The pre-, and post-market evaluation and outcome of Uncemented Total knee replacements and their effect on patient safety

Surveillance

Performance

Regulation

Safety

Adoption

Raymond Puijk

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The pre-, and post-market evaluation and outcome of Uncemented Total knee replacements and their effect on patient safety

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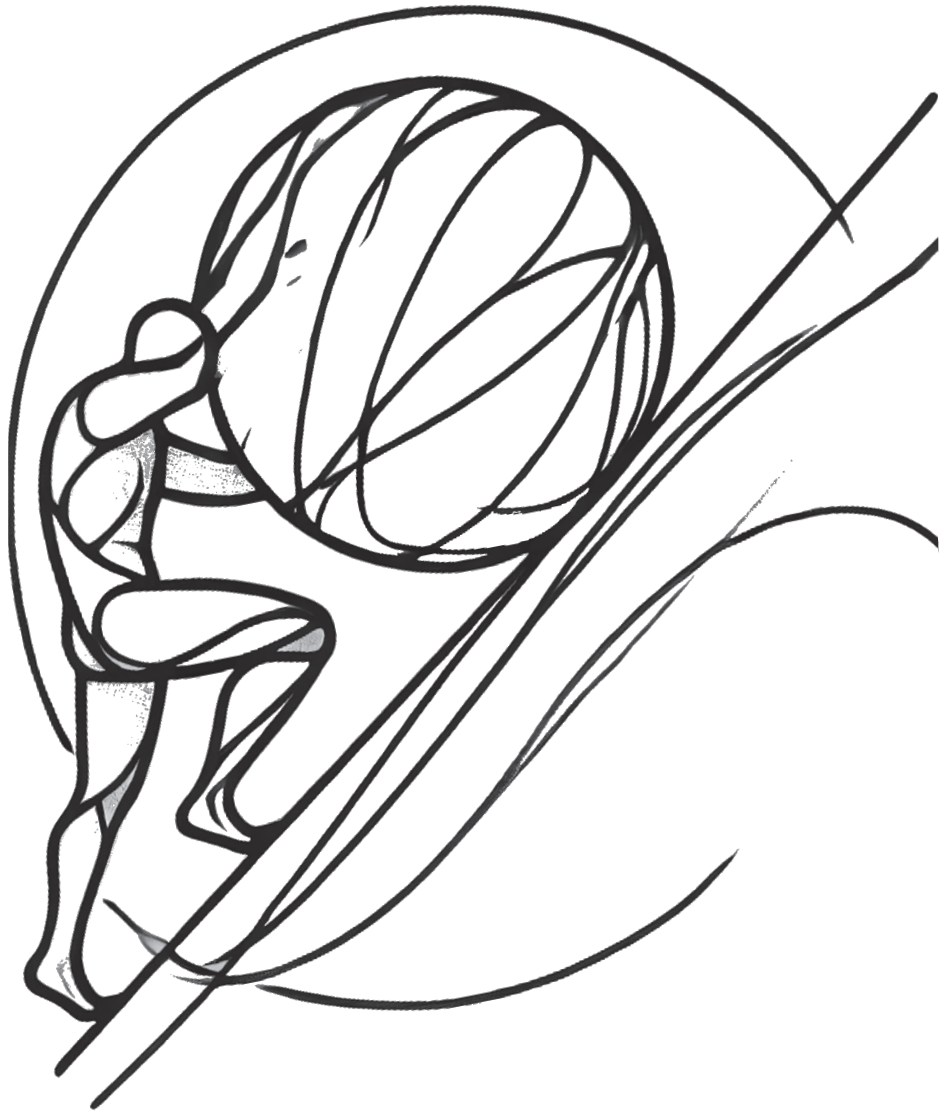


CHAPTER 1

GENERAL INTRODUCTION AND OUTLINE OF THIS THESIS

GENERAL INTRODUCTION

Osteoarthritis of the knee

Osteoarthritis (OA) is the most prevalent degenerative joint disease worldwide, affecting approximately 364 million people in 2019, with the knee being the most commonly affected joint. *[1]* This number is expected to rise by 75% by 2050. *[1]* OA is a progressive condition characterized by the gradual breakdown of cartilage and structural changes in the bone, including the formation of bone spurs and cysts (**Figure 1**). These degenerative changes lead to pain, stiffness, and reduced joint function, often necessitating total knee replacement (TKR) in the advanced stages of the disease. *[2]*

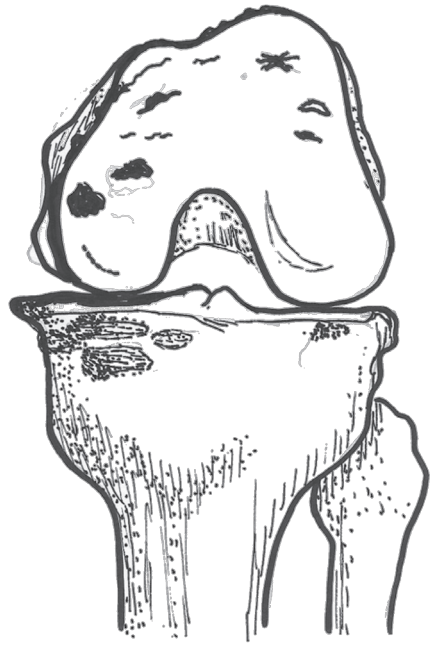


Figure 1. Illustration of a knee in flexion, depicting cartilage degeneration along with the formation of bony spurs and cysts. Reproduced with permission from: AmirQureshi.co.uk.

Total Knee Replacements

A TKR consists of a femoral and tibial metal alloy component, which can be fixated to the bone with or without bone cement, a polyethylene insert positioned between the metal components to facilitate knee movement, and optionally, a patella button that replaces the natural knee cap's articulating surface. Over the past five decades, TKRs have seen remarkable advancements. *[3]* Early designs resembled simple hinge mechanisms, but innovations have progressively evolved to create implants that closely mimic natural knee anatomy and biomechanics while ensuring a long implant lifespan. *[3]* In the past, these implants were primarily intended for older patients, for whom the expected implant lifespan of approximately 15 years was usually sufficient. However, the population requiring TKRs has gradually become younger and often heavier patients, who typically lead more active lifestyles. *[4–8]* This demographic shift places greater and longer mechanical stress on the implant, increasing the need for fixation methods that ensure both immediate stability and long-term durability. *[1]*

Total knee replacement fixation techniques

To achieve this, methods must provide long-term rigid fixation to maintain implant stability throughout the patient's lifetime. Cemented fixation, considered the gold standard, is used in approximately 88% of TKRs (95% Confidence interval [CI]: 78.6–97.5). *[4–9]* This method relies on polymethylmethacrylate (PMMA) bone cement, which acts as a grout, forming a strong bone-cement interlock upon hardening during surgery (**Figure 2**).

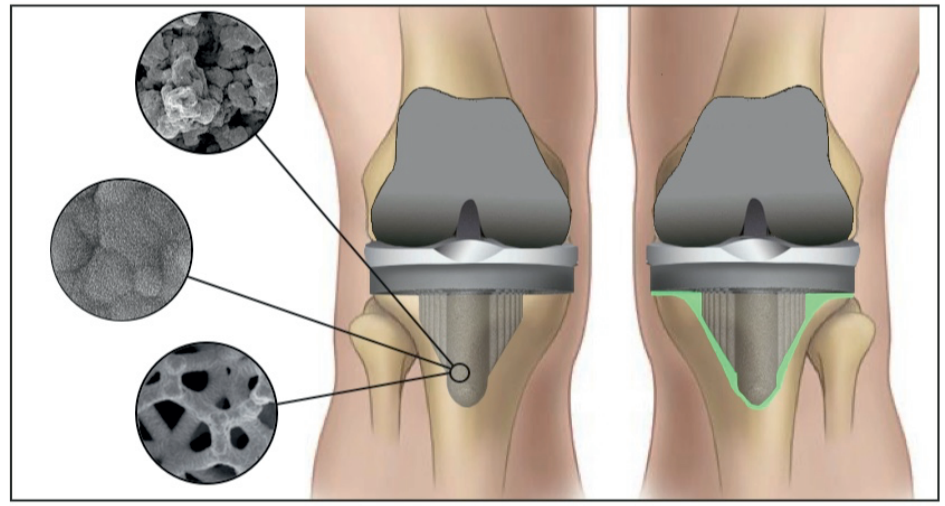


Figure 2. Schematic illustration of two total knee replacements, by uncemented fixation (left) by use of different surface modifications (e.g., vacuum plasma sprayed titanium, hydroxyapatite-coating, 3 dimensionally printed trabecular titanium) and by use of bone cement (right, in green).

In contrast, uncemented fixation was developed to rely more on the body's natural fixation mechanisms by utilizing bone ingrowth-promoting materials (**Figure 2**). *[10]* This approach employs a press-fit technique, where the implant is designed to fit tightly within the bone, providing initial stability. *[11]* Long-term fixation, however, relies on osseointegration—a process in which bone integrates into the implants' surface. This process begins with blood clot formation at the bone-implant interface immediately after implantation. *[12, 13]* Growth and differentiation factors released by activated blood cells initiate a biological cascade that promotes bone formation around the implant. A fibrin matrix forms first, serving as a scaffold for osteoblasts to deposit bone matrix. *[12, 13]* Failure of osseointegration can result in inadequate bone formation, ultimately compromising fixation and leading to implant loosening. *[13]* Currently, uncemented fixation is used in only 10% of TKRs (CI 1.2–18.8), largely due to poor outcomes observed with early TKR designs. *[3, 11, 14, 15]* These early failures, initially attributed to uncemented fixation, were later linked to design flaws, including lack of an

effective tibial keel, flat articulation insert surfaces, heat-pressed polyethylene, and reliance on polyethylene pegs, rather than inherent issues with the fixation method itself. *[3, 11, 14, 15]* Notably, uncemented fixation has become the most widely used and a reliable technique for total hip replacements, highlighting its potential for wider application in total knee arthroplasty. *[16]* Recent innovations in uncemented TKR have driven increased adoption.*[4–9]* Advancements such as rough or porous surfaces, as well as various forms of calcium phosphate coatings, facilitate cell attachment and bone integration at the implant interface, improving biological fixation and ensuring long-term stability. *[17–19]*

Functional outcome of uncemented total knee replacements

Functional outcome is one of the most important measures of TKRs success, as it directly reflects postoperative knee function and quality of life. *[20]* TKRs are widely recognized for providing significant functional improvement compared to the preoperative state. *[4–8]* Patient-reported outcome measures (PROMs) are commonly used in studies to assess functional outcomes, evaluating knee function, pain, and satisfaction through standardized questionnaires. *[4–8]* Despite the overall benefits of TKR, studies indicate that 10–20% of patients remain dissatisfied postoperatively due to residual pain, functional limitations, unmet expectations, mental health factors, or complications. *[21–23]* Ongoing research aims to further refine the interpretation of PROMs to better identify and address the causes of dissatisfaction. *[20]* Beyond patient outcomes, early PROM evaluations help monitor surgeon performance, surgical techniques, and implant effectiveness. They can serve as early indicators of complications *[21–23]* and provide valuable insights into the performance and risks of newly introduced prostheses, fixation methods, or surgical techniques.

Revision total knee arthroplasty

Implant failure significantly impacts the patient's well-being, with revision surgery often associated with prolonged recovery, increased morbidity, reduced mobility, a higher risk of re-revision, greater costs, and an elevated mortality risk compared to primary arthroplasty. *[24–26]* Due to these serious outcomes, revision surgery incidence and its causes are critical benchmarks in orthopedic research. Many national orthopedic associations adhere to an accepted standard for overall revision probability, with rates approximating 4.0% at 5 years, 5.0% at 10 years, and 6.5% at 15 years, as outlined by the Orthopaedic Data Evaluation Panel (ODEP) rating scale. *[27]*

Aseptic loosening of total knee replacements

Aseptic loosening, is defined as the failure of the fixation method in the absence of an infection or trauma, and is the most common cause of implant failure. *[4, 8]* While early revisions are often linked to prosthetic joint infections, the risk

of aseptic loosening progressively increases over time (**Figure 3**). *[4, 8]* Several factors contribute to its onset, including the inability to achieve proper fixation after surgery, degradation of fixation-interface material due to mechanical stress, or biological failure triggered by particulate debris (e.g., bone cement, metal alloy, or polyethylene). *[28]* These wear particles, generated through abrasive, adhesive, or fatigue wear within the joint space, are phagocytosed by macrophages, leading to a chronic inflammatory response. *[28]* The resulting inflammatory cytokines disrupt bone homeostasis, increasing bone resorption, osteolysis, and ultimately causing implant loosening. *[28]*

Early after surgery, the risk of aseptic loosening is higher in uncemented than cemented implants, due to the potential failure to establish biological fixation. *[29]* However, once osseointegration occurs, uncemented implants typically maintain strong long-term fixation, supported by continuous bone remodeling. *[28]* In contrast, cemented TKRs provide immediate stability through PMMA bone cement, reducing the risk of early loosening but making them more susceptible to early revisions due to infection. *[28]* Over time, cyclic loading and torque forces can induce cement fatigue and wear, increasing the risk of loosening in the long term. *[30]* As aseptic loosening remains a leading cause of revision surgery (**Figure 3**), accurate diagnosis is essential to avoid unnecessary procedures that may negatively impact patient outcomes and safety. *[24–26]* While aseptic loosening typically presents with pain and limited function, diagnosis can be challenging due to the numerous other potential causes of post-arthroplasty pain. *[31]* Differentiating between aseptic loosening and a prosthetic joint infection is particularly critical, as each requires a distinct surgical revision approach. *[32]*

Diagnostic evaluation for aseptic loosening begins with a thorough patient history, physical examination, and radiographic imaging. Each test contributes to the probability of aseptic loosening, which in turn influences the likelihood (pre-test) of obtaining a positive or negative result in subsequent tests. *[33]* Additional tests, such as infectious markers, joint aspiration, or advanced imaging techniques—including computed tomography (CT), magnetic resonance imaging (MRI), or bone scintigraphy with single-photon emission computed tomography/computed tomography (BS-SPECT/CT)—may be warranted based on initial findings. *[31]* BS-SPECT/CT employs a bisphosphonate tracer to detect increased osteoblastic activity, a potential indicator of implant loosening. *[34, 35]* However, the applicability of BS-SPECT/CT in uncemented TKR remains uncertain, as bone ingrowth and remodeling—both essential for uncemented fixation—may influence test results, particularly in the early postoperative years. *[34, 35]*

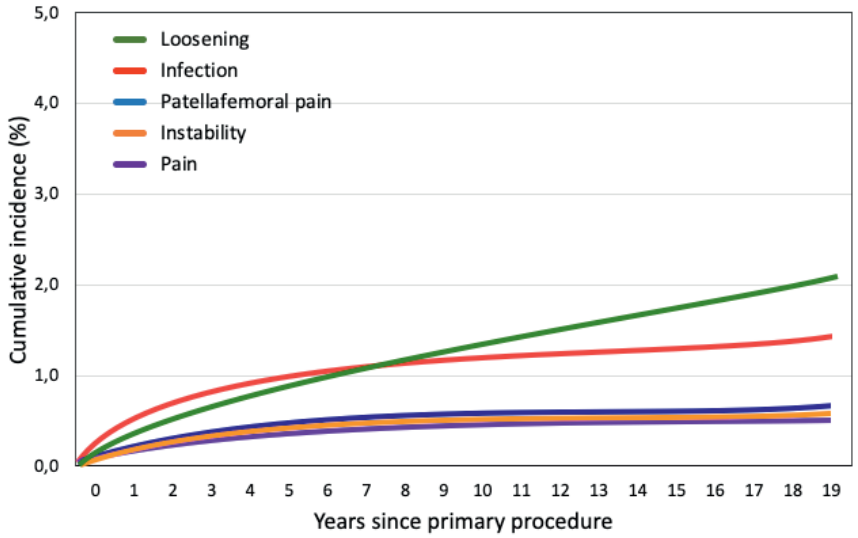


Figure 3. Cumulative incidence of revisions of primary TKR for different failure reasons, showing early revisions primarily due to infection, with aseptic loosening becoming increasingly prominent in later years (Image reproduced from the Australian Orthopaedic Association NJR: Annual Report 2020, without implant restrictions).

Radiostereometric analysis

Radiostereometric analysis (RSA) was introduced in the 1970s as an accurate method for assessing implant fixation, significantly improving upon conventional radiography. *[36]* Fixation is evaluated in RSA by measuring implant migration, which refers to changes in an implant's position and orientation relative to the bone over time. *[37]* Research shows that implant migration exceeding 0.1 mm per year in an individual is associated with a higher long-term risk of aseptic loosening. *[38]* A similar trend is observed when assessing the average 1-year migration of a group of implants. *[39]* This has led to the development of 1-year migration thresholds, classifying implants into acceptable, at-risk, or unacceptable categories based on their predicted 10-year risk of aseptic loosening. *[39]* However, these thresholds are primarily based on studies of cemented implants, which exhibit different migration patterns than uncemented designs. *[39]* Therefore, their applicability to uncemented implants remains uncertain. *[39]* RSA's high accuracy enables reliable results with small patient groups and short follow-up periods, making it a safe and efficient tool for evaluating implant performance. *[37]* Due to its predictive value, many researchers advocate for RSA assessments as a regulatory requirement for manufacturers before introducing new implants to the market. *[40–44]*

Prioritizing safety and performance

Historically, orthopedic implants have entered the market with minimal clinical evidence demonstrating their safety and performance. *[45]* This lack of robust pre-market testing, combined with ineffective post-market surveillance, has led to significant patient harm, with high failure rates often becoming apparent only after widespread adoption. *[44, 46–48]* The introduction of the new European Medical Device Regulation (MDR) ((EU) 2017/745) aims to address these issues by enforcing stricter requirements for clinical and preclinical evidence before market approval. *[48]* However, unlike pharmaceuticals, the regulation lacks a systematic and clearly defined framework specifying which aspects must be researched and how they should be evaluated to assess the risk of patient harm. *[48]* Therefore, a more structured approach to both pre-market evaluation and post-market surveillance is urgently needed to ensure patient safety and implant performance.

GENERAL AIM AND OUTLINE OF THIS THESIS

This thesis aims to provide insights into the short- and long-term performance and safety of modern uncemented TKR, with a particular focus on aseptic loosening. It follows a structured assessment pathway which should be required for newly introduced implants, encompassing both pre-market evaluation and post-market surveillance, to prevent underperforming designs from entering clinical practice and to systematically monitor the performance of implants already in use. By assessing osseointegration, fixation, migration patterns, safety, functional outcomes, and revision rates in uncemented TKR, this research aims to enhance the detection of early and late failures, support evidence-based surgical decision-making, and ultimately contribute to improved patient outcomes.

Part 1: Pre-market outcome of uncemented Total Knee Replacements

Before introducing new uncemented TKR implants into clinical practice, thorough pre-market evaluation is essential to assess their safety and long-term stability. This part of the thesis focuses on different assessments methods, including in-vitro and RSA investigations, to evaluate osseointegration, osteoclast activity, and early migration patterns, all associated to implant fixation.

To assess the biological response to uncemented TKR surfaces, **Chapter 2** investigates how human osteoblasts react to trabecular titanium and hydroxyapatite-coated surfaces, offering insights into their potential for osseointegration. Additionally, the influence of osteoblast-released factors on osteoclast formation is explored to understand the implications for implant fixation and bone resorption. **Chapter 3** updates a previous meta-analysis on RSA studies to evaluate the 5-year migration patterns of tibial components in primary TKR. The study also examines whether 6-month maximum total point motion (MTPM) could serve as an early predictor of long-term implant stability. Building on these findings, **Chapter 4** combines RSA and survival data in a meta-analysis to further evaluate the predictive value of early fixation-specific migration data. This chapter also validates and refines the RSA thresholds for phased TKR introduction, to prevent underperforming (uncemented) TKR from entering the market.

Part 2: Post-market outcome of uncemented Total Knee Replacements

Once uncemented TKR implants are introduced into clinical practice, continuous post-market surveillance is essential to monitor their performance, detect complications, and assess long-term outcomes. This part of the thesis focuses on evaluating functional outcomes, implant migration, revision rates, and diagnostic strategies for detecting uncemented implant-related complications.

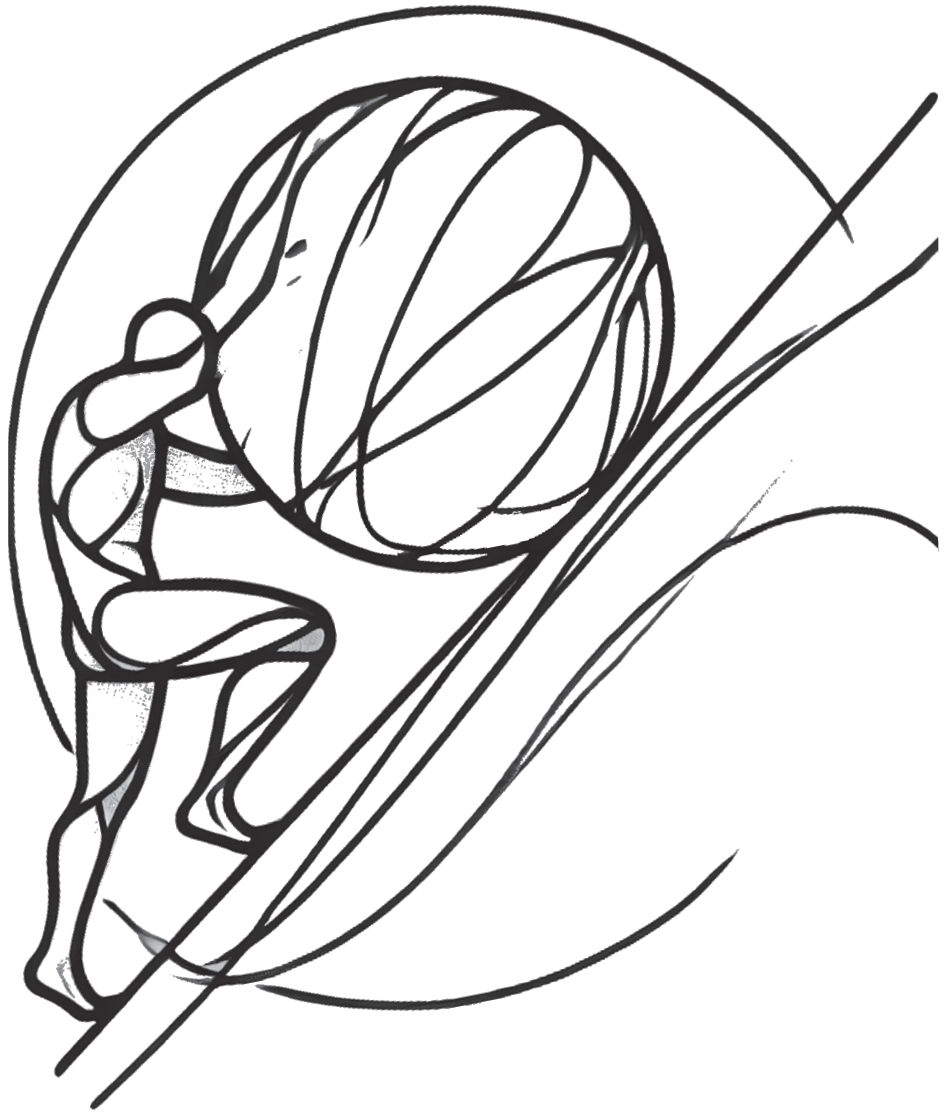
Chapter 5 investigates the early clinical performance of a new uncemented TKR, evaluating PROMs, clinical assessments, and revision rates up to three years postoperatively. **Chapter 6** follows up on an earlier randomized controlled trial (RCT) to analyze the migration patterns of a new uncemented TKR and its predecessor design, between two and five years postoperatively. Additionally, inducible displacement is assessed at five years to determine their current state of fixation. In **Chapter 7**, the role of BS-SPECT/CT in detecting implant loosening of uncemented TKR is evaluated by determining the diagnostic characteristics and reproducibility. To gain insights into long-term implant survival, **Chapter 8** presents a 15-year observational study on patients with end-stage knee osteoarthritis who received a modern uncemented TKR. This study examines revision rates, functional outcomes, and the impact of prior knee surgeries. Registry-based studies provide valuable large-scale data on implant performance and enable the identification of confounding factors. Therefore, in **Chapter 9**, the data from the Dutch Arthroplasty Registry was used to identify which surface modifications were used for uncemented TKR in the Netherlands, and their association with revision rates was investigated, particularly regarding aseptic loosening. Finally, **Chapter 10** presents a Dutch Arthroplasty Registry study that compared the revision rates of aseptic loosening between different constraint uncemented TKR designs, to evaluate their effect on long-term fixation.

General discussion and future perspectives

Chapter 11 discusses the findings of this thesis in the context of existing literature, highlighting their clinical implications and providing suggestions for future research directions.

PART 1

Pre-market outcome of uncemented total knee replacements



CHAPTER 2

Human Osteoblast Response to Uncemented Knee Implant Surface Structures and Osteoclast Formation in Vitro

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ABSTRACT

Background
Early bone ingrowth and minimal resorption ensure rigid fixation in uncemented total knee replacements. Trabecular titanium–aluminum–vanadium (Ti6Al4V) and hydroxyapatite (HA)-coated vacuum-plasma-sprayed (VPS) titanium with varying porosities and HA-coating thicknesses, have been developed to enhance fixation, though bone cellular response remains largely unknown. This study evaluated osteoblast responses to trabecular Ti6Al4V and three VPS titanium surfaces with 20–40% or 30–70% porosity and HA coatings of 60, 80, or 90µm.

Methods
Human primary osteoblasts were seeded and cultured for 29 days, to assess seeding efficiency, viability, metabolic activity, alkaline phosphatase activity, and the effect of osteoblast-released factors in conditioned medium during the last 4 days of culture on osteoclast formation. VPS-HA groups were first compared individually; when no differences were found, data were pooled for comparison with the trabecular group.

Results
Osteoblast seeding efficiency, viability, metabolic activity, and alkaline phosphatase activity were similar between VPS-HA surfaces. Moreover, osteoblast-conditioned medium did not affect osteoclast formation. Osteoblast seeding efficiency and viability were similar between the pooled VPS-HA and trabecular surface. Compared to the pooled VPS-HA, the trabecular surface increased osteoblast metabolic (1.5-2.7-fold) and alkaline phosphatase activity (6.5-15.2-fold). Osteoblast-conditioned medium reduced osteoclast formation (2.1-3.4-fold) on trabecular compared to the pooled VPS-HA surface.

Conclusion
In conclusion, these findings show that VPS-HA surfaces with various porosities and HA-coating thicknesses similarly affect osteoblast and osteoclast responses, while trabecular surfaces enhance osteoblast responsiveness and inhibit osteoclast formation. These results might help to further improve early stability and reduce long-term loosening risk in uncemented knee replacements.

INTRODUCTION

Total knee arthroplasty is one of the most commonly performed elective procedures worldwide, with approximately 1.5 million surgeries performed annually worldwide. *[49]* While cemented total knee replacements (TKR) are predominantly used, their long-term durability is a concern, particularly in younger, more active, and heavier patients who place greater mechanical stress on implants. *[49]* With total knee arthroplasty demand projected to grow 43–68% by 2050, and aseptic loosening as the leading cause of failure, uncemented TKR relying on biological fixation is considered a promising solution. *[49]*

Innovations in uncemented TKA focus on surface modifications to enhance biocompatibility, osteoinduction, and osseointegration. *[11]* Modifying surface morphology (i.e., roughness, porosity, pore size, interconnectivity), with or without coatings such as hydroxyapatite (HA), strongly influence osteoblast adhesion, proliferation, and differentiation. *[11, 50–52]* These advancements aim to enhance implant-bone fixation, reduce the risk of aseptic loosening, and improve implant longevity.

Radiostereometric analysis (RSA) is a precise imaging method used to measure implant migration in vivo. *[53]* RSA studies show that early migration within two years predicts late failure by aseptic loosening (5–15 years), supporting the theory that insufficient early bone ingrowth—due to fibrous membrane formation or osteoclast-induced bone resorption—is a key factor in implant loosening. *[38, 53]* Despite its importance for net bone gain, the role of osteoblast-released factors in regulating osteoclast formation and bone resorption remains underexplored. *[50, 51, 54]* In uncemented TKA, relatively new surface technologies include highly porous trabecular surfaces and vacuum-plasma-sprayed (VPS) titanium (Ti), often combined with hydroxyapatite (HA) coating. These technologies are applied in pockets (i.e., impressed areas on the implant), with pocket depth determining the thickness of the applied surface modification. Pocket depth itself varies along a component based on the required cross-sectional implant thickness to ensure adequate mechanical strength. *[55]* Previous RSA studies suggest that trabecular surfaces stabilize faster than porous HA-coated surfaces, potentially improving initial fixation, but mid- to long-term data on aseptic loosening risks are lacking due to their relatively recent introduction in clinical use.*[18, 56]*

The aim of this study was to evaluate the osteoblast response to trabecular titanium–aluminum–vanadium (Ti6Al4V) surfaces and hydroxyapatite (HA)-coated vacuum-plasma-sprayed (VPS) titanium (Ti) surfaces with varying pocket depths, porosity, and HA-coating thicknesses: 350 µm pocket depth with 20–40% porosity and 60 µm HA (VPS350-HA), 400 µm pocket depth with 30–70% porosity and 90 µm HA (VPS400-HA), and 1000 µm pocket depth with 30–70% porosity and 80 µm HA (VPS1000-HA). Trabecular Ti surfaces were applied to Ti6Al4V alloy discs,

while HA-coated VPS Ti surfaces were applied to cobalt–chromium–molybdenum (CoCrMo) alloy discs.

Both Ti6Al4V and CoCrMo alloys are commonly used in uncemented TKR in clinical practice, with different pocket depths applied based on implant location and mechanical requirements. *[11, 18]* Human primary osteoblasts were seeded on the trabecular Ti6Al4V or HA-coated VPS Ti surfaces and cultured for up to 29 days to assess seeding efficiency, viability, metabolic activity, alkaline phosphatase activity, and the effect of osteoblast-released factors in conditioned medium (CM) harvested during the last 4 days of culture on osteoclast formation. Comparisons were first made between the individual VPS-HA groups and subsequently pooled to compare with the trabecular surface. Our findings indicated a differential response of osteoblasts to HA-coated VPS surfaces on Ti with various porosity compared to trabecular-Ti surface.

MATERIALS AND METHODS

This study complies with the Preferred Reporting Items for Laboratory studies in Endodontology (PRILE) guidelines, and includes the PRILE checklist (**Table S-1**). *[57]*

Scaffolds and Surfaces

A total of 48 disc-shaped scaffolds (25 mm diameter, 3.5 mm height) were used, consisting of a base disc with distinct upper surfaces. Of these, 36 CoCrMo alloy discs featured a VPS of commercially pure Ti, coated with HA, and were divided into three groups: VPS350-HA (300 µm Ti-layer, 20–40% porosity, 60 µm HA), VPS400-HA (400 µm Ti-layer, 30–70% porosity, 90 µm HA), and VPS1000-HA (1000 µm Ti-layer, 30–70% porosity, 80 µm HA). These VPS-HA modifications are based on the "MectaGrip" technology *[58]* of Medacta International (Castel San Pietro, Switzerland), which is used in the uncemented Global Medacta Knee TKR. The remaining 12 scaffolds consisted of Ti6Al4V alloy discs with a 1000 µm 3D-printed trabecular Ti6Al4V honeycomb structure, corresponding to Medacta Internationals "3D-Metal" technology *[58]* which is being considered for use in their uncemented TKR. All scaffolds were provided by Medacta International, and their characteristics are summarized in **Table 1**. All scaffolds were sterilized using gamma radiation followed by UV sterilization prior to use.

Table 1. Characterizations of the different scaffolds, including the ground disc and surface.

	Pooled VPS-HA			Trabecular
Scaffold name	**VPS350-HA**	**VPS400-HA**	**VPS1000-HA**	
Ground disc				
Alloy	CoCrMo	CoCrMo	CoCrMo	Ti6Al4V
Surface				
Material/alloy	Ti	Ti	Ti	Ti6Al4V
Thickness, µm	350	400	1000	1000
Porosity, %	20-40	30-70	30-70	65-80
Pore void space, µm	100-350	100-350	100-350	450-900
Interconnecting pores	No	No	No	yes
Coating	HA	HA	HA	-
Coating thickness, µm	60	90	80	-

VPS vacuum plasma-spray; CoCrMo, cobalt–chromium–molybdenum; Ti6Al4V, titanium–aluminum–vanadium, Ti Titanium, HA Hydroxyapatite

Cell culture and seeding onto the scaffolds

Commercially obtained primary osteoblasts (passage 2) isolated from the femoral heads of 3 healthy female donors (aged 64–85 years) were used (Catalogue CC-12720; PromoCell, Huissen, The Netherlands). Osteoblasts were grown and maintained in phenol red-free Dulbecco's Modified Eagle Medium (DMEM) supplemented with 5% human platelet lysate (Sanquin, Amsterdam, The Netherlands), 1% penicillin/streptomycin/fungizone (PSF; Sigma-Aldrich, Saint Louis, MO, USA), and 0.2% heparin (5,000 IU/ml; LEO Pharma A/S, Ballerup, Denmark). They were maintained in a humidified incubator with 5% CO_2 in air at 37°C until they reached approximately 80% confluency, yielding a minimum of 5×10^6 cells per donor. At the time of, the mean passage number was 5 (range: 4–7). Cells were detached from culture flasks using 0.25% trypsin (Gibco, Invitrogen, Waltham, MA, USA), counted using a Muse Cell Analyzer (Merck, Burlington, MA, USA), and resuspended in culture medium with additives. Ten 100 µl drops of the cell suspension were carefully spread all over the scaffolds surface at 1.0×10^5 cells/cm^2 scaffold (VPS-Ti-HA of 5.0 cm^2; trabecular 25.0 cm^2) in 6-well culture plates (Greiner, Bio-One, Alphen aan de Rijn, The Netherlands). Attachment was allowed for 30 min, and osteogenic medium was added to cell/scaffold constructs. The osteogenic culture medium was composed of phenol red-free DMEM, 2% human platelet lysate, 1% PSF, 1% ascorbic acid (50 µg/ml), β-glycerophosphate (10 nM), and 0.2% heparin (5,000 IU/ml), and was refreshed twice a week. To obtain osteoblast-CM, the medium was changed to phenol red-free α-Minimum Essential Medium (α-MEM; Gibco, Life Technologies, Waltham, MA, USA), 10% fetal bovine serum (FBS; Gibco, Life Technologies), 1% PSF, 1% ascorbic acid, and 1% BGP at

day 25, and collected at day 29. This osteoblast-CM was used in experiments to compare the effect of soluble factors produced by osteoblasts cultured on the different scaffold surfaces on osteoclast formation.

Osteoblast Seeding Efficiency

To determine the number of cells that attached to the different scaffolds, seeding efficiency and viability were assessed after 16–24 hours. All scaffolds were transferred to new 6-well plates, and the cells remaining in the original plates were counted after trypsinization using a Muse Cell Analyzer (Merck, Burlington, MA, USA). Seeding efficiency was calculated by taking the number of initially seeded cells, subtracting the cells that attached to the original plate, dividing by the total cells attached to the scaffold, and multiplying by 100 to obtain a percentage. Data were obtained from three donors (n = 3), with experiments in duplicate.

Attachment of osteoblasts

To assure that cells were attached to the different scaffolds after 4 days, a total of three scanning electron microscope (XL20, Fei Company, Eindhoven, The Netherlands) images were carried from three replicates of each surface type. Cells were fixed with 4% formaldehyde, washed twice with PBS, dehydrated using a graded ethanol series (50%, 70%, 80%, 90%, 96%, and 100%), and air-dried overnight. To visualize the cells on the scaffolds, the discs were sputter-coated with gold, and examined using an accelerating voltage of 15 kV. Images were captured at randomly selected regions at 5000× magnification. An XFlash 6-30 Energy Dispersive Spectroscopy (EDS) system (Bruker, Billerica, Massachusetts, United States) was employed to detect carbon and confirm cells in contrast to scaffold material.

Metabolic activity of osteoblasts

The cell metabolic activity of osteoblasts was assessed using AlamarBlue® Cell Viability Reagent (Invitrogen, Rockford, IL, USA) at day 4 and 29. Cells were incubated with AlamarBlue® reagent in culture medium (1:10, v/v) in a humidified incubator with 5% CO_2 in air at 37°C for 4 h. After incubation, 200 µl of supernatant was transferred into a 96-well plate (Company, City, Country). The absorbance was measured at 530 nm using a Synergy HT® spectrophotometer (BioTek instruments, Winooski, VT, USA). Data were obtained from three donors (n = 3), with experiments in duplicate.

Alkaline phosphatase activity

Alkaline phosphatase (ALP) activity was determined to assess the osteoblastic phenotype of the cells cultured on different surface on day 4, 7, 11, 15, 19, 22, and 25. Cells were lysed with 1.5 ml milli-Q water, and stored at -20°C until use. 4-Nitrophenyl phosphate disodium salt (Merck, City, Country) at pH 10.3 was

used as a substrate for ALP, according to Lowry's method.*[59]* The absorbance was measured at 405 nm using a Synergy HT® spectrophotometer (BioTek Instruments, Santa Clara, United states). ALP activity was expressed as nmol/µg cellular protein. BCA Protein Assay Reagent Kit (Pierce™) was utilized to measure the amount of protein. The absorbance was read at 540 nm with a Syngergy HT® spectrophotometer. Data were obtained from three donors (n = 3), with experiments in duplicate.

Qualification of extracellular matrix mineralization

Mineral deposition in the extracellular matrix was visualized using tetracycline hydrochloride (TC)-staining.*[60]* A TC (Sigma-Aldrich) solution [10 mg/mL] was prepared in PBS and administered to the cells at a final concentration of 20 µg/mL in the culture medium, followed by overnight incubation on days 7, 14, and 21. After 29 days, all discs were fixed in 4% formaldehyde for 15 minutes and washed with PBS. Newly deposited mineralization was visualized using a Nikon AXR laser confocal microscope (Nikon Europe, Amstelveen, Netherlands), using a 405 nm laser for excitation and recording emission between 420-470 nm, as described before. *[60]* Overviews were captured using a Plan Apo λD 4x objective, and 3 random locations per disc were recorded using a Plan Apo λD 10x objective, with consistent acquisition settings. Linear adjustments to brightness and contrast were made using ImageJ *[61]*, and data were presented qualitatively with representative images.

CD14+ Monocyte Isolation

The number and differentiation of osteoclasts in response to osteoblast-CM were evaluated after culturing isolated CD14+ monocytes for 7, 14, and 21 days. CD14+ monocytes were obtained from a buffy coat containing peripheral blood mononuclear cells from one patient (Sanquin, Amsterdam, The Netherlands). The isolation of CD14+ monocytes was performed using Lymphoprep density gradient centrifugation (Alere Technologies, Oslo, Norway), a manual magnetic-assisted cell sorter (MACS), and iron-conjugated CD14 antibodies (Miltenyi Biotec, Bergisch Gladbach, Germany) to isolate CD14+ monocytes, as previously described. *[62]* The isolated CD14+ monocytes (10×10^3 cells/well) were seeded into 41 wells per plate across three 96-well plates (Greiner Bio-One), totaling 123 wells. For each plate, 5 wells were designated as the control group, and 9 wells (3 per osteoblast donor) were assigned to each surface modification from the osteoblast experiments. During the first 3 days, each well received 0.12 mL of culture medium (α-MEM, 10% FBS, 1% PSF) supplemented with 25 ng/mL Macrophage colony-stimulating factor (M-CSF; R&D Systems). After this period, the medium was replaced with group-specific formulations for the remaining 21 days. The control group received medium containing 10 ng/mL M-CSF and 5 ng/mL receptor activator of nuclear factor kappa-B ligand (RANKL; R&D Systems). In contrast, the wells assigned to surface modifications received a 1:1 ratio of culture medium (with 20 ng/mL

M-CSF and 10 ng/mL RANKL) and osteoblast-CM collected from the 3 osteoblast donors on day 29 of the experiment. Thus, between days 3 and 21, all wells received the same concentrations of M-CSF and RANKL. Media were replaced twice a week, and cells were incubated at 37°C and 5% CO2.

Osteoclast resorptive activity

The differentiation of the osteoclasts was quantified by measuring the extracellular secretion of Tartrate-resistant acid phosphatase (TRAP) during osteoclast culture. Supernatants were collected, and TRAP was measured using a colorimetric assay. The samples were incubated with p-nitrophenyl phosphate (pNPP) as a substrate in an acidic buffer at 37°C for 1 hour. After the reaction, the conversion of pNPP into p-nitrophenol was halted using sodium hydroxide. The resulting color change was measured at 405 nm using a Synergy HT® spectrophotometer, with a reference positive control for comparison. TRAP activity was quantified by comparing the absorbance to a standard curve of p-nitrophenol and expressed as nanomoles of p-nitrophenol produced per microgram of extracellular protein. Data were obtained from three independent experiments (n = 3) in duplicate.

Osteoclastogenesis and formation

The CM from each donor was applied in triplicate wells per group. After 7, 14, and 21 days, all cells from a single 96-well plate were fixed with 4% formaldehyde (Sigma-Aldrich) and stained with Tartrate Resistant Acid Phosphatase (TRACP), using a Leukocyte Acid Phosphatase staining kit (Sigma-Aldrich), as described previously. *[63]* Diamidino-2-phenylindole dihydrochloride (DAPI; Thermo Fisher Scientific) was used to counterstain cell nuclei. Osteoclasts were identified by positive TRACP staining, counted and categorized based on the number of nuclei per cell: 3-5 nuclei, and more than 5 nuclei. Bright field and fluorescent microscopy (Leica, Wetzlar, Germany) were used to capture microscopic images (10× magnification) from 5 consistent areas in each well: one from the center, two from the left and right edges, and two from the top and bottom along the vertical midline. Data were obtained from three donors (n = 3), with experiments in triplicate.

Statistical analysis

The distribution of data across all experiments and groups was evaluated using quantile-quantile (Q-Q) plots and the Shapiro-Wilk test. All experiments, except for the osteoclast count experiment, exhibited highly skewed distributions. To approximate normality, a log-transformation was applied to the skewed data. This transformation enabled the calculation of the mean and the log-transformed 95% confidence intervals (CI), as previously recommended in the literature. *[64]* In case of normally distributed data, the mean and CI were calculated. Non-overlapping CIs indicate a significant difference, whereas overlapping CIs indicate non-significance. The log-transformation and data visualization were performed using

RStudio (version 4.0.3; RStudio, Boston, MA, USA). If no significant differences were found between the three VPS-HA modifications, their data were pooled into a single VPS-HA group for comparison against the trabecular surface. For the osteoclastogenesis and activation analyses, the number of osteoclasts and multinucleation were also compared to the control group to evaluate the baseline effects of osteoblast-CM on osteoclasts. Each experimental unit (n = 1) corresponds to an independent osteoblast donor. Within each experiment, replicates were conducted under identical conditions to ensure data consistency and reliability.

RESULTS

Cell viability and seeding efficiency of osteoblasts

The mean percentage of viable osteoblasts prior to seeding was comparable across all surfaces: VPS350-HA (90.0%, CI 87.7–92.3), VPS400-HA (87.8%, CI 85.1–90.5), VPS1000-HA (91.0%, CI 88.0–93.9), and trabecular (88.1%, CI 84.2–92.1). Similarly, seeding efficiency was consistent between surfaces, with VPS350-HA at 87.3% (CI 81.1–93.4), VPS400-HA at 91.7% (CI 88.9–94.5), VPS1000-HA at 91.9% (CI 88.3–95.6), and trabecular at 92.0% (CI 87.3–96.6). On day 4, SEM imaging (**Figure 1**) confirmed osteoblast attachment on all scaffolds, regardless of surface type, at three random locations per scaffold.

Osteoblast metabolic activity and proliferation

The mean metabolic activity and CIs, measured by relative absorbance log, were similar at both day 4 and day 29 across the VPS350-HA, VPS400-HA, and VPS1000-HA surfaces (**Table S-2**), allowing the data from the three types to be pooled for comparison with the trabecular Ti6Al4V surface. The trabecular surface exhibited significantly higher metabolic activity, with a 1.5-fold increase over pooled VPS-HA values at day 4 and a 2.7-fold increase at day 29 (**Figure 2**, **Table S-2**)

Alkaline phosphatase activity and qualification of mineralization

Mean ALP activity (log nmol/µg protein) and CIs were similar across VPS350-HA, VPS400-HA, and VPS1000-HA surfaces at all measured timepoints (**Table S-3**), allowing the data to be pooled for comparison with the trabecular Ti6Al4V surface. The trabecular Ti6Al4V surface consistently exhibited significantly higher ALP activity throughout the experiment, with increases ranging from 6.5- to 15.2-fold compared to the pooled VPS-HA surfaces (**Figure 3, Table S-3**). By day 29, all scaffolds across surface types exhibited fluorescence under laser confocal microscopy at 10x magnification and overview captures, confirming mineral deposition (green), which indicates that osteoblasts maintained their phenotype throughout the experiment (**Figure 1**). The fluorescence intensity observed on

the trabecular surface was lower compared to the VPS-HA surfaces, requiring adjustments to the contrast range (0-1500 to 150-200 lux) for enhancing visualization (**Figure 1**).

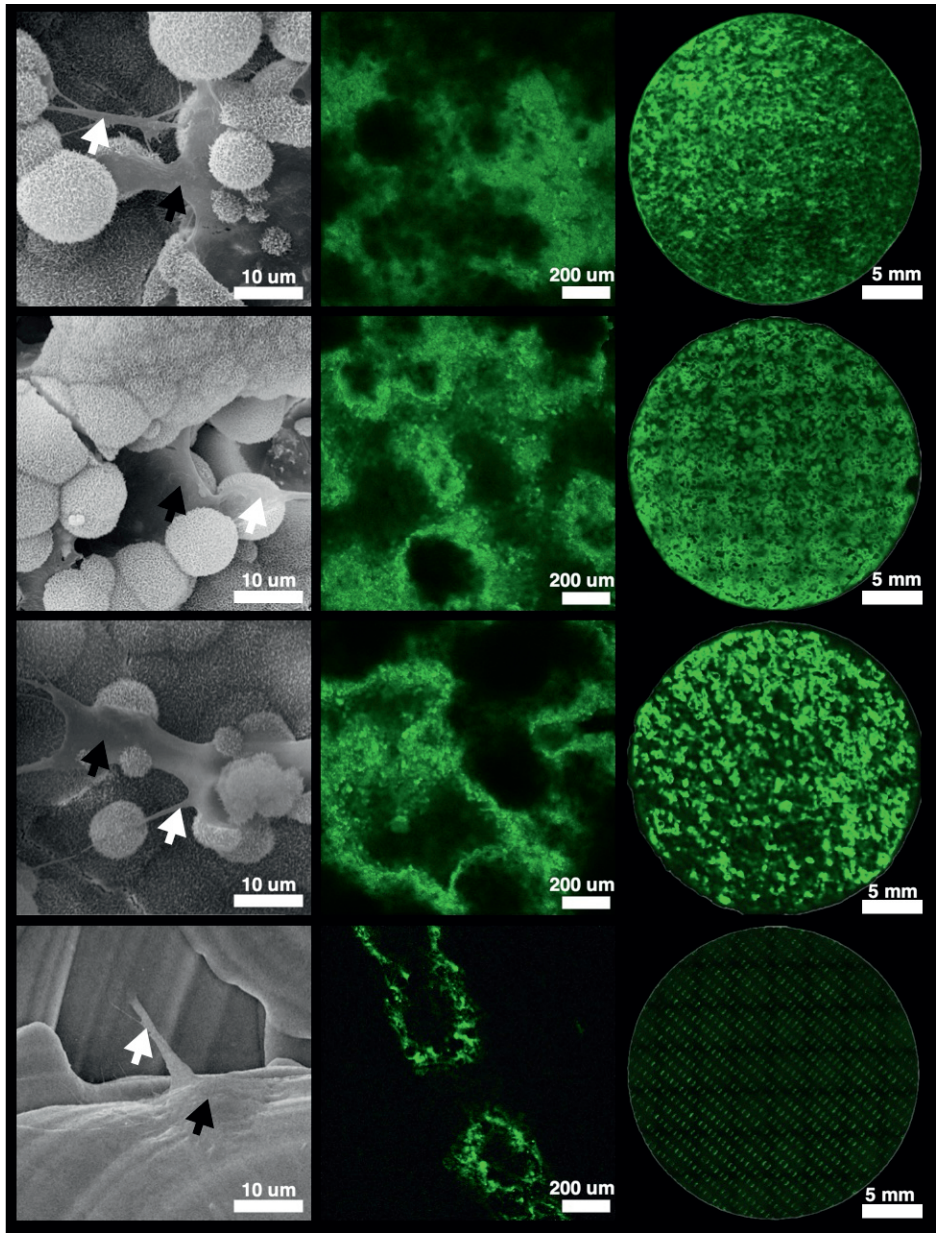


Figure 1. Scanning Electron Micrographs (SEM), laser confocal microscope single-view images at 10× magnification, and overview captures of mineralization patterns of osteoblast cultures on scaffold surfaces.

Scaffold rows (top to bottom): (1) VPS350-HA, (2) VPS400-HA, (3) VPS1000-HA, and (4) trabecular surface. **Left column:** SEM images showing scaffold surfaces on day 4. Black arrows indicate osteoblasts, and white arrows highlight filopodia interacting with the substrate. Energy Dispersive Spectroscopy confirmed that the observed material on the surfaces was of cellular origin. SEM settings: 20.00 kV accelerating voltage, ×5,000 magnification. **Middle column:** Laser confocal microscope images showing single-view fluorescent staining of mineral deposition by osteoblasts on day 29 using tetracycline hydrochloride. Tetracycline fluorescence was detected at 405 nm excitation, with emission recorded between 420–470 nm. **Right column:** Overview captures illustrating mineralization patterns across the entire scaffold surface on day 29. Fluorescent staining was achieved using tetracycline hydrochloride, which binds to newly deposited minerals, providing a precise visualization of active bone formation. Contrast ranges were set at 0–1500 lux for VPS-HA surfaces and 150–200 lux for trabecular surfaces to enhance visualization.

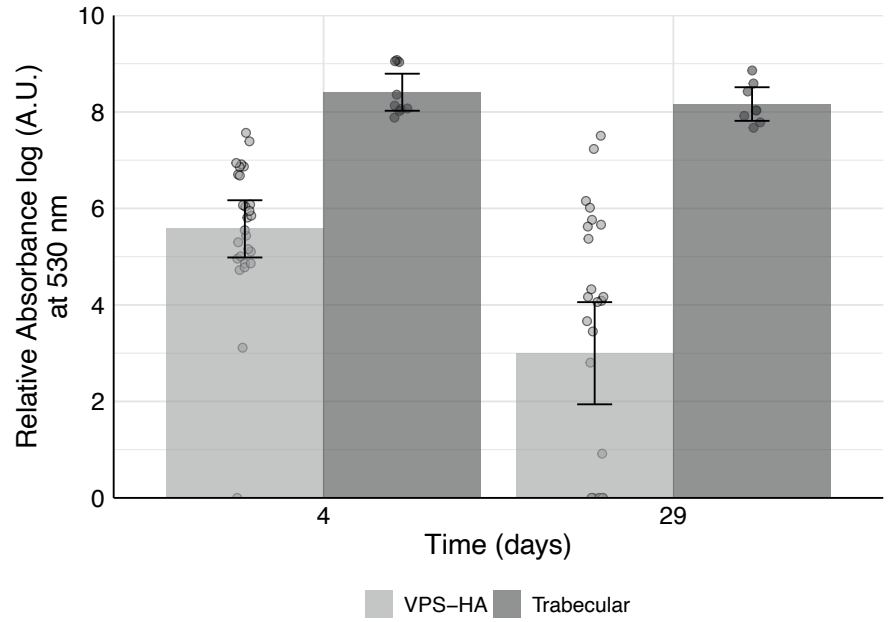


Figure 2. Metabolic activity and proliferation of human osteoblasts cultured on pooled VPS-HA (VPS350-HA, VPS400-HA, VPS1000-HA) and trabecular surfaces at days 4 and 29. Data from the three VPS-HA surfaces were pooled due to their comparable metabolic activity, with separate data presented in the supplemental file (**Table S-2**). The graph shows log-transformed data to account for distribution differences. Bars represent the mean absorbance (at 530 nm), while error bars indicate the 95% confidence intervals. Data points within the figure represent individual data values. Results were derived from three donors (n = 3), each performed in duplicate. The trabecular surface showed significantly higher absorbance at both day 4 and day 29 compared to the pooled VPS-HA surfaces.

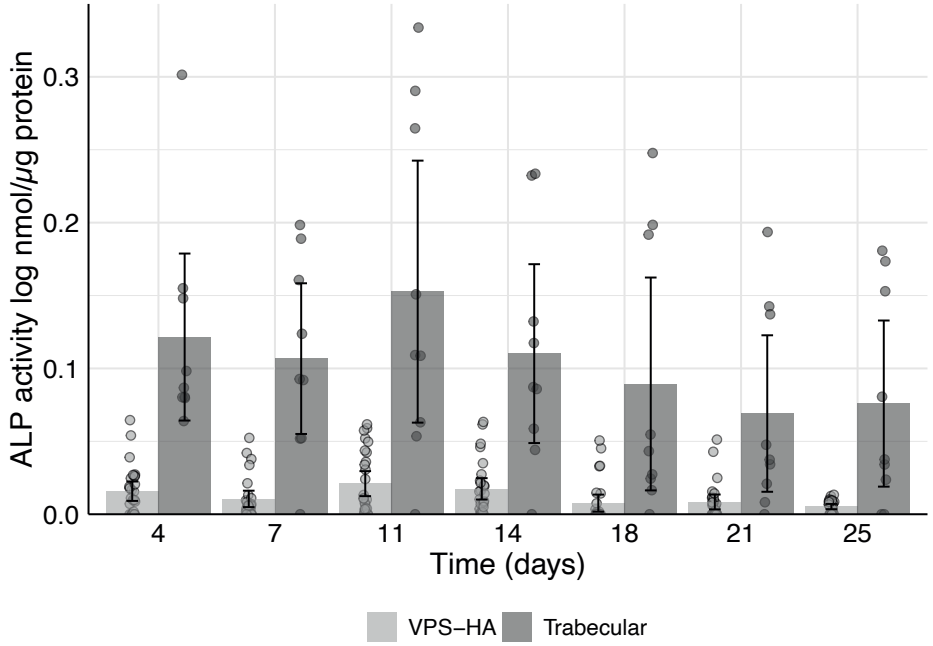


Figure 3. Alkaline phosphatase activity (ALP) of human osteoblasts cultured on pooled VPS-HA (VPS350-HA, VPS400-HA, VPS1000-HA) and trabecular surfaces. Data from the three VPS-HA surfaces were pooled due to their comparable ALP activity, with separate data provided in the supplemental file (**Table S-3**). Bars represent the mean log-transformed ALP activity to account for distribution differences, with error bars showing the 95% confidence intervals. Individual data points within the figure represent measurements from three donors (n = 3), each performed in duplicate. The trabecular surface demonstrated significantly higher ALP activity compared to the pooled VPS-HA surfaces, indicating enhanced osteoblast differentiation

Extracellular secreted tartrate-resistant acid phosphatase by osteoclasts

Osteoclasts cultured without osteoblast-CM (control) exhibited no detectable TRAP activity (log nmol/μg protein) at day 15, which increased to 0.09 (CI; 0.06–0.13) at day 19 and 0.34 (CI; 0.25–0.42) at day 21 (**Figure 4, Table S-4**). For the VPS350-HA, VPS400-HA, and VPS1000-HA surfaces, secreted TRAP activity values were comparable at days 15 and 19. However, at day 21, VPS350-HA exhibited significantly lower secreted TRAP activity (3.2- to 3.5-fold) compared to VPS400-HA and VPS1000-HA (**Table S-4**). The trabecular Ti6Al4V surface scaffolds demonstrated mean secreted TRAP activity levels comparable to those of the pooled VPS-HA surfaces throughout the experiment (**Figure 4, Table S-4**).

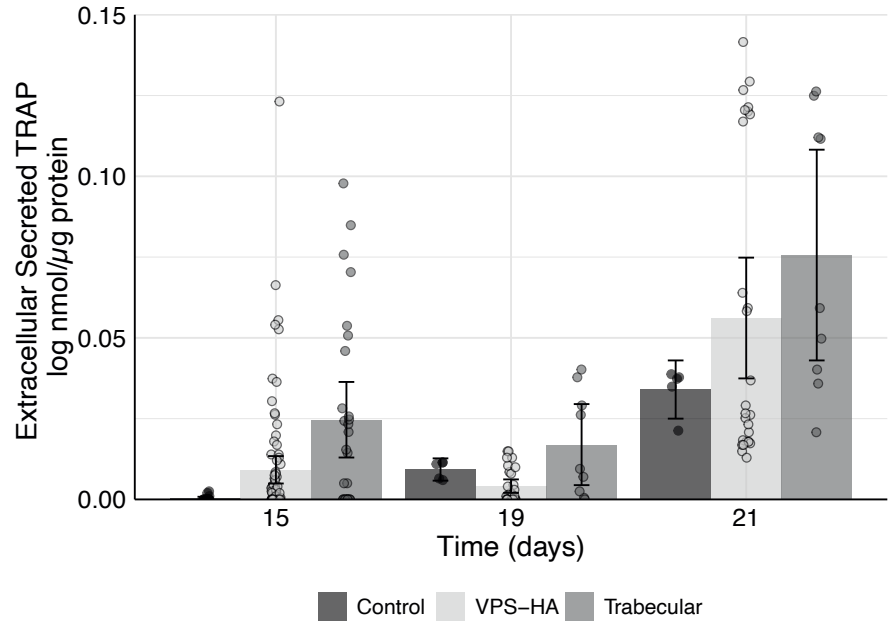
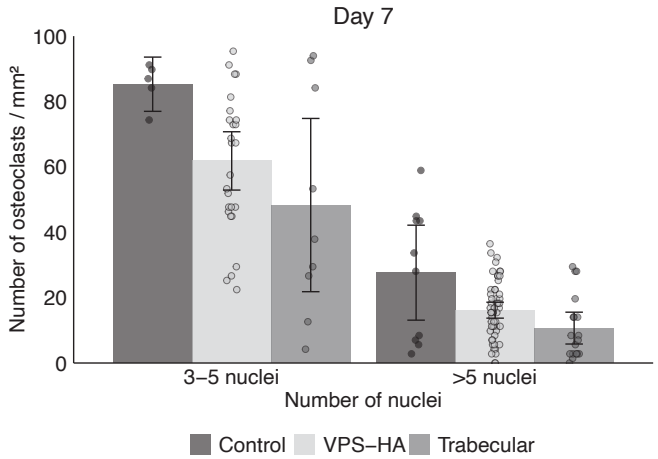
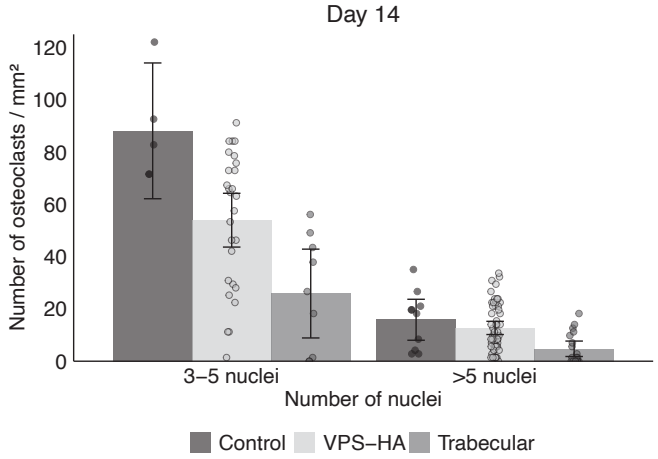


Figure 4. Extracellular secreted tartrate-resistant acid phosphatase (TRAP) activity of human osteoclasts cultured without conditioned medium (CM) (Control) and with CM of osteoblasts cultured on pooled VPS-HA (VPS350-HA, VPS400-HA, VPS1000-HA) and trabecular surfaces. Data from the three VPS-HA surfaces were pooled due to their comparable TRAP activity, with separate data provided in the supplemental file (**Table S-4**). Bars represent the mean log-transformed TRAP activity to account for distribution differences, with error bars showing the 95% confidence intervals. Individual data points within the figure represent measurements from three donors (n = 3), each performed in duplicate. Results indicate no significant differences in TRAP activity between groups. Osteoclasts cultured without osteoblast-CM (control) exhibited no detectable TRAP activity at day 15, but it increased over time, reaching the highest levels at day 21. The trabecular surface demonstrated comparable TRAP activity to the pooled VPS-HA surfaces throughout the experiment.

Osteoclastogenesis and formation

The mean number of osteoclasts per mm^2 cultured without osteoblast-CM (control) was consistently higher in the 3–5 nuclei category compared to the >5 nuclei category at day 7, 14 and 21 (**Figure 5, Table S-5**). This trend was also observed in the number of osteoclasts with osteoblast-CM from any other surface modification. Osteoclast counts per mm^2 were comparable across the VPS350-HA, VPS400-HA, and VPS1000-HA surfaces at each time point, regardless of nuclei category (**Table S-5**), allowing the data to be pooled for comparison with the trabecular Ti6Al4V surface (**Figure 5**). The pooled VPS-HA surfaces exhibited similar mean osteoclast counts per mm^2 across both nuclei categories compared to the trabecular surface at day 7 (**Figure 5, Table S-5**). However, at day 14, the VPS-HA surfaces showed significantly higher mean osteoclast counts, with 2.1-fold and 2.6-fold increases for the 3–5 and >5 nuclei categories, respectively. By day 21, these differences further increased to 3.1-fold and 3.4-fold, respectively, compared to the trabecular surface (**Figure 5, Table S-5**)





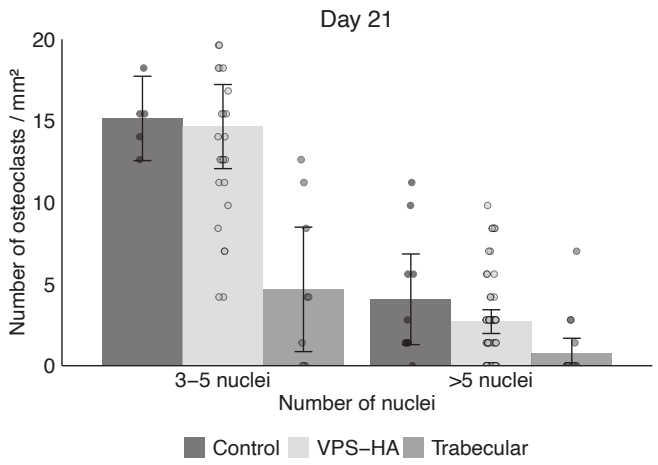


Figure 5. Osteoclastogenesis and formation of Tartrate-Resistant Acid Phosphatase (TRAP)-stained multinucleated human osteoclasts at Days 7, 14, and 21, cultured on polystyrene without conditioned medium (CM) (Control) and with CM from osteoblasts cultured on pooled VPS-HA (VPS350-HA, VPS400-HA, VPS1000-HA) and trabecular surfaces. Diamidino-2-phenylindole dihydrochloride (DAPI) was used to counterstain cell nuclei. Data from the three VPS-HA surfaces were pooled due to their comparable osteoclastogenic formation, with separate data provided in the supplemental file (Table S-5). Bars represent the mean number of osteoclasts per mm², with error bars showing the 95% confidence intervals. Individual data points within the figure represent measurements from three independent experiments (n = 3), each performed in triplicate. Results indicate that at Days 14 and 21, the trabecular surface exhibited a significantly lower number of osteoclasts compared to the pooled VPS-HA surfaces.

DISCUSSION

For successful rigid fixation in uncemented TKR, it is critical that bone formation by osteoblasts outweighs bone resorption by osteoclasts, ensuring a net gain in bone mass while minimizing resorptive activity. To model this, we used three human osteoblast donors with characteristics similar to typical TKR patients—older adults, predominantly women. These characteristics are particularly relevant, as aging significantly impacts osteosynthesis at the bone–implant interface, potentially influencing the success of uncemented TKR fixation. *[65]*The aim of this study was to evaluate human osteoblast differentiation and osteoclast activation mediated by CM from osteoblasts cultured on VPS-HA and trabecular surfaces.

Initially, we compared three VPS-HA surface types with varying porosity (20–40%, 30–70%, 30–70%) and HA-coating thickness (60, 90, and 80 µm, respectively), tailored to meet the depths of pockets on specific implant locations. Despite these differences, no significant variations were observed in osteoblast viability, seeding efficiency, metabolic activity, alkaline phosphatase activity, osteoclast-secreted TRAP, or osteoclast formation among the VPS-HA surfaces. This suggests that VPS-HA surface variations in porosity and HA-coating thickness minimally affect osteoblast and osteoclast behavior in these conditions, allowing data from the three surfaces to be pooled for comparison with the trabecular surface.

The comparability between the VPS-HA surfaces may result from the pore-filling effect of HA-coating application. Borsari et al. studied MG-63 osteosarcoma proliferation and differentiation on VPS-Ti scaffolds with varying porosities, both with and without HA coatings. *[51]* They found that HA coatings reduced porosity by 4- to 6-fold and concluded that HA coatings synergistically enhance cellular responses only when applied to surfaces with lower roughness. *[51]* Further, all scaffolds, regardless of porosity and coating, exhibited similar levels of differentiation, indicated by ALP activity and C-terminal type I procollagen (PICP). *[51]* Similarly, in our study, the HA coatings may have masked surface variations, resulting in similar osteoblast and osteoclast responses across the VPS-HA surfaces.

