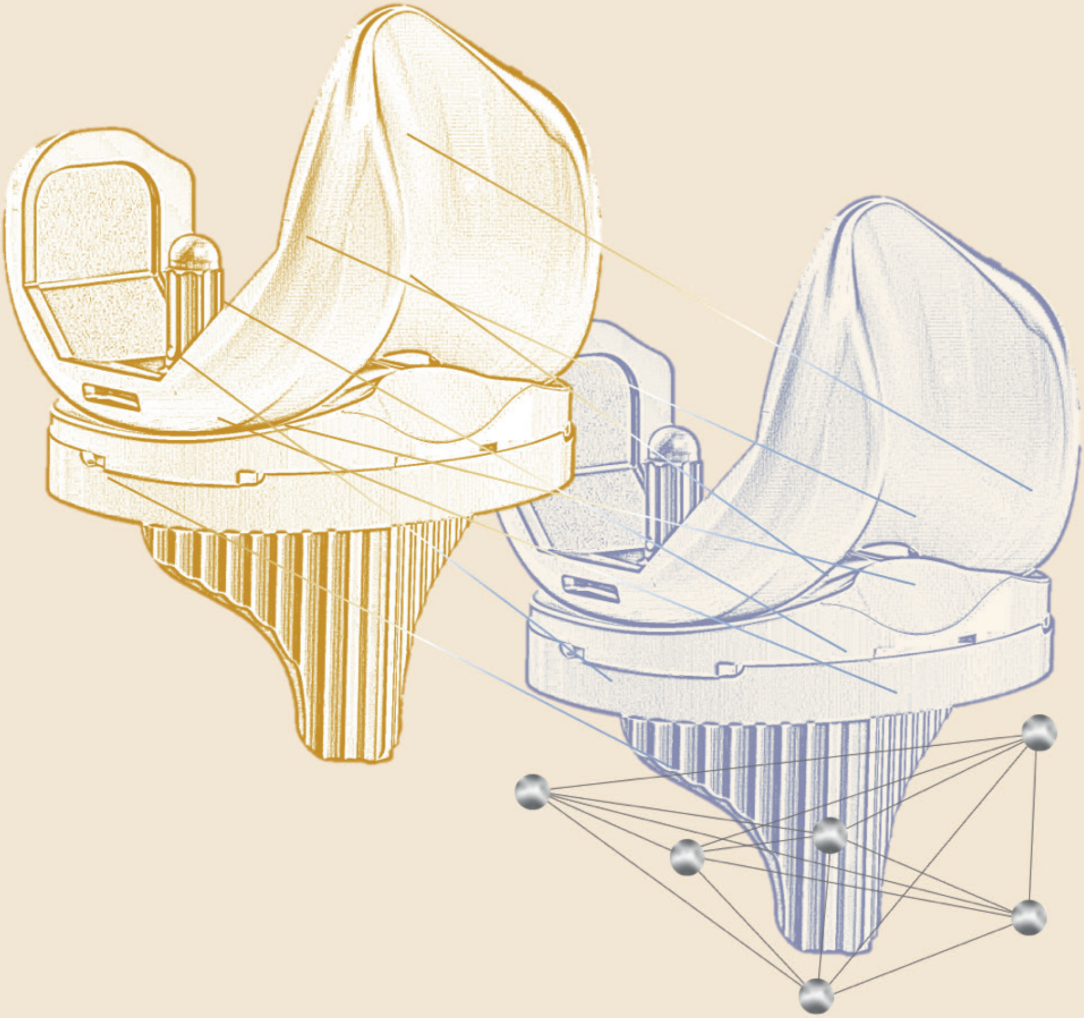
Safety of orthopedic implants: implant migration analysis a must

Hasan, S.



