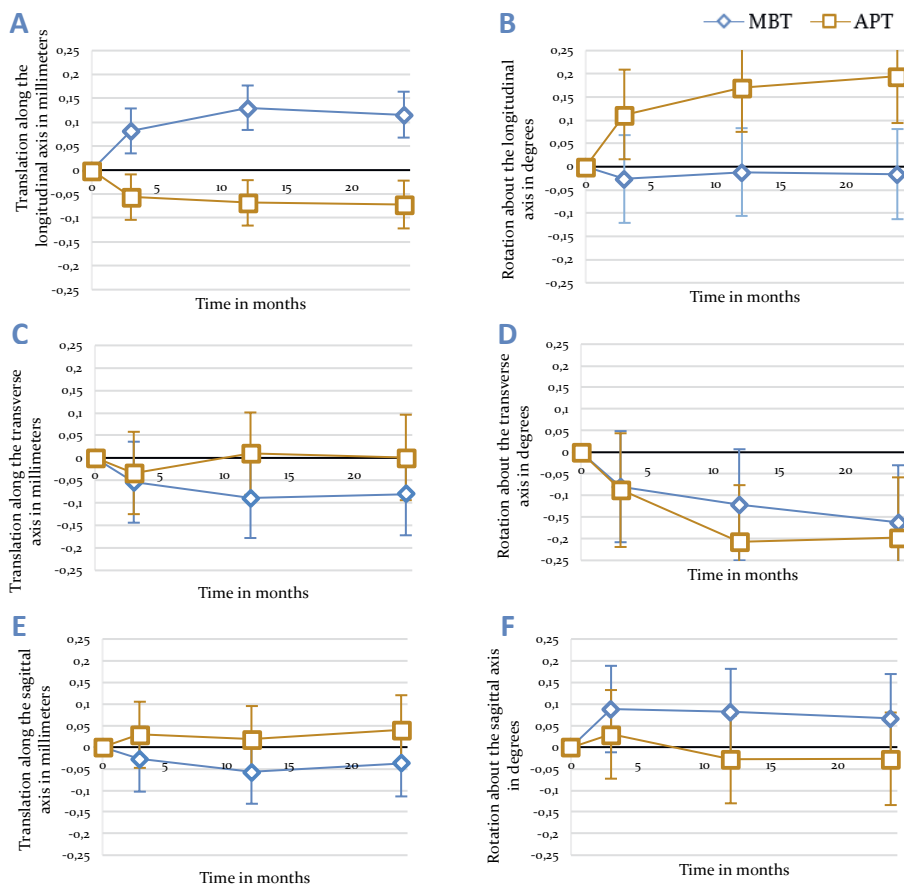
Figure IV.II Mean MTPM of the MBT and APT group with 95% CI over time. The MTPM of the 3 unstable implants are plotted and all 3 show continuous migration between 12 and 24 months follow-up.

MTPM: Maximum total point motion; MBT: metal-backed tibia; APT: all-polyethylene tibia



similar between groups with backward tilting (negative) being the most prominent direction of migration in both groups [Figure IV.III A,B, D, F]. None of the patients were scheduled for revision surgery. 50 double measurements were made at 1-year follow-up. The precision of the measurements of the translations and rotations were 0.1 mm and 0.1 degrees. The mean condition number of the tibial bone and the prosthesis was 42 (range 20-108) and 40 (range 21-114), respectively. The mean error of rigid body fitting was 0.14 (range 0.04-0.34) and 0.08 (range 0.01-0.47) of the tibial bone and the prosthesis, respectively.

Figure IV.III A-F Translation along and rotation about the transverse, longitudinal and sagittal axis. Means are represented with 95% confidence intervals (error bars).



The KSS-Knee scores across 3, 12, and 24 months were similar in both groups. KSS-Function score was also similar. Moreover, no statistically significant difference was found in the KOOS subscores or in the FJS [Table IV.III].

Table IV.III Clinical outcome scores with 95% confidence intervals [95%CI]

		Metal-backed	All-polyethylene
		Mean Score [95%CI]	Mean Score [95%CI]
KSS Knee	Preoperative	46 [43-50]	44 [42-46]
	3 months	93 [91-95]	86 [81-91]
	12 months	93 [90-96]	94 [90-97]
	24 months	98 [96-100]	95 [90-99]
KSS Function	Preoperative	54 [49-59]	52 [47-58]
	3 months	73 [68-78]	76 [71-82]
	12 months	85 [80-90]	85 [80-90]
	24 months	88 [83-93]	82 [77-88]
KOOS Symptoms	Preoperative	47 [41-53]	49 [42-55]
	3 months	67 [61-73]	62 [56-68]
	12 months	77 [71-83]	72 [66-79]
	24 months	80 [73-86]	75 [68-82]
KOOS Pain	Preoperative	38 [31-45]	41 [34-48]
	3 months	70 [63-77]	66 [59-73]
	12 months	82 [75-88]	80 [73-87]
	24 months	87 [80-94]	79 [72-86]
KOOS ADL	Preoperative	42 [35-48]	45 [38-52]
	3 months	75 [68-81]	67 [61-74]
	12 months	80 [73-86]	75 [68-82]
	24 months	82 [75-89]	75 [68-82]
KOOS Sports	Preoperative	9 [5-13]	12 [8-17]
	3 months	35 [26-44]	21 [14-29]
	12 months	42 [33-52]	40 [30-50]
	24 months	42 [35-50]	40 [29-50]
KOOS QoL	Preoperative	33 [27-38]	35 [30-40]
	3 months	46 [41-51]	43 [38-48]
	12 months	55 [50-60]	53 [48-58]
	24 months	54 [49-60]	53 [48-59]
FJS	3 months	36 [25-46]	35 [24-46]
	12 months	61 [50-72]	56 [45-67]
	24 months	58 [47-69]	51 [40-63]

KSS: Knee society score; KOOS: Knee osteoarthritis outcome score; ADL: Activities of daily living; QoL: Quality of Life; FJS: Forgotten joint score

Discussion

We found similar MTPM between the APT-PS and MBT-PS at 2-year follow-up, the translation and rotation along and about the 3 orthogonal axes were different for longitudinal translation and rotation. Van Hamersveld et al. (2018), who used a CS design, and other RSA studies on CR designs reported comparable MTPM values as in our study.¹⁴⁻¹⁸ These findings suggest that, although PS implants most likely experience different shear forces at the implant-bone interface, the MTPM values after 2-year follow-up are comparable to CR and CS designs. Furthermore, despite the relative elasticity of a full APT component, this did not result in a difference in migration compared to a MBT component. This may imply that the polyethylene insert within the metal baseplate gives enough peak stress absorption in the PS design. The difference in translation along the longitudinal axis was previously described by Adalberth et al. (2000) who compared a low-conforming APT and MBT with RSA and concluded that this finding might be explained by an increase in tensile forces in the less flexible MBT.^{15, 26} In our study, the subsidence of the APT and lift-off of the MBT stabilized after 3 months. The difference in rotation about the longitudinal axis (i.e. internal/external rotation) between the MBT and APT in our study might be due to unmeasured differences between the groups such as the alignment of the tibial component. Another explanation might be the minor differences in the postoperative HKA between groups, but the groups are too small to draw any valid conclusion. We reported signed migration values in contrast to several other RSA studies. In order to allow comparison between RSA studies and to understand the direction of migration, reporting signed values is preferred as was previously suggested by Valstar et al. (2005).²⁷

Gudnason et al. (2017) suggested that it was better to use the transversal rotation for analysis of RSA-migration data as it was a better predictor for aseptic loosening than MTPM. The rotation in the transverse plane was posterior for both groups (Figure 5, Rotation along the transverse axis).²⁸ The posterior rotation of the tibial implants in both groups could be due to anterior engagement of the cam-post mechanism of the

PS-design which engages in extension. Banks et al. (2002) found that TKAs are frequently aligned in relative hyperextension which might explain the rotation in the present study.²⁹ Another factor contributing to the posterior rotation might be the single radius design of the TKA used in our study which might play a role as the center of rotation lies more posteriorly compared to multi-radius designs.³⁰ Whether this migration pattern has clinical consequences remains unclear and should be studied further when longer follow-up data becomes available.

The KSS-Knee and -Function scores increased postoperatively and were comparable in both groups during follow-up, which is consistent with previous studies.^{15, 16} The KOOS subscales and the FJS also showed similar results. De Carvalho et al. (2013) used different clinical outcomes (the Oxford Knee Score, the Western Ontario and McMaster Universities Arthritis Index and the Short form-12 scores), but also found no difference between groups.³¹

Our study with an all-polyethylene PS design failed to show superiority of either APT nor MBT. Nevertheless, Chambers et al. (2016) estimated that a reduction of 42% in costs could be achieved if the APT were used.⁶ However, the actual costs of an implant differs widely and the total costs of TKA treatment consist of more than just the tibial component including personnel, equipment, and space costs. In addition, the financial benefit of the APT might not outweigh the limitations as it cannot be coated, and a liner exchange is not possible. These factors may be among the reasons why orthopedic surgeons continue to use the MBT TKA as the implant of first choice even though some suggest that the APT could be an acceptable treatment in patients above 70 years of age or with rheumatoid arthritis.³²

A limitation of this study is the lack of power to detect a difference in clinical scores between both groups. RSA studies, in general, include small groups and probably fail to detect any differences due to this small sample size. Including more patients, however, would nullify the strength of RSA studies as it can measure migration with high precision and, therefore, only a small sample size is needed to assess the

stability of implants. Another limitation is the difference in polyethylene as the polyethylene insert of the MBT tray was made of highly-crosslinked polyethylene and the APT was made from conventional polyethylene. Ideally, the polyethylene in both implants would be the same, but this was not possible due to manufacturing limitations.

In summary, the APT-PS TKA prosthesis has comparable migration as the MBT-PS TKA in terms of MTPM measured by RSA at 2-year of follow-up, even though there was a different pattern in longitudinal translation and rotation. No differences in complications or clinical outcomes were found between both groups.

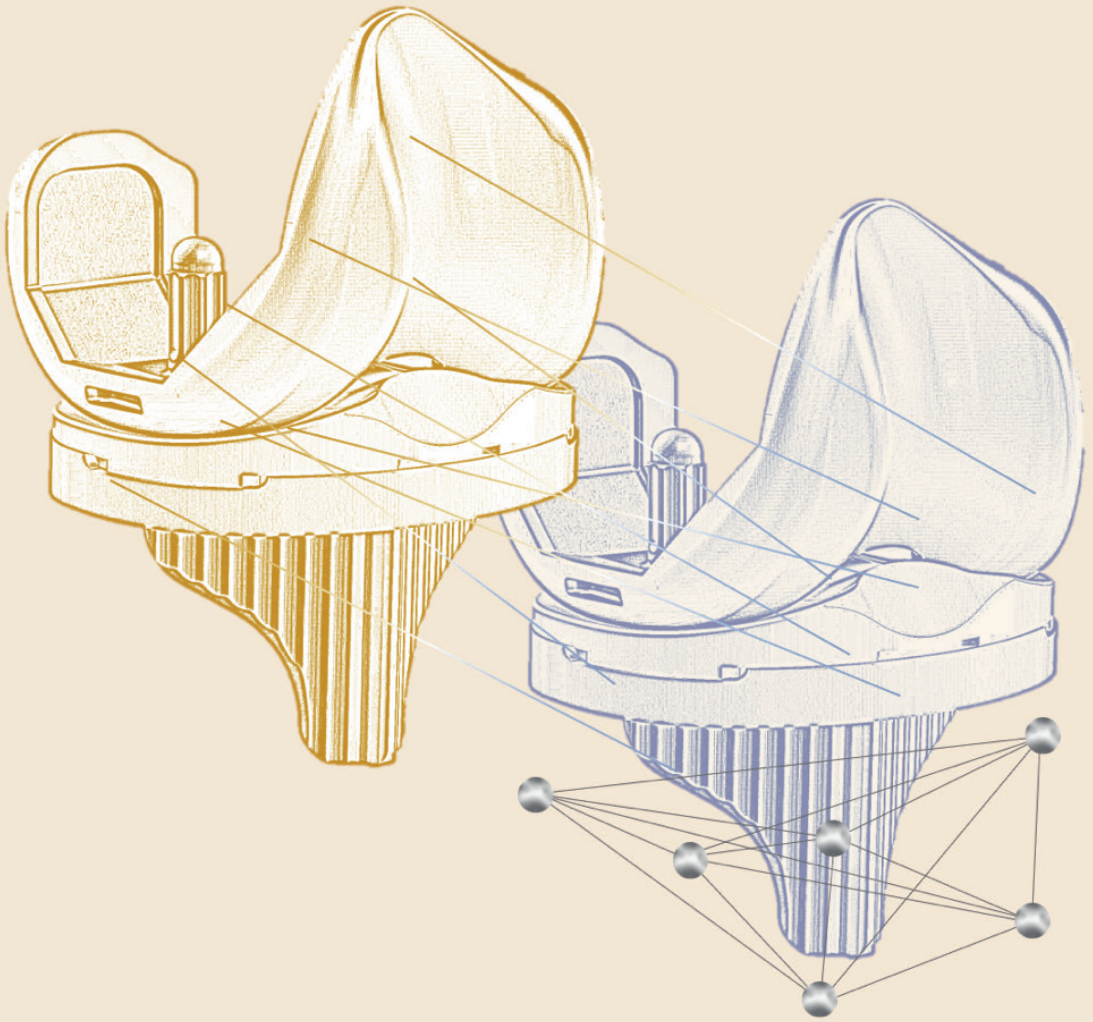
Acknowledgments

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Chapter V

Migration of a novel 3D-printed cementless versus a cemented total knee arthroplasty

Two-year results of a randomized trial using radiostereometric analysis

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Abstract

Aims

Although bone cement is the primary mode of fixation in total knee arthroplasty (TKA), cementless fixation is gaining interest as it has the potential of achieving lasting biological fixation. By 3D printing an implant, highly porous structures can be manufactured, promoting osseointegration into the implant to prevent aseptic loosening. This study compares the migration of cementless, 3D-printed TKA to cemented TKA of a similar design up to two years of follow-up using radiostereometric analysis (RSA) known for its ability to predict aseptic loosening.

Methods

A total of 72 patients were randomized to either cementless 3D-printed or a cemented cruciate retaining TKA. RSA and clinical scores were evaluated at baseline and postoperatively at three, 12, and 24 months. A mixed model was used to analyze the repeated measurements.

Results

The mean maximum total point motion (MTPM) at three, 12, and 24 months was 0.33 mm (95% confidence interval (CI) 0.25 to 0.42), 0.42 mm (95% CI 0.33 to 0.51), and 0.47 mm (95% CI 0.38 to 0.57) respectively in the cemented group, versus 0.52 mm (95% CI 0.43 to 0.63), 0.62 mm (95% CI 0.52 to 0.73), and 0.64 mm (95% CI 0.53 to 0.75) in the cementless group ($p = 0.003$). However, using three months as baseline, no difference in mean migration between groups was found ($p = 0.497$). Three implants in the cemented group showed a > 0.2 mm increase in MTPM between one and two years of follow-up. In the cementless group, one implant was revised due to pain and progressive migration, and one patient had a liner-exchange due to a deep infection.

Conclusion

The cementless TKA migrated more than the cemented TKA in the first two-year period. This difference was mainly due to a higher initial migration of the cementless TKA in the first three postoperative months after which stabilization was observed in all but one malaligned and early revised TKA. Whether the biological fixation of the cementless implants will result in an increased long-term survivorship requires a longer follow-up.

Keywords

3D printing; Radiostereometric analysis; Total knee arthroplasty.

Introduction

Although total knee arthroplasty (TKA) has a history of approximately 50 years, no consensus has been reached regarding the optimal fixation method. Cement fixation is the most common method, as reflected in national registries.¹⁻³ However, cementless fixation is gaining interest as it preserves bone stock, avoids cement debris, and has the potential of achieving lasting biological fixation of the prosthesis to the bone.⁴ Early cementless implants had poor survival and high revision rates but these results were mainly due to design flaws.⁵ In the last decade, new designs, coatings, and porous metals have been developed in an effort to overcome these problems and to facilitate bone ingrowth into the prosthesis.⁴ Another method to facilitate bone ingrowth is the application of 3D printing techniques which allows the manufacturing of highly porous implants which could mimic the stiffness and elasticity of bone.^{6, 7}

Several meta-analyses reported comparable survival and clinical outcomes of cementless and cemented TKA.⁸⁻¹⁰ One meta-analysis found superior survival of cemented TKA, but this difference was diminished when only randomized controlled trials (RCT) were included in the analysis.¹¹ In addition, cementless TKA have shown promising results in studies using radiostereometric analysis (RSA).¹²⁻¹⁴ RSA has the ability to measure micromotion of an implant and predict mechanical loosening as early as two years postoperatively.¹⁵⁻¹⁷ High initial migration and continuous migration is associated with early loosening of the implant, making RSA an effective tool for the evaluation of new implants.¹⁵⁻¹⁷ RSA studies reported that cementless implants typically show early migration in the first postoperative year (settling phase), after which stabilization is achieved which remains evident ten years postoperatively.^{13, 14, 18-21} By 3D printing a prosthesis with highly porous metal, cementless fixation might be enhanced due to the ingrowth of bone into the prosthesis and initial migration could be reduced to a level comparable to cemented TKA. To date, no RCT using RSA has evaluated the migration of a novel cementless

TKA with a 3D-printed highly porous metal called Tritanium (Stryker, Allendale, New Jersey, USA).

The aim of this RCT is to compare the cementless, 3D-printed Tritanium TKA with its cemented counterpart using RSA and clinical outcomes. The hypothesis is that the cementless TKA will be as stable as the cemented TKA during the two-year follow-up.

Methods

This RCT was conducted in the Hässleholm Hospital (Sweden) between October 2015 and October 2016. A total of 72 patients were randomized to either cementless Tritanium Triathlon Cruciate Retaining TKA or cemented Triathlon Cruciate Retaining TKA (Stryker, Warsaw, Indiana, USA). Inclusion criteria were osteoarthritis Ahlbäck stages II to IV, and males or non-pregnant females aged between 40 and 75 years, who had given informed consent.²² Exclusion criteria were a body mass index (BMI) > 38 kg/m², a bilateral operation, or a neuromuscular/neurosensory deficiency. Randomization was done by means of a computer-generated list using a blocked randomization scheme in a 1:1 ratio. To ensure concealment of treatment allocation, envelopes with randomization were opened just before surgery. Patients remained blinded to the treatment allocation during the study.

The prostheses were identical in geometrical shape except for the addition of 3D-printed in-growth foam, and four pegs onto the under-surface of the tibial baseplate in the cementless group to provide additional stability [Figure V.1].²³ The femoral component was press-fit and periapatite coated in the cementless group. Smartset GHV bone cement (DePuy CMW; DePuy Synthes, Blackpool, UK) was used in the cemented group, leaving the tibial

Figure V.1 3D-printed, cementless tibial base plate (Tritanium, Stryker, NJ, USA)



keel cementless in all cases. Both groups showed similar tibial preparation and the same jig was used. Patellae were reshaped but not resurfaced, and no tourniquet was used during surgery in both groups. The operation was performed according to the device-specific surgical protocol by a single experienced orthopaedic knee surgeon (STL). Both groups had identical postoperative treatments and follow-up.

The primary outcome measure was migration over the first two years measured by RSA. Migration was expressed as the Maximum Total Point Motion (MTPM), which estimates the length of the translational vector with the greatest migration along or about the transverse, longitudinal, or sagittal axis.²⁴ Secondary outcome measures were migration from three months onwards, the Knee Society Score (KSS), the Knee Injury and Osteoarthritis Outcome Score (KOOS), and the Forgotten Joint Score (FJS).²⁵⁻²⁷ These scores were collected preoperatively and at three months, one year, and two years postoperatively. All scores ranged from 0 to 100 with higher scores indicating better outcomes.

Eight spherical tantalum beads (\varnothing 0.8 mm; RSA Biomedical, Umeå, Sweden) were inserted into the tibia, and five beads were implanted in the polyethylene of the tibial insert in fixed positions to facilitate the RSA measurements. RSA radiographs were taken with a biplanar technique in a 90° angle (Cage 10, RSA Biomedical, Umeå, Sweden) with the patient supine. These radiographs were taken within two days postoperatively, and after three months, one year, and two years. Double examinations were made at one-year follow-up to determine the precision of the RSA measurements, which is expressed as the SD of the migration of these two subsequent RSA radiographs.²⁴ Long-leg standing anteroposterior radiographs were taken preoperatively and one-year postoperatively. The hip-knee-ankle angle was measured by a single observer (SH) using a standardized protocol.²⁸

The RSA radiographs were analyzed using Model-Based RSA (RSACore, Leiden, Netherlands) following the RSA guidelines.²⁴ All measurements were corrected to the right side.²⁹ Implants with > 0.2 mm MTPM between one- and two-year

postoperatively were classified as ‘continuously migrating’ and considered at greater risk for aseptic loosening.¹⁷ A marker configuration model was constructed in case markers were occluded by the metal implants.³⁰

Statistical analysis

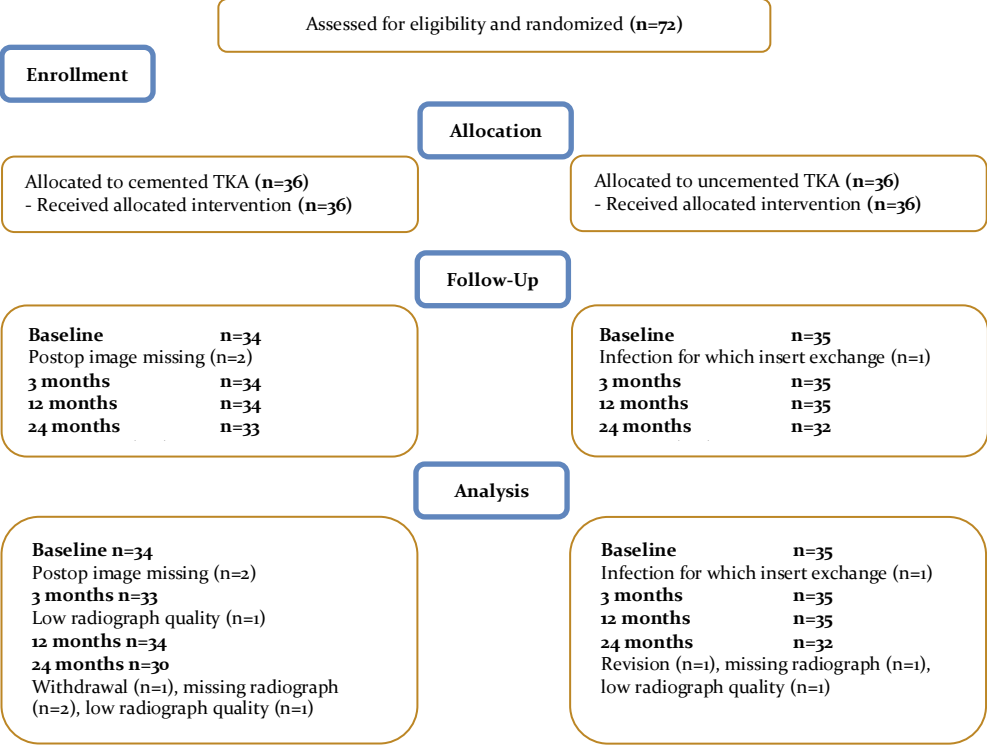
In a noninferiority study set-up, 23 subjects are needed for each group assuming a mean MTPM of 0.62 mm with SD 0.15 mm, and study power 80%.³¹ The two-sided 95% confidence interval (CI) will then exclude a difference beyond the 0.13 mm measurement error of the RSA-setup in MTPM.^{31, 32} To compensate for patients with inadequate marking and for loss to follow-up, 36 patients were recruited per study group. Migration and clinical scores were compared between groups using a linear mixed-model. This model deals effectively with missing data and takes the within-subject correlation into account.^{33, 34} The model consisted of a group variable, a time variable, and an interaction term between the time and group variable with a random intercept. MTPM was transformed using a logarithmic transformation to obtain a Gaussian distribution. The presented values were back-transformed to the original scale. The same analysis was repeated using the three-month measurements as baseline, to assess whether groups differed in migration after the settling phase. A post-hoc analysis was conducted to include any patient characteristics unevenly distributed by chance. A p-value < 0.05 was considered statistically significant. Analyses were performed using SPSS v. 25 (IBM, Armonk, New York, USA).

This study was approved by the Regional Ethical Review Board in Lund (entry no. 2015/8), was registered at clinicaltrials.gov (NCT02578446), and was conducted according to the CONSORT statement.³⁵ All patients provided informed consent. This study was funded by Stryker, but they had no part in the design, conduct, analysis, and interpretations stated in this paper.

Results

Of the 72 patients, two patients had missing baseline radiographs in the cemented group and could not be included in the analyses. In addition, the insert of one patient in the cementless group was exchanged to treat an infection three weeks postoperatively. As the markers were inserted in the polyethylene insert, no marker-based analysis could be performed for this patient after removal of the insert. As a result, 34 patients in the cemented and 35 patients in the cementless group were available for analysis [Figure V.II].

Figure V.II Consort Flowchart



During follow-up, one patient withdrew in the cemented group, four RSA examinations in the cemented group and two RSA examinations in the cementless group could not be analyzed due to technical issues or missing radiographs [Figure V.II]. BMI was slightly higher in the cemented group and there were more patients with lower ASA in the cementless group, but other characteristics were similar for both groups [Table V.I].