Nevertheless, HA-coatings are widely recognized for improving implant stability, as evidenced by reduced migration in RSA studies, and enhancing durability in uncemented TKR. *[66, 67]* The HA-coating thicknesses in the current study (60–90 µm) align with the optimal range (70–90 µm) reported for osseointegration. *[68]* In orthopedic surgery, however, thinner rather than thicker HA coatings are generally preferred due to concerns about coating fatigue, instability, and wear, which may compromise long-term implant performance. *[66, 69]*

Compared to VPS-HA surfaces, the trabecular surface exhibited significantly higher osteoblast metabolic activity and differentiation (ALP activity) throughout the experiment. Research shows that a minimum pore size of 300 µm is required to enhance osseointegration effectively, with osteoblasts growth occurring best in pore sizes of 600 µm diameter, rather than other diameters in the 300-1000 µm range. *[52, 70]* In our study, the trabecular surface features pores ranging from 450 to 900 µm, with the sizes varying throughout the interconnected pore network to facilitate cell attachment, migration, vascularization, and nutrient exchange, while also reducing the risk of growth arrest, making it particularly advantageous for early fixation and long-term stability. *[70, 71]* This structural advantage may also have contributed to the observed reduction in osteoclast multinucleation and formation, potentially through osteoblast-CM containing factors that suppressed resorption and promoted bone formation.

These findings align with a large RSA meta-analysis of 4,706 TKRs, which demonstrated superior early stability of trabecular and HA-coated implants compared to uncoated and porous-surfaced implants. *[67]*A long-term Dutch registry study reported a 10-year revision rate for aseptic loosening of 0.2% (CI 0.0–0.4) across 1,140 HA-coated TKR systems, encompassing multiple implant designs. *[56]* Trabecular implants were not included due to insufficient sample size. *[56]* The uncemented Global Medacta Knee TKR with 'MectaGrip' *[58]* (VPS-HA) surface technology has been used 1,934 times in Australia, as documented in the 2024 annual AOANJRR registry report. *[72]* Its 10-year revision rate for any reason is 5.8% (CI 4.4–7.6), exceeding the ODEP 10-year benchmark of 5.0%. *[27, 72]* This rate includes revisions for reasons beyond aseptic loosening. Unfortunately, the specific trabecular "3D-metal" technique has not yet been implemented for uncemented TKR by Medacta, and therefore no revision rates specific to this implant are currently available. However, other uncemented TKR implants featuring a similar trabecular surface design, such as the NexGen Trabecular Metal, have shown promising results. According to a Finnish registry study, the NexGen Trabecular Metal demonstrated a 7-year revision rate for any reason of 3.0% (CI 2.0–4.0) and 0.0% (CI 0.0–1.0) for aseptic loosening. *[73]* Regarding the Global Medacta Knee with 'MectaGrip' *[58]* (VPS-HA) surface technology, further clinical research into the failure mechanisms is required, ideally through RSA and survival studies. Such studies should ideally precede widespread clinical use to minimize the risk of unnecessary revisions.

In this study, all four surface groups demonstrated mineralization at day 29, shown by TC-staining; however, the fluorescence intensity was lower on the trabecular surface compared to the VPS-HA surfaces (**Figure 1**). This difference could be due to actual variations in mineralization, the inability of the laser confocal microscope to detect fluorescence from deeper pores in the trabecular structure, or the possibility of TC binding to the HA coating rather than newly formed minerals. Despite this, slower mineralization is unlikely to explain the findings, as previous RSA studies have shown earlier stabilization of trabecular-surfaced implants compared to other surface modifications. *[67]* In an attempt to ensure accurate visualization of mineralization, we used a TC-staining, as a previous study reported it to directly bind to newly deposited minerals, unlike other methods such as alizarin-red staining, which can stain pre-existing HA coatings or other matrix components. *[60, 74]* This approach enhances confidence that the observed fluorescence reflects active bone formation across the different surface types. *[60]*

Osteoclast differentiation and activity, as indicated by secreted TRAP levels in the supernatant, did not significantly differ between VPS-HA surfaces, nor between the pooled VPS-HA group and the trabecular surface in this study. TRAP secretion is a well-established marker of resorptive behavior in osteoclasts. However, Kirstein et al. demonstrated that a mineralized substrate is essential for the full activation and resorptive response of osteoclasts. *[75]* In our study, osteoclasts were cultured on polystyrene, which lacks a mineralized substrate and likely inhibited their resorptive response. This limitation is underscored by the observation that, despite similar secreted TRAP levels across surfaces, the osteoclast count was significantly lower on the trabecular surface compared to the pooled VPS-HA surfaces. This difference could be due to non-measured osteoblast-derived factors present in the osteoblast-CM, as osteoblasts are known to secrete factors that modulate osteoclast behavior beyond the effects of RANKL and M-CSF alone. *[76]*

This study has several limitations. First, the base alloys differed between groups (CoCrMo vs. Ti6Al4V). While cobalt ions are known to negatively impact osteoblast behavior *[77]*, their release is unlikely within such a short study duration. Moreover, CoCrMo alloys are widely used clinically, accounting for 47–96% of components in the Dutch Arthroplasty Registry, which justifies the clinically relevant comparison. *[5]* Second, the number of seeded osteoblasts varied due to the larger surface area of the trabecular surface, which may have influenced the results. However, in clinical applications, trabecular implants also provide greater surface area and bone contact, aligning with the comparisons made in this study. Third, meaningful statistical quantification of osteoblast attachment via SEM imaging or matrix deposition through laser confocal microscopy was not feasible due to the significant geographic differences among the surface modifications. However, the primary focus was to confirm the presence of mineralization across all surfaces,

ensuring that the osteoblast-CM contained osteoblast-derived factors necessary to provide a consistent baseline for the subsequent osteoclast experiments.

CONCLUSION

This study demonstrates that variations in VPS Ti surface porosity and HA-coating thickness have minimal impact on osteoblast differentiation and osteoclast activation. Conversely, the findings revealed that the trabecular Ti6Al4V surface provides a more favorable in-vitro environment than the VPS-HA surfaces, enhancing osteoblast differentiation and reducing osteoclast multinucleation, indicating a shift toward bone formation over resorption. These findings highlight the potential advantages of trabecular surfaces in promoting early implant stability and reducing long-term aseptic loosening risks in uncemented TKRs. Nonetheless, further research is required to confirm these in-vitro observations and assess their clinical implications in uncemented TKR applications.

SUPPLEMENTAL MATERIAL

Table S-1. PRILE 2021 checklist of items to be included when reporting laboratory studies in Endodontology.

Topic	Checklist item	Page number
Title	The Title must identify the study as being laboratory-based.	1
	The area/field of interest must be provided (briefly) in the Title	1
Keywords	At least two keywords related to the subject	3
Abstract	The rationale/justification of what the investigation contributes to the literature and/or addresses a gap in knowledge must be provided	2, 3
	The aim/objectives of the investigation must be provided	2, 3
	The body of the Abstract must describe the materials and methods used in the investigation and include information on data management and statistical analysis	2, 3
	The body of the Abstract must describe the most significant scientific results for all experimental and control groups	2, 3
	The main conclusion(s) of the study must be provided	2, 3
Introduction	A background summary of the scientific investigation with relevant information must be provided	4, 5
	The aim(s), purpose(s) or hypothesis(es) of an investigation must be provided ensuring they align with the methods and results	4, 5
Materials and Methods	A clear ethics statement must be described	19
	When harvesting cells and tissues for research, all the legal, ethical, and welfare rights of the subjects must be described	6, 7
	The use of reference samples must be included, as well as negative and positive control samples, and the adequacy of the sample size justified	8
	Sufficient information about the materials used in the study must be provided to enable it to be replicated	6, 27
	The use of categories must be defined	11, 28
	The numbers of replicated identical samples must be described within each test group.	6, 7
	The details of all the sterilization, disinfection, and handling conditions must be provided, if relevant.	6, 7, 8
	The process of randomization and allocation concealment, including who generated the random allocation sequence must be provided.	n/a
	The process of blinding the operator who is conducting the experiment must be provided.	n/a
	Information on data management and analysis including the statistical tests and software used must be provided.	11, 12

Table S-1. Continued

Topic	Checklist item	Page number
Results	The estimated effect and its precision for all the objective (primary and secondary) for each group including controls is provided.	12-14
	Information on the loss of samples during experimentation and the reasons must be provided.	n/a
	All the statistical results, including all comparisons between groups must be provided.	12-14
Topic	Checklist item	Page number
Discussion	The relevant literature and status of the hypothesis must be described	14-18
	The true significance of the investigation must be described	14-18
	The strength(s) of the study must be described	14-18
	The limitations of the study must be described	17, 18
	The implications for future research must be described	17, 18
Conclusion	The rationale for the conclusion(s) must be provided.	18
	Explicit conclusion(s) must be provided, i.e. the main 'takeaway' lessons	18
Funding and support	Sources of funding and other support (such as supply of drugs, equipment) as well as the role of funders must be acknowledged and described	19
Conflicts of interest	An explicit statement on conflicts of interest must be provided	19
Quality of images	Details of the relevant equipment, software and settings used to acquire the image(s) must be described in the text or legend	8, 9
	If an image(s) is included in the manuscript, the reason why the image(s) was acquired and why it is included must be provided in the text	n/a
	The circumstances (conditions) under which the image(s) were viewed and evaluated must be provided in the text	8, 9
	The resolution and any magnification of the image(s) or any modifications/ enhancements (e.g. brightness, image smoothing, staining) that were carried out must be described in the text or legend	8, 9
	An interpretation of the findings (meaning and implications) from the image (s) must be provided in the text	13, 14
	The legend associated with each image must describe clearly what the subject is and what specific feature(s) it illustrates	23-26
	Markers/labels must be used to identify the key information in the image(s) and defined in the legend	23
	If relevant, the legend of each image must include an explanation whether it is pre-experiment, intra-experiment or post-experiment and, if relevant, how images over time were standardized	N/a

Table S-2. Metabolic activity and proliferation of human osteoblasts cultured on VPS350-HA, VPS400-HA, VPS1000-HA and trabecular surfaces at days 4 and 29.

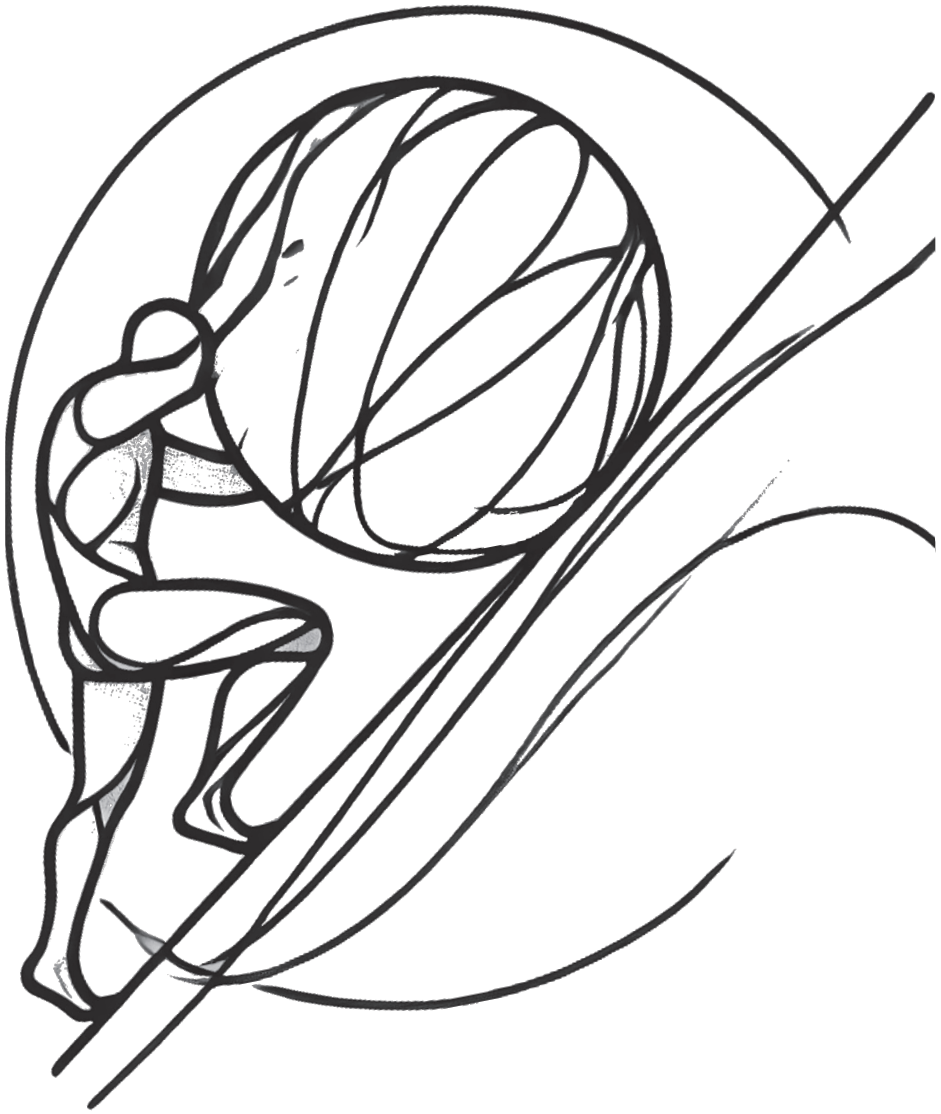
	Mean metabolic activity log (95%CI)	
	Time (day)	
Surfaces	**4**	**29**
VPS350-HA	5.04 (3.31; 6.77)	2.74 (0.63; 4.86)
VPS400-HA	6.12 (5.29; 6.95)	3.49 (0.99; 5.99)
VPS1000-HA	5.57 (5.07; 6.07)	2.77 (1.10; 4.44)
Pooled VPS-HA	5.58 (4.98; 6.17)	3.00 (1.94; 4.06)
Trabecular	8.41 (8.02; 8.80) [a]	8.16 (7.82; 8.51) [a]

Characteristics of surfaces are presented in Table 1. Statistically significant compared to other surfaces (a) based on overlap of 95%CI. VPS vacuum plasma-spray; Ha Hydroxyapatite; CI confidence interval

Table S-3. Alkaline phosphatase activity (ALP) of human osteoblasts cultured on VPS350-HA, VPS400-HA, VPS1000-HA and trabecular surfaces at different timepoints.

	Mean ALP activity log nmol/µg protein (95%CI) x 10^2						
	Time (day)						
Surfaces	**4**	**7**	**11**	**14**	**18**	**21**	**25**
VPS350-HA	0.12 (0.03; 0.23)	0.11 (0.01; 0.20)	0.18 (0.04; 0.31)	0.14 (0.02; 0.25)	0.05 (0.00; 0.17)	0.10 (0.00; 0.22)	0.05 (0.01; 0.09)
VPS400-HA	0.19 (0.03; 0.35)	0.09 (0.00; 0.19)	0.22 (0.04; 0.39)	0.25 (0.07; 0.43)	0.13 (0.00; 0.27)	0.10 (0.00; 0.23)	0.06 (0.02; 0.09)
VPS1000-HA	0.16 (0.24; 0.29) [a]	0.12 (0.00; 0.26)	0.23 (0.04; 0.43)	0.13 (0.01; 0.25)	0.05 (0.00; 0.13)	0.05 (0.01; 0.09)	0.05 (0.02; 0.09)
Pooled VPS-HA	0.16 (0.09; 0.22)	0.11 (0.05; 0.16)	0.21 (0.12; 0.30)	0.17 (0.10; 0.25)	0.08 (0.02; 0.13)	0.08 (0.03; 0.14)	0.05 (0.03; 0.07)
Trabecular	1.22 (0.64; 1.79) [a]	1.07 (0.55; 1.58) [a]	1.53 (0.63; 2.43) [a]	1.10 (0.49; 1.71) [a]	0.89 (0.16; 1.62) [a]	0.69 (0.15; 1.23) [a]	0.76 (0.19; 1.33) [a]

Characteristics of surfaces are presented in Table 1. Log-transformed data are shown as 10^2 in the table and 10^1 in Figure 3. Statistically significant compared to other surfaces (a) based on overlap of 95%CI. VPS vacuum plasma-spray; Ha Hydroxyapatite; CI confidence interval; ALP Alkaline phosphatase.



CHAPTER 3

6-month migration sufficient for evaluation of total knee replacements:

a systematic review and meta-analysis.

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ABSTRACT

Purpose

This updated meta-analysis evaluates the migration pattern of the tibial component of primary total knee replacements measured with radiostereometric analysis (RSA). We aimed to evaluate whether 6-month maximum total point motion (MTPM) values could be used instead of 1-year MTPM for RSA threshold testing and to present the pooled migration patterns for different implant designs that can be used as a benchmark.

Methods

The search included all published RSA studies on migration patterns of tibial components until 2023. Study groups were classified according to their prosthesis brand, fixation, and insert (PFI). Sub-analyses were performed to compare the mean tibial component migration patterns of different implant variables, stratified according to fixation.

Results

96 studies (43 new studies), including 197 study groups and 4,706 knees, were included. Most migration occurred within the first 6 postoperative months (126 study groups: mean 0.58 mm, 95% confidence interval [CI] 0.50–0.65), followed by minimal migration between 6 and 12 months (197 study groups: mean 0.04 mm, CI 0.03–0.06), irrespective of the fixation method used. Distinct migration patterns were observed among the different fixation methods. No differences were found in migration patterns among cemented components in any of the sub-group analyses conducted. For uncemented implants, trabecular metal surfaced components seemed to migrate less than porous-coated or uncoated components.

Conclusion

Based on the small difference between MTPM values at 6 months and 1 year, MTPM at 6 months could be used instead of MTPM at 1 year for RSA threshold testing. The pooled migration patterns can be used as benchmark for future evaluation of new implants and pave the way for defining fixation-specific RSA thresholds when combined with implant survival.

INTRODUCTION

Over the last few decades, total knee arthroplasty has increased globally, mainly attributable to demographic factors such as an aging population, escalating obesity rates, and enhanced access to medical healthcare [1]. As a direct consequence of this trend, national arthroplasty registries have reported a similar increased incidence of revisions, with aseptic loosening as one of the predominant causes [2-4]. In an effort to reduce the need for revisions, total knee replacements (TKR) are continuously being developed, occasionally introducing less favorable designs [5]. Global regulation of new devices through regulatory guidelines is inconsistent, with many countries having underdeveloped regulations that lack premarket testing or rely solely on manufacturers proving substantial equivalence to a legally marketed implant. These regulations do not guarantee high-quality evidence to ensure the safety, reliability, and quality of new medical devices [6-8].

To address the potential introduction of unfavorable designs, standardization of joint replacement screening has been proposed and endorsed by multiple studies as a crucial part of the evaluation of new prostheses [9-18]. Radiostereometric analysis (RSA) studies have established implant migration benchmarks and thresholds in the early postoperative period to identify TKRs with increased migration as a surrogate measure for increased risk of aseptic loosening [10,12]. It would be beneficial if previously published thresholds based on 1-year migration could be moved to 6 months postoperatively, given the minimal increase in migration after 6 months [19]. However, in light of the continuous advancements in implant technology and the increasing number of RSA studies, it is imperative to evaluate this proposal. Therefore, we aimed primarily to compare the pooled 6-month and 1-year maximum total point motion (MTPM) values to explore the applicability of the 6-month MTPM values for future RSA threshold testing. Secondarily we aimed to describe migration patterns of the different design features stratified by fixation.

MATERIAL AND METHODS

The reporting of this systematic review adheres to the standards of the updated Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Statement of 2020 [20]. This review serves as an update to the previous systematic review and meta-analysis published in 2018 [19]. The PRISMA checklist is itemized in **Table SM1** (see Supplementary data). This investigation was registered and embargoed in the Open Science Framework (OSF), a global study registry, accessible through the registration URL https://osf.io/96bnq/?view_only=0912275f5c364fffb3eec63921cf2925. During the study, there were protocol deviations, such as the decision not to use the software application “CADIMA” for screening purposes due to the time required for screening. As a

result, Excel (version 16.69.1, Microsoft Corp, Redmond, WA, USA [2022]) was utilized for screening.

Eligibility criteria

Studies were eligible for inclusion if they investigated the migration patterns of the tibial component through RSA in patients who underwent primary TKR. Unpublished studies, protocols, databases, or manuscripts were also considered eligible. Studies were included if they examined: (1) primary tibial components; (2) migration patterns of at least 2 MTPM measurements by RSA during the first 2 postoperative years. All included studies from the initial review were included [19]. Non-clinical studies (e.g., animal, phantom) and articles written in languages other than English, Dutch, or German were excluded. Multiple studies with the same patient cohorts remained eligible if they reported additional follow-ups for migration pattern measurements.

Search strategy

The literature search from the previous systematic review and meta-analysis [19] (up to July 2016) was updated by a medical librarian (JP) to ensure comprehensive retrieval of all relevant studies. Multiple medical bibliographic databases were searched, including PubMed, Embase, Web of Science, the Cochrane Library, and Google Scholar. Each bibliographic database was consulted on May 5, 2022 and December 28, 2022. The search targeted studies published between January 1, 2016 (slight overlap with prior search) and December 28,2022. The search strategy employed combinations of controlled vocabulary and free text terms that were associated with: (1) RSA, and (2) total joint arthroplasty. No differentiation between knee and hip arthroplasty was made, as some studies report on both. The full search strategies for all databases including utilized filters are detailed in **Table SM2** (see Supplementary data).

Study selection

After combining the references from the individual databases, duplicates were removed by using the software application CADIMA [21]. Automatically removed duplicates were double-checked by the first reviewer (RP). The merged references were transferred to Excel (version 16.69.1, Microsoft Corp, Armonk, NY, USA [2022]) for 2-stage screening, by 2 reviewers independently (RP, RHP). The screening was first based on the title and abstract, and, second, based on the full text. If the information in the abstract was insufficient or doubts existed, the study remained eligible for full-text screening. Any disagreement or uncertainty regarding study eligibility was resolved through consultation with a third reviewer (BP).

Data-collection process

Data from all newly included studies was collected by the first reviewer (RP) into an SPSS statistic database (version 27.0, IBM Corp, Armonk, NY, USA). No articles needed translation. Data from the initial meta-analysis was checked again by the first reviewer (RP), and the total database was independently checked by the second reviewer (RHP). Any missing or unclear information was obtained or confirmed by contacting the study investigators.

Data items

Data extracted from studies included migration in MTPM, and items regarding the study characteristics, patient demographics, RSA technique, and prosthesis characteristics. Details on extracted data items are presented in **Table 1**. In the case that a mean MTPM and corresponding SD were not reported, this was estimated from graphs by using the web application WebPlotDigitizer [22] or calculated from the reported median, interquartile range (IQR), or range by using an internationally accepted methodology [23]. MTPM data was considered at 6 weeks, 3 months, 6 months, 1 year, 2 years, 5 years, and 10 years postoperatively.

Statistics

A study group was defined as a group of patients in a study with the same prosthesis, fixation, and insert (PFI), according to the PFI methodology used in previously published meta-analyses [10,19]. Pooling of migration results at the PFI level was performed using random effects meta-analyses by using the maximum-likelihood estimator [24]. The pooled mean MTPM and associated 95% confidence interval (CI) was calculated, presented, and compared between 6 months and 1 year after stratification for the 3 main fixation types (i.e., cemented vs. uncemented without screws vs. uncemented with screws). This also allowed the calculation of the mean difference between time points and their CI. Additionally, the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles and the pooled mean of the MTPM means were determined up to 5-year follow-up and plotted separately for both cemented and uncemented implants. As part of the sub-analyses, the pooled 1-year MTPM and CI was calculated and presented by PFI at each time point (i.e., 6 weeks, 3 months, 6 months, 1 year, 2 years, 5 years, and 10 years). The 1-year MTPM was used for these analyses, as this was the most frequently reported value, which reduces the risk of potential reporting bias or bias by missing data. Finally, study groups of studies were categorized based on the groups' mean 1-year MTPM, according to the current RSA thresholds from 2012 [10] (1-year MTPM of < 0.5 mm [acceptable]; 0.5–1.6mm [at risk]; > 1.6 mm [unacceptable]). To address potential issues with multicollinearity, several analyses of uncemented implants were stratified by surface modifications when these groups were highly correlated with certain covariates. All statistical analyses were conducted using R

version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria) with the Metafor package (Maastricht University, Maastricht, Netherlands) [24].

Reporting bias assessment

The potential impact of publication bias and certainty of the results was evaluated by comparing the differences in MTPM values of certain implant characteristics (e.g., cruciate retaining [CR] and posterior stabilized [PS]) with the differences in revision rates for aseptic loosening of the same implant characteristics known from national registry reports.

Data sharing, funding, and disclosure

The data extraction of the RSA studies is available by contacting the corresponding author. Funding for the study was obtained from the author's institution. BP and JP were authors of the previous systematic review and meta-analysis[19]. EL, MD, and BP were part of an investigator team of multiple included studies. No author had any conflict of interest. Complete disclosure of interest forms according to ICMJE are available on the article page, doi: 10.2340/17453674.2023.24579

RESULTS

Inclusion of RSA studies

The literature search yielded 2,319 records, of which 810 were duplicates. From the remaining 1,509 records, 1,404 were excluded for such reasons as not being a clinical study (n = 322), not involving primary TKRs (n = 678), or not including RSA measurements (n = 404). An additional 2 records were excluded because the full text was not retrievable. After reviewing 103 reports for eligibility, a total of 57 reports were excluded for the reasons stated in the PRISMA flow diagram (**Figure 1**). The remaining 46 reports, related to 43 original studies published since 1 January 2016, were included [25-70]. The previous review included 63 reports, related to 53 original studies published before 2016, with their reference stated in the previous paper [19]. The current review includes 109 reports related to 96 studies, comprising 197 study groups and 4,706 knees.

From each study group, the median percentage of females was 62% (medians ranging from 30–100%), the median age was 68 years (medians ranging from 54–77 years), and the median percentage of osteoarthritis was 100% (medians ranging from 0–100%). Tibial components were fixated with cement without screw-fixation in 128, cement with screw-fixation in 1, uncemented without screw-fixation in 51, and uncemented with screw-fixation in 17 study groups. An overall breakdown of the number of study groups and knees for the 3 main fixation types for each follow-up moment is detailed in **Table 2**.

The pooled mean MTPM of all tibial components was at 1 month 0.39 mm (CI 0.33–0.44, 3 months 0.44 mm (CI 0.40–0.49), 6 months 0.58 mm (CI 0.50–0.65), 1 year 0.55 mm (CI 0.50–0.60), 2 years 0.60 mm (CI 0.54–0.65), 5 years 0.68 mm (CI 0.57–0.80), and 10 years 0.72 mm (CI 0.49–0.96).

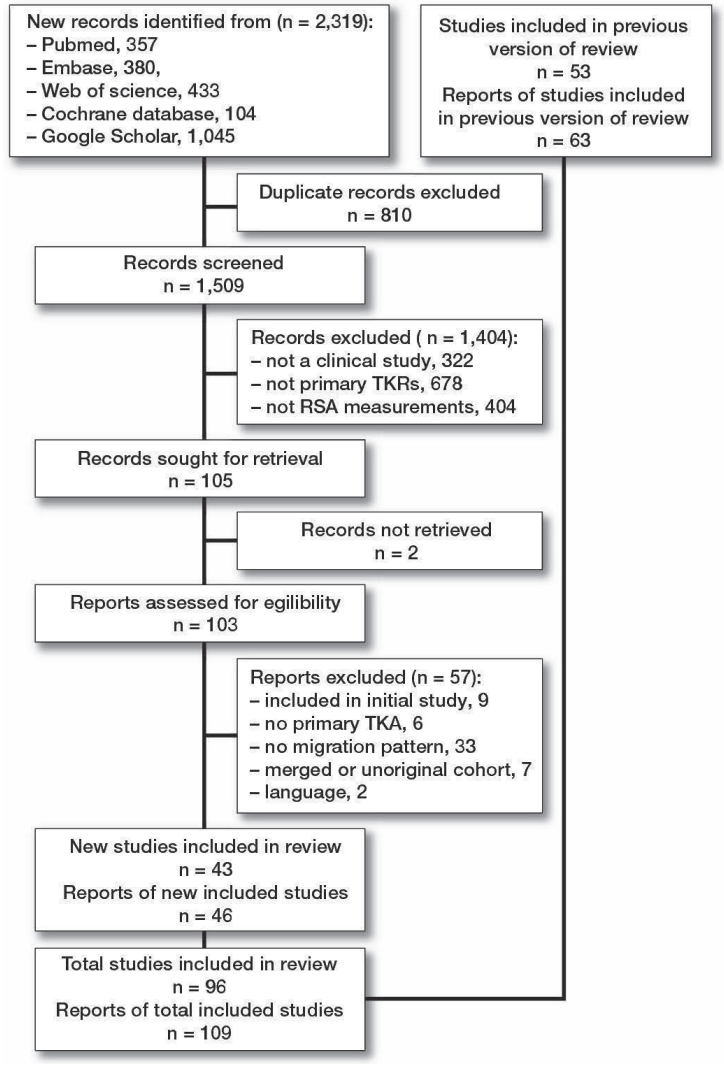


Figure 1. Flow diagram of articles screened, selected, and included in the systematic review and meta-analysis.

Table 1. Pooled mean 6-month and 1-year MTPM (mm) (95%CI) for cemented and uncemented without screw-fixation tibial components for different variables.

	Cemented		Uncemented	
	6-months	**1-year**	**6-months**	**1-year**
Decades				
80s	0.60 (0.32; 0.88)	0.71 (0.45; 0.97)	1.33 (1.03; 1.64)	1.27 (0.92; 1.62)
90s	0.50 (0.17; 0.84)	0.47 (0.37; 0.58)	1.55 (1.24; 1.86)	1.58 (1.26; 1.89)
00s	0.33 (0.25; 0.41)	0.39 (0.33; 0.46)	1.06 (0.57; 1.54)	0.91 (0.58; 1.24)
10s	0.38 (0.30; 0.46)	0.47 (0.39; 0.55)	0.85 (0.63; 1.06)	0.91 (0.70; 1.12)
Surface modification				
Trabecular metal	n/a	n/a	0.77 (0.56; 0.98)	0.74 (0.56; 0.93)
Hydroxyapatite	n/a	n/a	1.27 (0.71; 1.83)	1.15 (0.71; 1.58)
Porous coating	n/a	n/a	1.51 (1.22; 1.79)	1.46 (1.20; 1.73)
Uncoated	n/a	n/a	1.37 (1.07; 1.68)	1.43 (1.03; 1.84)
Trabecular surfaced				
Modular	n/a	n/a	0.84 (0.54; 1.15)	0.84 (0.57; 1.12)
Non-modular	n/a	n/a	0.70 (0.41; 0.99)	0.67 (0.42; 0.92)
Tibial component design				
Metal backed	0.37 (0.32; 0.43)	0.45 (0.40; 0.50)	n/a	n/a
All-poly	0.33 (0.12; 0.53)	0.38 (0.26; 0.49)	n/a	n/a
Bearing mobility				
Fixed	0.38 (0.32; 0.44)	0.44 (0.40; 0.49)	1.60 (1.26; 1.93)†	1.52 (1.23; 1.82)†
Mobile	0.36 (0.15; 0.58)	0.42 (0.20; 0.63)	1.22 (0.63; 1.81)†	1.24 (0.66; 1.81)†
Insert constraint				
Cruciate retaining	0.40 (0.30; 0.51)	0.45 (0.39; 0.51)	0.81 (0.51; 1.10)*	0.71 (0.51; 0.91)*
Posterior stabilized	0.43 (0.31; 0.55)	0.50 (0.40; 0.61)	0.72 (0.41; 1.03)*	0.90 (0.44; 1.35)*
Condylar stabilized	0.33 (0.22; 0.44)	0.39 (0.27; 0.50)	n/a	n/a
Insert material				
UHMWPE	0.38 (0.30; 0.45)	0.45 (0.40; 0.51)	0.73 (0.42; 1.04)*	0.67 (0.39; 0.95)*
HXLPE	0.34 (0.23; 0.45)	0.42 (0.34; 0.51)	0.81 (0.51; 1.10)*	0.82 (0.55; 1.08)*
RSA technique				
Model-based RSA	0.48 (0.35; 0.60)	0.56 (0.44; 0.68)	0.76 (0.30; 1.22)*	0.59 (0.38; 0.80)*
Fictive point	0.33 (0.24; 0.42)	0.39 (0.29; 0.49)	0.77 (0.49; 1.05)*	0.93 (0.59; 1.26)*
Tibial baseplate marker	0.39 (0.14; 0.64)	0.42 (0.27; 0.57)	n/a	n/a
All-poly/n-mod marker	0.36 (0.16; 0.56)	0.44 (0.32; 0.56)	n/a	n/a

Table 1. Continued

	Cemented		Uncemented
	6-months	**1-year**	**6-months**
Modular PE marker	0.38 (0.27; 0.49)	0.43 (0.36; 0.51)	n/a	n/a

† Restricted to implants with a porous-coating surface.
* Restricted to implants with a trabecular metal surface.
MTPM maximum total point motion; CI Confidence interval; UHMWPE Ultra high molecular weight polyethylene; HXLPE Highly crosslinked polyethylene; n-mod; non-modular; PE Polyethylene; n/a not applicable

Migration patterns between 6-month and 1-year follow-up

For the overall group, the majority of the migration occurred within the first 6 months post-surgery of 0.58 mm (CI 0.50–0.65), whereafter minimal additional migration was observed between 6 months and 1 year of 0.04 mm (CI 0.03–0.06). Similarly, for the different fixation methods, most tibial component migration was observed within the first 6 months and changed between 6 months and 1 year by 0.04 mm (CI 0.02–0.06) for cemented, 0.05 mm (CI –0.03 to 0.13) for uncemented screw-fixated, and 0.06 mm (CI 0.01–0.11) for uncemented without screw-fixation. When cemented and uncemented components were stratified for different design factors, the majority of migration also occurred within the first 6 months for all comparisons (**Table 1**). Overall, the MTPM values were reported in 127 (64%) study groups at 6 months, compared with 197 (100%) study groups at 1-year follow-up (**Table 2**).

Table 2. Number of study groups and knees for each follow-up moment.

Follow-up	**Baseline**	**1 month**	**3 months**	**6 months**	**1 year**	**2 years**	**5 years**	**10 years**
Cemented								
Study groups	128	41	93	75	128	125	28	6
Implants	3114	777	2077	1661	2863	2713	495	73
Uncemented without screw-fixation								
Study groups	51	24	48	39	51	46	13	6
Implants	1240	478	1078	798	1123	1003	290	84
Uncemented with screw-fixation								
Study groups	17	13	8	12	17	16	4	0
Implants	341	247	161	232	328	303	84	0

Numbers do not add up due to the exclusion of one study group with implants with a cement and screw fixation.

Migration patterns between fixation methods

The migration patterns of tibial components at 6 months showed that the pooled MTPMs were different between fixation groups: 0.37 mm (CI 0.31–0.42) for cemented, 0.67 mm (CI 0.47–0.86) for uncemented screw-fixated, and 1.13 mm (CI 0.96–1.31) for uncemented without screw-fixation (**Figure 2**). At 1-year follow-up, the differences in the pooled migration among all fixation methods remained: 0.43 mm (CI 0.38–0.47) for cemented, 0.77 mm (CI 0.56–0.98) for uncemented screw-fixated, and 1.08 mm (CI 0.9–1.24) for uncemented without screw-fixation. After 1 year, the slope of all 3 fixation methods changed, with a change between 1 and 5 years of 0.11 mm (CI 0.07–0.15) for cemented, 0.15 mm (CI 0.03–0.27) for uncemented screw-fixated, and 0.09 mm (CI –0.01 to 0.19) for uncemented without screw-fixation. The percentiles of the MTPM means were plotted separately up to a 5-year follow-up for cemented and uncemented without screw-fixation tibial components (**Figure 3**).

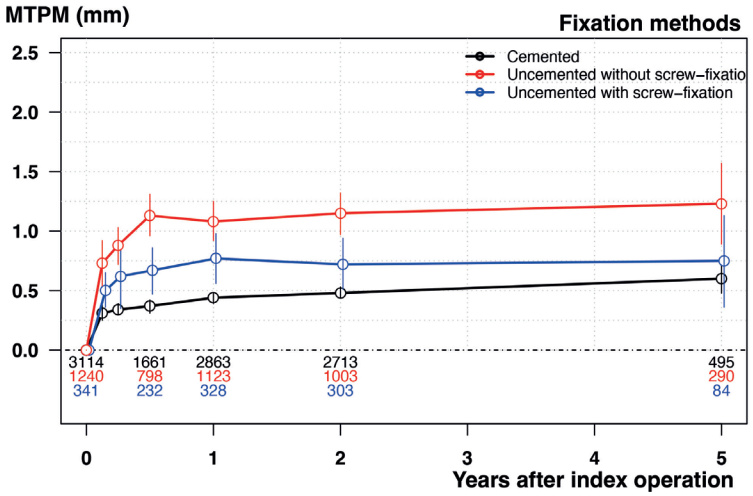
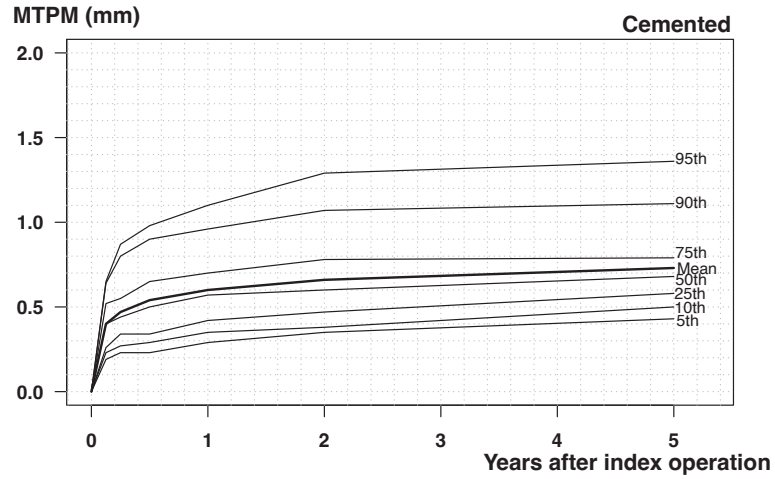


Figure 2. Migration patterns of all implants stratified by cemented, uncemented without screw fixation, and uncemented with screw fixation tibial components. The number of RSA examinations is given for each follow-up in color and order corresponding to the legend.

Migration patterns within cemented without screw-fixation tibial components

Migration patterns of cemented implants were lower in the last 3 decades than in the 1980s (**Figure 4A**). The migration of cemented metal-backed and all-poly implants seemed to be equal (**Figure 4B**). No variation in migration patterns seemed to exist between cemented implants with CR, PS, or CS inserts (**Figure 4C**), implants with UHMWPE or HXLPE insert material (**Figure 4D**), implants with fixed bearing (FB) or mobile bearing (MB) implants (**Figure 4E**), or when migration patterns were

measured by different RSA and marker techniques (model-based RSA [MBRSA], marker-based RSA with fictive points, markers fixed to the tibial component, marker in all-poly or non-modular PE or markers in modular PE) (**Figure 4F**).



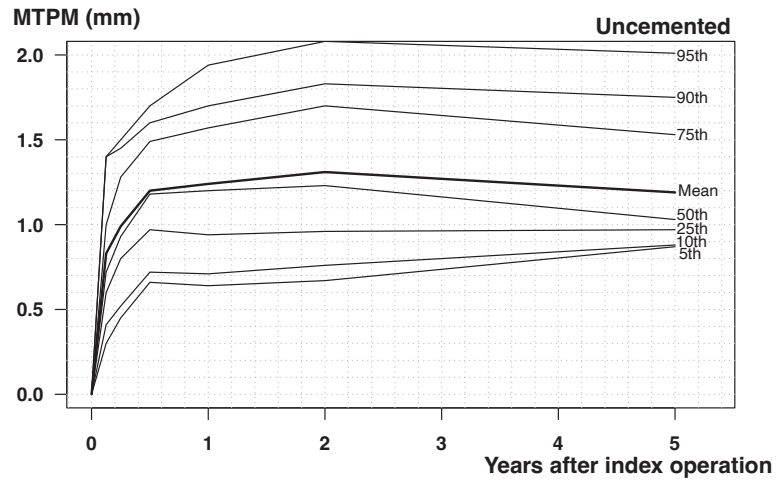


Figure 3. Early migration in percentiles of cemented and uncemented without screw-fixation tibial components.

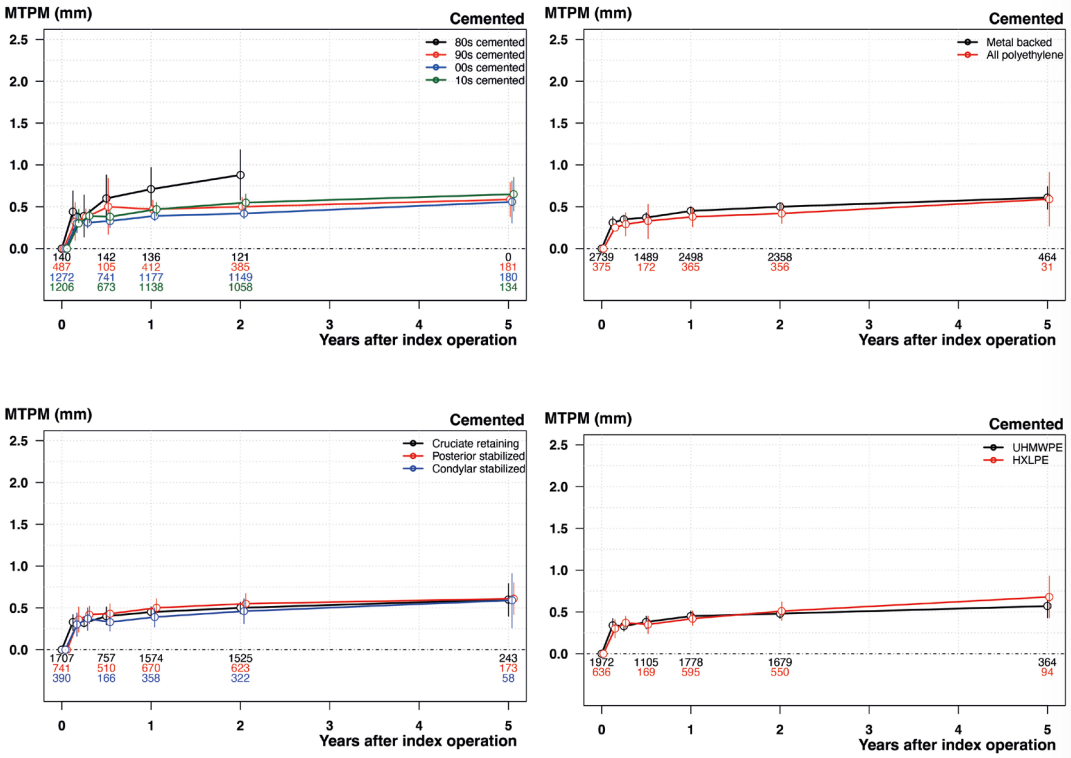


Figure 4. Migration patterns of cemented tibial components. The number of RSA examinations is given for each follow-up in color and order corresponding to the legend.

A. Migration patterns according to the decade in which the enrollment of the study started.
B. Migration patterns according to the design of the tibial baseplate.
C. Migration patterns according to the constraint of the insert.
D. Migration patterns according to the polyethylene material.
E. Migration pattern according to the mobility of the bearing.
F. Migration patterns according to the RSA technique used in the study.

Classification of implant migration

The migration was “acceptable” in 47 (37%) cemented, 0 (0%) uncemented screw-fixated, and 1 (2%) uncemented without screw-fixation implant study groups, when these 197 study groups were categorized. An “at-risk” migration was found in 81 (63%) cemented, 15 (88%) uncemented screw-fixated, and 39 (76%) uncemented without screw-fixation implant study groups. An “unacceptable” migration was found in 0 (0%) cemented, 2 (12%) uncemented screw-fixated, and 11 (22%) uncemented without screw-fixation implant study groups. Of the 13 study groups with implants whose migration was classified as unacceptable, 9 of 13 (62%) study groups contained implants comprising older models, which are no longer used today. The distribution of categories (acceptable, at risk, unacceptable) was similar before and after 2012 (the year the classifications were defined) for both cemented and uncemented tibial components.

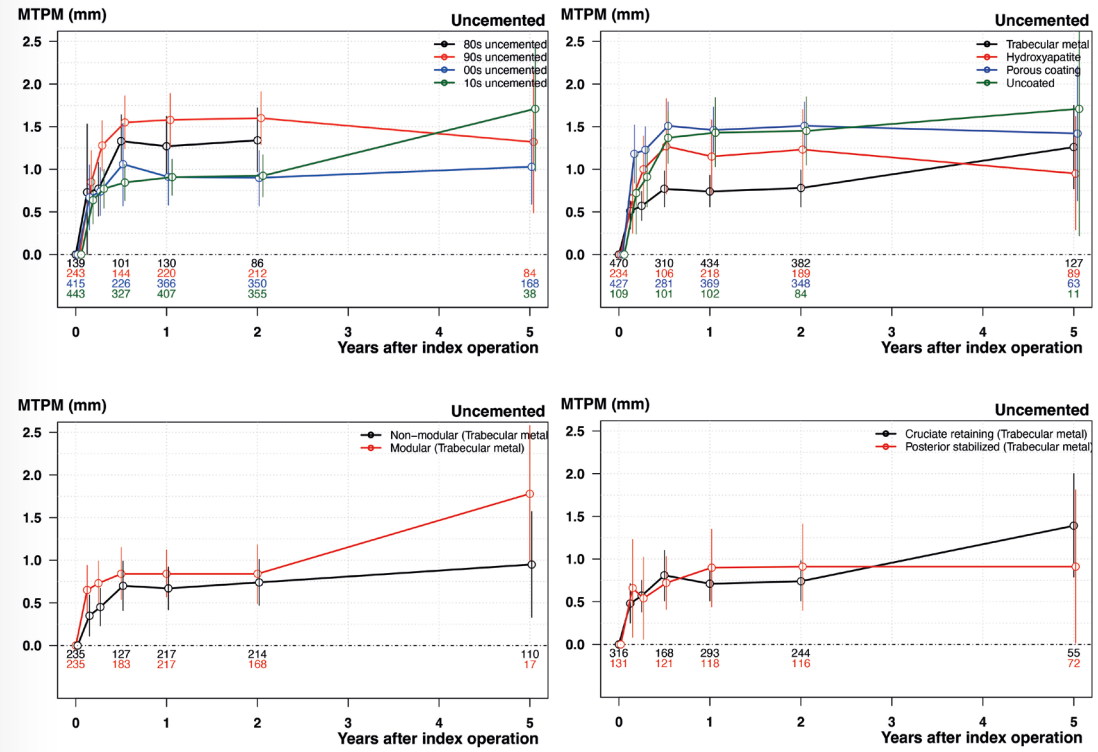


Figure 5. Migration patterns of uncemented without screw-fixation tibial components. The number of RSA examinations is given for each follow-up in color and order corresponding to the legend.

A. Migration patterns according to the decade in which the enrollment of the study started.
B. Migration patterns according to the components’ surface modification.
C. Migration pattern of modular and non-modular components, restricted to trabecular metal surfaced components.
D. Migration patterns according to the constraint of the insert, restricted to trabecular metal surfaced components.

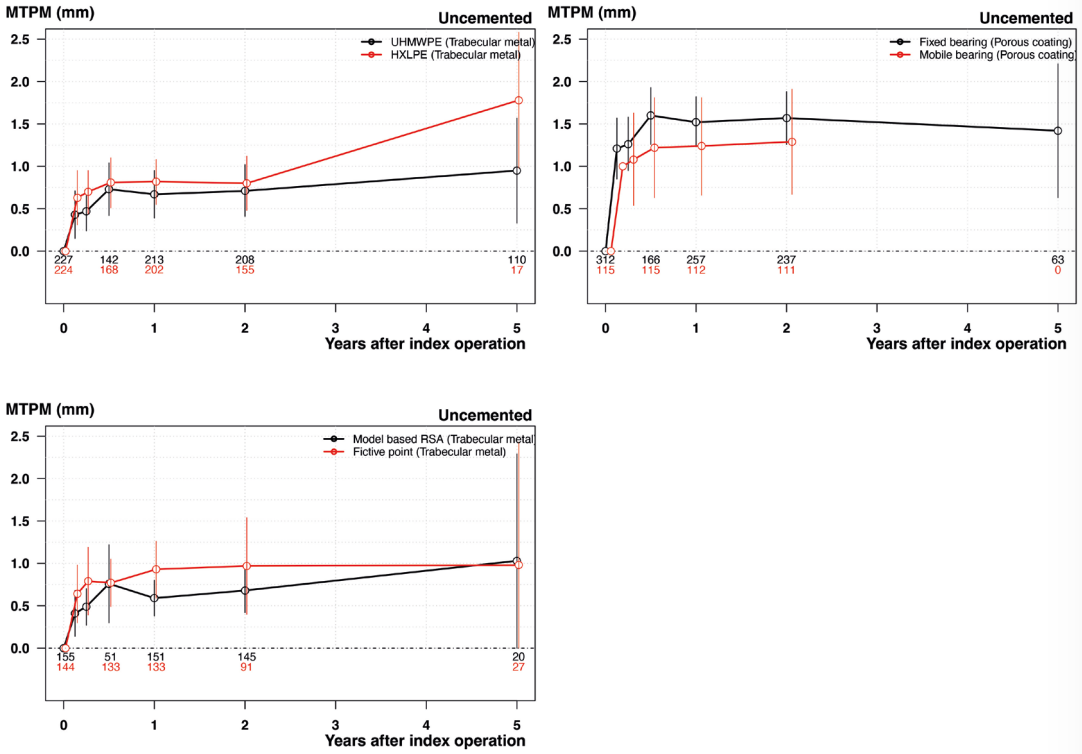


Figure 6. Migration patterns of uncemented without screw-fixation tibial components. The number of RSA examinations is given for each follow-up in color and order corresponding to the legend.

A. Migration patterns according to the polyethylene material, restricted to trabecular metal.
B. Migration patterns according to the mobility of the bearing, restricted to porous coating.
C. Migration patterns according to the RSA technique used, restricted to trabecular metal.

DISCUSSION

Our study aimed to investigate the suitability of the 6-month MTPM values, as opposed to the conventional 1-year values, for RSA threshold testing. Therefore, the pooled migration data at both time intervals was compared for different fixation methods independently. In our current systematic review and meta-analysis, which includes an expanded dataset of 96 studies compared with the previous 53 [19], we showed that the implant migration primarily occurs during the initial 6 months postoperatively, followed by a stabilization phase (6–12 months) with minimal movement. Notably, this pattern holds true for all three fixation methods, even when considering more recent RSA studies that explore contemporary TKA designs.

As the migration from 6 months to 1 year is almost negligible, employing the 6-month MTPM values for RSA threshold testing reduces the time needed for RSA studies to be completed. This could potentially reduce attrition bias when patients are revised or lost to follow-up after 6 months. When 6-month MTPM is used for the thresholds, the time between 6 months and 12 months could be used to assess implant stabilization. The findings of this review highlight the importance of regularly evaluating data and benchmarks to keep up with the evolving landscape of orthopedic implants. The current RSA thresholds from 2012 [10] (< 0.5 mm [acceptable]; 0.5–1.6mm [at risk]; > 1.6 mm [unacceptable]) were based on the mean migration of a group of patients at 1 year. The thresholds were developed with patient safety in mind, as the absence of any phased evidence-based introduction was shown to be unsuccessful and detrimental to patients [5,17]. Consequently, despite the limited number of studies available at the time, it was necessary to establish reliable thresholds for an early version of a phased evidence-based introduction that would be strict enough to prevent potentially harmful implants from entering the market [17,71]. When considering the current migration threshold [10], most uncemented tibial components in this study were at more risk for late-term aseptic loosening than cemented implants. However, the equivalent stabilization after 6 months seems to suggest that they are equally well fixed, which is in line with the findings of the meta-analyses of Prasad et al. (2020), which found no difference in revision rates for aseptic loosening between fully cemented and uncemented TKR, after including 6 randomized controlled trials (RCT) with mid- to long-term follow-up. *[147]*

For cemented implants, we found no substantial differences in migration patterns between all-poly and metal-backed tibial components; CR, PS, and CS implants; implants with UHMWPE and HXLPE inserts; FB and MB implants; or when measured by MBRSA or different marker-based RSA techniques. The results obtained in this study are in agreement with the outcomes found in our previous analysis [19] and suggest that comparable rates of revisions can be expected for aseptic loosening when assessing the impact of these variables through comparative research. These predictions are supported by the findings of systematic reviews and meta-analyses that include only RCTs with an extended follow-up period, which reported no difference in risk of revision for aseptic loosening between cemented all-poly and metal-backed TKR [73]; CR and PS TKR [74]; implants with UHMWPE and HXLPE inserts [75]; and between FB and MB implant designs [76].

For uncemented implants, our study showed a 0.28 mm increase in the 1-year pooled migration of HA-coated implants compared with the previous review[19]. This change was likely due to excluding a study group that used HA-coated implants but had an additional screw fixation. Furthermore, the distribution (95% CI) of the 1-year migration for TM-surfaced implants in the current study (0.74 mm; CI 0.56–0.93) was refined in contrast to that of the previous study (0.84

mm; CI 0.00–1.92) [19], which was attributed to the increasing number of studies investigating these implants. Additionally, we observed a substantial increase in the pooled continuous migration of modular TM implants from 2 to 5 years, compared with non-modular TM implants (**Figure 5C**). The reason for this difference might be the greater flexibility of non-modular implants, where the PE insert is molded into the TM, which can improve load sharing and weight distribution on the tibial bone and reduce the chance of lift-off[52,77]. Overall, the favorable migration of TM components does align with the 0% aseptic loosening revision rates reported in a meta-analysis by Hu et al. (2017) of 307 non-modular TM implants after 5 years and a Finnish Registry study of 1,143 primary TKRs after 7 years[78,79]. On the other hand, our study does not reveal differences in migration based on the other sub-analyses of uncemented components (CR vs. PS; UHMWPE vs. HXLPE; FB vs. MB; MBRSA vs. marker-based RSA with fictive points), while registry data suggests higher rates of aseptic loosening of metal-backed than all-poly implants [80]; non-porous than porous-coated implants [81]; PS than CR cemented implants [82]; UHMWPE than HXLPE in cemented and uncemented implants [3,83] and MB than FB cemented and uncemented implants [84].

Limitations

First, the 6-month MTPM values were reported in only 64% of the study groups, which causes a higher number of missing values than at 1 year. This, in turn, leads to a reduction in RSA examinations and analytical precision, and the potential introduction of bias into the analysis. Second, wide CIs were observed, suggesting multicollinearity. Therefore, migration patterns should be considered as exploratory and not a formal comparison. To ensure the validity of the results, migration patterns were presented for each variable separately, stratified for the most influential independent variable (e.g., TM surface or porous coating) if necessary. Third, we did not account for translations and rotations when considering the migration in this study, while some authors have suggested it could also be used as a predictor of aseptic loosening [85]. However, inconsistent reporting of these parameters prompted us to focus on MTPM, a well-documented parameter for predicting loosening. Finally, because survival data was not incorporated into the study, no conclusions could be drawn regarding the suitability of the current migration thresholds. Combining rates with migration data is a massive undertaking that is beyond the scope of the present review. Therefore, we intend to update and re-evaluate the RSA thresholds using the migration data from this review.

CONCLUSION

This study demonstrates that the majority of implant migration occurs within the initial 6 months following arthroplasty, regardless of fixation method. These results advocate for employing the RSA threshold testing at 6 months, rather than at the traditional 1-year mark. By shortening this interval, potentially unsafe implants could be identified earlier, thereby protecting patients from unfavorable outcomes. Moreover, this study provided pooled migration patterns of different implant variables that can be used as a benchmark for future evaluation of new implants.

SUPPLEMENTAL MATERIAL

Table SM1. PRISMA 2020 checklist.

Section	Item	Paragraph
Title/Abstract	Identify it as a systematic review and use the PRISMA 2020 checklist for abstracts.	Title/ abstract
Introduction		
Rational	Describe the rationale for the review in the context of existing knowledge.	1
Objectives	Provide an explicit statement of the objective(s) or question(s) the review addresses.	1
Methods		
Eligibility criteria	Specify the inclusion and exclusion criteria and groupings.	3
Information sources	Specify all sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	4
Search strategy	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	4/SM2
Selection process	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	5
Data collection process	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	6
Data items	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	7
	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	7
Risk of bias assessment	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	8
Effect measures	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	8

Table SM1. Continued

Section	Item	Paragraph
Synthesis methods	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	8
	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	8
	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	8
	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	8
	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	8
	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	8
Reporting bias assessment	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	9
Certainty assessment	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	9
Results		
Study selection	Describe the results of the search and selection process, ideally using a flow diagram.	10
	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study characteristics	Cite each included study and present its characteristics.	Fig1. / 10
Risk of bias in studies	Present assessments of risk of bias for each included study.	n/a
Results of individual studies	For all outcomes, present, for each study: (a) summary statistics for each group and (b) an effect estimate and its precision, ideally using structured tables or plots.	n/a
Results of syntheses	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	11-15
	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision and measures of statistical heterogeneity.	11-15

Table SM1. Continued

Section	Item	Paragraph
	Present results of all investigations of possible causes of heterogeneity among study results.	n/a
	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	n/a
Reporting biases	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	n/a
Certainty of evidence	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	n/a
Discussion	Provide a general interpretation of the results in the context of other evidence.	16-20
	Discuss any limitations of the evidence included in the review.	21
	Discuss any limitations of the review processes used.	21
	Discuss implications of the results for practice, policy, and future research.	22
Other information	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	23
	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	23
	Describe and explain any amendments to information provided at registration or in the protocol.	23
	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	24
	Declare any competing interests of review authors.	24
	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	25

Table SM2. Details of the literature search strategy.

PubMed

((“Photogrammetry”[Mesh:NoExp] OR Radiostereometric Analysis [Mesh] OR “roentgen stereophotogrammetric analysis”[tiab] OR “RSA” [tiab] OR “Radiostereometric” [tiab] OR “Radiostereometrics” [tiab] OR “stereophotogrammetric” [tiab] OR “stereophotogrammetrics” [tiab] OR “stereophotogrammetry” [tiab] OR “stereo-photogrammetric” [tiab] OR “stereophotogrammetrics” [tiab] OR “stereophotogrammetry” [tiab] OR “Photofluorography” [Mesh] OR “roentgen fluoroscopic”[tiab] OR “roentgen fluoroscopics”[tiab] OR “roentgen fluoroscopy”[tiab])) AND ((“Joint Prosthesis”[Mesh:NoExp] OR “Hip Prosthesis”[Mesh] OR “Knee Prosthesis”[Mesh] OR “hip prosthesis”[tiab] OR “knee prosthesis”[tiab] OR “hip prostheses”[tiab] OR “knee prostheses”[tiab] OR “prosthetic hip”[tiab] OR “prosthetic knee”[tiab] OR “TKA”[tiab] OR “THA”[tiab] OR “THR”[tiab] OR “TKR”[tiab] OR “joint replacement”[tiab] OR “Arthroplasty, Replacement”[mesh:NoExp] OR “total knee replacement”[tiab] OR “total hip replacement”[tiab] OR “total knee arthroplasty”[tiab] OR “total hip arthroplasty”[tiab] OR “Arthroplasty, Replacement, Hip”[Mesh] OR “Arthroplasty, Replacement, Knee”[Mesh])) AND (“2016”[Date - Publication] : “2023”[Date - Publication])

Web of Science

TS=(“Photogrammetr*” OR “RSA” OR “radiostereometr*” OR “radio-stereometr*” OR “stereophotogrammetr*” OR “stereo-photogrammetr*” OR “roentgen fluoroscop*” OR “Photofluorograph*” OR “Photo-fluorograph*”) AND TS=(“Joint Prosthe*” OR “hip prosthe*” OR “knee prosthe*” OR TKA OR TKR OR THA OR THR OR “hip arthroplast*” OR “knee arthroplast*” OR “knee replacement*” OR “hip replacement*”) AND PY=(2016-2023)

Cochrane database

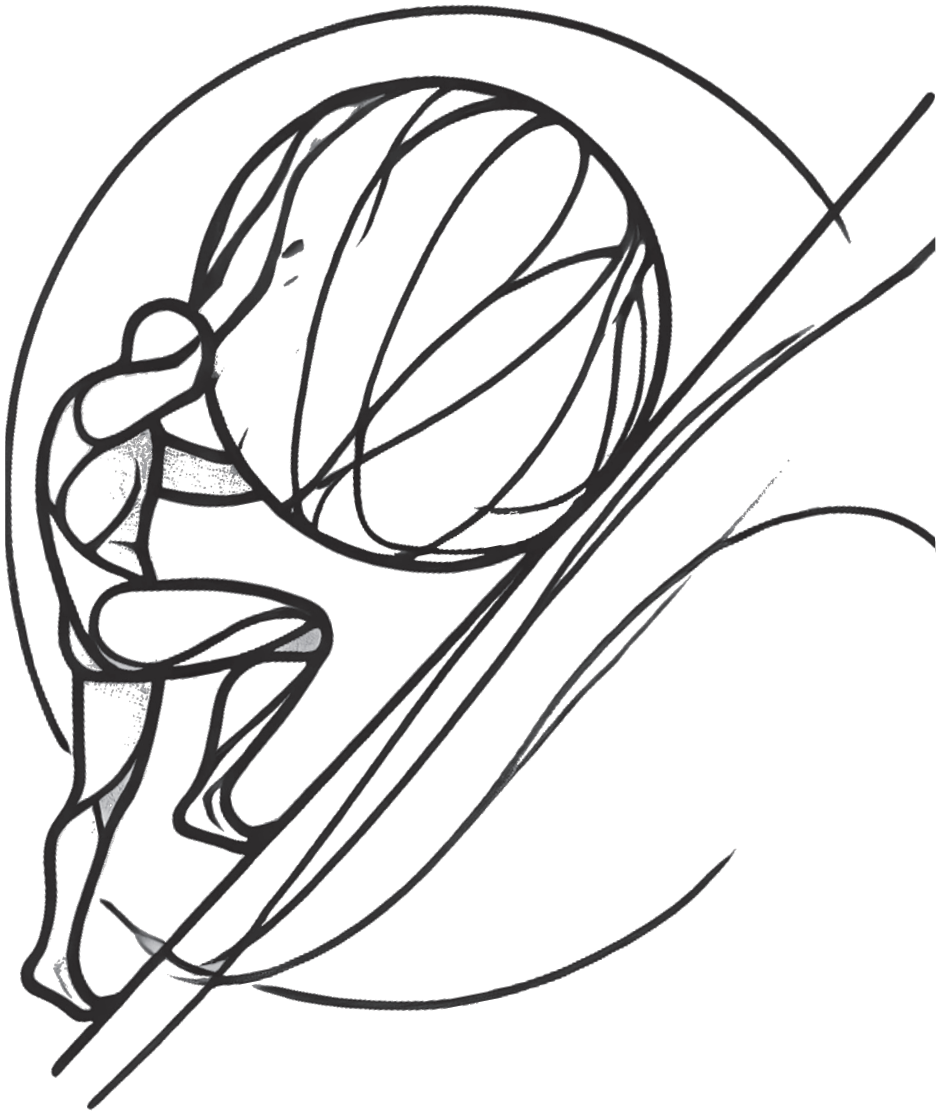
(“Photogrammetr*” OR “RSA” OR “radiostereometr*” OR “radio-stereometr*” OR “stereophotogrammetr*” OR “stereo-photogrammetr*” OR “roentgen fluoroscop*” OR “Photofluorograph*” OR “Photo-fluorograph*”):ti,ab,kw AND (“Joint Prosthe*” OR “hip prosthe*” OR “knee prosthe*” OR TKA OR TKR OR THA OR THR OR “hip arthroplast*” OR “knee arthroplast*” OR “knee replacement*” OR “hip replacement*”):ti,ab,kw

Embase

(Stereophotogrammetry/ OR exp radiostereometric analysis/ OR “RSA”.ti,ab. OR “Radiostereometr*”.ti,ab. OR “Radio-stereometr*”.ti,ab. OR “stereophotogrammetr*”.ti,ab. OR “stereo-photogrammetr*”.ti,ab. OR exp fluorography/ OR “Photofluorograph*”.ti,ab. OR “Photo-fluorograph*”.ti,ab. OR “roentgen fluoroscop*”.ti,ab.) AND (joint prosthesis/ OR exp hip prosthesis/ OR exp knee prosthesis/ OR “hip prosthe*”.ti,ab. OR “hip arthroplast*”.ti,ab. OR “hip replacement*”.ti,ab. OR “knee prosthe*”.ti,ab. OR “knee arthroplast*”.ti,ab. OR “knee replacement*”.ti,ab. OR “prosthetic hip*”.ti,ab. OR “prosthetic knee*”.ti,ab. OR “TKA”.ti,ab. OR “TKR”.ti,ab. OR “THA”.ti,ab. OR “THR”.ti,ab. OR “joint replacement*”.ti,ab. OR replacement arthroplasty/ OR exp hip replacement/ OR exp knee replacement/) AND 2016:2023.(sa_year). NOT (conference OR conference abstract OR “conference review”).pt.

Google Scholar

“Total knee arthroplasty” AND “radiostereometric” from 2016 to 2023, no citations, no patents



CHAPTER 4

Evaluation and refinement of thresholds for early migration of total knee replacements as an estimator of late aseptic loosening

an updated systematic review of RSA and survival studies

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ABSTRACT

Purpose

This study updates 2 parallel systematic reviews and meta-analyses from 2012, which established the 1-year radiostereometric (RSA) migration thresholds for tibial components of total knee replacements (TKR) based on the risk of late revision for aseptic loosening from survival studies. The primary aim of this study was to determine the (mis)categorization rate of the 2012 thresholds using the updated review as a validation dataset. Secondary aims were evaluation of 6-month migration, mean continuous (1- to 2-year) migration, and fixation-specific thresholds for tibial component migration.

Methods

One review comprised early migration data, measured by maximum total point motion (MTPM), from RSA studies, while the other focused on revision rates for aseptic loosening of tibial components from survival studies. Studies were matched based on prosthesis, fixation (i.e., cemented and uncemented, and uncemented with screw fixation), and insert (PFI). For the primary aim, newly included study group combinations were compared with the 2012 RSA thresholds to determine the (mis)categorization rate. For the secondary aims, new thresholds were determined based on revision rates for any reason in national registries (5-year < 3%, 10-year < 5%, 15-year < 6.5%).

Results

After matching studies on PFI, a total of 157 survival and 82 RSA studies were included, comprising 504 study group combinations, 51 different PFIs, and 186,974 TKRs. We found that the 2012 thresholds were valid, with a misclassification rate of 0.5% at 5 and 0.3% at 10 years. Mean continuous migration could not be used to identify safe or unsafe implants. For cemented TKR, the 6-month mean MTPM was acceptable below 0.30 mm and unacceptable above 1.10 mm. For uncemented TKR, it was acceptable below 1.10 mm and unacceptable above 1.55 mm.