Chapter I

General introduction

Chapter I General introduction and outline

Total knee arthroplasty

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

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

Implant design and surgical technique – principles and improvements

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

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

#1	No more bone should be removed as needed for a primary arthrodesis
#2	Loosening should be avoided. This could be minimized by the following principles
	a. The femoral and tibial component should be incompletely constrained to prevent load transfer from the prosthesis to the bone during movement b. Minimalization of friction between both components; Metal-on-polyethylene is therefore preferred over metal-on-metal c. Hyperextension limit should be progressive and not abrupt d. Components should have the largest possible contact area with the bone to spread the load; large bone surfaces on which the prosthesis can sit and the use of cement
#3	The rate of wear debris production should be limited
#4	The produced wear debris should be as harmless as possible
#5	Compact implants with minimal dead spaces should be used to reduce the probability of
#6	The consequence of an infection should be minimized (short stems, avoid intramedullar
#7	A standard procedure protocol should be available
#8	The implant should be able to function from 5° extension to 90° flexion; function above 120
#9	Some freedom in rotation and ad- or abduction should be possible
#10	Soft tissue should resist excessive movements without breaking the bone-prosthesis
#11	It is unwise to depend on the mechanical functioning of the cruciate ligaments for
#12	The prosthesis should permit the removal of intercondylar tissues and should restore
#13	The tibio-femoral replacement should be able to accommodate the patella itself or a
#14	The cost should be minimized by making the smallest practicable number of sizes and versions. This objective is last on the list but should not be forgotten entirely

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

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

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

Although, in the Australian Orthopaedic Association National Joint Replacement Registry a higher survival rate of HXLPE TKA was found for specific TKA designs.[57]

Apart from improvements in material composition, uncemented fixation methods have improved substantially. Ever since the early years of TKA, one of the main reasons for TKA failure was implant loosening.[11, 12, 36, 58] Therefore, fixation methods of implants have been discussed for several decades. The most common fixation method is cementing of the components using polymethyl methacrylate (PMMA).[11,]

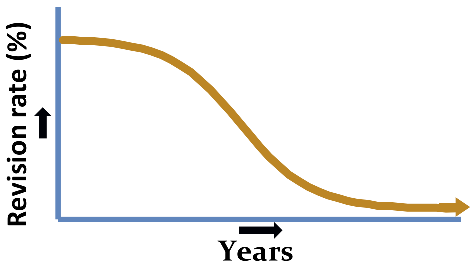
[12, 58] As a consequence, more complex reconstructions may be needed requiring the use of bone grafts or larger implants for revision surgery.[59] Other disadvantages are the production of cement debris, the slow degradation of cement with long-term loosening as consequence and the time needed for cement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

Evaluation of novel implant designs

Most 50-year-old implant design principles are still valid nowadays. However, minimizing the number of implant designs and sizes is one of the neglected principles while using multiple different implants could be associated with an increased risk of revision [#14, Table I.I].[24,68] TKAs could differ in several characteristics. First, every manufacturer has his own TKA design or several different TKA designs. Second, the fixation method could either be cemented (i.e., cemented femoral and tibial component), hybrid (i.e., cemented femoral and uncemented tibial component or vice versa), or uncemented (i.e., uncemented femoral and tibial component). Further, the constraint could differ between designs (e.g., CR or PS). Also, the tibial component could be MBT or APT. Last, MBT components could have fixed- or mobile-bearing inserts. Every different combination of these characteristics could theoretically influence revision rates and functional outcomes even though the differences between these implant characteristics could be small. A study comparing cemented PS designs to cemented CR designs using data from the Dutch Arthroplasty Registry, for example, found that cemented PS designs were 1.5 times more likely to be revised compared to cemented CR designs.[69]

One could question whether further improvements of TKA designs are needed as revision rates have dropped considerably since the introduction of TKA and are relatively low (i.e., ten-year revision rate 4-6%).[11, 12, 58] While initially a novel design had the potential to significantly reduce the revision rate, the chance of reducing revision rates even further is limited. The evolution of the performance of TKAs in terms of revision rates could be illustrated by a reversed S-curve: an initial slow reduction of revision rate followed by a period of fast reduction [Figure I.I]. After this period, the curve flattens, and further improvements have minimal or even a detrimental effect on the revision rate [Figure I.I].[62] However, a reason to continue innovation of TKA designs could be to increase patient satisfaction. Whereas the revision rates have dropped significantly over the past decades, patient satisfaction trails behind as approximately one in five patient is not satisfied following TKA.[22] Many efforts have been put into understanding the reason for this relatively high rate of unsatisfied patients, but unfortunately, the reasons remain unclear. Hence, novel implant designs have been developed aiming to increase patient satisfaction by, for example,

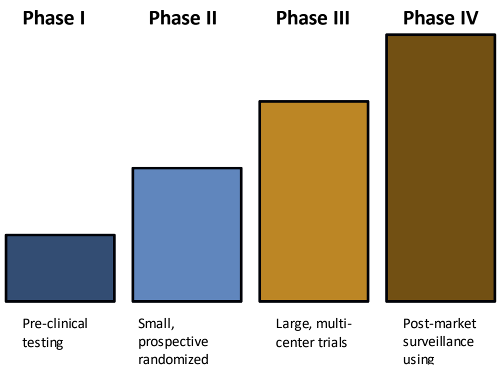
Figure I.I A reversed S-curve illustrating revision rates (y-axis) over time (x-axis).