Table V.I Baseline characteristics

		Cemented	Cementless
Age, years (SD)		66 (6.3)	65 (5.7)
Male, n (% of group)		18 (53%)	18 (51%)
BMI, kg/m² (SD)		30 (3.1)	28 (3.1)
Right, n (% of group)		15 (44%)	19 (54%)
Surgery duration, minutes (SD)		45 (4.6)	43 (6.0)
HKA preoperative, n (% of group)			
	Neutral	1 (3%)	4 (11%)
	Varus	30 (88%)	23 (66%)
	Valgus	3 (9%)	8 (23%)
HKA postoperative, n (% of group)			
	Neutral	23 (68%)	20 (57%)
	Varus	6 (18%)	9 (26%)
	Valgus	5 (15%)	6 (17%)
ASA classification, n (% of group)			
	I	4 (12%)	13 (37%)
	II	26 (77%)	21 (60%)
	III	4 (12%)	1 (3%)
Ahlbäck grade, n (% of group)			
	I	1 (3%)	0 (0%)
	II	7 (21%)	8 (23%)
	III	25 (74%)	27 (77%)
	IV	1 (3%)	0 (0%)
KSS-Knee Score, points (SD)		30 (8.9)	33 (9.2)
KSS-Function score, points (SD)		61 (4.4)	61 (5.9)

SD = Standard Deviation. HKA = Hip-Knee-Ankle angle. Neutral = -3° - 3° , varus $<-3^{\circ}$, valgus $>3^{\circ}$. ASA classification = American Society of Anesthesiologists. KSS = Knee Society Score.

The precision of the translations and rotations was 0.1 mm and 0.1°, respectively. The mean error of rigid body fitting was 0.1 mm (0.02 to 0.30) and 0.1 mm (0.02 to 0.33) for the prosthesis and the tibial bone, respectively. The mean condition number was 35 (21 to 103) and 38 (24 to 93) for the prosthesis and the tibial bone, respectively.

MTPM differed between groups during the two-year follow-up period ($p = 0.003$, linear mixed model). The MTPM at three months, one-year, and two-year follow-up was 0.33 mm (95% CI 0.25 to 0.42; 0.09 to 0.93), 0.42 mm (95% CI 0.33 to 0.51; 0.19 to 1.34), and 0.47 mm (95% CI 0.38 to 0.57; 0.14 to 1.07) in the cemented group, versus 0.52 mm (95% CI 0.43 to 0.63; 0.10 to 2.24), 0.62 mm (95% CI 0.52 to 0.73; 0.13 to 3.63) and 0.64 mm (95% CI 0.53 to 0.75; 0.18 to 2.03) in the cementless group, respectively (Figure V.III). Using three months as reference, the between-group difference in increase of the MTPM up to two years of follow-up was 0.01 mm (95% CI 0.01 to 0.03; $p = 0.497$, linear mixed model).

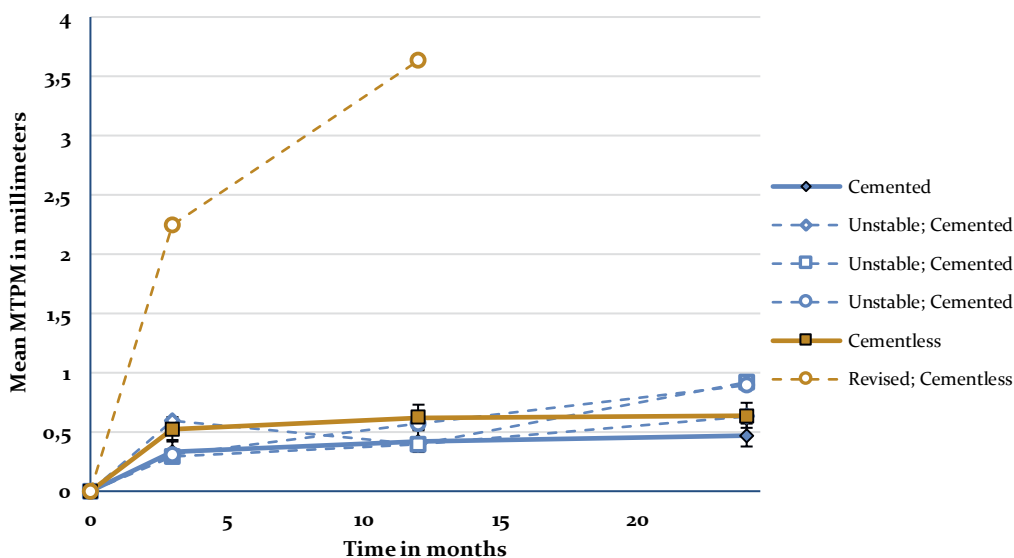


Figure V.III Mean MTPM of the cemented and cementless group with 95% confidence intervals. The MTPM of 3 continuously migrating cemented TKAs and one revised cementless TKA were plotted.

One patient in the cementless group had a revision 20 months postoperatively due to progressive pain and migration of the tibial component. This patient was a 71-year-old female with a BMI of 30 kg/m² and was classified as ASA 2. The pre- and

postoperative hip-knee-ankle (HKA) angle was 10° (i.e. valgus) and -11° (i.e. varus), respectively. The Medial Proximal Tibial Angle was 3° (i.e. valgus) preoperatively and was -5° (i.e. varus) postoperatively. Main mode of failure was posterior tilting of the tibial component [Figure V.IV]. Three cemented tibial components showed continuous migration [Figure V.III].

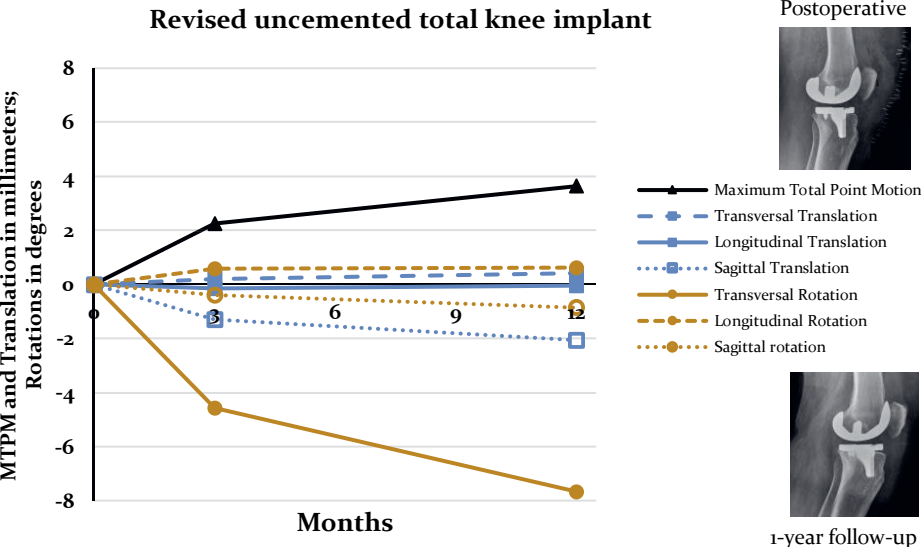


Figure V.IV Migration pattern of the revised cementless total knee implant. Most prominent mode of failure is the rotation about the transverse axis. Backward tilting of the tibial component is also visible on the lateral knee radiograph 1-year postoperative.

Apart from the revised implant, none of the cementless implants was considered unstable. The initial migration observed in the cementless group primarily consisted of tibial component subsidence [Figure V.V]. There were no differences in translations or rotations in any other direction [Figure V.VI A-E].

Figure V.V Translation along the longitudinal axis. Error bars represent 95% confidence intervals. Lift-off is represented by a positive value and subsidence by a negative value.

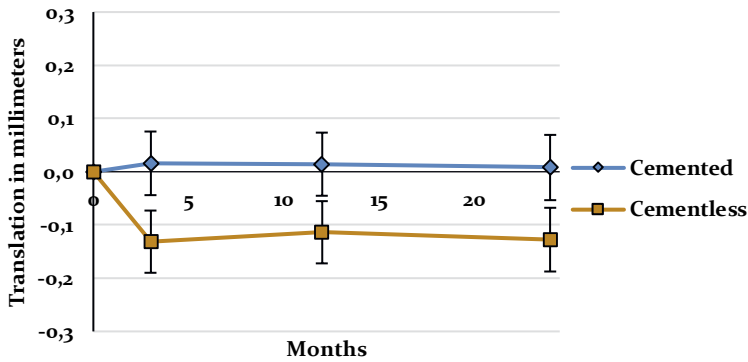
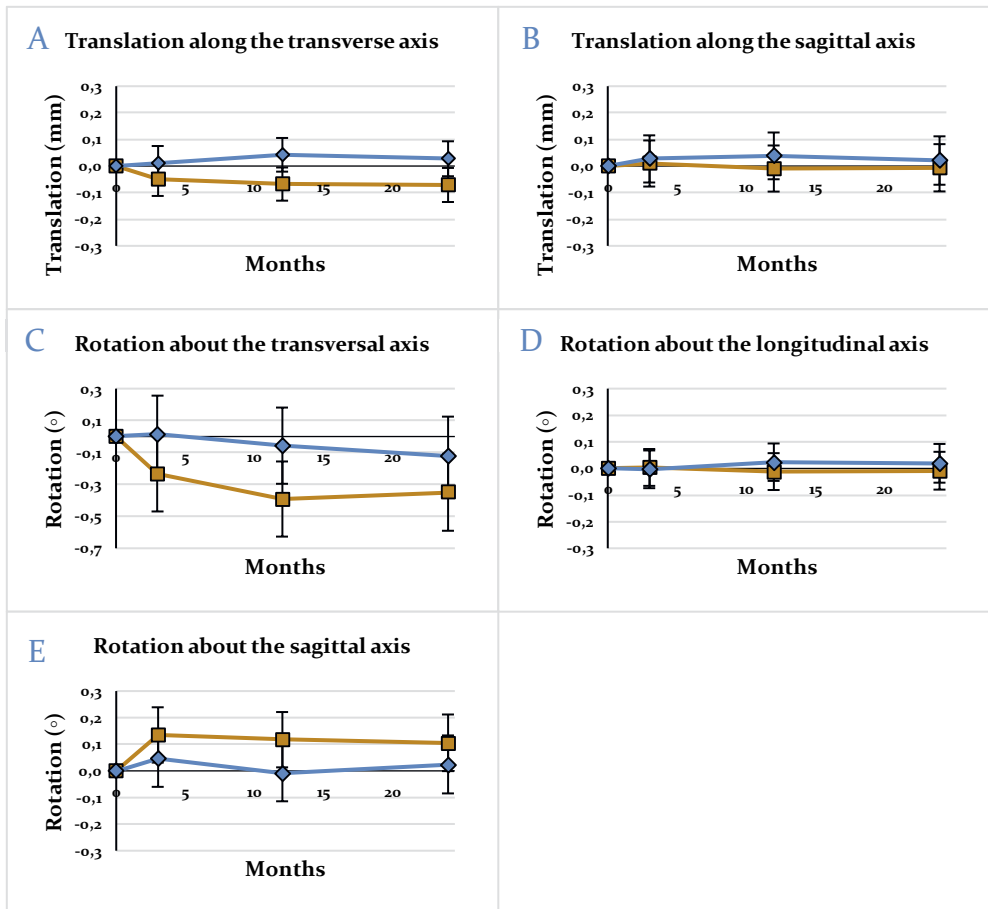
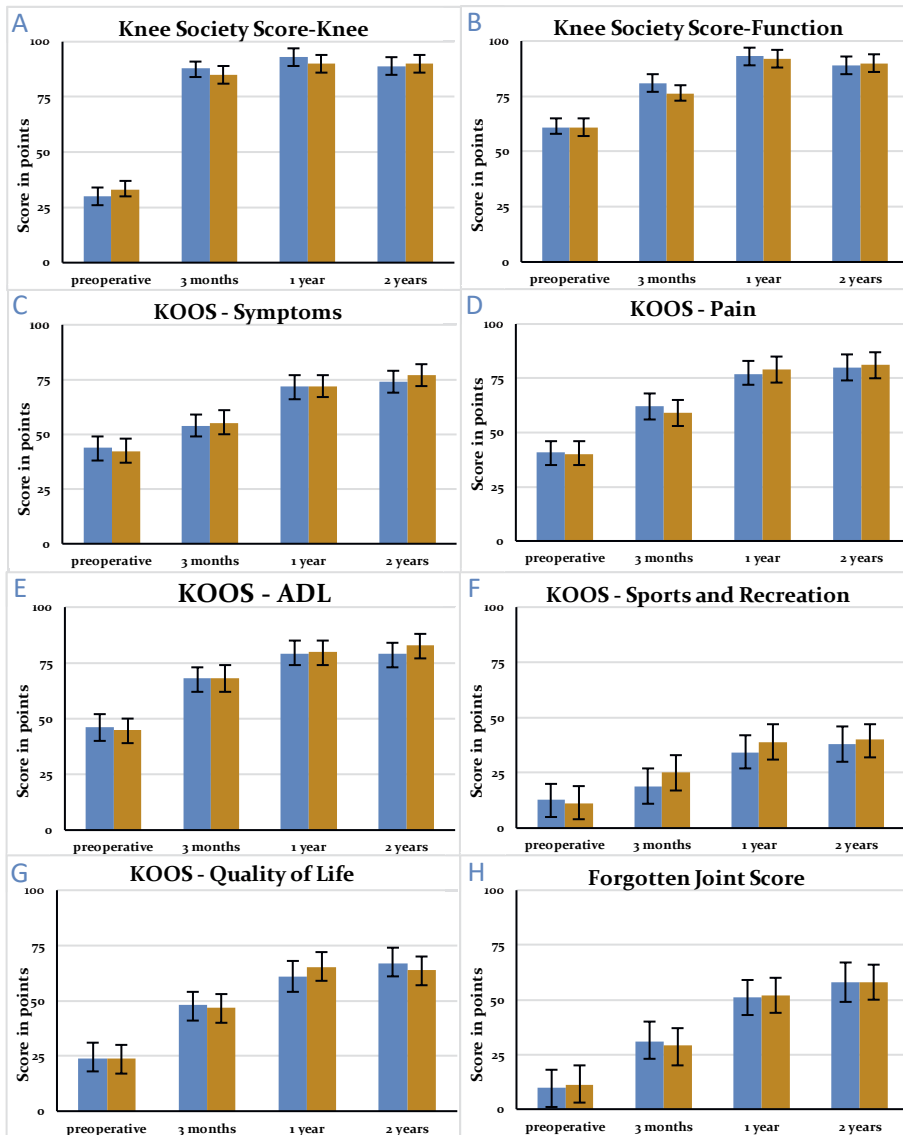


Figure V.VI A-E Translation along the transverse and sagittal axis, and rotation about the transverse, longitudinal and sagittal axis. Means are presented with 95% confidence intervals.



The KSS-Knee ($p = 0.117$) and -Function ($p = 0.459$) showed no statistical difference between groups, nor did the KOOS Symptoms ($p = 0.806$), Pain ($p = 0.740$), Activities of daily living ($p = 0.676$), Sports and recreation ($p = 0.546$), Quality of life ($p = 0.725$), and the FJS ($p = 0.922$) at any interval, using a linear mixed model [Figure V.VII A-H].

Figure V.VII A-H Clinical scores per domain. Error bars are 95% confidence intervals. KOOS = Knee Injury and Osteoarthritis Outcome Score; ADL = Activities Daily Living.

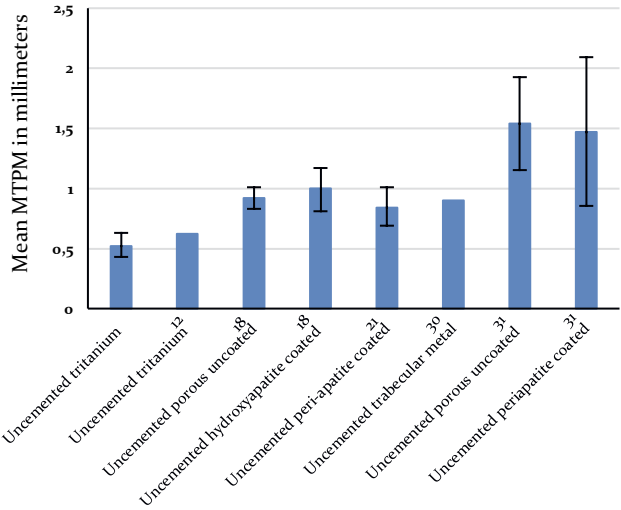


Discussion

The present study compared the migration of a novel, cementless, 3D-printed tibial component, and a cemented tibial component of a TKA with a similar design. Over the two-year period, the cementless implants had a higher initial migration. However, as expected, this difference was caused by initial settling of the cementless implants during the first three months after which stabilization was observed in all but one (revision) implant. These results are in line with previously reported RSA results using the same cementless implant.¹² In comparison, three cemented implants were initially stable but showed continuous migration between one and two years of follow-up. Using recently proposed six-month thresholds (MTPM < 0.5 mm acceptable; 0.5 mm to 1.6 mm at risk; > 1.6 mm unacceptable), the cemented and cementless implants in the present study would be classified as acceptable and at risk, respectively.¹⁶ However, as Laende et al. (2019) suggested, because these thresholds do not discriminate between fixation methods, different thresholds should be implemented as higher early migration of cementless TKA was not associated with more instability.¹³

When comparing our results for the cementless TKA with those from other studies, the mean MTPM at three months in the present study was lower (0.52 mm, 95% CI 0.43 to 0.63) than previously reported MTPM values ranging between 0.82 mm and 1.52 mm [Figure V.VIII].^{12, 18, 21, 36, 37} This might be related to the tibial component design as well as material properties for initial

Figure V.VIII Mean MTPM at 3 months follow-up of uncemented total knee implants. Error bars represent the 95% confidence interval



optimal bone fixation. The main direction of migration was subsidence in the first three months, which mirrored other RSA studies using cementless implants.^{19, 20}

The HKA of the patient with the revised implant changed from 10° preoperatively (i.e. valgus) to -11° (i.e. varus) postoperatively, with the tibial component positioned more in varus postoperative. The revised patient had the greatest pre- and postoperative difference in HKA, and the greatest postoperative varus HKA. The influence of pre- and postoperative alignment on implant failure is still unclear, as conflicting results have been published.^{38, 39} A recent study found that varus aligned TKA resulted in a higher migration than in-range aligned TKA, while another study showed that varus aligned tibial components show more migration.^{40, 41} Hence, early failure of the cementless TKA requiring revision might be attributed to malalignment contributing to increased micromotion resulting in failure to obtain bone ingrowth.

This was the first RCT presenting RSA results of this novel 3D-printed, cementless TKA. This relatively new manufacturing technique is becoming more accessible for broader use and the costs of 3D printing decreased substantially between 2001 and 2011.⁷ Another benefit of 3D-printed implants, beyond the ability to manufacture highly porous implants to allow osseointegration into the bone, is the ability to match better the elasticity and stiffness of the bone, which could result in less stress-shielding around the implant.^{7, 42} The 3D-printed, cementless TKA in this study shows promising results as the initial migration seems to be lower than other cementless designs. Likewise, several other studies using a similar implant-reported excellent short-term survival rates and clinical scores.⁴³⁻⁴⁵

Limitations of this study are that we could not separate the effect of the cementless design from the four additional pegs onto the under-surface of the tibial plateau. Theoretically, these pegs could provide more rotational stability, but this has not been studied before in vivo so that a study comparing a cementless knee implant with and without pegs is needed. Moreover, patients with a BMI of > 38 kg/m² were

excluded even though in a previous study they have been shown to benefit from cementless coated TKA.⁴⁶ Future studies should assess the benefits for this specific population. In addition, the cementless implants were slightly more malaligned postoperatively compared with the cemented TKA. It is unclear whether this difference is due to the fixation method or a more demanding surgical technique. As the procedures were performed by a single surgeon (STL), there is a limit to the generalizability of the results, although the observed differences between groups cannot be attributed to a surgeon effect as found in a previous RSA study.⁴⁷ In addition, marker-based RSA analysis was used instead of model-based RSA, which may have introduced slight measurement errors due to micromotion at the locking mechanism of the polyethylene. Lastly, this study was single blinded as it was impossible to blind clinicians given the differences in radiological appearance of both implants. However, RSA is an objective method of assessing implant migration and no influence on these results would be expected. The current study underscores the importance of evaluation of new techniques such as 3D printing.^{48, 49} In conclusion, the cementless TKA migrated more than the cemented TKA in the first two years. This difference was mainly due to a higher initial migration of the cementless TKA in the first three postoperative months after which stabilization was observed in all but one malaligned and early revised TKA. Whether the biological fixation of the cementless implants will result in an increased long-term survival will become clear when longer follow-up results become available.

Take home message

- The cementless total knee arthroplasty (TKA) showed more migration compared to the cemented TKA due to higher initial migration the cementless implant. After three months, both the cemented and cementless TKA were stable.
- The most prominent direction of migration for the cementless implants was tibial subsidence.

Funding statement

This study was funded by Stryker but had no part in the design, conduct, analysis, and interpretations stated in this paper. Although none of the authors has received or will receive benefits for personal or professional use from a commercial party related directly or indirectly to the subject of this article, benefits have been or will be received but will be directed solely to a research fund, foundation, educational institution, or other non-profit organization with which one or more of the authors are associated.

ICMJE COI statement

S. Hasan and B. L. Kaptein report an institutional grant, money paid to support travel, and payment for writing or reviewing the manuscript, all from Stryker, related to this study. K. T. van Hamersveld and P. J. Marang-van de Mheen report money paid to their institution from Stryker to support travel, related to this study. R. G. H. H. Nelissen reports an institutional grant and money paid to support travel from Stryker, related to this study. S. Toksvig-Larsen reports an institutional grant from Stryker, related to this study, as well as institutional grants/grants pending from Stryker, and money paid to their institution and personal payments from Stryker, Smith & Nephew, and Johnson & Johnson for consultancy and payment for lectures, all unrelated to this study.

Ethical review statement

This study was approved by the Regional Ethical Review Board in Lund (entry no. 2015/8), was registered at clinicaltrials.gov (NCT02578446), and was conducted according to the CONSORT statement.

Trial registration number

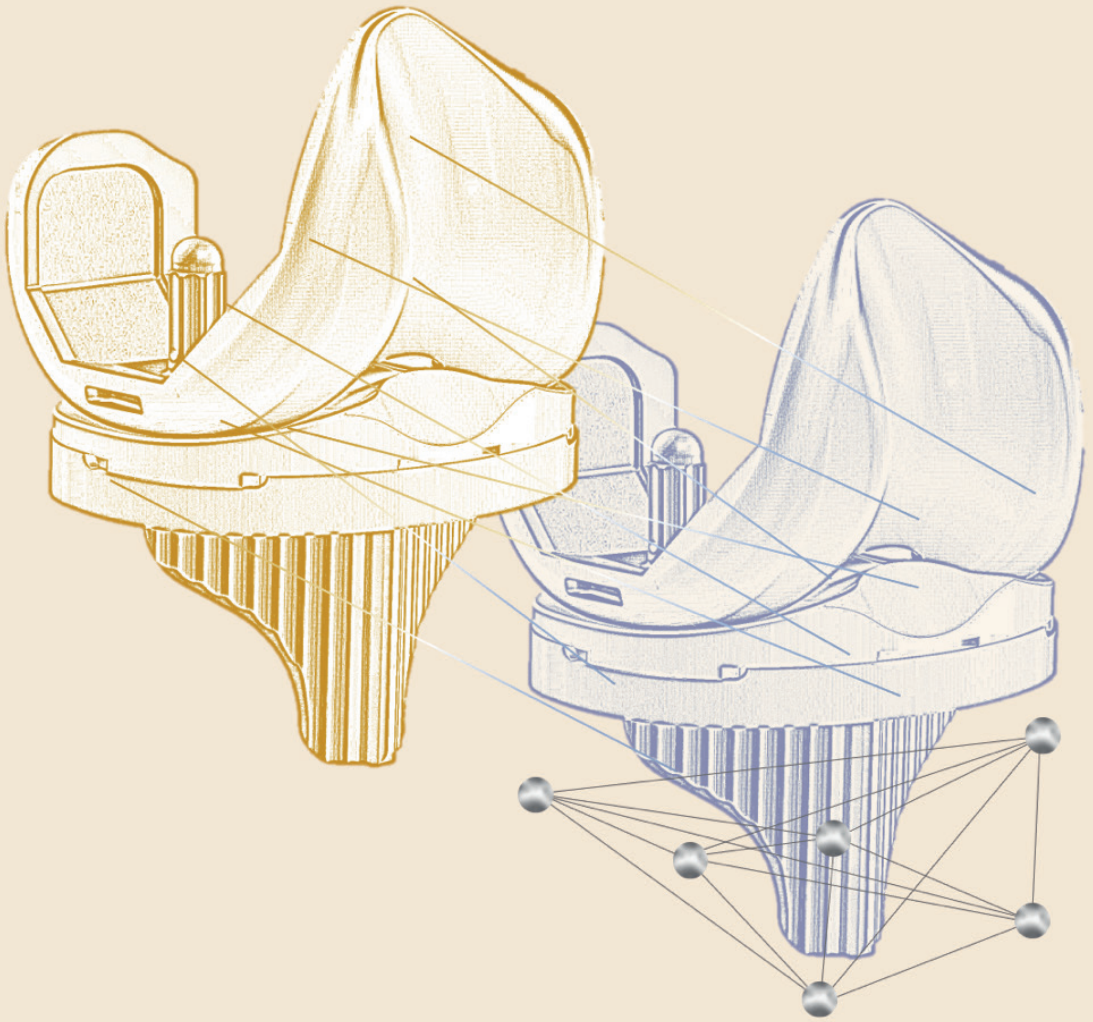
[Clinicaltrials.gov](https://clinicaltrials.gov) NCT02578446.