Conclusion

The updated data reaffirm the 2012 RSA thresholds, confirming their validity in estimating revision risks for tibial component aseptic loosening. The newly proposed fixation-specific 6-month migration thresholds were found to be reliable for early identification of unsafe TKR designs, while 1- to 2-year mean continuous migration data were found not to be reliable for this purpose. These findings support and refine the migration thresholds to improve the evidence-based introduction of new TKR systems.

INTRODUCTION

Since 2017, the European Union has implemented new medical device regulations mandating implant manufacturers to provide clinical evidence of whether the performance of newly introduced implants outweighs the risks to patient safety *[159]*. Radiostereometric analysis (RSA) has emerged as a valuable surrogate for assessing long-term outcomes of implants in a small group of patients with a follow-up of 1 year *[39, 160–162]*. The effect of RSA testing can be observed in national joint registries, showing an approximate 1% decrease in the mean all-cause revision rate for total knee replacements (TKR) after 5- and 10-year follow-up among RSA-tested compared with non-RSA-tested TKRs *[161]*. This reduction translates to a 10–35% reduction in the total number of TKR revisions *[162]*. RSA has been proposed as a necessary tool in preclinical testing to provide early warnings and protect patients from newly introduced implants, fixation methods, or inserts that potentially have inferior outcomes *[39, 40, 160, 161]*

Over a decade ago, the RSA and survival study meta-analysis conducted by Pijls et al. (2012) established 1-year migration thresholds for tibial components of TKR. These thresholds categorized migration as acceptable, at-risk, or unacceptable based on their corresponding revision rates at 5 and 10 years *[39]*. However, with the ongoing development and introduction of new TKRs, one may wonder whether the 2012 thresholds are still valid and whether they apply to modern designs including new uncemented fixations *[67]*. Therefore, the primary aim of this study was to determine the categorization rate of the 2012 thresholds using the updated review as a validation dataset. Secondary aims were the evaluation of thresholds based on 6-month migration, based on mean continuous migration (difference between first and second year), and fixation-specific (i.e., cemented and uncemented without screw fixation, uncemented with screw fixation) thresholds.

METHODS AND MATERIALS

We performed a 2-sided parallel systematic review of the literature for both RSA and survivorship studies on TKR tibial components, which serves as an update to the previous meta-analysis published in 2012 *[39]*. The reviews considered the literature for: (i) early migration of tibial components of TKR from RSA studies, and (ii) revision rates for aseptic loosening of tibial components of TKR from survival studies. The results of the reviews were matched for tibial component design, including all technical factors mentioned by studies on the prosthesis, fixation (e.g., cemented, uncemented with or without screw fixation), and insert (e.g., cruciate retaining or posterior stabilized) (PFI) *[39]*. The reporting of this systematic review adheres to the standards of the updated Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Statement of 2020 *[95]*. The PRISMA

checklist is available in **Table SM1** (see Supplementary data). The protocol, and its amendments, has been registered a priori in the Open Science Framework (OSF): URL https://osf.io/96bnq/?view_ only=0912275f5c364fffb3eec63921cf2925.

Review of survival studies

Eligibility criteria
Studies were considered eligible based on the following criteria: (i) primary TKR; (ii) revisions or indications for revision surgery related to aseptic loosening of the tibial component as an endpoint; (iii) a follow-up duration of 5, 10, 15, 20, or 25 years; and (iv) reporting of revision percentages at the 5-year interval follow-up points. Studies were excluded if: (i) there were fewer than 75 TKRs in each treatment arm at baseline; (ii) the follow-up of a complete cohort was less than 5 years; (iii) studies were not written in English, Dutch, or German; (iv) studies lacked sufficient information on the PFI used; (v) studies lacked adequate information concerning revisions; and (vi) used a PFI that did not match any of the PFIs included in the updated RSA review. Studies that were initially excluded from the previous review due to the inability to find matching PFIs with any of the RSA studies have been reevaluated for potential inclusion.

Search strategy
The previous search strategy was updated by the same medical librarian (JP) for the same medical bibliographic databases (i.e., PubMed, Embase, Web-of-Science, and the Cochrane Library), with the addition of Google Scholar. To identify new results, the search was limited to publications from 2008 to 2023, with a controlled vocabulary and free-text terms related to (i) joint replacement; (ii) implant failure; and (iii) survival analysis. No differentiation between knee and hip arthroplasty was utilized, as some studies report on both *[39]*. The full search strategies for all databases including utilized filters are detailed in **Table SM2** (see Supplementary data).

Study selection
After merging the records of individual databases and removal of duplicates, references were transferred to Excel (version 16.69.1, Microsoft Corp, Redmond, WA, USA), in which screening was first performed in duplicate by 2 reviewers (RP, JS) based on the title and abstract, and thereafter on the full text. A third reviewer (BP) was consulted to resolve study eligibility disagreements, and articles remained eligible for full-text screening in case of insufficient information stated in the abstract.

Data collection, items, and synthesis
Data extraction from 2008–2023 publications were performed in Excel (version 16.69.1, Microsoft) in duplicate by 2 reviewers (RP, JS) independently. Data extraction of articles included in the meta-analysis of 2012 was checked by 1 reviewer (RP). Any missing or unclear information was obtained or clarified by contacting the study investigators, and each item of correspondence was archived. Extracted data items included the study, patient, and implant characteristics, and revision rates for aseptic loosening of the tibial component at 5-year intervals, all similar to those of the previous meta-analysis from 2012 *[39]*. For each included study, study groups were categorized according to the PFI methodology *[39]*.

Review of RSA studies
The methodology for the literature review of RSA studies that investigated the migration of tibial components was defined in our previous meta-analysis from 2023 *[67]*, which applied to all RSA studies published before 2023. Briefly, implant migration was recorded, quantified as mean maximum total point motion (MTPM) as this was the most commonly reported metric. The full search strategies for all databases including utilized filters are detailed in **Table SM3** (see Supplementary data). Similarly, study groups were categorized according to the PFI methodology *[39]*. RSA studies were secondarily excluded if they investigated a PFI not matching any included in the survival study review.

Data synthesis of combined reviews
A study group is defined as a group of patients in a study with the same PFI, and a single study can have multiple study groups. To mitigate confounding related to prosthesis factors, study groups from RSA and survival studies were matched by their shared PFI. A single PFI might have multiple "RSA-survival combinations" based on the number of study groups with a similar PFI *[39]*. For instance, if 2 RSA study groups and 4 survival groups shared a PFI, this resulted in 8 combinations (i.e., 2 times 4 = 8 combinations).

Quality assessment
To appraise the internal validity of a study, the AQUILA methodological score was used, which was specifically constructed for cohort studies regarding lower limb arthroplasty *[163]*. The score could vary between 11 (excellent) and 0 (poor) for survival studies, and 8 (excellent) and 0 (poor) for RSA studies *[39, 163]*. The AQUILA score was independently assigned for each publication by 2 reviewers (JS, RHP).

The external validity across study groups was addressed by using a match score to assess the similarity of populations between RSA and survival studies *[39]*. The match score was based on several factors, including age, sex, diagnosis, hospital type, and continent, and could vary between 5 (excellent) and 0 (poor) *[39]*. The

match score calculation by each item is detailed in **Table SM4** (see Supplementary data). By evaluating these characteristics, we aimed to quantify and describe the degree of similarity between the populations involved in the RSA and survival study combinations, enhancing the generalizability of the findings.

Computation of migration thresholds

The migration thresholds in this study were based on migration categories, defined as acceptable, at risk, and unacceptable early migration measured by MTPM, aligning with nationally accepted revision rate standards *[39]*. Because no nationally established standards exist specifically for the revision rates of aseptic loosening in tibial components, we have used nationally established revision rates for any cause as a benchmark. The rationale for this approach is that newly introduced tibial components should, at a minimum, perform as well as the current all-cause revision standards. This aligns with the goal of RSA benchmarks, which is to identify high-risk "disaster" implants that pose a significant risk of patient harm. The revision standards that are used as benchmarks are sourced from national registries for 5 years (< 3%) and 10 years (< 5%) post-surgery (NJR 2023, SKAR 2023, AJR 2023, NZJR 2023 *[4, 6–8]*), and for 15 years (< 6.5%) post-surgery the standard of the Orthopaedic Data Evaluation Penal (ODEP) Rating System *[27]*. Similar to the previous review, we solely extracted revision rates due to aseptic loosening of the tibial component from studies for our analysis *[39]*. By using the revision rate standards, 3 migration categories (acceptable, at risk, and unacceptable) were determined. A migration was defined as "acceptable" when all revision rates of tibial components did not exceed the revision standard of the specific follow-up (3%, 5%, or 6.5%). Component migration was defined as "unacceptable" when all revision rates exceeded the revision standard of the specific follow-up. The "at risk" category encompasses the migration range falling between the "acceptable" and "unacceptable" thresholds, including studies with both lower and higher revision rates than the standards at a specific follow-up.

Statistics

As the purpose of this implant safety study is to prevent unsafe implants from entering the market, the study leverages the established association between early migration, as measured by RSA, and late revision due to aseptic loosening *[39, 143]*. Both factors are significantly influenced by the type of PFI. However, due to the challenges inherent in conducting studies that investigate both early migration and late revision, this study indirectly compares these factors using data from separate studies, similar to the descriptive method of the previous review (2012) *[39]*. For comparisons, scatterplots were created with revision rates (y-axis) and migration data (x-axis), alongside the calculated limits of the migration categories *[39]*. First, the 2012 fixation-independent 1-year migration thresholds (5 years: 0.54 and 1.60 mm; 10 years: 0.45 and 1.60 mm) were validated, by evaluating how

many current study combinations were miscategorized. Additionally, the internal validity and similarity of the miscategorized study combinations were evaluated, by use of the AQUILA methodological-quality *[163]* and match-score, respectively. Second, the usability and meaningfulness of the mean difference between 1- and 2-year migration (Δ1–2-year) for migration thresholds was evaluated, considering all study combinations together, and only the "at-risk" categorized combinations, as proposed by Pijls et al. (2018) *[164]*. The Δ1–2-year MTPM was preferably obtained directly from the studies when it was reported. However, if it was not reported, we calculated this difference by subtracting the mean 1-year MTPM from the mean 2-year MTPM, both referenced to the baseline. Lastly, fixation-specific scatterplots were created and evaluated for migration thresholds, by using 6-month and 1-year migration, and 5-, 10-, and 15-year revision data. All analyses were performed with RStudio version 2023.12.0+369 (Rstudio, PBC, Boston, MA, USA) and the "ggplot2" package.

Because the 10- and 15-year data for TKRs with high revision rates may not always be published once the 5-year or 10-year results are available, we estimated the missing data to account for a potential effect of publication bias *[39]*. To estimate the missing data, we analyzed the average increase in revision rates for aseptic loosening from 5 to 10 years, based on the available data of studies that did report at these follow-up points. This analysis showed a multiplying factor of 1.5, indicating a 50% increase in revision rates for aseptic loosening at 10 years compared with at 5 years. As for the 15 years missing results, the same approach was performed, resulting in a multiplying factor of 1.7, indicating a 70% increase in revision rates at 15 years compared with at 10 years. Accordingly, missing values were calculated by use of these multiplying factors. To verify whether the estimated revision rates followed the correct pattern, we compared the estimated 10-year results with the actual 10-year results for the complete cases. Similarly, we compared the estimated and actual results for the 15-year data *[39]*. The analyses showed a minimal difference between the estimated and actual results: 0.3% (SD 1.0) for the 10-year revision rates and 0.2% (SD 1.4) for the 15-year revision rates. This indicates minimal systematic error and minimal influence on the thresholds. Also, the calculated multiplying factors were found to be comparable with the 10-year pattern of revision rates for aseptic loosening reported by the New Zealand Joint Registry (NZJR) *[6]*. Overall, the proportions of study combinations with estimated data were 0.0% at 5 years, 46.0% at 10 years, and 86.1% at 15 years. A breakdown of the actual and estimated data for the 3 main fixation types at the different follow-up points is provided in **Table 1**. As sensitivity analyses, we reported the migration thresholds when the estimated data was calculated with a multiplying factor of 1.0, representing no change in revisions after the previous follow-up.

Data sharing, funding and disclosure
The data extraction of the RSA and survival studies is available by contacting the corresponding author. Funding for the study was obtained from the author's institution. BP and JP were authors of the previous systematic review and meta-analysis *[39]*. RP, EL, PN, and BP were part of an investigator team for 1 or more of the included studies. No author had any conflict of interest to declare. Complete disclosure of interest forms according to ICMJE are available on the article page, doi: 10.2340/17453674.2024.42574

Table 1. Breakdown of number of reported and estimated study combinations and implants by each follow-up mark, used for analyses (1-year migration data). Values are count (%)

Follow-up	Reported data by studies			Estimated data			Final data used [a]
	5 years	10 years	15-years	5 years	10 years	15 years	
Cemented							
Study combinations	399 (100)	224 (54)	56 (14)	0 (0.0)	187 (45)	355 (86)	399 (100)
Implants	132,360	107,351	23,917	0	50,369	133,803	132,360
Uncemented without screw fixation							
Study combinations	82 (100)	41 (50)	12 (15)	0 (0.0)	41 (50.0)	70 (85)	82 (100)
Implants	15,163	7,324	3,548	0	7,839	11,615	15,163
Uncemented with screw fixation							
Study combinations	11 (100)	7 (64)	2 (18)	0 (0.0)	4 (36)	9 (82)	11 (100)
Implants	1,242	810	248	0	432	994	1,242

[a] Final data includes the data used for analyses, which is an accumulation of the reported and estimated data.

RESULTS

Included studies and matched PFIs

The inclusion of reports and studies of both meta-analyses is depicted in **Figure 1**. A study was defined as a study cohort, on which multiple reports (follow-up papers) could be published. For the survival review, the updated literature search yielded 3,680 records, of which 1,212 were duplicates. A total of 127 new reports, related to 98 original studies, were eligible for matching the RSA studies. Together with the previous survival study review, and studies that were previously excluded because no RSA study with a matching PFI existed, a total of 186 reports related to 149 studies were included. For the RSA review, the updated review of RSA studies

included 109 reports related to 96 original studies *[67]*. After matching the eligible survival and RSA studies, a total of 85 RSA reports (82 studies) *[15, 100, 103, 108, 110, 111, 113–115, 117–119, 121, 122, 125–127, 129–136, 138, 139, 141, 142, 144, 165–220]* and 186 survival reports (157 studies) *[221–406]* were included, comprising 504 study group combinations, and 186,974 knee arthroplasties of 51 different PFIs (**Figure 1**). All different PFIs that were found and matched are reported in **Table 2**.

The mean AQUILA methodological-quality score was 5.3 (SD 1.3) on an 8-point scale for the RSA studies, and 6.6 (SD 1.5) on an 11-point scale for the survival studies. The mean match-score of RSA survival combinations was 1.9 (SD 1.1) on a 5-point scale. All included studies were separately referenced in alphabetical order in the supplementary file (see Supplementary data).

Evaluation of the 2012 thresholds based on 1-year MTPM

Of the 415 newly included study combinations, 2 (0.5%) at 5 years and 1 (0.3%) at 10 years were misclassified based on their 1-year MTPM when using the 2012 thresholds for estimating the risk of aseptic loosening of the tibial component (**Figure 2**). The 2012 thresholds (based on the 1-year MTPM and 5- and 10-year revision rates of 89 study combinations) *[39]* are displayed for clarity (**Figure 2).** One study combination (**Figure 2**; at 5 and 10 years with a 0% revision rate and 1.63 mm migration at 1 year) was incorrectly categorized as unacceptable, instead of at-risk, in the 2012 study, despite having a 0% revision rate. Consequently, this miscategorized study combination was excluded when calculating the miscategorization rate to validate the 2012 1-year migration thresholds.

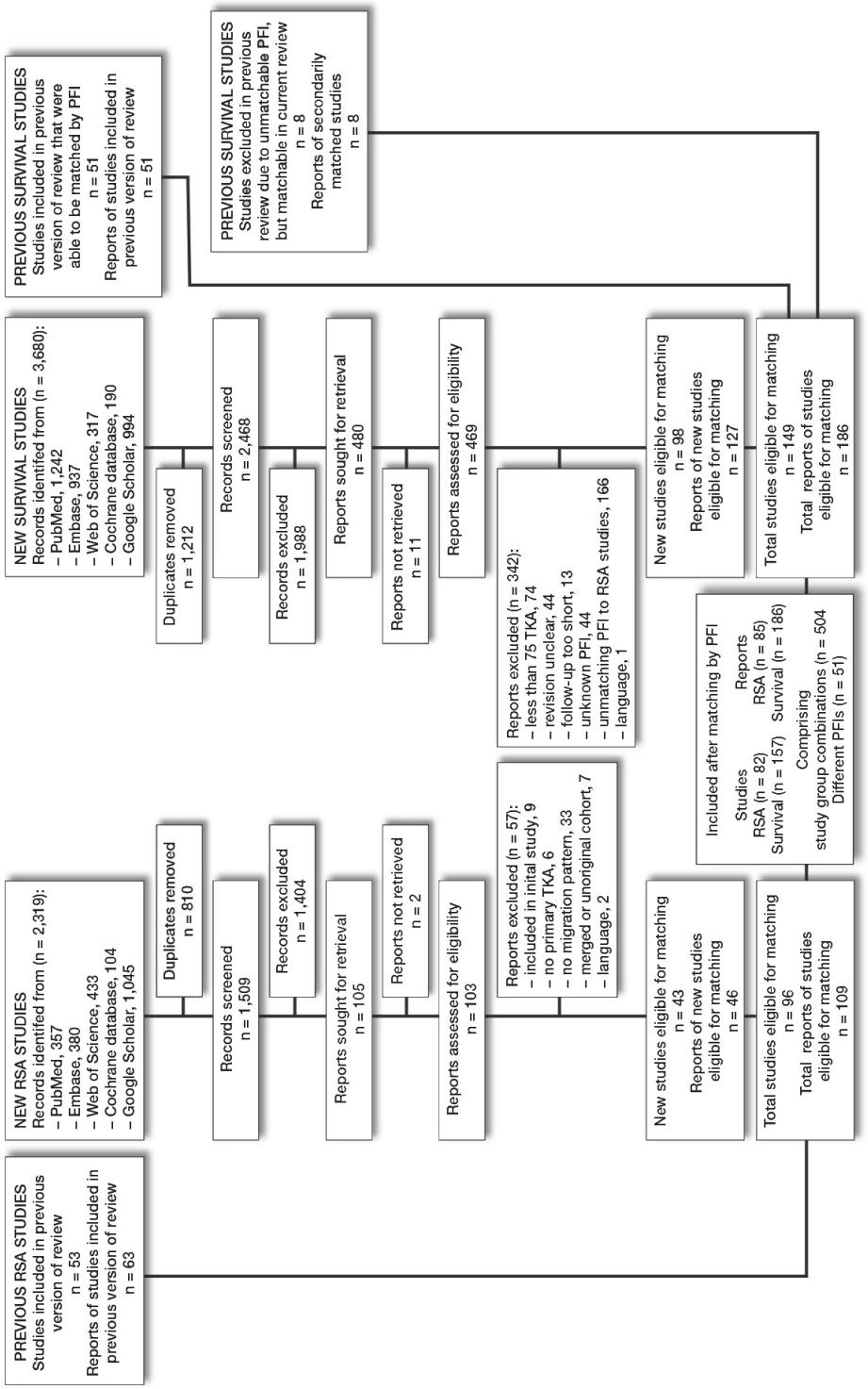


Figure 1. Flow diagram of articles screened, selected, included, and combined from both systematic reviews and meta-analyses. The definition of a report is that multiple (follow-up) reports can be published concerning a single study (cohort).

Table 2. Prosthesis, fixation, and insert (PFI) characteristics

				Number of study groups		
	Prosthesis	**Fixation**	**Insert**	**RSA**	**survival**	**combined**
1	ACS, PS, MB	Cemented	FB, Mod	1	1	1
2	ACS, CS, MB	Cemented	MoB, Mod	2	1	2
3	ACS, CS, MB	Porous + TiN [a]	MoB, Mod	1	2	2
4	Advance, CS, MB	Cemented	FB, Mod	1	6	6
5	AGC, CR, MB	Cemented	FB non-Mod	2	5	10
6	AGC 2000, CR, MB	Porous [a]	FB, non-Mod	1	2	2
7	Anatomic Modular Knee, CR, MB	Cemented	FB, Mod	3	2	6
8	Duracon, CR, MB	Cemented	FB, Mod	2	2	4
9	Duracon, CR, MB	Porous + PA [a]	FB, Mod	4	1	4
10	Freeman-Samuelson, CR	Uncoated [a]	All-poly (HDP)	2	2	4
11	Freeman-Samuelson, PE pegs, CR, MB	Uncoated [a]	FB, non-Mod	2	1	2
12	Freeman-Samuelson, metal pegs, CR, MB	Cemented	FB, Mod	2	2	4
13	Freeman-Samuelson, PE pegs, CR, MB	Cemented	FB, non-Mod	1	2	2
14	Genesis II, PS, MB	Cemented	FB, Mod	3	5	15
15	Interax, CR, MB	Uncoated [a]	FB, MenB	2	1	2
16	Kinematic condylar, CR, MB	Cemented	FB, non-Mod	1	7	7
17	Kinemax plus, CR,	Cemented	All-poly	1	2	2
18	LCS, CS, MB	Porous [a]	MB, Mod	1	11	11
19	Maxim, I-beam stem, CR, MB	Cemented	FB, Mod	1	1	1
20	Miller Galante I, CR, MB	Porous + screws [a]	FB, Mod	2	2	4
21	Miller Galante I, CR, MB	Cemented	FB, Mod	1	2	2
22	Miller Galante II, CR, MB	Cemented	FB, Mod	2	1	2
23	Miller Galante II, CR, MB	Porous + screw [a]	FB, Mod	3	1	3
24	NexGen CR, MB	Cemented	FB, Mod	5	12	60
25	NexGen CR flex, MB	Cemented	FB, Mod	2	5	10
26	NexGen legacy PS, MB	Cemented	FB, Mod	4	10	40
27	NexGen legacy PS flex, MB	Cemented	FB, Mod	2	15	30
28	NexGen legacy PS flex, MB	Cemented	MoB, Mod	2	4	8
29	NexGen option stemmed, CR, MB	Cemented	FB, Mod	3	2	6

Table 2. Continued

	Prosthesis	Fixation	Insert	Number of study groups		
				RSA	survival	combined
30	NexGen monoblock Legacy, PS, MB	Trabecular [a]	FB, non-Mod	4	4	16
31	NexGen monoblock, CR, MB	Trabecular [a]	FB, non-Mod	5	3	15
32	Optetrak, PS, MB	Cemented	FB, Mod	1	2	2
33	Porous Coated Anatomic, CR, MB	Porous + screw [a]	FB, Mod	4	1	4
34	Porous Coated Anatomic, CR, MB	Cemented	FB, Mod	1	1	1
35	Profix, CR, MB	Cemented	FB, Mod	6	1	6
36	Profix, CR	Cemented	All-poly	1	3	3
37	Persona, PS, MB	Cemented	FB, Mod	2	2	4
38	Persona, CR, MB	Cemented	FB, Mod	2	1	2
39	Press Fit Condylar, CR, MB	Cemented	FB, Mod	1	10	10
40	Press Fit Condylar, CR, MB	Porous *	FB, Mod	1	1	1
41	Press Fit Condylar Sigma, CR, MB	Cemented	FB, Mod	3	11	33
42	Press Fit Condylar Sigma, CR, MB	Cemented	MoB, Mod	1	4	4
43	Total Condylar, PS	Cemented	All-poly	1	5	5
44	Triathlon cruciform, CR, MB	Cemented	FB, Mod	10	5	50
45	Triathlon cruciform, PS, MB	Cemented	FB, Mod	5	3	15
46	Triathlon cruciform, PS, MB	Porous + PA [a]	FB, Mod	2	1	2
47	Triathlon tritanium, CR, MB	Trabecular [a]	FB, Mod	4	4	16
48	Tricon M, PE pegs, MB	Porous [a]	FB, non-Mod	3	1	3
49	Vanguard complete, CR, MB	Cemented	FB, Mod	8	7	56
50	Vanguard complete, CR, MB	Porous [a]	FB, Mod	1	2	2
51	Vanguard XP, MB	Cemented	FB, Mod	2	1	2
Total				127	183	504

[a] Uncemented fixation, surface modification specified. AGC = Anatomic Graduated Component, CR = cruciate retaining; PS = posterior stabilized; CS = condylar stabilized; MB = metal backed; PE = polyethylene; TiN = titanium-nitride; HA = hydroxyapatite; PA = periapatite; FB = fixed bearing; MoB = mobile bearing; Mod = modular; MenB = meniscal bearings.

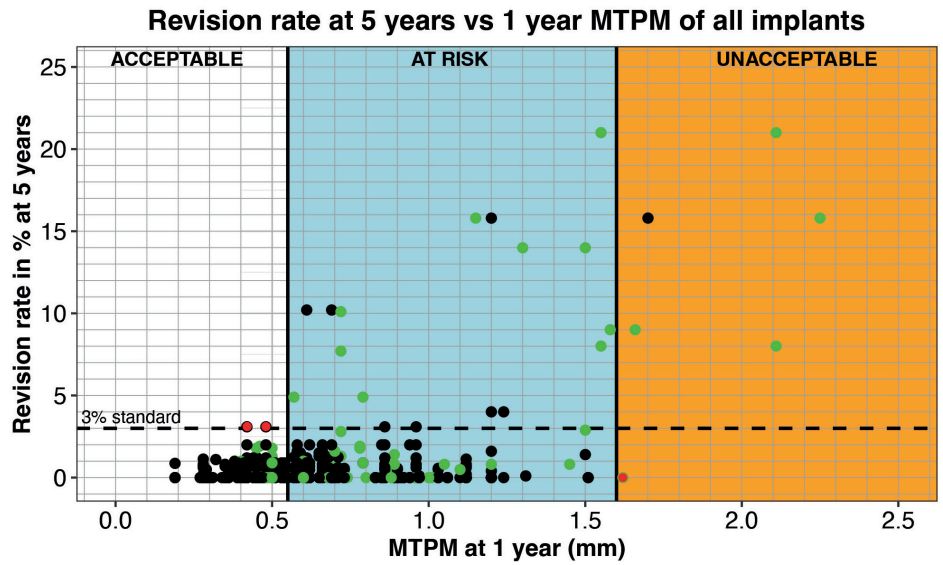


Figure 2. Scatterplots presenting the 2012 migration thresholds for 5 years and 10 years post-surgery, including the 3 migration categories (acceptable, at risk, unacceptable) and all 504 study group combinations. The 2012 migration thresholds were defined at 0.55 and 1.60 mm (5 years) and at 0.45 and 1.60 mm (10 years) [5]. Green dots indicate previously included study combinations, black dots newly included study combinations. Red dots indicate study combinations that were miscategorized by the 2012 thresholds.

Threshold based on the mean Δ 1–2-year continuous migration

When considering all tibial components together, no relationship was found between the mean magnitude of migration during the second postoperative year and the revision rate for follow-ups at 5, 10, or 15 years postoperatively. Despite exhibiting low mean continuous migration values, many tibial components still presented a heightened risk of revision due to aseptic loosening, as evidenced by the revision rates observed at the 15-year point (**Figure 3**). The lack of correlation held true regardless of whether all study group combinations or only the combinations with an at-risk 1-year MTPM were considered.

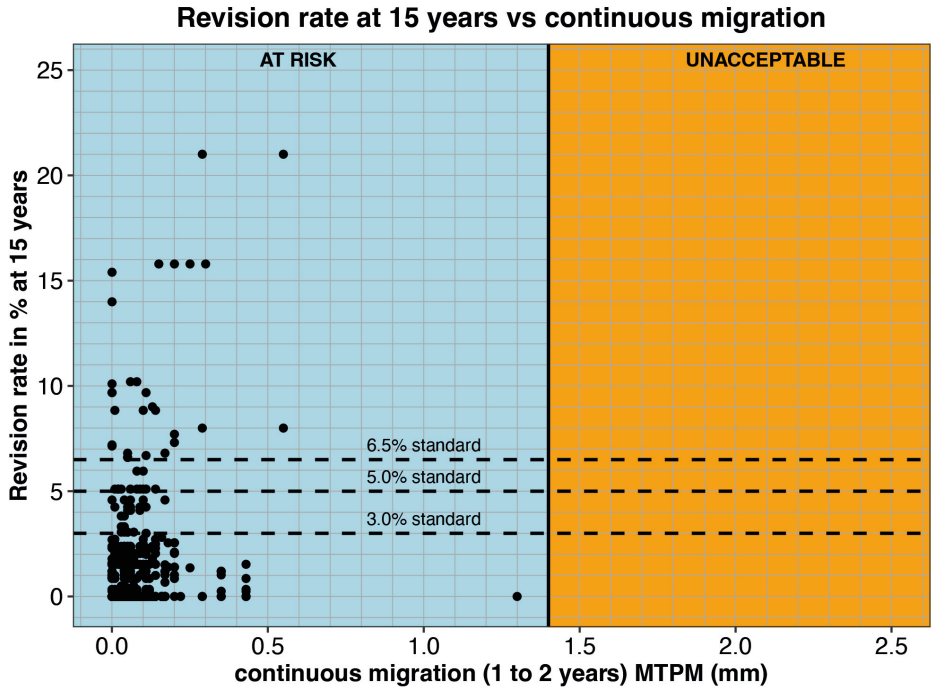
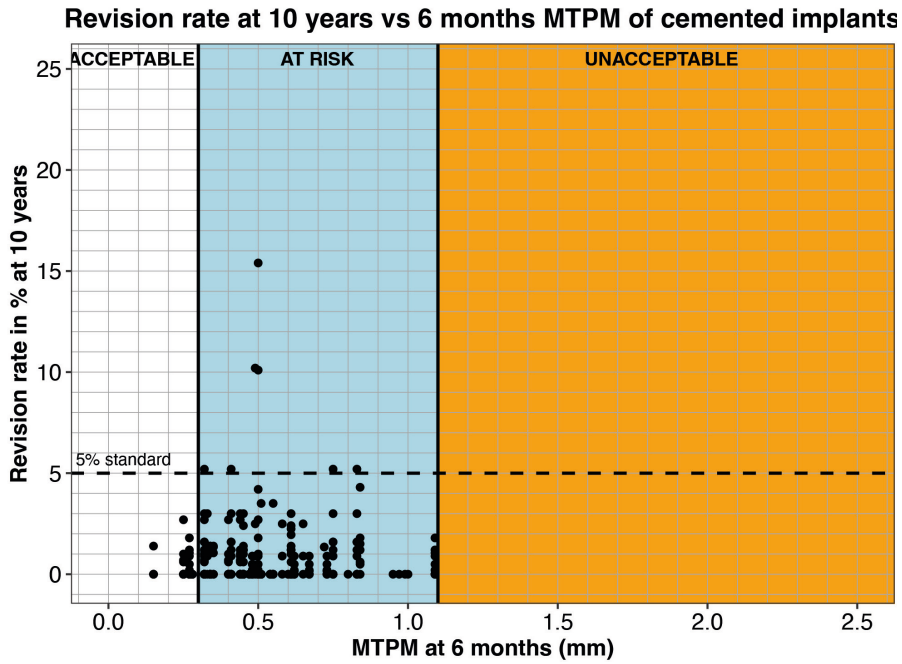


Figure 3. Scatterplot presenting no correlation between the mean Δ 1–2-year MTPM and revision of the tibial component for aseptic loosening at 10 and 15 years. All study combinations are considered in the figure.



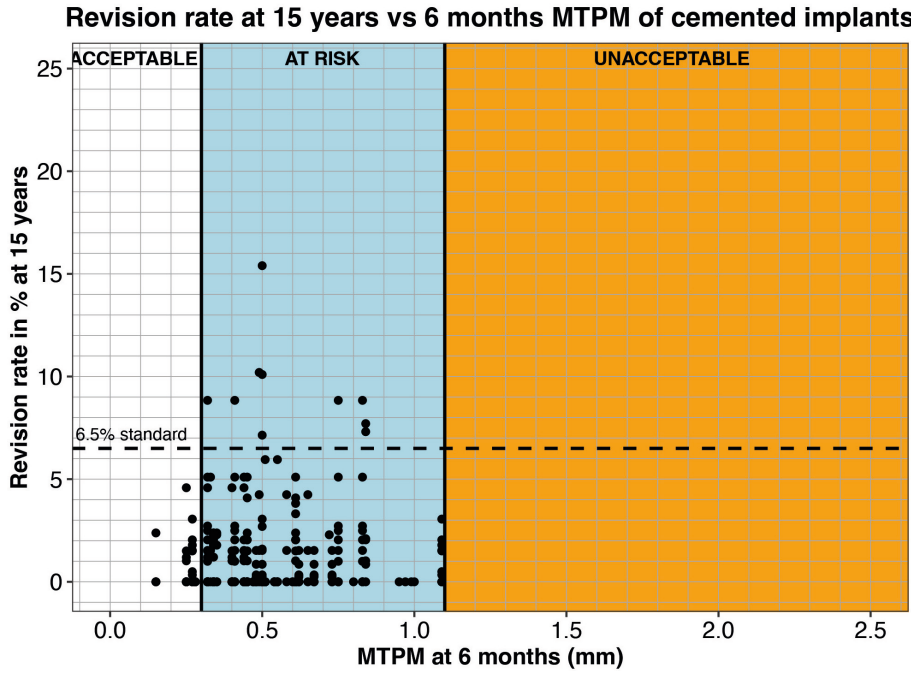


Figure 4. Relation between MTPM at 6 months and the revision rate of cemented tibial components for aseptic loosening at 10 and 15 years, including the 3 migration categories (acceptable, at risk, unacceptable) and corresponding thresholds at 0.30 and 1.10 mm.

Uncemented fixation without screw fixation

14 different PFIs were found in 82 RSA-survival study combinations that included 15,163 uncemented tibial components without screw fixation (**Tables 1 and 2**). Based on a 6-month MTPM, the revision rates for aseptic loosening were below 3%, 5%, or 6.5% when components migrated below 1.10 mm for all 3 follow-up points (5, 10, and 15 years). However, at all 3 follow-up moments, the revision rates exceeded the standards when the migration surpassed 1.55 mm. These findings establish 6-month migration thresholds for uncemented tibial components to be at 1.15 mm and 1.55 mm (**Table 3, Figure 5**). For the 1-year MTPM, these thresholds were slightly higher than those based on the 6-month MTPM (**Table 3**).

As for the sensitivity analysis, the 6-month migration thresholds for at-risk implants would be 1.15 mm, instead of 1.10 mm, for 15 years postoperatively only. The 1-year thresholds would not change.

Uncemented with screw fixation

3 different PFIs were found in 11 RSA-survival study combinations that included 1,242 uncemented components with screw fixation (**Tables 1 and 2**). Regarding the 6-month MTPM, revision rates did not exceed 3%, 5%, or 6.5% when the component migration was below 0.56 mm. However, the revision rates were not below 3%, 5%, or 6.5% when the component migration was higher than 1.00 mm (**Figure 6, Table 3**). For the 1-year MTPM, these thresholds were found at 0.56 mm and 1.10 mm after 5, 10, and 15 years (**Table 3**).

Regarding the sensitivity analysis, no changes in the thresholds were observed for the 10-year follow-up. For the 15-year follow-up, an at-risk category could not be determined, resulting in similar thresholds of 1.00 mm after 10 years and 1.10 mm after 15 years. However, these thresholds would delineate the acceptable and unacceptable categories.

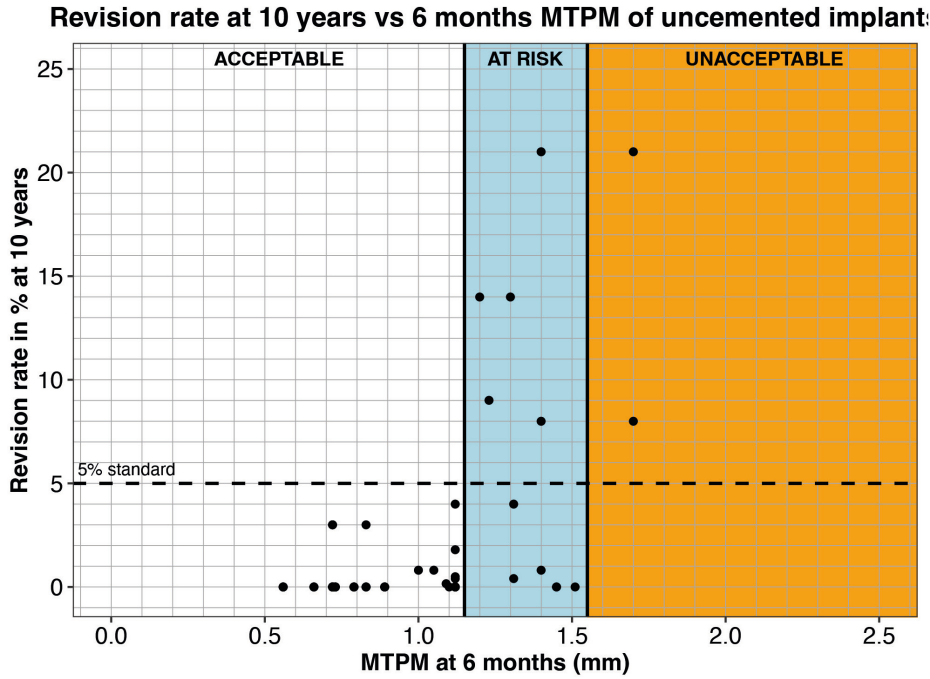
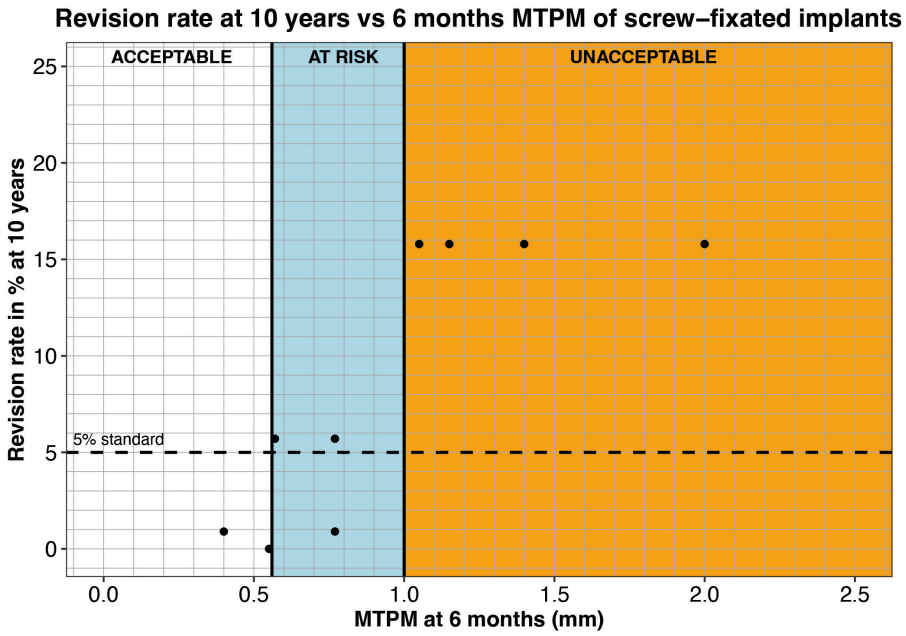


Figure 5. Relation between MTPM at 6 months and the revision rate of uncemented tibial components for aseptic loosening at 10 and 15 years, including the 3 migration categories (acceptable, at risk, unacceptable) and corresponding thresholds at 1.20 and 1.55 mm (10 years) and at 1.10 and 1.55 mm (15 years).



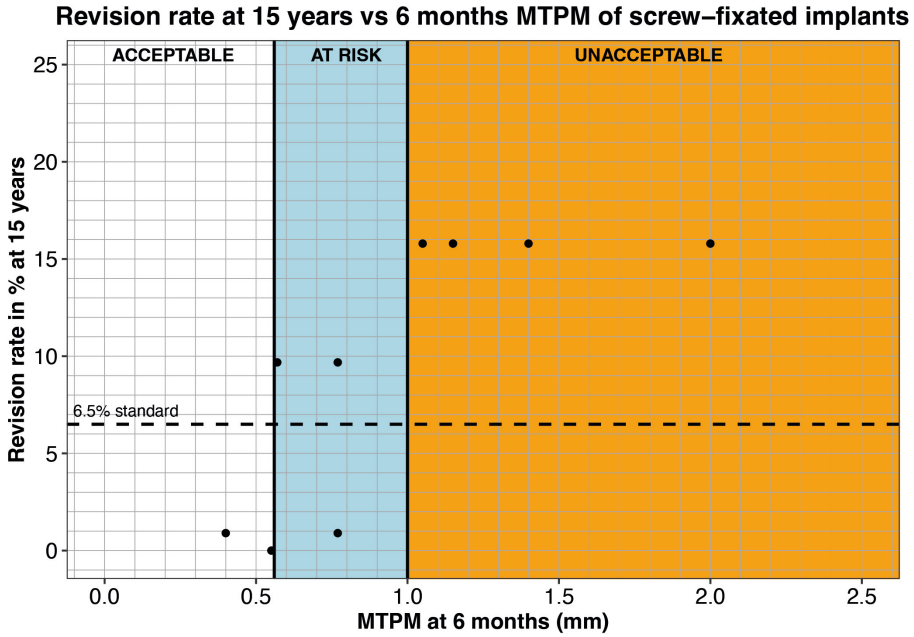


Figure 6. Relation between MTPM at 6 months and the revision rate for aseptic loosening of uncemented tibial components with screw fixation at 10 and 15 years including the 3 migration categories (acceptable, at risk, unacceptable) and corresponding thresholds at 0.56 and 1.00 mm at 10 and 15 years.

Table 3. Overview of the migration category thresholds.

	5-year		10-year		15-year	
	Acceptable – at risk	**At risk - unacceptable**	**Acceptable – at risk**	**At risk - unacceptable**	**Acceptable – at risk**	**At risk - unacceptable**
1-year migration thresholds						
2012 thresholds*	0.54 mm	1.60 mm	0.45 mm	1.60 mm	n/a	n/a
Overall	0.40 mm	1.65 mm	0.40 mm	1.65 mm	0.40 mm	1.65 mm
Cemented	0.40 mm	1.15 mm	0.40 mm	1.15 mm	0.40 mm	1.15 mm
Uncemented without screw-fixation	1.15 mm	1.65 mm	1.30 mm	1.65 mm	1.10 mm	1.65 mm
Uncemented with screw-fixation	0.56 mm	1.10 mm	0.56 mm	1.10 mm	0.56 mm	1.10 mm
6-months migration thresholds						
Overall	0.30 mm	1.65 mm	0.30 mm	1.65 mm	0.30 mm	1.65 mm
Cemented	0.30 mm	1.10 mm	0.30 mm	1.10 mm	0.30 mm	1.10 mm
Uncemented without screw-fixation	1.10 mm	1.55 mm	1.15 mm	1.55 mm	1.10 mm	1.55 mm
Uncemented with screw-fixation	0.56 mm	1.00 mm	0.56 mm	1.00 mm	0.56 mm	1.00 mm

* Based on the thresholds defined in the previous meta-analysis from 2012 (39).

DISCUSSION

Our study aimed to evaluate the 2012 tibial component 1-year migration thresholds, which were defined to provide early identification of unsafe TKRs *[39]* against more recent migration and survivorship data. The results from our updated review ratify the 2012 migration thresholds with miscategorization rates of less than 1% on 415 newly included study combinations. We also explored alternative metrics such as 6-month migration, mean continuous migration, and fixation-specific migration thresholds. We found that it was possible to identify safe and unsafe implants based on 15-year follow-up using 6-month migration data. Fixation-specific thresholds made these predictions more precise by left-shifting the "at-risk" category for cemented implants and converging the limits of the "at-risk" category for uncemented implants. The difference in the change of limits for both fixations is most likely due to combining the fixations for threshold determination in the previous study. Specifying both fixations is important,

especially for uncemented tibial components, given the renewed interest in their use.

For our first objective, the 2012 thresholds for acceptable, at risk, and unacceptable 1-year MTPM migration based on the original 89 study group combinations performed very well overall with the additional 415 study group combinations. The 2 miscategorized study combinations (i.e., i. Dunbar et al., 2009 *[152]* – Pulido et al., 2015 *[320]* 5-year thresholds; and ii. Laende et al., 2022 *[119]* – Pulido et al., 2015 *[320]* for the 5- and 10-year thresholds) of new data relative to the original 2012 thresholds had no obvious reasons underlying the misclassifications. Both combinations employed a similar PFI, the NexGen legacy posterior stabilized, metal-backed, cemented, fixed-bearing, modular TKR design. In the survival study by Pulido et al. *[320]* 135 patients were included, with 3.1% and 7.4% of the tibial components revised for aseptic loosening after 5 and 10 years, respectively. However, specific reasons for the revisions were not reported. The RSA study by Dunbar et al. *[152]* analyzed 21 TKRs over 2 years, with baseline migration analysis performed within the first 4 days postoperatively. They reported a mean 1-year MTPM of 0.48 mm. The RSA study by Laende et al. *[119]* involved the analysis of 9 TKRs over 2 years, with baseline analysis conducted immediately postoperatively, and a reported mean 1-year MTPM of 0.42 mm. Neither RSA study reported revisions for aseptic loosening. The AQUILA methodological-quality *[163]* scores were 4 and 8 for the survival studies and 4 for both the RSA studies, respectively, with a match score of 3 for both combinations. Ultimately, the miscategorized combinations slightly exceeded the threshold limits, which raises the question of whether this deviation was due to magnified migration or random variation.

Regarding our second objective, the 6-month thresholds were similar to the 1-year migration thresholds. The minimal differences observed between the 6-month and 1-year migration thresholds suggest that 6-month migration assessment may offer comparable accuracy, but has earlier detection capabilities than 1-year assessment. These findings support the recommendations of the study of Pijls et al. (2018) and Puijk et al. (2023) *[67, 164]*. Furthermore, the fixation-specific thresholds found in this study could help give manufacturers and researchers more guidance and healthcare institutions more certainty on the performance of their TKR. Additionally, our study did not find suitability of the mean continuous migration (Δ 1–2-year) identified at-risk implant groups in RSA threshold testing. The concept of utilizing continuous migration and associated thresholds for a phased introduction of implants was initially proposed by Ryd et al. (1995) and confirmed by Molt et al. (2016) *[38, 123]*. They found that an individual implant carries an 85% predictive risk of mechanical loosening within 10 years, when it surpasses a Δ 1–2-year MTPM of 0.1 mm/year *[38]*. While the Δ 1–2-year MTPM is effective at the individual level, it is not suitable for group-level risk assessment. This is likely because an increased Δ 1–2-year MTPM in 1

or 2 patients has minimal impact on the overall cohort's mean Δ 1–2-year MTPM. As previously mentioned by Ryd et al. *[38]*, the migration pattern of implants will likely play a substantial role in the future of implant safety, as this metric considers early migration as well as continuous migration. For future studies, the "at risk" group requires more effort to narrow down the risk of loosening, perhaps by measuring inducible displacement, as it directly measures the fixation of the implant. To consolidate all thresholds in this study, we recommend that the phased introduction of new implants should include fixation-specific thresholds at 6 months and 1 year.

Limitations

First, due to the methodological approach of using 2 types of studies, individual patient variations are less accounted for, which can potentially lead to an aggregation bias. Individual patient and study variability could affect the accuracy of group-level conclusions *[407]*; unfortunately, we were only able to descriptively estimate the RSA thresholds, and were not able to conduct statistical inferential methods, or consider individual patient data, due to the design of our study. Therefore, it is very important to consider that the study's purpose is to identify unsafe implants and thus should be interpreted on a group level, rather than on an individual level *[37]*. Therefore, the reported thresholds should not be attributed to the implant's performance on an individual patient level. Besides, as the migration and revision rates were sourced from different studies, migration data were not available in the survival studies to influence the decision to perform a revision. Therefore, our results do not suffer from an incorporation bias.

Second, the nationally established revision rate benchmarks used in this study considered revision rates for any cause, while the extracted data focused solely on rates for aseptic loosening of the tibial component. Ideally, benchmark rates for aseptic loosening of tibial components would have been used, to more accurately estimate their long-term revision risk for aseptic loosening based on migration. However, the approach used in this study is still effective in identifying disaster implants that pose a significant risk of patient harm.

Third, we estimated future revision rates based on reported data from previous follow-up periods. While this approach may lead to less accurate thresholds, it accounts for publication bias, which could affect the results more than the data estimation. Therefore, we performed sensitivity analyses that demonstrated nearly equal thresholds, indicating that the data estimation followed a correct pattern. Additionally, it also accounted for a potential selection bias, as the available reported data would represent less data on modern implants compared with older implants, if no estimations were conducted.

Fourth, the study included separate migration thresholds for uncemented components with screw fixation, although with a much lower number of data points compared with the other fixation-specific thresholds. Although this may

result in less accurate and reliable thresholds, they were found to lie between the cemented and uncemented thresholds, which is consistent with the results of our previous meta-analysis indicating that the early migration of screw-fixated implants falls between fully cemented and uncemented implants *[67]*.

Fifth, our study may face attrition bias due to potential revisions of high-migrating implants between 1 and 2 years postoperatively, possibly resulting in missing data at the 2-year mark and underestimating mean continuous migration. Additionally, if studies did not specifically report the 1- to-2-year migration, this was calculated, which could mean the 2 follow-up moments represent different locations and directions of migration, introducing less accurate results. However, it is unlikely that these factors influenced our results significantly. High-migrators could only minimally alter the average Δ 1–2-year migration data. Also, as MTPM represents the greatest motion vector, which mainly occurs in markers experiencing the greatest biological effect, it is likely the same markers were used at both follow-up moments. Lastly, our study did not account for other migration parameters such as translations in directions and rotations, which are also considered predictors of aseptic loosening. However, inconsistent reporting of these parameters led to a focus solely on the MTPM.

CONCLUSION

This study reaffirms the validity of the 2012 RSA thresholds for predicting revision risk due to aseptic loosening of tibial components up to 15 years, as the majority of the newly included data was correctly categorized. Additionally, the results support the use of our newly proposed fixation-specific 6-month migration thresholds for early identification of unsafe TKR designs, while highlighting that mean continuous migration from 1 to 2 years is less reliable for such estimations.

In perspective, the implementation of the 6-month fixation-specific migration thresholds could enhance the evidence-based introduction of new TKR designs, fixations, and inserts by providing early identification of unsafe TKRs. Nevertheless, these estimations might carry some inherent uncertainties and potential sources of bias.

SUPPLEMENTAL MATERIAL

Table SM1. PRISMA 2020 checklist.

Section	Item	Page
Title/Abstract	Identify it as a systematic review and use the PRISMA 2020 checklist for abstracts.	1-2
Introduction		
Rational	Describe the rationale for the review in the context of existing knowledge.	3
Objectives	Provide an explicit statement of the objective(s) or question(s) the review addresses.	3
Methods		
Eligibility criteria	Specify the inclusion and exclusion criteria and groupings.	3,3
Information sources	Specify all sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	4
Search strategy	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	4
Selection process	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	4
Data collection process	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	4
Data items	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	4
	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	5
Risk of bias assessment	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	5
Effect measures	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	5,6
Synthesis methods	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	5,6

Table SM1. Continued

Section	Item	Page
	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	5,6
	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	5,6
	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	5,6
	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	5
	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	-
Reporting bias assessment	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	6
Certainty assessment	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	5
Results		
Study selection	Describe the results of the search and selection process, ideally using a flow diagram.	7
	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	7
Study characteristics	Cite each included study and present its characteristics.	7
Risk of bias in studies	Present assessments of risk of bias for each included study.	n/a
Results of individual studies	For all outcomes, present, for each study: (a) summary statistics for each group and (b) an effect estimates and its precision, ideally using structured tables or plots.	7,8
Results of syntheses	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	n/a
	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision and measures of statistical heterogeneity.	7,8
	Present results of all investigations of possible causes of heterogeneity among study results.	7
	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	n/a
Reporting biases	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	n/a

Table SM1. Continued

Section	Item	Page
Certainty of evidence	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	n/a
Discussion	Provide a general interpretation of the results in the context of other evidence.	9
	Discuss any limitations of the evidence included in the review.	10
	Discuss any limitations of the review processes used.	10
	Discuss implications of the results for practice, policy, and future research.	10
Other information	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	3
	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	3
	Describe and explain any amendments to information provided at registration or in the protocol.	3
	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	6
	Declare any competing interests of review authors.	6
	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	6

Table SM2. Details of the literature search strategy for survival studies.

PubMed
("Joint Prosthesis"[Mesh:NoExp] OR "Hip Prosthesis"[Mesh] OR "Knee Prosthesis"[Mesh] OR "hip prosthesis"[tiab] OR "knee prosthesis"[tiab] OR "hip prostheses"[tiab] OR "knee prostheses"[tiab] OR "prosthetic hip"[tiab] OR "prosthetic knee"[tiab] OR "TKA"[tiab] OR "THA"[tiab] OR "THR"[tiab] OR "TKR"[tiab] OR "joint replacement"[tiab] OR "Arthroplasty, Replacement"[mesh:NoExp] OR "total knee replacement"[tiab] OR "total hip replacement"[tiab] OR "total knee arthroplasty"[tiab] OR "total hip arthroplasty"[tiab] OR "Arthroplasty, Replacement, Hip"[Mesh] OR "Arthroplasty, Replacement, Knee"[Mesh]) AND ("Prosthesis Failure"[Mesh:NoExp] OR "Prosthesis Failures" [tiab] OR "Prosthesis Failure"[tiab] OR "Prosthetic Failure"[tiab] OR "Prosthetic Failures"[tiab] OR "Prosthesis Survival" [tiab] OR "Prosthesis Survivals"[tiab] OR "Prosthesis Durability" [tiab] OR "Prosthesis Durabilities" [tiab] OR "Prosthesis Loosening" [tiab] OR "Prosthesis Loosenings" [tiab] OR "prosthetic loosening" [tiab] OR "aseptic loosening" [tiab] OR "implant loosening" [tiab] OR "implant failure" [tiab] OR "Prosthesis migration"[tiab] OR "Prosthesis migrations"[tiab]) AND ("survival analysis"[MeSH:NoExp] OR "Survival Analyses" [tiab] OR "Survival Analysis"[tiab] OR "Survival Rates" [tiab] OR "Survival Rate"[tiab]) Filters: from 2008 - 2022/12/28
Web of Science
TS=("Joint Prosthe*" OR "hip prosthe*" OR "knee prosthe*" OR TKA OR TKR OR THA OR THR OR "hip arthroplast*" OR "knee arthroplast*" OR "knee replacement*" OR "hip replacement*") AND TS=("Prosthesis Failure*" OR "Prosthetic Failure*" OR "Prosthesis Survival*" OR "Prosthetic Survival*" OR "Prosthesis Durab*" OR "Prosthesis Loosening*" OR "prosthetic loosening*" OR "aseptic loosening*" OR "implant loosening*" OR "implant failure*" OR "Prosthesis migration*" OR "Prosthetic migration*") AND TI=(surviv*) AND PY=(2008-2023)
Cochrane database
("hip prosthesis" OR "knee prosthesis" OR "hip prostheses" OR "knee prostheses" OR TKA OR THA OR "hip arthroplasty" OR "knee arthroplasty" OR "knee replacement" OR "hip replacement"):ti,ab,kw AND ("Prosthesis Failure*" OR "Prosthetic Failure*" OR "Prosthesis Survival*" OR "Prosthetic Survival*" OR "Prosthesis Durab*" OR "Prosthesis Loosening*" OR "prosthetic loosening*" OR "aseptic loosening*" OR "implant loosening*" OR "implant failure*" OR "Prosthesis migration*" OR "Prosthetic migration*"):ti,ab,kw AND (surviv*):ti,ab,kw
Embase
(joint prosthesis/ OR exp hip prosthesis/ OR exp knee prosthesis/ OR "hip prosthe*".ti,ab. OR "hip arthroplast*".ti,ab. OR "hip replacement*".ti,ab. OR "knee prosthe*".ti,ab. OR "knee arthroplast*".ti,ab. OR "knee replacement*".ti,ab. OR "prosthetic hip*".ti,ab. OR "prosthetic knee*".ti,ab. OR "TKA".ti,ab. OR "TKR".ti,ab. OR "THA".ti,ab. OR "THR".ti,ab. OR "joint replacement*".ti,ab. OR replacement arthroplasty/ OR exp hip replacement/ OR exp knee replacement/) AND (exp prosthesis loosening/ OR "Prosthesis Failure*".ti,ab. OR "Prosthetic Failure*".ti,ab. OR "Prosthesis Survival*".ti,ab. OR "Prosthesis Durab*".ti,ab. OR "Prosthesis Loosening*".ti,ab. OR "prosthetic loosening*".ti,ab. OR "aseptic loosening*".ti,ab. OR "implant loosening*".ti,ab. OR "implant failure*".ti,ab. OR "Prosthesis migration*".ti,ab. OR "Prosthetic migration*".ti,ab.) AND (exp survival analysis/ OR "Survival Analyses".ti,ab. OR "Survival Analysis".ti,ab. OR "Survival Rate*".ti,ab.) NOT (conference OR conference abstract OR "conference review").pt. AND 2008:2023.(sa_year).
Google Scholar
"Total knee arthroplasty" AND "loosening" AND "survival" from 2008 to 2023, no citations, no patents

Table SM3. Details of the literature search strategy for RSA studies.

PubMed
(("Photogrammetry"[Mesh:NoExp] OR Radiostereometric Analysis [Mesh] OR "roentgen stereophotogrammetric analysis"[tiab] OR "RSA" [tiab] OR "Radiostereometric" [tiab] OR "Radiostereometrics" [tiab] OR "stereophotogrammetric" [tiab] OR "stereophotogrammetrics" [tiab] OR "stereophotogrammetry" [tiab] OR "stereo-photogrammetric" [tiab] OR "stereophotogrammetrics" [tiab] OR "stereophotogrammetry" [tiab] OR "Photofluorography" [Mesh] OR "roentgen fluoroscopic"[tiab] OR "roentgen fluoroscopics"[tiab] OR "roentgen fluoroscopy"[tiab])) AND (("Joint Prosthesis"[Mesh:NoExp] OR "Hip Prosthesis"[Mesh] OR "Knee Prosthesis"[Mesh] OR "hip prosthesis"[tiab] OR "knee prosthesis"[tiab] OR "hip prostheses"[tiab] OR "knee prostheses"[tiab] OR "prosthetic hip"[tiab] OR "prosthetic knee"[tiab] OR "TKA"[tiab] OR "THA"[tiab] OR "THR"[tiab] OR "TKR"[tiab] OR "joint replacement"[tiab] OR "Arthroplasty, Replacement"[mesh:NoExp] OR "total knee replacement"[tiab] OR "total hip replacement"[tiab] OR "total knee arthroplasty"[tiab] OR "total hip arthroplasty"[tiab] OR "Arthroplasty, Replacement, Hip"[Mesh] OR "Arthroplasty, Replacement, Knee"[Mesh])) AND ("2016"[Date - Publication] : "2023"[Date - Publication])
Web of Science
TS=("Photogrammetr*" OR "RSA" OR "radiostereometr*" OR "radio-stereometr*" OR "stereophotogrammetr*" OR "stereo-photogrammetr*" OR "roentgen fluoroscop*" OR "Photofluorograph*" OR "Photo-fluorograph*") AND TS=("Joint Prosthe*" OR "hip prosthe*" OR "knee prosthe*" OR TKA OR TKR OR THA OR THR OR "hip arthroplast*" OR "knee arthroplast*" OR "knee replacement*" OR "hip replacement*") AND PY=(2016-2023)
Cochrane database
("Photogrammetr*" OR "RSA" OR "radiostereometr*" OR "radio-stereometr*" OR "stereophotogrammetr*" OR "stereo-photogrammetr*" OR "roentgen fluoroscop*" OR "Photofluorograph*" OR "Photo-fluorograph*"):ti,ab,kw AND ("Joint Prosthe*" OR "hip prosthe*" OR "knee prosthe*" OR TKA OR TKR OR THA OR THR OR "hip arthroplast*" OR "knee arthroplast*" OR "knee replacement*" OR "hip replacement*"):ti,ab,kw
Embase
(Stereophotogrammetry/ OR exp radiostereometric analysis/ OR "RSA".ti,ab. OR "Radiostereometr*".ti,ab. OR "Radio-stereometr*".ti,ab. OR "stereophotogrammetr*".ti,ab. OR "stereo-photogrammetr*".ti,ab. OR exp fluorography/ OR "Photofluorograph*".ti,ab. OR "Photo-fluorograph*".ti,ab. OR "roentgen fluoroscop*".ti,ab.) AND (joint prosthesis/ OR exp hip prosthesis/ OR exp knee prosthesis/ OR "hip prosthe*".ti,ab. OR "hip arthroplast*".ti,ab. OR "hip replacement*".ti,ab. OR "knee prosthe*".ti,ab. OR "knee arthroplast*".ti,ab. OR "knee replacement*".ti,ab. OR "prosthetic hip*".ti,ab. OR "prosthetic knee*".ti,ab. OR "TKA".ti,ab. OR "TKR".ti,ab. OR "THA".ti,ab. OR "THR".ti,ab. OR "joint replacement*".ti,ab. OR replacement arthroplasty/ OR exp hip replacement/ OR exp knee replacement/) AND 2016:2023.(sa_year). NOT (conference OR conference abstract OR "conference review").pt.
Google Scholar
"Total knee arthroplasty" AND "radiostereometric" from 2016 to 2023, no citations, no patents

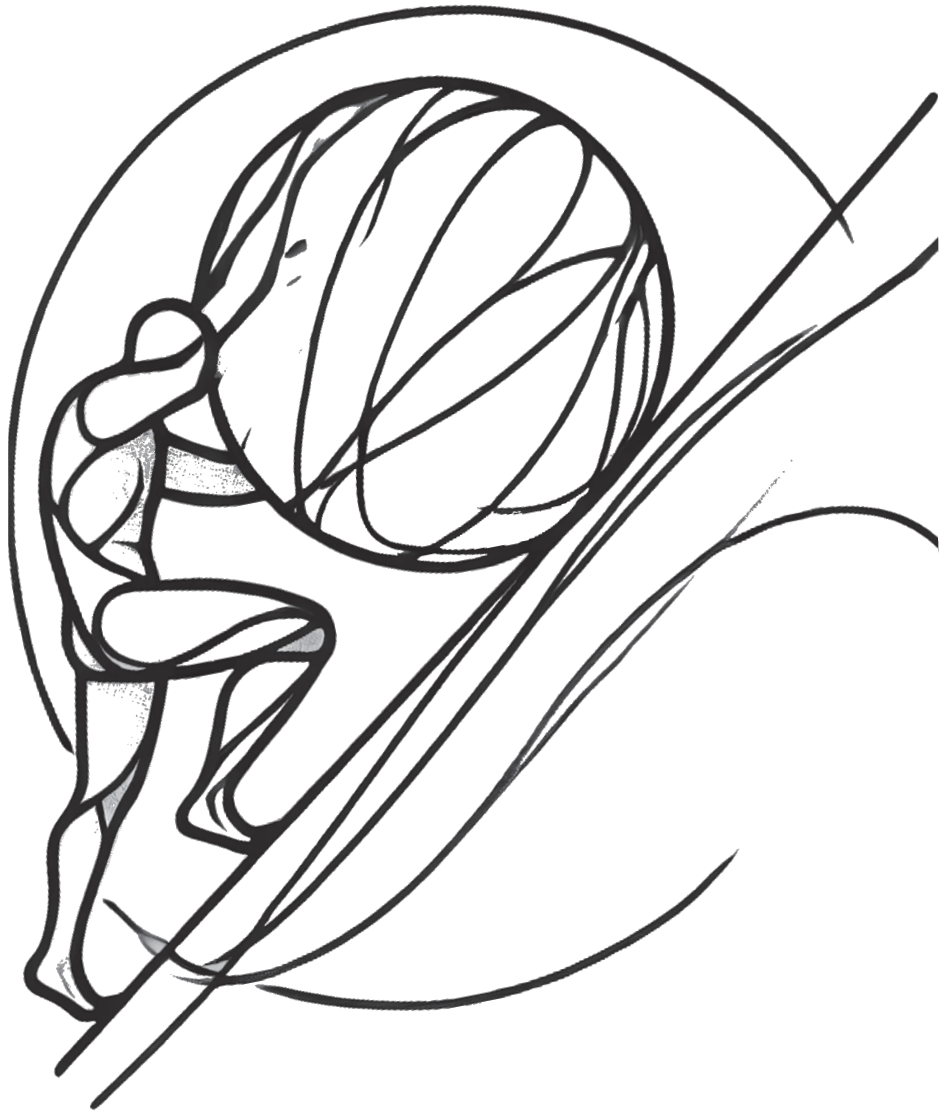
Table SM4. Match score item calculation

Age	Studies score 1 point for age if the mean age difference between matching studies is < 5 years; otherwise, 0 points if it exceeds 5 years or when it is not reported.
Gender	Studies score 1 point if the percentage difference between matching studies in females is < 10%; otherwise, 0 points if it exceeds 10% or when it is not reported.
Diagnosis	Studies score 1 point if the percentage difference between matching studies in diagnosis (osteoarthrosis) is < 10%; otherwise, 0 points if it exceeds 10% or when it is not reported.
Hospital type	Studies score 1 point if the studies were performed in similar type of hospitals (i.e. Academic, Developer, Special institute, High volume, Public); otherwise, 0 points if not or when it is not reported.
Continent	Studies score 1 point if the studies were performed on the same continent; otherwise, 0 points if not or when it is not reported.

The match score was determined by a Delphi-study among 37 independent experts (Pijls et al. 2011 (doi: 10.1186/1471-2474-12-173). The score ranges from 0 (poor) to 5 (excellent) points and is based on age, gender, diagnosis, hospital type, and continent.