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Chapter VI

Late stabilization after initial migration of patients undergoing cemented total knee arthroplasty

**A five-year follow-up paper of two randomized
controlled trials using radiostereometric analysis**

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Abstract

Background and purpose

In total knee arthroplasty (TKA), metal-backed (MBT) and all-polyethylene (APT) designs have shown comparable implant migration up to 2 years using radiostereometric analysis (RSA). However, studies comparing mid-term migration of both designs are lacking. Furthermore, continuously migrating TKAs up to 2 years may continue to migrate or stabilize hereafter. Therefore, we compared 5-year migration of MBT and APT using either cruciate-stabilizing (CS) or posterior-stabilizing (PS) designs and specifically assessed migration profiles of continuously migrating TKAs beyond 2 years.

Patients and methods

The present study includes results from 2 randomized trials comparing migration of cemented MBT with APT of either CS (CS-study, n=59) or PS (PS-study, n=56) design. 2 surgeons performed all surgeries. We used a linear mixed model for the analyses.

Results

The overall migration between MBT and APT TKAs was similar for either the CS- or PS-design over a 5-year period. In both studies combined, 9 implants showed continuous migration in the second postoperative year, of which 1 (APT-CS) was revised for instability, 4 (2 MBT-CS, MBT-PS, APT-PS) stabilized and 4 (2 MBT-CS, APT-CS, MBT-PS) missed 5-year data.

Interpretation

Overall migration was similar between MBT and APT TKAs up to 5 years, for both the CS- and PS-design. 4 initially migrating TKAs stabilized between 2- and 5-year follow-up, stressing the need for longer-term follow-up to determine whether second-year continuous migration correctly predicts loosening.

Introduction

Several total knee arthroplasty (TKA) design characteristics could influence migration. TKA designs include either metal-backed tibial (MBT) or all-polyethylene tibial (APT) components. MBT designs are currently the gold standard because of intra-operative flexibility and the possibility of applying a coating to increase bone ingrowth, but APT TKAs are gaining interest as these designs could reduce costs with approximately 40%.^{1, 2}

Despite disappointing revision rates of APT designs in the early 1970s, contemporary studies showed comparable revision rates and clinical outcomes for MBT and APT TKAs.³⁻⁴ Also, studies comparing migration using radiostereometric analysis (RSA) between MBT and APT designs found comparable 2-year results for both designs.⁵⁻¹⁰ However, mid-term results are needed to confirm whether migration is still comparable and, particularly for implants showing continuous migration in the first 2 years, to assess whether migration is progressive over time or stabilizes. These mid-term results are needed for both unconstrained TKA designs (e.g., cruciate-stabilizing (CS)) and posterior stabilizing (PS) designs as migration could differ between these designs due to the post-cam design of PS implants which could induce greater stress to the tibial component compared with unconstrained designs.¹¹

Therefore, we (1) compared overall 5-year migration between MBT and APT using TKAs with either CS or PS design, and (2) evaluated continuously migrating TKAs in the second postoperative year in their migration profiles up to mid-term follow-up.

Patients and methods

We describe 5-year results of 2 randomized controlled trials (RCTs) using RSA. The 2-year results as well as the patient selection and surgical procedures for these RCTs have been described in detail previously.^{9, 10} Both RCTs were conducted in Hässleholm, Sweden and all patients in both studies were operated by 2 surgeons. The study compared the MBT-cruciate stabilizing (CS) Triathlon Total Knee System with the APT-CS Triathlon, while the other study compared the MBT-posterior stabilizing (PS) Triathlon with the APT-PS (Stryker, Warsaw, NJ, USA). For the CS-study, 60 consecutive patients were included between June 2014 and November 2014. Another 60 patients were included between November 2014 and June 2015 in the PS-study. 1 patient in the CS-study and 4 patients in the PS-study were excluded before the first postoperative assessment [Fig. VI.1]. Thus, 115 patients were available for follow-up.

Outcome measures

The primary outcome measure was migration as measured with RSA over a 5-year period. RSA radiographs were taken 1-2 days postoperatively, and at 3 months, 1 year, 2 years and 5 years. Migration was expressed as transverse, longitudinal, and sagittal translation, and rotation as well as maximum total point motion (MTPM) which is the length of the translational vector of the marker with the greatest migration. TKAs migrating >0.2 -millimeter (mm) MTPM between 1 year and 2 years were classified as continuously migrating.¹² Analyses and reporting were performed in concordance with the ISO 16087 Standard and the RSA guidelines.^{13, 14} Precision of RSA measurements were assessed through double measurements and expressed as $2 \times \text{SD}$ of these measurements. The precision of the translation and rotation in the APT-CS study was ≤ 0.13 mm and $\leq 0.15^\circ$, respectively, and was ≤ 0.15 mm and $\leq 0.23^\circ$ in the APT-PS study.^{9, 10} A mean error of rigid body fitting < 0.35 mm and a condition number < 120 were set as cut-off points.¹³ Marker-based migration was calculated using MB-RSA version 4.2014 (RSAcore, Leiden, the Netherlands). If < 3 markers were

visible on specific RSA radiographs (occurred in 13 patients), a marker-configuration model was used to migration and prevent loss of data.¹⁵

Statistics

First, we assessed possible attrition bias by comparing baseline characteristics of patients with missing and available data at 5 years within each study group (i.e., MBT-CS, APT-CS, MBT-PS, APT-PS). Transverse, longitudinal, and sagittal translations and rotations, and MTPM were then compared using a linear mixed model per study. MTPM was log-transformed and presented MTPM values were back-transformed in the original scale. A mixed model was used as it takes the within-subject correlation into account and deals with missing values¹⁶. The model consisted of a group variable (i.e., CS-study: MBT-CS versus APT-CS or PS-study: MBT-PS versus APT-PS), a time variable (i.e., baseline, 3 months, 1 year, 2 years, 5 years), and an interaction term of group and time as fixed effects. Furthermore, operating surgeon was added as a fixed variable (i.e., surgeon 1, surgeon 2) as well as an interaction term of surgeon and time because the surgeon significantly influenced migration for the 2-year results and was unevenly distributed between groups in the CS-study.⁹ The distribution of sex was also skewed in the CS-study, but was not included in the analysis as results at 2 years showed no influence of sex on migration.⁹ An Autoregressive Order-1 covariance matrix was used to model remaining variability. Besides overall migration, the migration profiles beyond 2 years of continuously migrating TKAs at risk for aseptic loosening were examined. Means were reported with 95% confidence intervals without p-values.¹⁷ We used SPSS version 25 (IBM SPSS Statistics 25.0; IBM Corp, Armonk, NY, USA) for all analyses.

Ethics, registration, funding, and potential conflicts of interest

For both studies, approval of the Regional Review Board in Lund was obtained before recruitment (entry no. 2013/434; 2014/513) and were registered at the ISRCTN

Registry (ISRCTN04081530; ISRCTN10744502). The present study is reported in concordance with the CONSORT guidelines. Stryker funded both studies but did not take part in the design, conduct, analysis nor interpretations stated in this paper. The authors declare no other conflicts of interest.

Figure VI.I Consort Flowchart

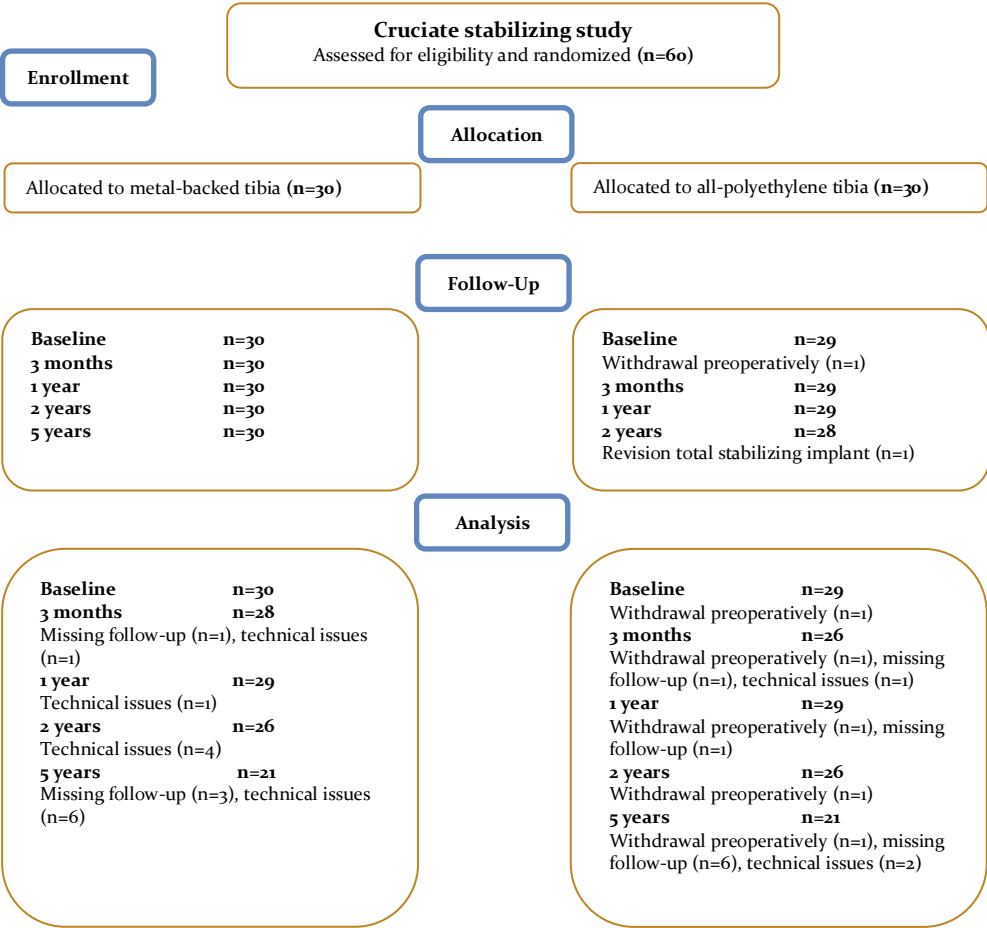
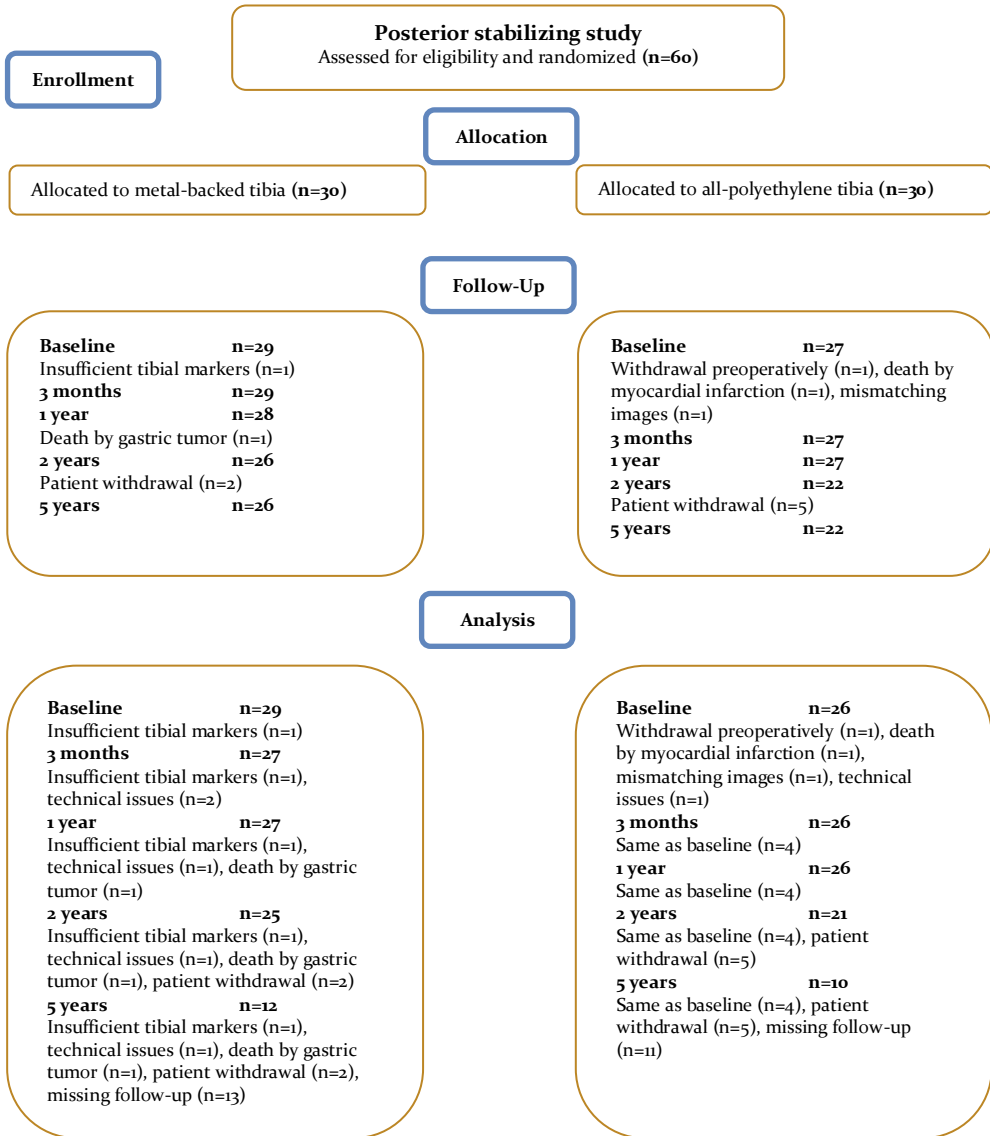


Figure VI.I Consort Flowchart (continued)



Results

42 patients in the CS-study and 22 patients in the PS-study were analyzed at 5-year follow-up [Fig. VI.I, Table VI.I]. Patients in the PS-study missed their 5 years follow-up visit mainly due to the COVID-19 pandemic which prohibited patients to visit the hospital or resulted in patients refusing follow-up. No differences in baseline characteristics were found between patients with and without 5-year RSA data within study groups (data not shown). Given the reason for missing 5-year follow-up measurements, it seems likely that any loss-to-follow-up was random and therefore attrition bias was considered unlikely.

	Cruciate-stabilizing (CS)		Posterior-stabilizing (PS)	
	Metal-backed	All-polyethylene	Metal-backed	All-polyethylene
Age, mean years (SD)	68 (5)	69 (5)	68 (4)	68 (4)
BMI, mean (SD)	29 (3)	28 (4)	28 (4)	29 (3)
Sex, N				
Female	13	22	17	13
Male	17	7	12	14
Surgeon, N				
#1	16	9	15	13
#2	14	20	14	14
Ahlbäck classification, N				
II	10	6	5	4
III	19	21	23	23
IV	1	2	1	0
HKA postoperative, N				
Varus (<177°) ^z	7	4	7	3
Neutral (177-183°)	22	19	15	17
Valgus (>183°)	1	6	2	4
Missing ^a	0	0	5	3
Size of femoral component, N				
1-3/4/5/6/7-8	3/9/7/8/3	7/14/7/1/0	5/12/5/6/1	6/9/7/4/1
Size of tibial component, N				
2-3/4/5/6/7-8	0/11/4/10/5	3/11/10/5/0	6/9/4/7/3	4/6/7/9/1
Thickness of polyethylene, N				
9/11/13/16 mm	2/18/10/0	1/17/9/2	5/18/6/0	11/9/7/0

Table VI.I Baseline characteristics

Migration up to 5 years of MBT and APT designs

No statistically significant differences in MTPM were found between MBT-CS and APT-CS TKAs nor between MBT-PS and APT-PS TKAs over a 5-year period [Fig. IV.II]. The operating surgeon, however, influenced migration significantly in the CS-study but not in the PS-study [Fig. VI.III]. Although differences were small, both MBT groups translated in positive direction along the longitudinal axis (i.e., lift-off) while both APT groups translated in negative direction along the longitudinal axis (i.e., subsidence; Fig. VI.IV). The APT-CS group tended to rotate more about the transverse axis in posterior direction (i.e., negatively) compared with MBT-CS TKAs [Supplementary data Table VI.II]. Also, a trend towards positive rotation about the longitudinal axis (i.e., internal rotation) was found for APT-PS implants while MBT-PS TKAs tended to rotate negatively about the longitudinal axis (i.e., external rotation; Supplementary data Table VI.II). No statistically significant differences were found in transverse or sagittal translation, nor in sagittal rotation [Supplementary data Table VI.II]. The operating surgeon had no influence on any of the translations or rotations (data not shown).

Figure VI.II Mean maximum total point motion in millimeters per group. Error bars represent 95% confidence intervals. CS = cruciate stabilizing, PS = posterior stabilizing, mm = millimeters

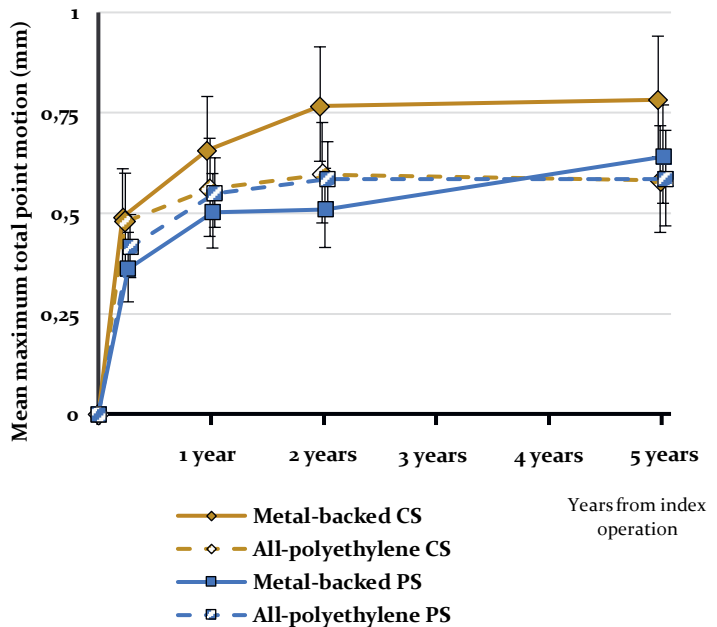


Figure VI.III Mean maximum total point motion (MTPM) stratified by surgeon at 3 months, 1 year, 2 years, and 5 years. Error bars represent 95% confidence intervals.

CS = Cruciate-stabilizing; PS = Posterior-stabilizing; mm = millimeters

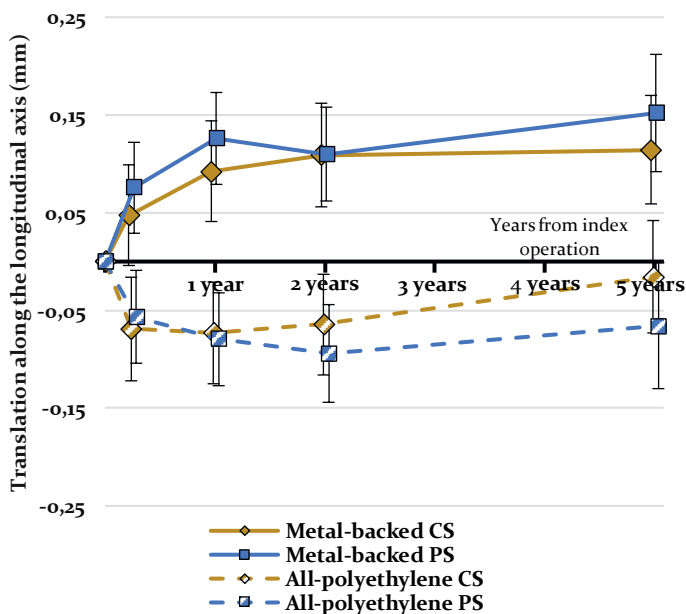
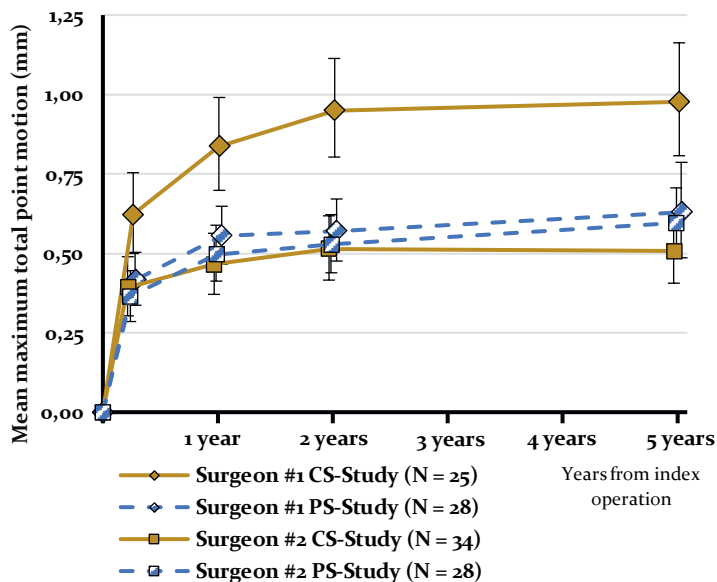


Figure VI.IV Mean translation along the longitudinal axis of the metal-backed tibial implant groups and the all-polyethylene tibial implant groups at 3 months, 1 year, 2 years, and 5 years. Error bars represent 95% confidence intervals. Positive values indicate lift-off of the tibial implant and negative values subsidence.

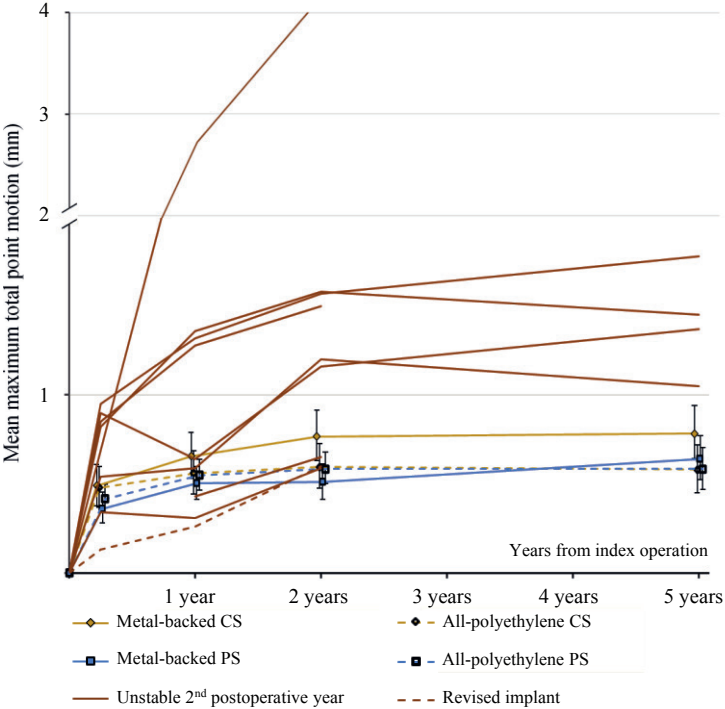
CS = Cruciate-stabilizing; PS = Posterior-stabilizing; mm = millimeters

Continuously migrating TKAs

In both studies combined, 9 tibial components showed continuous migration up to 2 years of which 4 (2 MBT-CS, MBT-PS, APT-PS) stabilized between 2 and 5 years, 1 (APT-CS) was revised for persistent pain and instability, 1 (MBT-CS) could not be analyzed due to a condition number >120 (i.e., technical issue), and 3 (MBT-CS, APT-CS, MBT-PS) were missing at 5 years [Fig. VI.V]. The latter 3 implants had a similar magnitude and slope of migration up to 2 years compared to implants with 5-year data available that stabilized. The other component (MBT-CS design) where 5-year RSA data could not be analyzed due to a condition number >120 had a different migration pattern with high migration at 1 year and 2 years (i.e., MTPM 2.7 mm and 4.2 mm respectively). This patient was a female of 67 years who had a BMI of 27. Walking distance at 2 and 5 years was unlimited, and she experienced no pain. Also, one of the continuous migrating implants was revised (ATP-CS). The MTPM of the revised patients increased >0.2 mm MTPM between 1-and 2-year follow-up and was therefore classified as continuously migrating. This revised patient was a female of 65 years with a BMI of 34. She was initially treated with an APT-CS design and was revised to a total-stabilizing TKA after 4 years to treat her complaints of persistent pain and instability [Fig. VI.V].

Figure VI.V Mean maximum total point motion (MTPM) of the continuously migrating (i.e. >0.2 mm MTPM between 1 and 2 years) implants at 3 months, 1 year, 2 years, and 5 years. Error bars represent 95% confidence intervals.

CS = Cruciate-stabilizing; PS = Posterior-stabilizing; mm = millimeters



Discussion

This study is the first study comparing migration of MBT TKAs with APT TKAs up to 5 years and showed similar migration between MBT and APT TKAs for either the CS or the PS design. Consistent with the 2-year results, the operating surgeon still had a statistically significant effect on overall migration in the CS-study but not systematically on any of the translations or rotations. Even though overall migration was similar, MBT and APT designs tended to have a different migration direction, especially along the longitudinal axis where APT designs subsided while MBT implants showed lift-off. Moreover, mid-term results showed that 4 (3 MBT TKAs; 1 APT TKA) out of 9 continuously migrating TKAs up to 2 years showed late stabilization. That these implants stabilized after initial migration was unexpected as cement fixation mostly provides strong initial fixation which weakens over time (i.e., cement-debonding). It is unclear how this can be explained, which requires further research to unravel potential mechanisms provided that longer-term follow-up shows that these implants remain stable.