PART 2

Post-market outcome of uncemented total knee replacements



CHAPTER 5

The uncemented ATTUNE Knee Outcome study (ATKOS):

short-term clinical improvements in advanced knee osteoarthritis

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ABSTRACT

Background
The functional patient-reported outcome measures (PROMs) of the newly introduced uncemented cruciate-retaining rotating-platform ATTUNE total knee replacement (TKR) have not yet been documented. This preliminary study aims to evaluate the short-term functional PROMs. Secondary objectives include evaluating the clinical outcomes, and rates of revisions and reoperations.

Method
Preliminary data from an ongoing 10-year multi-center observational study on patients with osteoarthritis receiving an uncemented ATTUNE were analyzed. Surgeries were performed with mechanical alignment and without patellar resurfacing. PROMs (Oxford-knee-score [OKS], Forgotten-joint-score [FJS], Anterior-Knee-Pain-Scale [KUJALA], EQ-5D-5L, NRS-pain-scale, TEGNER and UCLA) and clinical examination results were collected at 6 weeks, 6 months, and 1 year. Linear-mixed-models analyzed PROMs and clinical data, while revision rates were estimated using Kaplan-Meier survival analysis.

Results
After excluding 171 knees with less than one year of follow-up, a total of 260 knees were included in the analysis. The cohort comprised 57% women, of 67 years (standard deviation [SD]= 9.5) old, with a follow-up of 2.0 years (SD 0.9). All measured PROMs showed significant improvements at 6 months and 1 year compared to baseline. At 1 year postoperatively, the scores were as followed: OKS 36.8 (CI 35.7–38.0), FJS 53.1 (CI 49.7–56.6), KUJALA 71.7 (CI 69.5–73.8), EQ-5D-5L index 0.88 (CI 0.86–0.90), NRS at rest 1.2 (CI 0.9–1.4), NRS during movement 2.2 (CI 1.8–2.5), TEGNER 3.4 (CI 3.1–3.6), and UCLA 5.6 (CI 5.3–5.9). The revision rate was 1.9% (CI 1.9–1.9) at 1 and 2 years, and 2.8% (CI 2.8–2.8) at 3 years. Revisions included one case of aseptic loosening of the tibial component.

Conclusions
The results suggest that the uncemented cruciate-retaining rotating-platform ATTUNE TKR provides substantial short-term functional improvements compared to the preoperative state, which are at least equivalent to other well-established TKRs. Longer follow-up is necessary to determine if these findings are sustained, particularly regarding revision rates.

INTRODUCTION

To date, 10–20% of patients remain dissatisfied after knee arthroplasty (TKA), driving manufacturers to develop new implant designs with enhanced biomechanics to better meet the needs of a growing population of younger, more active patients anticipated in the coming years. *[21, 49]* Uncemented TKA rely on biological fixation through osseointegration, which is thought to benefit this changing patient demographic by preserving bone stock and potentially reducing risks associated with cement wear debris and loosening in the mid-to-long term. *[10, 18]*

In response to dissatisfaction rates, the ATTUNE TKA (DePuy Synthes, Warsaw, Indiana, USA) was introduced to replace its predecessor, the Low Contact Stress (LCS) TKA (DePuy Synthes, Warsaw, Indiana, USA), which had an excellent clinical track record of low revision rates and good patient-reported outcome measures (PROMs). *[408]* The cemented version of the ATTUNE was launched in 2012, followed by the uncemented version in 2017, which differs in fixation methods, surgical techniques, and potential reasons for revision, all of which could impact clinical and functional outcomes. *[409–411]*

The ATTUNE system is designed to provide smooth knee flexion and enhance anteroposterior stability through its gradually reduced femoral radius. *[409]* As for the cemented ATTUNE, it demonstrated equal to slightly better PROMs compared to previous designs. *[412]* For the uncemented design, only 3 studies have investigated PROMs: one investigated the cruciate-retaining (CR) mobile-bearing (MB) design, but had an insufficient sample size due to it focusing on implant migration, another solely investigated the Knee Injury and Osteoarthritis Outcome Score (KOOS-PS) of the CR MB design, and the third studied only the Forgotten-joint-score (FJS) of the posterior-stabilized (PS) MB design. *[182, 413, 414]* All three studies reported equal to slightly better scores compared to their respective comparisons in national registries after 1 year. Moreover, it is of utmost importance to thoroughly evaluate the early functional outcomes of newly introduced implants, regardless of their fixation method, as poor outcomes identified at later term comes at the expense of patients' well-being.

This study aims to report the preliminary short-term outcomes of the "follow-up uncemented ATTUNE Knee Outcome Study" (ATKOS) *[409]* with a primary focus on assessing a broad overview of different 6-month and 1-year PROMs to provide a thorough evaluation of patient outcomes. Secondarily, it evaluates the clinical and functional outcomes, revision rates, and complications in patients with end-stage primary or secondary osteoarthritis who received the uncemented CR MB ATTUNE total knee system.

PATIENTS AND METHODS

Study design

This study reports short-term findings from the multicenter ATKOS study *[409]*, adhering to STROBE and AQUILA guidelines *[415, 416]*. Ethical approval was obtained from the Amsterdam UMC (CME NL71274.029.19), and the protocol was preregistered on ClinicalTrials.gov (NCT04247672) and published. *[409]*

Settings

The ATKOS study aims to assess revision and reoperation rates of the uncemented ATTUNE knee system over 10 years, with a target enrollment of 900 patients. *[409]* Recruitment began in 2019 and is ongoing across four hospitals in the Netherlands, namely:

- Spaarne Gasthuis, Hoofddorp (4 surgeons)
- Bergman Clinics, Rijswijk (2 surgeons)
- Maastricht Universitair Medisch Centrum, Maastricht (3 surgeons)
- Alrijne Ziekenhuis, Leiderdorp (2 surgeons)

According to the ATKOS protocol, all recruited patients undergo physical examinations and complete questionnaires at predefined intervals: at 6 weeks (physical examination only, except at Bergman Clinic), 6 months, 1 year, 5 years, and 10 years. *[409]*

Implant and surgical procedure

This study investigates the uncemented, MB (rotating platform), CR ATTUNE total knee system by DePuy Synthes, designed for anatomic patellar tracking and enhanced anteroposterior stability up to 150° flexion. The cobalt-chromium-molybdenum alloy tibial tray features radially positioned pegs and a central keel for fixation, with a spherical bead coating to minimize migrations and support bone ingrowth. The polyethylene insert incorporates antioxidants for wear resistance and stability. Patella resurfacing was not performed.

Surgical techniques followed manufacturer guidelines, including medial arthrotomy without a tourniquet and mechanical alignment via intramedullary femoral and extramedullary tibial guides. Rotational alignment adhered to Akagi's line for the tibia and the transepicondylar axis and Whiteside's line for the femur. To minimalize bias, all surgeons were uniformly trained in the ATTUNE system. Further implant and surgical details are available in the published study rationale. *[409]*

Participants

All patients between 21 and 90 years, with end-stage primary or secondary osteoarthrosis of the knee that necessitates a primary TKA, and able to comply with the study schedule, were consecutively asked for participation. Patients were

excluded from the ATKOS study if they withdrew prior to surgery or if surgery with the uncemented ATTUNE could not proceed, or when there was an indication for a cemented fixation (e.g., decreased bone stock or quality of the cancellous bone), a stemmed component or a fixed posterior-stabilized insert. For the current short-term study, patients were secondarily excluded if their follow-up was less than 1 year. Demographic details of included patients were presented in **Table 1**.

Variables and measurements

Since the main study commenced in 2019 and is still ongoing, the primary outcomes of the current preliminary study include the PROMs measured preoperatively, and at 6 months and 1 year postoperatively. The PROMs include:

1. Knee and health-related PROMs, assessed preoperative, 6 months and 1-year post-surgery.
    - Oxford Knee Score (OKS): assessing the pain and function of the knee; 0 = most severe problems; 48 = least severe. *[417]*
    - Forgotten Joint Score (FJS): assessing artificial knee joint awareness during daily living, by use of a 5-point Likert scale, with a score of 0 = most aware; 100 = least aware. *[418]*
    - Anterior Knee Pain Scale (KUJALA) assessing patellofemoral function and pain; 0 = worst; 100 = best. *[419]*
    - EuroQol 5-dimension 5-level (EQ-5D-5L): assessing general health; 0 = worst; 1 = best. *[420]*
    - Numerical rating scale (NRS-rest; NRS-activity): assessing pain at rest and during activity; 0 = no pain; 10 = worst pain imaginable).
    - Anchor scales by 3 likert-cales, assessing satisfaction (0 = not satisfied; 10 = very satisfied), change in pain and daily function since the index surgery (0 = much deteriorated; 7 = much improved).

2. Return to sport and work, assessed preoperative and 1-year post-surgery.
    - University of California Los Angeles activity scale (UCLA): an ordinal rating scale from 0 to 10; 0 = no physical activity or dependency on others; 10 = regular participation in impact sports.
    - Tegner rating scale, an ordinal rating scale from 0 to 10; 0 n= o physical activity or disability; 10 = participating in highly competitive sports.

The secondary outcomes of the study encompass the clinical outcomes from physical examination, performance-based measurements (PBMs), complications, and the rate of planned or performed revisions and reoperations. Clinical outcomes were registered during physical examination, including measurements of range of motion (ROM), anteroposterior and mediolateral stability, and anteroposterior alignment. The anteroposterior alignment was measured by use of full-leg, full weight-bearing conventional radiographs preoperatively and 1 year postoperatively.

Performance-based measurements were performed preoperatively and at 1-year, including the 30-second chair stand test (30-CST), 40-meter fast-paced walk test (40-FPWT), and the stair climb test (SCT). *[421]* Patients performed as many repetitions of standing up and sitting down in 30 seconds for the 30-CST, walked 40 meters while timing was recorded for the 40-FPWT, and ascended and descended a set of stairs while timing was recorded for the SCT. Additionally, planned or performed revision and reoperation surgeries were registered. A major revision was defined as the implantation, explantation, or exchange of at least the femoral or tibial component, and a minor revision in case if only the insert was exchanged and/or patella was added. A reoperation was defined as all interventions or procedures that did not qualify for a minor or major revision. Complications encompass any adverse events related to knee surgery occurring during the postoperative period. All data were collected on paper or electronically, by using Research Manager (Cloud9 software, Deventer, Netherlands) and exported for analysis to SPSS Statistics 26.0 (IBM SPSS, New York, USA).

Statistical methods

Baseline characteristics were presented as means with standard deviations (SD), medians with interquartile ranges (IQR), or frequencies with proportions, depending on the data distribution. PROM scores and clinical outcomes were presented as means with corresponding 95% confidence intervals (CI) or frequencies with proportions. The mean and CI of PROMs and clinical outcomes were calculated using a linear mixed-effects model (LMM) to effectively account for missing values and within-patient correlations. In the LMM, postoperative time was set as a fixed effect, while patient cases were treated as random effects. Since PROMs were the primary objective, the CI of scores were compared with those from previous follow-up moments (i.e., baseline vs. 6 months and 1 year, 6 months vs. 1 year). Non-overlapping CIs indicate a significant difference between PROM values at the different follow-up moments, whereas overlapping CIs indicate non-significance. *[64, 422]* To assess the potential impact of attrition bias, PROMs of patients excluded due to missing 1-year follow-up data but with available 6-month scores were compared to those of included patients. Cumulative crude revision incidences were assessed using Kaplan-Meier survival analyses for major and minor revision for any reason. Time was characterized from primary TKA to first revision, patient death, or the date of data export (April 5, 2024). Deaths were censored observations, assuming independence from the risk of revision. Revision rates were presented with corresponding CIs. Complications and adverse events were described.

A post-hoc sample size calculation was performed to determine whether the study had adequate power to evaluate the PROMs. Based on a minimal important clinical difference of 5 points and a SD of 9.74 for the Oxford Knee Score *[423]*,

the current study with 260 knees had 99% power to detect a 5-point difference at a significance level of 0.05.

Funding

The study was funded by DePuy Synthes (DPS-JMP-2020–018), but the company had no involvement in design, data collection, analysis, interpretation, or manuscript writing. All authors declare no conflict of interest.

RESULTS

Out of 444 cases enrolled in the ATKOS study by April 2024, 431 knees met the inclusion criteria (**Figure 1**). Thirteen cases were excluded post-recruitment for various reasons (**Figure 1**). Additionally, 145 knees were secondarily excluded as they had less than one year of follow-up (of which 51 patients had 6-monthts values). Ultimately, 241 patients (260 knees) with at least one year of follow-up were included (**Figure 1**). Missing PROM scores were noted for 24 preoperatively and 47 at both 6-month and 1-year follow-ups.

Patient-reported outcomes measures

All mean PROM scores measured at 6 months and 1 year significantly improved compared to the preoperative scores (**Table 2**). Additionally, all PROM scores, except for the EQ5D-5L index, EQ5D-5L VAS scale, and NRS for pain at rest, showed significant improvement between the 6-month and 1-year postoperative periods (**Table 2**). Majority of scores improved the most during the first 6 months following surgery. Patients rated their satisfaction on a 0 to 10 scale, with scores of 7.8 (CI 7.6–8.1) at 6 months and 8.2 (CI 7.9–8.5) at 1 year.

The risk of attrition bias was deemed minimal. Assessment of attrition bias showed that the 51 patients with 6-month data but excluded due to missing 1-year follow-up had a mean OKS of 27.1 (CI 21.8–32.9), which was significantly lower than that of the included patients (34.5 [CI 33.4–35.6]). All other PROMs were comparable between the two groups.

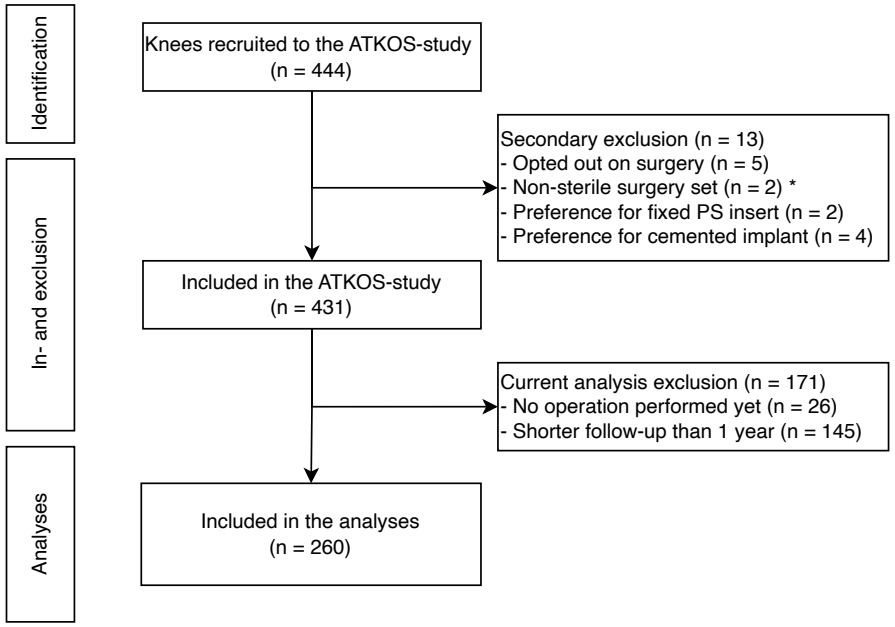


Figure 1. Flowchart of recruitment and inclusion of patients to the AKTOS study.

* Cases where the usual sterile surgical set for the ATTUNE knee system was found to be inadequately packaged, leading to the use of an alternative knee system.

Clinical outcomes

The mean range of motion reached was 119.3 (CI 117.7–120.3) at 1-year, which was comparable to the preoperative range of motion (**Table 3**). The proportions of patients with deformations (e.g., extensor lag, mediolateral and anteroposterior instability) decreased after surgery (**Table 3**). The mean coronal mechanical alignment was corrected from 180.1 (CI 179.3–181.0) preoperatively to 182.1 (CI 181.1–183.1) after 1 year. All 3 PBM exercises demonstrated significantly improved 1-year scores compared to preoperatively (**Table 3**).

Table 1. Demographic, clinical and perioperative characteristics of the included population.

Number of patients	241
Number of knees	260
Performed in hospitals, n (%)	
Spaarne Gasthuis	94 (36.2)
Bergman Clinics	130 (50.0)
Alrijne hospital	18 (6.9)
Maastricht university medical center	18 (6.9)

Table 1. Continued

Duration of symptoms, median years (IQR)	3.5 (2.0 – 6.0)
Secondary osteoarthritis, n (%)	8 (3.1)
Sex, woman, n (%)	149 (57.3)
Mean age, years (SD)	66.6 (9.5)
< 50 years, n (%)	5 (1.9)
50 – 59 years, n (%)	53 (20.4)
60 – 69 years, n (%)	93 (35.8)
70 – 79 years, n (%)	94 (36.2)
80 > years, n (%)	15 (5.7)
Mean BMI, (SD)	29.3 (5.4)
ASA grade, n (%)	
I	40 (15.7)
II	161 (63.1)
III to IV	54 (21.2)
Surgery duration in minutes, mean (SD)	55.0 (18.0)
Follow-up in years, mean (SD)	2.0 (0.9)

Proportions do not add up due to missing values
n Number, BMI Body mass index, IQR Interquartile range, SD Standard deviation

Table 2. Repeated outcome of patient-reported outcome measures 6-months and 1-year postoperative, compared to preoperative values, calculated by use of linear mixed-model analyses.

	Preoperative	**Postoperative**	
		6-months	**1-year**
	Mean (95%CI)	**Mean (95%CI)**	**Mean (95%CI)**
Cases	236	213	213
OKS score	24.8 (23.7 – 25.9)	34.5 (33.4 – 35.6) [A]	36.8 (35.7 – 38.0) [A, B]
FJS (%)	16.9 (13.6 – 20.2)	44.7 (41.3 – 48.1) [A]	53.1 (49.7 – 56.6) [A, B]
KUJALA score	46.3 (44.3 – 48.4)	66.3 (64.2 – 68.4) [A]	71.7 (69.5 – 73.8) [A, B]
EQ5D-5L index	0.64 (0.62 – 0.66)	0.84 (0.82 – 0.86) [A]	0.88 (0.86 – 0.90) [A]
VAS-scale	69.8 (67.6 – 72.0)	78.9 (76.6 – 81.2) [A]	79.4 (77.1 – 81.7) [A]
NRS rest	5.1 (4.8 – 5.3)	1.7 (1.4 – 2.0) [A]	1.2 (0.9 – 1.4) [A]
NRS activity	6.8 (6.5 – 7.1)	2.9 (2.6 – 3.2) [A]	2.2 (1.8 – 2.5) [A, B]
TEGNER	2.4 (2.2 – 2.6)	n/a	3.4 (3.1 – 3.6) [A, B]
UCLA	4.5 (4.2 – 4.7)	n/a	5.6 (5.3 – 5.9) [A, B]

p-values were calculated for values compared to baseline.
[A] Significantly different compared to baseline values, based on non-overlapping 95%CIs.
[B] Significantly different compared to 6-months values, based on non-overlapping 95%CIs.
CI Confidence interval

Table 3. Baseline and repeated measurements of physical examination and performance-based measurements.

	Preoperative	Postoperative		
		6-weeks *	6-months	1-year
Number of knees	259	120	210	223
ROM, mean degrees (CI)	119.2 (117.7; 120.8)	108.0 (105.8; 110.1) [A]	116.0 (114.3; 117.8)	119.3 (117.7 – 120.3)
Extension lag, n (%)	92 (35.4)	56 (46.7)	45 (21.4)	33 (14.9)
Anteroposterior stability				
< 5 mm, n (%)	225 (86.5)	112 (95.7)	207 (98.6)	219 (98.2)
5-10 mm, n (%)	25 (9.6)	5 (4.3)	2 (1.0)	4 (1.8)
> 10 mm, n (%)	5 (1.9)	0 (0.0)	1 (0.5)	0 (0.0)
Mediolateral stability				
< 5 degrees, n (%)	174 (66.9)	115 (95.8)	196 (96.6)	208 (94.5)
5 – 9 degrees, n (%)	75 (28.8)	3 (2.5)	7 (3.4)	12 (5.5)
10 – 14 degrees, n (%)	5 (1.9)	2 (1.7)	0 (0.0)	0 (0.0)
> 14 degrees, n (%)	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Performance based measurements				
30-CST, mean reps (CI)	9.3 (8.8–9.8)	n/a	n/a	12.2 (11.7–12.7) [A]
40-FPWT, mean sec (CI)	34.5 (33.2–35.8)	n/a	n/a	27.7 (26.3–29.1) [A]
SCT, mean sec (CI)	14.5 (13.5–15.6)	n/a	n/a	11.7 (10.6–12.8) [A]

n Number, SD Standard deviation, CI Confidence interval, Sec seconds, Reps repetitions, ROM Range of motion. [A] Significantly different compared to baseline values, based on non-overlapping 95%CIs.
* Fewer patients were examined at 6 weeks, as this was not standard clinical practice at one institute.

Revision and adverse events

As for the survival, 9 revisions (3 major, 6 minor) and 12 reoperations were planned or performed (**Table 4**). The minor revision rate was 1.5% (CI 1.5–1.5) at 1 year, and 2.1% (CI 2.1–2.1) at 2 and 3 years. For major revisions, the rates were 0.8% (CI 0.8–0.8) at 1 and 2 years, and 1.6% (CI 1.6–1.6) at 3 years. The rate of aseptic loosening was 0.9% (CI 0.9–0.9) at three years, with one case occurring at year two. The overall revision rate was 1.9% (CI 1.9–1.9) at 1 and 2 years, and 2.8% (CI 2.8–2.8) at 3 years. A total of 243 patients were at risk at 2 years, and 130 at 3-years. Additionally, a total of 18 cases withdrew and 2 patients died. As for reoperations, a total of 11 manipulations under anesthetic (MUA) were performed after an average of 6.1 months (SD 5.9), with a 1-year incidence of 3.9% (CI 3.9–3.9). Nine serious adverse events occurred, excluding revisions and reoperations, all listed in **Table 5**.

Table 4. Reasons for revisions and reoperations

Reasons	intervention	n	Mean months, (SD)
Reoperation			
Stiffness or flexion contracture	Manipulation under anesthetic	11	6.1 (5.9)
Periprosthetic fracture	Plate osteosynthesis	1	9.6 (-)
Minor revision			
Insert spinout	insert exchange to thicker size	3	0.5 (0.8)
Patellofemoral osteoarthritis	Adding a patella component	2	10.3 (9.7)
Acute prosthetic joint infection	DAIR with insert exchange	1	1.0 (-)
Major revision			
Femoral fissure and lateral tibial plateau fracture	Revision to cemented sleeved implant	1	1.4 (-)
Expected aseptic loosening	Exchange to cemented sleeved TKR	1	25.8 (-)
Medial collateral ligament rupture	Revision to hinged cemented implant	1	0.7 (-)

Table 5. Adverse events occurred during the study up to April 2024.

Number of knees	Event
1	Direct postoperative collapse resulting from hypotension and bradycardia, requiring an extended hospital stay.
1	Distal patellar fracture, treated conservatively.
2	Hospitalization for bilateral pulmonary embolism.
1	Hospitalization for urosepsis.
1	Shoulder fracture from a fall, requiring total shoulder arthroplasty.
1	Death due to complications of endometrial carcinoma.
1	Hospitalization for treatment of an ankle wound.
1	Endoscopic repair of an inguinal hernia.

DISCUSSION

The most important finding of the current study was that all PROMs, including the OKS, FJS, KUJALA, EQ5D-5L, NRS scores, and Tegner and UCLA activity scores, improved significantly at 6-months and 1-year postoperatively, compared to baseline. This was the first study with a sufficient sample size that was able to provide insight into the short-term functional outcomes of the uncemented CR MB ATTUNE TKA. These findings suggest that the uncemented ATTUNE TKA

can deliver short-term substantial functional benefits and pain relief to patients with end-stage primary or secondary osteoarthrosis of the knee.

Due to the recent introduction of the uncemented ATTUNE TKA system, literature and available PROMs on the device are limited. This scarcity makes it challenging to compare scores accurately and assess the generalizability of our findings.

The 5-year radiostereometric analysis (RSA) RCT by Puijk et al. (2025) compared 30 uncemented ATTUNE implants with 31 uncemented LCS implants. *[424]* Although underpowered for robust PROM evaluation, their study reported KUJALA scores of 76.9 (SD 15.3) for ATTUNE and 79.9 (SD 17.6) for LCS, both slightly higher than the 1-year score of 71.8 (CI 69.5–74.1) in the current study, suggesting continued improvement beyond 5 years. *[424]* Their OKS and NRS-rest and NRS-activity scores were significantly better for ATTUNE compared to LCS up to 3 months, with no differences observed at later follow-ups. *[424]* One possible explanation for ATTUNE's early improvement could be its anatomical femoral design, enhancing anteroposterior stability throughout knee flexion. *[182]* When comparing their 6-month and 1-year PROM scores to ours, or those (OKS and KOOS) reported by national registries, similar results were observed. *[4–6, 424]* However, as our study did not assess PROMs earlier than 6 months, we could not verify the results of these early (i.e., <3 months) improvements found in Puijk *[424]* The OKS and KOOS scores are widely used in studies and registries but are acknowledged to have a high ceiling effect, making them less effective in distinguishing between good and excellent outcomes compared to scores like the FJS and KUJALA. *[419, 425–427]* Unfortunately, these outcomes are not yet registered by national arthroplasty registries. Additionally, this study investigated functional improvement using PBMs, as recommended by previous research. *[421]* This outcome is rarely explored in other studies, highlighting a unique strength of the current investigation in evaluating patient recovery comprehensively.

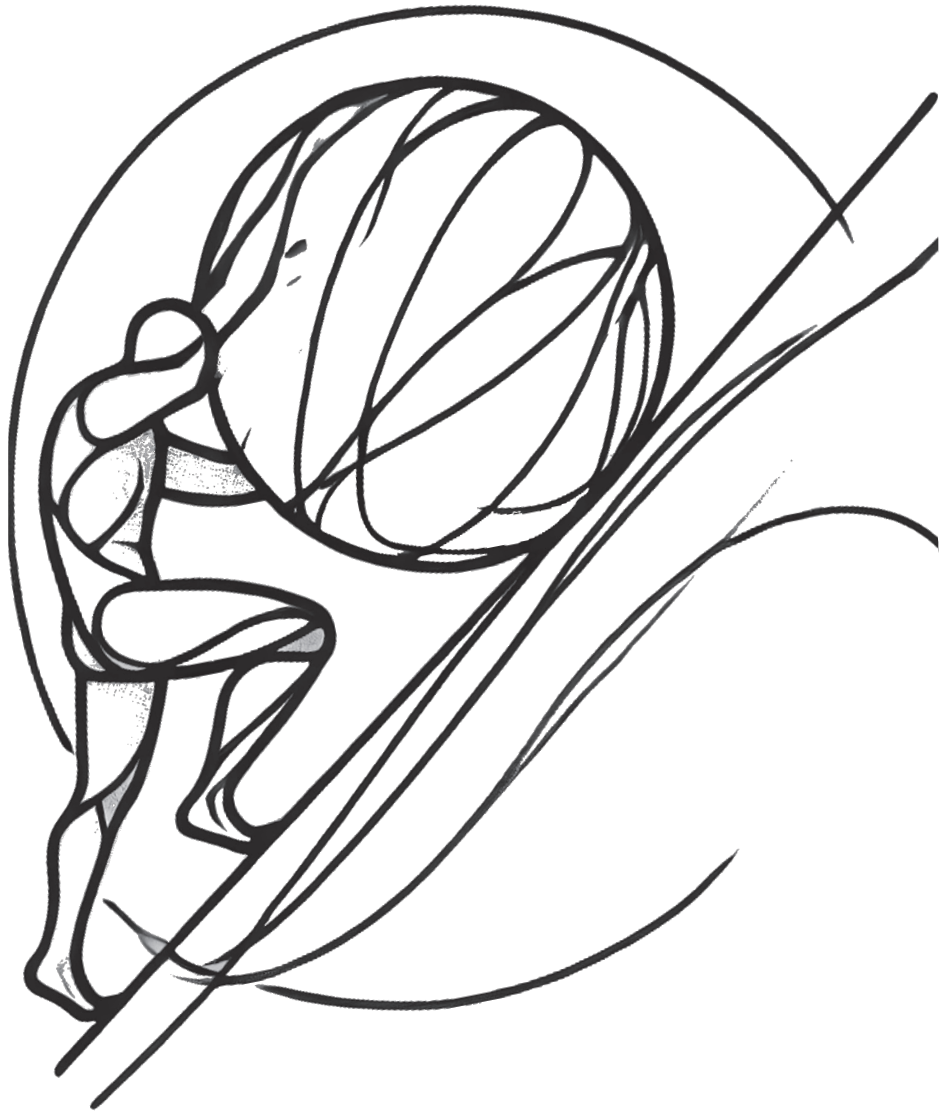
We observed an overall revision rate of 1.9% (CI 1.9–1.9) at 3 years, with most revisions due to insert spinout—a recognized complication of TKAs with MB inserts. Keogh *[413]* (2020) reported a 2.9% spinout rate in 332 uncemented CR MB ATTUNE implants, with spinouts occurring only in cases using the measured resection technique, not gap-balancing. *[413]* In contrast, our study exclusively used the gap-balancing technique, which may explain the lower spinout rate observed. One implant in our cohort required revision for aseptic loosening of both components. This aligns with the 5-year RSA RCT by Puijk (2025), which demonstrated equal to superior implant migration stability for the uncemented ATTUNE compared to the LCS, indicating effective long-term fixation. *[424]* We observed a 1-year MUA rate of 3.9% (CI 3.9–3.9), higher than the 1.7% reported in a Swedish registry study of 64,840 TKAs and 1,061 MUAs. *[428]* That study highlighted variation in MUA incidence (0–5%) across hospitals, mainly in younger patients (65%), women (64%), and those with ASA scores ≤2 (88%), reflecting a

lack of universal indications for MUA. However, the current study lacks the power to assess these factors or rates conclusively. Furthermore, no data exist on MUA rates for the cemented ATTUNE design, underscoring the need for longer-term studies with larger cohorts, including a comparison group.

This study has several limitations. The uncemented ATTUNE TKA is exclusively used for research in the Netherlands and is not the sole implant in each center, potentially introducing selection bias by excluding patients with major deformities requiring cemented, hinge, or PS implants. This may result in a healthier study population compared to the general arthroplasty population. However, the pre- and postoperative demographics and PROM scores were comparable to those in the Dutch arthroplasty registry, suggesting minimal bias. *[5]* Additionally, The ATKOS study lacks a comparison group, making it difficult to attribute PROM improvements solely to the uncemented ATTUNE, warranting cautious interpretation. Nevertheless, it is the first study with a sufficient sample size, making it valuable for benchmarking to other implants. Further, the study remains small for detecting rare complications, conducting subgroup analyses, or calculating reoperation and revision rates. However, given the recent adoption of the uncemented ATTUNE, we deemed it essential to evaluate its performance at an early stage to detect any potential issues with failure rates or clinical performance.

CONCLUSION

The 6-month and 1-year PROMs from this preliminary study suggest that the uncemented CR MB ATTUNE TKA provides substantial short-term functional improvements compared to the preoperative state, which are at least equivalent to other well-established TKAs. The significant improvements in PROMs at 6 months and 1 year postoperatively indicate that it can deliver clinically relevant benefits and pain relief to patients in the short term. The larger follow-up study is necessary to determine if these findings are sustained over the long term, particularly regarding revision rates.



CHAPTER 6

5-year migration and inducible displacement of the uncemented LCS and ATTUNE rotating platform knee systems:

a secondary report of a randomized controlled RSA trial.

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ABSTRACT

Purpose

Early migration of the uncemented cruciate-sacrificing rotating platform ATTUNE and Low Contact Stress (LCS) tibial components was classified as at-risk for aseptic loosening rates exceeding 6.5% at 15 years based on recent fixation-specific migration thresholds. In this secondary report of a randomized controlled trial (RCT) we aimed to evaluate whether the 5-year migration, inducible displacement, and the clinical outcome of the ATTUNE components were comparable with those of the LCS.

Methods

Patients from the initial 2-year radiostereometric analysis (RSA) RCT were recruited for a 5-year follow-up. At 5 years, participants underwent 2 supine and 1 loaded RSA examination, clinical assessments, and questionnaires. Migration was analyzed using maximum total point motion (MTPM), translations, and rotations, focusing on 5-year migration, continuous migration (>0.10 mm/year), and inducible displacement. Revisions, along with clinical and functional outcomes, were also evaluated.

Results

At 5 years, 24 ATTUNE and 24 LCS implants were analyzed. The mean MTPM was similar for tibial components (ATTUNE 1.13mm [confidence interval (CI) 0.94–1.33]; LCS 1.24 mm [CI 1.05–1.46]) but significantly lower for the ATTUNE femoral component (1.14 mm [CI 0.92–1.39]) than LCS 1.87 mm [CI 1.57–2.21]). 2-to-5-year migration rates were comparable, but 11 ATTUNE and 7 LCS exceeded 0.10 mm MTPM/year, indicating a higher risk of loosening. Inducible displacement was similar, although, 1 patient with a tibial ATTUNE showed excessive displacement (3.34 mm MTPM) with focal osteolysis but no symptoms. 1 revision 10 days post-surgery was performed for an ATTUNE insert spinout, resolved with an isolated insert exchange. Clinical and functional outcomes were comparable.

Conclusion

At the 5-year follow-up, ATTUNE tibial components showed similar migration, while the femoral component migrated significantly less than the LCS, what mainly occurred during the first 2 years. 2-to-5-year migration rates, inducible displacement, clinical and functional outcomes were comparable. These findings suggest a comparable long-term risk of aseptic loosening between the uncemented ATTUNE and LCS knee systems.

INTRODUCTION

The introduction of new total knee replacements (TKRs) or fixation methods carries the potential risk of higher revision rates, with several examples of newer implants showing inferior results compared with their predecessors *[41, 46, 429, 430]* A prominent case is the original cemented ATTUNE knee system from 2012 (DePuy Synthes, Warsaw, Indiana, USA), which exhibited a higher failure rate than earlier designs due to debonding at the tibial implant-cement interface *[431, 432]* To address this, the ATTUNE S+ design was introduced in 2017, incorporating an improved "macrolock" cement-locking mechanism and "microblast" surface, to enhance stability *[431, 432]* For this reason, it remains crucial to closely study performance at an early stage, while wide usage of the implants is still limited. Radiostereometric analysis (RSA) is a method that can accurately measure the 3-dimensional micromotions of an implant relative to the bone, requiring only a small number of patients to study *[37]* When measured over time, implant migration patterns can provide valuable insight on the implants long-term quality of fixation and potential risk of loosening up to 15 years *[53, 143]* Additionally, inducible displacement is an RSA method that assesses the current state of the implant–bone fixation, by comparing its position under loading conditions, such as standing, to its position in an un-loaded condition, e.g. non-weight-bearing supine position *[143, 200, 207, 433–436]* In our previously performed RSA randomized controlled trial (RCT), we analyzed the 2-year migration of the newly introduced uncemented ATTUNE TKR and its predecessor, the uncemented Low Contact Stress (LCS) implant (DePuy Synthes, Warsaw, Indiana, USA) *[182]* The study revealed similar improvements in patient-reported outcome measures (PROMs), a significantly lower femoral component migration of the ATTUNE compared with the LCS, and comparable migration patterns for both tibial components. However, according to the newly defined fixation-specific migration thresholds by Puijk et al. (2024), the 6- and 12-month migrations of both tibial components would be identified as at-risk for a revision rate higher than 6.5% due to aseptic loosening at 15 years *[53]* While the uncemented LCS implant has been used for several decades, demonstrating excellent long-term revision rates for aseptic loosening *[5, 311, 321]*, the uncemented ATTUNE system, first introduced in 2016, does not yet have similarly reassuring long-term data. This is a secondary report of an RCT aiming to investigate whether the uncemented ATTUNE TKR exhibits a comparable migration pattern with the LCS system in patients with end-stage primary osteoarthritis over a 5-year follow-up period. Secondarily, it compares the inducible displacement, clinical, and functional outcomes between implants.

METHODS

Trial design

This follow-up study assesses the 5-year follow-up data, extending the analysis of a prior 2-year follow-up, single-center, single-blinded, noninferiority RCT in the Netherlands *[182]* The conduct and reporting of this study adhere to the RSA (2024) *[37]* and CONSORT (2010) guidelines *[437]*. The RSA item checklist is provided in **Table S1** (see Supplementary data).

Participants

All patients with primary osteoarthritis who participated and underwent arthroplasty by 3 surgeons in the original study between July 2017 and April 2019 were deemed eligible. Patients were excluded in case they underwent major revision (exchange of the tibial or femoral component), or when they were not able or unwilling to participate. No exclusions were conducted when patients passed the recommended ± 4 weeks examination window. *[37]* Data was collected in the Spaarne Gasthuis Hospital (Hoofddorp, the Netherlands) and migration data further analyzed in the Leiden University Medical Center (Leiden, the Netherlands).

Intervention, randomization and blinding

Patients were randomly assigned to receive either uncemented cruciate-sacrificing rotating platform LCS or ATTUNE TKR in a 1:1 allocation ratio. Detailed information on the design differences, randomization, allocation, surgical techniques, and postoperative care is stated in the initial study (Koster et al. 2023) *[182]* Patients were unblinded to the type of implant they received after 2 years. At the 5-year follow-up, the researchers (RP, JS) who performed the clinical assessments were blinded to the type of implant each patient had received.

Radiostereometric technique

At the 5-year follow-up, available patients underwent 2 sequential non-loaded supine examinations and 1 loaded single-leg stance examination. The first supine examination was used for the migration pattern, while the second supine examination was used to calculate the measurement error (i.e., precision). Inducible displacement was calculated by comparing the displacement between the first supine and the loaded examination. For the single-leg stance, patients were instructed to fully bear their body weight on the operated-on leg, placing the contralateral foot on a diagonally positioned chair in front of them with their knee bent at a 90° angle.

Radiographs were taken by use of 2 DX radiology detectors (35 × 43 cm, Siemens Healthcare, Germany, and Carestream Health, USA) and an acrylic biplanar calibration cage (Baat Medical, Netherlands). Baseline reference examinations were undertaken on the first postoperative day after weightbearing. Migration

was expressed using maximum total point motion (MTPM) and translations measured in millimeters (mm), and rotations in degrees (°). Migration of implants was measured using the right knee as the reference side. Positive translations were defined as proximal translation in the y-axis, medial translation in the x-axis, and anterior translation in the z-axis. Positive rotation directions were defined as internal rotation about the y-axis, anterior tilt about the x-axis and varus rotation about the z-axis. Component migration was calculated using the consistent-marker method, by use of model-based RSA software (v.4.2, RSAcore, Netherlands), utilizing computer-aided design models. The migration of previous follow-ups was recalculated by the same researcher (LAK) to ensure the same markers were used over the 5-year period. Condition numbers were limited to 120, and the mean error of rigid body fitting was restricted to 0.35 *[37]*

Outcome measures

The primary outcome measure of this follow-up study was the 5-year migration pattern (MTPM) of both components and implants. The secondary outcome was the inducible displacement and clinical and functional outcome. For the clinical outcome, all complications up to 5 years were recorded. The functional outcome was measured by range of motion and stability of the joint. PROMs were collected by questionnaires, including the Oxford Knee Score (OKS), KOOS-PS, the Anterior Knee Pain Scale (KUJALA), EQ-5D-3L, the numeric rating scale for pain at rest (NRS-rest) and activity (NRS-activity) *[182]* The KUJALA score was introduced for additional assessment of PROM outcomes after the 2-year report *[182]*.

Sample size

A sample size calculation for the initial 2-year RCT determined that 26 total knee replacements (TKRs) per group were necessary to confirm the non-inferiority of the ATTUNE system, with 80% power ($\alpha = 0.01$, SD = 0.6 mm) *[182]*.

Statistics

All migration and displacement values were presented as means and 95% confidence intervals (CI). MTPM values were log-transformed (log10) for analyses and back-transformed for presentation in Tables and Figures. All repeated migration measures were calculated by use of a linear mixed-effects model (LMM). The number of implants that had a higher 2-to-5-year migration than the 0.1 mm/year threshold were evaluated, since this has been suggested to be associated with a higher risk of loosening, according to Ryd et al. *[38]*. Measurement error statistics from double examinations at 5 years were provided for each migration direction *[37]* The mean inducible displacement at 5 years was compared with this measurement error to assess actual inducible displacement. The inducible displacement of cases with a greater than 0.30 mm (>0.1 mm/year) 2-to-5-year

migration was evaluated. The distribution of the CIs of migration values were compared to evaluate significance.
The differences in clinical and functional outcomes were evaluated for clinical relevance, and presented in boxplot diagrams besides the previous interval scores. Analyses were performed R software (v.4.2.1, R Foundation for Statistical Computing, Vienna, Austria).

Sensitivity analysis

Sensitivity analyses were conducted to evaluate whether patients outside ±4 weeks examination window or using the second instead of the first supine examination at 5 years altered results. The potential influence of attrition bias was assessed by comparing the 2-year migration patterns for patients with and without 5-year follow-up.

Ethics, registration, data sharing, funding, and disclosure

The Committee for Medical Ethics of Leiden University Medical Center (LUMC) approved the study (Protocol ID P22.065, ABR NL82000.058.22) and the study was registered in Clinical Trials (ClinicalTrials.gov ID NCT05623215). All patients provided informed consent. Data is available by contacting the corresponding author. Both the original and current studies were investigator-initiated. In the original trial, DePuy Synthes provided funding for the radiostereometric analysis. In the current study, no external funding was received, and DePuy Synthes played no role in the study's design, analysis, interpretation, or manuscript preparation. No author had any conflicting interest. Complete disclose of interest forms according to ICMJE are available on the article page, doi: 10.2340/17453674.2024.42744.

RESULTS

24 LCS (14 females) and 24 ATTUNE (11 females) uncemented TKR systems were included (**Figure 1**). For the patients available at the 5-year follow-up, the ATTUNE group had a mean age of 72.6 years (SD 8.6) and BMI of 30.1 (SD 5.3), while the LCS group had a mean age of 73.2 years (SD 6.3) and BMI of 27.6 (SD 2.6) at the 5-year follow-up. The mean follow-up duration was 61.3 months (SD 3.1). 8 patients were examined outside the recommended ± 4 weeks window, with a follow-up range of 59–73 months. The systematic measurement error (precision) of the double examinations at 5-years were similar for the two systems (**Table 1**).

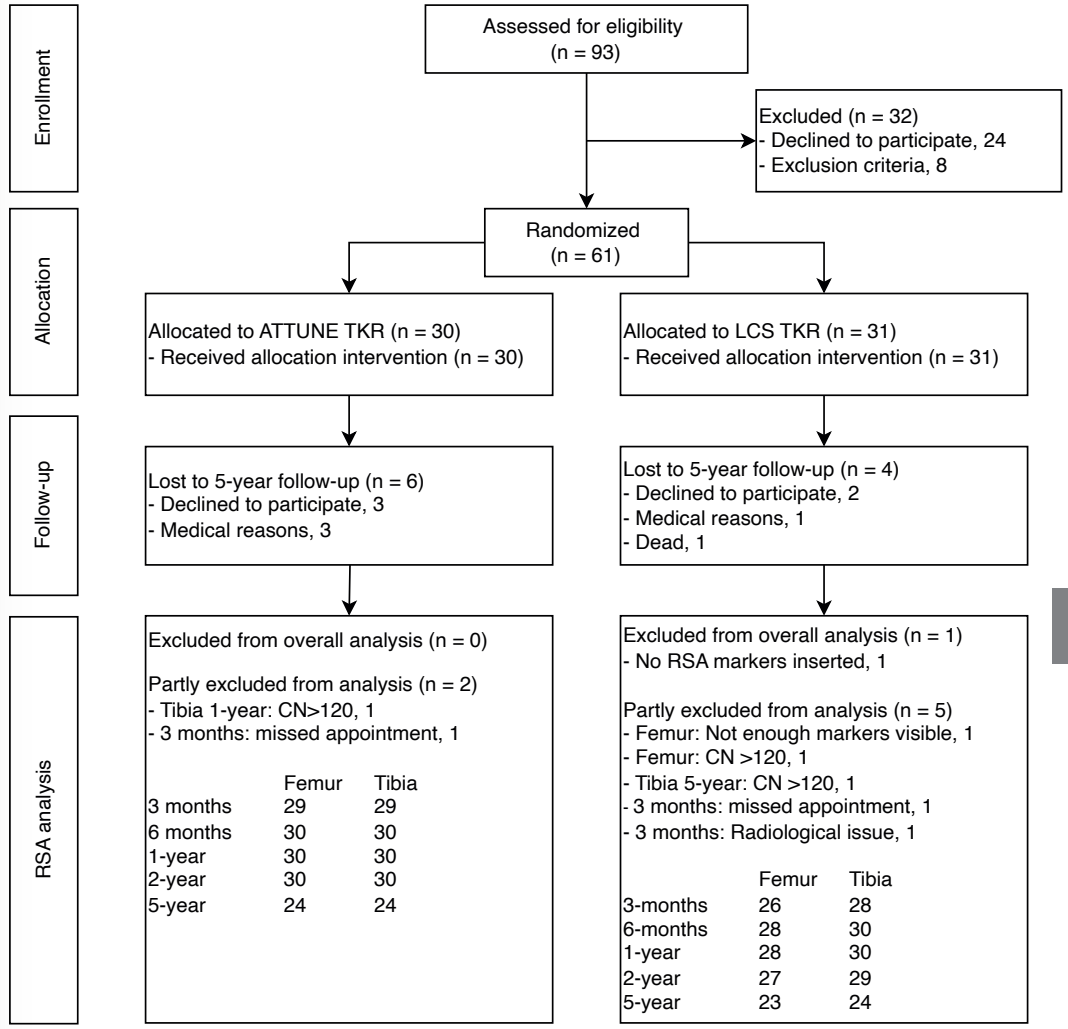


Figure 1. Flow diagram of the patients through each stage of the study. CN. condition number; LCS. Low Contact Stress; RSA. radiostereometric analysis; TKA. total knee arthroplasty.

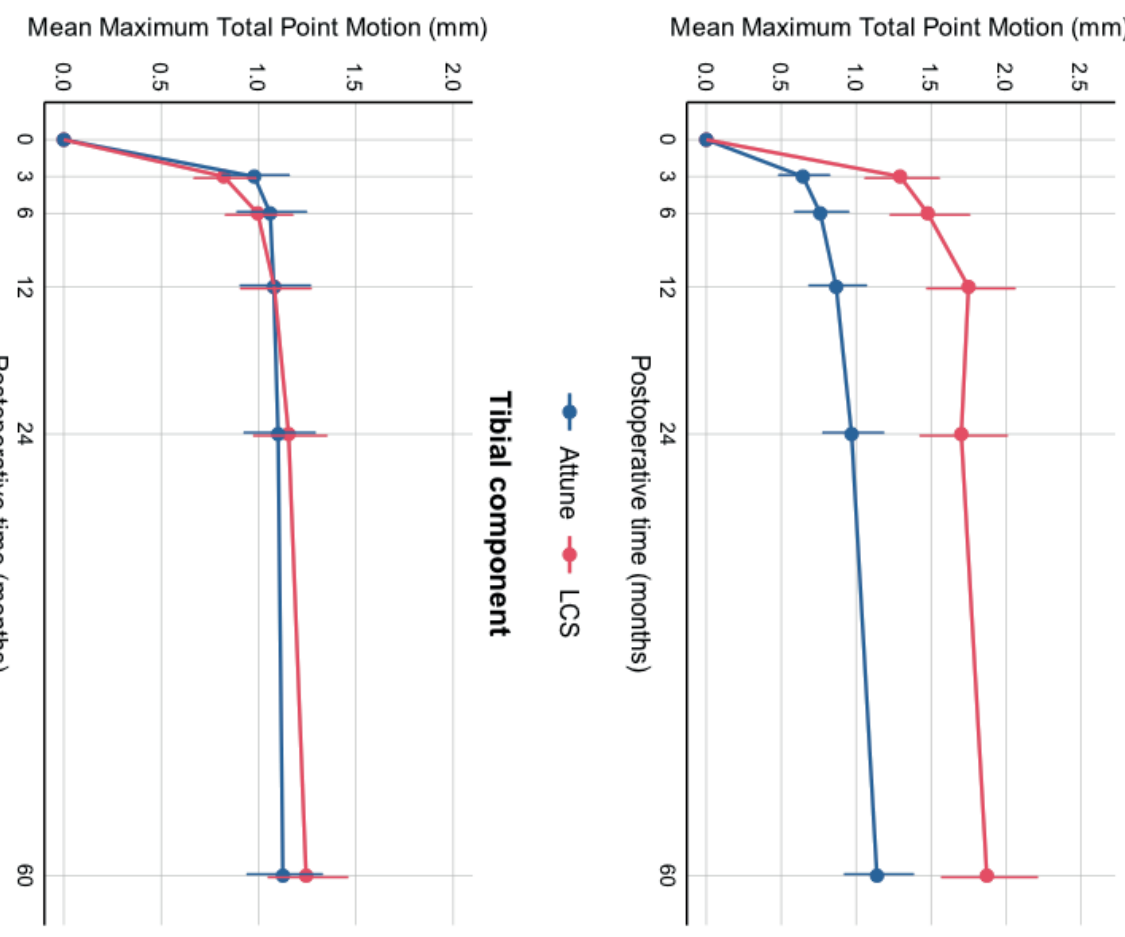


Figure 2. Postoperative time after surgery versus longitudinal mean migration patterns of the Attune and LCS femoral components, measured by maximum total point motion (MTPM) in millimeter. Migration was derived from the linear-mixed model analyses. Error bars and dotted lines indicate 95% confidence intervals.

Table 1. Values of measurement error statistics (i.e., precision) of both components of the uncemented ATTUNE and LCS total knee system, based on double examinations at 5-years postoperative. Values are mean (standard deviation).

Component	Tx, mm	Ty, mm	Tz, mm	Rx, °	Ry, °	Rz, °	MTPM, mm
Femoral component							
ATTUNE	−0.04 (0.12)	0.01 (0.05)	−0.07 (0.43)	0.07 (0.41)	−0.02 (0.14)	−0.07 (0.17)	0.30 (0.63)
LCS	0.00 (0.05)	−0.01 (0.04)	−0.01 (0.08)	−0.02 (0.12)	0.00 (0.16)	−0.06 (0.10)	0.22 (0.12)
Tibial component							
ATTUNE	0.02 (0.06)	0.00 (0.03)	0.01 (0.05)	0.01 (0.07)	−0.04 (0.20)	−0.01 (0.11)	0.18 (0.11)
LCS	−0.01 (0.04)	0.01 (0.04)	0.03 (0.08)	0.00 (0.17)	0.01 (0.34)	0.00 (0.10)	0.27 (0.17)

Rx, Ry, and Rz represent rotations around, and Tx, Ty, and Tz represent translations along the x-, y-, and z-axes. For a right-sided knee, positive translations are medial (x), proximal (y), and anterior (z) movements; positive rotations (°) are anterior tilt about the x-axis, internal rotation about the y-axis, and varus rotation about the
z-axis. LCS Low Contact Stress; MPTM, maximal total point motion; SD, standard deviation.

Migration pattern

Tibial components

The mean MTPM was 1.13 mm (CI 0.94–1.33) and 1.24 mm (CI 1.05–1.46) for the ATTUNE and LCS after 5 years, respectively (**Figure 2**). The LCS translated significantly in lateral, distal and posterior direction, and rotated counterclockwise for any direction at 5 years compared with baseline (**Table S2**, see Supplementary data). The ATTUNE showed a significant distal translation at 5 years compared with baseline. The CIs of all directions deemed comparable at the 5-year examination mark (**Table S2, Figure S1**, see Supplementary data). Between 2 and 5 years, no significant migration was detected in any direction, with similar outcomes observed for both components (**Table 2**). 4 ATTUNE and 4 LCS tibial components migrated more than 0.30 mm (>0.1 mm MTPM/year) between 2 and 5 years postoperative (**Figure 2**). 1 of the 4 ATTUNE components showed a clear focal osteolysis on the lateral and posterior side of the component, without any complaints of pain (NRS of 0 in rest, and 1 during movement) (**Figure S4**, see Supplementary data). Other implants had no obvious reasons for their increased continuous migration.

Femoral components

At 5 years postoperative, the ATTUNE had a lower mean MTPM of 1.14 mm (CI 0.92–1.39) than the 1.87 mm (CI 1.57–2.21) of the LCS femoral component (**Figure 2**). Additionally, the ATTUNE translated less proximally (0.27 mm [CI 0.17–0.37] vs. 0.77 mm [0.67–0.88]), and had less external rotation (–0.24° [CI –0.45 to –0.03] vs. –0.70° [CI –0.92 to –0.49]), compared with the LCS component at 5 years (**Table S2, Figure S2**, see Supplementary data). Between 2 and 5 years postoperative, no significant migration was observed in any direction, with comparable results for both components (**Table 2**). A total of 7 ATTUNE and 3 LCS implants had a larger 2-to-5-year migration (MTPM) than 0.30 mm (**Figure 3**), which would indicate a higher risk of loosening according to the 0.1 mm/year thresholds. In 1 femoral LCS component, a migration (MTPM) of 4.99 mm was measured between 2 and 5 years, which was attributed to a lateral femoral condyle fracture, 4 months prior to the 5-year examination. This patient showed no complaints of pain (NRS of 0 in rest, and 1 during movement). Other implants showed no clear reason for their increased continuous migration.

Sensitivity analyses showed no differences in mean migration results when excluding cases with their 5-year examination outside the ± 4 weeks window. The 2-year mean migration patterns suggested an attrition bias, with both LCS components without a 5-year follow-up showing slightly higher MTPM compared with other groups with and without 5-year follow-up (**Figure S3**, see Supplementary data).

Table 2. Differences in 2-to-5-year migration between components of the ATTUNE and LCS prostheses. Mean values with the 95% confidence intervals (CI), as derived from the linear mixed-effects model.

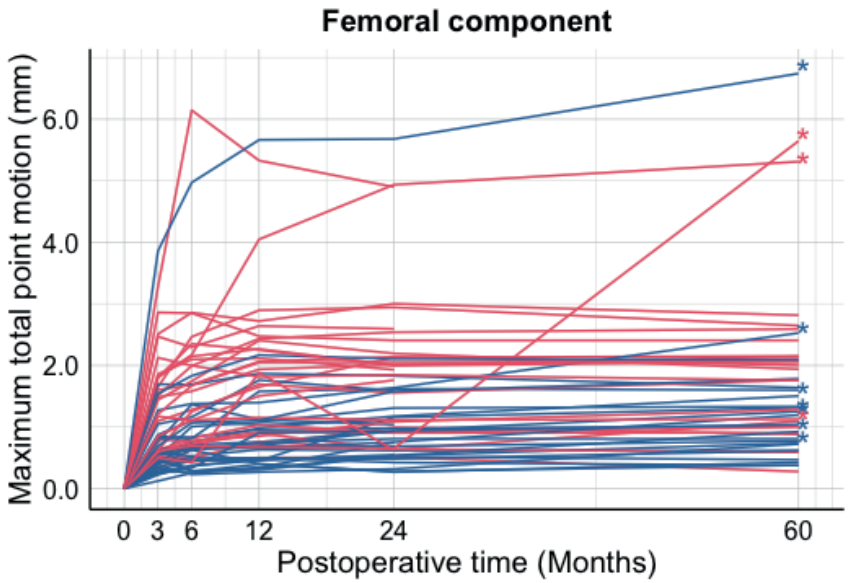
	ATTUNE	LCS
	Mean (CI)	**Mean (CI)**
Femoral component		
Tx, mm	0.05 (–0.10 to 0.21)	–0.02 (–0.18 to 0.14)
Ty, mm	0.02 (–0.11 to 0.16)	0.05 (–0.09 to 0.19)
Tz, mm	–0.02 (–0.32 to 0.28)	–0.10 (–0.41 to 0.21)
Rx, °	0.05 (–0.33 to 0.42)	0.16 (–0.23 to 0.55)
Ry, °	0.00 (–0.29 to 0.29)	–0.15 (–0.45 to 0.15)
Rz, °	0.10 (–0.22 to 0.42)	–0.06 (–0.39 to 0.28)
MTPM, mm	0.20 (–0.26 to 0.67)	0.22 (–0.26 to 0.70)
Tibial component		
Tx, mm	–0.01 (–0.14 to 0.12)	–0.01 (–0.14 to 0.12)
Ty, mm	0.03 (–0.15 to 0.21)	0.05 (–0.13 to 0.24)
Tz, mm	–0.01 (–0.19 to 0.17)	0.01 (–0.17 to 0.19)
Rx, °	0.07 (–0.33 to 0.48)	–0.04 (–0.46 to 0.36)
Ry, °	–0.07 (–0.33 to 0.19)	–0.23 (–0.49 to 0.03)
Rz, °	–0.03 (–0.26 to 0.20)	–0.08 (–0.31 to 0.14)
MTPM, mm	0.02 (–0.27 to 0.30)	0.13 (–0.16 to 0.42)

For abbreviations, see Table 1

Table 3. Inducible displacement and the measurement error at 5 years postoperatively, between the ATTUNE and LCS components. Values are mean MTPM (in mm) and (CI).

	n	Inducible displacement	Measurement error at 5 years (supine doubles)
Femoral component			
ATTUNE	24	0.28 (0.21–0.35)	0.23 (0.17–0.30)
LCS	22	0.30 (0.23–0.36)	0.27 (0.18–0.36)
Tibial component			
ATTUNE	24	0.37 (0.22–0.53)	0.24 (0.16–0.32)
LCS	24	0.39 (0.29–0.51)	0.30 (0.25–0.35)

MTPM maximal total point motion; mm millimeter; CI 95% confidence interval.



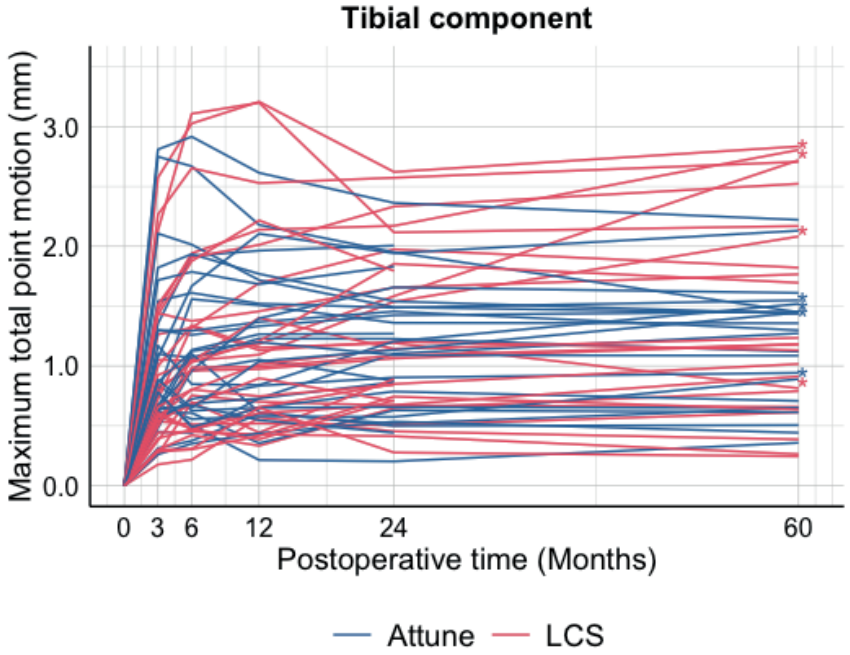


Figure 3. Longitudinal individual 5-year migration patterns of the Attune and LCS tibial components, measured by maximum total point motion (MTPM) in millimeter.
* A 2-to-5-year migration (MTPM) of more than 0.1 mm/year (0.3 mm).

Inducible displacement
No differences in inducible displacement (MTPM) and corresponding CIs were observed between the femoral and tibial components of both implants (**Table 3**). The mean inducible displacements (MTPM) of all components were larger than the measurement errors from the double examinations at 5-year follow-up, although all had overlapping CIs (**Table 3**). Detailed inducible displacement data, including the translations and rotations, were provided in **Table S3**.

For the ATTUNE implant, the femoral component showed a significant displacement along the y-axis of 0.03 mm (CI 0.01–0.04), and –0.05 mm (CI –0.07 to –0.03) for the tibial component. For the LCS femoral component, a significant posterior translation along the z-axis of –0.03 (CI –0.06 to –0.01) was observed compared with the measurement error (**Table S3**). When only the inducible displacement of components with >0.30 mm (MTPM) 2–5-year migration rate was considered, the mean displacement was 0.21 mm (SD 0.07) for the 7 femoral ATTUNE, 0.19 mm (SD 0.02) for the 3 femoral LCS, 1.01 mm (SD 1.50) for the 4 tibial ATTUNE, and 0.29 mm (SD 0.04) for the tibial 4 LCS component. Of these tibial ATTUNE components, 1 had an inducible internal rotation of 4.73° and MTPM of 3.34 mm. Additionally, the patient who suffered from a femoral lateral condyle fracture 4 months before the examination had an inducible displacement of 0.11 mm MTPM.

A sensitivity analysis showed that when the second supine examination at 5 years was used as a reference, no relevant differences were observed compared with the original analyses.

Clinical outcomes
There were no differences between both components in clinical and functional outcomes at 5 years (**Table S4 and S5**). The KUJALA score, added additionally after the 2-year report *[182]*, was 76.9 (SD 15.3) for the ATTUNE and 79.9 (SD 17.6) for the LCS after 5-years, indicating similarity. From 2 to 5 years, the mean scores for OKS, KOOS-PS, EQ-5D-3L, and NRS (rest and activity) were comparable and showed no further improvement. One ATTUNE insert spin-out occurred 10 days post-arthroplasty in a patient with valgus deformity and was revised to a thicker insert, with no further issues reported after. Another patient with an LCS had a femoral lateral condyle fracture 4 months before the 5-year RSA exam, treated with a plaster sleeve and hinged brace for 12 weeks. The 5-year migration data of both patients was included in the analyses.

DISCUSSION

In this follow-up RCT we aimed to evaluate whether the 5-year migration, inducible displacement, and clinical outcome of the ATTUNE components were comparable with those of the LCS. We observed comparable mean 5-year migration of the tibial components in all directions. However, the ATTUNE femoral components showed less migration at 5 years compared to the LCS components. This difference was primarily attributed to the greater proximal translation and external rotation observed in the LCS femoral components. The higher averages of both directions were largely influenced by 2 LCS components: 1 showed substantial proximal and anterior translation, posterior tilt, and external and valgus rotation after 2 years but stabilized by 5 years; the other experienced a significant proximal and posterior translation, anterior tilt and external rotation due to trauma 4 months before the 5-year examination. Additionally, the mean 2-to-5-year migration rate showed no clinically relevant differences between the components, despite the 11 ATTUNE (4 tibia) and 7 LCS (4 tibia) components that had a higher rate of 0.30 mm (>0.1 mm MTPM/year).

To date, there are no other studies comparing the migration patterns of the ATTUNE and LCS knee systems beyond this and the previous study, making it difficult to compare our results with other research. However, the migration patterns of both tibial components fell within the 25th to 75th percentile range for all uncemented implants, and for similar porous-coating or mobile-bearing characteristics, as determined by a meta-analysis of RSA studies up to 2023 *[67]* Recent findings indicate that relying on the mean continuous migration of study groups is not valuable for estimating the collective risk of revision of aseptic loosening, and thus also not for the use in a phased introduction of implants. *[53]* However, by employing an RCT design, this study is optimally positioned to enable reliable conclusions regarding comparability in fixation, encompassing both early migration and 5-year inducible displacement. Additionally, considering excellent long-term revision rates established by the uncemented LCS system, there is a strong likelihood that the uncemented ATTUNE system will exhibit comparable performance in this regard. For instance, the Dutch Arthroplasty Register (LROI) recorded a major revision rate (e.g., not exclusively aseptic loosening) of 3.3% (CI 2.8–3.7) for 9,032 uncemented LCS implants after 14 years of follow-up *[5]* Similarly, the NRJ registry reported a revision rate of 4.0% (CI 3.6–4.4) for 16,494 LCS knees *[8]* However, the Australian registry reported a higher all-cause revision rate of 7.3% (CI 6.2–8.5) for 2,379 LCS knees after 15 years, without specific reasoning known *[4]* As for the uncemented ATTUNE system, the LROI reported a revision rate of 1.4% (CI 0.0–3.1) for 467 implants, and the Australian registry reported a rate of 1.2% (CI 0.5–2.8) for 1,632 implants after 3 years of follow-up *[4, 5]* Although no long-term follow-up revision rates for the ATTUNE system are available yet, the mean rates at 3 years are so far lower than those known for the

LCS at the same interval: 2.2% (CI 1.8–2.5) (LROI), 1.8% (CI 1.6–2.0) (NJR), and 3.4% (CI 2.7–4.2) (Australia) *[4, 5, 8]*

In the current study, the mean inducible displacement was similar to that observed in other uncemented implants from studies with comparable long-term follow-up *[143, 435]* Laende's 10-year follow-up study (2019) reported a significantly lower mean displacement of 0.18 mm (SD 0.18) in 21 uncemented implants compared with 0.38 mm (SD 0.37) in cemented implants *[143]* Similarly, Wilson et al. (2010) found a displacement of 0.19 mm (SD 0.06) in trabecular metal uncemented implants compared with 0.34 mm (SD 0.13) in cemented implants *[435]* Both studies suggesting comparable or better fixation of uncemented implants at the time of inducible displacement measurement *[143, 435]* While the utility of inducible displacement shows great promise for detecting loosened implants, its role in risk assessment during phased implant introduction remains uncertain *[143, 433–436]* In the current study, 1 ATTUNE tibial component with substantial inducible displacement showed a significant post hoc risk for aseptic loosening *[37]*, given the increased prior probability due to the presence of focal osteolysis (**Figure S4**, see Supplementary data). Nevertheless, the patient has not presented any symptoms yet, and therefore, no revision has been performed. Notably, this tibial component was 1 of 18 components with continuous migration of 0.10 mm/year, which would suggest a higher risk of loosening for more implants. One possible explanation, which we propose, is that uncemented implants may possess the ability to re-establish bone ingrowth and fixation even after an initial loosening event. This hypothesis is supported by our study's findings, where the LCS femoral component, which exhibited a migration rate of 4.99 mm (MTPM) between 2 and 5 years following a distal femoral fracture sustained 4 months earlier, demonstrated only an inducible displacement of 0.11 mm at the 5-year follow-up, with no reports of pain in the PROM assessment. However, further research would be needed to confirm this hypothesis. In the study by Lam Tin Cheung et al. (2018), which included 15 cemented implants followed up for 10 years, no correlation was found between inducible displacement and the 2-to-10-year migration rate *[436]* A longer follow-up of this trial would be required to determine whether the components with higher migration rates and inducible displacement, could re-achieve fixation.

Limitations

First, a notable portion of patients were lost to follow-up, primarily due to medical reasons (n = 5) or unwillingness to participate (n = 5). A sensitivity analysis to assess the impact of this attrition bias showed slightly higher migration at 2 years for the group without a 5-year follow-up. Although this indicates some attrition bias, the minimal difference in migration and non-overlapping CIs suggest that this bias likely did not influence our conclusions. Nevertheless, the 5-year LCS migration data would likely be slightly higher without any attrition bias. Second, the

researcher (LAK) who performed the RSA measurements was aware of the TKR design during analyses, thus these measurements were not blinded. However, RSA measurements are inherently objective rather than subjective, so it is expected that this would not lead to different results. Third, this study did not include a point motion analysis of fictive points, which could have provided more detailed insights into specific movement patterns such as subsidence or lift-off *[37]* However, all mean rotations and translations are presented in the supplemental materials to give a clearer understanding of implant movements. Fourth, the study was underpowered to detect differences in PROMs. Hence, we focused solely on describing their changes since the 2-year period. For a clearer understanding of functionality scores associated with the uncemented ATTUNE TKR, observational studies with adequate statistical power, such as The ATTUNE Knee Outcome Study (ATKOS) *[409]*, can provide more definitive insights.

CONCLUSION

We showed that the ATTUNE femoral component exhibited significantly lower mean 5-year migration than the LCS femoral component, while this was comparable between tibial components. The mean 2-to-5-year migration rate and mean inducible displacement at 5-year were similar between both TKR components and there was no difference in PROM's.

From a clinical perspective, the mean migration metrics suggest that the uncemented cruciate-sacrificing rotating platform ATTUNE has an equivalent long-term fixation compared with the LCS knee system.

SUPPLEMENTAL MATERIAL

Table S1. RSA REPORTING CHECKLIST

Serving as a checklist table specifically for prosthesis migration studies as an addition to the CONSORT guidelines.

Section	Checklist item	Page
Title Abstract Methods	1. Identification as a radiostereometric analysis (RSA) study in title, abstract and keywords	1, 2, 3
Study details	1. Report papers/references where prior results or partial results can be found	5
	2. First and last inclusion. Location and surgery information.	5
	3. Number of surgeons that performed the surgeries.	5
Study groups	1. Detailed descriptions of prosthesis, cementation, and liner characteristics for each study group.	5
Follow-up	1. Information on weightbearing before or after first postoperative examination.	6
	2. Mean number and SD of postoperative time and baseline RSA examinations.	Previous study
	3. Mean number and SD of postoperative time and endpoint RSA examination.	9
RSA technique	1. Migration measurement method.	6
	2. Patient position (supine, weightbearing).	6
	3. Software used, including version number.	6
	4. Location and orientation of the migration coordinate system.	6
	5. Use of fiducial/reference points to calculate MTPM.	n/a
Marker/ model-based RSA technique	1. Image resolution (DPI) and type (CR, DR, film) or X-ray detectors.	Previous study
	2. Material and size of markers.	
	3. Calibration cage used, including type (uniplanar, bi-planar).	6
	4. Cutoff values for condition number and mean error of rigid-body fitting.	7
	5. Consistent or alternating X-ray method for RSA analysis.	6
Results		
Study flow	1. Number of migration examinations at different follow-up moments.	8
	2. Number and reasons why migration examinations were missing or excluded.	Figure 1.
Outcome	1. All migration data should be presented in millimeters and degrees.	Suppl file; Table A.
	2. Double examinations, mean, SD, and n for all outcome variables in the study.	Table 1.
	3. Mean and SD of number of markers, CN and mean error of rigid-body fitting for each rigid body at the primary follow-up timepoint.	9

Table S1. Continued

Section	Checklist item	Page
	1. Unmodelled results: mean, n and CI for each study group and follow-up timepoint presented in a table or figure or both.	Suppl file; Table A.
Revision/ failures	1. Number of prosthesis revision/failures in each treatment group. 2. Migration values at last follow-up before revision or failure.	9 9

RSA: Radiostereometric analysis; CT: Computed tomography; DPI: Dots per inch; CR: Computed radiography; DR: Digital radiography; SD: Standard deviation; n: Number (of measurements); MTPM: Maximum total point motion; CI: 95% confidence interval.

Table S2. The mean migration and corresponding 95% confidence intervals of the uncemented Attune and LCS total knee replacements, as derived from the linear mixed-effects model

Follow-up	Tx, mm	Ty, mm	Tz, mm	Rx, °	Ry, °	Rz, °	MTPM. mm
Attune femoral component							
3 months	0.03 (−0.07; 0.14)	0.17 (0.08; 0.27) [a]	0.03 (−0.18; 0.24)	−0.02 (−0.28; 0.24)	−0.19 (−0.39; 0.02)	−0.03 (−0.25; 0.20)	0.64 (0.48; 0.83) [a]
6 months	0.05 (−0.06; 0.15)	0.19 (0.09; 0.28) [a]	0.05 (−0.16; 0.26)	−0.01 (−0.27; 0.26)	−0.24 (−0.44; −0.04)	−0.02 (−0.24; 0.21)	0.76 (0.59; 0.95) [a]
12 months	0.06 (−0.05; 0.17)	0.22 (0.12; 0.32) [a]	0.06 (−0.15; 0.27)	−0.01 (−0.27; 0.25)	−0.25 (−0.45; −0.05)	0.01 (−0.21; 0.23)	0.87 (0.78; 1.07) [a]
24 months	0.05 (−0.05; 0.16)	0.25 (0.15; 0.34) [a]	0.04 (−0.17; 0.25)	0.05 (−0.21; 0.31)	−0.23 (−0.43; −0.03)	0.01 (−0.22; 0.23)	0.97 (0.78; 1.19) [a]
60 months	0.11 (−0.01; 0.22)	0.27 (0.17; 0.37) [a]	0.02 (−0.19; 0.24)	0.10 (−0.18; 0.37)	−0.24 (−0.45; −0.03)[a]	0.10 (−0.13; 0.34)	1.14 (0.92; 1.39) [a]
LCS femoral component							
3 months	0.01 (−0.01; 0.12)	0.51 (0.41; 0.61) [a]	0.10 (−0.11; 0.32)	−0.02 (−0.49; 0.05)	−0.34 (−0.55; −0.13)	0.26 (0.03; 0.50)	1.29 (1.06; 1.56)[a]
6 months	0.00 (−0.11; 0.11)	0.60 (0.51; 0.70) [a]	0.19 (−0.02; 0.41)	−0.38 (−0.70; −0.11)	−0.43 (−0.64; −0.22)	0.26 (0.03; 0.49)	1.48 (1.22; 1.76) [a]
12 months	0.00 (−0.10; 0.12)	0.68 (0.58; 0.77) [a]	0.18 (−0.04; 0.40)	−0.46 (−0.73; −0.19)	−0.61 (−0.82; −0.40)	0.18 (−0.05; 0.41)	1.75 (1.47; 2.06) [a]
24 months	0.02 (−0.09; 0.13)	0.72 (0.63; 0.82) [a]	0.18 (−0.04; 0.40)	−0.51 (−0.79; −0.24)	−0.55 (−0.76; −0.35)	0.28 (−0.05; 0.41)	1.70 (1.42; 2.01) [a]
60 months	−0.00 (−0.11; 0.12)	0.77 (0.67; 0.88) [a]	0.08 (−0.15; 0.30)	−0.35 (−0.63; 0.07)	−0.70 (−0.92; −0.49)[a]	0.12 (−0.12; 0.36)	1.87 (1.57; 2.21) [a]
Attune tibial component							
3 months	0.00 (−0.09; 0.09)	−0.31 (−0.43; −0.18)	0.07 (−0.06; 0.19)	−0.46 (−0.74; −0.17)	−0.01 (−0.19; 0.17)	−0.01 (−0.16; 0.15)	0.98 (0.81; 1.16)
6 months	−0.01 (−0.10; 0.08)	−0.34 (−0.47; −0.22)	0.10 (−0.02; 0.22)	−0.48 (−0.76; −0.10)	0.03 (−0.15; 0.21)	−0.04 (−0.19; 0.12)	1.06 (0.89; 1.25)
12 months	−0.02 (−0.11; 0.07)	−0.32 (−0.45; −0.19)	0.09 (−0.04; 0.21)	−0.34 (−0.62; 0.06)	0.00 (−0.18; 0.18)	−0.06 (−0.22; 0.10)	1.08 (0.90; 1.27)
24 months	−0.04 (−0.13; 0.07)	−0.31 (−0.48; −0.18)	0.10 (−0.03; 0.22)	−0.22 (−0.50; 0.06)	−0.01 (−0.19; 0.17)	−0.06 (−0.21; 0.11)	1.10 (0.92; 1.29)
60 months	−0.05 (−0.14; 0.04)	−0.28 (−0.41; −0.15)	0.08 (−0.04; 0.21)	−0.15 (−0.44; 0.15)	−0.08 (−0.27; 0.11)	−0.09 (−0.25; 0.08)	1.13 (0.94; 1.33)
LCS tibial component							
3 months	−0.10 (−0.19; −0.01)	−0.24 (−0.37; −0.11)	−0.09 (−0.21; 0.03)	−0.38 (−0.67; −0.10)	−0.04 (−0.22; 0.14)	0.03 (−0.13; 0.18)	0.82 (0.67; 0.99)
6 months	−0.13 (−0.22; −0.04)	−0.23 (−0.36; −0.11)	−0.13 (−0.25; 0.00)	−0.49 (−0.77; −0.21)	−0.09 (−0.27; 0.09)	0.01 (−0.15; 0.17)	1.00 (0.83; 1.18)

Table S2. Continued

Follow-up	Tx, mm	Ty, mm	Tz, mm	Rx, °	Ry, °	Rz, °	MTPM. mm
12 months	−0.13 (−0.22; −0.04)	−0.25 (−0.38; −0.12)	−0.14 (−0.27; −0.02)	−0.46 (−0.74; −0.18)	−0.08 (−0.26; 0.10)	−0.04 (−0.20; 0.12)	1.08 (0.91; 1.27)
24 months	−0.14 (−0.23; −0.05)	−0.26 (−0.39; −0.13)	−0.14 (−0.26; −0.02)	−0.31 (−0.59; −0.03)	−0.17 (−0.35; 0.01)	−0.12 (−0.28; 0.04)	1.15 (0.97; 1.35)
60 months	−0.15 (−0.24; −0.06)	−0.21 (−0.34; −0.07)	−0.13 (−0.25; 0.00)	−0.36 (−0.65; −0.06)	−0.40 (−0.59; −0.21)	−0.20 (−0.36; −0.04)	1.24 (1.05; 1.46)

Rx, Ry, and Rz represent rotations around, and Tx, Ty, and Tz represent translations along the x-, y-, and z-axes. For a right-sided knee, positive translations are medial (x), proximal (y), and anterior (z) movements; positive rotations (°) are anterior tilt about the x-axis, internal rotation about the y-axis, and varus rotation about the z-axis. CI confidence interval; LCS Low Contact Stress; MTPM maximal total point motion. [a] Parameters that are different between the 2 designs based on 95% confidence intervals.

Table S3. Inducible displacement and measurement error at 5 years postoperative, between the Attune and LCS components. Values are mean (95% confidence interval)

	Knees	Inducible displacement	Measurement error at 5 years (supine doubles)
Femoral component			
Attune	24		
Tx, mm		−0.03 (−0.09 to 0.02)	0.04 (−0.03 to 0.11)
Ty, mm		0.03 (0.01 to 0.04)	−0.01 (−0.03 to 0.01)
Tz, mm		−0.02 (−0.07 to 0.03)	−0.01 (−0.05 to 0.02)
Rx, °		0.01 (−0.05 to 0.08)	0.09 (0.00 to 0.19)
Ry, °		−0.04 (−0.12 to 0.04)	−0.02 (−0.09 to 0.04)
Rz, °		−0.07 (−0.15 to 0.01)	−0.02 (−0.07 to 0.02)
MTPM, mm		0.28 (0.21 to 0.35)	0.25 (0.17 to 0.30)
LCS	22		
Tx, mm		0.01 (−0.03 to 0.05)	−0.02 (−0.04 to 0.01)
Ty, mm		−0.01 (−0.05 to 0.03)	−0.01 (−0.04 to 0.02)
Tz, mm		−0.03 (−0.06 to −0.01)	0.03 (−0.01 to 0.08)
Rx, °		0.03 (−0.06 to 0.11)	−0.04 (−0.10 to 0.01)
Ry, °		−0.02 (−0.10 to 0.07)	0.12 (0.00 to 0.24)
Rz, °		−0.06 (−0.14 to 0.01)	0.01 (−0.07 to 0.10)
MTPM, mm		0.30 (0.23 to 0.36)	0.28 (0.18 to 0.36)
Tibial component			
Attune	24		
Tx, mm		−0.04 (−0.08 to 0.00)	−0.05 (−0.14 to 0.03)
Ty, mm		−0.05 (−0.07 to −0.03)	−0.02 (−0.05 to 0.00)
Tz, mm		−0.01 (−0.05 to 0.03)	−0.01 (−0.02 to 0.01)
Rx, °		−0.01 (−0.1 to 0.11)	−0.01 (−0.06 to 0.41)
Ry, °		0.20 (−0.21 to 0.62)	0.04 (−0.06 to 0.14)
Rz, °		0.04 (−0.03 to 0.12)	0.07 (−0.04 to 0.18)
MTPM, mm		0.37 (0.22 to 0.53)	0.28 (0.16 to 0.32)
LCS	24		
Tx, mm		−0.02 (−0.06 to 0.02)	−0.01 (−0.03 to 0.01)
Ty, mm		−0.04 (−0.09 to 0.01)	−0.01 (−0.03 to 0.01)
Tz, mm		−0.01 (−0.05 to 0.03)	0.02 (−0.01 to 0.04)
Rx, °		0.03 (−0.09 to 0.14)	−0.03 (−0.12 to 0.05)
Ry, °		0.05 (−0.15 to 0.24)	−0.06 (−0.21 to 0.09)
Rz, °		0.05 (−0.12 to 0.22)	0.02 (−0.01 to 0.05)
MTPM, mm		0.39 (0.29 to 0.51)	0.30 (0.25 to 0.35)

Rx, Ry, and Rz represent rotations around, and Tx, Ty, and Tz represent translations along the x-, y-, and z-axes. For a right-sided knee, positive translations are medial (x), proximal (y), and anterior (z) movements; positive rotations (°) are anterior tilt about the x-axis, internal rotation about the y-axis, and varus rotation about the z-axis.
LCS Low Contact Stress; MTPM maximal total point motion; CI confidence interval.

Table S4. Functional outcome measures of the patients with an uncemented Attune and LCS implant at 5-years postoperative

	Attune	LCS
Number of knees	24	24
Mean ROM, ° (SD)	123.8 (5.9)	120.0 (8.6)
Anteroposterior stability, n (%)		
< 5 mm	24 (100)	25 (100)
5–10 mm	0 (0.0)	0 (0.0)
> 10 mm	0 (0.0)	0 (0.0)
Mediolateral stability, n (%)		
< 5 °	20 (83)	20 (80)
5–9 °	4 (17)	4 (16)
10–14 °	0 (0.0)	1 (4.0)
> 14 °	0 (0.0)	0 (0.0)

ROM Range of motion; mm millimeter

Table S5. Scores of patient-reported outcome measures of patients with an uncemented Attune (n = 24) and LCS (n = 24) implant at 5-years postoperative

	Mean (SD)		Median (IQR)	
	Attune	LCS	Attune	LCS
Oxford Knee score	41.6 (7.0)	41.5 (7.6)	44.0 (37.3–47.8)	44.0 (39.0–47.0)
KOOS-PS	21.3 (14.9)	21.8 (17.8)	22.0 (10.5–32.7)	18.6 (5.6–36.6)
KUJALA	76.9 (15.3)	79.9 (17.6)	76.0 (68.0–88.0)	82.0 (70.8–97.3)
EQ-5D-3L	0.9 (0.1)	0.9 (0.2)	1.0 (0.8–1.0)	1.0 (0.8–1.0)
NRS at rest	1.0 (1.9)	1.2 (2.5)	0.0 (0.0–1.0)	0.0 (0.0–2.0)
NRS during movement	1.5 (2.1)	1.4 (2.5)	0.5 (0.0–2.8)	0.0 (0.0–2.0)

KOOS-PS; Knee injury and Osteoarthritis Outcome Score Physical Function shortform, KUJALA; anterior Knee Pain Scale.

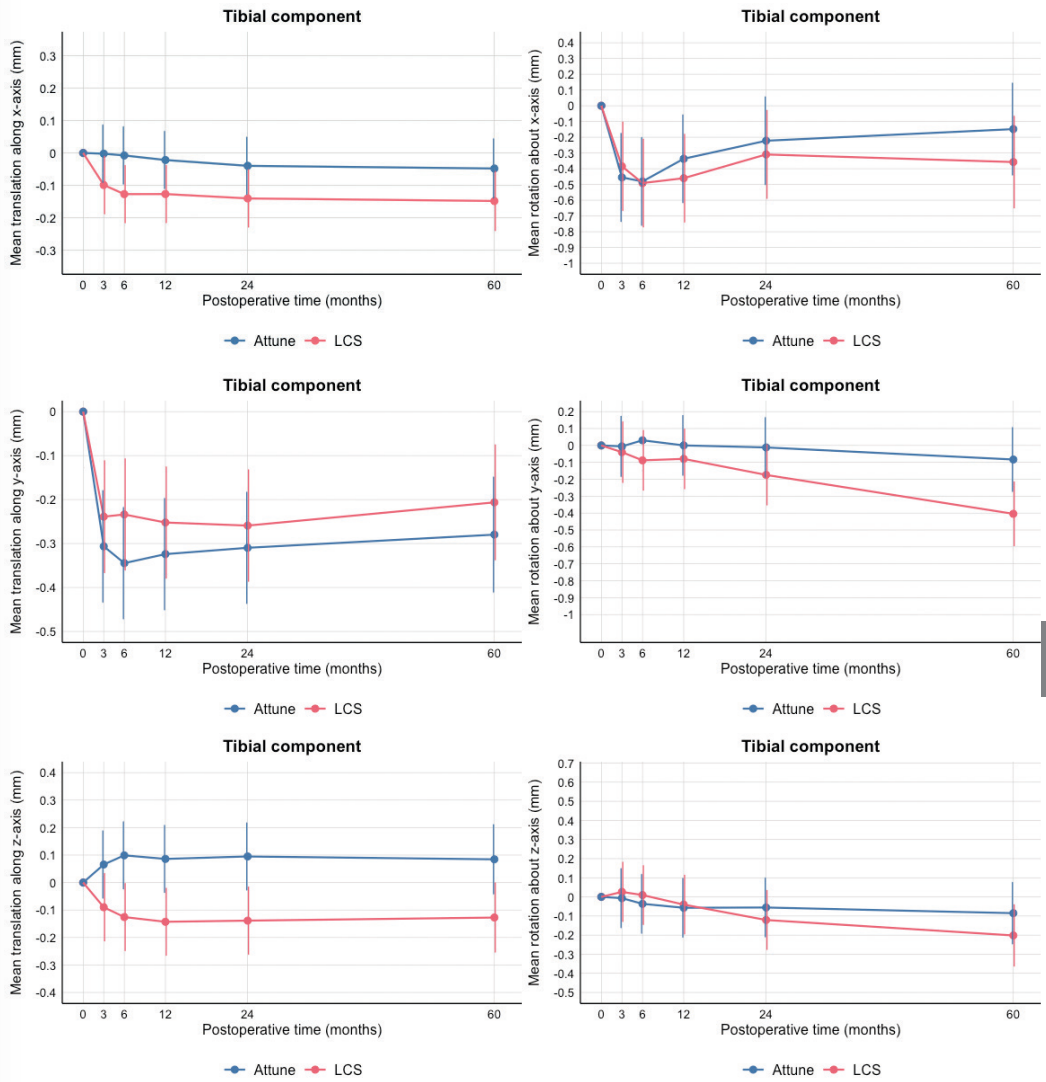


Figure S1. 5-year migration patterns of translations and rotations of the Attune and LCS tibial components.

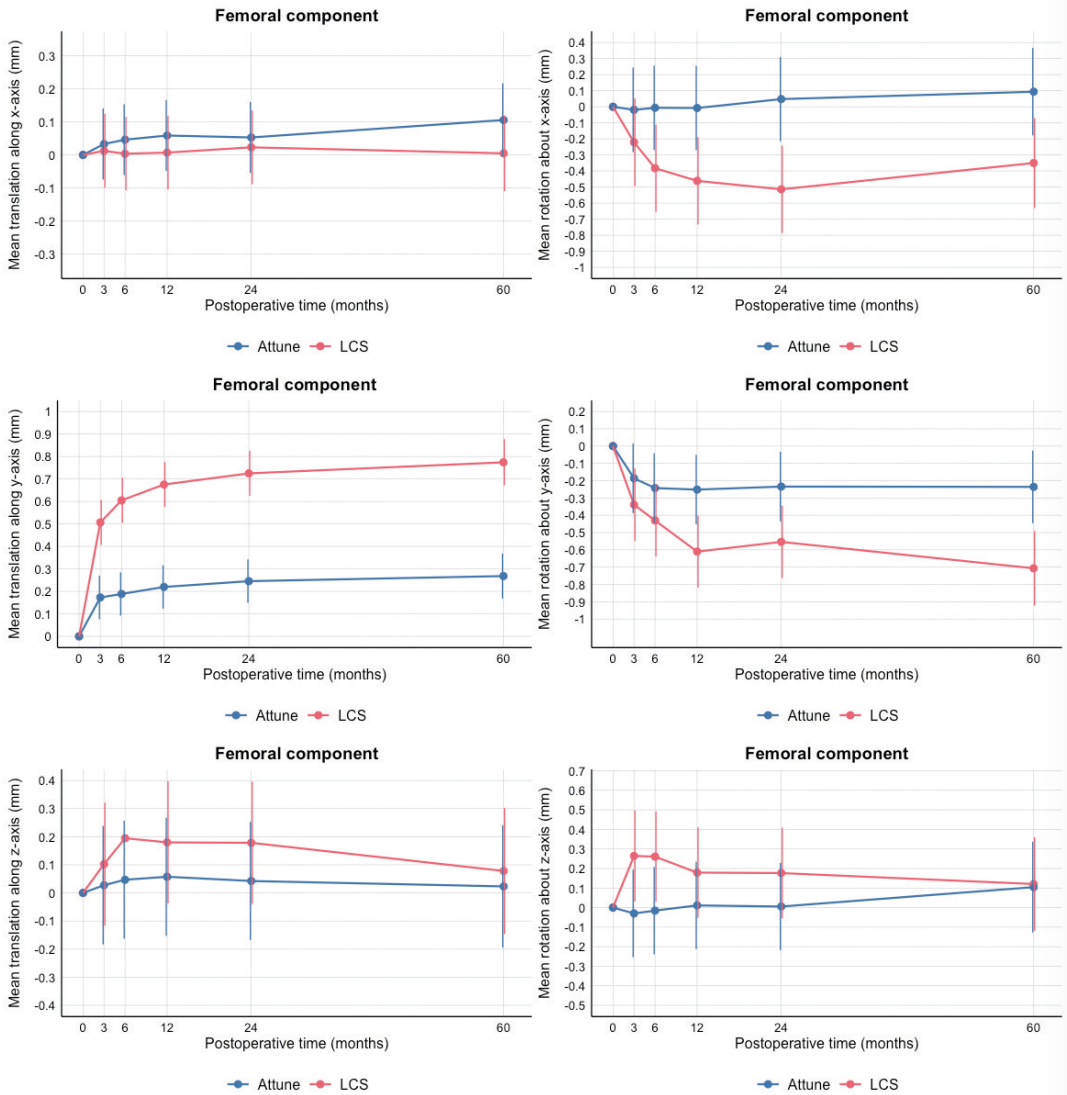
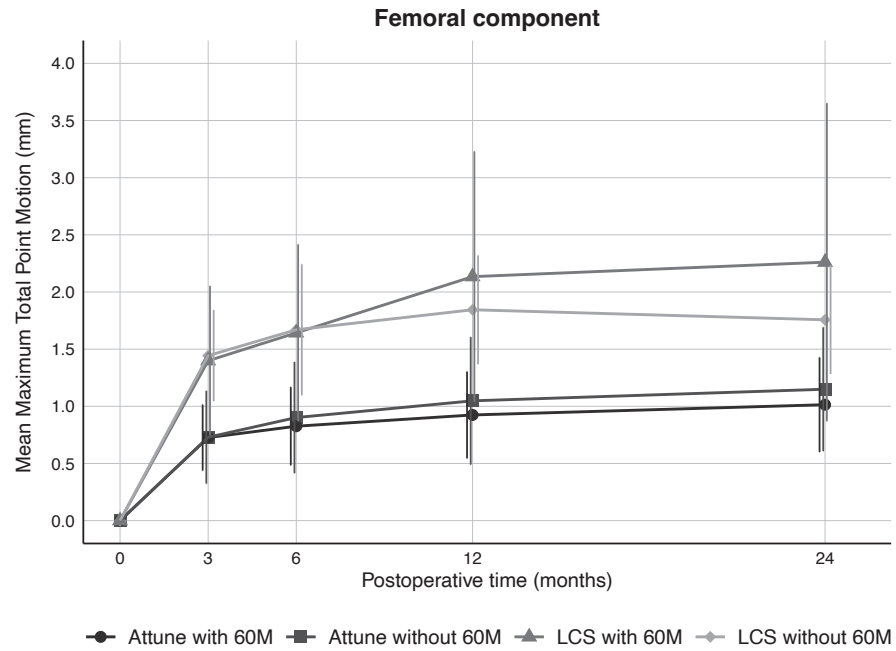


Figure S2. 5-year migration patterns of translations and rotations of the Attune and LCS femoral components.



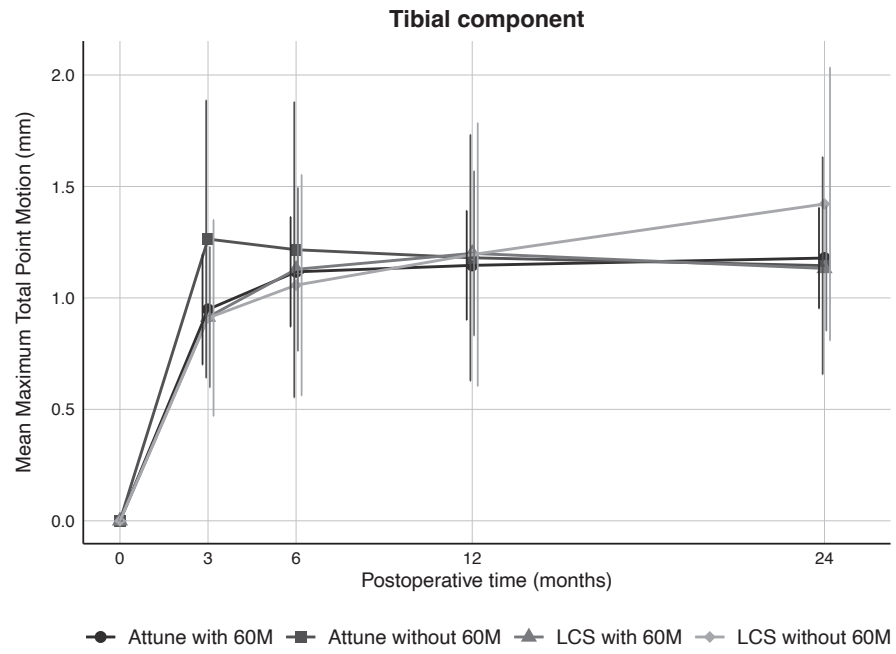


Figure S3. 2-year migration patterns of maximum total point motion of the Attune and LCS tibial and femoral components, concerning patients with and without 5-year migration data.

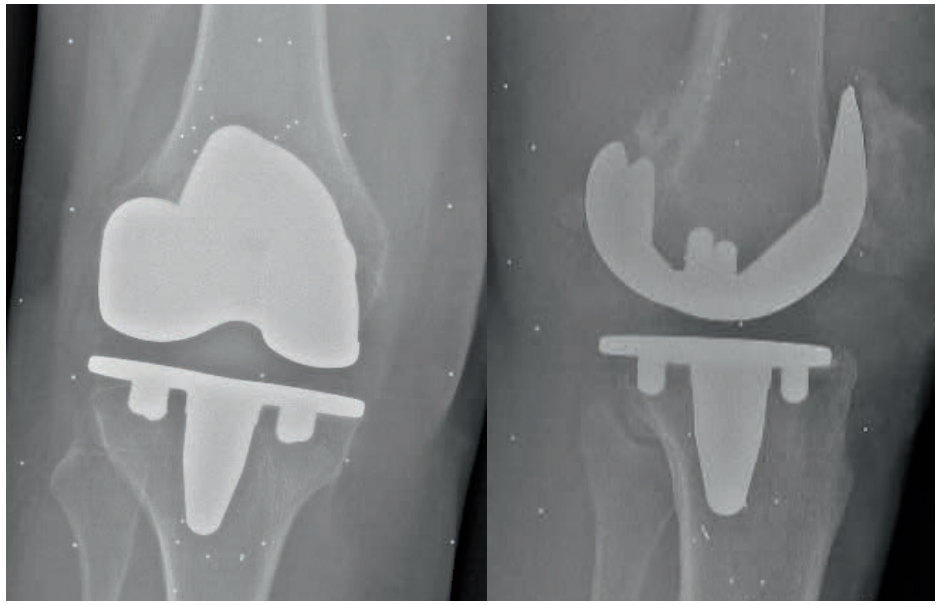
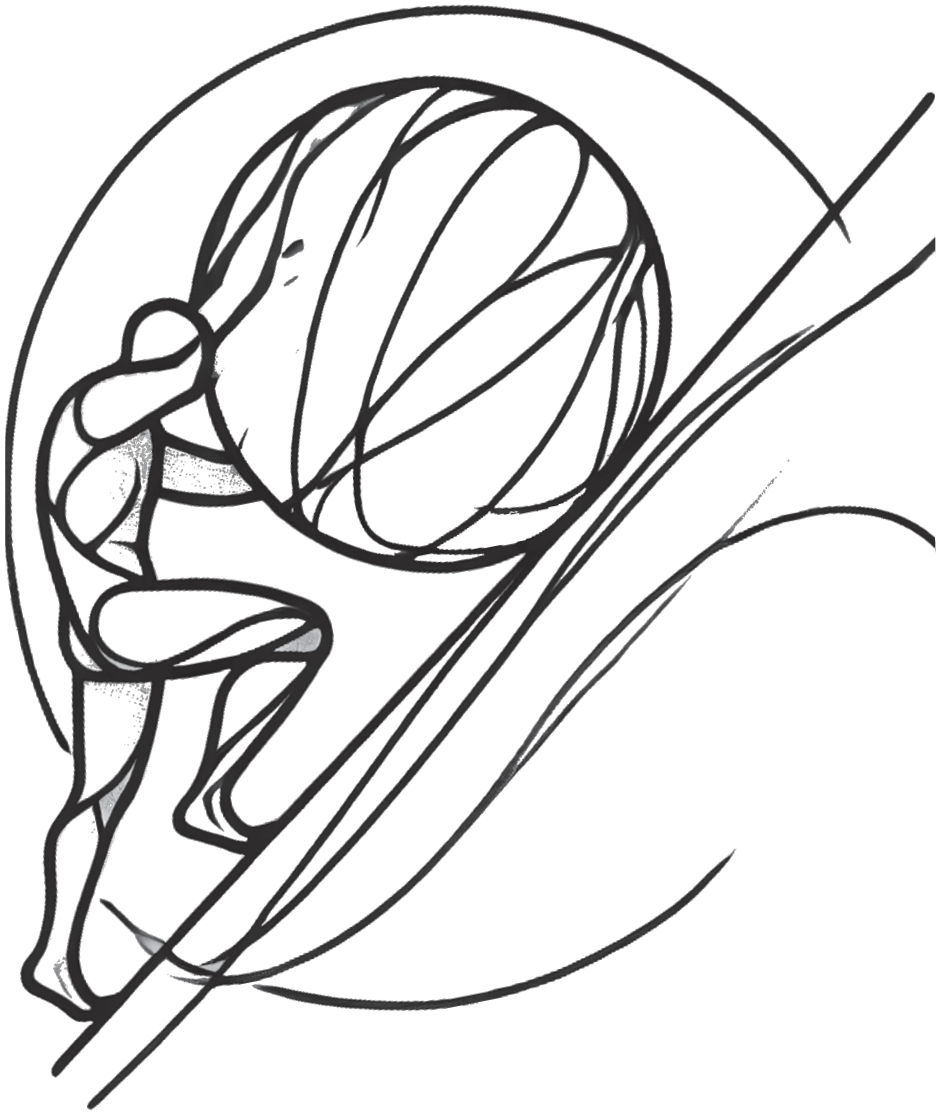


Figure S4. Radiostereometric radiographs of the ATTUNE total knee replacement with an inducible external rotation of 4.73° and 3.34 mm maximum total point motion. Both radiographs show a focal osteolysis on the lateral and posterior side of the tibial plateau.



CHAPTER 7

The Diagnostic Characteristic and Reproducibility of Bone Scintigraphy Single-Photon Emission Computed Tomography/Computed Tomography for Diagnosing Aseptic Loosening of Uncemented Total Knee Arthroplasty.

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ABSTRACT

Purpose
The primary objective of this study was to investigate the diagnostic characteristics of bone scintigraphy SPECT/CT (BS-SPECT/CT) for diagnosing aseptic loosening after uncemented total knee arthroplasty (TKA), and to evaluate the following aspects: how to manage inconclusive results, the inter-observer reliability, and the location of tracer uptake between symptomatic cases with and without aseptic loosening.

Methods
In this study, 180 patients who had uncemented total knee arthroplasty (TKA) and persistent knee pain suspected of aseptic loosening were included. As part of routine medical care, BS-SPECT/CT was utilized, and its results were compared with the reference standard, which involved revision surgery for aseptic loosening or a 12-month follow-up without revision or imaging. Inconclusive BS-SPECT/CT results were considered either negative (best-case scenario) or positive (worst-case scenario). Sensitivity, specificity, positive/negative likelihood ratios (LR), and positive/negative predictive values (PPV and NPV) were calculated. Sensitivity analyses were conducted by comparing the diagnostic characteristics between cases with a follow-up of less and more than 2 years follow-up. The anatomical distribution of tracer uptake and interobserver reliability were also evaluated.

Results
Out of the 180 BS-SPECT/CT scans conducted, 22 were determined positive, 113 negative, and 45 inconclusive. The best-case scenario showed a sensitivity of 66.7%, specificity of 93.8%, +LR 10.8, -LR 0.4, PPV 54.6%, and NPV 96.2%. In contrast, the worst-case scenario had a sensitivity of 94.4%, specificity of 69.1%, +LR 3.1, -LR 0.1, PPV 25.4%, and NPV 99.1%. Sensitivity analyses revealed no significant differences in characteristics between the two TKA-interval groups. The interobserver reliability was fair-to-moderate (κ = 0.39; 95%CI 0.18 to 0.60), with an estimated agreement of 79% (95%CI 70 to 87). Four prosthetic zones had a notably higher proportion of cases with tracer uptake in those with aseptic loosening compared to those without.

Conclusion
The test characteristics of BS-SPECT/CT were deemed appropriate in patients who have complaints of uncemented TKA suspected of aseptic loosening. Inconclusive cases were best categorized as negative, especially in patients who have a short interval between TKA and the first BS-SPECT/CT. Increased tracer uptake in four prosthetic zones was observed in cases of aseptic loosening, although interobserver reliability was fair to moderate.

INTRODUCTION

Complications following total knee arthroplasty (TKA) can markedly impact patient outcomes, with aseptic loosening being a notable concern. *[6, 438]* Aseptic loosening is detected through symptoms of pain and progressive radiolucencies, or osteolysis on radiographic imaging in clear-cut instances. *[439]* However, in the subgroup of patients where the osteolysis is not yet apparent, the differentiation of aseptic loosening from other complications [13], or the undiagnosed pain experienced by 10 to 20% of patients *[23]*, is particularly challenging. Given this challenge, definitive recommendations for revision TKA in cases lacking a clear cause becomes complex, as patient satisfaction, pain reduction, and functional improvement following revision TKA cannot be guaranteed. *[440, 441]*

Nuclear imaging techniques such as bone scintigraphy single-photon emission computed tomography/computed tomography (BS-SPECT/CT) have been described as a valuable diagnostic tool for detecting bone-remodeling by use of a radioactive tracer, in cases suspected of a low-grade infection or aseptic loosening. *[442–444]* However, a tendency for bone remodeling is also expected in early non-failed implants as part of the fixation process, especially for uncemented total knee arthroplasties (TKA) due to their reliance on osseointegration. *[445]* Previous studies examining the diagnostic accuracy of BS-SPECT/CT for detecting aseptic loosening have yielded diverse results in terms of sensitivity and specificity *[34, 35, 439, 443, 446]* However, these studies have been associated with several limitations, resulting in a wide range of interpretations. For instance, some studies have reported characteristics without providing confidence intervals *[35]*, while others have had small sample sizes *[439, 446]*, or excluded patients in analyses that received a BS-SPECT/CT, but not a reference standard *[35, 443]*. Additionally, certain studies have combined cohorts of hip and knee *[447]* or cemented and uncemented TKA *[34, 35, 443]*, or evaluated a variety of different or unknown implant designs *[442]*.

The purpose of this study was to investigate the diagnostic characteristics of BS-SPECT/CT for aseptic loosening after uncemented TKA, and to evaluate (1) the most appropriate way to manage inconclusive SPECT/CT results, (2) the inter-observer reliability, and (4) the locations of tracer uptake between symptomatic cases with and without aseptic loosening.

PATIENTS AND METHODS

Study design
This diagnostic cross-sectional study was approved by the internal review board (ACLU: 2022.0058) of the Spaarne Gasthuis Hospital, Hoofddorp, The Netherlands. This hospital is a high-volume institution with over 300 TKAs

performed annually. Data collection was conducted retrospectively. Informed consent was not necessary as this study was an evaluation of routine medical care. Reporting of data was performed according to the Standards for Reporting Diagnostic Accuracy Studies (STARD) 2015 guidelines *[448]*, with all aspects noted in the STARD checklist in the supplemental file.

Patient selection

All patients with a TKA in situ who had undergone a BS-SPECT/CT between the 1st of January 2009 and the 1st of June 2022 were identified by using International Classification of Primary Care (ICPC) and operation codes. Patients were included in case the BS-SPECT/CT was performed following a diagnostic workup that excluded other commonly occurring diagnoses for symptomatic TKAs (e.g., high-grade infection, arthrofibrosis, instability of ligaments, malposition), to evaluate whether aseptic loosening was the cause of their complaints. The workup included a physical examination, radiographs, and blood tests. Patients were excluded from the study in cases where the imaging was unrelated to a primary TKA, the imaging included solely a BS instead of a BS-SPECT/CT, the imaging was of a cemented implant, or when patients were not followed up for at least one year after their last BS-SPECT/CT.

Test methods

In every case, a 600MBq Tc-99m labeled Oxidronate tracer injection (CIS Bio International Sur Yvette, France) was used to target the bones in proportion to their osteoblastic activity, to reveal an increased uptake in the bone as a result of a higher bone turnover (e.g., osteolysis, inflammation, metastases). The imaging consisted of three phases, with the first-phase scintigraphy images (perfusion phase) being acquired using planar detectors positioned from the anterior and posterior angles, obtained in four-time frames of 30 seconds each. The second phase image (diffusion phase) acquisition followed by using the same detector positions, but in a single frame lasting 180 seconds. At least two hours after the injection, the third phase (bone phase) planar images were obtained using unchanged detector positions, acquired in a single frame of 180 seconds per body part position, ranging from the lumbar spine to the feet. Subsequently, SPECT acquisition of the knees was performed, using detectors in a 180-degree rotation consisting of 64 viewpoints with 20 seconds per view. A Symbia™ T2 SPECT/CT (Siemens Healthineers Erlangen, Germany) was used with a matrix of 128 x 128, combined with a 130kV 45 mAs low-dose CT for anatomical mapping and attenuation correction.

Test interpretation

The index test was the first BS-SPECT/CT to diagnose aseptic loosening of the uncemented TKA, after the exclusion of other common complications. The

outcome of the index test was determined by the researchers (RP, PL) by consulting the imaging reports of the patient's electronic medical records (EMR), assessed by the nuclear radiologists of the institute. The outcome was categorized as positive (i.e., suspicion of aseptic loosening), negative (i.e., no suspicion of aseptic loosening), or inconclusive (i.e., no clear suspicion, or being able to rule loosening out, therefore, recommended to evaluate changes in tracer uptake pattern or intensity by performing a following BS-SPECT/CT).

The reference standard for aseptic loosening of the TKA depended on the outcome of the index test. In the case of a positive primary index test, a revision TKA was generally performed. Otherwise, the decision for a revision was based on follow-up scans or the progression of the complaints of the patient. The reference standard was considered positive when implant loosening was documented in the revision surgery report, while the potential of loosening due to infection was determined minimal. The chance of an infection was determined minimal in cases where physical examination showed no signs of infection, low levels of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were present in the patient's blood tests, and a negative result from either preoperative joint aspiration or intra-operative cultures was obtained. In order to conduct a thorough analysis, the Dutch Arthroplasty Registry (LROI) was consulted to verify information regarding the reasons for revisions. This was necessary as surgeons could provide a clearer view of indication for revision on the LROI registration forms compared to the information reported in the surgery reports. The reference test was considered negative if (1) a patient had undergone a revision without aseptic loosening confirmed as the final diagnosis according to the previously mentioned criteria, or (2) a patient had not undergone revision surgery, but was monitored for at least one year after their last imaging, during which they experienced relief or no progression of pain. The rationale for the one-year follow-up was based on the assumption that symptoms of aseptic loosening would typically worsen over time due to the further progression of osteolysis. Therefore, a patient not visiting the outpatient clinic for their pain would suggest relief of pain and therefore, the absence of aseptic loosening. A similar rationale and follow-up period were also used in other studies. *[447, 449, 450]*

Patient population

A total of 439 patients were identified, of which 180 patients were included for evaluation. A flow diagram of the inclusion and exclusion reasons is presented in **Figure 1**. The population had a mean age at surgery of 66 years (range, 43 to 86) and consisted of 106 (59%) women. All TKA systems were uncemented mobile-bearing LCS (DePuy Synthes, Warsaw, Indiana) implants. The median time interval between TKA and the first BS-SPECT/CT was 2.1 (IQR 1.1 to 4.3) years. Overall, aseptic loosening of the implant was confirmed in 18 cases (10.0%). All 180 cases were not suspected for infection through physical examination and low infection

parameters. Intra-articular aspirations were performed in 6 patients, without any showing bacterial growth. A knee radiograph was taken from all patients, with radiolucent lines present in 36 cases (19.4%), from which 5 were determined to be loosened by the reference standard.

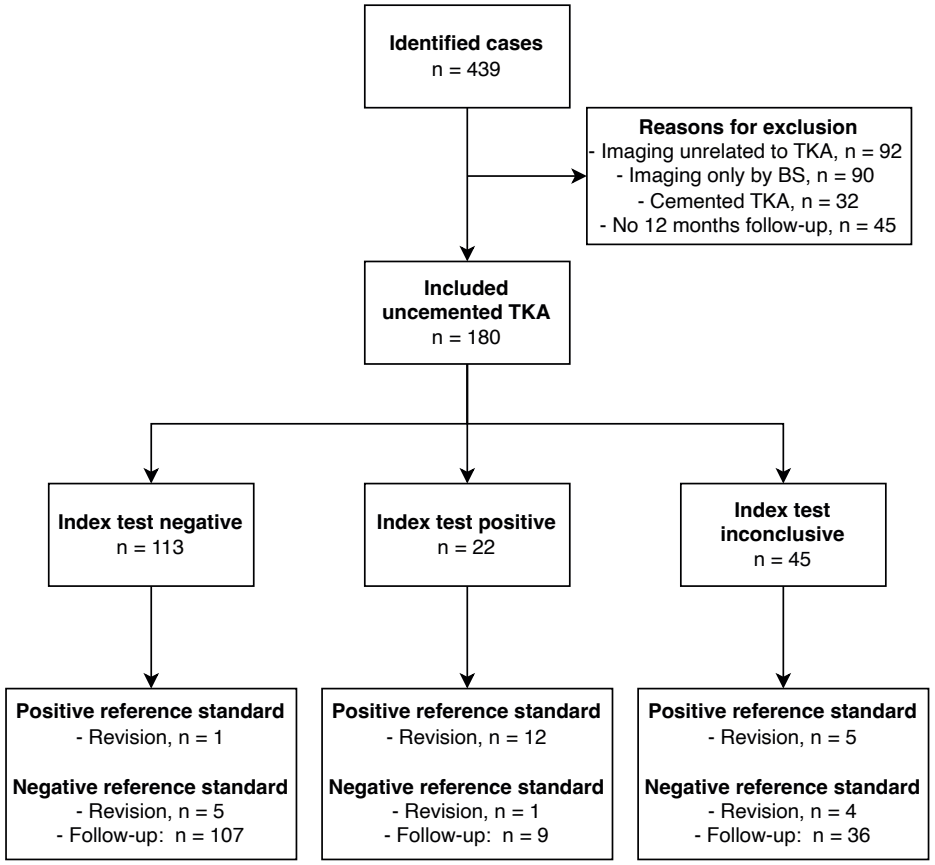


Figure 1. Flow diagram of inclusion and exclusion and test details of the study population. n Number; TKA total knee arthroplasty; BS bone scintigraphy.

Interobserver reliability and tracer location

To assess the consistency in interpreting nuclear imaging results, a nuclear radiologist (Observer 1 (JB) with 10 years of experience) and a physician assistant (Observer 2 (AK) with 2 years of experience) independently reviewed 100 selected cases. These cases were chosen independently by one of the authors (PL). For each case, the observers identified any areas of increased uptake and recorded the location of this uptake using the zones for radiolucencies according to the Knee Society roentgenographic scoring system. *[451]*

Data Analyses

Baseline characteristics are presented as means and standard deviation (SD), median and interquartile range (IRQ), or frequency and percentage, depending on the distribution of the data. To calculate the diagnostic characteristics (i.e., sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPV], positive likelihood ratio [+LR], negative likelihood ratio [-LR]) of the index test, the result of the index test was compared with the results of the reference standard, and presented with 95% confidence intervals (CI). The definitions of the different characteristics are presented in **Table 1**. Since this study included all patients who had uncemented TKA that underwent BS-SPECT/CT for diagnosing aseptic loosening, the prevalence of aseptic loosening observed in our study population can serve as a reliable estimate of the pre-test probability. Therefore, explicit application of Bayes' rule for updating probabilities was deemed not necessary in the analyses. *[33]*

Diagnostic characteristics were determined using two scenarios: the 'best-case' and 'worst-case.' In the 'best-case' scenario, inconclusive results were treated as negative, while in the 'worst-case' scenario, they were treated as positive. The terms 'best' and 'worst' reflect the patient's viewpoint. Also, both scenarios are easily implementable in regular practice. Furthermore, considering that uncemented implants may exhibit prolonged tracer uptake following primary TKA due to physiological bone remodeling, a sensitivity analysis was conducted to assess the diagnostic characteristics when stratifying the cases based on the duration of the interval between the primary TKA and first BS-SPECT/CT (i.e., < 2.0 years and > 2.0 years). As most of the inconclusive cases in the <2.0 and >2.0 analyses were advised to undergo a follow-up BS-SPECT/CT, these analyses were performed similarly to the 'best-case' scenario. Also, since both sensitivity analyses (< 2.0 years and > 2.0 years) included fewer patients than the analyses of the best- and worst-case scenarios (entire cohort), the disease prevalence was set equally as that of the analyses of the best- and worst-case scenarios. The Interobserver reliability was evaluated by calculating Cohen's kappa (κ) coefficient and the absolute agreement with Clopper-Pearson confidence intervals. Interpretation of the κ coefficient was according to the criteria of Landis and Koch (e.g., κ = > 0.8 (almost perfect), κ = 0.6–0.8 (substantial), κ = 0.4–0.6 (moderate), κ = 0.2–0.4 (fair), and κ = < 0.2 (slight agreement)). *[452]* All Statistical analyses were performed by use of Statistical Package for the Social Sciences (SPSS); statistical package version 26.0 (IBM SPSS Statistics, Armonk, New York: IBM Corp) and MedCalc Statistical Software version 19.2.6 (MedCalc Software B.V., Ostend, Belgium).

Table 1. Definitions of the evaluated diagnostic characteristics of BS-SPECT/CT for diagnosing aseptic loosening after uncemented total knee arthroplasty.

Sensitivity	The true positive rate, representing the proportion of patients with aseptic loosening correctly detected by the BS-SPECT/CT.
Specificity	The true negative rate, representing the proportion of patients without aseptic loosening correctly detected by the BS-SPECT/CT.
Positive likelihood ratio	Represents the ratio of the probability of obtaining a positive SPECT/CT result in patients with aseptic loosening to the probability of obtaining a positive BS-SPECT/CT result in patients without aseptic loosening
Negative likelihood ratio	Represents the ratio of the probability of obtaining a negative BS-SPECT/CT result in patients with aseptic loosening to the probability of obtaining a negative BS-SPECT/CT result in patients without aseptic loosening.
Positive predictive value	It represents the likelihood that a positive result (aseptic loosening) from the BS-SPECT/CT is an accurate indication of the presence of aseptic loosening.
Negative predictive value	It represents the likelihood that a negative result (no aseptic loosening) from the BS-SPECT/CT is an accurate indication of the absence of aseptic loosening.

BS-SPECT/CT = Bone Scintigraphy Single-Photon Emission Computed Tomography/Computed Tomography

RESULTS

Diagnostic characteristics

All diagnostic characteristics of each scenario are presented in **Table 2**. In the 'best-case' scenario, 12 cases were classified as true positive (TP), 10 cases as false positive (FP), 152 cases as true negative (TN), and 6 cases as false negative (FN). In this scenario, the likelihood of a patient having aseptic loosening was 54.6% (95% confidence interval (CI) 32.2 to 75.6) after a positive, and 3.8% (CI 1.4 to 8.1) after a negative test. Of the 6 FN cases, 3 cases (50%) were diagnosed with aseptic loosening by use of a follow-up BS-SPECT/CT. In the 'worst-case' scenario, 17 cases were identified as TP, 50 as FP, 112 as TN, and 1 as FN. The post-test probability of a patient having aseptic loosening was 25.4% (CI 15.5 to 37.5) after a positive, and 0.9% (CI 0.0 to 4.8) after a negative test.

As for the sensitivity analyses, a total of 84 cases were assigned to the < 2.0 years interval group (median follow-up; 1.1 years [IQR 0.9 to 1.5]), and 96 to the > 2.0 years interval group (median follow-up; 4.0 years [IQR 2.6 to 5.8]). Both analyses resulted in test accuracies with overlapping 95%CI, with no substantial differences in diagnostic characteristics between both interval groups (**Table 3**).

Table 2. Diagnostic characteristics of the combined three-phase scintigraphy and BS-SPECT/CT performed for aseptic loosening after uncemented total knee arthroplasty.

	Inconclusive results interpreted according to	
	'Best-case' scenario (95%CI)	**'Best-case' scenario (95%CI)**
Total cases, n	180	180
Inconclusive cases, n (%)	45 (25)	45 (25)
Disease prevalence, %	10.0 (6.0 - 15.3)	10.0 (6.0 - 15.3)
Sensitivity, %	66.7 (41.0 - 86.7)	94.4 (72.7 - 99.9)
Specificity, %	93.8 (88.9 - 97.0)	69.1 (61.4 - 76.2)
Positive likelihood ratio	10.8 (5.5 - 21.4)	3.1 (2.4 - 4.0)
Negative likelihood ratio	0.4 (0.2 - 0.7)	0.1 (0.0 - 0.5)
Positive predictive value*, %	54.6 (32.2 - 75.6)	25.4 (15.5 - 37.5)
Negative predictive value*, %	96.2 (91.9 - 98.6)	99.1 (95.2 - 100.0)
Accuracy*, %	91.1 (86.0 - 94.8)	71.7 (64.5 - 78.2)

BS-SPECT/CT = Bone Scintigraphy Single-Photon Emission Computed Tomography/ Computed Tomography; CI = Confidence Interval
* Values are dependent on disease prevalence.

Table 3. Sensitivity analyses regarding diagnostic characteristics of BS-SPECT/CT to diagnose aseptic loosening after uncemented total knee arthroplasty, stratified for cases with a shorter and longer interval of 2.0 years between total knee arthroplasty and imaging.

	Inconclusive results interpreted as negative	
	< 2.0 years interval (95%CI)	**> 2.0 years interval (95%CI)**
Total cases, n	84	96
Inconclusive cases, n (%)	34 (40.5)	11 (11.5)
Disease prevalence, %	15.5 (8.5 – 25.0)	5.2 (1.7 - 11.7)
Sensitivity, %	69.2 (38.6 – 90.9)	60.0 (14.7 - 94.7)
Specificity, %	97.2 (90.2 – 99.7)	91.2 (83.4 - 96.1)
Positive likelihood ratio	24.6 (6.0 – 101.0)	6.8 (2.6 - 18.1)
Negative likelihood ratio	0.3 (0.1 – 0.7)	0.4 (0.2 - 1.3)
Positive predictive value*	73.2 (39.9 – 91.8)	43.1 (22.3 – 66.8)
Negative predictive value*	96.6 (92.6 – 98.5)	95.4 (87.5 - 98.4)
Accuracy*, %	94.4 (87.1 – 98.2)	88.1 (79.9 - 93.8)

For abbreviations see table 2. * Values are dependent on disease prevalence, wherefor the same disease prevalence was used as was calculated in the 'best and worst' case scenario of 10%.

Interobserver reliability and tracer uptake localizations

From the 100 re-evaluated cases, 82 cases had a negative, and 18 had a positive reference standard. The interobserver reliability between observers 1 and 2 was fair to moderate, estimated at κ = 0.39 (CI; 0.18 to 0.60), with an absolute agreement of 79% (CI; 70 to 87). The localization of the tracer uptake was presented in **Figure 2**. Mainly, a similar localization tracer uptake distribution was found between the cases with and without aseptic loosening found by the reference standard. The proportion of tracer uptake was considerably larger in the cases with aseptic loosening found by the reference standard, in zone T6 and T7 of the tibial component (anterior-posterior view) and zone F5 and F7 of the femoral component (lateral view).

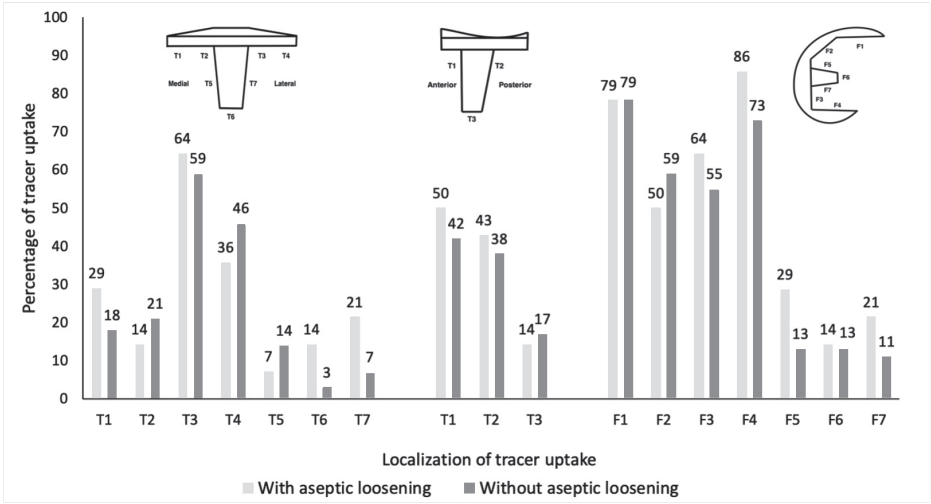


Figure 2. Proportions of tracer uptake of 18 cases with aseptic loosening and 82 cases without aseptic loosening, according to the locations of the Knee Society roentgenographic scoring system.

DISCUSSION

The most important finding of the present study was that the best diagnostic characteristics of BS-SPECT/CT for diagnosing aseptic loosening of uncemented TKA were obtained with the best-case scenario, in which unclear results were assumed to be negative. This resulted in a sensitivity of 66.7%, specificity of 93.8%, a +LR of 10.8, a -LR of 0.4, PPV of 54.6%, and NPV of 96.2%. Furthermore, the diagnostic characteristics identified were not much affected by the duration of the postoperative interval between TKA and the performed BS-SPECT/CT.

In regular clinical practice prior to undergoing BS-SPECT/CT, patients who have a symptomatic TKA typically undergo a combination of diagnostic tests

as part of the step-by-step approach to failure analysis. *[453]* These tests may include a thorough physical examination, regular radiography, assessment of inflammatory blood parameters, and sometimes intra-articular aspiration. This sequential approach is employed to rule out the more common complications, with the purpose of correctly diagnosing patients by using fewer invasive tests, and ideally, to increase the pre-test probability of the following test. *[33]* Due to the distinct roles of specificity in reducing false positives and sensitivity in minimizing false negatives, a BS-SPECT/CT conducted during the final stages of the diagnostic workup requires a high level of specificity. This is particularly crucial as a positive result would suggest aseptic loosening of the implant, necessitating revision TKA. In this study (best-case scenario), 9 cases were FP by follow-up and 1 by revision. During this revision, no loosened component was found and only a patellar resurfacing for patellofemoral arthrosis was carried out. Minimizing false-positive outcomes in the diagnostic approach for aseptic loosening is of utmost importance, considering that most patients are likely to experience poorer function and increased pain compared to the outcome of primary TKAs, and have an elevated risk of subsequent revision or reoperation, especially when the underlying cause of implant failure has not yet been fully determined. *[26, 440, 441, 454, 455]* Therefore, based on specificity values found in this study, we conclude that the interpretation of inconclusive BS-SPECT/CT results as positive (worst-case scenario) would be inappropriate, as it could result in unnecessary or wrongly indicated revisions. The specificity values obtained in the 'best-case' scenario and sensitivity analyses are in agreement with their specificity reported in previous investigations, ranging from 86.6 to 100% *[34, 35, 443, 447]*. Nevertheless, the sensitivity values of this study are notably lower compared to previous studies, exhibiting a range of 86.2 to 100% *[34, 35, 443, 447]*. This disparity likely arises from the use of "inconclusive index test results" in this study, from which it is important to note that the use of inconclusive conclusions by nuclear radiologists on a single BS-SPECT/CT is not uncommon in routine medical care. In this study, 3 of 6 (50%) inconclusive cases in the best-case scenario, were found to be positive for aseptic loosening, and confirmed by revision, based on a follow-up BS-SPECT/CT. Another factor that could play a role in the differences in diagnostic characteristics is the dispersed performance of nuclear radiologists, which is supported by the 'fair-to-moderate' interobserver reliability found in this study. In the study of Arican et al. *[443]* a 'substantial to almost perfect' interobserver reliability of κ = 0.80 was found. However, it is likely that this is a result of the patient population that was used, in which patients that were not revised were excluded. It remains important to the analyses to also include patients that did not undergo a revision. Even though, this could assemble to incorporate bias.

In contrast to other studies, the primary focus of this study was specifically on analyzing the BS-SPECT/CT results of uncemented implants. This unique focus was motivated by concerns raised by physicians regarding the fading of tracer uptake in

cemented implants after a year, which could potentially impact the interpretation and clinical relevance of the scan results, leading to an increased number of false positives. However, the sensitivity analyses conducted in this study demonstrate that the diagnostic characteristics of BS-SPECT/CT for uncemented TKA remained mostly consistent when comparing cases irrespective of the postoperative duration (<2.0 and >2.0 years) between TKA and the first BS-SPECT/CT. Although it is important to note that the <2.0 group had substantially more inconclusive cases, caution should be warranted when interpreting the findings of these analyses. An increasingly popular innovative technique mentioned in the literature is the [^{18}Fluoride] positron emission tomography, which offers the advantage of quantitatively measuring osteoblast activity. *[456]* This hybrid modality might hold the potential to reduce the number of inconclusive, false-positive cases and improve inter-observer reliability. *[456, 457]* Even though current studies assessing this modality face similar limitations as those that assessed the BS-SPECT/CT diagnostic characteristics.

As for the likelihood of aseptic loosening after a positive BS-SPECT/CT result, this study found a PPV of 54.6 % (CI: 32.2 to 75.6), meaning that 45.4% (CI: 24.4 to 67.8) of cases would actually not have aseptic loosening of their implant. Therefore, in accordance with the principle of "primum non nocere" (do no harm first), it is not recommended to implement BS-SPECT/CT in an early stage of the diagnostic workup, as in an early stage, the pre-test probability, and thus the post-test probability would be lower.

This study has several potential limitations that should be acknowledged. The presence of incorporation bias is possible, as the decision to revise TKA was primarily based on the BS-SPECT/CT results. Therefore, not all patients received the same reference standard (i.e., revision or follow-up), which can cause the misclassification of false negatives into true negatives, consecutively leading to an overestimation of the diagnostic accuracy. However, it is important to note that the diagnostic characteristics obtained in this study were comparatively lower than those reported in previous studies, thereby reducing the likelihood of overestimation. Also, the presence of verification bias within the outcome of the reference standard should be acknowledged. As the surgeons were not blinded to the BS-SPECT/CT results, there is a possibility that they inadvertently engaged in selective verification of the findings. For instance, they may have reported a "loosened" prosthesis in the surgical report because the BS-SPECT/CT indicated a high probability of loosening, without being consciously aware of this bias and thereby enhancing the likelihood of overestimation. In addition, a total of 32 patients who had cemented implants were excluded, despite their experiencing similar complaints to the included patients. While their exclusion was justified due to the study's specific focus on uncemented implant loosening, it is important to note that none of these 32 excluded cases were found to have aseptic loosening. Consequently, the pre-test disease probability is slightly overestimated

by 8.5 to 10%. Nonetheless, it is worth emphasizing that this limitation has minimal impact on both the negative predictive value (NPV) and positive predictive value (PPV) of the study's findings. Furthermore, the utilization of inconclusive cases sets this study apart from other studies, as the research group believed it would be more representative of the reality of daily practice to include these cases. Mainly because scans are not always conclusive, which is likely a result of lacking quantitative measurements of tracer uptake intensity. For instance, when tracer uptake intensity could be measured, thresholds for tracer uptake intensity could potentially be determined in future studies, providing a more precise and objective assessment. Nevertheless, in this study, scan reports were interpreted by physicians, which would also be the most representative of the common practice in daily healthcare settings. Additionally, it is important to exercise caution when interpreting the data due to the wide confidence intervals associated with the results in this study. The broad range of these intervals indicates a level of uncertainty and highlights the need for further research to obtain more precise estimates and validate the findings.

CONCLUSION

The test characteristics of BS-SPECT/CT in patients who have complaints of uncemented TKA suspected of aseptic loosening showed a sensitivity of 66.7% and a specificity of 93.8%. The positive and negative likelihood ratios were 10.8 and 0.4, respectively, with positive and negative predictive values of 54.6 and 96.2%. Inconclusive cases were best categorized as negative, especially in patients who have a short interval between TKA and the first BS-SPECT/CT. Increased tracer uptake in four prosthetic zones was observed in cases of aseptic loosening, although interobserver reliability was fair to moderate.