Both APT designs had comparable mid-term MTPM migration compared to their respective MBT designs in the present study. These results are in line with several short-term (i.e., 2-year) RSA studies as well as with clinical studies assessing survival and clinical outcomes between both designs and prior systematic reviews and meta-analyses.^{3-8, 18-23} Beside clinical studies, a study using 10-year revision rates in the Swedish registry showed superior TKA survival when using revision for any reason as endpoint in favor of APT designs.²⁴ Despite these excellent results of modern APT designs, orthopedic surgeons are still hesitant to use these components which is reflected in national registries where APT designs account for less than 15% of all TKAs.^{1, 25-27} As APT designs are less expensive than MBT designs, increasing the share of APT designs globally could reduce arthroplasty costs without risking patient safety.²

As we found earlier in our 2-year results, the CS-study showed a difference in migration up to 5-years between the 2 surgeons.⁹ This difference in tibial migration between surgeons was absent in the PS-study. These findings suggest that migration might be influenced by the surgeon for specific designs e.g., a technically more demanding CS design due to surgeon skill or experience, although both orthopedic surgeons were experienced knee surgeons. However, other RSA studies have not reported such an effect of surgeon on tibial component migration. A difference between both surgeons was found for MTPM while no differences were found in translations or rotations. These findings suggest that minor differences in the direction of migration could result in an overall difference in migration between surgeons. Whether these differences could be due to unmeasured variables such as tibial undersizing or surgical technique should be explored in future studies. Also, future comparative RSA studies should take differences between surgeons across groups into account when designing and evaluating studies.

Although the MTPM was comparable between MBT and APT designs, we found several differences in translations and rotations. First, both APT designs tended to subside in contrast with the MBT designs which tended to show lift-off. This phenomenon has suggested to be due to a difference in tensile forces between the flexible APT and the rigid MBT TKA.⁵ Second, all groups rotated posteriorly over a 5-year follow-up. Given the post-cam mechanism of PS-designs which engages in extension, posterior rotation was expected to be higher in the PS-designs, but this could not be confirmed in the present study. Unfortunately, comparison of translations and rotations with other RSA studies comparing MBT with APT designs was not possible as these studies reported unsigned values.^{5, 6, 8} Also, the differences in translation along the longitudinal axis, and rotations about the transverse axis were mainly due to differences in the first 3 months. Therefore, it is quite uncertain whether these differences influence long-term migration which should be further investigated e.g. by assessing migration using certain feature points of the implant (e.g., medial border of the tibial component). However, minor changes in TKA

design could have clinical effects as a recent study comparing revision rates of CR designs with PS designs in the Dutch arthroplasty registry found that PS designs had higher revision rates.²⁸

A limitation of our study was that several patients missed their 5-year follow-up visit due to COVID-19 restrictions. These missing RSA examinations resulted in not being able to determine whether 4 continuously migrating TKAs up to 2 years continued to migrate or stabilized. As we did not have the resources to both reschedule these follow-up visits and continue regular follow-up for other running studies, we had to accept these missing follow-up visits. However, patients who have missed their 5-year follow-up visit due to COVID-19 restrictions are scheduled for regular follow-up at 7 years and 10 years, so that migration profiles of these implants (including possible stabilization) can at those time points. It seems promising that 3 of the 4 patients with missing data showed similar migration profiles up to 2 years compared to patients who stabilized.

In conclusion, we found similar overall 5-year migration between MBT and APT TKAs. Differences in tibial migration were present between the 2 operating surgeons in the CS study at mid-term follow-up, which may be due to the CS design being technically more challenging. In addition, we found that 4 continuously migrating MBT and APT TKAs up to 2 years showed late stabilization in the period hereafter. This highlights the need for mid- and long-term RSA studies to confirm predictions made at 2 years follow-up.

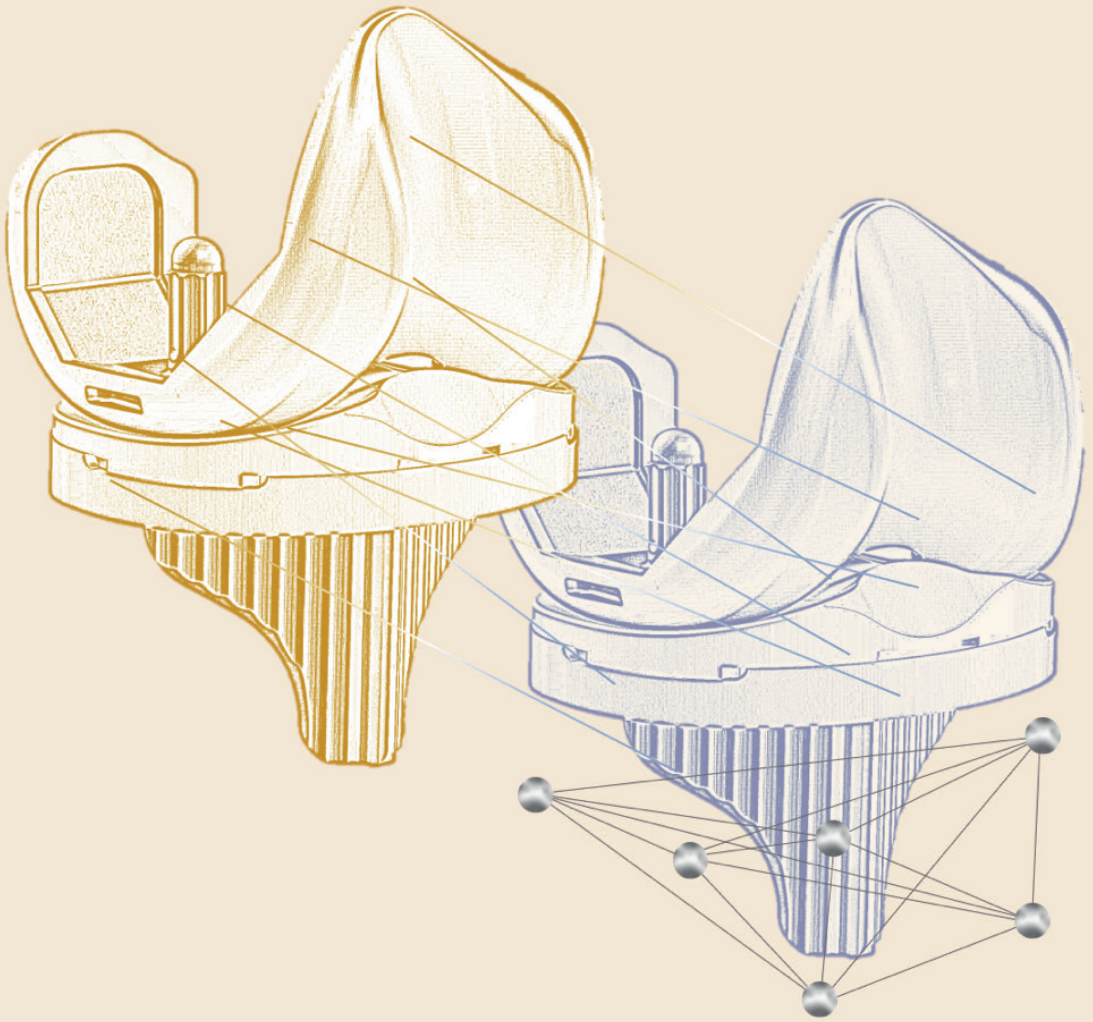
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Supplementary data; Table VI.II Mean translation along and rotation about the transverse, longitudinal, and sagittal axis with 95% confidence intervals. Statistically significant differences were highlighted in bold.

		Mean (95% confidence interval) <i>Signed values</i>			
	Visit (months)	Metal-backed CS	All-polyethylene CS	Metal-backed PS	All-polyethylene PS
Transverse Translation millimeters	3	0.00 (-0.09; 0.10)	-0.04 (-0.14; 0.06)	-0.04 (-0.14; 0.05)	-0.03 (-0.13; 0.06)
	12	-0.04 (-0.13; 0.06)	0.01 (-0.08; 0.11)	-0.05 (-0.14; 0.05)	0.01 (-0.08; 0.11)
	24	-0.08 (-0.18; 0.01)	0.01 (-0.10; 0.11)	-0.08 (-0.18; 0.01)	0.01 (-0.09; 0.11)
	60	-0.02 (-0.13; 0.08)	0.05 (-0.06; 0.15)	-0.11 (-0.22; 0.01)	0.01 (-0.11; 0.13)
Longitudinal Translation millimeters	3	0.05 (0.00; 0.10)	-0.07 (-0.12; -0.02)	0.08 (0.03; 0.12)	-0.06 (-0.10; -0.01)
	12	0.09 (0.04; 0.14)	-0.07 (-0.13; -0.02)	0.13 (0.08; 0.17)	-0.08 (-0.13; -0.03)
	24	0.11 (0.06; 0.16)	-0.06 (-0.12; -0.01)	0.11 (0.06; 0.16)	-0.09 (-0.14; -0.04)
	60	0.11 (0.06; 0.17)	-0.02 (-0.07; 0.04)	0.15 (0.09; 0.21)	-0.07 (-0.13; 0.00)
Sagittal Translation millimeters	3	-0.06 (-0.23; 0.10)	-0.10 (-0.26; 0.07)	-0.03 (-0.12; 0.05)	0.04 (-0.05; 0.12)
	12	-0.01 (-0.17; 0.16)	-0.15 (-0.31; 0.02)	-0.07 (-0.16; 0.01)	0.06 (-0.03; 0.14)
	24	0.03 (-0.14; 0.19)	-0.16 (-0.33; 0.01)	-0.04 (-0.13; 0.05)	0.07 (-0.02; 0.16)
	60	-0.03 (-0.20; 0.15)	-0.14 (-0.32; 0.03)	-0.01 (-0.11; 0.09)	0.09 (-0.02; 0.19)
Transverse Rotation degrees	3	-0.13 (-0.32; 0.06)	-0.33 (-0.53; -0.14)	-0.12 (-0.26; 0.02)	-0.08 (-0.22; 0.07)
	12	-0.13 (-0.32; 0.06)	-0.42 (-0.62; -0.22)	-0.23 (-0.36; -0.09)	-0.11 (-0.25; 0.03)
	24	-0.10 (-0.29; 0.10)	-0.47 (-0.67; -0.28)	-0.24 (-0.38; -0.10)	-0.11 (-0.25; 0.04)
	60	-0.19 (-0.39; 0.02)	-0.42 (-0.63; -0.21)	-0.23 (-0.40; -0.06)	-0.14 (-0.32; 0.04)
Longitudinal Rotation degrees	3	-0.03 (-0.16; 0.09)	0.13 (0.01; 0.26)	-0.04 (-0.13; 0.05)	0.10 (0.01; 0.20)
	12	-0.01 (-0.13; 0.12)	0.14 (0.01; 0.27)	-0.07 (-0.16; 0.02)	0.13 (0.03; 0.22)
	24	-0.03 (-0.15; 0.10)	0.12 (-0.01; 0.25)	-0.05 (-0.14; 0.04)	0.13 (0.03; 0.22)
	60	0.01 (-0.13; 0.14)	0.08 (-0.06; 0.22)	-0.12 (-0.23; -0.01)	0.15 (0.03; 0.27)
Sagittal Rotation degrees	3	-0.06 (-0.20; 0.08)	0.02 (-0.13; 0.16)	0.11 (0.00; 0.21)	-0.01 (-0.12; 0.10)
	12	-0.04 (-0.18; 0.10)	-0.17 (-0.31; -0.03)	0.09 (-0.02; 0.20)	-0.09 (-0.20; 0.02)
	24	-0.05 (-0.19; 0.10)	-0.20 (-0.33; -0.06)	0.10 (-0.01; 0.20)	-0.10 (-0.22; 0.01)
	60	-0.06 (-0.21; 0.09)	-0.27 (-0.42; -0.12)	0.18 (0.05; 0.31)	-0.09 (-0.22; 0.05)



Chapter VII

RSA migration of unicondylar knee arthroplasties is comparable to migration of total knee arthroplasties

A meta-analysis

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Abstract

Importance

Aseptic loosening is a major cause of failure for unicondylar knee arthroplasty (UKA). In total knee arthroplasty (TKA), early migration as measured with radiostereometric analysis (RSA) is a strong predictor of late revision for aseptic loosening of the tibial component. Migration in the first two years provides information on the fixation of an implant. However, the migration pattern of UKAs has not been systematically determined and it is unclear if the migration pattern of UKAs is similar to TKAs. Therefore, the present meta-analysis aims to evaluate the migration patterns of tibial components of UKAs.

Evidence review

All RSA studies reporting on migration at two or more postoperative moments of an UKA were included. Pubmed, Web of Science, Cochrane and Embase were searched up to April 2021. The risk of bias was assessed using the methodological score of the Assessment of Quality in Lower Limb Arthroplasty tool. All phases of the review were performed by two reviewers independently. A random effects model was applied to pool the migration data.

Findings

The literature search yielded 3187 hits of which ten studies were included, comprising 13 study groups and 381 UKAs. The majority of the early migration occurred in the first 6 months postoperatively followed by a period of very little migration, similar to what is reported for TKAs. The pooled mean migration expressed as the maximum total point motion of all UKAs at three months, six months, one year, and two years was 0.43 mm (95%CI 0.38-0.48), 0.54 mm (95%CI 0.40-0.67), 0.59 mm (95%CI 0.52-0.66), and 0.61 mm (95%CI 0.55-0.68), respectively. Migration at one- and two-year was higher than migration of TKAs as reported in

previous studies. All-polyethylene UKAs migrated more at one year (0.69 mm; 95%CI 0.58-0.80) than metal-backed UKAs (0.52 mm; 95%CI 0.46-0.58).

Conclusions and Relevance

The migration pattern of UKAs is comparable to the migration pattern of TKAs in the first two years as both show initial migration in the first few months and very little migration thereafter. However, UKAs had higher migration at one- and two-year follow-up.

Level of evidence

Level II

Funding

None

Registration

Not registered

Bullet Points

What is already known?

- Migration profiles of TKA include high initial migration in the first few months and stabilization thereafter
- TKA migrating >0.2 mm maximum total point motion (MTPM) between year one and year two are at risk for failure due to aseptic loosening
- Three other thresholds for migration at one year have been proposed to assess the risk of tibial loosening of total knee arthroplasty (TKA): <0.54 mm MTPM, 0.54 - 1.6 mm MTPM, and >1.6 mm MTPM.
- No migration profiles or thresholds for unicondylar knee arthroplasty (UKA) are reported

What are the new findings?

- The migration pattern of UKA was comparable to TKA with high initial migration followed by a stabilization phase between one- and two-year follow-up
- Migration of the UKA tibial components was higher at one- and two-year follow-up compared to TKA
- Future studies should assess whether TKA thresholds are applicable for UKAs

Introduction

Unicondylar knee arthroplasty (UKA) has the potential to treat medial and lateral knee osteoarthritis without replacement of the entire knee joint.¹ Although the popularity of UKA is increasing, isolated medial or lateral osteoarthritis of the knee is mostly treated with total knee arthroplasty (TKA). This is reflected in arthroplasty registries where 90147 TKA and 11916 UKA surgeries were registered in the National Joint Registry (NJR; England, Wales, Northern Ireland) in 2019.² UKA has several advantages over TKA such as shorter operation time, shorter length of stay, decreased risk of early complications (e.g., deep infection, myocardial infarction), greater range of motion, and higher patient reported outcome scores.³ However, one of the major disadvantages is a higher mean revision rate of UKAs with reported rates between 8.3-11.0% for UKA compared to a mean TKA revision rate of 3.4-4.2%.² The main reason for revision of an UKA is aseptic loosening followed by dislocation or subluxation, and pain.²

In TKA, early migration (i.e., one to two years) has been associated with late (i.e., five to ten years) revision for aseptic loosening.⁴ Additionally, continuous migration after the first post-operative year has been associated with early onset of aseptic loosening.⁵ Moreover, three thresholds for migration at one year have been proposed to assess the risk of tibial loosening of TKA and to classify in TKAs in an acceptable group (i.e., <0.54 mm maximum total point motion (MTPM)), at-risk group (i.e., 0.54-1.6 mm MTPM), and an unacceptable group (i.e., >1.6mm MTPM).⁴ Therefore, the migration pattern provides important information on implant safety. The migration pattern can be measured very accurately with radiostereometric analysis (RSA), which has an accuracy of 0.2mm.⁵ While the migration pattern has been established for TKA it is unknown for UKAs and it is unclear how the UKA migration pattern compares to the TKA migration pattern. Therefore, the present meta-analysis aimed to evaluate the migration patterns of tibial components of UKAs. The question was whether the postoperative migration pattern and magnitudes of migration of UKAs were the same as earlier reported for TKAs. The hypothesis that

UKAs had a comparable migration pattern as well as comparable magnitude of migration up to two years as TKAs was tested.

Methods

This study is a meta-analysis and was performed in concordance with the PRISMA statement.⁶ The systematic review comprised migration patterns from RSA studies. The methodology of the review is the same as previously described for TKAs.⁷ The present review was not registered.

Literature Search

The literature search was conducted with a medical librarian (JP). RSA studies were searched up to October 2019 and was updated for studies up to April 2021 using Pubmed, Web of Science, Cochrane and Embase. The search included a combination of the terms defining 'RSA' and 'Joint Replacement' (Appendix A). It was decided to conduct a broad search including all joint replacements instead of focusing on UKA to minimize the possibility of missing studies. Studies in English, Dutch, German, French, Spanish and Italian were considered.

Inclusion and exclusion analysis

All RSA studies reporting migration patterns of an UKA were identified. A migration pattern was defined as the reporting of migration at two or more postoperative follow-up moments within the first two years of follow-up using the maximum total point motion (MTPM).⁷ The MTPM is defined as the point on the implant with the highest migration relative to the bone and is the most frequently reported outcome measure in RSA studies to report migration.^{4, 5} Titles and abstracts were screened by two reviewers (SH, LD) independently. If the reviewers disagreed, the study remained eligible, and the full-text was screened. The eligible full-texts were screened by the same two reviewers independently, and any disagreements were resolved by discussion or after consulting a third reviewer (BP). Inclusion criteria for the RSA studies were: (1) primary UKA and (2) MTPM measured with RSA. Studies with less than five UKA or non-clinical studies (e.g., phantom or animal studies) were excluded. If the same cohort was reported in multiple publications, the

publication with the longest follow-up was formally included, while the other publications were used for additional data if required.

Data extraction

SH and LD independently extracted the data using a predefined SPSS database (IBM SPSS Statistics 26.0; IBM Corp, Armonk, NY, USA). Data extracted were first author, journal, year of publication, implant design, fixation method (i.e., cemented, uncemented), anatomical compartment (i.e., medial, lateral, both), insert (i.e., fixed, mobile), material (i.e., metal-backed, all-polyethylene), follow-up in years, and RSA technique (i.e., marker-based, model-based). Marker-based RSA is a technique which relies on movements between markers attached to or inserted into the prosthesis and markers positioned in the surrounding bone. In contrast to marker-based RSA, model-based RSA measures migration by comparing movements between a prosthesis model and markers positioned in the surrounding bone. Although these techniques have obvious differences, calculated MTPM from these different techniques do not show significant differences and can be pooled.⁸ The number of patients at baseline and during follow-up was extracted as well as the age, sex, RSA results comprising of the MTPM at time intervals up to and including three months, four months, six months, one year, and two years. For the purpose of pooling data, MTPM at 3 and 4 months were combined as a single time point. The standard deviation or standard error was extracted. Some studies reported the MTPM graphically. In these studies, the MTPM was measured in the graphs by both reviewers and the average of both measurements was taken.

Quality assessment

Risk of bias was assessed using the methodological score of the Assessment of Quality in Lower Limb Arthroplasty (AQUILA) tool.^{4, 9} The AQUILA is a tool which was designed to assess the quality of observational studies in lower limb

arthroplasty. SH and LD assessed the risk of bias individually and any discrepancy was resolved by discussion.

Data analysis

Migration patterns of included UKAs were plotted up to 2 years. A pooled mean was calculated using a random-effects model, weighting means according to their standard error (se).¹⁰ If se was missing, this was calculated by subtracting the lower limit of the 95% confidence interval from the upper limit of the 95% confidence interval, and by dividing this difference by 3.92 (2×1.96). If the standard deviation was missing, this was calculated by dividing the standard error by the square root of the number of included patients.¹¹ To assess the migration pattern of UKAs, MTPM of UKAs were pooled at each time point (i.e., three-four months, six months, one year, two years). Secondary, migration of metal-backed tibial (MBT) and all-polyethylene tibial (APT) components were separately analyzed and compared. In a post-hoc analysis, mean migration at one year was plotted against publication year in order to assess the influence of time on migration of UKAs. The Metafor Package in R Statistics (version 3.6.1; R Foundation for Statistical Computing, Vienna, Austria) was used for the analysis.¹⁰

Figure VII.I PRISMA flowcharts of the selection and inclusion process of the review. UKA: unicondylar knee arthroplasty; TKA: total knee arthroplasty; RSA: radiostereometric analysis; MTPM: maximum total point motion

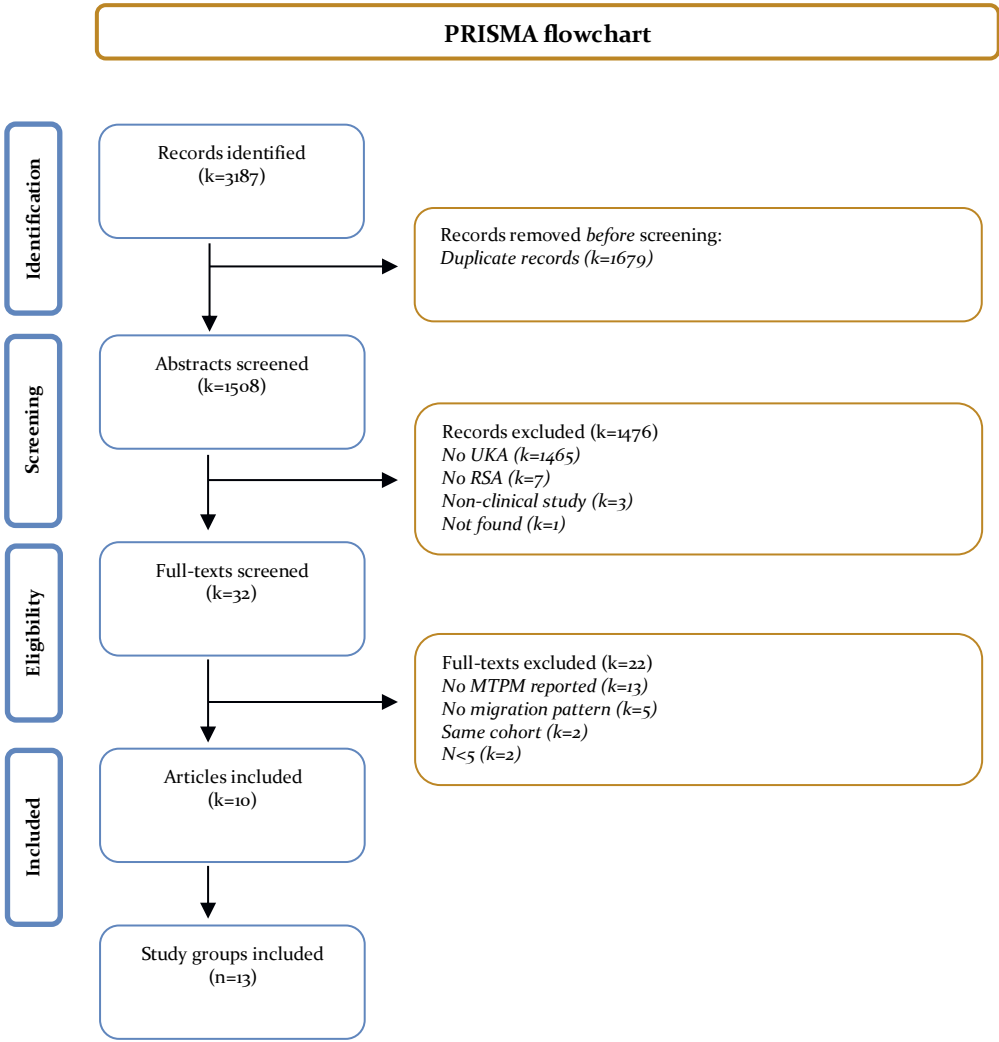


Table VII.1 Study characteristics of RSA studies. RSA: radiostereometric analysis; MTPM: maximum total point motion; se: standard error; NR: not reported

Author (Year)	Unicondylar knee arthroplasty	Patients Total, N	Age Mean, years	MTPM 3-4 months Mean, millimeters (se)	MTPM 6 months Mean, millimeters (se)	MTPM 1 year Mean, millimeters (se)	MTPM 2 years Mean, millimeters (se)
Linde (2019) ⁷	Oxford Phase III cemented medial mobile-bearing metal-backed tibial component	53	65			0.47 (0.04)	0.54 (0.05)
Koppens (2019) ⁶	Oxford Phase III cemented medial mobile-bearing metal-backed tibial component	33	64	0.42 (0.06)		0.54 (0.07)	0.55 (0.06)
	Sigma cemented medial fixed-bearing metal-backed tibial component	32	61	0.44 (0.06)		0.51 (0.08)	0.50 (0.06)
Koppens (2018) ¹⁵	Sigma High-Performance cemented medial fixed-bearing metal-backed tibial component	45	64	0.47 (0.08)		0.53 (0.09)	0.65 (0.09)
Bruni (2015) ³	Duracon cemented medial/lateral (unclear) (fixed) bearing all-polyethylene tibial component	36	71			1.12 (0.27)	1.35 (0.39)
Ensini (2013) ²¹	Optetrak cemented medial (fixed) bearing all-polyethylene tibial component	23	69	0.46 (0.08)	0.67 (0.08)	0.70 (0.14)	0.77 (0.17)
Bragonzoni (2005) ¹²	Duracon cemented medial+lateral all-polyethylene tibial component	16	NR	0.47 (0.09)	0.55 (0.08)	0.61 (0.16)	0.67 (0.18)
Soavi (2002) ²⁰	Duracon cemented medial all-polyethylene tibial component	20	72			0.60 (0.15)	0.60 (0.17)
Hydahl (2001) ¹⁴	Miller-Galante cemented medial metal-backed tibial component	18	NR			0.61 (0.10)	0.96 (0.20)
	Miller-Galante cemented medial all-polyethylene tibial component	20	NR			0.78 (0.14)	0.78 (0.14)
Lindstrand (2000) ⁸	Duracon cemented medial+lateral all-polyethylene tibial component	49	72	0.39 (0.04)	0.41 (0.03)	0.65 (0.10)	0.61 (0.07)
Ryd (1992) ¹⁹	Marmor cemented medial+lateral metal-backed tibial component	24	NR			0.95 (0.23)	1.09 (0.24)
	Lund tibial component cemented medial+lateral metal-backed tibial component	12	NR			0.77 (0.23)	0.80 (0.26)

Results

Inclusion of RSA studies

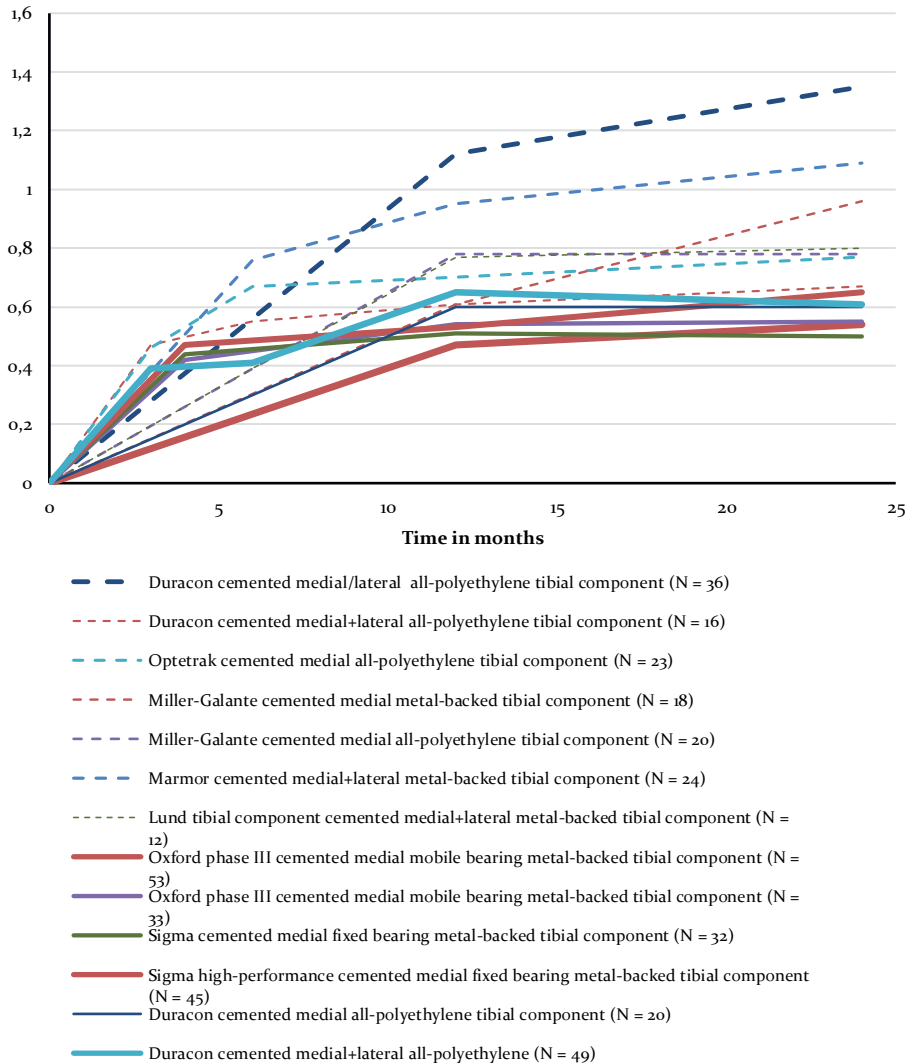
A total of 3187 records were found in the initial search of which 1679 duplicates leaving 1508 records to be screened based on title and abstract. Another 1476 records were excluded due to not involving an UKA ($k=1465$), not being an RSA study ($k=7$), not being a clinical study ($k=3$) and one full-text could not be found ($k=1$). The full-texts of 32 records were screened for eligibility, and 22 records were excluded as 13 records did not report the MTPM, 5 records did not report a migration pattern, 2 records used the same cohort, and 2 records included less than 5 UKAs, leaving ten records to be included [Fig. VII.I, Table VII.I]. Risk of bias of included studies is included in Appendix B. Follow-up was predefined in all studies and almost all studies ($k=9$) included more than 20 UKA. None of the studies were excluded based on the risk of bias.

Migration results

Ten studies comprising thirteen study groups were included [Table VII.I].¹²⁻²¹ The number of UKAs per study group ranged between 12 and 53 with a median of 24. All implants in the studies were cemented. The pooled mean migration of all UKAs at three-four months, six months, one year, and two years was 0.43 mm (95% CI 0.38 to 0.48), 0.54 mm (95% CI 0.40 to 0.67), 0.59 mm (95% CI 0.52 to 0.66), and 0.61 mm (95% CI 0.55 to 0.68), respectively [Fig. VII.II-VII.III]. UKAs migrated predominately in the first three-four months. Migration of UKAs at one year and two years was higher than migration of TKAs at these time points [Fig. VII.III].⁷ The increase in migration between six months and one year was 0.17 mm (95% CI 0.03 to 0.32) based on five study groups.

Figure VII.II The mean maximum total point motion (MTPM) of the included UKA by group over a 2-year period. The thickness of the lines are relative to the number of patients included with larger studies having thicker lines and smaller studies having thinner lines. Number of included patients, mean age, and mean MTPM with standard errors are reported in table 1. UKA: unicondylar knee arthroplasty

Migration (mm)



After one year there was little migration: pooled increase in MTPM migration between one year and two years was 0.05 mm (95% CI -0.03 to 0.12) based on 13 study groups. This increase was comparable to the increase of TKAs between one year and two years: 0.04 mm (95% CI 0.02-0.06).⁷ Secondary, migration of MBT and APT were compared. MBT and APT UKAs showed a comparable migration pattern up to 6 months follow-up, but APT had a statistically significant higher MTPM at one year ($p=0.007$), while this difference was less prominent at two years ($p=0.09$; Fig. VII.IV). The influence of publication year on migration was plotted post-hoc. This figure suggests that migration of metal-backed UKAs have decreased over time in contrast to migration of all-polyethylene UKAs [Fig. VII.V].

Figure VII.III Mean migration expressed as the maximum total point motion in millimetres. The blue bold line represents the pooled mean of all UKA and the black lines represent the 10th, 25th (interrupted line), 50th (bold line), 75th (interrupted line) and 90th percentiles. The yellow line represents the mean migration of cemented TKA as previously reported.⁷ UKA: unicondylar knee arthroplasty; TKA: total knee arthroplasty

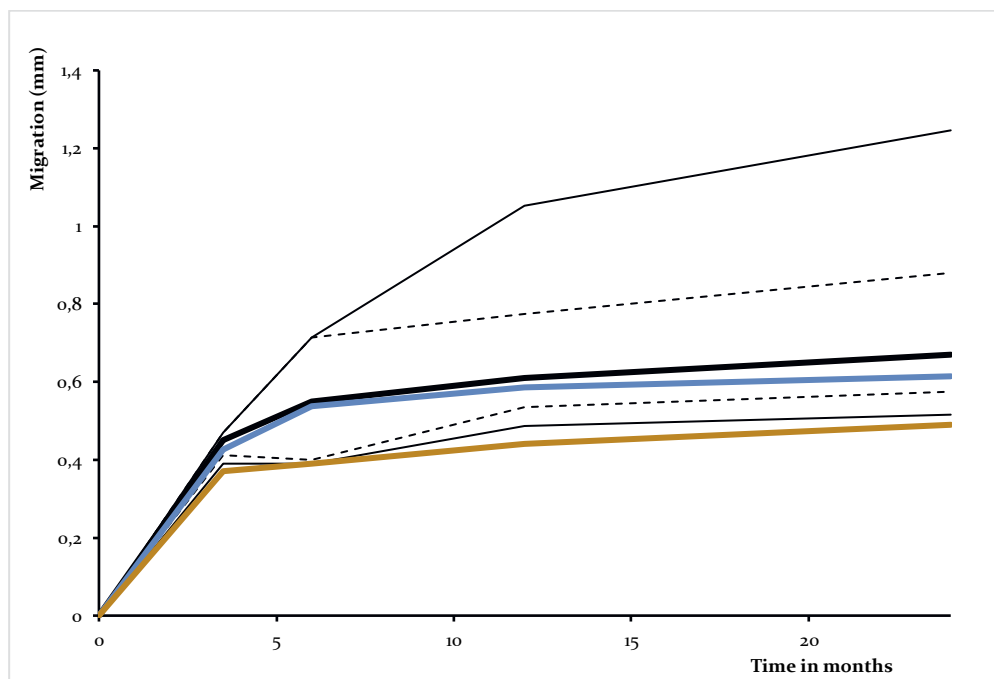


Figure VII.IV Mean migration with 95% confidence intervals (vertical error bars) expressed as the maximum total point motion in millimetres (mm) of all-polyethylene and metal-backed UKA over a 2-year period. The red, interrupted line represents the all-polyethylene UKAs, and the blue, continuous line represents the metal-backed UKAs. The yellow, interrupted line represents the mean migration of cemented all-polyethylene TKAs, and the yellow, solid line represents the mean migration of cemented metal-backed TKAs as previously reported.⁷

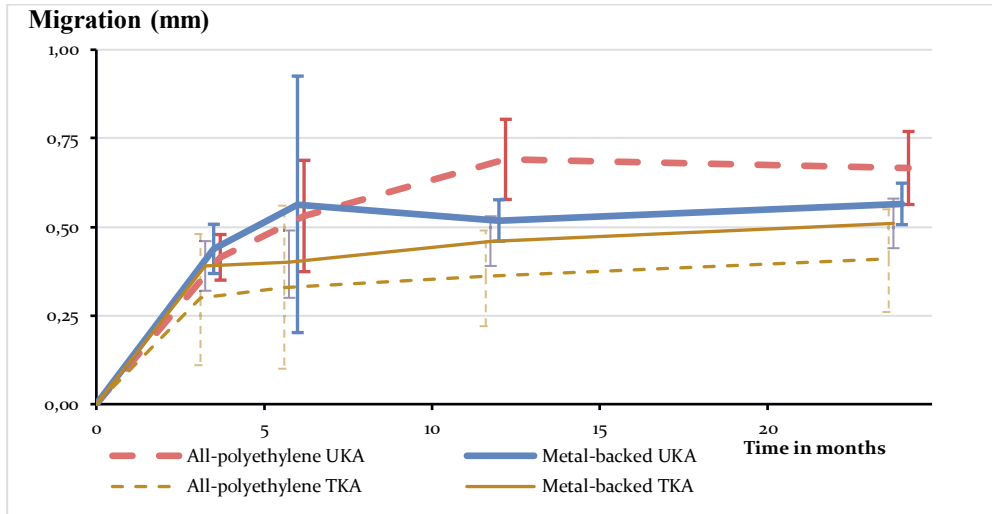
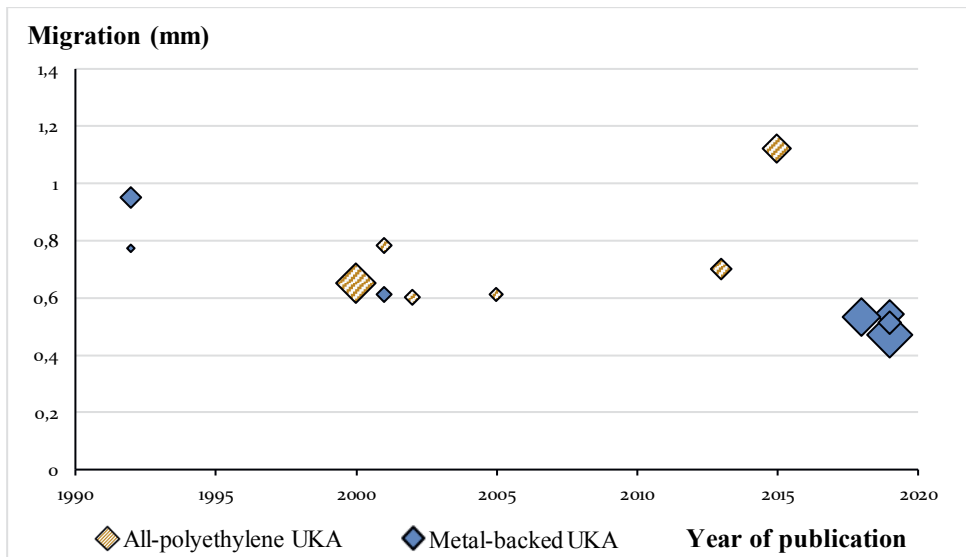


Figure VII.V Mean migration expressed as the maximum total point motion at one year in millimetres (mm) presented over time by publication year. Diamond size corresponds to the number of included patients with larger diamonds having more patients than smaller diamonds. Red, line-filled diamonds represent all-polyethylene UKAs, and the blue, solid-filled diamonds represent metal-backed UKAs. UKA: unicondylar knee arthroplasty



Discussion

The present review aimed to assess the migration profile of UKAs and found that these were comparable with the migration profile of TKAs with high initial migration and little migration between one year and two years. However, UKAs had a higher initial migration at one-year and two-year compared with TKAs. In addition, APT UKAs migrated more than MBT UKAs. Last, a trend towards a decrease of migration of MBT UKAs over the past three decades was found.

These findings suggest that the threshold used to identify implants at risk for early loosening (i.e., >0.2 MTPM from the first to the second postoperative year) could be used for UKAs as has been done by several UKA RSA studies.^{13, 15-17, 21} Beside this threshold, Pijls et al. (2012) proposed a classification of TKAs into three groups based on one-year MTPM and long-term survival of TKAs: <0.54 mm one-year MTPM (i.e., acceptable), $0.54 - 1.6$ mm one-year MTPM (i.e., at risk), and >1.6 mm one-year MTPM (i.e., unacceptable).⁷ If this classification was to be used to classify the included UKAs of the present meta-analysis, three UKAs would have been classified as acceptable, ten as at risk, and none as unacceptable. However, the one-year MTPM was higher for UKAs compared to TKAs which would naturally result in a higher number of UKAs classified as at risk or unacceptable. Whether it is justified to use this classification for UKAs remains unclear and long-term RSA UKA studies are needed to address this question. Moreover, the clinical relevance of the found difference in migration between UKAs and TKAs is unclear and should be studied further.

Our review did not include any migration studies comprising uncemented UKAs. There was one RSA study comparing uncemented and cemented UKAs, but this study did not report MTPM and was therefore not included.²² This study found a comparable migration of uncemented and cemented UKAs.²² Kerens et al. (2017) found no difference in revision or clinical scores, but found less radiolucent lines and a shorter operative time for uncemented UKAs,²³ while two recent registry studies

found a lower revision rate for uncemented UKAs compared to cemented UKAs using 14814 and 8733 UKAs.^{24, 25} The popularity of uncemented UKAs is increasing: in the Dutch arthroplasty register, 3% of UKA was uncemented in 2010 while 54% was uncemented in 2019.²⁶ RSA studies assessing the migration of uncemented UKAs are thus required, especially for new UKAs or UKAs without long-term follow-up either in registries or published studies.

The results of our review showed that APT UKAs migrated more than MBT UKAs at one year and two years follow-up. This finding is in line with the results from a recent meta-analysis which found a 2.13 higher risk of all-cause revision and a 1.66 higher risk for revision due to aseptic loosening for APT compared to MBT.²⁷

There are several UKA designs available and only some of these UKA designs have been evaluated with RSA and were included in this systematic review. The five-year all-cause revision rates of these UKAs varies between 3.3% and 16.8%.^{2, 26} Considering this variation of revision rate, a phased introduction is especially needed for UKAs to ensure patient safety. It is, therefore, highly recommended to test novel UKA designs with RSA in addition to cohort studies for mid- and long-term survival.²⁸⁻³⁰

Some limitations of this review should be considered. First, the number of included RSA studies was small compared to a previous review on TKAs. Ten RSA studies compared to 50 RSA studies for TKAs were included.^{4, 7} In order to obtain a better understanding of the migration profiles of different implant designs, studies including novel UKA designs are needed. Moreover, some studies used medial and lateral UKAs or did not specify whether medial or lateral UKAs were included without further specifying outcomes for the medial or lateral UKAs separately. It would be helpful if future studies clearly specify the design, fixation method, insert and the anatomical compartment of UKAs to allow comparison between studies and facilitate future systematic reviews. Last, the present review did not assess the influence of specific patient characteristics or surgical technique on migration nor was the influence of publication year statistically analysed as the number of groups

was limited and further subgroup analysis was deemed inappropriate. Future studies should pool individual patient data to assess the influence of patient characteristics on UKA migration.

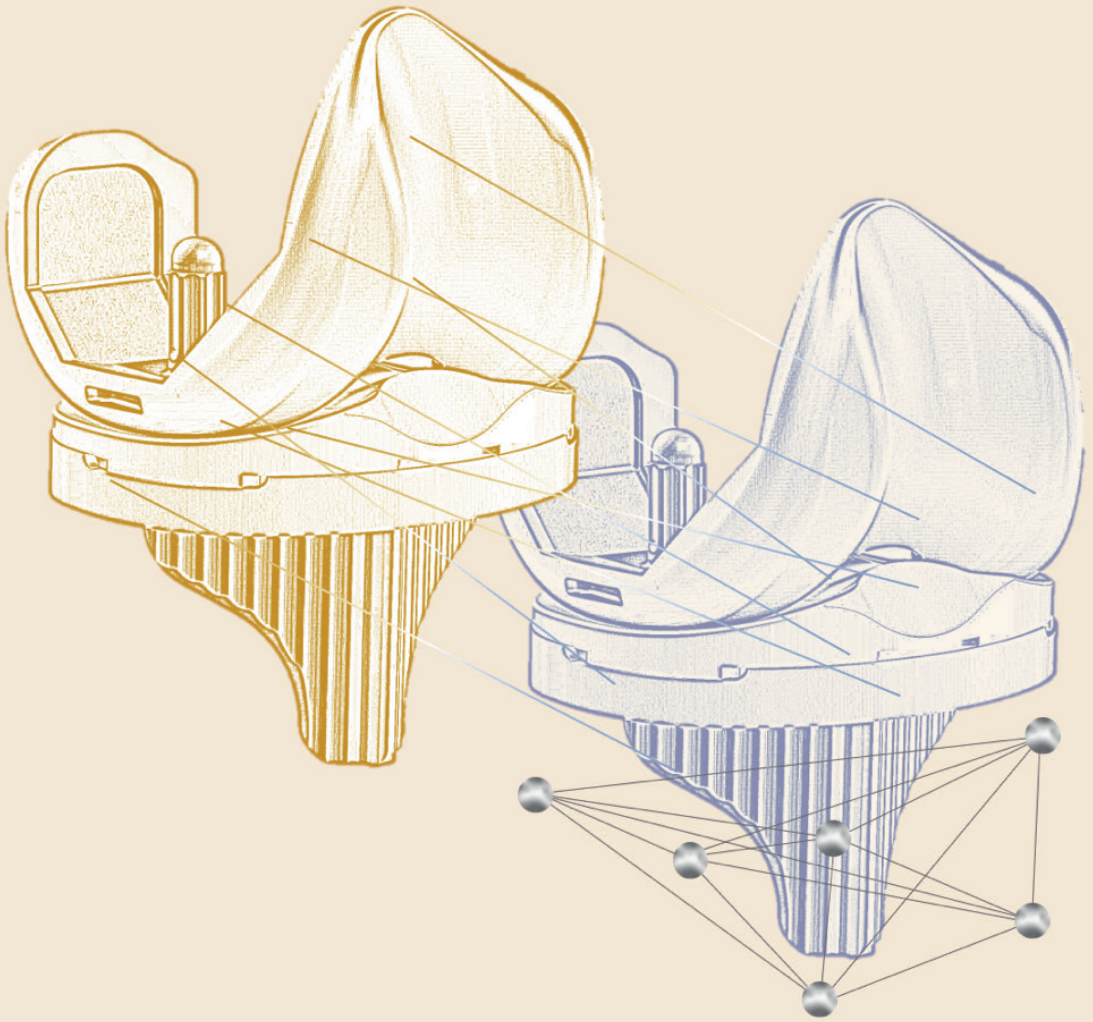
Conclusion

The migration pattern of UKAs is comparable to the migration pattern of TKAs in the first two years as both show initial migration in the first few months and limited migration hereafter. However, UKAs had higher migration at one- at two-year.

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Chapter VIII

The influence of postoperative coronal alignment on tibial migration after total knee arthroplasty in preoperative varus and valgus knees

A secondary analysis of 10 randomized controlled trials using radiostereometric analysis

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Abstract

Background

Orthopaedic surgeons aim for mechanical alignment when performing total knee arthroplasty (TKA) as malalignment is associated with loosening. Loosening may be predicted by migration as measured with radiostereometric analysis (RSA), but previous RSA studies on postoperative alignment have shown contradictory results and have been limited to cemented implants and small numbers of patients. Therefore, we performed a secondary analysis of 10 previously published randomized controlled trials (RCTs) to compare migration between postoperative in-range and out-of-range cemented and uncemented TKA implants among patients with a preoperative varus or valgus knee.

Methods

All RCTs involving the use of RSA that had been conducted at 2 centers were included. Alignment was classified, with use of the hip-knee-ankle angle (HKA), as in-range ($0^\circ \pm 3^\circ$) or out-of-range ($<-3^\circ$ or $>3^\circ$). The fixation methods included cemented, uncemented-coated, and uncemented-uncoated. Migration was measured at 3, 12, and 24 months. A linear mixed model was used, with adjustment for fixation method and clustering of patients within centers.

Results

Of 476 TKA implants that had been out-of-range preoperatively, 290 were in-range postoperatively and 186 were out-of-range in either varus ($n = 143$) or valgus ($n = 43$) postoperatively. The mean migration at 3, 12, and 24 months was 0.73 mm (95% CI, 0.66 to 0.79 mm), 0.92 mm (95% CI, 0.85 to 1.00 mm), and 0.97 mm (95% CI, 0.90 to 1.05 mm), respectively, for the in-range group and 0.80 mm (95% CI, 0.72 to 0.87 mm), 0.98 (95% CI, 0.90 to 1.07 mm), and 1.04 mm (95% CI, 0.95 to 1.13 mm), respectively, for the out-of-range group ($p = 0.07$). The fixation method significantly

influenced migration, with uncemented-uncoated implants migrating more than cemented and uncemented-coated implants ($p < 0.001$).

Conclusions

Postoperative alignment did not influence migration of TKAs in the first 2 postoperative years in patients with preoperative varus or valgus alignment of the knee. However, the fixation method significantly influenced migration, with uncemented-uncoated implants showing the greatest migration.

Level of Evidence

Level III. See Instructions for Authors for a complete description of levels of evidence.

Background

The debate regarding the optimal coronal alignment of total knee arthroplasty (TKA) implants is ongoing. Traditionally, mechanical alignment as defined as a hip-knee-ankle angle (HKA) of $0^\circ \pm 3^\circ$ (that is, in-range) has been considered the so-called gold standard as studies have shown that malaligned implants are associated with an increased risk of loosening and lower clinical scores.^{1,2} Mechanical alignment is considered to be optimal because the weight-bearing load is distributed evenly on the medial and lateral sides of the prosthesis, which in turn reduces wear and loosening.^{3,4} However, some patients naturally have some degree of varus or valgus preoperatively³, and achieving mechanical alignment can be challenging.⁵

The main concern associated with malalignment is the risk of loosening and wear. Loosening can be predicted with radiostereometric analysis (RSA), a highly accurate technique for measuring migration, a factor that has been shown to be associated with the risk of revision TKA.⁶⁻⁸ Three previous studies assessed the effect of postoperative alignment on migration. Laende et al., in a study of 47 patients who were randomized to mechanical alignment with use of computer-assisted surgery or to kinematic alignment with use of patient-specific instruments, found no difference between the groups in terms of migration or clinical outcomes.⁹ Van Hamersveld et al., in a study of 85 TKA implants that had in-range, varus, or valgus alignment postoperatively, found that out-of-range implants, especially those with varus alignment, migrated more than in-range implants.¹⁰ In contrast, Teeter et al., in a small series of 15 TKAs, found no difference in migration between implants with in-range, varus, or valgus postoperative alignment¹¹. Besides the limited numbers of patients, those studies included both patients with preoperative neutral alignment and those with preoperative varus or valgus alignment. As achieving postoperative in-range alignment is more straightforward for knees with neutral alignment preoperatively, the influence of failing to achieve mechanical alignment during TKA on migration is of particular interest for patients with preoperative varus or valgus alignment as more releases and larger resections have to be done. Moreover, the

above 3 studies were limited to cemented implants. As the interest in uncemented TKA is growing, studies assessing the influence of alignment strategies on migration are needed for both uncemented and cemented implants. Therefore, the aim of the present study was to compare tibial component migration for 2 years postoperatively for TKA implants with in-range or out-of-range (varus or valgus) alignment in patients with preoperative varus or valgus alignment.