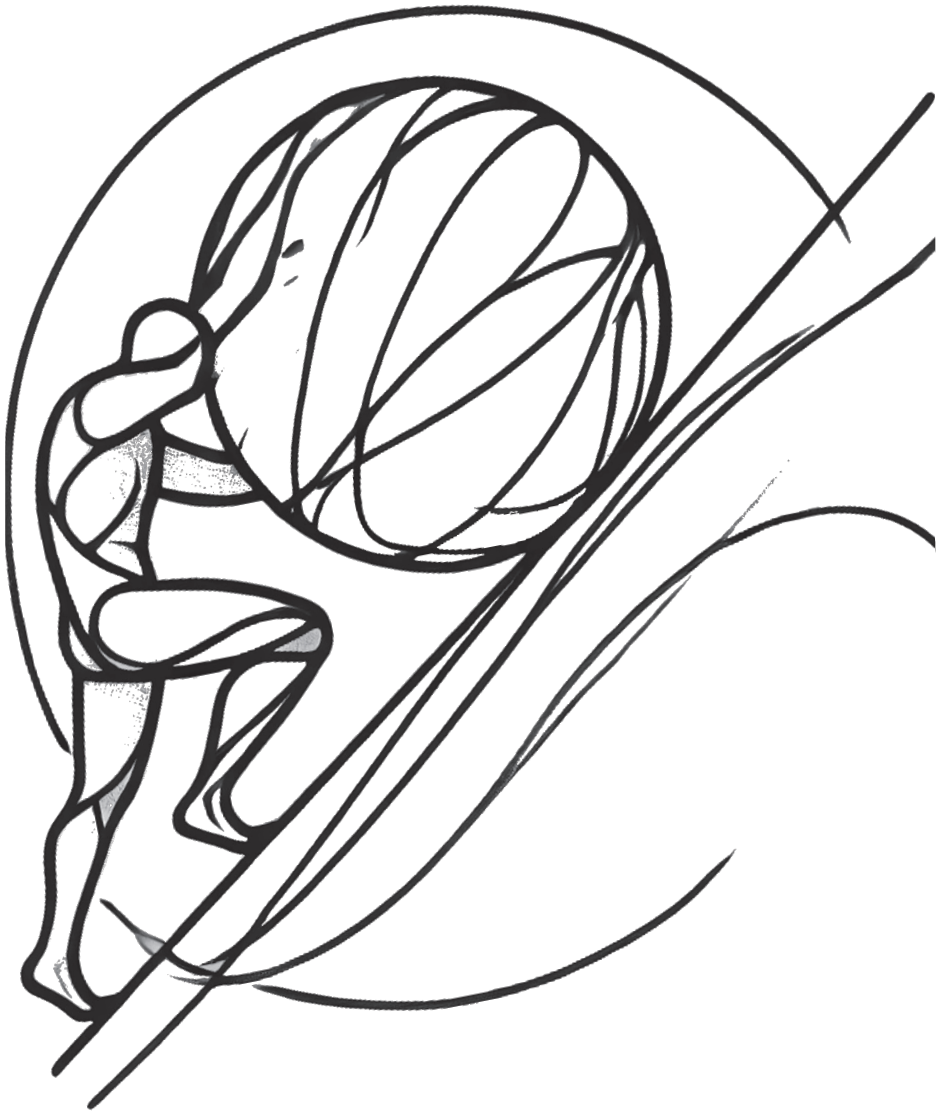
SUPPLEMENTAL MATERIAL

Table S1. STARD 2015 CHECKLIST

Section	Item	Page
Title	Identification as a study of diagnostic accuracy using at least one measure of accuracy	1
Abstract	Structured summary of study design, methods, results, and conclusions	1
Introduction	Scientific and clinical background, including the intended use and clinical role of the index test	1-2
	Study objectives and hypotheses	2
Methods		
Study design	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after	2
Participants	Eligibility criteria	2-3
	On what basis potentially eligible participants were identified (Such as symptoms, results from previous tests, and inclusion in the registry)	2-3
	Where and when potentially eligible participants were identified (setting, location and dates)	2-3
	Whether participants formed a consecutive, random, or convenience series	2-3
Test	Index test, in sufficient detail to allow replication	3
	Reference standard, in sufficient detail to allow replication	3
	Rationale for choosing the reference standard	3
	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	3
	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	3
	Whether clinical information and reference standard results were available to the performers/readers of the index test	3
	Whether clinical information and index test results were available to the assessors of the reference standard	3
Analysis	Methods for estimating or comparing measures of diagnostic accuracy	4
	How indeterminate index test or reference standard results were handled	4
	How missing data on the index test and reference standard were handled	n/a

Table S1. Continued

Section	Item	Page
	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	4
	Intended sample size and how it was determined	-
Results	Flow of participants, using a diagram	4-5
Participants	Baseline demographic and clinical characteristics of participants	4-5
	Distribution of severity of disease in those with the target condition	n/a
	Distribution of alternative diagnoses in those without the target condition	n/a
	Time interval and any clinical interventions between index test and reference standard	4-5
Test results	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	4-5
	Estimates of diagnostic accuracy and their precision (95% confidence intervals)	4-5
	Any adverse events from performing the index test or the reference standard	n/a
Discussion	Study limitations, including sources of potential bias, statistical uncertainty, and generalizability	5-6
	Implications for practice, including the intended use and clinical role of the index test	5-6
Other information	Registration number and name of registry	n/a
	Where the full study protocol can be accessed	n/a
	Sources of funding and other support; role of funders	n/a



CHAPTER 8

Long-Term Clinical Performance of an Uncemented, Mobile Bearing, Anterior Stabilized Knee System and the Impact of Previous Knee Surgery.

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ABSTRACT

Background
The aim of this study is to report long-term survival and patient-reported outcome measures (PROMs) of the uncemented low contact stress total knee system and explore the potential as- sociation between prior knee surgery and outcomes.

Methods
A total of 1,289 procedures in 1,068 patients performed between 2000 and 2010 (mean follow-up 11.1 years) were retrospectively identified. All patients received an uncemented, mobile bearing, anterior stabilized (cruciate sacrificing) knee implant with a porous coating on th1e bone-prosthesis surface. Implant survival was calculated using competing risk analyses at 5, 10, and 15 years. PROMs include the Oxford Knee Score, Knee Society Score (domain function), EuroQol 5D-3L, and Numeric Rating Scale for pain during rest and activity, and for overall satisfaction. The association between previous surgery (no surgery versus meniscectomy versus arthroscopy versus corrective osteotomies) and implant survival was assessed with multivariable Cox proportional hazards analysis; the association with PROMs was assessed with multivariable linear regression analyses.

Results
Survival after 5, 10, and 15 years was 97.0% (95%CI 96.0-98.0), 96.3% (95%CI 95.3-97.3), and 96.0% (95%CI 94.8-97.2), respectively. The most common reason for revision was aseptic loosening of the tibial tray (23/49 revisions, 47%). All PROMs were comparable with the reference values of the Dutch Arthroplasty Register. History of knee surgery prior to TKA was not associated with survival or PROMs.

Conclusion
The low contact stress uncemented mobile bearing knee implant provides excellent survival and patient satisfaction in our cohort. Previous surgery does not seem to compromise results in our population.

INTRODUCTION

Total knee arthroplasty (TKA) is the gold standard for treatment of end-stage symptoms of knee joint destruction. *[410]* It has grown to one of the most performed surgeries in the world and is expected to rise in light of the current obesity epidemic. *[410, 458]* The number of young patients demanding TKA has risen in parallel. *[459]* Aided by recent improvements in implant design and manufacturing technology, this sparked a renewed interest in uncemented implant fixation. Although heavily debated *[460, 461]*, the potential of biological ingrowth of the implant is slowly getting recognized as a potential better fixation strategy in (younger) patients receiving TKA. *[462–464]*

The most frequently registered uncemented implant in the United Kingdom and New Zealand is the low contact stress (LCS) (DePuy, Warsaw, IN). *[6, 8]* One of its key features is a congruent, rotating, mobile bearing that is designed to minimize contact stress and thus reduce mechanical wear. *[465, 466]* Clinical studies on survival and knee function achieved with the uncemented LCS have shown excellent results. *[315, 467–471]* The prospective cohort study by co-designer Sr Buechel represents the first long-term study on the uncemented LCS, presenting results of 309 cruciate retaining ("meniscal bearing") and anterior stabilized ("rotating platform," cruciate sacrificing) knee implants followed up for a minimum of 10 years (mean 12.4 years). *[468]* Besides reporting excellent results at long term, this article also highlights that previous knee surgery does not influence survival and knee function achieved with uncemented TKA. *[468]* This is in accordance with another study by Lim et al *[472]*, showing that prior knee surgery did not compromise revision rates or knee function of 303 patients at a minimum follow-up of 2 years after cemented TKA. Both these studies *[468, 472]* are, however, flawed by small sample sizes and are therefore underpowered to detect differences in implant survival due to the small incidence of revisions after TKA.

The primary aim of the current retrospective cohort study is to evaluate the long-term clinical results achieved with the uncemented, mobile bearing, anterior stabilized ("rotating platform") cruciate sacrificing configuration of the LCS knee implant. We furthermore sought to explore the potential impact of prior knee surgery on the results achieved with this uncemented knee system.

MATERIALS AND METHODS

Between May 1, 2000 and January 1, 2010, a total of 1,510 mobile bearing LCS (DePuy Synthes, Warsaw, IN) primary TKAs were performed at our institution (Spaarne Gasthuis, Hoofddorp, the Netherlands) and were considered for inclusion. Cemented/hybrid fixated implants, cruciate retaining implants, conversions from unicondylar or patellofemoral arthroplasty, and procedures utilizing revision

components were excluded. Our hospital database was searched with CTcue (CTcue B.V., Amsterdam, the Netherlands) to identify and select eligible patients. After review and approval by the institutional review board of our institution (ACLU 2018.0105), all eligible patients were retrospectively contacted and invited for participation in the current study starting from February 2020. In case of unwillingness to participate in the study, the patient was asked on potential reoperations regarding the implant system elsewhere.

A total of 1,289 implants in 1,068 patients (769 females [72%]; 221 bilateral procedures) were uncemented, anterior stabilized ("rotating platform") constructs and were included in the current analysis (**Figure 1**). The mean follow-up was 11.1 years (standard deviation 3.9 years, range 10.6-20.2). Patients were consented for joint replacement therapy after failed conservative treatment for invalidating symptoms of osteoarthritis (1,253 knees), rheumatoid arthritis (20 knees), post-traumatic arthritis (13 knees), or secondary arthritis (3 knees) and had a mean age of 70.8 years (range 39-95) at surgery. A total of 336 knees (26%) had a history of knee surgery (**Table 1**). All 1,289 included implants had complete information on survival of the prosthesis and patient (using mortality information from the Dutch population register [Basisregistratie personen]; date accessed February 9, 2021) and 318 knees had complete questionnaires available at final follow-up (**Figure 1**).

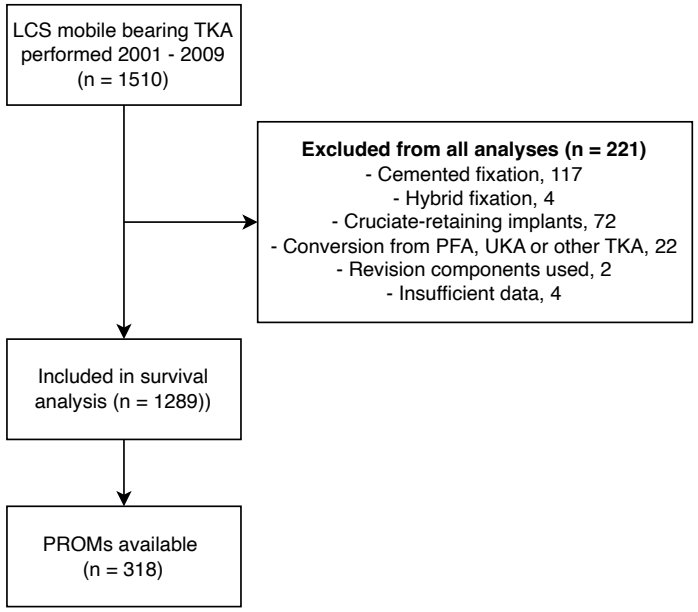


Figure 1. Flowchart illustrating the inclusion of implants and the reasons for exclusion. LCS, low contact stress; PFA, patellofemoral arthroplasty; UKA, unicondylar knee arthroplasty; TKA, total knee arthroplasty; PROMs, patient-reported outcome measures.

All patients were operated using a medial parapatellar approach without tourniquet usage. Gap balancing was used to ensure proper mechanical alignment and measurement of the appropriate mobile bearing size. After placement of trial components, trial reduction was performed to ensure acceptable range of motion, stability, and absence of impingement. All implants were uncemented with a porous coating on the bone-prosthesis surface; no bioactive coating was used. Patellar resurfacing was not routinely performed (only 7/ 1,290 knees [<1%] received a metal-backed patellar prosthesis). Knees with fixed varus deformity had additional medial soft tissue release (n = 2); knees with fixed valgus deformity underwent attenuation of the medial collateral ligament (n = 2) or lateral soft tissue release (n = 2). There were 4 perioperative tibial shaft fractures and 1 patellar fracture, all receiving additional osteosynthesis except for 1 tibial shaft fracture that was treated conservatively. A total of 9 bone defects were encountered during surgery, treated with bone graft impaction without osteosynthesis (n = 5), bone graft impaction with additional osteosynthesis (n = 3), and 1 cm distal extension of the tibial cut (n = 1). A simultaneous patellar realignment procedure was performed in 2 knees (1 lateral release, 1 tibial tuberosity osteotomy) and simultaneous removal of osteosynthesis from a previous coronal correctional osteotomy in 1 knee. After surgery, all patients received a rehabilitation program under the supervision of a physical therapist pursuing active range of motion movement and mobilization starting from the first day postoperative. One patient sustained injury to the patellar ligament, for which immobilization with a brace was recommended for 6 weeks after surgery. Postoperative controls with radiographic evaluation are done after 6 weeks, 1 year, 5 years, and 10 years in the outpatient clinic.

Table 1. Baseline Characteristics of All 1,068 Patients Receiving 1,289 Uncemented LCS Knee Systems Between May 2000 and January 2010.

Gender, n Patients (%)	
Female	769 (72)
Male	299 (28)
Diagnosis, n Knees (%)	
Osteoarthritis	1,253 (97)
Rheumatoid arthritis	20 (2)
Post-traumatic arthritis	13 (1)
Secondary arthritis[1]	3 (<1)
Age (y), mean (SD)	70.8 (9.5)
BMI (kg/m²), mean (SD)	28.8 (5.8)
Total hospital stay (d), median (IQR)	5 (5–6)

Table 1. Continued

Previous surgery, n Knees (%)	
Meniscectomy	233 (18)
Arthroscopy	67 (5)
Coronal corrective osteotomies	44 (3)
Ligament reconstruction	12 (1)
Patella realignment procedures	9 (1)
Other arthrotomies	16 (1)

LCS, low contact stress; BMI, body mass index; IQR, interquartile range.

The primary outcome was implant survival, with failure (ie, implantation, explantation, or exchange of any component) of the implanted knee as an end point. Survival was recorded for revision for any reason and for aseptic loosening. Secondary outcomes that were collected include re-revision rate, functional outcome measures, reoperation rate, need for mobilization under anesthetics (MUA), and the incidence of radiolucent lines. Re-revision rate is defined as subsequent failure of any revised knee implant after first revision. Functional outcome measures (patient-reported outcome measures; PROMs) were collected through physical or electronic questionnaires and included the Oxford Knee Score (OKS; 0, worst to 48, best), the Knee Society Score for Function (0, worst to 100, best), the Knee injury and Osteoarthritis Outcome Score Physical Function Short Form (0, best to 100, worst), the EuroQol 5D-3L index (EQ5D; 0, worst to 1, best), and a Numeric Rating Scale (NRS) for pain (0, no pain to 10, worst pain), during rest (NRS-R) and activity (NRS-A), and for overall satisfaction (NRS-S; 0, very un- satisfied to 10, very satisfied). *[473–477]* These PROMs were supplemented with two 7-point Likert scales asking patients to rate their change in daily functioning ("very deteriorated" to "very improved," scores ranging from 1 to 7) and knee pain ("very deteriorated" to "very improved," scores ranging from 1 to 7) since their TKA surgery. Reoperations were defined as any intervention to the operated knee without alteration of the implanted components. MUA was always subsequent to impaired range of motion, incidence and time to MUA were reported. Radiolucent lines were scored by 2 independent examiners (R.R. and J.S.) based on their presence and potential progression on the most recent short-leg radiograph according to the zones described in the Knee Society roentgenographic scoring system. *[451]* Interobserver reproducibility was assessed by test-retest analysis of 30 randomly selected radiographs and calculation of the agreement (%) on radiolucent lines in the tibia and femur separately with the accompanying Kappa statistic. *[478]* The agreement was 92% for radiolucent lines in the tibia with a Kappa statistic of 0.83 (95% confidence interval 0.69-0.97) and 93% for radiolucent lines in the femur with a Kappa statistic of 0.84 (95% confidence interval 0.63-1.0).

Statistical Analysis

A post hoc power analysis based on noninferiority of the uncemented LCS compared to real-world survival data were performed. A noninferiority margin of 2% was assumed. Ten-year survival of all primary knee arthroplasties registered in the Dutch Arthroplasty Register (LROI Landelijke Registratie Orthopedische Implantaten) is 94.1% according to the 2019 annual report. *[479]*Based on alpha = 0.05, power (1-B) of 0.90, and both true proportion (p) and null hypothesis proportion (p0) of 94.1%, a sample size of n = 1,188 was calculated with a one-sided test. *[480, 481]*

Data analysis was done with SPSS 24.0 (IBM SPSS, New York, NY). Survival at 5, 10, and 15 years after index surgery was deter- mined using Kaplan-Meier curves and competing risk analysis (with death as the competing risk). Patients lost to follow-up or death due to other reasons were censored from the survival analysis. Re-revisions were described and expressed in frequencies and percentages. Calculated functional outcome measures were assessed for normality and then expressed as means and standard deviations or medians and interquartile ranges in case of non- normal distribution. Reported 1-year functional outcome measures of all cemented and uncemented implants registered from 2014 to 2019 in the LROI are presented as a comparison. Reoperation rates and the need for MUA were described and expressed in frequencies and percentages. Radiolucent lines were expressed in frequencies and percentages. The impact of previous surgery (no surgery versus meniscectomy versus arthroscopy versus corrective osteotomies) on implant survival was explored by plotting Kaplan-Meier curves separately for all groups and log-rank test. Adjusted survival comparisons were done with multivariate Cox proportional hazards analysis, with correction for age, gender, and pre- operative diagnosis (osteoarthritis versus others). The influence of previous surgery on functional outcomes was determined by construction of multivariate linear regression analyses, with correction for age, gender, and preoperative diagnosis. A P-value <.05 was considered statistically significant in all analyses.

RESULTS

Survival Analysis and Description of (Re-)Revision Procedures

At final follow-up, a total of 49 out of 1,289 implants were revised. Calculated survival rates at 5, 10, and 15 years were 97.0% (95% CI 96.0-98.0), 96.3% (95% CI 95.3-97.3), and 96.0% (95% CI 94.8-97.2) respectively (**Figure 2**). Survival with revision for aseptic loosening as an end point was 98.4% (95% CI 97.6-99.2), 98.2% (95% CI 97.4-99.0), and 98.2% (95% CI 97.4-99.0) at 5, 10, and 15 years, respectively. Aseptic loosening of the tibia was the most common reason for revision (47%), followed by anterior knee pain (18%) and instability (14%). All patients with anterior knee pain (n = 9) had no primary resurfaced patellae and

underwent secondary patellar resurfacing. Insert spin-out occurred 2 times (6%) and 1 patient had a fractured insert (2%), all 3 underwent solitary insert exchange. In our cohort, the most common intervention during a revision procedure was an isolated exchange of the tibial tray with a stemmed component (39%), followed by secondary patellar resurfacing (22%) and an isolated insert ex- change (18%) (**Table 2**).

Of the 49 implants that were revised, a total of 6 knees (12%) underwent a second revision. Most common reasons for re-revision were instability (50%) and arthrofibrosis (33%) (**Table 2**).

Table 2. Failure modes and interventions performed during revision (n = 49) and re-revision (n = 6) procedures.

Failure Modes and Interventions	Revisions, n (%)	Re-Revisions, n (%)
Reasons for revision		
Aseptic loosening	23 (47)	-
Anterior knee pain	9 (18)	-
Instability	7 (14)	3 (50)
Persisting knee pain (no loosening)	3 (6)	
Patella baja	3 (6)	1 (17)
Patellar maltracking	2 (4)	-
Malalignment	2 (4)	-
Insert spin-out	2 (4)	-
Suspicion of PJI	2 (4)	-
Loose body	1 (2)	-
Insert fracture	1 (2)	-
Arthrofibrosis	-	2 (33)
Polyethylene wear	-	1 (17)
Symptomatic osteophytes	-	1 (17)
Interventions during revision procedures		
Tibial tray revision with stemmed component	19 (39)	-
Secondary patellar resurfacing	11 (22)	-
Isolated insert exchange	9 (18)	6 (100)
Tibial tray revision with primary cemented component	5 (10)	-
Soft tissue release	3 (6)	1 (17)
Tibial tuberosity osteotomy	2 (4)	1 (17)
DAIR (with exchange of insert)	1 (2)	-
Removal revision with stemmed component	1 (2)	-
Removal of all component and arthrodesis	0 (0)	-
Revision of all components with stemmed components	1 (2)	1 (17)

Table 2. Continued

Failure Modes and Interventions	Revisions, n (%)	Re-Revisions, n (%)
Revision of all components with stemmed tibial tray, posterior stabilized insert, and primary stemless femur	1 (2)	-
Removal of loose body/osteophytes	1 (2)	-
Resection lateral patella	1 (2)	-
Two-staged revision of all components (with cement spacer and reimplantation of stemmed components)	1 (2)	-

PJI Prosthetic Joint Infection, DAIR Debridement antibiotics, and implant retention.
a Numbers do not add up due to multiple reasons for revisions or interventions during the procedure.
b Twenty-two isolated tibial loosening and 1 tibial and femoral component loosening.

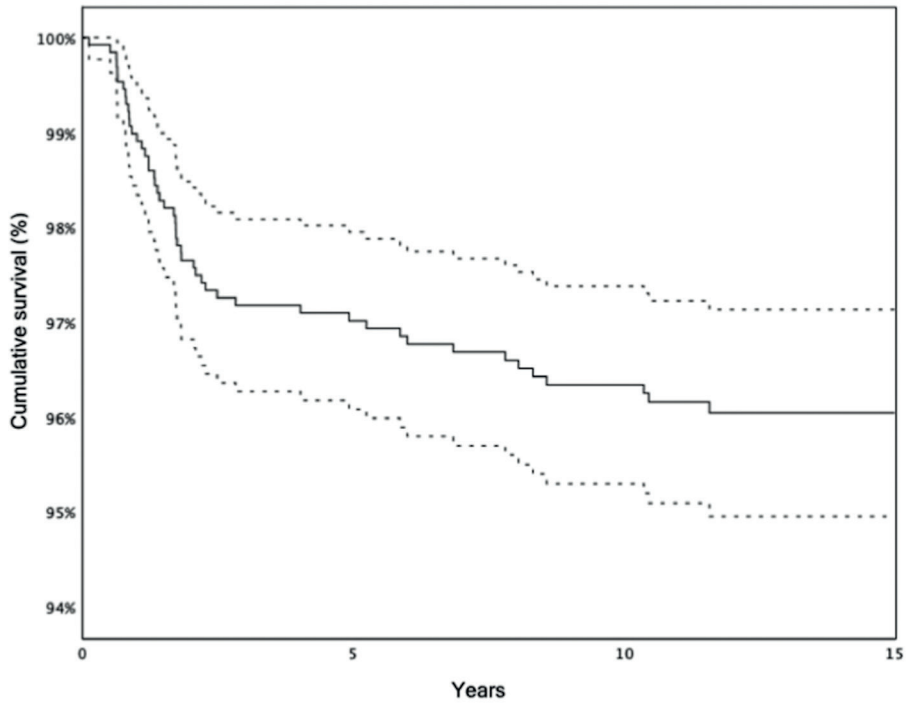


Figure 2. Kaplan-Meier survival curve (with 95% confidence interval) of the uncemented, mobile bearing, anterior stabilized ("rotating platform") low contact stress total knee system.

Functional Outcomes

A total of 318 patients had available PROMs for analysis. **Table 3** summarizes calculated scores and also includes 1-year scores reported in the LROI for the Netherlands. *[482]* The mean OKS, Knee injury and Osteoarthritis Outcome Score

Physical Function Short Form, EQ5D index, and NRS for pain during rest and activity of our cohort were comparable with the reference values of the LROI. In our cohort, 78% of the patients reported improvement in their daily functioning, while 85% reported improvement in their knee pain.

Table 3. An Overview of Functional Outcome Measures of All Included Patients who responded to the questionnaires.

	Current Cohort	LROI Report 2019 [482]
OKS	39.7 (38.6–40.8)	38.6 (38.5–38.7)
KOOS-PS	26.8 (24.7–28.9)	28.3 (28.1–28.5)
EQ5D	0.84 (0.81–0.87)	0.84 (0.84–0.84)
NRS-PR	1.4 (1.14–1.66)	1.5 (1.5–1.6)
NRS-PA	1.8 (1.50–2.10)	2.3 (2.3–2.4)
NRS-S	8.1 (7.81–8.39)	7.9 (7.9–8.0)
Improvement in general functioning	5.6 (5.4–5.8)	5.7 (5.6–5.7)
Improvement in knee pain	5.9 (5.8–6.0)	6.0 (6.0–6.0)

Reported values of the LROI are included for reference.

Reoperations, Mobilization Under Anesthetics, and Radiolucent Lines

A total of 47 reoperations (47/1,290) in 42 implants (5-second reoperations) were undertaken in the included cohort (**Table 4**). Mean time to reoperation was 3.1 years (SD 3.8 years). Most patients were reoperated for suspicion of prosthetic joint infection (30%) and periprosthetic fracture (28%). Of the 5 patients undergoing a second reoperation, 3 were suffering of persistent prosthetic joint infections and underwent a second debridement. The remaining 2 patients had a second peri-prosthetic fracture and failure of previous osteosynthesis for periprosthetic fracture. A total of 35 knees (3%) underwent MUA for impaired range of motion after a mean of 12 months (SD 7.2 months) after index surgery. All patients were admitted and additionally treated with motorized range of motion for 1-2 days after MUA. Six of these patients (17%) remained symptomatic and underwent a revision procedure (for aseptic loosening [4] and persistent pain [2]). Six more patients (17%) still had invalidating symptoms after the MUA, 1 underwent a patella realignment procedure, 2 had invalidating functional impairment, and the last 3 were referred to the pain specialist. The other 23 patients (66%) had significant improvement of their knee pain and function, of which 14 occasionally experienced some mild symptoms (mild swelling, pain, or functional impairment). A total of 296 implants (23%) demonstrated radiolucent lines in one or more zones, of which 52 (18%) demonstrated progression during the minimum follow-up of 10 years. **Figure 3** schematically shows the prevalence of radiolucent lines in all different zones. The most prevalent radiolucent line was found in zone 1 under the tibial component

in the lateral view (15%), followed by zones 4 (13%) and 1 (11%) under the tibial component in the anteroposterior view.

Table 4. Overview of All 47 Reoperations (in 42 Knees) That Were Undertaken During the Complete Follow-up Period of the Included Cohort.

	n (%)
Suspicion of prosthetic joint infection, treated with DAIR	14 (30)
Periprosthetic fracture, treated with ORIF	13 (28)
Arthrofibrosis, treated with arthrolysis	6 (13)
Removal of symptomatic osteophytes	4 (9)
Hydrops or bursitis, treated with arthroscopic debridement	2 (4)
Malalignment, treated with bone graft impaction	1 (2)
Compartment syndrome, treated with fasciotomy	1 (2)
Patella realignment procedure	1 (2)
Surgical site infection, treated with wound debridement and antibiotics	1 (2)
Removal of osteosynthesis	1 (2)
Unexplained pain, treated with diagnostic arthroscopy and biopsy	1 (2)
Failed osteosynthesis, treated with open reduction internal refixation	1 (2)
Neuropathy of cutaneous nerves distal side of the scar, treated with neurolysis	1 (2)

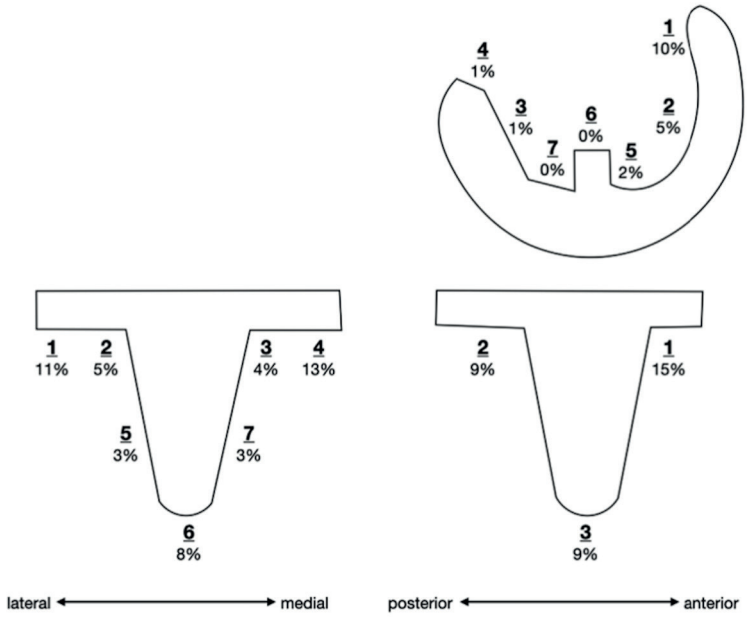


Figure 3. Prevalence of radiolucent lines in the different zones according to the Knee Society roentgenographic scoring system. *[451]*

Association Between Previous Surgery and Survival/Patient-Reported Outcome Measures

Ten-year survival of patients with no history of previous surgery, history of meniscectomy, history of arthroscopy (i.e., excluding meniscectomy and ligament reconstructions), and history of coronal corrective osteotomies was 96.7% (CI 95.5-97.9), 95.7 (CI 93.0-98.4), 93.5% (CI 87.3-99.8), and 95.4 (CI 89.1-100), respectively (P = .58). After adjustment for confounders (i.e., age, gender, preoperative diagnosis), patients with previous meniscectomy, arthroscopy, or corrective osteotomy were not at increased risk for revision compared to patients with no history of previous surgery (**Table 5**). Furthermore, after correction for the aforementioned confounders, we found no differences between the groups with regard to postoperative PROMs (**Table 5**).

Table 5. Cox Regression analysis (revision) and Linear regression analysis (PROMs) that were used to analyze differences in implant survival and functional outcome, respectively, between patients with and without (reference) history of previous surgery.

		Meniscectomy, (95%CI)	Arthroscopy, (95%CI)	Coronal Corrective Osteotomy, (95%CI)
All-cause revision	Crude HR	1.38 (0.68; 2.79)	1.87 (0.66; 5.29)	1.30 (0.31; 5.40)
	Adjusted HR	1.28 (0.61; 2.68)	1.49 (0.51; 4.33)	0.99 (0.23; 4,21)
OKS	Crude B	-1.32 (-3.82; 1.18)	-0.84 (-4.67; 2.99)	0.93 (-4.50; 6.35)
	Adjusted B	-0.84 (-2.64; 2.48)	0.11 (-3.73; 3.94)	2.03 (-3.38; 7.44)
KOOS-PS	Crude B	-2.94 (-7.76; 1.88)	-1.38 (-8.99; 6.23)	-0.86 (-11.06; 9.35)
	Adjusted B	-0.23 (-5.09; 4.64)	0.52 (-5.99; 6.04)	2.22 (-7.87; 12.32)
EQ5D	Crude B	0.03 (-0.03; 0.08)	0.02 (-0.08; 0.11)	-0.04 (-0.17; 0.09)
	Adjusted B	0.00 (-0.06; 0.06)	-0.02 (-0.11; 0.08)	-0.07 (-0.20; 0.06)
NRS-PR	Crude B	-0.33 (-0.95; 0.29)	-0.05 (-1.00; 0.90)	0.14 (-1.11; 1.38)
	Adjusted B	-0.30 (-0.95; 0.35)	-0.09 (-1.06; 0.89)	0.10 (-1.16; 1.37)
NRS-PA	Crude B	-0.26 (-0.95; 0.43	-0.49 (-0.61; 1.59)	0.16 (-1.23; 1.54)
	Adjusted B	-0.12 (-0.84; 0.60)	0.49 (-0.61; 1.59)	0.16 (-1.23; 1.54)
NRS-S	Crude B	0.52 (-0.17; 1.21)	-0.15 (-1.20; 0.89)	0.39 (-1.04; 1.81)
	Adjusted B	0.45 (-0.27; 1.16)	-0.25 (-1.32; 0.81)	0.27 (-1.19; 1.72)

No history was used as reference. All analyses were corrected for age, gender and diagnosis. PROMs Patient-reported outcome measures PROMs; HR Hazard ratio; B B-coefficient.
a Arthroscopic procedures included debridement of the joint space, synovectomy, diagnostic arthroscopy, and unknown interventions (i.e., meniscectomy and ligament reconstruction excluded)

DISCUSSION

The current retrospective cohort study reports on the clinical performance of an uncemented, mobile bearing, cruciate sacrificing (anterior stabilized) knee implant. We report a 15-year survival rate of 96% and functional outcomes comparable to the Dutch population receiving a TKA. In our cohort, there was no association between previous surgery (meniscectomy, arthroscopy, or corrective osteotomy) and inferior survival or functional outcome.

All-cause survival after 15 years was 96.0% (95% CI 94.8-97.2) in our cohort, using aseptic loosening as an end point survival was 98.2% (95% CI 97.4-99.0). Hopley et al *[408]* report a similar 12-year survival of 96.3% (95% CI 91.6-98.4) in their meta-analysis of studies describing the survival of both cemented and uncemented LCS rotating platform implants. The most common criticism of uncemented fixation in TKA is the risk of early aseptic loosening, which was the main failure mode in our study (23/1,289 implants, 2%; 23/49 revisions, 47%). Besides fixation, several patient factors (e.g., obesity, inflammatory arthritis, previous fracture around the knee) are known to influence TKA survival. *[483, 484]* Several registry analyses and cohort studies show slightly better survival of cemented compared to uncemented tibial trays. *[461, 485–487]* In these observational studies, however, uncemented implants with either design- related failures or an absence of a bioactive coating are included and may skew results. *[190, 486]* The implant used in the current study (LCS; DePuy Synthes) did not employ any bioactive coatings (e.g., hydroxyapatite) but did have a porous structure of the bone- implant surface of the implant. Studies on this specific implant show that an additional bioactive coating is not needed with the porous structure of the bone-implant surface metal. *[270]* However, studies on other uncemented implants tend to show a beneficial effect of these bioactive coatings in terms of revision risks *[19]*, possibly implying that the need of a bioactive coating is influenced by the structure of the bone-implant surface metal. Furthermore, surgeons often tend to choose uncemented fixation in younger patients with higher risk of revision*[488, 489]*, which subsequently introduces the possibility of treatment-by-indication bias in observational studies. *[490]* Another important note is the fact that the timing of aseptic loosening tends to be significantly different between cemented and uncemented fixation, with cemented fixation showing a higher risk of future aseptic loosening. In contrast to observational evidence, randomized clinical trials tend to show similar revision rates when comparing both fixation modes. *[445, 491]* Future studies should focus on long-term comparisons between modern cemented and uncemented implants to accurately estimate the risk of aseptic loosening of each mode of fixation.

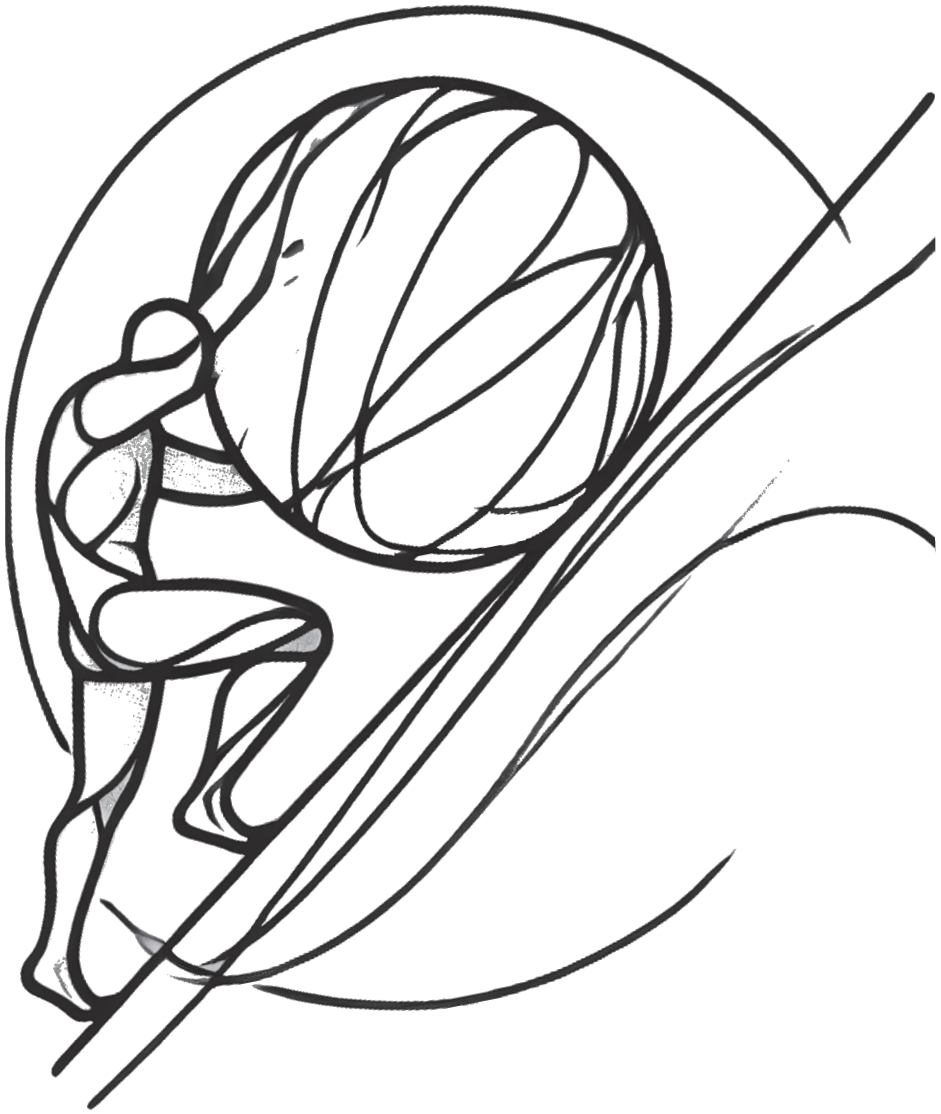
In our cohort, we found similar functional outcomes and knee pain compared to published results of all cemented and uncemented implants registered in the LROI from 2014 to 2019 (**Table 3**). *[482]* A recent comparison of 60 cemented

and 50 uncemented mobile bearing implants reported similar OKS, NRS pain, and EQ5D scores in both groups after 1 year. *[492]* Similarly, high-level evidence reports no significant differences in functional outcomes and knee pain between both fixation methods. *[147]* A meta-analysis of 6 randomized clinical trials in patients 65 years old, however, re- ports a statistically significant difference in functional outcomes in favor of uncemented fixation. *[463]* Due to the limited follow-up in some studies included in this meta-analysis (range 2-16.6 years) and the lack of clinical significance of the differences in functional outcomes that were found, more evidence is needed to assess the optimal fixation method for younger patients undergoing TKA.

We found no difference between patients with history of previous surgery (meniscectomy, arthroscopy, or corrective osteotomy) compared to patients without previous knee surgery. To our knowledge, literature on the impact of previous surgery on subsequent TKA is limited to retrospective studies. *[493–500]* In accordance with our findings, most studies report no influence on functional outcomes or survival achieved with TKA after soft tissue interventions (e.g., arthroscopic debridement, meniscectomy). *[493, 496, 499]* The influence of prior bony interventions (e.g., osteotomies, open reduction internal fixation of tibial plateau fractures, patellar realignment procedures) on the outcomes of TKA, however, is less unambiguously. Two recent meta-analyses report conflicting results on the influence of prior tibial osteotomy on TKA outcomes. *[500, 501]* Sun et al *[500]* show that 10-year survival and functional outcomes are not related to prior osteotomy in 16 studies reporting on 99,597 procedures. In contrast, Seo et al *[501]* conclude that patients with prior osteotomy are at higher risk for revision surgery after >10 years in 15 studies including 74,844 procedures. The inferior survival may be a reflection of the patient population rather than detrimental effects of the osteotomy on subsequent TKA results (e.g., patients who have received an osteotomy have more deformity). However, surgeons should consider the possible difficulties a prior osteotomy presents when performing TKA (e.g., ligamentous imbalance, anatomical distortion of the proximal tibia) and counsel patients appropriately. *[502, 503]*

As all studies, there are limitations that need be discussed. First, the retrospective design of this study limits the strength of our conclusions. Our main outcome (survival), however, is less influenced by this design due to its objectivity and accurate estimates can be made with a retrospective design. Second, a substantial number of patients had no available PROMs (75%). Considering the long follow-up (minimum 10 years), and therefore increasing chances of death or (mental and physical) comorbidity, this is to be expected. In the quest for longevity in TKA, uncemented fixation and mobile bearings have been proposed as possible solutions. Especially with the rising demand of TKA in young patients, there is a need for durable knee implants to contain the already increasing revision burden in the future. *[459, 482]* This sparked a reinterest in uncemented fixation as a

possibility to promote biological ingrowth and provide durable fixation without the risks of cement wear and thus long-term aseptic loosening. *[445]* Older uncemented implants had problems, particularly with the initial fixation of the tibial tray and screw-track osteolysis *[504, 505]*, but most modern uncemented implants have comparable track records to their cemented counterparts. *[29, 491, 506, 507]* In tandem, mobile bearings were introduced in 1979 to address wear-related failure of implants by reducing contact stresses during knee kinematics. *[508]* Early results were promising *[509]*, but randomized clinical trials show no clear clinical difference between mobile bearings and conventional fixed bearings *[510]*. Even though the concern of bearing dislocation remains for mobile bearing implants, the incidence is low (0.3%) and overall revision rates are similar for mobile and fixed bearing implants. *[510–512]* Furthermore, a revision procedure for bearing dislocation is a relatively minor procedure with good outcomes. *[512]* Altogether, future research should specifically focus on long- term (>10-15 years) comparisons between both fixation and bearing options, in order to accurately assess the incidence of late aseptic loosening and wear-related failure. Furthermore, future research efforts should focus on exploring the ideal circumstances for reliable biological ingrowth in uncemented fixation, including elements such as bone-implant surface materials and the presence of a bioactive coating.



CHAPTER 9

Association Between Surface Modifications for Biologic Fixation and Aseptic Loosening of Uncemented Total Knee Arthroplasties.

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ABSTRACT

Background
Various surface modifications are used in uncemented total knee arthroplasties (TKA) to enhance bony ingrowth and longevity of implants. This study aimed to identify which surface modifications are used, whether they are associated with different revision rates for aseptic loosening, and which are underperforming compared to cemented implants.

Methods
Data on all cemented and uncemented TKAs used between 2007 and 2021 were obtained from the Dutch Arthroplasty Register. Uncemented TKAs were divided into groups based on their surface modifications. Revision rates for aseptic loosening and major revisions were compared between groups. Kaplan-Meier, Competing-Risk, Log-rank tests, and Cox regression analyses were used. In total, 235,500 cemented and 10,749 uncemented primary TKAs were included. The different uncemented TKA groups included; 1,140 porous-hydroxyapatite (HA), 8,450 Porous-uncoated; 702 Grit-blasted-uncoated; and 172 Grit-blasted-Titanium-nitride (TiN) implants.

Results
The 10-year revision rates for aseptic loosening and major revision of the cemented TKAs were 1.3 and 3.1%, and for uncemented TKAs 0.2 and 2.3% (porous-HA), 1.3 and 2.9% (porous-uncoated), 2.8 and 4.0% (grit-blasted-uncoated), and 7.9% and 17.4% (grit-blasted-TiN) respectively. Both type of revision rates varied significantly between the uncemented groups (log-rank tests, P<0.001, P<0.001). All grit-blasted implants had a significantly higher risk of aseptic loosening (P <0.01), and porous-uncoated implants had a significantly lower risk of aseptic loosening than cemented implants (P=0.03) after ten years.

Discussion
There were four main uncemented surface modifications identified, with different revision rates for aseptic loosening. Implants with porous-HA and porous-uncoated had the best revision rates, at least equal to cemented TKAs. Grit-blasted implants with and without TiN underperformed, possibly due to the interaction of other factors.

INTRODUCTION

Total knee arthroplasty (TKA) used to be mainly done on elderly patients using implants that lasted mainly around 10 to 15 years. However, as TKA becomes more prevalent among younger patients who continue to engage in demanding activities after TKA, it is anticipated that there will be an increase in the number of revisions performed, particularly those occurring 10 to 15 years after the initial surgery. *[513]* Given the reports from national registries showing that aseptic loosening is the leading reason for late revision procedures, it is important to find ways to extend the life of prostheses to reduce the number of late revisions required. *[4–6]*

In an effort to overcome this ambition, manufacturers have been developing their implants, with the most prominent advances made in modern uncemented implants. Studies of previously used, now outdated, uncemented TKA designs showed underperformance, resulting in a condemnation of cementless fixation by some researchers and clinicians. However, recent high-level evidence suggests that modern cementless implants show similar durability and outcomes to cement-fixated implants at a mean follow-up of 7 to 12 years. *[445, 485, 491, 514]* The fixation of uncemented implants primarily focuses on improving osseointegration, which refers to the biological ingrowth process. This method eliminates the presence of cement wear particles associated with cemented TKA, which can lead to reduced instances of implant loosening and foreign body reactions. *[515–517]* Moreover, most modern uncemented TKAs have a modified surface or coating to improve the biological properties of the implant, such as promoting cell attachment, spreading, growth, and the formation of new bone tissue. *[518–520]*

Although aseptic loosening is multifactorial in nature, it can roughly be classified as a result of an early lack of osseointegration, or a later failure of the implant-bone interface due to periprosthetic osteolysis. The theory that aseptic loosening is caused by a lack of osseointegration is supported by the association found between magnified early migration and late revision for aseptic loosening. *[39]*

This was measured by Radiostereometric analyses (RSA), which refers to a radiographic technique that allows 3-dimensional measurement of migration of prosthesis components over time. To test whether new implants are safe for patients, an implant's early migration pattern is often evaluated with RSA to benchmark against migration patterns of former implants. Previous studies utilizing RSA reported that the use of hydroxyapatite (HA) coating can improve early implant stabilization compared to non-HA-coated or cemented implants. *[19, 66, 109, 521]* Although RSA can accurately measure differences in migration patterns, it is challenging to actually measure the variations in late revisions for aseptic loosening because the incidence is relatively low, and mainly occurs late in follow-up.

Therefore, the purpose of this study was to utilize the national arthroplasty register of the Netherlands, in order to investigate the following questions: 1) What

are the prevalent surface modifications utilized in uncemented implants in the Netherlands? 2) Are there any variations in the revision rates for aseptic loosening among uncemented implants with different surface modifications? 3) Does any surface modification exhibit inferior performance in terms of revision for aseptic loosening when compared to cemented implants?

MATERIALS AND METHODS

Data source

This observational study used routinely collected data from the Dutch Arthroplasty Register (Landelijke Registratie Orthopedische Implantaten [LROI)]). The register collects data since 2007 and covers all Dutch hospitals since 2012, with overall completeness of collected data of 99% for primary TKAs and 98% for revision TKAs in 2020. *[5]* Specifications of implant surface modifications are registered by scanning the product and batch numbers of implants during TKA and reported according to the names used in the international prosthesis library of the International Society of Arthroplasty Registers (ISAR). *[522]* Patient informed consent is perceived by the use of an opt-out system. Encrypted social security numbers are linked to the Dutch national insurance database, to connect primary and revision TKAs and identify deaths. *[5]*

Patient selection

All patients who underwent a fully cemented or uncemented TKA for osteoarthritis in the Netherlands between 2007 and 2021 were eligible for inclusion. Patients were excluded in case implant batch or product information was missing; revision components were used; cemented implant brands that had not also been used uncemented; the number of implants per brand was less than 50; or when one component of an implant had a different surface modification than the other component. The flowchart of in-and exclusion is presented in **Figure 1**. After inclusion, uncemented implants were categorized into groups, based on the matching surface modification of the femoral and tibial components of every implant. For each procedure, the following characteristics were extracted: age, gender, Body Mass Index (BMI), Charnley classification (A, B1, B2 and C), American Society of Anesthesiologists grade ([ASA] I, II, III to IV), smoking status, previous knee surgeries, surgical approach (medial parapatellar or other), bearing type (fixed or mobile), hospital (anonymously coded) and revision information. Data on BMI, smoking status, and Charnley classification had only been registered since 2014.

Study population

A total of 245,971 primary TKAs were included in this study, comprising 235,500 cemented and 10,471 uncemented implants. In total, six different surface

modifications could be distinguished. After excluding uncemented implants of which the femoral and tibial components had different surface modifications (**Figure 1**), four groups were included:1) porous metal with a HA coating (n = 1,140); (2) porous metal without coating (n = 8,450); (3) grit-blasted metal without coating (n = 702); and (4) grit-blasted metal with Titanium nitride (TiN) coating (n = 179). Uncemented implants that were not included in the analysis were implants with a porous-TiN or grit-blasted-polymethylmethacrylate surface modifications. Uncemented implants with trabecular metal were not included due to a low number of TKAs. Demographic details and clinical characteristics per group are presented in **Table 1**. The populations' overall median follow-up was 5.1 years (IQR 2.6 – 8.2, range 0 to 14). The groups differed in the distribution of fixed and mobile bearings, the variety of hospitals, the variety of implant designs, and the median follow-up.

Outcome measures

The primary outcome in this study was the five and 10-year revision rate for aseptic loosening per group. Revision is defined as the removal or exchange of at least one component due to aseptic loosening. The secondary outcome was the major revision rate at five and ten years. A major revision was defined as the removal or exchange of at least the femoral or tibial component for any reason. Major revision as an outcome measure was used to provide a crude estimation of the internal validity regarding the primary outcome. It was proposed that surface modification of implant materials may only impact osseointegration and thus the rate of aseptic loosening, not other reasons of revision. If a specific group exhibits a significantly higher rate of major revisions compared to other groups, regardless of whether there is an increased rate of revisions due to aseptic loosening, it suggests that factors beyond surface modification might be contributing to performance of that particular group.

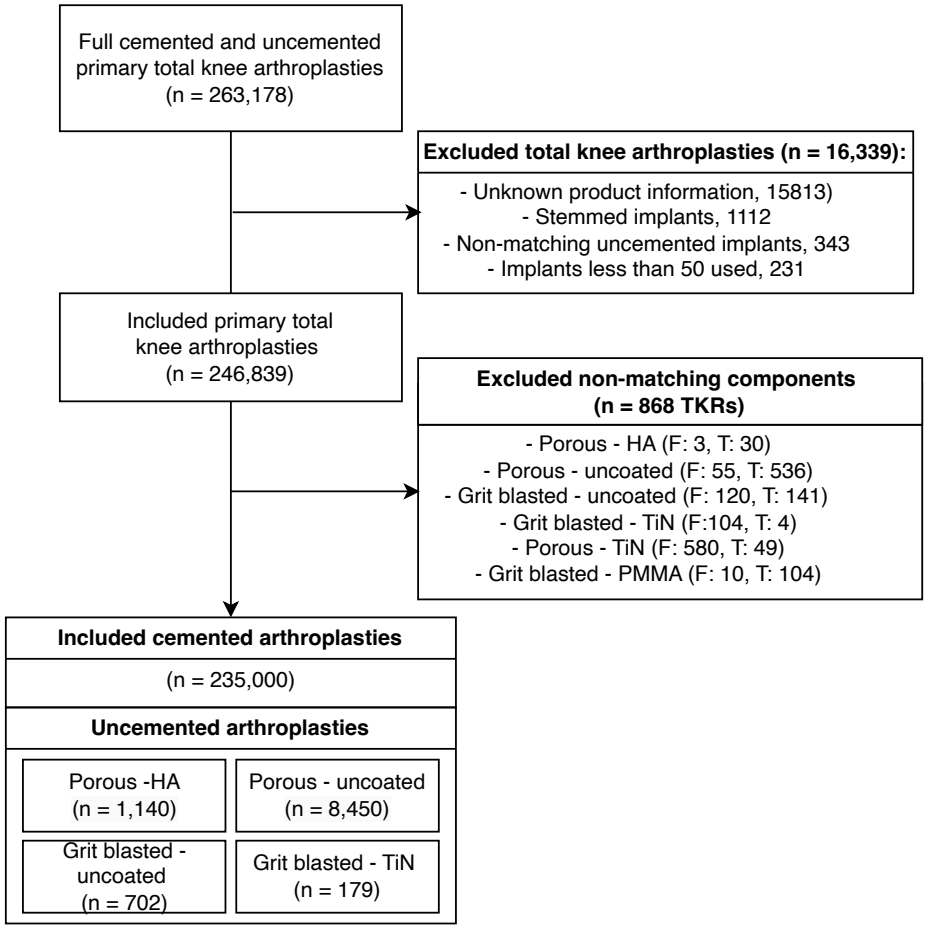


Figure 1. Flow chart of in-and exclusion, and creation of groups.

Table 1. Demographic details and clinical characteristics of included population.

	Prosthesis Type				
	Cemented	Uncemented			
		Porous - HA	Porous - Uncoated	Grit blasted - Uncoated	Grit blasted - TiN
Knees, n	235,500	1,140	8,450	702	179
Median follow-up, years (IQR)	5.5 (2.6; 8.1)	4.8 (2.8; 7.8)	6.6 (3.1; 9.6)	7.2 (3.8; 9.6)	8.7 (4.5 - 10.5)
Sex, n (%)					
Woman	152,853 (64.9)	744 (65.3)	5,478 (64.8)	474 (67.5)	85 (47.5)
Mean age, years (SD)	68.8 (9.2)	68.7 (9.3)	69.0 (9.3)	69.9 (9.1)	68.5 (11.1)
Mean BMI, (SD) *	29.8 (5.4)	29.0 (4.1)	29.5 (4.9)	29.8 (4.6)	n/a
Previous knee surgery, n (%) †	67,900 (28.8)	383 (33.6)	2,104 (24.9)	123 (17.5)	46 (25.7)
ASA grade, n (%)					
I	3,7190 (15.8)	103 (9.0)	1,370 (16.2)	142 (20.2)	102 (57.0)
II	153,722 (65.3)	824 (72.3)	5,783 (68.4)	386 (55.0)	66 (36.9)
III to IV	39,784 (16.9)	211 (18.5)	1,130 (13.4)	100 (14.2)	10 (5.6)
Charnley classification, n (%) §*					
A	56,571 (24.0)	257 (22.5)	1,650 (19.5)	129 (18.4)	n/a
B1	49,090 (20.8)	293 (25.7)	1,110 (13.1)	99 (14.1)	n/a
B2	30,680 (13.0)	155 (13.6)	831 (9.8)	43 (6.1)	n/a
C	4,361 (1.9)	6 (0.5)	179 (2.1)	7 (1.0)	n/a
Smoking, n (%) *					
Yes	131,645 (55.9)	81 (7.1)	382 (4.5)	16 (2.3)	n/a
No	12,119 (5.1)	691 (60.6)	3,547 (42.0)	280 (39.9)	n/a
Surgical approach, n (%)					
Medial parapatellar	231,657 (98.4)	1,103 (96.8)	8,240 (97.5)	639 (91.0)	178 (99.4)
Bearing type, n (%)					
Fixed	212,014 (90.0)	1,093 (95.9)	17 (0.2)	581(82.8)	0 (0.0)
Mobile	22,890 (9.7)	47 (4.1)	8,433 (99.8)	121 (17.2)	179 (100.0)
Performed in hospitals, n (%)	102 (98.1)	8 (7.7)	24 (23.1)	67 (64.4)	1 (1.0)
N of implant designs	34	8	3	13	2
Years in use (range)	2007-2020	2007-2020	2007-2020	2007-2020	2007-2013

Numbers do not add up to total due to missing data. * Not registered before 2014.
†Previous surgeries defined as any surgical procedure (e.g., meniscectomy, osteotomy, ACL reconstruction, osteosyntheses, synovectomy, arthroscopy, and patellar realignment).
§ Charnley score: (A) only one affected knee joint, (B1) both knee joints affected, (B2) a knee prosthesis in the contralateral knee joint, and (C) multiple joints affected.
HA Hydroxyapatite; TiN Titanium nitride; ASA American Society of Anesthesiologists; IQR interquartile range; SD standard deviation; n/a not applicable.

Data analyses

Baseline characteristics are presented as means and standard deviations (SD), medians and Interquartile ranges (IRQ), or frequencies and percentages. Kaplan-Meier (KM) and competing risk (CR) (supplementary file) analyses were performed to calculate the revision rate per group for aseptic loosening and major revision after 5- and 10-year follow-up. Patients were censored from KM analyses in case they died before the end of the study follow-up (January 1, 2021). Competing-risk analyses were also performed since the proportion of patients experiencing the competing event (death) was equal to or greater than those experiencing the outcome of interest (revision). *[523]* Implant revision probability was reported with 95% confidence intervals (CI). The impact of the surface modification on the revision rate was explored by plotting KM curves for all groups. Log-rank tests were performed to assess if there were differences in revision rates among the uncemented surface modification groups. In case of a group with a substantially high major revision rate, a KM curve for different reasons for revisions of that group was plotted, to assist in identifying whether there are additional factors that have contributed to the outcome of the group. Additionally, crude and multivariate Cox proportional hazard models were used to compare the likelihood of revision with reference to the cemented group. Since some groups contained only fixed or mobile bearings, the Hazard Ratios (HR) of each group were stratified by bearing mobility. HRs were calculated with 95% Confidence intervals (CI) and adjustment for age, gender, ASA classification, and previous knee operations was, like in other LROI studies, performed. *[29]* As data on smoking status, BMI, and Charnley classification were only available after 2014, sensitivity analyses were performed to assess the confounding effects of these variables. All statistical analyses were performed using IBM® statistical Package for the Social Sciences (SPSS) version 26.0 (IBM Corp. Armonk, New York: IBM Corp.) A P-value <0.05 was considered statistically significant.

Funding, conflicts of interest, and ethical approval

This research did not receive any grants. None of the authors declare any competing interests. Ethical approval was not required for this study. Routinely collected data from the LROI were extracted for this study. Ethics approval and consent to participate were not applicable, as all data received was completely anonymous.

RESULTS

Revision rate for aseptic loosening

Overall, a total of 121 uncemented implants were revised for aseptic loosening of at least one component, including 24 (19.8%) femoral and 112 (92.6%) tibial components. The mean cumulative revision rates varied among the groups after

ten years, including the; porous-HA group (0.2% [95%CI 0.0 – 0.4]); porous-uncoated group; (1.3% [95%CI 1.0 – 1.6]); grit-blasted-uncoated group (2.8% [95%CI 1.3 – 4.3]) and grit-blasted-TiN group (7.9% [95%CI 3.5 – 12.3]). All mean cumulative revision rates at five and ten years are presented in **Table 2 and Figure 2**. The results of KM analyses were similar to competing-risk analyses (**Table S1**). Revision rates varied significantly between the uncemented groups (log-rank test, p <0.001). The revision rates for aseptic loosening of the porous-HA and porous-uncoated groups were the lowest two of the four groups. The grit-blasted TiN-coated implants had a higher revision rate for aseptic loosening than all other groups at every follow-up point. The grit-blasted-Tin coated group was the only group in which the ratio of revised femoral and tibial components was 1:1.

The mean cumulative major revision rates of all groups after five and ten years are presented in **Table 3 and Figure 3.** All groups, except the grit-blasted TiN coating group, had similar major revision rates and 95% CI. The cumulative major revision rate of the grit-blasted-TiN coated group was substantially higher than in all other groups at every follow-up moment (log-rank test, P <0.001). The reasons for major revisions of the grit-blasted-TiN coated group are plotted in **Figure 4**, showing aseptic loosening and instability as the most prevalent reasons for major revision. The results of KM analyses were similar to competing-risk analyses (**Table S2**).

Table 2. Five- and ten-year revision rates by Kaplan-Meier analysis for aseptic loosening of at least one component of the total knee arthroplasty.

		Events				
	Total N	**Total TKAs**	**Femoral component**	**Tibial component**	**KM revision rate, % (95% CI)**	**N at risk**
5-year estimate						
Cemented TKA	235,500	1,373	291	1,269	0.8 (0.8 – 0.8)	120,079
Uncemented TKA						
Porous - HA	1,140	2	0	2	0.2 (0.0 – 0.4)	553
Porous - Uncoated	8,450	85	10	82	1.2 (1.0 – 1.4)	5,194
Grit Blasted - Uncoated	702	10	1	9	1.6 (0.6 – 2.6)	443
Grit Blasted - TiN	179	10	7	6	5.9 (2.4 – 9.4)	131
10-year estimate						
Cemented TKA	235,500	1,766	405	1,648	1.3 (1.2 – 1.4)	30,970
Uncemented TKA						
Porous - HA	1,140	2	0	2	0.2 (0.0 – 0.4)	118
Porous - Uncoated	8,450	93	14	90	1.3 (1.0 – 1.6)	1,839
Grit Blasted - Uncoated	702	14	2	12	2.8 (1.3 – 4.3)	172
Grit Blasted - TiN	179	12	8	8	7.9 (3.5 – 12.3)	53

N Number; CI Confidence Interval; KM Kaplan-Meier; TKA Total Knee Arthroplasty; HA Hydroxyapatite; TiN Titanium Nitride

Underperforming surface modifications

The revision rates for aseptic loosening of the porous-HA and porous-uncoated groups were lower and equal to the revision rate of cemented implants at ten years (**Table 2, Figure 2**). Crude and adjusted HRs, stratified by bearing mobility, showed no significant difference in the likelihood of revision for aseptic loosening between cemented and porous metal HA-coated implants (P = 0.07) (**Table 4**). Porous metal-uncoated implants had a significantly lower likelihood of revision than cemented implants (0.76 [95%CI 0.60 – 0.98]) (P = 0.03). Patients with grit blasted-uncoated and grit blasted-TiN coated implants were 2.71 (95% CI 1.46 – 5.05) (P < 0.01) and 4.60 (95% CI 2.56 – 8.25) (P < 0.01) times more likely to undergo a revision than patients with cemented implants, respectively. Sensitivity analysis showed no differences in risk of revision after adding the covariates smoking status, BMI, and Charnley score to the model.

Table 3. Five- and ten-year major revision rates by Kaplan-Meier analysis rates of all total knee arthroplasty groups.

	Total N	Total events	KM revision rate, % (95% CI)	N at risk
5-year estimate				
Cemented TKA	235,500	4,055	2.2 (2.1 – 2.3)	120,079
Uncemented TKA				
Porous - HA	1,140	11	1.2 (0.5 – 1.9)	553
Porous - Uncoated	8,450	193	2.6 (2.2 – 3.0)	5,194
Grit Blasted - Uncoated	702	18	2.8 (1.5 – 4.1)	443
Grit Blasted - TiN	179	21	12.7 (7.6 – 17.8)	131
10-year estimate				
Cemented TKA	235,500	4,801	3.1 (3.0 – 3.2)	30,970
Uncemented TKA				
Porous - HA	1,140	15	2.3 (0.9 – 3.7)	118
Porous - Uncoated	8,450	206	2.9 (2.5 – 3.3)	1,839
Grit Blasted - Uncoated	702	22	4.0 (2.3 – 5.7)	172
Grit Blasted - TiN	179	27	17.4 (11.3 – 23.5)	53

N Number; CI Confidence Interval; KM Kaplan-Meier; TKA Total Knee Arthroplasty; HA Hydroxyapatite; TiN Titanium Nitride

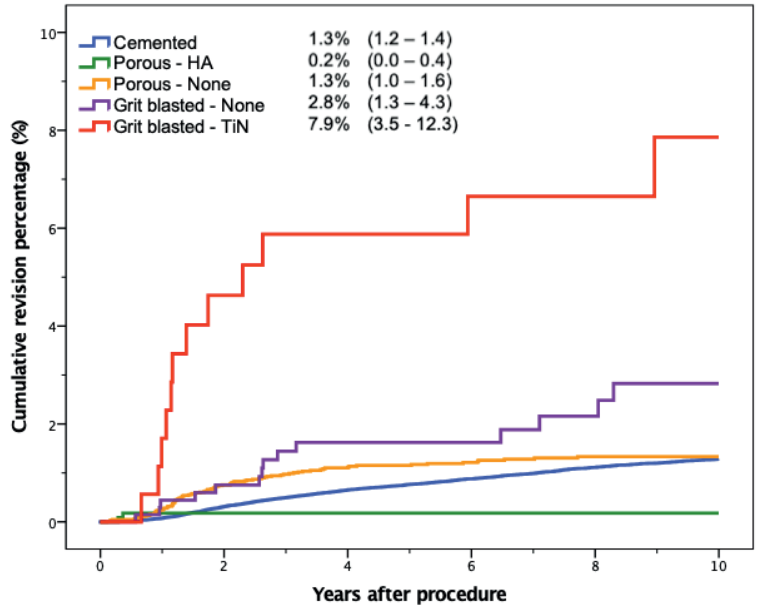


Figure 2. Cumulative revision rates (95% CI) of cemented and uncemented implants stratified by their surface modifications, with as endpoint aseptic loosening of at least one component.

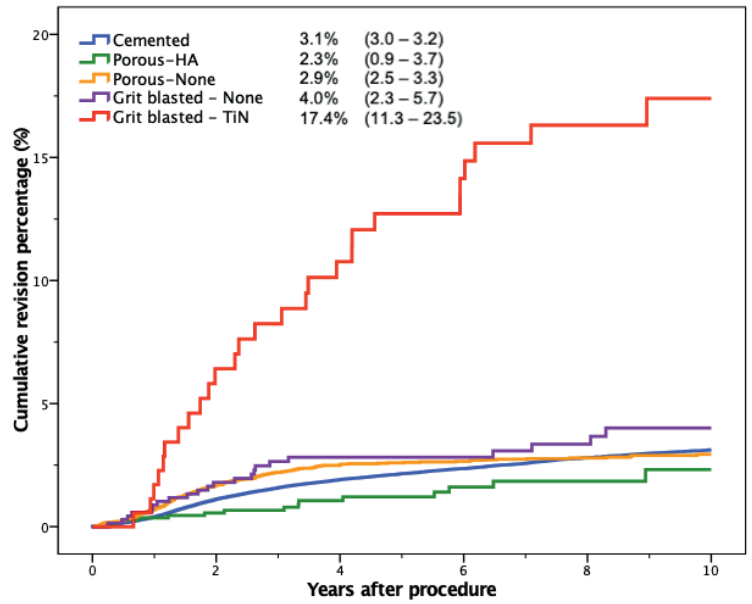


Figure 3. Cumulative revision rates (95% CI) of cemented and uncemented implants stratified by their surface modifications, with as endpoint major revision.

Table 4. Stratified crude and multivariable survival analyses of cemented and uncemented total knee arthroplasties with different surface modification, with revision for aseptic loosening of any component as an endpoint.

	Crude HR (95% CI)	Adjusted HR * (95% CI)
Stratum: fixed bearing		
Cemented	REF	REF
Uncemented		
Porous – HA	0.28 (0.07 – 1.10)	0.28 (0.07 – 1.12)
Porous – Uncoated	n/a	n/a
Grit blasted – Uncoated	2.50 (1.41 – 4.40)	2.71 (1.46 – 5.05)
Grit blasted – TiN	n/a	n/a
Stratum: Mobile bearing		
Cemented	REF	REF
Uncemented		
Porous – HA	n/a	n/a
Porous – Uncoated	0.75 (0.60 – 0.95)	0.76 (0.60 – 0.98)
Grit blasted – Uncoated	n/a	n/a
Grit blasted – TiN	4.27 (2.40 – 7.60)	4.60 (2.56 – 8.25)

*Adjusted for age, gender, ASA classification and previous operations on the affected knee. HR Hazard ratio; CI Confidence interval; REF Reference; HA Hydroxyapatite; TiN Titanium Nitride; n/a not available.