Materials and Methods

Design

The present study was a secondary analysis of all randomized controlled trials (RCTs) involving RSA for the analysis of primary TKAs that were performed in the last 2 decades at 2 centers (Hässleholm, Sweden; Leiden, the Netherlands). Ten published RSA studies including 636 patients undergoing TKA from 2002 to 2016 were pooled [Table VIII.I].¹²⁻²¹ Seven studies were conducted in Hässleholm (432 TKAs)¹⁴⁻²⁰ and 3 in Leiden (204 TKAs).^{12,13,21} Two studies with cemented TKA implants were included in a recently published study on alignment.^{10,12,13} One study had 4 treatment arms¹², and 9 studies had 2 treatment arms.¹³⁻²¹ The number of TKAs per study ranged from 52 to 78. TKA implant designs included cemented, uncemented-coated, and uncemented-uncoated Triathlon implants (Stryker), uncemented-coated Tritanium implants (Stryker), cemented NexGen implants (Zimmer), and cemented Persona implants (Zimmer).

Patients

For a patient to be included in the present study, preoperative and postoperative anteroposterior standing full-leg radiographs, as well as a direct postoperative RSA radiograph and at least 1 RSA radiograph during follow-up, needed to be available for the measurement of alignment. Patients were excluded if

Table VIII.I Study characteristics

Reference	Center	Inclusion period	Number of patients	Implant design	Registration
12	Leiden, The Netherlands	2002-2005	78	NexGen ¹ LPS cemented fixed bearing NexGen ¹ LPS cemented mobile bearing NexGen ¹ LPS High-flexion cemented fixed bearing NexGen ¹ LPS High-flexion cemented mobile bearing	Dutch Trial register NTR3287
13	Leiden, The Netherlands	2008-2010	52	Triathlon ² PS cemented fixed bearing Triathlon ² PS cemented mobile bearing	ClinicalTrials.gov NCT02024961
14	Hässleholm, Sweden	2006-2006	60	Triathlon ² CR cemented fixed bearing Triathlon ² PS cemented fixed bearing	ClinicalTrials.gov NCT00436982
15	Hässleholm, Sweden	2007-2008	60	Triathlon ² CR uncemented-unc coated fixed bearing Triathlon ² CR uncemented-coated (PA) fixed bearing	ClinicalTrials.gov NCT03198533
16	Hässleholm, Sweden	2008-2010	60	Triathlon ² standard-stem CR cemented fixed bearing Triathlon ² short-stem CR cemented fixed bearing	ClinicalTrials.gov NCT00436982
17	Hässleholm, Sweden	2009-2010	60	Triathlon ² CR cemented fixed bearing Triathlon ² CR uncemented-coated (PA) fixed bearing	ClinicalTrials.gov NCT02525601
18	Hässleholm, Sweden	2014-2014	60	Triathlon ² CR cemented fixed bearing Triathlon ² CR cemented fixed bearing all-polyethylene	ISRCTN Registry ISRCTN04081530
19	Hässleholm, Sweden	2014-2015	60	Triathlon ² PS cemented fixed bearing Triathlon ² PS cemented fixed bearing all-polyethylene	ISRCTN Registry ISRCTN10744502
20	Hässleholm, Sweden	2015-2016	72	Triathlon ² CR cemented fixed bearing Tritanium ³ Triathlon ² CR uncemented-coated fixed bearing	ClinicalTrials.gov NCT02578446
21	Leiden, The Netherlands	2014-2015	74	NexGen ¹ LPS cemented fixed bearing Personal ⁴ PS cemented fixed bearing	ClinicalTrials.gov NCT02269254

Table VIII.I. Study characteristics. Reference numbers correspond to the reference list. ¹Zimmer Inc, Warsaw, IN, USA; ²Stryker Inc, Mahwah, NJ, USA. LPS = Legacy posterior stabilizing; PS = posterior stabilizing; CR = Cruciate retaining; PA = Peri-apatite coated;

the knee had a preoperative neutral alignment (an HKA of $0^\circ \pm 3^\circ$). Age, sex, American Society of Anesthesiologists (ASA) score, body mass index (BMI), Ahlbäck classification, primary diagnosis, and fixation method (cemented, uncemented-coated, or uncemented-uncoated) were collected.

Alignment

Preoperative and postoperative alignment was measured on anteroposterior standing full-leg radiographs in concordance with a standardized protocol; the postoperative radiographs were made at a median of 3 months (interquartile range, 2 to 5 months)²²In short, the femoral mechanical axis was drawn from the center of the femoral head up to the center of the femoral notch, and the tibial mechanical axis was drawn from the center of the talus up to the center of the tibial plateau. The HKA was the angle between these 2 lines.^{10,23} A postoperative HKA of $0^\circ \pm 3^\circ$ was considered in-range, and a postoperative HKA of $<-3^\circ$ (varus) or $>3^\circ$ (valgus) was considered out-of-range. Two observers conducted the measurements regardless of the site. Interobserver variability was assessed by means of measurement of the HKA independently by 2 different observers who were blinded to each other's measurements. The intraclass correlation coefficient (ICC) for measuring the preoperative HKA with use of 208 radiographs was 0.97 (95% confidence interval [CI], 0.96 to 0.97), and the ICC for measuring the postoperative HKA with use of 205 radiographs was 0.94 (95% CI, 0.93 to 0.96). A random set of 44 preoperative and postoperative radiographs was selected to measure intraobserver variability. These double measurements were performed after an interval of 2 months to eliminate the memory effect. In this sample, the ICC for intraobserver variability was 0.96 (95% CI, 0.92 to 0.98) preoperatively and 0.99 (95% CI, 0.98 to 0.99) postoperatively.

Radiostereometric Analysis

The primary outcome of interest was tibial component migration as measured with RSA over a 2-year follow-up period, which is a common follow-up period for RSA

studies. RSA radiographs were made within 2 to 3 days postoperatively and at 3 months, 1 year, and 2 years in all studies but one. In that study, RSA radiographs were not made at 3 months and were only made at the other time points.¹³ UmRSA software (RSA Biomedical) was used in 4 studies, and Model-Based RSA software (RSACore) was used in 6 studies. Migration was calculated with use of marker-based analysis in 8 studies and model-based analysis in 2 studies. Migration was expressed as the maximum total point motion (MTPM), which estimates the length of the translational vector with the largest migration.²⁴ As a secondary outcome, implants migrating >0.2 mm in the second postoperative year were considered at risk for early failure.⁶ All analyses were performed following the ISO standard and RSA guidelines.^{24,25}

Statistics

An independent t test was used for normally distributed continuous variables, and a chi-square test was used for categorical variables, to assess baseline differences. A linear mixed model was used to analyse MTPM over a 2-year follow-up period.^{26,27} This model included the group (in-range and out-of-range) and time (baseline, 3 months, 1 year, and 2 years) as fixed effects and an interaction term of group with time. Fixation method (cemented, uncemented-coated, uncemented-uncoated) was included as a fixed effect to adjust for known differences in migration patterns, and the surgical centre (Hässleholm, Leiden) was included as a random effect to account for clustering of patients within these centres. MTPM was log-transformed to obtain a normal distribution. Presented values were back-transformed to the original scale. Remaining variability was modelled with an autoregressive order-1 covariance matrix. As a secondary analysis, the percentage of at-risk implants (an MTPM of >0.2 mm between the 1 and 2-year follow-ups) was compared between both groups with use of a chi-square test.⁶ In addition, the out-of-range group was stratified into varus (HKA <-3°) and valgus (HKA >3°) groups, and the primary analysis was repeated. Sensitivity analyses were performed to check whether the results differed if a stricter (HKA 0° ± 1°) or a less strict (HKA 0° ± 6°) threshold was used to classify implants as

being in-range. As a post hoc analysis, both the preoperative alignment (that is, varus or valgus) and postoperative alignment (that is, in-range, varus, or valgus) were considered, creating 6 groups (for example, varus-to-valgus alignment). Mean migration was compared between these groups. Means were reported with 95% CIs or standard deviations (SDs), and the level of significance was set at $p < 0.05$. Analyses were performed with use of SPSS statistical software (version 26.0; IBM).

Ethics

All studies were approved by an ethical review board before recruitment of the patients, and all patients provided informed consent. The protocol for pooling of the data was presented to the medical ethics committee of Leiden, who waived the need for approval under Dutch law (P.15.198).

Source of Funding

No funding was received for the current study. Seven of the included studies were funded by Stryker; 2 studies, by the Dutch Arthritis Association; and 1 study, by Zimmer Biomet. The sponsors did not take part in the design, conduct, analysis, or interpretations in the current study.

Figure VIII.I Inclusion Flowchart

RSA = radiostereometric analysis, TKA = total knee arthroplasty, HKA = hip-knee-ankle angle

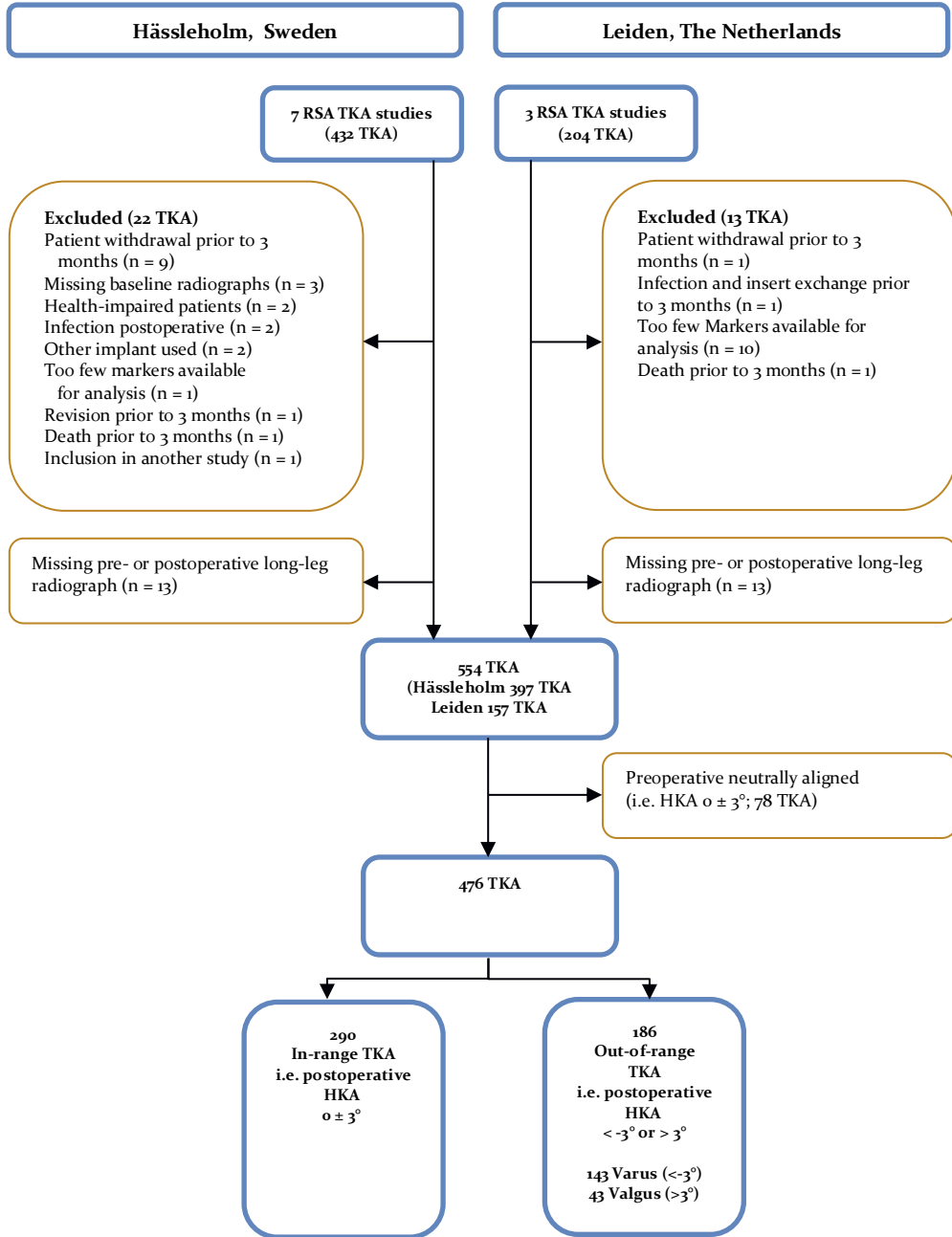


Table VIII.II Baseline characteristics

		Postoperative Hip-Knee-Ankle angle			
		In-range (i.e. HKA $0\pm 3^\circ$; n=290)	Out-of-range (i.e. HKA $<-3^\circ$ or $>3^\circ$; n=186)	p-value	Total (n=476)
Center, n (%)	Hässleholm	229 (79)	123 (66)	0.002	352 (74)
	Leiden	61 (21)	63 (34)		124 (26)
Age, years (SD)		67 (7.3)	67 (8.2)	0.9	67 (8.0)
BMI, kg/m² (SD)		29 (4.4)	29 (4.0)	0.3	29 (4.2)
Sex, n (%)	Female	172 (59)	105 (57)	0.5	277 (58)
	Male	118 (41)	81 (43)		199 (42)
Alignment preop, n (%)	Varus	240 (83)	154 (83)	1.0	394 (83)
	Valgus	50 (17)	32 (17)		82 (17)
Diagnosis, n (%)				0.4	
	Osteoarthritis	269 (93)	171 (92)		440 (93)
	Post-traumatic	1 (0)	0 (0)		1 (0)
	Rheumatoid arthritis*	19 (7)	11 (6)		30 (6)
	Missing	1 (0)	4 (2)		5 (1)
Ahlbäck, n (%)				0.2	
	I	2 (1)	1 (1)		3 (1)
	II	67 (23)	34 (18)		101 (21)
	III	146 (50)	86 (46)		232 (49)
	IV	14 (5)	2 (1)		16 (3)
	Missing	61 (21)	63 (34)		124 (26)
ASA, n (%)				0.3	
	I	59 (20)	37 (20)		96 (20)
	II	193 (67)	129 (69)		322 (68)
	III	36 (12)	16 (9)		52 (11)
	Missing	2 (1)	4 (2)		6 (1)
Fixation, n (%)				0.3	
	Uncemented- uncoated	13 (5)	8 (4)		21 (4)
	Uncemented-coated	54 (19)	24 (13)		78 (16)
	Cemented	223 (77)	154 (83)		377 (79)

Table VIII.II. Baseline characteristics. HKA = Hip-Knee-Ankle angle. SD = Standard Deviation. Varus: HKA $<-3^\circ$; Valgus: HKA $>3^\circ$. ASA classification = American Society of Anesthesiologists. *Rheumatoid arthritis or another inflammatory disease.

Results

Of the 636 TKAs that were included in the original 10 RSA studies, 476 TKAs were included in the present study [Fig. VIII.I]. Of these, 290 TKAs were in-range postoperatively (HKA $0^\circ \pm 3^\circ$) and 186 were out-of-range postoperatively (HKA $<-3^\circ$ [varus, n = 143] or HKA $>3^\circ$ [valgus, n = 43] [Fig. VIII.I]. Relatively more patients underwent the operation in Hässleholm in the in-range group as compared with the out-of-range group (79% compared with 66%; p = 0.002). The primary diagnoses included osteoarthritis (440 knees), rheumatoid arthritis or another inflammatory disease (30 knees), and trauma (1 knee); the diagnosis was missing for remaining 5 knees [Table VIII.II]. The mean postoperative HKA was $-1^\circ \pm 3.7^\circ$, and the median postoperative HKA was also -1° (interquartile range, -3.5° to 0.8°) [Fig. VIII.II].

Figure VIII.II Distribution of the hip-knee-ankle angle

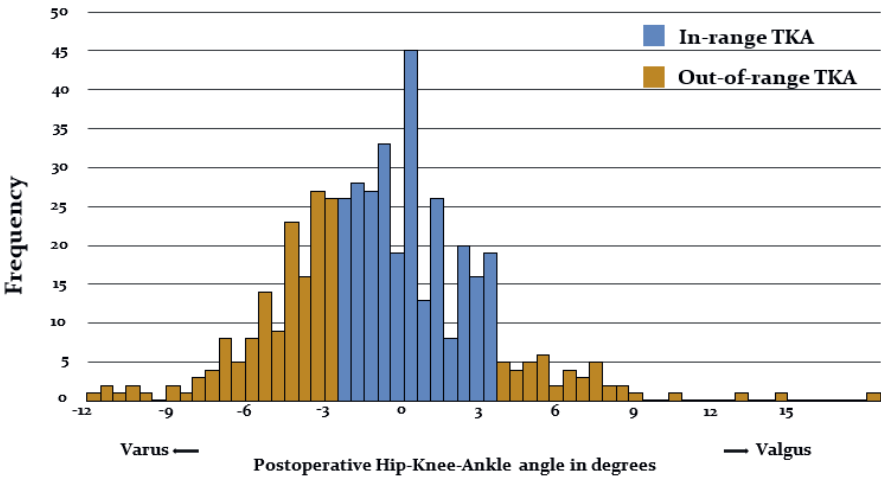


Figure VIII.II Histogram showing the distribution of the postoperative hip-knee-ankle angle (HKA). The blue bars represent the number of in-range TKA implants, and the yellow bars represent the number of out-of-range TKA implants in the primary analysis. An HKA of $<-3^\circ$ is considered varus alignment, and an HKA of $>3^\circ$ is considered valgus alignment. TKA = total knee arthroplasty

No significant difference in MTPM was observed between the alignment groups over the 2-year follow-up period ($p = 0.07$). The MTPM at 3, 12, and 24 months was 0.73 mm (95% CI, 0.66 to 0.79 mm), 0.92 (95% CI 0.85, to 1.00 mm), and 0.97 mm (95% CI, 0.90 to 1.05 mm), respectively, for the in-range group and 0.80 mm (95% CI, 0.72 to 0.87 mm), 0.98 mm (95% CI, 0.90 to 1.07 mm), and 1.04 mm (95% CI, 0.95 to 1.13 mm), respectively, for the out-of-range group (Fig. VIII.III).

Figure VIII.III Mean migration expressed as the maximum total point motion (MTPM) over time

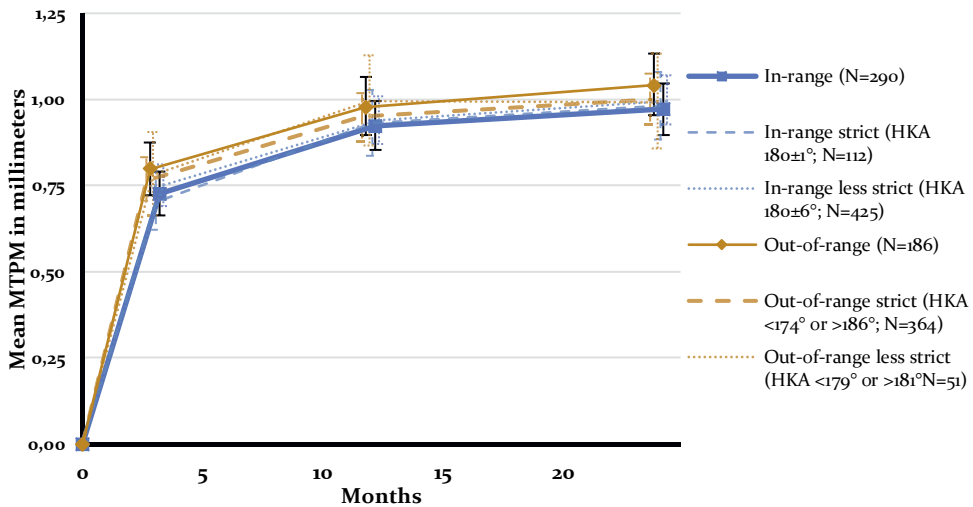


Figure VIII.III. The mean MTPM in millimeters over the 2-year follow-up period labelled by postoperative alignment (In-range: HKA $0 \pm 3^\circ$; Out-of-range: HKA $< -3^\circ$ or $> 3^\circ$). Error bars represent 95% confidence intervals. The interrupted lines represent the MTPM over time using a strict (i.e. HKA $0 \pm 1^\circ$) or a less strict (i.e. HKA $0 \pm 6^\circ$) threshold to determine TKA in-range and out-of-range. MTPM = Maximum total point motion; HKA = Hip-Knee-Ankle angle; TKA = Total knee arthroplasty

No difference between groups was observed when using a stricter (HKA $0^\circ \pm 1^\circ$) or less strict (HKA $0^\circ \pm 6^\circ$) threshold for the classification of in-range (Fig. VIII.III). Similarly, further stratification of the out-of-range group into varus (HKA $< -3^\circ$) and valgus (HKA $> 3^\circ$) showed no difference between postoperative alignment groups ($p = 0.4$), including when varus implants were compared with in-range implants ($p = 0.08$) [Fig. VIII.IV]. The fixation method itself had a significant effect on migration, with uncemented-unc coated implants migrating the most and cemented implants migrating the least ($p < 0.001$) [Fig. VIII.V]. Both cemented and uncemented-coated

implants showed limited migration between 3 months and 2 years [Fig. VIII.V]. The difference in migration between the uncemented-uncoated out-of-range group and

Figure VIII.IV Mean MTPM in a 2-year follow-up period with the out-of-range group subdivided in a varus and valgus group. The mean MTPM in

millimeters over the 2-year follow-up period labelled by postoperative alignment (In-range: HKA $0 \pm 3^\circ$; Varus: HKA $< -3^\circ$; Valgus: HKA $> 3^\circ$). The error bars represent 95% confidence intervals.

MTPM = Maximum total point motion; HKA = Hip-Knee-Ankle angle

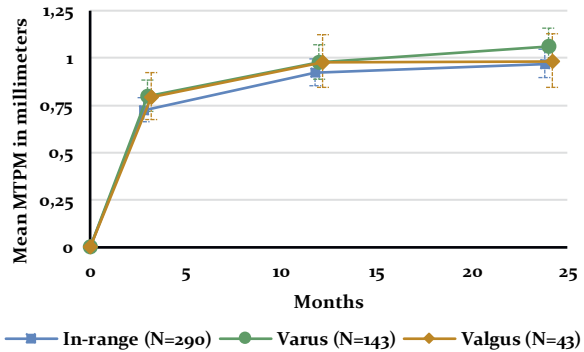


Figure VIII.V Mean MTPM in millimeters over the 2-year follow-up period stratified according to the fixation method

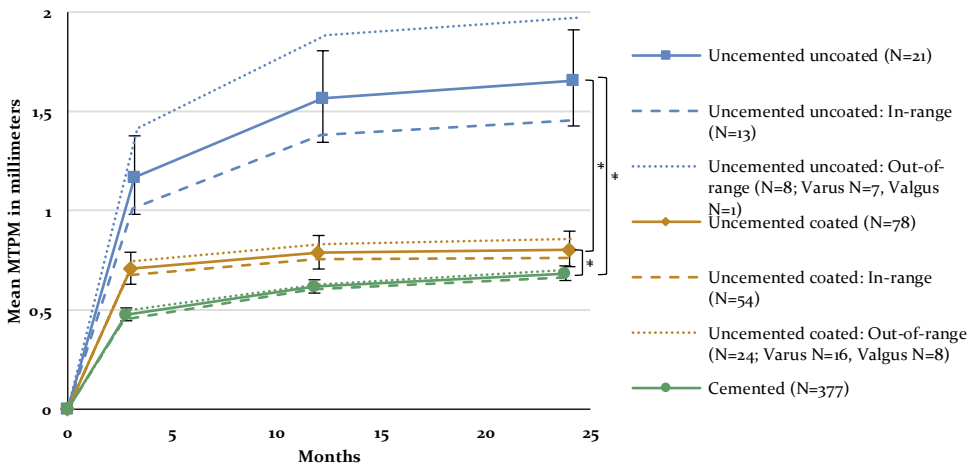


Figure VIII.V. The mean MTPM in millimeters over the 2-year follow-up period stratified by the fixation method of the TKA. The error bars represent 95% confidence intervals. The means are subdivided into an in-range group (i.e. HKA $0 \pm 3^\circ$), and an out-of-range group (i.e. HKA $< -3^\circ$ or $> 3^\circ$) which are represented by interrupted lines. Statistical significant differences are marked with an asterisk (*). MTPM = Maximum total point motion; HKA = Hip-Knee-Ankle angle

the uncemented-uncoated in-range group did not reach significance as the MTPM at 3, 12, and 24 months was 1.01 mm (95% CI, 0.74 to 1.33 mm), 1.38 mm (95% CI, 1.05 to 1.76 mm), and 1.49 mm (95% CI, 1.14 to 1.90 mm), respectively, for the in-range group

and 1.42 mm (95% CI, 1.00 to 1.92 mm), 1.82 mm (95% CI, 1.31 to 2.43 mm), and 1.97 mm (95% CI, 1.46 to 2.59 mm), respectively, for the out-of-range group ($p = 0.4$) (Fig. VIII.V). Thirty-two implants (13%) in the in-range group and 25 (16%) in the out-of-range group were considered to be at risk for early failure as the migration between the one and two-year follow-up intervals was >0.2 mm ($p = 0.3$). Stratifying the out-of-range group into varus and valgus groups showed that 22 implants (19%) were at risk for early failure in the varus group and three implants (8%) were at risk for early failure in the valgus group.

The post hoc analysis, including six groups based on preoperative and postoperative alignment (for example, varus-to-valgus alignment), showed that there was a significant difference in migration between groups ($p = 0.04$) and that patients with preoperative valgus and postoperative varus alignment (that is, valgus-to-varus) had the most migration [Fig. VIII.VI].

Figure VIII.VI Mean migration according to pre- and postoperative alignment

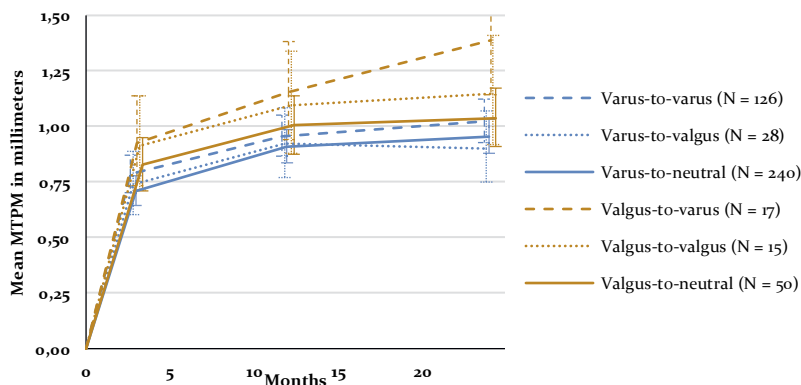


Figure VIII.VI. The mean MTPM in millimeters over the 2-year follow-up period stratified by pre- and postoperative alignment. Varus was defined as an HKA $< -3^\circ$, valgus as an HKA $> 3^\circ$, and neutral as an HKA $0 \pm 3^\circ$. MTPM = Maximum total point motion; HKA = Hip-Knee-Ankle angle

Discussion

The present study of knees with preoperative varus or valgus alignment showed that there was no significant difference between those with postoperative in-range alignment and those with out-of-range alignment in terms of implant migration as measured with RSA during the first 2 postoperative years. The number of implants at risk for early failure was comparable between the groups. These results did not change when stricter or less-strict thresholds were used to define in-range implants or when implants with postoperative varus and valgus alignment were analyzed separately. Post hoc analysis indicated that knees with preoperative valgus alignment that was over-corrected into varus had significantly more migration. In all analyses, the fixation method influenced migration, with uncemented-uncoated implants migrating the most and cemented implants migrating the least. Both cemented and uncemented-coated implants showed limited migration from 3 months onward.

The long-held belief that coronal alignment has a significant influence on results after TKA has been challenged both because the evidence supporting this belief is limited and because studies have demonstrated contradictory results. The results of the present study, which included a larger number of patients than in previous studies, provide further evidence to challenge this belief. This is in line with a case series comparing 7 in-range and 6 varus-aligned TKA implants, which showed no difference in migration at up to 10 years of follow-up.¹¹ However, another study demonstrated that 29 varus-aligned implants had more migration in comparison with 47 in-range implants over a 5-year period.¹⁰ Likewise, studies comparing survival or clinical outcomes between in-range and out-of-range implants have demonstrated ambiguous results. Rhee et al. found no differences in terms of clinical outcome or survivorship between computer-assisted and conventional TKAs, even though better postoperative alignment with fewer outliers was seen in the computer-assisted group.²⁸ Several studies have shown no difference between in-range and out-of-range implants in terms of clinical scores or survivorship²⁹⁻³¹, whereas other

studies have shown better clinical outcomes for in-range implants.^{32,33} Despite these inconsistent findings, much effort has been put into the development of novel methods to perfectly align implants, such as robot-assisted surgery and patient-specific instrumentation. However, those novel surgical techniques have not resulted in less migration or increased patient satisfaction.³⁴⁻³⁶ Future studies should assess whether other factors, such as implant size or bone quality, may be important when considering alignment strategies and migration of TKA implants.

The present study found that uncemented-uncoated implants migrated the most and cemented implants migrated the least. Studies assessing migration for different fixation methods at up to 5 and 10 years have shown comparable results.^{37,38} The present study also showed that uncemented-coated implants tended to migrate more initially but were as stable as cemented implants beyond 3 months, which is in agreement with the findings of several studies.^{20,39-42} A long-term RSA study comparing different fixation methods suggested that biological fixation of uncemented-coated implants could outperform cemented implants in terms of migration.⁴³ Those results further strengthen the case for using uncemented-coated TKA implants. The present study adds to that literature indicating that postoperative in-range versus out-of-range alignment does not influence migration of implants at 2 years of follow-up but that it is the fixation method, particularly uncemented-uncoated fixation, that influences migration. Long-term follow-up of the patients in the included studies is needed to address whether postoperative alignment influences migration across a 5 or 10-year period.

To our knowledge, the present study is one of the few multicenter, pooled RSA studies involving the use of individual patient-level data. In most RSA studies, RSA is used to assess the initial migration of a novel implant design as compared with its predecessor. The benefits of using RSA for this purpose are that small groups of approximately 30 patients each are needed, and results become available after 1 or 2 years of follow-up. However, as such studies are powered to compare the migration between 2 groups of specific implants, they are mostly underpowered to answer

other clinical questions requiring subgroup analyses. Future studies should consider pooling RSA studies to address such unanswered questions, including the impact of alignment on long-term migration.

Several limitations should be noted. First, all TKA procedures were performed with the intention to achieve mechanical alignment, and reasons why this was not achieved were not registered. Second, preoperative and postoperative anteroposterior standing full-leg radiographs, which were used to define in-range and out-of-range groups, were not made at standardized time points. In theory, the HKA could change preoperatively and postoperatively over time because of progressive osteoarthritis or migration of an implant. Third, although migration was corrected for the originating center and fixation method, there may have been residual confounding due to factors such as osteoporosis if these were distributed differently across the groups. Fourth, migration may depend on implant design, so ideally the impact of alignment would be investigated within the same implant design. Fifth, the group of uncemented-uncoated implants was small ($n = 21$), which could have resulted in a type-II error as the point estimates of in-range and out-of-range implants seemed different but had large confidence intervals. Finally, the present study assessed migration up to 2 years as a proxy for tibial loosening. Studies assessing the long-term effect of varus or valgus alignment on revision rates are needed before drawing conclusions regarding the longevity of out-of-range TKA implants.

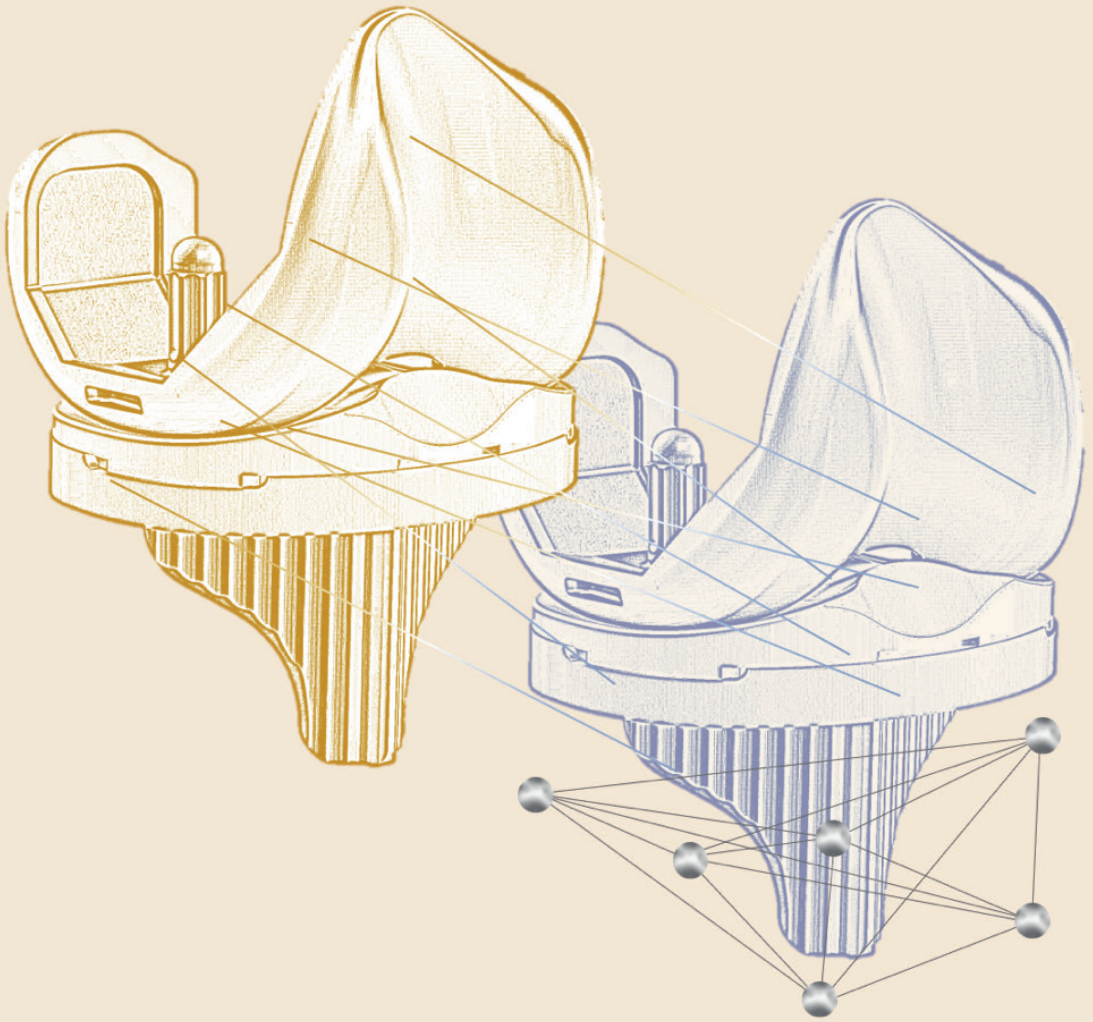
In conclusion, the present study showed that for patients with preoperative varus or valgus knees, postoperative alignment did not influence the mean tibial component migration in the first 2 postoperative years or the number of implants at risk for early loosening. Applying stricter or less-strict thresholds for defining an in-range aligned TKA implant gave similar results. The fixation method significantly influenced implant migration, with uncemented-uncoated implants showing the most migration.

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Chapter IX

General Discussion and
Future Perspectives

Total knee arthroplasties (TKAs) have excellent short- and long-term results considering its low revision rates which are 4 - 6% at ten years and 8-10% at 20 years, and patient reported outcome measures (PROMs) are good to excellent in the majority of patients.¹⁻¹¹ Even though TKA designs have achieved these excellent results for the last 3 decades, the results are less favourable in a subgroup of patients. For that matter in patients younger than 60 years the lifetime risk for a revision is 30% and up to 15-20% of these relative young patients are not satisfied with their overall outcome.⁵⁻¹¹ For these reasons, novel TKA designs are introduced on a regular basis. However, clinical evidence supporting superiority of these novel designs is frequently lacking.¹² Concerns on implants being introduced onto the market without sufficient clinical evidence have increased, particularly after some medical devices created disasters to patients, like the metal-on-metal hip prostheses in orthopaedics and the PIP-breast implants and vaginal meshes in other fields.¹³⁻¹⁶ The metal-on-metal hip prostheses were introduced with the promise that they would benefit younger and more active patients.^{17, 18} Short-term results of these prostheses were promising, but then studies reported pseudo-tumours, an adverse reaction to metal debris, which lead to up to fourfold increased revision rates in young patients as reported by the Australian Registry and NORE (Network of Orthopaedic Registries of Europe).¹⁹⁻²⁴ These bad outcomes in total hip as well as worse performance for some total knee implants stress again the necessity of a phased introduction of new implants as has been advocated for several decades.^{15, 24-27}

To prevent these less favourable outcomes in patients, the EU commission implemented the medical device regulation (MDR) in 2017, which became effective in 2021.²⁸⁻³⁰ The main difference between the medical devices directive (MDD) and the MDR included: 1) stricter requirements of clinical evidence for access to the EU market, including post-market surveillance, 2) a comprehensive EU database of high-risk medical devices and its adverse events (EUDAMED), and 3) independent

expert panels to evaluate new medical devices who need to be consulted on these high-risk medical devices. The “new” requirements of clinical evidence prior to market introduction has been suggested for decades.^{27, 31-34} Pre-market studies ideally subject a minimum number of patients to a novel implant while providing objective strong evidence on their performance. In orthopaedics, evaluating clinical results of novel implants can be challenging as the primary outcome often involves all-cause revision, which is relatively rare for orthopaedic hip and knee implants within the first ten years. Due to the low frequency of occurrences, large patient cohorts with extensive follow-up are required to gather sufficient clinical evidence to demonstrate the superiority of a novel implant design. Since loosening of the implant within the supporting bone is the major reason for failure, revision due to loosening is the main endpoint when evaluating orthopaedic implants. Thus, methods providing objective results on implant fixation are most important for evaluating new implants in the pre-market evaluation phase, ideally with an objective and highly accurate technique requiring a minimum of patients to be exposed to the new implant.

Radiostereometric analysis (RSA), which measures implant migration, is such a method as it can identify implants at risk of aseptic loosening as early as one- or two-year follow-up.^{35, 36} It does so by measuring implant migration with high accuracy (up to 0.1mm and rotation up to 0.1°).³⁷ Implants with high initial or continuous migration after one year are known to be prone to failure.^{35, 36} Therefore, RSA is an ideal tool to assess novel implants prior to massive market introduction.

This thesis contributes to the existing literature by expanding our understanding of TKAs performance by measuring implant migration using RSA at two-, five- and ten-year follow-up. Furthermore, this thesis conducted a comprehensive pooled analysis to examine the impact of surgical alignment on implant migration. Additionally, the present thesis explored alternative biomarkers of implant migration, which have potential to serve as early indicators for detecting implant loosening. Presented studies in this thesis strengthen the importance of highly accurate measurement tools of implant migration for providing short-term clinical evidence on the

performance of TKA implants, to ensure the best possible outcomes for patients in the long run.

Migration thresholds

If RSA would be used to evaluate implants prior to market entry, the key question is when is early migration too high, i.e., which migration threshold is clinically relevant for long-term performance. In this thesis, we used the threshold proposed by Ryd et al. (1995) to assess the number of implants at risk for early aseptic loosening, defined as an increase of 0.2 mm MTPM or more between one year and two years of follow-up.³⁵ This threshold dates from 1995 and was determined by assessing 158 patients who had different TKA implants with either cemented or uncemented designs (N = 120) or even UKAs (N = 38). In this series 15 implants (14 TKAs; 1 UKA) were revised for mechanical loosening of the tibial component within 1 to 11 years after the primary surgery. All the revised implants showed continuous migration over time and had higher migration at one year compared to the control group (i.e., non-revised implants). The authors used the difference in migration between both groups to define thresholds as >0.2 mm MTPM migration between one year and two years. In **Chapter IV**, **Chapter V**, and **Chapter VI**, we used this threshold to identify the number of continuously migrating implants for the different types of design i.e., MBT and APT designs, and for cemented and 3D-printed uncemented designs. We also used this threshold to identify the number of continuously migrating implants for postoperative in-range (femorotibial angle of $0^{\circ} \pm 3^{\circ}$) and out-of-range (femorotibial angle of $<-3^{\circ}$ or $+3^{\circ}$) TKAs (**Chapter VIII**). In a post-hoc analysis, the number of continuously migrating implants were similar in these studies for the different implant designs, and for postoperative in-range and out-of-range TKAs. Given that these migration thresholds date from nearly three decades ago in a very heterogenous group of knee implants and considering the substantial improvements in implant design and fixation methods since then, it is important to conduct mid- and long-term RSA studies to assess the external validity of predictions regarding

continuously migrating implants made at two years as every implant design is likely to have a distinct migration profile. In **Chapter VI**, we contribute further evidence on this matter by investigating whether continuously migrating implants at two years continued to migrate up to five years postoperatively. We found that one TKA was revised due to continuous migration, four showed late stabilization and four could not be analysed due to missing data at five years. These results suggest that implants can stabilize after an initial period of continuous migration and highlight the importance of five- and 10-year follow-up in RSA studies to assess long-term migration profiles of different TKA designs. This raises the question whether long-term results should be considered in a phased introduction of novel implants. Incorporating long-term results would negate the advantage of RSA studies, which provides early (i.e., at two years) insights into the migration profile of a novel implant, but they may be required for implants with progressive migration at two years.

Furthermore, it should be noted that the a-priori chance of developing aseptic loosening of the tibial component in the study by Ryd et al. (1995) was about 10% at ten years.³⁵ The chance of all cause revision has since then decreased to approximately 5% at 10 years of which approximately 20% is due to tibial loosening.¹ This small a-priori risk of tibial loosening of TKA implies that large patient cohorts are needed to validate the threshold proposed by Ryd et al.³⁵ In this context, we increased the sample size by combining data from ten RSA studies comprising 636 TKAs at baseline (**Chapter VIII**). However, when the revision rate is around 1% at 10 years, this would require approximately 1500 TKAs (across RSA studies) to be included to have 15 revisions due to tibial loosening and to compare the migration of these revised TKAs to non-revised TKAs. The latter implies that network analysis across RSA centres and sharing individual patient data is the way forward.^{38, 39} Ideally, a global registry of RSA studies should be established, for example by The International Radiostereometry Society.

Surgical alignment technique influencing migration

Besides using RSA to assess novel implants prior to market introduction, RSA can also be used to evaluate the effect of surgical techniques on implant migration. Traditionally, orthopaedic surgeons aim for neutral coronal alignment (i.e., mechanical alignment hip-knee-ankle angle or femorotibial angle is 0 degrees).⁴⁰ While this 'one size fits all' principle has resulted in low revision rates for modern TKAs, the number of patients who are not satisfied after TKA is 15-20%, which is higher compared to total hip arthroplasty.⁴¹ Possible reasons for patients not being satisfied include the management of patient expectations but could also be that the TKA prosthesis is neutrally aligned even in patients who had a preoperative varus or valgus knee alignment. This is a substantial group as the native knee alignment in men and women is varus in 32% and 17%, respectively.⁴⁰ Changing the alignment of these patients to neutral, could result in a change in soft tissue balance, which may cause an unnatural feeling of the knee.⁴⁰ Other alignment principles have been proposed, like kinematic alignment, which aims to insert the knee implants in a similar fashion as the preoperative alignment.⁴⁰ Proponents of this technique state that this alignment technique respects the soft-tissue balance and requires less soft-tissue releases to balance the TKA.⁴²⁻⁴⁴ By respecting the preoperative alignment and the native soft-tissue balance, patients could experience their 'new' knee as more natural which theoretically could increase patient satisfaction. But the reality is more complex than just focussing on individual preoperative alignment as varus positioning of TKA could cause more migration and in turn more loosening in the long term.^{45, 46}

In the past years, several variations to kinematic alignment have been introduced such as "kinematic alignment plus" or "mild kinematic alignment".^{47, 48} These variants have the same principles as kinematic alignment but differ slightly in terms of the acceptable amount of varus or valgus. Opponents of this technique state that malalignment (i.e., varus or valgus alignment) could result in an unfavourable load

transfer through the implant which in turn could increase the risk of loosening and revision.^{40, 49-53} Research in this thesis contributes to this debate. We showed that failing to achieve postoperative neutral mechanical alignment did not affect tibial migration up to two years in patients with a preoperative varus or valgus aligned knee (**Chapter VIII**). Therefore, our findings suggest that postoperative varus or valgus aligned TKAs do not have an increased risk of failure due to aseptic loosening in contrast to prior findings of van Hamersveld et al. (2019) who found increased migration of postoperative varus aligned TKAs.⁴⁶ Difference between both studies was however that we excluded preoperative neutrally aligned knees and therefore only assessed preoperative varus and valgus aligned knees. For these patients, postoperative neutral, varus or valgus alignment was not related to increased implant migration. Our study suggests that kinematic alignment could thus be a safe treatment option as it does not increase the risk of aseptic loosening but has the advantage that it requires less soft tissue release. Unfortunately, we did not assess functional outcome nor patient reported outcome measures (PROMs) in our study so that we could not test whether kinematic alignment resulted in better patient satisfaction. Another limitation of our study was that the aim of TKA positioning was neutral mechanical alignment and any deviation from neutral postoperative alignment was due to a combination of random variation as well as intra-operative assessment of the soft tissue balance by the orthopedic surgeon, making it difficult to assess a causal relationship in our study.

Other studies report ambiguous results regarding postoperative patient satisfaction and function, with some studies suggesting better clinical outcomes following kinematic alignment and others suggesting no difference between both alignment principles.^{48, 54-58} These findings also highlight the complexity of determining the optimal alignment for an individual patient when this is based only on PROMs and functional outcome. For that matter functional outcome and survival of TKAs are influenced by many other factors besides coronal alignment, like preoperative expectations, preoperative functionality and kinematics.⁵⁹ So what the optimal

coronal and sagittal alignment should be for an individual patient in order to have good long-term bone-implant fixation as well as subjective outcomes is determined by a complex of multifactorial variables. Novel techniques aimed at improving the precision of implant positioning, such as robot-assisted surgery, machine learning algorithms or AI, may prove advantageous, but they still need to undergo validation through implant migration analysis studies and other clinical research.⁶⁰⁻⁶⁴

Future perspectives

In recent years, both implant design and measurement techniques of implant performance, like implant migration techniques, have improved considerable and in turn have improved implants and thus patient safety and outcomes. Biomarkers for example could monitor or identify implants at risk for loosening. Furthermore, an improvement in implant migration assessment could be the development of CT-based RSA, which has emerged as a promising technique in implant-bone migration assessment.⁶⁵⁻⁶⁸ Last, the introduction of 3D-printing technology has enabled the creation of customized and patient-centred implants, but whether this is favourable in the long run for implant fixation, also has to be shown by implant migration studies.⁶⁹

An early warning signal

As mentioned earlier, TKAs have an excellent survival of approximately 94-96% at ten-years.^{1, 2} Although the risk of TKA failure is low, it is associated with severe morbidity and frequently results in extensive revision surgery.^{70, 71} This low revision rate in the overall TKA population, but not in the younger population (e.g., 60 years), makes it difficult to improve outcomes. Where RSA can only be used in specific and a limited number of patients, it is frequently only used in patients included in studies. It also requires additional steps intra-operatively, in contrast with other biological markers that could be assessed relatively easy in large patient cohorts. This thesis contributes further evidence by demonstrating that serum tumour necrosis factor α (TNF α), serum interleukin-1b (IL-1b), serum osteocalcin, and urinary N-terminal telopeptide (NTX) were significantly increased in loosened implants compared with stable implants at time of diagnosis or prior to revision surgery (**Chapter III**). These findings suggest that these biomarkers may have the potential to act as early indicators for loosened implants, as well as for monitoring progression of loosening.^{72, 73} Advantages of such biomarkers are: first, sampling from patients with implant-related complaints, thus differentiating between

implant-bone interface problems (e.g. loosening), soft-tissue problems, infection or other factors. Also, longitudinal studies could establish biomarker values that predict loosening. If the association between specific biomarker levels and implant loosening is further confirmed, these biomarkers could be used to monitor treatment modalities aimed at preventing or delaying implant loosening, like gene-directed therapy to fixate loosened implants or the use of bisphosphonates.⁷⁴⁻⁷⁷

To conclude

No innovation without evaluation is a common saying. In the case of new implant designs, evaluation should include clinical studies prior to market introduction among which implant migration studies (e.g., RSA studies). The latter safeguards good implants and thereby, enabling good to excellent patient outcomes.