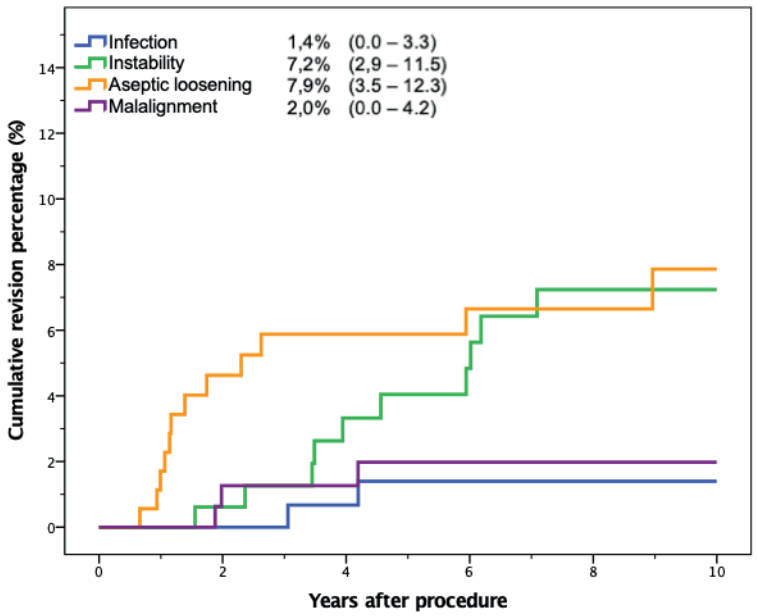


Figure 4. Cumulative revision rates (95% CI) of different major revision reasons of the grit-blasted-TiN group.

DISCUSSION

In this nationwide registry study, four main types of surface modifications on uncemented implants were found to be used in the Netherlands between 2007 and 2021. The most important finding was the variation in revision rates for aseptic loosening between the uncemented implants with different surface modifications.

As the primary objective of uncemented implants is to promote osseointegration at the bone-implant interface, it is noteworthy that significant variations in the rate of aseptic loosening were observed between different groups. These variations ranged from 0.2 to 7.9% after ten years. These results emphasize the significance of identifying the most effective surface modifications to achieve better outcomes. In this study, we found an exceptionally low revision rate for aseptic loosening after ten years, attributed to the porous-HA (0.2% [95%CI 0.0 - 0.4]) and porous-uncoated (1.3% [95%CI 1.0 – 1.6]) group. It is important to mention that the exceptional results of the porous-HA group may have been influenced by the lower sample size, however, the sample size was larger than most cohort studies and the rate of completeness of the LROI register minimizes the possibility of any missed revisions. Additionally, previous studies support the good performance of implants with a similar surface modification. The recent study by Harwin et al. *[269]*, retrospectively evaluated 805 uncemented porous-HA coated implants and reported a revision rate of 0.1% for aseptic loosening after an average of 4.4 years (range, 2 to 9). Another recent study, which retrospectively examined 1,289 uncemented porous-uncoated Low Contact Stress (LCS) prostheses, reported a revision rate for aseptic loosening of 1.8% (95% CI 1.0 – 2.6) after a mean follow-up of 11.1 years (range, 11 to 20). *[321]*This population is comparable to the porous-uncoated group in the current study, since the LCS implant is also the most commonly used uncemented porous-uncoated prosthesis in the Netherlands, accounting for over 60% of all uncemented prostheses, as reported by the LROI. *[5]* Similar positive results for porous and HA-coated implants have been observed in studies using RSA. Modern uncemented implants, containing a highly interconnecting porous (trabecular) metal or HA coating, have been found to have lower implant migration and better fixation than other uncemented implants and some cemented implants. *[19, 128, 152]* Although trabecular metal implants were not included in the groups of the current study, these studies do indicate what porosity can mean for the results of an implant. In our study, a significantly lower HR for the likelihood of revision for aseptic loosening was found in the porous-uncoated group compared to cemented implants. However, this was not confirmed by the KM analysis, which showed overlapping 95%CI. Based on the results of this study, it can be inferred that implants featuring a porous-uncoated surface modification perform at least as well as cemented implants.

Besides identifying high-performing implants, it is even more important to identify low-performing implants, especially because of patient safety. The disparity

between the best and least-performing groups in this study might be attributed to the different underlying purposes of the surface modifications. The HA coating and porous metal aim to promote osseointegration, likely more than grit-blasted metal, while ceramic coatings such as TiN are designed to enhance properties such as hardness, wettability, wear resistance, and friction reduction of an implant. *[524]* This difference in the use of purpose, could be a factor in the observed variation in performance. However, it remains difficult to draw a firm conclusion from these results, since the differences in population characteristics between groups are major. It is recognized that the low sample size (n = 179), the restricted number of hospitals utilizing these prostheses (n = 1), and the limited variety of prostheses with this surface modification (n = 2) likely exerted a significant influence on the results of this group. This is supported by the fact that the major revision rate is also substantially higher than that of other groups, which could indicate that factors other than surface modification, such as prosthesis, surgical, or hospital failure may have contributed to the results. For example, the grit-blasted-TiN implants are the only group that is not used after 2013 (**Table 1**), which might be a consequence of bad results due to a failing implant design, rather than failing surface modification. However, surgical failure can also be responsible, since outlier-performing hospitals with significantly higher revision rates are not rare. *[525]* Despite the poor results in this study, TiN coatings are commonly used on uncemented implants, within the literature reported, a substantially lower reported revision rate for aseptic loosening at ten years (3.9 *[308]* and 0.9% *[526]*) than was found in this current study. Although, both these revision rates are from studies that used implants with a porous metal and TiN coating, instead of a Grit-Blasted-TiN coated implant. For that reason, a direct comparison is complicated. Other registry studies could perform similar comparisons, to ascertain the correctness of these results. Until the results of this group can be validated, it is advised to interpret the results with caution, as they may not be representative of all uncemented implants with a grit-blasted surface and TiN coating. To gain a more comprehensive understanding of the effects of surface modifications, future RSA and in vitro studies are necessary to evaluate early migration and surrogates for osseointegration.

This study has several potential limitations to acknowledge. The study was observational and subject to confounding by indication. Only a limited number of variables are collected by the LROI, more detailed information on prosthesis types, brands, applications, and coating thickness could have improved the evaluation of the surface modification effects. Also, not all kinds of surface modifications used in the Netherlands were analyzed. Two other surface modifications (porous-TiN and grit-blasted-polymethylmethacrylate) could not be included, as the proportion of femoral and tibial components with a similar surface modification was below 10%. Incorporating these groups would have heightened the risk of misclassification bias, as it would not have been possible to determine which surface modification was responsible for a certain revision. Furthermore, although the group populations

were not the same, making it likely that confounding occurred, this study provides valuable insight into the various surface modifications used and the variations between them. Moreover, the best-performing uncemented groups appeared to be least affected by confounding, indicating that innovation in uncemented implants is ongoing and beneficial.

CONCLUSION

There were four of the six main surface modifications in the Netherlands analyzed and revealed varying revision rates for aseptic loosening. Porous metal-HA coated and uncoated uncemented implants had the best revision rates, at least comparable to cemented implants. Grit-blasted uncoated and TiN-coated implants showed underperformance, although other factors may have contributed to these results.

SUPPLEMENTAL MATERIAL

Table S1. Five- and ten-year revision rates by Competing Risk analysis for aseptic loosening of at least one component of the total knee arthroplasty.

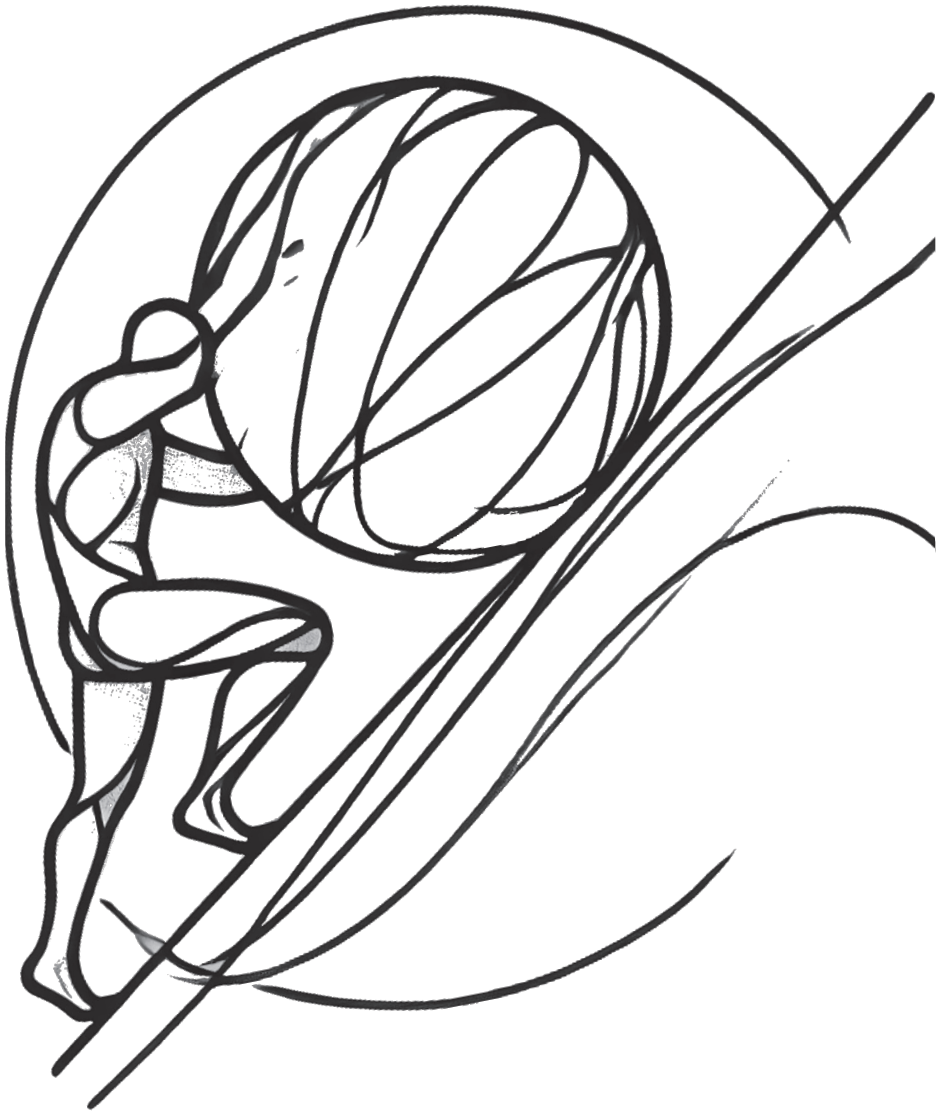
		Events				
	Total N	Total TKAs	Femoral component	Tibial component	KM revision rate, % (95% CI)	N at risk
5-year estimate						
Cemented TKA	235,500	1,373	291	1,269	0.7 (0.7 – 0.8)	120,079
Uncemented TKA						
Porous - HA	1,140	2	0	2	0.2 (0.1 – 0.7)	553
Porous - Uncoated	8,450	85	10	82	1.1 (0.9 – 1.4)	5194
Grit Blasted - Uncoated	702	10	1	9	1.6 (0.9 – 3.0)	443
Grit Blasted - TiN	179	10	7	6	5.8 (3.2 – 10.5)	131
10-year estimate						
Cemented TKA	235,500	1,766	405	1,648	1.2 (1.1 – 1.3)	30,970
Uncemented TKA						
Porous - HA	1,140	2	0	2	0.2 (0.1 – 0.7)	118
Porous - Uncoated	8,450	93	14	90	1.3 (1.1 – 1.6)	1,839
Grit Blasted - Uncoated	702	14	2	12	2.7 (1.6 – 4.5)	172
Grit Blasted - TiN	179	12	8	8	7.3 (4.2 – 12.7)	53

N Number; CI Confidence Interval; KM Kaplan-Meier; TKA Total Knee Arthroplasty; HA Hydroxyapatite; TiN Titanium Nitride

Table S2. Five- and ten-year major revision rates by Competing Risk analysis of all total knee arthroplasty groups.

	Total N	Total events	KM revision rate, % (95% CI)	N at risk
5-year estimate				
Cemented TKA	235,500	4,055	2.1 (2.0 – 2.2)	120,079
Uncemented TKA				
Porous - HA	1,140	11	1.2 (0.7 – 2.2)	553
Porous - Uncoated	8,450	193	2.6 (2.2 – 2.9)	5,194
Grit Blasted - Uncoated	702	18	2.8 (1.8 – 4.4)	443
Grit Blasted - TiN	179	21	12.2 (8.2 – 18.2)	131
10-year estimate				
Cemented TKA	235,500	4,801	3.0 (2.9 – 3.1)	30,970
Uncemented TKA				
Porous - HA	1,140	15	2.2 (1.2 – 3.8)	118
Porous - Uncoated	8,450	206	2.9 (2.5 – 3.3)	1,839
Grit Blasted - Uncoated	702	22	3.8 (2.5 – 5.9)	172
Grit Blasted - TiN	179	27	16.0 (11.3 – 22.7)	53

N Number; CI Confidence Interval; KM Kaplan-Meier; TKA Total Knee Arthroplasty; HA Hydroxyapatite; TiN Titanium Nitride



CHAPTER 10

Increased risk of aseptic loosening for posterior stabilized compared with posterior cruciate-retaining uncemented total knee replacements:

a cohort study of 13,667 knees from the Dutch Arthroplasty Registry.

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ABSTRACT

Background
While registry studies have suggested a higher risk of revision for posterior-stabilized (PS) compared with posterior cruciate-retaining (CR) total knee replacements (TKR) using cement, it is unknown whether this is also the case for uncemented TKR. We aimed to compare the revision rates of PS and CR designs in patients receiving primary uncemented TKR.

Patients and methods
Data from the Dutch arthroplasty register (LROI) was analyzed, comprising 12,226 uncemented primary CR TKRs and 750 uncemented PS TKRs registered between 2007 and 2022. Competing risk and multivariable Cox regression analyses were used to compare revision rates, risks of revision, and reasons for revision between groups. Sensitivity analyses were performed to analyze the risk, concerning the 5 most commonly used implants and performing hospitals for each group.

Results
Uncemented PS TKRs had higher 10-year revision rates for any reason and aseptic loosening (6.5%, 95% confidence interval [CI] 4.6–9.2 and 3.9%, CI 2.6–6.7) compared with uncemented CR TKRs (4.2%, CI 3.8–4.7 and 1.4%, CI 1.2–1.7). PS TKRs were 1.4 and 2.5 times more likely to be revised for any reason and aseptic loosening, respectively. These results remained consistent after adjustment for age, sex, BMI, previous surgeries, bearing mobility, and surface modification, with sensitivity analyses.

Conclusion
We found that uncemented PS implants have a higher rate of revision than uncemented CR implants, mainly due to a higher risk of aseptic loosening.

INTRODUCTION

In general, the 2 most commonly used total knee replacement (TRK) designs are posterior cruciate-retaining (CR) and posterior stabilized (PS) systems*[527]* The use of a PS system is mainly indicated in cases of posterior cruciate ligament (PCL) insufficiency but is currently in most cases dependent on the surgeon's preference and training. High-evidence studies have shown no clinically significant differences regarding the patient-reported outcome, pain, and function between the systems *[528, 529]* Yet it is hypothesized that PS systems may increase stress transmission to their interfaces with the polyethylene (PE) and bone, leading to a greater risk of wear, osteolysis, and aseptic loosening *[7]* This theory was confirmed by large observational studies, finding a higher revision rate of PS compared with CR implants, but including only cemented implants *[530, 531]* Recent registry reports from Australia and the Netherlands have also reported a higher risk of revision for cemented implants with a PS compared with CR designs *[4, 5]* However, no analysis was performed restricted to uncemented implants. The National Joint Registry from the United Kingdom identified a higher revision rate for uncemented TKR with a PS design compared with a CR design, but the analysis lacked correction for confounders and information on reasons for revisions *[8]*.

We aimed to investigate the likelihood of revision for uncemented PS implants compared with CR implants while adjusting for potential confounders and to establish the primary causes of revision. Our hypothesis was that uncemented PS implants have a higher risk of revision than uncemented CR implants, mainly due to aseptic loosening.

PATIENTS AND METHODS

Study design
Our study is an observational study using data from the Dutch Arthroplasty Register (Landelijke Registratie Orthopedische Interventies [LROI]). Data is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines *[532]*

Setting
Since the inception of the LROI in 2007, data on all patients and procedures is anonymized and routinely collected unless patients opt out from the data collection. All Dutch hospitals participated in the data registration from 2012, with a current total data completeness of 97% for both primary and revision TKAs. *[5]* Reasons for revisions are documented through an online form immediately postoperatively. To validate outcomes, revision rates for various reasons are anonymously compared among healthcare providers, aiming to identify outliers

based on performance or registration practices. Encrypted social security numbers are linked to the Dutch national insurance database twice a year, to connect primary and revision TKAs and identify deaths. *[5]*

Participants

All patients who received an uncemented primary TKR for end-stage osteoarthritis between 2007 and 2022 were eligible for the study. Cases were excluded from the study if the fixation was not uncemented, the TKA was neither CR nor PS, or in any case where this was unknown.

Variables

The primary outcome measure was the revision rate for any reason as an endpoint. A revision was defined as the removal, exchange, or addition of 1 or more components. Reasons for revision were registered in the LROI at the time of revision surgery, without incorporation of the results of intraoperative cultures, as these most often were not yet available at the moment of registration. Revisions that include only patellar resurfacing, or debridement, antibiotics, and implant retention (DAIR), with or without insert exchange, were excluded from the endpoint. The secondary outcome measure was the revision rate for aseptic loosening, with removal or exchange of at least a femoral or tibial component (major revision), without the presence of signs of infection. Either endpoint was assessed at 5- and 10-year follow-up.

For each patient, demographic and surgical details, including age, sex, body mass index (BMI), Charnley classification (A, B1, B2, or C), American Society of Anesthesiologists grade (ASA I, II, or III–IV), smoking status, previous surgeries to the index knee (e.g., meniscectomy, osteotomy, ACL reconstruction, osteosynthesis, synovectomy, arthroscopy, and patellar realignment), surgical approach, anonymized implant design, bearing mobility (fixed bearing [FB] or mobile bearing [MB]), polyethylene (PE) material (ultrahigh molecular weight PE [UHMWPE] or highly crosslinked PE [HXLPE]), component surface modification (porous metal—hydroxyapatite (HA), porous metal—uncoated, grit-blasted uncoated, or grit-blasted-titanium-nitride, trabecular metal), and anonymized performing hospital were collected. All data has been collected since 2007, except BMI, smoking status, and Charnley classification, which have only been registered since 2014.

Potential confounders were identified, based on the criteria of Rothman et al *[533]* and depicted in a directed acyclic graph (DAG) *[534]* Demographic factors such as age, BMI, ASA classification, smoking, and Charnley score have been found to be associated with revision [14]. However, these factors do not affect the choice between CR or PS implants (except possibly for age and BMI). Previous knee surgery was considered a potential confounder because a previous high tibial osteotomy or removed or damaged PCL during an earlier procedure could interfere with the choice between a CR or PS implant. Bearing mobility (e.g.,

FB or MB) *[535]* and surface modification *[56]* are considered to be associated with revision rates but are also part of implant design and hence associated with PS or CR (criteria 3). However, as many manufacturers have multiple bearing-constraint options for the same implant, this is considered minimally influential. Taken together, potential confounders included in the model were considered and visualized in a DAG (**Figure 1**).

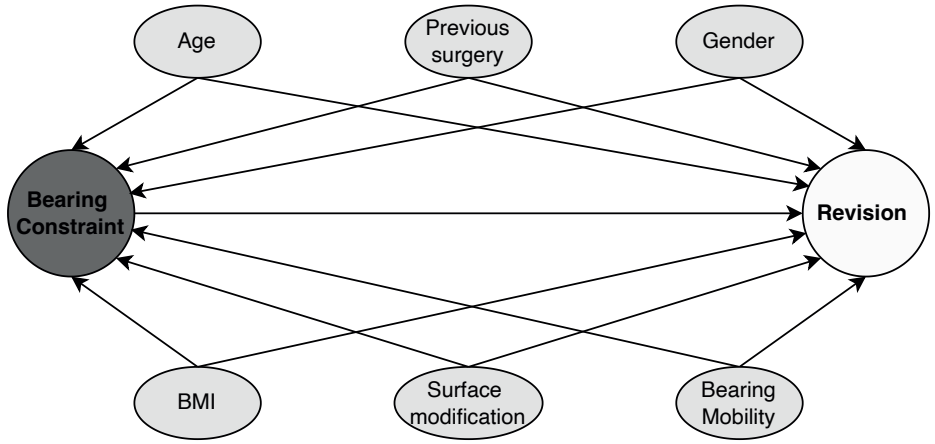


Figure 1. Directed acyclic graph representing the direct causal and associations between variables, the exposure (bearing constraint), and outcome (implant revision risk). Arrows represent the direction of causality or association between variables.

Statistics

Baseline characteristics are presented as means and standard deviation (SD), median and interquartile range (IRQ), or frequency and percentage. Cumulative crude revision incidences were assessed using Kaplan–Meier (KM) and competing-risk time-to-event survival analyses for revision for any reason and aseptic loosening at 5 and 10 years. Survival time was defined as the time from primary TKA to first revision, patient death, or the end of the study period (January 1, 2022). For KM analyses, deaths were censored observations, assuming that the risk of revision is independent of the risk of death. For competing risk analyses, deaths were considered a competing event *[523]* Tables and graphs show revision risks for any reason and aseptic loosening and their associated 95% confidence intervals (CI). Furthermore, an overview of other risks of various revision reasons has been calculated and presented. A log-minus-log transformation (with continuity correction in case of zero events) was employed to calculate the CI for the revision

risks for different reasons, as the event rates were small. The KM and competing-risk cumulative revision incidences were compared to determine the possible influence of death as a competing risk. Since both analyses gave similar results, this justified using Cox regression models for the univariate and multivariate analyses to estimate hazard ratios (HR) associated with implant revision rates and their corresponding CI. We therefore only used the competing risk model to calculate the revision risks. Schoenfeld residuals were checked to ascertain model fit *[536]*, which showed no violation of the proportional hazard assumption for both models (revisions for any reason and aseptic loosening). KM revision risks are presented in **Table S1** (see Supplemental material). In the Cox regression models, the CR group was used as the reference group. An HR above 1.0 indicates that the PS group had a higher likelihood of revision compared with the CR group, while an HR below 1.0 suggests a lower likelihood of revision for the PS group. The model was adjusted for possible confounders that were included in the DAG (**Figure 1**). The models' multicollinearity was assessed using the variance inflation factor (VIF), indicating no significant issues when the VIF is lower than 5.0. *[537]* To mitigate potential bias from underutilized prostheses or low-volume hospitals, 2 sensitivity analyses were conducted. Multivariable Cox regression analyses were performed on 2 restricted databases, each including only the 5 most commonly used implants and the 5 highest volume hospitals within each group over the follow-up period. Missing data was addressed by omitting cases with a majority of unknown variables. For variables with feasible imputation, a multiple imputation method was used to generate plausible imputed values based on observed data. This approach aimed to reduce the impact of missing data while considering the probability of incorrect results *[538]* R software version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria) using R packages "mstate" and "survival" were used to perform the analyses *[539, 540]*

Ethics, funding, and disclosures

The study was approved by the institutional Scientific Advisory Board (WAR) of the LROI (LROI2022-100) after a comprehensive evaluation regarding the feasibility, relevance, compliance with ethical standards, privacy protection of patients and caregivers, and sound methodology of any study before data was obtained. The protocol of the study (LROI2022-100) can be provided by the authors upon request. Regarding potential conflicts of interest, 2 authors, BP (medical director) and AS (research and quality control), are employees of the LROI. The authors received no financial support for conducting the research and declare no conflict of interest. Complete disclosure of interest forms according to ICMJE are available on the article page, doi: 10.2340/17453674.2023.33283

RESULTS

13,667 uncemented primary TKRs initially met the inclusion criteria. Exclusions were made for 32 cases with different bearing designs and 659 cases where it was not possible to determine if the TKR was of CR or PS type. Consequently, the study focused on 12,976 uncemented primary TKRs, of which 12,226 were CR implants and 750 PS implants (**Figure 2**).

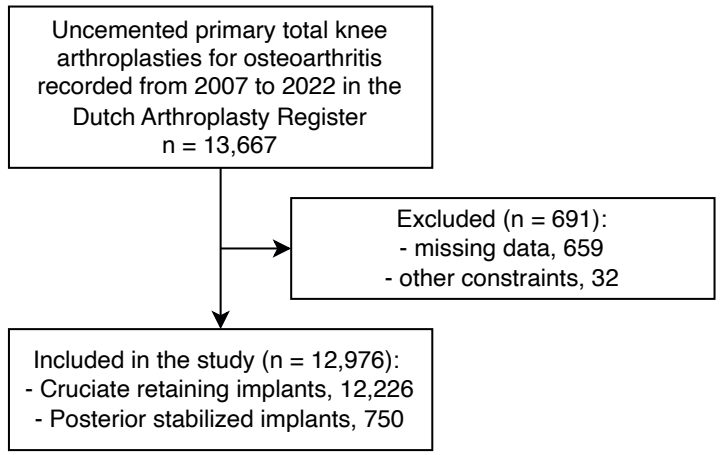


Figure 2. Flowchart of in- and exclusion.

Baseline

The median follow-up was 7 years (IQR 3–10) for the CR group and 5 years (IQR 2–10) for the PS group. Patient demographics were comparable between the groups (**Table 1**). The data was derived from 88 different hospitals, of which 22 (25%) never utilized a CR TKR system, and 20 (23%) never utilized a PS TKR system. In comparison with the PS group, the CR group had a greater variety of implants available with 24 designs compared with the PS group with 16 designs. The CR group comprised a larger proportion of cases with previous surgery on the same knee (25% vs. 16%), a substantially greater number of mobile bearing cases (82% vs. 13%), and a higher percentage of components with a porous metal-uncoated surface modification (**Table 1**).

There was some missing data for relevant variables such as insert mobility (48 CR [1%]; 12 PS [2%]), surface modification (982 CR [8%]; 205 PS [27%]), previous surgery on the same knee (678 CR [6%]; 69 PS [9%]), BMI (CR 5,756 implants [47%]; PS 290 implants [39%]), smoking (CR 5,970 [49%]; PS 291 [39%]), and Charnley score (CR 5,706 implants [47%]; PS 284 implants [38%]).

Table 1. Baseline characteristics.

	Cruciate retaining	Posterior stabilized
Patients, n	10679	747
Knees, n	12226	750
Implant designs, n	24	16
Follow-up in years, median (IQR)	7 (3–10)	5 (2–10)
Age at surgery, n (%)		
< 50 years	243 (2)	22 (3)
50–59 years	1,800 (15)	121 (16)
60–69 years	4,191 (34)	266 (36)
70–79 years	4,423 (36)	254 (34)
> 80 years	1,562 (13)	85 (11)
Sex, n (%)		
Female	7,894 (65)	486 (65)
Male	4,314 (35)	261 (35)
BMI, mean (SD)	29 (5)	30 (5)
Preoperative smoking, n (%)	582 (5)	35 (5)
Charnley score [a], n (%)		
A	2,775 (23)	228 (30)
B1	2,072 (17)	151 (20)
B2	1,415 (12)	73 (10)
C	258 (2)	14 (2)
ASA-classification, n (%)		
I	2,047 (17)	108 (14)
II	8,295 (68)	485 (65)
III/IV	1,642 (13)	107 (14)
Previous knee surgery [b], n (%)	3,099 (25)	116 (16)
Bearing mobility, n (%)		
Fixed	2218 (18)	644 (86)
Mobile	9960 (82)	94 (13)
PE material, n (%)		
UHMWPE	10345 (85)	585 (78)
Highly crosslinked PE	1474 (12)	146 (20)
Highly crosslinked PE + AO	260 (2)	14 (2)
Femur component surface, n (%)		
Porous-HA	1905 (15)	99 (13)
Porous-uncoated	8935 (73)	23 (3)

Table 1. Continued

	Cruciate retaining	Posterior stabilized
Porous-TiN	697 (6)	2 (0)
Grit-blasted-uncoated	447 (4)	555 (74)
Grit-blasted-TiN	199 (2)	30 (4)
Trabecular metal	0 (0)	0 (0)
Tibial component surface, n (%)		
Porous-HA	1879 (15)	100 (13)
Porous-uncoated	9502 (78)	20 (3)
Porous-TiN	81 (1)	5 (1)
Grit-blasted-uncoated	514 (4)	470 (63)
Grit-blasted-TiN	186 (2)	1 (0)
Trabecular metal	13 (0)	20 (3)

Numbers do not add up to total due to missing data.; BMI: body mass index; HA: hydroxyapatite; IQR: interquartile range; n: number; PE: polyethylene; AO: Antioxidant; SD: standard deviation; TiN: titanium nitride; TKA: total knee arthroplasty.

Revision for any reason

The 10-year revision rate for any reason was higher for the PS group (6.5%, CI 4.6–9.2) compared with the CR group (4.2%, CI 3.8–4.7) (**Table 2 and Figure 3**). Revision risks for infection and aseptic loosening were also higher for the PS implants compared with the CR implants (**Table 3**). Multivariable Cox regression analyses revealed that PS implants had a higher risk of revision for any reason than CR implants (crude HR 1.4, CI 1.0–2.0; **Table 4**, model 1). Also, after multivariable adjustment, the risk of revision for any reason was higher for PS implants than for CR implants (adjusted HR 1.4, CI 0.6–3.2; **Table 4**, model 8).

Table 2. 5- and 10-year revision rates for any reason and aseptic loosening of uncemented implants with cruciate-retaining and posterior stabilized inserts.

	Total knees, n	Revision for aseptic loosening, n	Revisions for any reason, n	Revision rate for aseptic loosening, % (CI)	Revision rate for any reason, % (CI)	n at risk [a]
5-year estimate						
Cruciate retaining	12,226	119	366	1.1 (0.9–1.3)	3.4 (3.1–3.7)	7,535
Posterior stabilizing	750	13	26	2.1 (1.2–3.5)	4.1 (2.8–6.0)	370
10-year estimate						
Cruciate retaining	12,226	139	422	1.4 (1.1–1.6)	4.2 (3.8–4.7)	3,238
Posterior stabilizing	750	19	34	3.9 (2.4–6.0)	6.5 (4.6–9.2)	170

[a] Total number of knees remaining in the study at the specified follow-up.
n: number; CI: confidence interval

Table 3. Reasons for revision for uncemented implants with cruciate-retaining and posterior stabilized implants at 10-year follow-up.

	Cruciate retaining n = 12,226		Posterior stabilized n = 750	
	revision [a]	% (CI)	revisions [a]	% (CI)
Infection	23	0.2 (0.1-0.3)	6	0.9 (0.4-2.0)
Instability	183	1.9 (1.7-2.3)	7	1.4 (0.6-3.0)
Polyethylene wear	18	0.3 (0.2-0.5)	1	0.3 (0.0-2.4)
Aseptic loosening	139	1.4 (1.1-1.6)	19	3.9 (2.4-6.0)
Arthrofibrosis	33	0.3 (0.2-0.5)	0	0.0 (0.0-2.4)
Patellofemoral pain	50	0.6 (0.5-0.8)	4	1.1 (0.4-3.3)

[a] The number of revisions does not add up to the total number of revisions of Table 2 due to the presence of multiple reasons for a single revision.
* Continuity correction (1 event)

Revision for aseptic loosening

Competing risk analysis, with aseptic loosening as the endpoint, over 10 years, revealed a higher rate of revision for PS implants (3.9%, CI 2.4–6.0) than for CR implants (1.4%, CI 1.1–1.6) (**Table 2 and Figure 4**). Using multivariable Cox regression analyses, the crude risk of revision for aseptic loosening was estimated to be 2.5 times higher for PS implants than for CR implants (crude HR 2.5, CI 1.5–4.0; see **Table 5**, model 1). After multivariable adjustment, an approximately 3-fold increased risk (adjusted HR 2.6, CI 0.6–11; **Table 5**, model 8) of revision due to aseptic loosening was found for PS implants compared with CR implants.

The results of sensitivity analyses were consistent with the analyses of the full dataset when restricted to the 5 most commonly used implants or the 5 highest-volume hospitals (**Tables 4 and 5**).

Table 4. Multivariable Cox regression model on full and restricted dataset for revision rates for any reason of PS compared with CR implants (reference) after 10 years follow-up.

Use of PS	Full dataset HR (CI)	Restricted to implants [a] HR (CI)	Restricted to hospitals [a] HR (CI)
Crude [b]	1.4 (1.0–2.0)	1.6 (1.1–2.4)	2.0 (1.2- 3.2)
Adjusted for			
Model 1: Age (5 categories [c])	1.4 (1.0–2.0)	1.6 (1.1–2.4)	1.8 (1.1–2.9)
Model 2: Sex	1.4 (1.0–2.0)	1.6 (1.1–2.4)	2.0 (1.2–3.2)
Model 3: BMI	1.3 (0.8–2.2)	n/a [d]	n/a [d]
Model 4: Previous knee surgery	1.5 (1.1–2.2)	1.7 (1.1–2.6)	2.2 (1.3–3.7)
Model 5: Bearing mobility	2.1 (1.4–3.1)	2.2 (1.4–3.5)	2.6 (1.3–5.0)
Model 6: Surface modification femur	1.3 (0.9–1.8)	1.4 (1.0–2.2)	2.1 (1.3–3.4)
Model 7: Surface modification tibia	1.5 (1.3–1.7)	1.2 (0.8–2.0)	2.5 (1.4–4.2)
Model 8: All above	1.4 (0.6–3.2)	1.7 (0.8–3.4)	2.1 (1.0 –4.5)

[a] The restricted datasets contain only data of 1) the 5 most commonly used implants (CR 11,214 [92%]; PS 562 [75%]), 2) the 5 most performing hospitals per group (CR 8,596 [70%]; PS 267 [36%]).
[b] Crude = HR from univariable model.
[c] The 5 age categories include < 50; 50–59; 60–69; 70–79; ≥ 80 years.
[d] BMI has been registered by the LROI since 2014 resulting in a small sample size that do not allow any meaningful analyses.
PS posterior stabilized; CR: cruciate retaining; HR: hazard ratio; CI: confidence interval; BMI: body mass index;

Table 5. Multivariable Cox regression model on full and restricted dataset for revision rates for aseptic loosening of PS compared with CR implants (reference) after 10 years follow-up.

Use of PS	Full dataset HR (CI)	Restricted to implants [a] HR (CI)	Restricted to hospitals [a] HR (CI)
Crude [b]	2.5 (1.5–4.0)	2.3 (1.3–4.2)	3.6 (1.8–7.2)
Adjusted for			
Model 1: Age (5 categories [c])	2.4 (1.5–3.8)	2.3 (1.3–4.3)	3.3 (1.7–6.6)
Model 2: Sex	2.5 (1.5–4.0)	2.3 (1.3–4.2)	3.6 (1.8–7.2)
Model 3: BMI	3.0 (1.3–6.7)	n/a [d]	n/a [d]
Model 4: Previous knee surgery	2.6 (1.6–4.3)	2.4 (1.3–4.5)	4.4 (2.2–8.8)
Model 5: Bearing mobility	4.1 (2.3–7.4)	3.9 (1.8–8.3)	7.9 (3.5–17.6)
Model 6: Surface modification femur	2.2 (1.3–3.5)	2.3 (1.2–4.4)	4.5 (2.3–9.0)
Model 7: Surface modification tibia	1.9 (1.1–3.2)	1.8 (0.9–3.5)	5.6 (2.8–11.1)
Model 8: All above	2.6 (0.6–11.0)	4.0 (1.4– 11.4)	9.9 (4.0–24.7)

For abbreviations, see Table 4

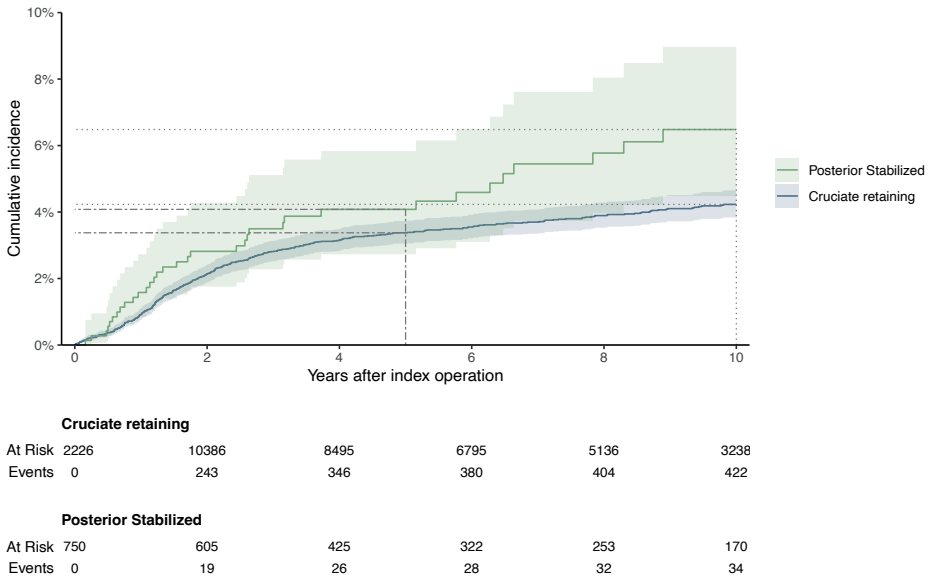


Figure 3. Cumulative incidence with 95% confidence intervals of revisions for any reason of cruciate-retaining and posterior stabilized implants, calculated by Competing Risk analysis.

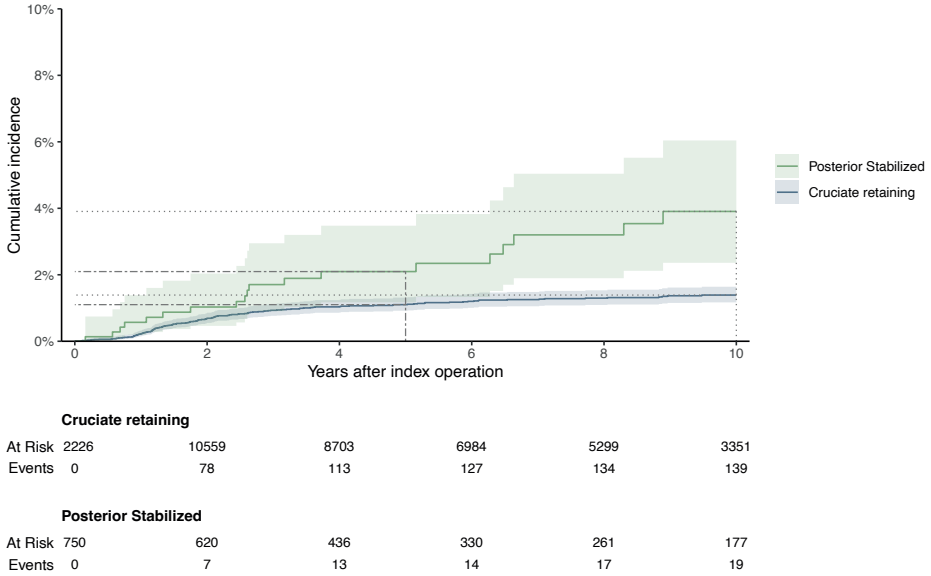


Figure 4. Cumulative incidence with 95% confidence intervals of revisions for aseptic loosening of at least one component, of cruciate-retaining and posterior stabilized implants, calculated by Competing Risk analysis.

DISCUSSION

We aimed, in this registry study, to compare the revision rates of PS and CR designs in patients receiving primary uncemented TKR. The main finding was that uncemented PS implants had a 1.4 times higher risk of revision for any reason and a 2.5 times higher risk for revision for aseptic loosening compared with uncemented CR implants used in the Netherlands from 2007 to 2022 during follow-up of 10 years.

This study represents the first large observational analysis that compares the risks of revision between PS and CR constraints, focused only on uncemented TKR systems. However, our findings are in line with previous observational studies that included only cemented CR and PS TKR systems. The recent Dutch registry study by Spekenbrink-Spooren et al. (2018) found PS cemented TKR systems to be 1.3 (CI 1.2–1.4) times more likely to receive a major revision than the CR cemented TKR systems after a median follow-up of 8 years. Moreover, the most common reason for the revision of both systems was aseptic loosening (PS (41%), CR (27%); P < 0.001) [*[541]* Similar conclusions were drawn by the Australian registry study of Vertullo et al. (2017), in their effort to circumvent confounding by indication, who compared patient groups treated by high-volume surgeons who preferred CR systems with those who preferred PS systems*[531]* The authors found that the PS implants were more at risk of revisions for any reason (HR 1.6, CI 1.3–1.8]), aseptic loosening (HR 1.9, CI 1.6–2.4), and infection (HR 1.5, CI 1.3–1.8), compared with CR implants. Unfortunately, an analysis of uncemented implants was not performed due to an insufficient number of PS implants *[531]* In the single high-volume institute study of Abdel et al. (2011), the all-cause revision rate of CR implants was found to be significantly lower than that of PS implants (CR 4.3%, CI 4.9–3.7 vs. PS 7.8%, CI 6.6–9.0, P < 0.001) *[530]* This difference remained statistically significant after they attempted to remove a potential selection bias, by stratifying for knees with and without preoperative deformity, which was at the time the main medical indication for using a PS design *[530]*

Contrary to our findings, the most recent meta-analysis based on 14 randomized controlled trials (RCTs), involving 1,453 patients with follow-up ranging from 0.5 to 6 years, reported equivalent revision rates and functional outcomes between PS and CR designs *[149]* However, it is important to note that the present and preceding meta-analyses are based solely on RCTs involving cemented implants and may lack sufficient statistical power and follow-up duration to adequately compare revision rates. In an RCT on uncemented TKR with trabecular metal, Wojtowicz et al. compared PS with CR in terms of fixation, measured with radiostereometric analyses (RSA), and found no clinically relevant differences *[542]* Their results predicted that, for trabecular metal, there would be no differences in revision rates of aseptic loosening for PS compared with CR tibial baseplates *[542]* Notably, 3 observational studies, which together assessed more than 450 uncemented PS TKRs with trabecular metal, reported no revisions for aseptic loosening after a

follow-up period of 5 years *[301, 328, 543]*, reinforcing the robustness of the RSA results of the study of Wojtowicz et al. *[542]* These finding may seem to contradict our observed higher revision rates for any reason and for aseptic loosening of PS systems. However, only 33 trabecular metal tibial baseplates were included in our study, so the type of uncemented fixation may be an effect modifier. One notable distinction between the 2 groups in our study is that the CR group predominantly consisted of implants with a porous-uncoated surface, whereas the PS group had grit-blasted-uncoated surfaces. This disparity may be associated with the presence of different implant designs in each group, with potentially more modern designs having porous metal surfaces.

The reason why PS implants could be more at risk of revision has not yet been determined, but it is theorized that several factors may contribute to an increased risk. One possible factor could be the release of microparticles by increased post-wear, which can cause inflammation, ultimately leading to implant loosening *[544]* Another potential factor is the post and cam mechanism used in PS implants, which can increase load transfer to the tibial tray and result in micromotion at the bone–implant interface. Also, suboptimal implant positioning might increase stress on the bone–implant interface and contribute to the development of micromotion and aseptic loosening *[544]* While further research is needed to fully understand the reasons for the increased risk of revision in PS uncemented implants, addressing these potential factors through improved implant designs (e.g., use of trabecular metal implant surface) and surgical techniques could help reduce the risk of aseptic loosening of PS TKR systems.

Limitations

First, the study employs an observational design and there is a notable discrepancy in sample sizes between the PS group (n = 750) and the larger CR group (n = 12,226). This size difference may raise concerns about potential confounding by indication. However, we anticipate that this risk is low, as 2 previous registry and observational studies, in which a possible indication bias was deliberately investigated, reported results consistent with our study. One study included only high-volume surgeons who exclusively employed either a CR or PS design *[531]*, while the other corrected for preoperative deformities *[530]*. Second, the LROI registers only the indication for revision, without incorporating feedback on the intraoperative cultures. Therefore, it is likely that low-grade infections were misclassified as revisions for aseptic loosening, but it is expected that this misclassification was equal between both groups. Also, the proportion of unsuspected low-grade infections in cases with a preoperative diagnosis of aseptic loosening appears to be low (4–13%) in total hip or TKA *[545, 546]* Third, the inclusion of underutilized prostheses with suboptimal outcomes and the involvement of hospitals with low annual volumes or limited experience in utilizing uncemented TKR, irrespective of design, may contribute to a risk of bias in the

study's findings *[525]* However, the sensitivity analyses conducted on the restricted databases yielded results consistent with those obtained from the full database analyses, indicating a minimal risk of introducing bias. Also, unmeasured residual confounding effects may have influenced our findings due to missing variables. For instance, BMI data was available only from 2014 onwards, limiting the sample size for specific analyses. However, after correcting for BMI in the full dataset, our results remained consistent, suggesting that any BMI imbalances between CR and PS groups did not affect the study outcomes. Fourth, it is important to note that the generalizability of the study findings is limited to the specific implants used in this study.

CONCLUSION

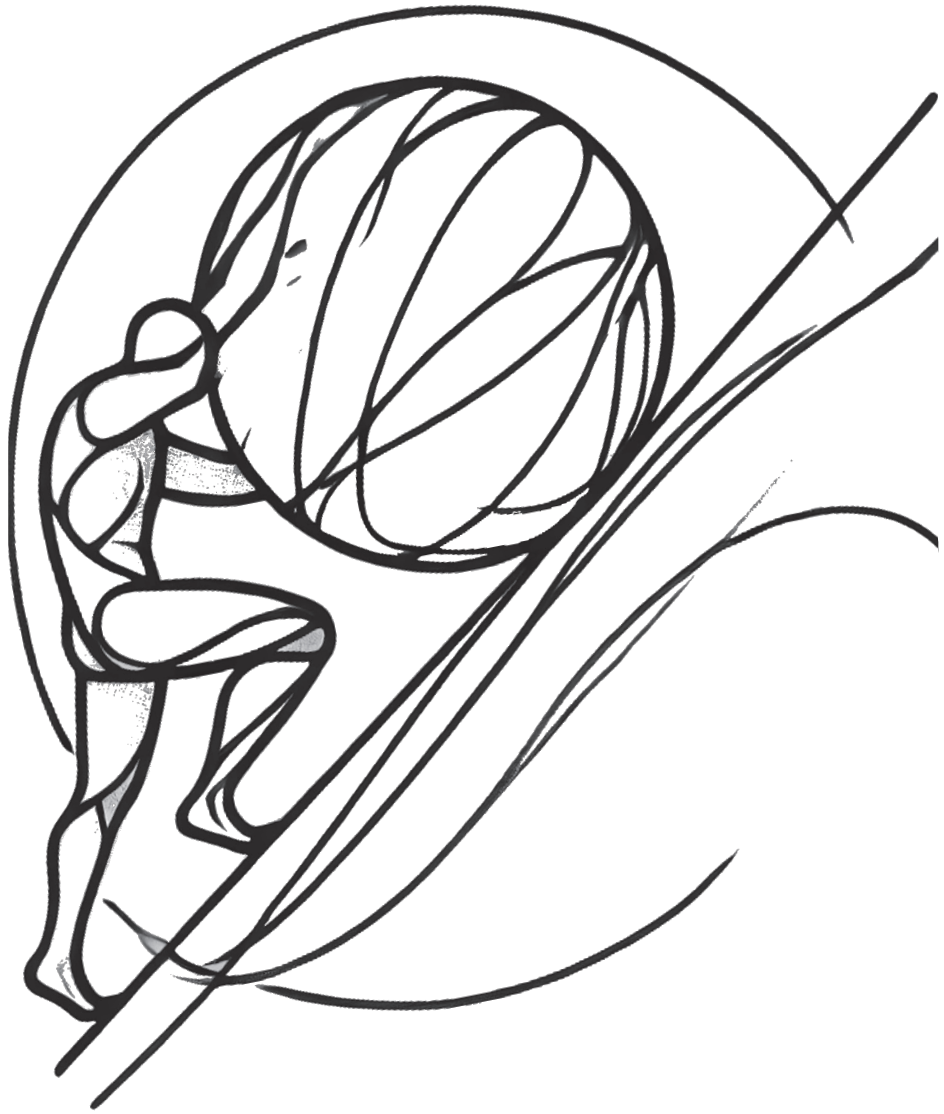
We showed that, during 10 years of follow-up, uncemented PS implants were 1.4 times more at risk of a revision for any reason, and 2.5 times more for aseptic loosening compared with uncemented CR implants. These results remained consistent after adjustment for confounders and sensitivity analyses.

SUPPLEMENTAL MATERIAL

Table S1. Five- and ten-year revision rates for any reason and aseptic loosening of uncemented implants with cruciate-retaining and posterior stabilized inserts by Kaplan Meier survival analysis.

	Total knees, n	Revision for aseptic loosening, n	Revisions for any reason, n	Revision rate for aseptic loosening, % (95% CI)	Revision rate for any reason, % (95% CI)	n at risk*
5-year estimate						
Cruciate retaining	12 226	119	366	1.1 (0.9 – 1.3)	3.4 (3.1 – 3.8)	7535
Posterior stabilizing	750	13	26	2.1 (0.9 – 3.3)	4.1 (2.5 – 5.7)	370
10-year estimate						
Cruciate retaining	12 226	139	422	1.4 (1.2 – 1.7)	4.4 (4.0 – 4.8)	3238
Posterior stabilizing	750	19	34	4.2 (2.2 – 6.2)	6.8 (4.4 – 9.2)	170

* Total number of knees remaining in the study at this specific follow-up moment.
n Number; CI Confidence Interval



CHAPTER 11

General discussion and future perspectives

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Joint replacement surgery has transformed Orthopaedic care by turning debilitating conditions into manageable ones, restoring patients' mobility and quality of life. *[2]* Like any medical innovation, its adoption hinges on a critical question: do the benefits outweigh the risks? In a field where patient safety is paramount, this question shapes the balance between progress and caution.

Innovation and adaptation of TKR in terms of patient safety

The S-curve framework, which illustrates how technological innovations progress from early experimentation to maturity and widespread adoption, provides a valuable perspective on the evolution of total knee replacement (TKR) technology (**Figure 1**). *[547]* The development of TKR dates back to the 1890s, when the first hinged knee implant was introduced. Made from ivory and fixed with plaster of Paris, this early design was unsuccessful due to high failure rates. *[3]* Nearly 70 years later, in 1958, bulky metal-hinged implants were developed, but they were only used in the most severe cases, as no better alternative treatments were available at the time. However, also their rigid constraint resulted in high mechanical loosening rates, limiting their long-term success. *[3]* A breakthrough came in the 1970s with the introduction of less constrained condylar designs, which more closely replicated natural knee movement that contributed to improved kinematics and patient outcomes. *[3]* Together with advancements in surgical techniques, these innovations improved the reliability and effectiveness of TKR, ultimately establishing it as the gold standard for treating end-stage knee osteoarthritis. *[2]*

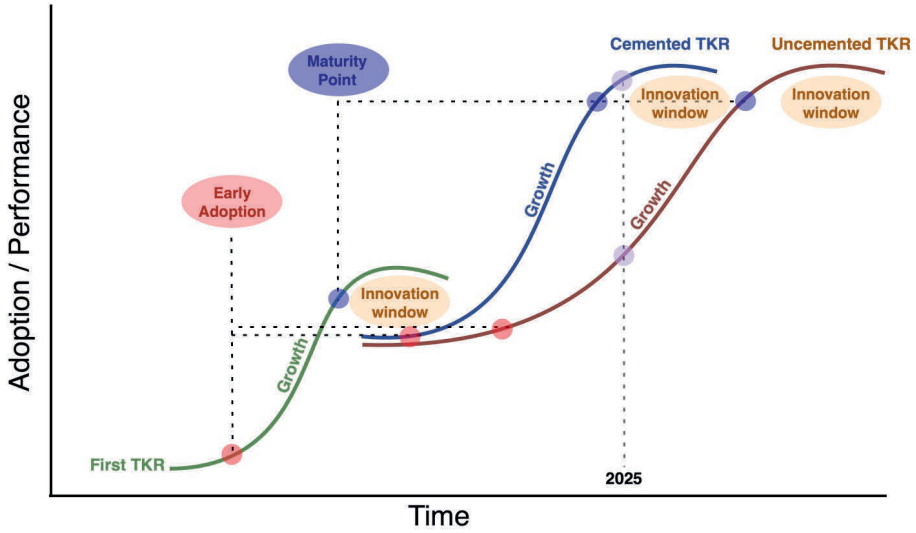


Figure 1. Traditional S-curve illustrating patterns of technological growth and adoption (adapted from Ashkenazi (2022) *[547]*.

As with any technological advancement, the pace of innovation naturally slows as it approaches the end of the S-curve, marking the plateau phase (**Figure 1**). Rather than signaling an endpoint, this stage creates opportunities for further refinement. Innovations in modularity, fixation methods, and implant constraints have continued to drive new waves with technological development, shaping the ongoing evolution and adoption of TKR technology as we currently know it. *[547]* For instance, the S-curve framework can highlight distinct innovation trajectories for cemented and uncemented TKR (**Figure 1**). Cemented fixation has reached maturity on its S-curve, as evidenced by **Chapter 3** (Figure 4.A), which shows no improvements in early migration or stabilization over the past three decades. With predictable stability and long-term performance, it remains the gold standard and accounts for approximately 88% of procedures (Confidence Interval [CI]: 78.6–97.5). While its long-term stability is well-established, this also means fewer opportunities for improvement, and any modifications may introduce new risks rather than significant benefits. Also, cemented fixation is not without its drawbacks. Challenges such as longer surgery times *[492]*, bone-cement implantation syndrome *[548]*, and more complex revision procedures *[549]* remain significant and can impact both patient safety and surgical efficiency. Longer surgery times increase the risk of infection *[550]*, while bone-cement implantation syndrome—though rare—can cause serious cardiovascular complications due to embolization of cement particles into the bloodstream. Additionally, revision procedures for failed cemented implants are often more complex and technically demanding, requiring extensive cement removal and potentially compromising bone stock. *[549]*

While cemented fixation remains the gold standard, uncemented methods offer an opportunity to address its limitations and provide more tailored solutions for specific patient populations. *[147, 445, 491, 551–553]* This trend mirrors the debate in total hip replacements, where uncemented fixation has gained increasing interest, particularly among younger and more active patients. *[554]* Uncemented TKR is still in its growth phase (**Figure 1**) due to its later adoption, presenting significant potential for further development and possibly involving a different, potentially higher, risk-reward ratio compared to cemented TKRs. Uncemented implants eliminate concerns related to bone cement, but introduce other challenges, including variability in osseointegration (**Chapter 2)** and revision rates (**Chapter 9**) among designs. Overall, as shown in **Chapter 3** (Figure 5.A), uncemented TKR has demonstrated clear improvements in early migration over recent decades, reinforcing its ongoing evolution and improvement. Additionally, in the Netherlands alone, four different types of uncemented TKR with distinct surface modifications are currently in use (**Chapter 9**). Given these variations, it is reasonable to assume that each type follows its own S-curve framework, progressing at a different pace depending on the design and the time it has been in use. Moreover, promising innovations—such as trabecular-surfaced implants—have not even been considered in most registry studies, due to the yet limited clinical use (**Chapter 9 and 10**).

This gap in large-scale registry data may hinder further adoption, as clinicians and policymakers rely on registry evidence for implant selection and approval. *[27]*

The stakes of innovation in healthcare are exceptionally high. Unlike other industries, where trial and error are more tolerable, failures in medical devices can have profound, life-altering consequences. For high-volume, high-risk devices like TKR, relied upon by millions of patients annually, even minor design flaws or packaging problems can result in chronic pain, reduced mobility, or complex revision surgeries. *[24–26]* Both historical and recent cases of implant failures underscore the critical importance of regulation and post-market surveillance. *[431, 555]* For instance, the Optetrak implant (Exactech, USA) was initially considered an outlier in multiple national registries but was later found to have a three- to seven-fold higher revision rate compared to other TKR systems due to polyethylene wear (e.g., loosening, lysis, pain), likely caused by oxidation resulting from packaging issues present since 2004. As a result, the FDA issued a recall to prevent further patient harm. *[431, 555]* Consequently, a phased market introduction framework for implants is essential, forming the foundation of this thesis on uncemented TKR.

Premarket assessments and outcomes of uncemented TKR

The pre-market phase is critical to ensuring the safety and effectiveness of high-risk devices like TKR. The European Medical Device Regulation (MDR 2017/745) requires clinical proof of concept for CE-mark certification, but its flexibility in the type of proof accepted has allowed underperforming implants to enter the market. *[84, 159]* Studies show that 30% of new implants fail to outperform their predecessors in functionality, underscoring the need for stricter and more robust pre-market frameworks, including in-vitro and radiostereometric analysis (RSA) studies. *[46]* A study by Hoogervorst et al. (2024) found that 25% of underperforming TKR systems identified in registries were not addressed by manufacturers, revealing gaps in post-market surveillance and reinforcing the need for stronger pre-market assessments. *[47]* Moreover, registry data indicates that RSA-tested implants have a 1% lower revision rate at 5- and 10-year follow-ups compared to non-RSA-tested implants, further highlighting the value of rigorous pre-market evaluation methods. *[161, 162]*

This thesis explored pre-market outcomes related to uncemented TKR in **Chapters 2, 3, and 4**. **Chapter 2** found that a trabecular surface elicited a stronger osteoblastic response and reduced osteoclast formation compared to a hydroxyapatite-coated (HA) vacuum plasma-sprayed (VPS) surface, the latter of which is used for the uncemented Global Medacta Knee (GMK) implant. This finding aligns with **Chapter 3's** results (Figure 5.B), which showed faster implant stability for trabecular-surfaced compared to other tibial components. The GMK implant, implanted 1,934 times in Australia, had a 10-year revision rate of 5.8% (CI 4.4–7.6%) *[72]*, exceeding the Orthopaedic Data Evaluation Panel (ODEP) 10-year benchmark of 5.0%. *[27]* This elevated revision rate may be linked to aseptic loosening; however, no RSA pre-

market evaluations were conducted on the GMK to assess its early migration and long-term stability. Had such testing been performed, it might have identified an unacceptable or at-risk early migration using the fixation-specific thresholds from **Chapter 4**, potentially preventing the implant from reaching the market and nearly 2,000 Australian patients from exposure. *[72]* This evaluation would have required only 25–30 patients *[37]* in an RSA trial lasting of only six months (as demonstrated in **Chapter 4**), a significantly lower patient burden compared to the widespread clinical use that followed. A limitation of the current thresholds (**Chapter 4**) is the existence of an at-risk category, as there is still no established method to estimate whether an implant categorized as at-risk will ultimately fail or remain stable. This uncertainty highlights the need for future research to continue investigating this matter, ideally working toward a two-category system—acceptable vs. unacceptable—to provide clearer clinical guidance and improve decision-making in regulatory assessments. In this context, the recent proposal to use the full migration pattern of tibial components using a Michaelis-Menten curve introduces the MTPMemax parameter as a promising alternative. [556] This method allows for a binary classification (safe vs. unsafe), opens the possibility for implant brand and fixation-specific thresholds, and requires only two follow-up measurements, with a reduced accuracy to the exact timing of RSA exams. [556] However, the method has thus far only been validated using five-year revision rates from an earlier systematic review published in 2012 [39], and future validation using more recent datasets including modern implant designs, like the dataset of **Chapter 4**, remains necessary.

Fortunately, healthcare facilities increasingly rely on evidence-based frameworks, such as the ODEP rating system, to guide implant selection by evaluating implant quality and revision rates. *[27]* Integrating RSA and in-vitro assessments could strengthen these frameworks, offering deeper insights for patients, surgeons, and manufacturers. Nevertheless, when applying the new migration thresholds from **Chapter 4**, researchers should recognize the potential for outcome reporting bias when evaluating migration data using multiple thresholds (**Chapter 4**; Table 3) instead of a single, preregistered threshold. To prevent cherry-picking, only predefined thresholds stated in the study protocol should be used. Additionally, the traditional RSA work-up faces challenges for such integration, due to its reliance on tantalum markers and high setup costs. However, computed tomography (CT)-RSA addresses these issues by using standard CT scanners, eliminating the need for bone markers, specific surgical considerations, and templates, thereby simplifying the work-up and analyses. *[37, 557]* This makes CT-RSA a more accessible and cost-effective alternative, particularly for uncemented TKR, which is often performed with robotic assistance to ensure precise bone cuts. *[558]* Standardized preoperative and 1-year postoperative CT scans assess robotic accuracy in these procedures already. *[558]* Integrating additional scans immediately post-surgery and at 6 months could effortlessly track early migration, providing valuable data on aseptic loosening risk in uncemented TKR.

Post-market surveillance and outcomes of uncemented TKR

Post-market surveillance complements pre-market assessments by evaluating actual implant performance, patient functional outcome and identifying rare or unexpected failures. These assessments rely on early cohort studies and robust joint registries with large patient cohorts and long follow-up. *[559]* In this context, this thesis examined revision rates, patient-reported outcome measures (PROM) scores, patient satisfaction, and advanced diagnostics for aseptic loosening in uncemented TKR.

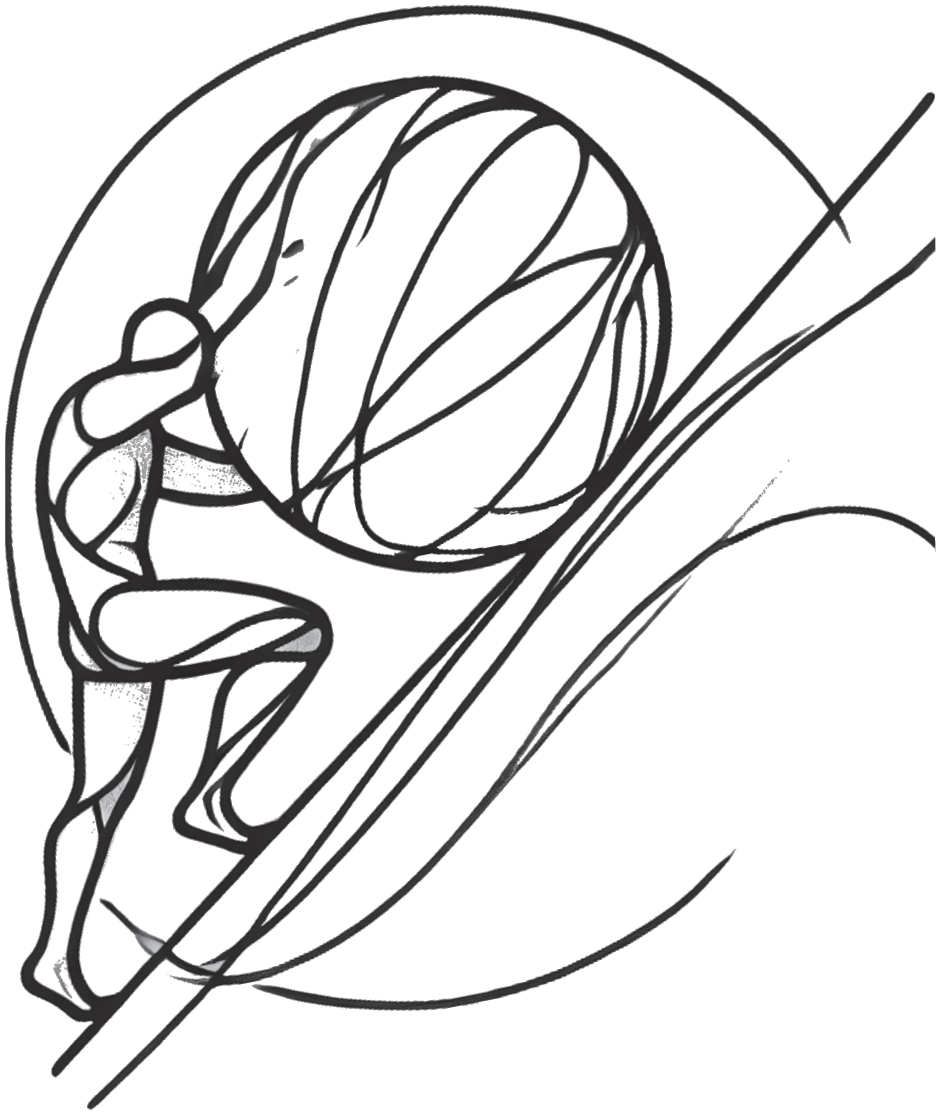
The literature includes numerous randomized controlled trials (RCTs) comparing uncemented and cemented TKR (the gold standard), which generally report similar outcomes in PROMs, knee function, patient satisfaction, and short-term revision rates. *[147, 445, 491, 551–553]* However, PROMs often receive less focus than revision rates in orthopedic research, despite the 10–20% of patients reporting dissatisfaction after surgery. *[20]* While patient satisfaction is an important factor for the decisions to conduct a revision *[20, 560]*, its underlying causes are still being explored. Some dissatisfied patients may experience complications that initially go undetected but gradually affect joint function, potentially becoming apparent over time. *[560]* These may include subtle implant instability, low-grade infection, or progressive loosening, which could eventually lead to functional impairment or implant failure. For instance, **Chapter 6** found that the initial 3-month migration of the femoral component in the newly introduced uncemented ATTUNE TKR was lower than in its predecessor, the uncemented LCS TKR. Both implants, however, stabilized under similar conditions up to 5 years postoperatively. The reason for this difference remains unclear and warrants further research. One possibility is the formation of a fibrous membrane at the femoral interface, which could disrupt osseointegration and increase the risk of loosening, according to previous RSA, - and MRI studies. *[434, 561]* These findings emphasize the need for a deeper understanding of this process, and to establish specific migration thresholds for (uncemented) femoral components, similar to those defined for tibial components. Such thresholds would enhance the precision of pre-market assessments and improve the interpretation of post-market evaluations, advancing diagnostics for implant fixation and loosening.