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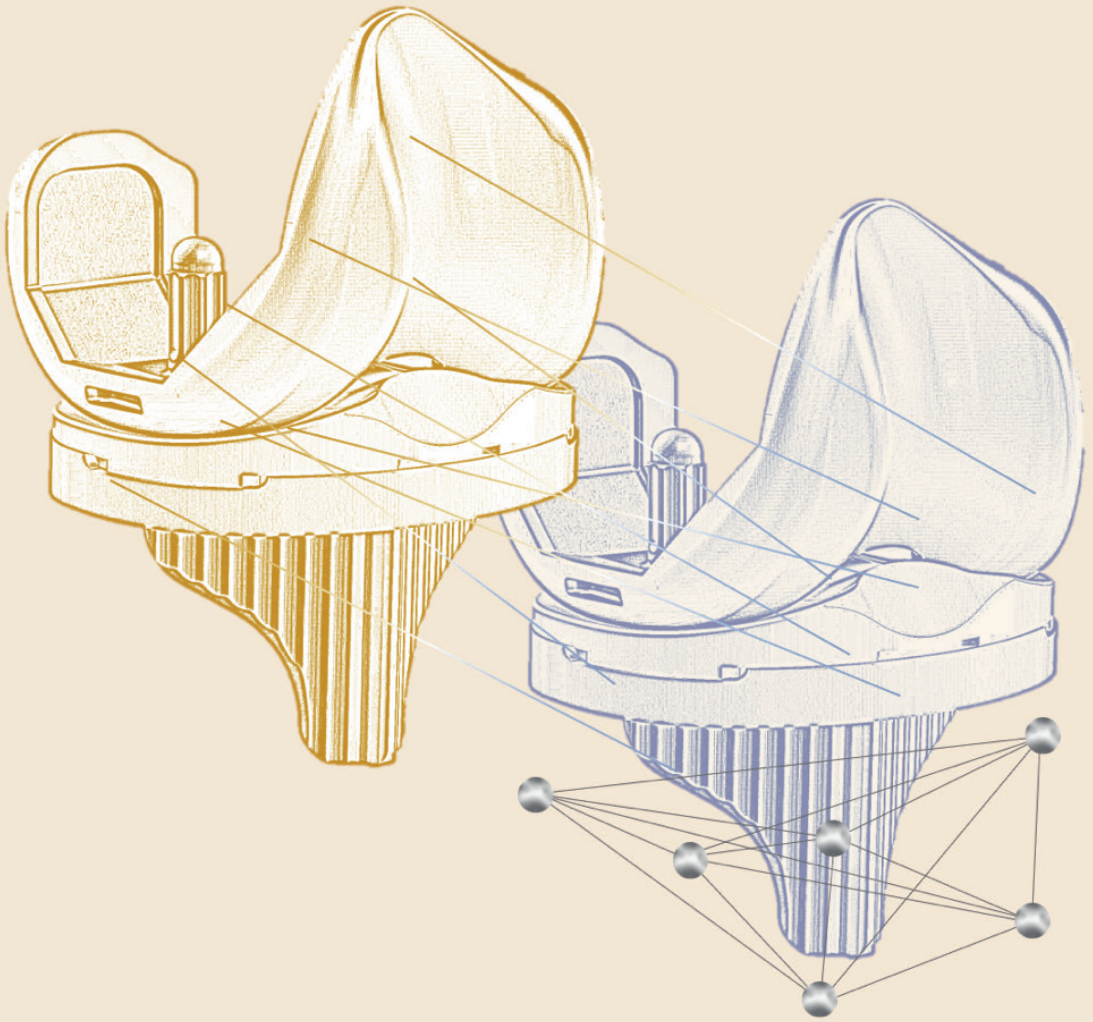
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Chapter X

Summary

The aim of the present thesis was to contribute to better understand the influence of differences in implant design and surgical techniques on migration of TKA, and more broadly on the effect of using RSA and other markers to detect loosening early.

In [Chapter II](#), we compared revision rates of RSA-tested TKA designs with non-RSA-tested TKA designs using national and regional arthroplasty registries. Seven registries comprising of 339 TKA designs were included. These TKA designs were compared to TKA designs used in RSA studies on three characteristics: prosthesis model, fixation method and insert type. TKA designs from registries matching a design used in an RSA study were classified as RSA-tested. All remaining TKA designs were classified as non-RSA-tested. The RSA-tested and non-RSA-tested groups included 236 and 103 TKA designs, respectively. The pooled revision rate of RSA-tested TKAs at five years was 2.9% and at ten years was 4.4%. The pooled revision rate of non-RSA-tested TKAs at five years was 3.6% and was 5.5% at ten years. Revision rates were 0.6% and 0.9% lower at five and ten years in favor of RSA-tested TKAs. This absolute reduction of revision risk could translate in a relative reduction of approximately 20% at ten years.

In [Chapter III](#), we conducted a systematic review to identify serum and urine markers which could discriminate between aseptic loosened and stable hip and knee implants. Twenty-eight studies assessing these biomarkers were included. Serum and urine markers were studied in 22 and in ten studies, respectively. Serum tumor necrosis factor α , interleukin-1 β and osteocalcin as well as urinary N-terminal telopeptide were significantly elevated in loosened implants compared to stable implants. These biomarkers should be studied further as they potentially could open strategies to not only prevent severe implant loosening by acting as a therapeutic target, but also have the potential to monitor disease progression.

In [Chapter IV](#), migration and patient reported outcome scores (PROMs) of two implant designs were compared in a randomized controlled trial (RCT) conducted in Hässleholm, Sweden. Sixty patients were randomized to either a cemented metal-

backed tibial (MBT) posterior-stabilizing (PS) TKA or an all-polyethylene tibial (APT) PS TKA. Primary outcome was migration measured with RSA and secondary outcomes were the knee society score (KSS), knee osteoarthritis outcome score (KOOS) and the forgotten joint score (FJS). Patient follow-up was at three months, one year and two years postoperative. No differences in migration between MBT and APT TKAs was found. Further, no significant differences were found in KSS, KOOS or FJS scores between both implant designs. These findings suggest that the risk of aseptic loosening is comparable for MBT and APT TKAs.

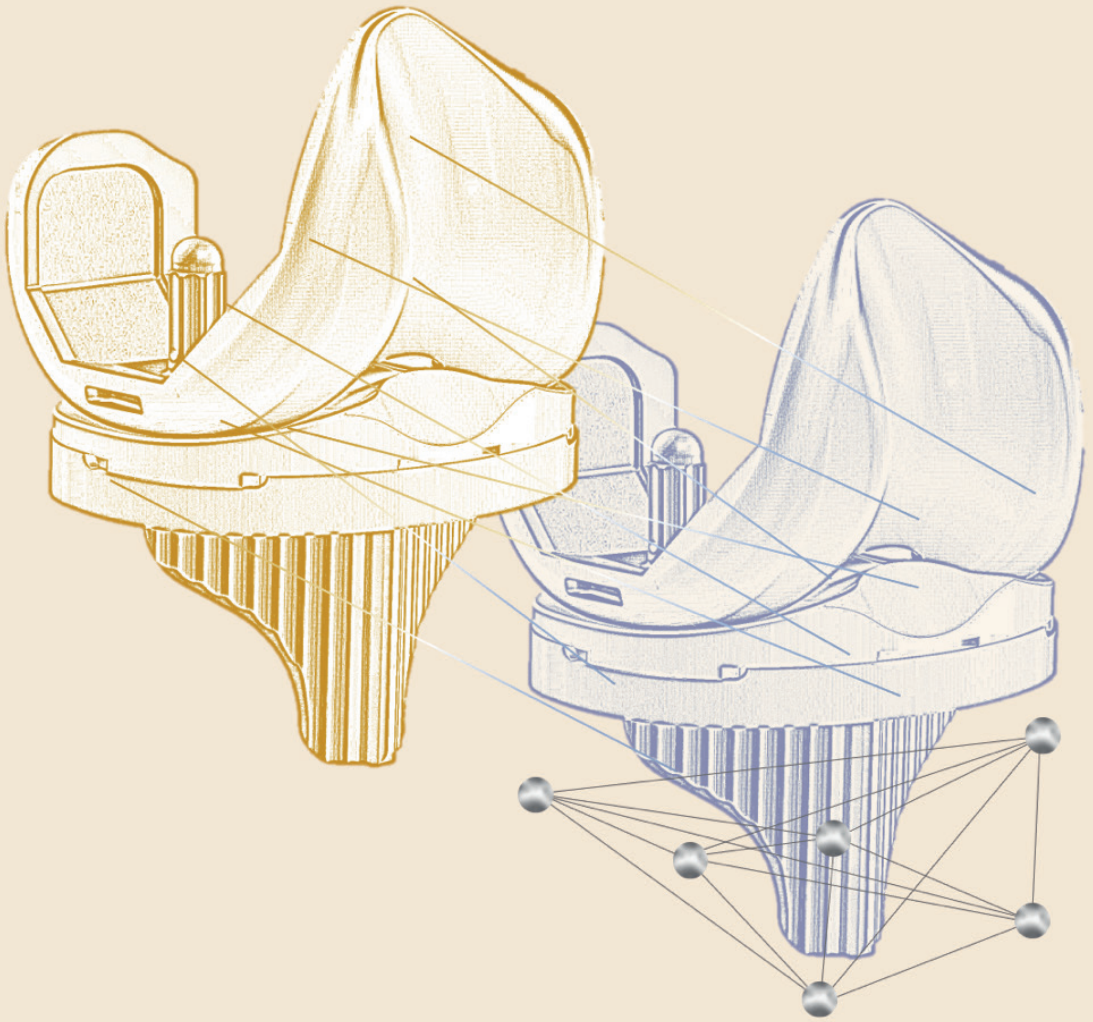
In [Chapter V](#), two different fixation methods were compared using migration measured with RSA and PROMS. This RCT was conducted in Hässleholm, Sweden. Seventy-two patients were randomized to either a cemented or an uncemented, 3D-printed TKA. RSA radiographs were taken within two-three days postoperative, at three months, at one year and at two years. Secondary outcome measures were the KSS, KOOS and FJS. The 3D-printed, uncemented TKAs migrated more over the two-year period than their cemented counterparts. The difference was due to higher migration of the uncemented TKAs in the first three months. After three months, cemented and 3D-printed, uncemented TKAs showed comparable migration. No differences were found in KSS, KOOS and FJS between both fixation methods. These findings suggest that 3D-printed, uncemented TKAs are as stable as cemented TKAs after an initial period of settling.

In [Chapter VI](#), two RCTs were pooled and migration of MBT and APT TKAs were compared up to five years. In this study, MBT cruciate-stabilizing (CS) TKAs were compared with APT CS TKAs, and MBT PS TKAs were compared with APT PS TKAs. Further, migration profiles of continuously migrating implants were evaluated beyond two years. Sixty patients were randomized in each study, but five patients were excluded due to various reasons, leaving 115 patients to be analysed. No differences in migration between MBT-CS and APT-CS nor between MBT-PS and APT-PS TKAs was found. However, the surgeon had a significant influence on implant migration in the CS-study. Further, nine TKAs showed continuously

migration in both studies combined. Of these TKAs, one was revised for instability, four stabilized, and four had missing five-year data. These findings suggest that the risk of aseptic loosening is comparable between MBT and APT TKAs using data up to five years. Further, the surgeon seems to influence migration in particular implant designs. Last, the finding that four TKAs showed late stabilization stresses the need for mid- and long-term RSA studies to determine whether predictions at two years are correct.

In [Chapter VII](#), we conducted a meta-analysis to evaluate migration patterns of tibial components of unicondylar knee arthroplasties (UKAs). Ten studies comprising of 13 study groups and 381 UKAs were included. We found that the majority of migration occurred in the first 6 months postoperatively followed by a period of very little migration, similar to what is reported for TKAs. However, migration at one year and two years was higher for UKAs than for TKAs. These findings suggest that migration profiles of UKAs are comparable to TKA migration.

In [Chapter VIII](#), ten RCTs conducted in Hässleholm, Sweden or Leiden, The Netherlands were pooled to compare migration of in-range TKAs with out-of-range TKAs in patients with a preoperative varus or valgus knee. In-range was classified as a hip-knee-ankle angle (HKA) of $0 \pm 3^\circ$ and out-of-range as a HKA of $< -3^\circ$ or $> 3^\circ$. The in-range group consisted of 290 TKAs and 186 TKAs were included in the out-of-range group. We found no difference in migration up to two years between in-range and out-of-range TKAs. However, the fixation method (i.e., cemented, uncemented-coated, or uncemented-uncoated) had a significant influence on migration with uncemented-uncoated implants showing the highest migration. Thus, failing to achieve an in-range TKA in patients with a preoperative varus or valgus knee did not increase migration up to two years, suggesting that leaving residual varus or valgus has no impact on TKA migration.



Chapter XI

Summary in Dutch

(Nederlandse Samenvatting)

Het doel van deze thesis was om bij te dragen aan een beter begrip van de invloed van verschillen in implantaatontwerp en chirurgische technieken op de migratie van totale knieprothesen (TKPs) en, in bredere zin, het effect van het gebruik van Radiostereometrische Analyse (RSA) en andere markers om vroegtijdige loslating te detecteren.

In [Hoofdstuk II](#) hebben de revisiepercentages van RSA-geteste TKPs vergeleken met niet-RSA-geteste TKPs met behulp van nationale en regionale prothese registers. Zeven registers met in totaal 339 TKP-ontwerpen werden geïnccludeerd. Deze TKP-ontwerpen werden vergeleken met TKP-ontwerpen die gebruikt werden in RSA-studies op basis van drie kenmerken: prothesemodel, fixatiemethode en type insert. TKP-ontwerpen uit registers die overeenkwamen met een ontwerp dat gebruikt werd in een RSA-studie werden geclassificeerd als RSA-getest. Alle overige TKP-ontwerpen werden geclassificeerd als niet-RSA-getest. De RSA-geteste en niet-RSA-geteste groepen omvatten respectievelijk 236 en 103 TKP-ontwerpen. Het samengevoegde revisiepercentage van RSA-geteste TKPs na vijf jaar was 2,9% en na tien jaar was dit 4,4%. Het samengevoegde revisiepercentage van niet-RSA-geteste TKAP na vijf jaar was 3,6% en na tien jaar was dit 5,5%. De revisiepercentages waren respectievelijk 0,6% en 0,9% lager na vijf en tien jaar in het voordeel van RSA-geteste TKPs. Deze absolute vermindering van het revisierisico zou kunnen resulteren in een relatieve vermindering van ongeveer 20% na tien jaar.

In [Hoofdstuk III](#) hebben we een systematische review uitgevoerd om serum- en urinemarkers te identificeren die onderscheid kunnen maken tussen aseptisch losgelaten en stabiele heup- en knie-prothesen. Achtentwintig studies die deze biomarkers beoordeelden, werden geïnccludeerd. Serummarkers werden bestudeerd in 22 studies en urinemarkers in tien studies. Serumentumor necrosis factor α , interleukine-1b en osteocalcine, evenals urine N-terminaal telopeptide, waren significant verhoogd bij losgelaten prothesen in vergelijking met stabiele prothesen. Deze biomarkers zouden verder onderzocht moeten worden, omdat ze mogelijk strategieën kunnen bieden om niet alleen ernstige loslating van het implantaat te

voorkomen door te fungeren als een therapeutisch doelwit, maar ook omdat ze het potentieel hebben om de ziekteprogressie te monitoren.

In [Hoofdstuk IV](#) hebben we de migratie en patiëntgerapporteerde uitkomsten (PROMs) van twee protheseontwerpen vergeleken in een gerandomiseerde gecontroleerde studie (RCT) uitgevoerd in Hässleholm, Zweden. Zestig patiënten werden willekeurig toegewezen aan ofwel een gecementeerde 'metal-backed' tibia component (MBT) posterieur-gestabiliseerde (PS) TKP of een volledig polyethyleen tibia component (APT) PS TKP. Het primaire resultaat was migratie gemeten met RSA en secundaire resultaten waren de Knee Society Score (KSS), de Knee Osteoarthritis Outcome Score (KOOS), en de forgotten joint score (FJS). Patiënten werden gevolgd op drie maanden, één jaar en twee jaar na de operatie. Bovendien werden er geen significante verschillen gevonden in KSS, KOOS of FJS tussen beide groepen. Deze bevindingen suggereren dat het risico op aseptische loslating vergelijkbaar is voor MBT en APT TKPs.

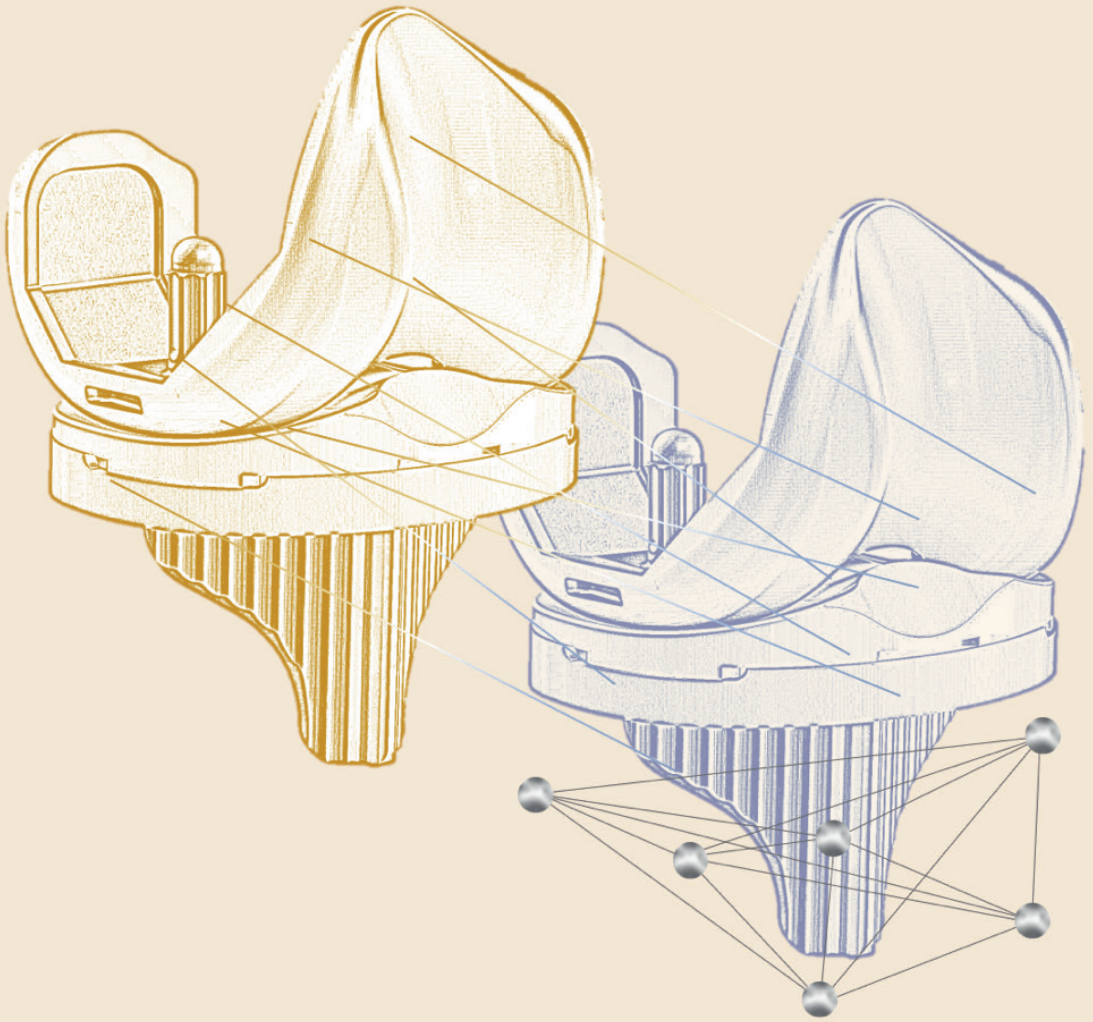
In [Hoofdstuk V](#) werden twee verschillende fixatiemethoden vergeleken aan de hand van migratie gemeten met RSA en PROMS. Deze gerandomiseerde gecontroleerde studie werd uitgevoerd in Hässleholm, Zweden. Tweeënzeventig patiënten werden willekeurig toegewezen aan ofwel een gecementeerde of een ongecementeerde, 3D-geprinte TKP. RSA-röntgenfoto's werden genomen binnen twee tot drie dagen na de operatie, op drie maanden, op één jaar en op twee jaar. Secundaire uitkomstmaten waren de KSS, KOOS en FJS. De ongecementeerde, 3D-geprinte TKPs vertoonden gedurende de tweejarige periode meer migratie dan hun gecementeerde tegenhangers. Het verschil werd veroorzaakt door een hogere migratie van de ongecementeerde TKPs in de eerste drie maanden. Na drie maanden vertoonden gecementeerde en ongecementeerde, 3D-geprinte TKPs vergelijkbare migratie. Er werden geen verschillen gevonden in KSS, KOOS en FJS tussen beide fixatiemethoden. Deze bevindingen suggereren dat 3D-geprinte, ongecementeerde TKPs net zo stabiel zijn als gecementeerde TKPs na een initiële periode van settling.

In **Hoofdstuk VI** werden twee gerandomiseerde gecontroleerde studies samengevoegd en werd de migratie van MBT- en APT-TKPs vergeleken over een periode van vijf jaar. In deze studie werden MBT-kruisbandstabiliserende (CS) TKPs vergeleken met APT-CS TKPs, en MBT-PS TKPs werden vergeleken met APT-PS TKAs. Bovendien werden migratieprofielen van voortdurend migrerende implantaten geëvalueerd na twee jaar. In elk van de twee studies werden zestig patiënten willekeurig toegewezen, maar vijf patiënten werden om verschillende redenen uitgesloten, waardoor 115 patiënten werden geanalyseerd. Er werden geen verschillen gevonden in migratie tussen MBT-CS en APT-CS, noch tussen MBT-PS en APT-PS TKPs. De chirurg had echter een significante invloed op de migratie van het implantaat in de CS-studie. Bovendien vertoonden negen TKPs voortdurende migratie in beide gecombineerde studies. Van deze TKPs werd er één gereviseerd vanwege instabiliteit, stabiliseerden er vier en ontbraken er gegevens van vijf jaar bij vier TKPs. Deze bevindingen suggereren dat het risico op aseptische loslating vergelijkbaar is tussen MBT- en APT-TKPs op basis van gegevens tot vijf jaar. Bovendien lijkt de chirurg invloed te hebben op de migratie bij bepaalde implantaten. Ten slotte benadrukt de bevinding dat vier TKPs laat stabiliseerden, de noodzaak van middellange- en lange termijn RSA-studies om te bepalen of voorspellingen na twee jaar juist zijn.

In **Hoofdstuk VII** hebben we een meta-analyse uitgevoerd om migratiepatronen van tibiale componenten van unicondylaire knieprothesen (UKPs) te evalueren. Tien studies met 13 onderzoeksgroepen en 381 UKPs werden geïncludeerd. We ontdekten dat de meeste migratie plaatsvond in de eerste 6 maanden na de operatie, gevolgd door een periode van zeer weinig migratie, vergelijkbaar met wat wordt gerapporteerd voor TKPs. Migratie na één jaar en twee jaar was echter hoger voor UKPs dan voor TKPs. Deze bevindingen suggereren dat migratieprofielen van UKPs vergelijkbaar zijn met migratie van TKPs.

In **Hoofdstuk VIII** werden tien RCTs uitgevoerd in Hässleholm, Zweden, of Leiden, Nederland, samengevoegd om migratie van neutraal gepositioneerde ('in-range')

TKPs met varus of valgus ('out-of-range') TKPs te vergelijken bij patiënten met een voorafgaande varus- of valgus knie. In-range werd geclassificeerd als een heup-knie-enkelhoek (HKA) van $0 \pm 3^\circ$ en out-of-range als een HKA van $< -3^\circ$ of $> 3^\circ$. De in-range groep bestond uit 290 TKPs en 186 TKPs werden geïncludeerd in de out-of-range groep. We vonden geen verschil in migratie tot twee jaar tussen in-range en out-of-range TKPs. De fixatiemethode (gecementeerde, ongecementeerd-gecoat of ongecementeerd-niet-gecoat) had echter een significante invloed op migratie, waarbij ongecementeerde-niet-gecoate implantaten de hoogste migratie vertoonden. Het niet bereiken van een in-range TKP bij patiënten met een voorafgaande varus- of valgus knie verhoogde migratie tot twee jaar niet, wat suggereert dat een resterende varus- of valgus stand geen invloed heeft op TKP-migratie bij patiënten met een pre-operatief varus of valgus stand van de knie.



Chapter XII

Appendices

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Hasan S, Kaptein BL, Marang-van de Mheen PJ, Nelissen RGHH, Toksvig-Larsen S. *Patients with a continuously migrating total knee arthroplasty do not have inferior patient reported outcome scores: 10-year follow-up of 5 randomized controlled trials using radiostereometric analysis. RSA meeting, virtual congress, 2021 (oral presentation).*

Hasan S, Kaptein BL, Marang-van de Mheen PJ, van Hamersveld KT, Nelissen RGHH, Toksvig-Larsen S. *Stabilization of continuous migrating tibial components*

between two and five years: the need for longer term follow-up in RSA studies. RSA meeting, virtual congress, 2021 (oral presentation).

Hasan S, Kaptein BL, Marang-van de Mheen PJ, Nelissen RGHH, Toksvig-Larsen S. Patients with a continuously migrating total knee arthroplasty do not have inferior patient reported outcome scores: 10-year follow-up of 5 randomized controlled trials using radiostereometric analysis. European Federation of National Associations of Orthopaedics and Traumatology (EFORT) congress, virtual congress, 2021 (oral presentation).

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Curriculum Vitae

Shaho Hasan was born in Alkmaar on the 6th of July in 1992. He graduated from Stedelijk Gymnasium in Breda and started studying Medicine in Leiden at the Leiden University in 2010. During his bachelor's degree, he worked part-time as a poker croupier at Holland Casino and as a scribe at the Orthopedics department at Alrijne Hospital. His motivation for the study Medicine grew during the third year of his bachelor's degree when he first performed a medical examination of a patient under supervision of a trauma surgeon. Together they initiated research assessing the benefits and satisfaction of using a medical scribe at the outpatient clinic. This study evolved into a research internship at the Trauma Surgery Department of the Leiden University Medical Centre (LUMC). He presented this study at the yearly symposium for Trauma surgery and at the symposium for surgical residents, where it was rewarded with the price for the best presentation.

During his master's degree, he started his internships and concluded it with a five-week internship at the Orthopedics department at the Alrijne Hospital and a final internship at the Surgery department of the Haaglanden Medical Centre (HMC).

His career as a medical doctor began in 2018 as a PhD-student at the Orthopedics department of the LUMC in close collaboration with the Hässleholm Sjukhaus in Sweden. During his PhD, he participated in a COVID study, worked shifts at the COVID ward, and took shifts at a mobile COVID post. Moreover, he was active in training medical students and guiding them with research within the Orthopedics department. After approximately 3.5 years, he transitioned in 2021 from full-time research to a residency Orthopedics (not in training) at the Alrijne Hospital. After he got admitted for an Orthopedic surgery residency, he commenced his training with one-and-a-half-year general surgery training at the HMC. In July 2024, he will continue his residency at the Orthopedic department of the LUMC.