The diagnostic work-up for detecting loosening in uncemented TKR could be improved by incorporating bone scintigraphy with single-photon emission computed tomography/computed tomography (BS-SPECT/CT) at later stages of diagnosis, as shown in **Chapter 7**. A novel finding of this study is that the time interval between surgery and imaging was not associated with diagnostic outcomes, which might provide greater flexibility for diagnostics in clinical practice. However, recognizing inconclusive outcomes as negative is crucial to preventing unnecessary revisions and minimizing patient harm. Serum and urine biomarkers (e.g., TNFα, IL-1β, osteocalcin, and urinary N-telopeptide) show promise for the early detection of aseptic loosening, particularly due to their non-invasive nature

and their potential to enhance the pre-test probability of subsequent diagnostic tests. *[33, 562]* Additionally, implant characteristics—such as surface modifications and constraint designs—should be considered in both implant selection and diagnostic evaluations, as **Chapters 9 and 10** demonstrated their significant variation in loosening risk. For instance, **Chapter 9** showed that grit-blasted uncoated and grit-blasted titanium-nitride-coated implants were associated with a two- to eight-fold higher incidence of loosening within 10 years compared to other implants in the Netherlands. Similarly, **Chapter 10** found that posterior-stabilized designs had a 2.5-fold higher risk of loosening than cruciate-retaining designs. These findings highlight that the term "uncemented TKR" oversimplifies the diversity in uncemented design and performance, emphasizing the need for more precise categorization in future research. A clearer classification system would improve the accuracy of evaluations and prevent underperforming prostheses from being camouflaged within the broader group. *[563]*

Finally, PROM scores at 1-year for the novel uncemented ATTUNE (**Chapter 5**) and at 15 years for the uncemented LCS (**Chapter 8**) were excellent, comparable to outcomes consistently reported in high-quality RCTs for uncemented TKR. *[147, 445, 491, 551–553]* Since manufacturers refine newer implant models based on previous designs, early short-term cohorts play a crucial role in assessing their safety and performance before widespread clinical use. Short-term revision rates of the newer ATTUNE design (i.e., 0.4% at 3 years) in **Chapter 5** were in line with the longer-term rates for loosening of its predecessor, the LCS (i.e., 1.8% at 15 years). Both studies demonstrate the potential success rate of modern uncemented TKR. Although the ATTUNE study was underpowered (n = 260) for complication rates, **Chapter 5** reported a higher incidence of manipulations under anesthesia (MUA) (3.9%), compared to its predecessor the LCS in **Chapter 8** of 3.0%. Both were notably higher than the overall 1.7% reported in a Swedish registry study. *[428]* This discrepancy may arise due to variations between hospitals, differences in standardized procedural indications, patient characteristics, or the implementation of fast-track postoperative protocols to enhance recovery. *[428]* These findings underscore the critical importance of both short- and long-term surveillance and consistent outcome reporting to ensure the safety, durability, and clinical effectiveness of uncemented TKR.

In conclusion, as uncemented TKR continues to evolve, this thesis highlights the need for robust pre-market evaluations and short- to long-term post-market surveillance to prevent underperforming implants from reaching or expanding in widespread clinical use. For policymakers and regulatory bodies, this thesis supports the implementation of pre-market RSA testing with fixation-specific thresholds to enhance (uncemented) implant safety. For surgeons, the data-driven insights from this thesis on modern uncemented TKR can guide implant selection and inform surgical decision-making. From a patient perspective, optimizing implant selection can reduce the risk of implant-related complications and improve patient safety.



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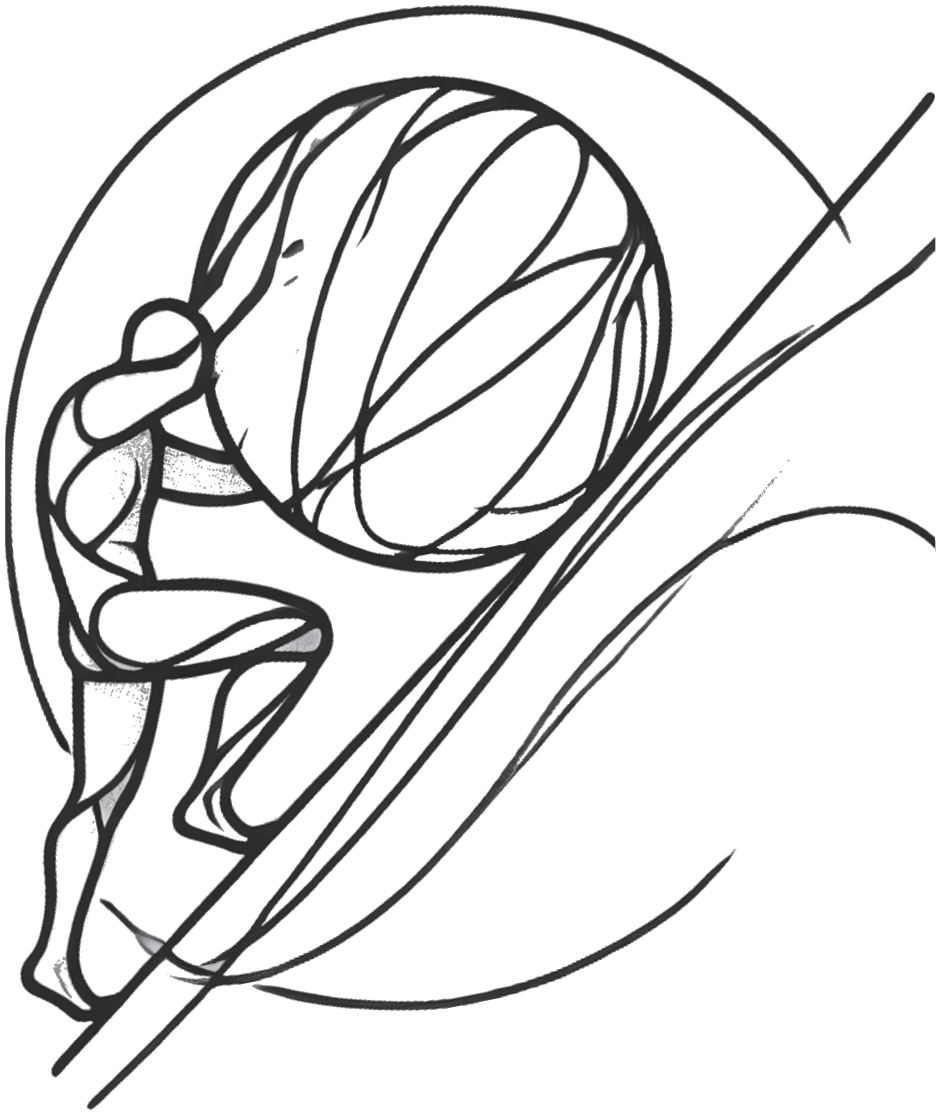


APPENDICES

SUMMARY

Osteoarthritis is a common degenerative joint disorder that causes progressive damage to cartilage and bone. In advanced stages, a total knee replacement (TKR) may be necessary. Traditionally, TKR fixation is achieved using bone cement, but uncemented techniques are increasingly being used worldwide, particularly in younger and more active patients. While cement fixation provides immediate stability, uncemented fixation relies on bone ingrowth, which may offer a more durable long-term solution. As the number of younger patients requiring TKR continues to grow, uncemented fixation may be a valuable option to extend implant longevity, reduce revision surgeries, and enhance patient safety.

This thesis investigates the performance and durability of modern uncemented TKR, with a specific focus on the risk of aseptic loosening—a complication where the prosthesis detaches from the bone without infection. The research consists of both pre-market and post-market evaluations. The pre-market evaluation aims to identify early warning signs of potential long-term failure, allowing high-risk implants to be recognized before widespread clinical use. The post-market evaluation assesses the real-world performance of uncemented TKR, examining functional outcomes, migration patterns, and revision risks. This structured approach provides valuable insights into long-term fixation and implant survival, contributing to a better understanding of clinical applicability and supporting the continued development of safe and effective uncemented TKR.

Part I: Premarket assessments and outcomes of uncemented TKR

Since bone ingrowth is the foundation of uncemented TKR fixation, it is crucial to evaluate this process as early as possible in new uncemented TKR designs. Ideally, this should be done with minimal patient burden, using the smallest possible patient sample and within the shortest possible time frame. Pre-market studies play an essential role in identifying potential failure risks at an early stage, before an implant is widely adopted in clinical practice. Experimental laboratory studies can help assess and optimize the biological and mechanical properties of new uncemented implants. Additionally, radiostereometric analysis (RSA) is a powerful clinical tool to evaluate early fixation and stability in a small number of patients, typically followed for one to two years. RSA enables microscopic implant migration to be measured within the first months to years after implantation. Previous research has shown that early migration is a strong predictor of late aseptic loosening. These methods allow reliable long-term performance estimations within a relatively short time frame, reducing the likelihood of introducing implants with poor outcomes.

In **Chapter 2**, the biological response of bone cells to different uncemented TKR surfaces was investigated. A comparison was made between trabecular titanium-aluminum-vanadium (Ti6Al4V) and hydroxyapatite (HA)-coated vacuum plasma spray (VPS)-Ti surfaces, both of which are relatively new for uncemented TKR. Human osteoblasts (bone-forming cells) were cultured on these surfaces for 29 days, and their metabolic activity, differentiation, and bone mineralization were evaluated. Additionally, the activation of osteoclasts (bone-resorbing cells) was assessed, as this could indicate potentially induced bone-resorption. The results showed that all surfaces induced bone mineralization, but trabecular Ti6Al4V surfaces exhibited significantly higher osteoblast activity and lower osteoclast activity than HA-VPS surfaces. This suggests that trabecular surfaces provide a more favorable environment for bone ingrowth and long-term fixation. However, the clinical relevance of these findings requires further validation in patient studies.

Since early implant migration is a key predictor of aseptic loosening, **Chapters 3 and 4** focused on the use of RSA to assess the fixation of uncemented TKR. **Chapter 3** presented a meta-analysis of 96 RSA studies, analyzing migration patterns from 4,706 tibial components. The results confirmed that most implant migration occurs within the first six months after surgery, regardless of fixation method. However, migration patterns differed among cemented, uncemented non-screw-fixed, and uncemented screw-fixed components. Among uncemented implants, trabecular surfaces exhibited the lowest early migration, comparable to HA-coated implants but more stable than non-coated or porous-coated surfaces. Previously, one-year migration patterns were used to predict the long-term risk of aseptic loosening. However, this study suggested that six-month migration patterns could already provide sufficient predictive value. This led to the recommendation that fixation-specific migration thresholds should be established for a more accurate risk assessment. **Chapter 4** built upon these findings by correlating migration data from **Chapter 3** with revision rates from 157 clinical studies. By analyzing 186,974 tibial components, six-month and one-year fixation-specific migration thresholds were able to be defined. These thresholds enable more accurate risk assessment and serve as a critical tool for evaluating new TKR designs, allowing pre-market studies to predict long-term outcomes within six months, thereby ensuring a safer introduction of new implants.

Part II: Post-market surveillance and outcomes of uncemented TKR

While pre-market studies provide valuable insights into the early stability and fixation of uncemented TKR, long-term clinical evaluation is essential to confirm their effectiveness and durability in real-world practice. Post-market studies play a crucial role by collecting and analyzing data on functional outcomes, implant migration, and revision risks. This not only helps identify potential complications but also contributes to the continuous optimization of uncemented prostheses.

Post-market evaluations include observational cohort studies and registry analyses, which assess various clinical outcomes, such as patient-reported outcome measures (PROMs), the diagnostic accuracy of imaging tools for detecting aseptic loosening, and revision risks. Additionally, national implant registries offer valuable epidemiological insights by tracking trends in revision rates and identifying key factors influencing these outcomes. In this thesis, post-market evaluations are used to analyze the short-, mid-, and long-term outcomes of uncemented TKR.

In **Chapter 5**, the short-term functionality of a new uncemented TKR design was investigated. This study, based on preliminary data from an ongoing multicenter follow-up study, assessed clinical outcomes, complications, and revision rates in patients with a minimum follow-up of one year. The results showed significant improvements in knee function, pain relief, and activity level at six months and one year compared to preoperative levels. Furthermore, revision rates were low (1.9% after two years and 2.8% after three years), with only one case of aseptic loosening. The functional performance and early survival of this uncemented TKR were comparable to those of widely used cemented and uncemented implants. Although these findings are promising, it remains crucial to understand the long-term behavior of these implants. Therefore, **Chapter 6** continued a previously conducted randomized controlled RSA study to assess the five-year migration patterns and stability of this new uncemented TKR compared to its predecessor. The results demonstrated that both implants exhibited similar migration patterns, stabilizing after six months for the tibial component and after twelve months for the femoral component. However, the femoral component of the older prosthesis migrated more during the first three months. These findings suggested that the new design was not inferior to the previous implant. Additionally, implant analyses revealed that some components had an increased risk of aseptic loosening based on their individual migration patterns. These findings highlight the need for longer follow-up periods and the importance of fixation-specific migration thresholds (as defined in **Chapter 4**) to improve long-term risk predictions for uncemented TKR.

In **Chapter 7**, the diagnostic role of nuclear imaging, specifically bone scintigraphy with SPECT/CT, was investigated in patients presenting with symptoms suggestive of aseptic loosening. The study demonstrated that SPECT/CT had a high specificity (93.8%) for detecting aseptic loosening. This means that a positive scan was highly reliable, whereas a negative scan was less predictive. For this reason, the study suggested that inconclusive results should be interpreted as negative to reduce false-positive diagnoses and unnecessary revision surgeries. These findings support the use of SPECT/CT as an additional imaging tool for evaluating symptomatic uncemented TKR, particularly in patients with persistent knee pain and an elevated risk of aseptic loosening based on other diagnostic tests.

To gain a comprehensive understanding of the long-term performance of uncemented TKR, long-term outcomes were analyzed through observational cohort and registry studies. In **Chapter 8**, revision rates and functional outcomes

were assessed in 1,289 patients with the previously studied longer-in-use uncemented TKR (also examined in **Chapter 5**) with a follow-up of up to 15 years. The results showed that this uncemented TKR provides durable fixation and excellent functional outcomes, with an overall revision incidence of 4.0%, and 1.8% for aseptic loosening after 15 years. The study further demonstrated that previous knee surgeries had no significant impact on revision risk or functional outcomes after 15 years, suggesting that uncemented TKR is suitable for a wide range of patients.

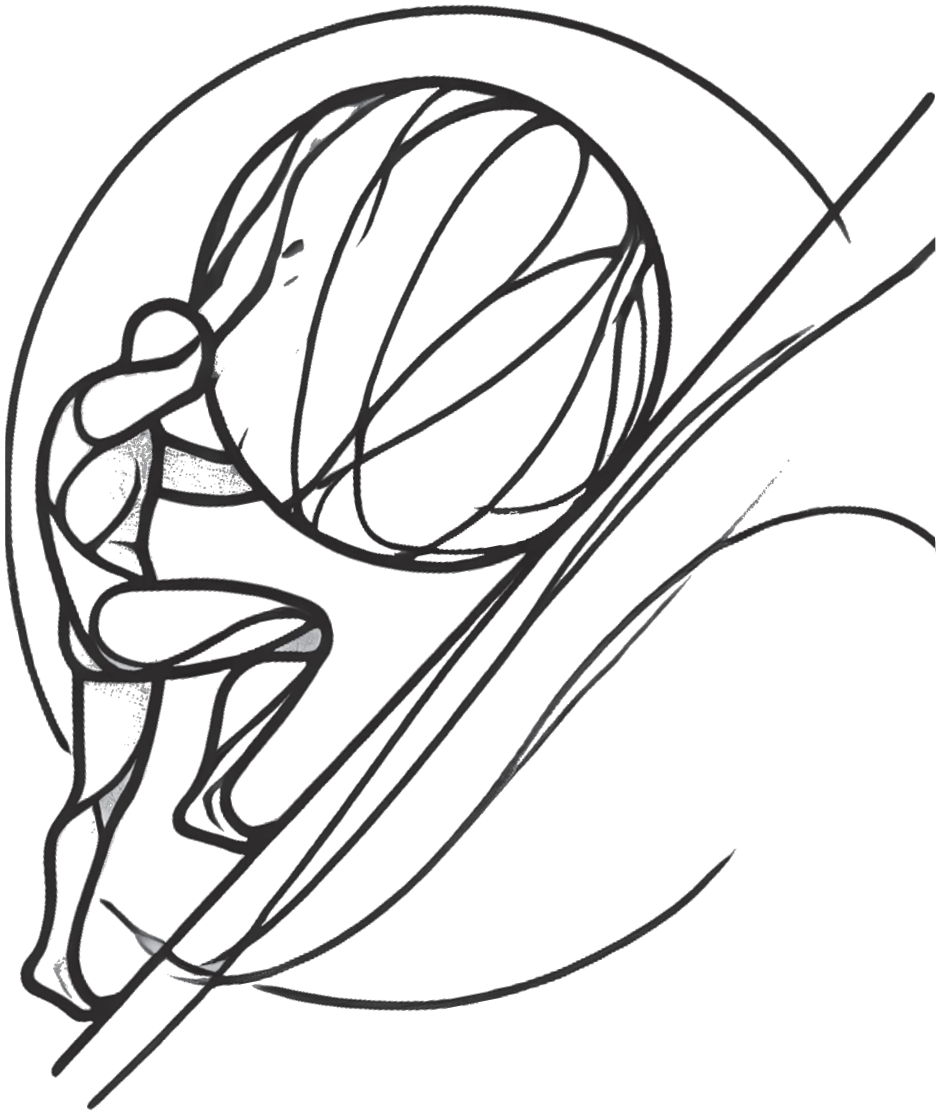
Finally, the association of prosthesis design on aseptic loosening in uncemented TKR was investigated in **Chapter 9 and 10** using data from the Dutch Arthroplasty Register (LROI). **Chapter 9** examined the impact of surface treatments on the risk of aseptic loosening. The study identified four main surface treatments currently used in the Netherlands, namely; Porous implants with hydroxyapatite (HA) coating, porous implants without coating, grit-blasted implants without coating, grit-blasted implants with titanium-nitride (TiN) coating. The results showed that porous implants with HA coating had the lowest revision incidence, whereas grit-blasted implants, with and without TiN coating, exhibited a significantly higher risk of loosening when used in uncemented TKR. In **Chapter 10**, the association of posterior-cruciate retaining versus sacrificing designs in uncemented TKR on the revision risk for aseptic loosening was investigated. The study found that cementless posterior cruciate ligament-sacrificing designs had a higher risk of aseptic loosening compared to cruciate-retaining designs. This increased risk was potentially caused by greater stress transfer to the components of the uncemented TKR.

The discussion in **Chapter 11** highlights the main findings and potential implications of this thesis, including:

- Uncemented TKR are on an innovative growth trajectory. Pre-market and post-market surveillance are essential to identify underperforming implants and optimize future innovations.
- The term “uncemented TKR” is overly broad due to the variety of designs and outcomes it encompasses. Future research and clinical practice should adopt more specific terminology based on the surface modifications employed.
- Variations among uncemented TKR systems are detectable in in-vitro studies. Future research should focus on translating these findings into clinical practice to better align experimental results with real-world applications.
- Refined migration thresholds for uncemented TKR offer a more accurate tool for pre-market assessments, enabling early detection of uncemented implants at risk for late-term aseptic loosening. The increasing adoption of CT-RSA could simplify the integration of mandatory RSA analyses into pre-market frameworks.

- Modern uncemented TKRs are an effective treatment for advanced knee osteoarthritis, with revision rates and functional outcomes that vary depending on insert constraints and surface modifications. Given the ongoing innovation process of uncemented TKR, further research is essential to evaluate their performance and ensure patient safety.
- BS-SPECT/CT improves the diagnosis of aseptic loosening in symptomatic uncemented TKR, regardless of the time since surgery, as long as inconclusive results are treated as negative. However, its utility is maximized when used in later diagnostic stages with higher pre-test probability. Future research should explore the potential of biomarkers to enhance pre-test probability and reduce unnecessary revision procedures.

This thesis provides new insights into the evaluation of uncemented TKR and contributes to the further development of guidelines for their safe and effective application in clinical practice.



APPENDICES

NEDERLANDSE SAMENVATTING

Artrose is een veelvoorkomende degeneratieve gewrichtsaandoening die progressieve schade aan kraakbeen en bot veroorzaakt. In gevorderde stadia kan een totale knieprothese (TKP) noodzakelijk zijn. Traditioneel wordt een TKP gefixeerd met cement, maar cementloze technieken worden wereldwijd steeds vaker toegepast, met name bij jongere en actievere patiënten. Waar cementfixatie directe stabiliteit biedt, steunt cementloze fixatie op botingroei, wat op lange-termijn een duurzamere oplossing kan zijn. Aangezien steeds meer patiënten op jongere leeftijd een TKP nodig hebben, kan de cementloze techniek een waardevolle optie zijn om de levensduur van de prothese te verlengen, revisieoperaties te beperken en daarmee de patiëntveiligheid te waarborgen.

Dit proefschrift onderzoekt de prestaties en duurzaamheid van moderne cementloze TKP, met aandacht voor het risico op aseptische loslating. Aseptische loslating is een complicatie waarbij de prothese loslaat van het bot, zonder dat er sprake is van een infectie. Het onderzoek bestaat uit een pre-market en een post-market evaluatie. De pre-market evaluatie richt zich op het identificeren van vroege signalen voor mogelijke risico's op revisies op de lange-termijn, zodat implantaten met een hoog risico op falen tijdig kunnen worden geïdentificeerd. De post-market evaluatie analyseert de prestaties van cementloze TKP in de klinische praktijk, waarbij functionele uitkomsten, migratiepatronen en revisierisico's worden geëvalueerd. Dit proces helpt bij het waarborgen van patiëntveiligheid en biedt waardevolle inzichten in factoren die een rol spelen in de lange-termijn fixatie en prestaties van cementloze TKP. Door deze gestructureerde aanpak draagt dit proefschrift bij aan een beter begrip van de klinische toepasbaarheid en kan het handvatten bieden voor verder gebruik, onderzoek en patiëntveiligheid rondom cementloze TKP.

Deel I: Pre-market evaluatie van cementloze TKP

Omdat botingroei de basis vormt voor de fixatie van cementloze TKP, is het cruciaal om dit proces bij nieuwe implantaten zo vroeg mogelijk te evalueren. Idealiter gebeurt dit bij zo min mogelijk patiënten, met minimale belasting en binnen een zo kort mogelijke tijd. Pre-market studies spelen hierin een essentiële rol, omdat ze helpen potentiële faalrisico's in een vroeg stadium te identificeren, nog voordat een implantaat breed wordt toegepast in de klinische praktijk. Experimentele laboratoriumstudies kunnen hierbij uitkomst bieden, doordat ze de biologische en mechanische eigenschappen van nieuwe cementloze implantaten kunnen testen en optimaliseren. Daarnaast is radiostereometrische analyse (RSA) een krachtig klinisch instrument om de vroege fixatie en stabiliteit van een TKP te beoordelen, met deelname van een klein aantal patiënten gedurende maximaal één tot twee jaar. RSA maakt het mogelijk om de microscopische migratie van implantaten te meten in de eerste maanden tot jaren na implantatie. Eerdere onderzoeken hebben

aangetoond dat vroege TKP-migratie een sterke voorspeller is voor aseptische loslating op de lange-termijn. Deze methoden maken het mogelijk om in een relatief korte periode betrouwbare voorspellingen te doen over de lange-termijn prestaties van implantaten, waardoor de introductie van implantaten met slechte uitkomsten kan worden beperkt.

In **Hoofdstuk 2** werd onderzocht hoe botcellen reageren op verschillende prothese-oppervlakken die worden gebruikt bij cementloze TKP. Er werd een vergelijking gemaakt tussen trabeculair titanium-aluminium-vanadium (Ti6Al4V) en hydroxyapatiet (HA)-gecoate vacuüm-plasmaspray (VPS)-Ti-oppervlakken, beide relatief nieuwe oppervlaktebehandelingen voor cementloze TKP. Humane osteoblasten (botvormende cellen) werden gedurende 29 dagen gekweekt op deze oppervlakken, waarbij metabole activiteit, differentiatie en botmineralisatie werden gemeten. Daarnaast werd onderzocht in hoeverre deze cellen osteoclasten (bot afbrekende cellen) activeren, wat kan leiden tot botafbraak. De resultaten toonden aan dat alle oppervlakken botmineralisatie induceerden, maar trabeculaire Ti6Al4V-oppervlakken een aanzienlijk hogere osteoblastactiviteit en lagere osteoclastactiviteit vertoonden in vergelijking met HA-VPS-oppervlakken. Dit suggereert dat trabeculaire oppervlakken een gunstigere omgeving creëren voor botingroei en botbehoud, en mogelijk bijdragen aan een betere fixatie en langere levensduur van cementloze TKP. De relevantie en klinische implicaties van deze bevindingen vereisen echter validatie in een patiëntgebonden setting.

Omdat vroegtijdige implantaatmigratie een belangrijke voorspeller is voor aseptische loslating, richtten **Hoofdstuk 3 en 4** zich op het gebruik van RSA als methode om de stabiliteit van cementloze TKP te beoordelen. In **Hoofdstuk 3** werd een meta-analyse uitgevoerd van 96 RSA-studies, waarin migratiepatronen van 4.706 tibia componenten werden geanalyseerd. De resultaten bevestigden dat de meeste migratie plaatsvond in de eerste zes maanden na implantatie, ongeacht de fixatiemethode. Echter, gecementeerde, cementloze implantaten zonder schroeffixatie en cementloze implantaten met schroeffixatie vertoonden verschillende migratiepatronen. Onder de cementloze, lieten implantaten met een trabeculair oppervlak de minste vroege migratie zien, vergelijkbaar met HA-gecoate implantaten, maar stabieler dan implantaten zonder coating of met poreuze oppervlakken. Voorheen werden migratiepatronen na één jaar gebruikt om het lange-termijn risico op aseptische loslating te voorspellen. Echter, op basis van deze studie kon worden gesuggereerd dat migratiepatronen na zes maanden al voldoende voorspellend zijn, en dat fixatie-specifieke migratiedrempelwaarden moeten worden opgesteld om een meer accurate risicoschatting te kunnen maken.

Hoofdstuk 4 bouwde voort op deze bevindingen door migratiegegevens uit **Hoofdstuk 3** te koppelen aan revisiepercentages voor aseptische loslating uit 157 klinische studies. Door gegevens van 186.974 tibia componenten te analyseren, konden fixatie-specifieke migratiedrempelwaarden worden gedefinieerd voor zowel zes maanden als één jaar na implantatie. Deze drempelwaarden maken een

nauwkeurigere risicoschatting mogelijk en vormen een belangrijk instrument voor de evaluatie van nieuwe TKP-ontwerpen. Door deze inzichten kunnen pre-market studies met een relatief klein aantal patiënten toch betrouwbare voorspellingen doen over de lange-termijn prestaties van cementloze TKP, binnen 6 maanden, wat bijdraagt aan een veilige introductie van nieuwe implantaten.

Deel 2: Post-market onderzoeken en uitkomsten van cementloze TKP.
Hoewel pre-market studies waardevolle inzichten bieden in de vroege stabiliteit en fixatie van cementloze TKP, is langdurige klinische evaluatie noodzakelijk om hun effectiviteit en duurzaamheid in de praktijk te bevestigen. Post-market studies spelen hierin een cruciale rol door het verzamelen en analyseren van gegevens over functionele uitkomsten, implantaatmigratie en revisierisico's. Dit helpt niet alleen bij het identificeren van mogelijke problemen, maar draagt ook bij aan de voortdurende optimalisatie van cementloze prothesen.

Post-market evaluaties bestaan uit observationele cohort of register studies, die verschillende uitkomsten kunnen analyseren, waaronder patiënt-gerapporteerde uitkomsten (PROMs), diagnostiek precisie van instrumenten om aseptische loslating aan te tonen, of revisie risico's. Daarnaast kunnen nationale implantaatregisters, waardevolle epidemiologische inzichten bieden door trends in revisiepercentages te volgen, en factoren aan te wijzen die een rol kunnen spelen in het behalen van deze uitkomsten. In dit proefschrift worden post-market evaluaties gebruikt om de uitkomsten van cementloze TKP te analyseren op korte-, midden- en lange-termijn.

In **Hoofdstuk 5** werd de korte-termijnfunctionaliteit van een nieuw cementloos TKP-ontwerp onderzocht. Deze studie, gebaseerd op voorlopige gegevens uit een lopende multicenter follow-upstudie, evalueerde klinische uitkomsten, complicaties en revisiepercentages bij patiënten met een minimale follow-up van één jaar. De resultaten toonden significante verbeteringen in kniefunctie, pijnverlichting en activiteitsniveau na zes maanden en één jaar, vergeleken met preoperatieve metingen. Bovendien waren de revisiepercentages laag (1,9% na twee jaar en 2,8% na drie jaar), met één geval van aseptische loslating. De functionele prestaties en vroege overleving van deze cementloze TKP waren vergelijkbaar met die van veelgebruikte gecementeerde en cementloze implantaten. Hoewel bemoedigend, blijft het cruciaal om te begrijpen hoe deze implantaten zich op de langere termijn gedragen. Daarom werd in **Hoofdstuk 6** een eerdere gerandomiseerde gecontroleerde RSA-studie vervolgd tot een vijfjarige follow-up, om de stabiliteit en migratiepatronen van deze nieuwe cementloze TKP te vergelijken met zijn voorganger. De resultaten toonden aan dat beide implantaten vergelijkbare migratiepatronen vertoonden, waarbij stabilisatie plaatsvond na zes maanden voor de tibia component en na twaalf maanden voor het femur component. Echter, bleek het femur component van de langer bestaande prothese meer te migreren gedurende de eerste 3 maanden. Dit suggereerde dat het nieuwe ontwerp niet inferieur was aan het bestaande implantaat. Verder bleek uit individuele implantaat

analysen dat enkele componenten een verhoogd risico hadden op aseptische loslating, op basis van hun migratie. Dit gegeven benadrukt de noodzaak van langere follow-upperioden en de waarde van fixatie-specifieke migratiedrempelwaarden (zoals gedefinieerd in **Hoofdstuk 4**) om betere voorspellingen te doen over de lange-termijn betrouwbaarheid van cementloze TKP.

In **Hoofdstuk 7** werd de diagnostische rol van nucleaire beeldvorming, namelijk botscintigrafie met SPECT/CT, onderzocht bij patiënten met klachten voor de detectie van aseptische loslating bij cementloze TKP. De studie toonde aan dat SPECT/CT een hoge specificiteit (93,8%) had bij het identificeren van aseptische loslating. Dit betekent dat een positieve scan betrouwbaar is, maar dat een negatieve scan minder voorspellend is. Om die reden werd gesuggereerd dat dat inconclusieve resultaten beter als negatief konden worden geïnterpreteerd om fout-positieve diagnoses en onnodige revisieoperaties te minimaliseren. Deze resultaten ondersteunen het gebruik van SPECT/CT als aanvullende beeldvorming in de diagnostische beoordeling van cementloze TKP, vooral bij patiënten met aanhoudende pijnklachten waarbij een verhoogd risico op aseptische loslating wordt vermoed door andere diagnostische testen.

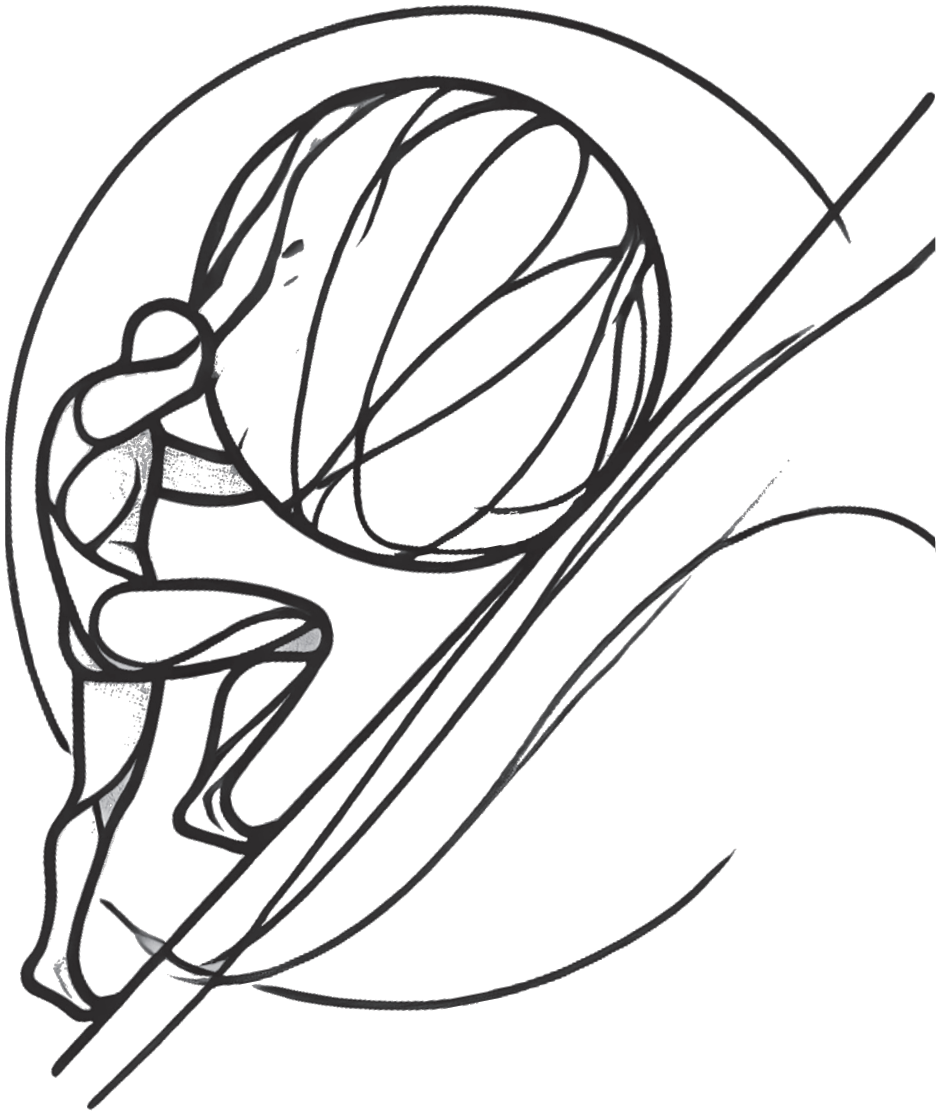
Voor een volledig inzicht in de duurzaamheid van cementloze TKP werden lange-termijn resultaten bestudeerd, doormiddel van observationele cohort en register studies. In Hoofdstuk 8 werd daarom de revisiepercentages en functionele uitkomsten van 1.289 patiënten met de langer-bestaande cementloze TKP (ook bestudeerd in **Hoofdstuk 5**) geanalyseerd met een follow-up van maximaal 15 jaar. De resultaten bevestigden dat cementloze TKP een duurzame fixatie en uitstekende functionele uitkomsten bieden, met een totale revisie-incidentie van 4,0% en slechts 1,8% specifiek voor aseptische loslating na 15 jaar. De studie liet zien dat eerdere knieoperaties geen invloed hadden op het revisierisico of functionele uitkomsten na 15 jaar, wat suggereert dat de cementloze TKP geschikt is voor een breed scala aan patiënten.

Tot slot werd de invloed van protheseontwerpen op aseptische loslating van cementloze TKP onderzocht, door gebruik te maken van data van het Nederlandse Register voor Orthopedische Interventies (LROI). **Hoofdstuk 9** liet hierbij zien dat oppervlaktebehandelingen van cementloze TKP een grote invloed hebben op het risico op loslating. De resultaten toonden aan dat er momenteel vier soorten oppervlaktebehandelingen gebruikt worden in Nederland, waarbij poreuze implantaten met HA-coating de laagste revisie-incidentie hadden, en grit-blasted implantaten een erg verhoogd risico op loslating vertoonden onder cementloze TKP. In **hoofdstuk 10** werd een vergelijking gemaakt tussen achterste kruisband-behoudende en opofferende cementloze implantaten. Ook deze factor bleek van invloed te zijn, waarbij kruisband-opofferende cementloze TKP een hoger risico op aseptische loslating lieten zien, wat mogelijk door een verhoogde bewegings-stressoverdracht naar de componenten veroorzaakt kan worden.

In **Hoofdstuk 11** worden de belangrijkste kernpunten en toekomstperspectieven van dit proefschrift besproken. Dit zijn:

- Cementloze TKP bevinden zich nog in een fase van innovatie, wat continue pre-market en post-market evaluatie vereist om onderpresterende implantaten te identificeren en toekomstige ontwerpen te optimaliseren.
- De term “cementloze TKP” omvat een brede variatie aan ontwerpen en klinische uitkomsten. Een meer gespecificeerde terminologie, gebaseerd op oppervlaktemodificaties, is wenselijk voor toekomstig onderzoek en klinische toepassingen.
- Verschillen tussen cementloze TKP-systemen kunnen al in in-vitro studies worden waargenomen. Toekomstig onderzoek zou zich kunnen richten op de relevantie van experimentele bevindingen voor de klinische praktijk.
- De verfijnde migratiedrempels voor cementloze TKP maken een nauwkeurigere pre-market risicobeoordeling mogelijk, met vroege detectie van implantaten met een verhoogd risico op aseptische loslating.
- Moderne cementloze TKP zijn een effectieve behandeling voor gevorderde knieartrose, maar revisierisico en functionele uitkomsten variëren in ieder geval op basis van insert-ontwerp en oppervlaktemodificaties.
- BS-SPECT/CT verbetert de diagnostiek van aseptische loslating bij symptomatische cementloze TKP, vooral in latere diagnostische stadia. Toekomstig onderzoek naar andere diagnostische tools kan helpen om de diagnostische nauwkeurigheid verder te verbeteren en onnodige revisies te verminderen.

Dit proefschrift biedt nieuwe inzichten in de evaluatie van cementloze TKP en draagt bij aan de verdere ontwikkeling van richtlijnen voor hun veilige en effectieve toepassing in de klinische praktijk.



APPENDICES

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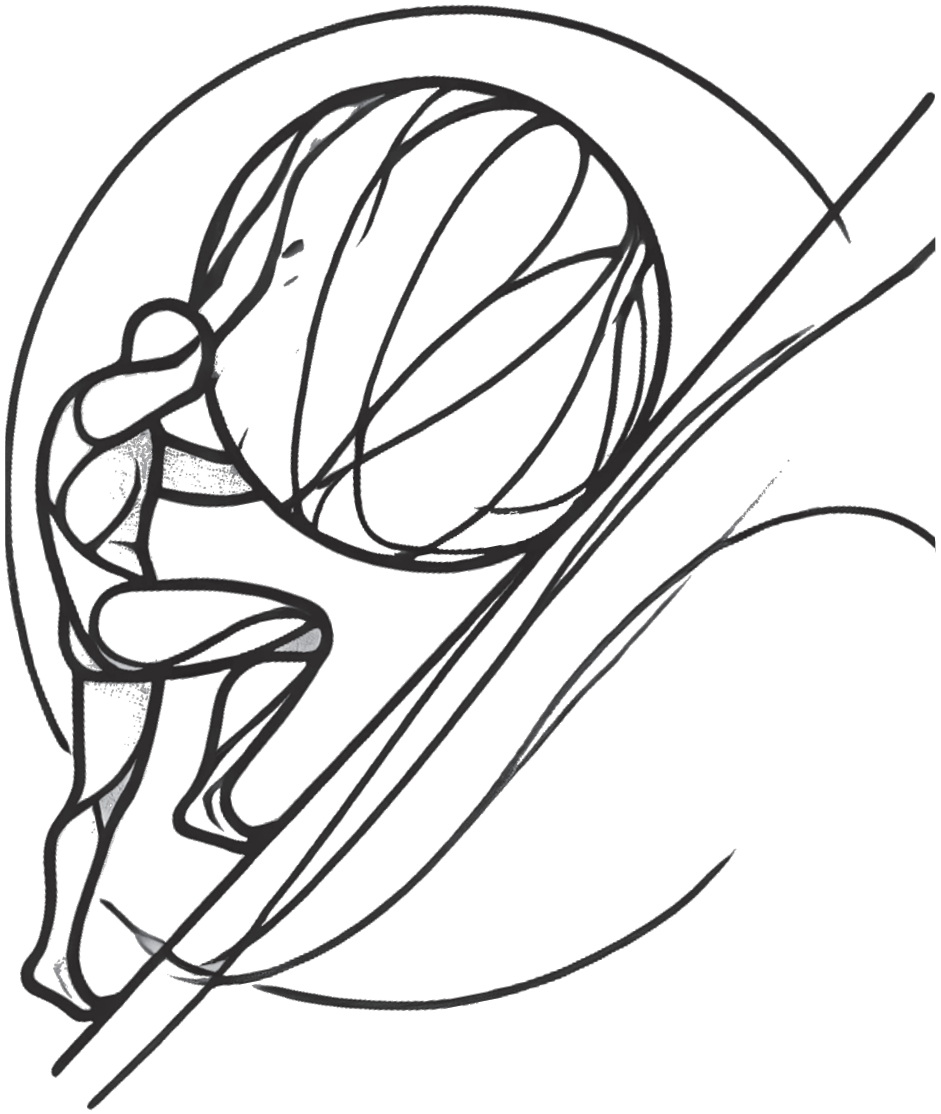

APPENDICES

LIST OF PUBLICATIONS

Publications of this thesis

1. **R. Puijk**, B. Zandieh-Doulabi, W.J.A.M Runderkamp, B.G.C.W. Pijls, J. Klein-Nulend, P.A. Nolte. Human Osteoblast Response to Uncemented Knee Implant Surface Structures and Osteoclast Formation in Vitro. Journal of Biomaterials Applications. 2025 May; 39: 1261-1272.
2. **R. Puijk**, R.H. Puijk, E.K Laende, M.J Dunbar, J.W.M Plevier, P.A Nolte, B.G.C.W Pijls. 6-month migration sufficient for evaluation of total knee replacements: a systematic review and meta-analysis. Acta Orthop. 2023 Nov 30:94:577-587.
3. **R. Puijk**, J. Singh, R.H. Puijk, J.W.M. Plevier, P.A. Nolte, B.G.C.W. Pijls. Evaluation and refinement of thresholds for early migration of total knee replacements as an estimator of late aseptic loosening: an updated systematic review of RSA and survival studies. Acta Orthopaedica. 2025 Jan; 96:1–10.
4. **R. Puijk**, I.N. Sierevelt, R. Rassir, J. Singh, M. Schager, ATKOS-group, P.A. Nolte. The uncemented ATTUNE Knee Outcome study (ATKOS); short-term clinical improvements in advanced knee osteoarthritis. Journal of Orthopaedic Reports. 2025 Mrt; 100647.
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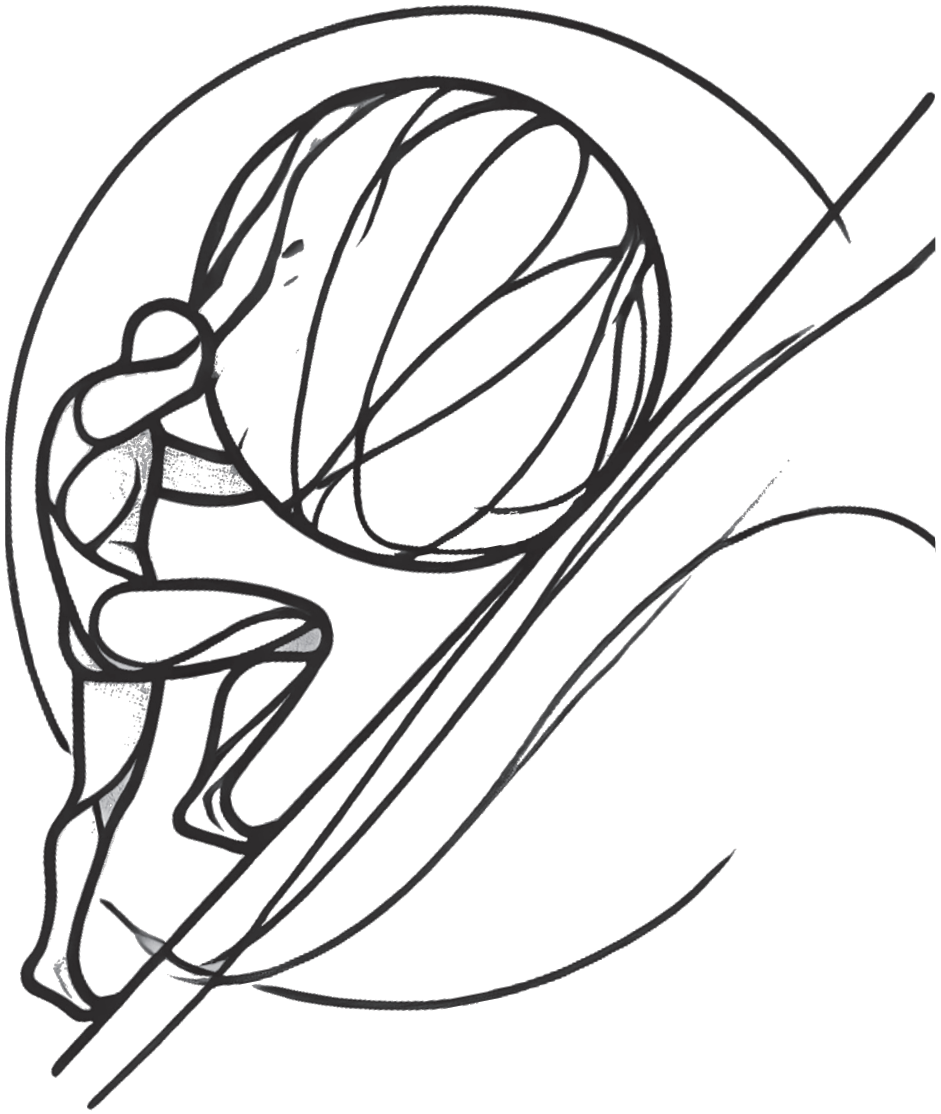
6. **R. Puijk***, P. Lubbe*, I.N. Sierevelt, A.E. Kristians, J. Boer, P.A. Nolte. The Diagnostic Characteristic and Reproducibility of Bone Scintigraphy Single-Photon Emission Computed Tomography/Computed Tomography for Diagnosing Aseptic Loosening of Uncemented Total Knee Arthroplasty. J Arthroplasty. 2024 Jul;39(7):1707-1713.e1.
   * Co-first authors
7. Rassir, R., **R. Puijk**., I.N. Sierevelt, M. Schager., D.A. Vergroesen., P. A. Nolte. Long-term survivorship and clinical results of the uncemented Low Contact Stress Rotating Platform knee system. J Arthroplasty. 2022 Oct;37(10):2041-2048.
8. **R. Puijk***, R. Rassir*, I.N. Sierevelt, A. Spekenbrink-Spooren, R.G.H.H. Nelissen, P.A. Nolte. Association Between Surface Modifications for Biologic Fixation and Aseptic Loosening of Uncemented Total Knee Arthroplasties. J Arthroplasty. 2023 Jun 8: S0883-5403(23)006344.
   * Co-first authors
9. **R. Puijk**, B.G.C.W. Pijls, I.N. Sierevelt, A. Spekenbrink-Spooren, P.A. Nolte. Increased risk of aseptic loosening for posterior stabilized compared to posterior cruciate-retaining uncemented Total Knee Replacements; a Dutch Arthroplasty Registry study. Acta Orthop. 2023 Dec 13:94:600-606.

Other publications

1. **R. Puijk**, R. Rassir, JKG Louwerens, IN Sierevelt, T de Jong, PA Nolte. Evaluation of the 'Spaarne soft tissue procedure' as a treatment for recurrent patellar dislocations: a four-in-one technique. J Exp Orthop. 2021 Apr 20;8(1):31.
2. **R. Puijk**, R. Rassir, L.M. Kok, I.N. Sierevelt, P.A. Nolte. Common Peroneal Nerve Palsy after TKA in valgus deformities; a Systematic Review. J Exp Orthop. 2022 Jan 20;9(1):12.
3. **R. Puijk**, R. Rassir, L.M. Kok, I.N. Sierevelt, P.A. Nolte. No common peroneal nerve palsies found after a peroneal nerve release prior to TKA in fixed valgus deformities (a retrospective cohort study). Knee Surg Sports Traumatol Arthrosc. 2022 Dec;30(12):4010-4014.
4. **Puijk R**, Rassir R, Sierevelt IN, Vergroesen DA, de Jong T, Nolte PA. Eighteen-Year Outcome of an Uncemented "Meniscal Bearing", Cruciate-Retaining Total Knee System. J Arthroplasty. 2022 Aug;37(8):1586-1593.
5. **Puijk R**, Rassir R, LW Kaufmann LW, P.A Nolte. A Pseudoaneurysm of the Inferior Lateral Geniculate Artery Following Total Knee Arthroplasty. Arthroplast Today. 2022 Apr 26; 15:120-124.
6. J.H. Hinloopen, **R. Puijk**, P.A. Nolte, J.W. Schoones, R. de Ridder, B.G. Pijls. The efficacy and safety of patient-specific instrumentation in primary total knee replacement: a systematic review and meta-analysis. Expert Rev Med Devices. 2023 Mar;20(3):245-252.
7. R.J.M. Vossen, **R. Puijk**, I.N. Sierevelt, A. Van Noort. Diagnostic Acromioclavicular Joint Infiltration Prior to Distal Clavicle Resection for Acromioclavicular Osteoarthritis: A Retrospective Study. Clin Shoulder Elb. 2024 Jan 15;27(1):45–51.



APPENDICES

PhD PORTFOLIO

PhD student:	Raymond Puijk
PhD promotor	Prof. dr. P. A. Nolte
PhD co-promotor	Dr. B. G. C. W. Pijls
PhD period	Jul 2021- Mrt 2025

1. PhD Training

Courses	Year	ECTS*
e-BROK	2021	1.0
Research Integrity for PhD	2022	2.0
Practical Biostatistics - blended e-learning	2022	1.4
HarvardX PH559x: Causal Diagrams (e-learning)	2022	1.0
Training European Clinical Trial Regulation "Expert"	2022	3.0
Clinical epidemiology: Observational epidemiology	2022	0.6
Clinical epidemiology: Systematic reviews	2022	0.7
Clinical epidemiology: Evaluation of medical tests	2022	0.7
Project Management (Team Based Learning)	2022	0.6
Talents in PhD	2022	0.2
Scientific writing and presenting in English	2023	3.0
Searching for a systematic review	2023	0.9
Dentistry for non-dentists	2023	1.0

Oral presentations	Event	Year	ECTS*
Association Between Surface Modifications for Biologic Fixation and Aseptic Loosening of Uncemented Total Knee Arthroplasties.	"Week van de wetenschap" - Spaarne gasthuis	2022	0.5
6-month migration sufficient for evaluation of the total knee replacement: a systematic review and meta-analysis.	iRSA meeting – Nijmegen, the Netherlands	2023	0.5
No common peroneal nerve palsies found after a peroneal nerve release prior to TKA in fixed valgus deformities (a retrospective cohort study)	EFORT congress - Vienna, Austria	2023	0.5

Poster presentations	Event	Year	ECTS*
No common peroneal nerve palsies found after a peroneal nerve release prior to TKA in fixed valgus deformities (a retrospective cohort study)	European Knee society - Germany	2022	0.5
Association Between Surface Modifications for Biologic Fixation and Aseptic Loosening of Uncemented Total Knee Arthroplasties.	ISAR congress – Canada	2023	0.5
Association Between Surface Modifications for Biologic Fixation and Aseptic Loosening of Uncemented Total Knee Arthroplasties.	EFORT congress - Austria	2023	0.5

Attending (inter)national conferences	Year	ECTS*
Nederlandse Orthopaedische Vereniging congress	2022	0.5
European Knee Society (EKS)	2022	1.0
iRSA meeting conference	2023	1.0
International society of Arthroplasty Registries (ISAR)	2023	1.0
European Federation of National Associations of Orthopaedics and Traumatology	2023	1.0

Guidance and supervision by supervisors	Year	ECTS*
Daily guidance and supervision	2021-2024	6.0

Other scientific activities	Year	ECTS*
Member of "Association for Young Orthopedic & Sports Medicine Netherlands" (VEJOS)	2022	1.0

* Workload was calculated in ECTS (European Credit Transfer System), with 1 ECTS equal to 28 study hours

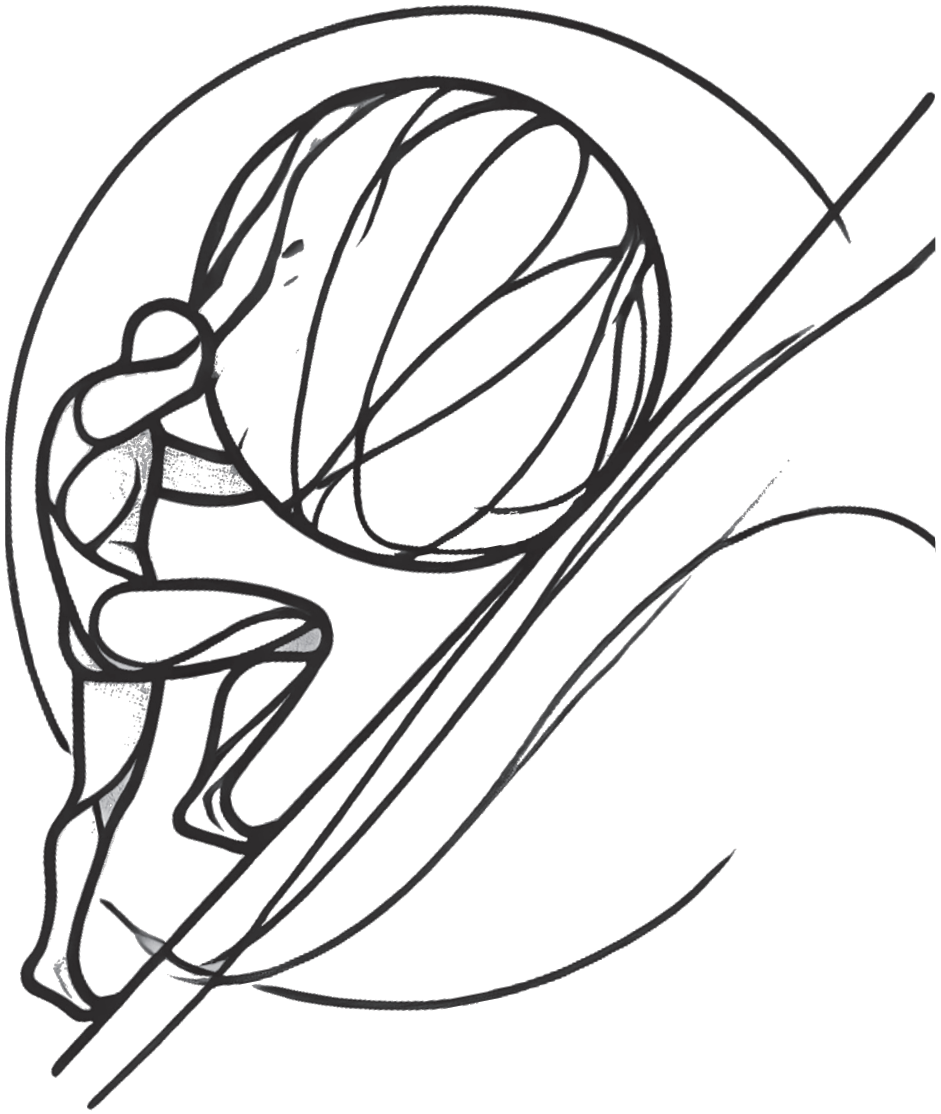
2. Teaching

Mentoring	Year	ECTS*
Mentoring a master student with their master scientific thesis	2023	1.0
Mentoring a master student with their master scientific thesis and publication	2023	1.0

3. Parameters of Esteem

Awards	Event	Year
Edward Valstar award, representing the best research group who established international collaboration on implant migration or related issues. "6-month migration sufficient for evaluation of the total knee replacement: a systematic review and meta-analysis."	iRSA meeting – Nijmegen, the Netherlands	2023
Awarded for best poster presentation: "Association Between Surface Modifications for Biologic Fixation and Aseptic Loosening of Uncemented Total Knee Arthroplasties."	ISAR congress –Canada	2023
Awarded for best poster presentation: "Association Between Surface Modifications for Biologic Fixation and Aseptic Loosening of Uncemented Total Knee Arthroplasties."	EFORT congress - Austria	2023

* Workload was calculated in ECTS (European Credit Transfer System), with 1 ECTS equal to 28 study hours



APPENDICES

ACKNOWLEDGEMENTS – DANKWOORD

Working on this thesis often felt like rolling Sisyphus' boulder: fulfilling, yet demanding, heavy, and seemingly endless. But unlike his fate, mine was not eternal. Time passed, progress was made, and the task eventually came to an end. While much of this work required solitary focus, it was far from a lonely endeavor. Along the way, many people offered their guidance, inspiration, and support, and for that, I am deeply grateful.

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Beste **Peter**, Ik herinner me nog goed hoe ik als student jouw kantoor binnenstapte, enthousiast om meer over onderzoek te leren. Jouw grenzeloze enthousiasme, nieuwsgierigheid en passie voor zowel orthopedie als onderzoek waren een enorme inspiratiebron voor mij. Je was een fantastische promotor. Geen enkel idee was te gek, en je wist vaak andere specialismen en instellingen te betrekken om het werk naar een hoger niveau te tillen. Bedankt voor het vertrouwen, de vrijheid in mijn keuzes en jouw vriendschap. Dankzij jou kon ik niet alleen mijn proefschrift, maar ook mezelf als persoon verder ontwikkelen.

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To my **co-authors** not mentioned earlier, thank you for your time, effort, and valuable guidance. Your collaboration and teamwork truly helped bring each paper to a higher level. I'm grateful for the opportunity to have worked alongside you.

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Dear **OK-Corral Crew**, the freedom to be ourselves, the inspiration to embrace who we are, the fun, the love, and the perfect weirdness, this is what makes our Burningman camp so special. Grateful to be part of this wild, and beautiful family. I'm OK, You're OK.

Beste **vrienden die er tijdens deze periode voor me waren,** ik wil jullie bedanken voor alle mooie momenten die we samen hebben gedeeld. De afleiding die jullie boden was soms precies wat ik nodig had om weer op te laden. Ik ben ontzettend dankbaar dat ik zulke lieve en betrokken vrienden om me heen heb, zowel de oude vertrouwde als de nieuwe uit Amsterdam. Jullie hebben deze periode voor mij zoveel mooier gemaakt.

Dear friends of **OnlyButtLove**, if there's one group that truly understands what this journey has been like, it's all of you. We started out as a group of young medical students, but over time, with significant others joining in, we've let this group grow into our own little community; a close, warm, and diverse circle of amazing people who support each other every step of the way. I'm proud of what we share and excited for who we will become together.

Beste **Mark & Max,** Onze vriendschap gaat terug tot de beginjaren van de middelbare school, en daar ben ik ontzettend trots op. Ondanks onze verschillende interesses en het feit dat we elkaar tegenwoordig wat minder vaak zien, voel ik nog steeds de diepe band en verbondenheid die we samen hebben opgebouwd. Jullie hebben mij door alle fases heen zien gaan, en het betekent me veel dat jullie er nog steeds voor me zijn. Op naar nog veel meer bijzondere momenten samen!

Dear **Family Hansen**, I want to express my deepest gratitude for all the warmth and support you've given me. I know this period hasn't always been easy, especially with Carley living so far away across the big pond. I'm truly proud to be part of your family and really cherish all our gatherings. Backyard get-togethers, cozy Christmas celebrations, and visits have been such highlights every year. Thank you for your unwavering kindness, love, and support.

Lieve **Mam**, ik waardeer hoe we weer dichter bij elkaar zijn gekomen. We lijken op elkaar, meer dan ik vroeger doorhad, en wat ik nu des te meer koester. Je hebt me laten zien hoe belangrijk het is om naar mijn gevoel te luisteren, mezelf te zijn en

plezier te maken. Ik ben dankbaar dat we samen mogen blijven groeien en nieuwe herinneringen mogen maken. Ik hou van je.

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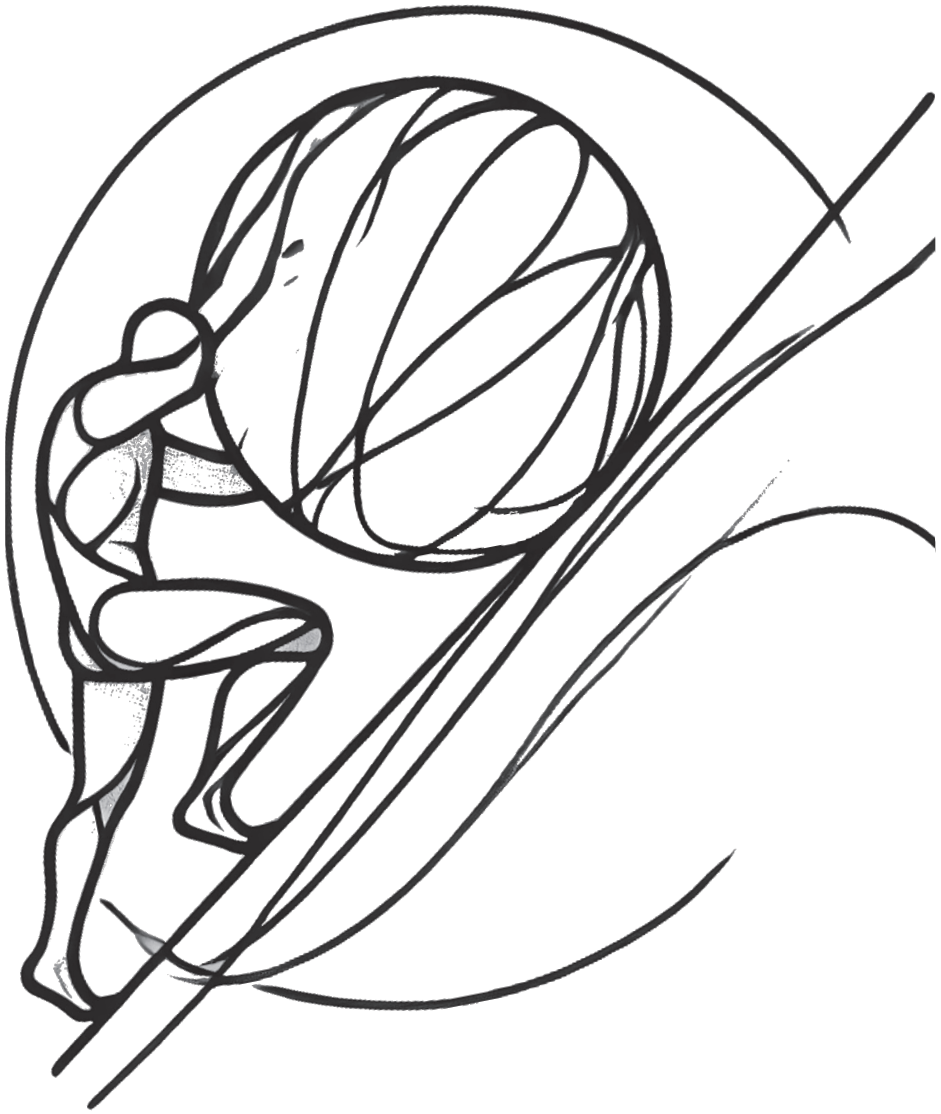
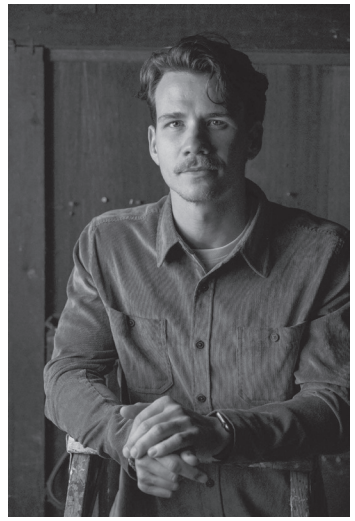


APPENDICES

ABOUT THE AUTHOR



Raymond Puijk was born on October 12, 1994, in Houten, the Netherlands, where he grew up with an older sister and a younger brother. He began his secondary education at College de Heemlanden in Houten, starting at the Pre-vocational Secondary Education (VMBO) level. However, his strong interest in biology motivated him to advance through Higher General Secondary Education (HAVO) and Pre-university Education (VWO), eventually leading him to study medicine at the Vrije University of Amsterdam.

During his bachelor's and master's medical studies, Raymond lived in Amsterdam with two other medical students who were close friends from his hometown. After completing his bachelor's degree, he spent nine months backpacking through Southeast Asia. During this journey, he met his future wife, Carley Rae Hansen, from California, USA.

As part of his master's program, Raymond completed internships in various specialties, including gynecology and pediatrics at the Sint Maarten Medical Center in the Caribbean, as well as family medicine and surgery in the Netherlands. His fascination with the musculoskeletal system sparked his initial interest in orthopedic surgery. During his research internship, amid the COVID-19 pandemic, Raymond lived with Carley in California for three months and worked remotely. This period allowed him to write his first systematic review and fueled his passion for research. Afterwards, Professor Dr. Peter A. Nolte invited him to pursue a PhD in orthopedic surgery, focusing on uncemented implants.

Raymond completed his PhD efficiently, driven by his passion for answering research questions and collaborating with co-authors. To maintain clinical practice during his PhD, he worked evening and night shifts in elderly healthcare. Toward the end of his PhD, he worked as a resident not in training (ANIOS) in orthopedic surgery at Spaarne Gasthuis Hospital. Although rewarding, he realized that the limited patient interaction and its fit with his personal life did not align with his goals and aspirations. While finishing his PhD, Raymond explored family medicine, which provided fulfillment through treating a wide range of patients, meaningful patient interactions, and hands-on procedures. This experience confirmed his decision to pursue a career as a general practitioner. In March 2025, he began his General Practitioner residency in Amsterdam.

Raymond currently lives in Amsterdam with his wife, Carley Hansen. Outside of work, he enjoys staying active through fitness and yoga, traveling, and spending quality time with family and friends.

My deepest fear,
My deepest fear is not that I am inadequate.
My deepest fear is that I am powerful beyond measure.
It is my light, not my darkness that most frightens me.
I ask myself 'Who am I to be brilliant, gorgeous, talented, fabulous?'
Actually, who am I not to be?
Me playing small does not serve the world.
There is nothing enlightened about shrinking so that other people won't feel insecure around me.
I am meant to shine, as children do.
I was born to make manifest the glory of what is within me.
It's not just in me; it's in everyone.
And as I let my own light shine,
I unconsciously give other people permission to do the same.
As I am liberated from my own fear,
My presence automatically liberates others.

— Marianne Williamson—

Amsterdam Movement Sciences

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Amsterdam Movement Sciences conducts scientific research to optimize physical performance in health and disease based on a fundamental understanding of human movement in order to contribute to the fulfillment of a meaningful life.