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

These novel TKA designs are introduced on a regular basis and often without (sufficient) evidence of lower revision rates or better clinical outcomes compared to their predecessor.[70] An evidence-based approach is needed when introducing novel TKA designs to expose a minimal number of patients to a novel treatment to ensure patient safety. Therefore, several authors suggested the introduction of novel implants in a phased fashion.[6, 71-76] A phased introduction includes several phases which are considered necessary to safely implement novel TKA designs without compromising patient safety [Figure I.II].[6, 71-76] The first phase includes pre-clinical testing which is followed by a phase that should include prospective, randomized controlled clinical trials. These clinical trials preferably include a limited number of patients to minimalize the risks associated with a novel TKA design. Results from phase II could be used to assess whether it is beneficial to continue to phase III. In the next clinical phase (i.e., phase III), large, multicentre studies are conducted to assess whether the novel design improves patient outcomes in a more generic population before this novel implant is widely implemented in clinical practice and is then continued to be monitored for any unintended consequences (as part of post-marketing surveillance). A phased introduction is needed to prevent implant failures which have previously been shown to result in severe patient morbidity.[77, 78]

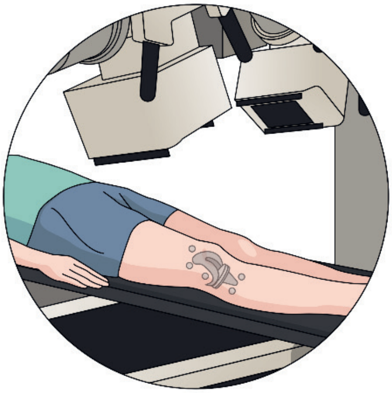
Figure I.II A phased introduction including four steps: 1) pre-clinical testing, 2) small, prospective randomized clinical trials, 3) large, multicentre trials, and 4) post-market surveillance using registries[6]



The role of Radiostereometric Analysis in evaluation of implant designs

Radiostereometric analysis (RSA) is suggested to be implemented as an early detection tool in the first clinical step of a phased implant introduction.[6, 71, 73, 74, 76, 79] The reason for this is that RSA could provide accurate objective results on the performance of novel implants after one or two years. These studies frequently compare well-performing design with a novel design in a randomised trial and it requires only a limited number of approximately 30 patients per treatment arm. RSA uses two 2D radiographs taken in a stereo fashion to reconstruct a 3D image to estimate migration of implants [Figure I.III].[79] RSA calculates the position of the implant by measuring the position of radiopaque tantalum markers, which are inserted in the bone surrounding the implant during surgery, relative to predefined markers positioned on a calibration box.[79] These radiopaque tantalum beads have a varying diameter (0.5-, 0.8-, or 1.0-mm).[79-83] During follow-up visits, the position of the implant relative to the tantalum markers in the bone is again calculated and any change in relative implant position over time is considered to be migration.[79] The position of the implant can be determined by attaching tantalum beads to the implant before surgery, by inserting tantalum beads in the polyethylene (marker-based RSA) or by using a model of the implant (model-based RSA), which has the advantage that it does not require markers in or attached to the implant.[84] The change of implant position is called migration and expressed as translation along or rotation about the transverse, longitudinal, and sagittal axis. Maximum total point motion (MTPM) is used as a summary measure and is an estimate of the length of the translational vector of the point with the greatest

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



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

Outline of this thesis

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

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

Although RSA is an objective method to assess clinical outcome following TKA, a disadvantage of RSA as a diagnostic tool for implant loosening is that it can only be used if RSA markers are inserted during surgery. A few other non-operative markers to identify loosened implants have been described. Having pre-emptive markers of implant loosening could potentially open strategies to not only prevent more severe implant loosening, but also has the potential to monitor disease progression. **Chapter III** aimed to identify the most frequently studied markers which can discriminate between loosened and stable THAs and TKAs, and therefore have the most promising results in differentiating between these groups.

Any change in implant design or surgical technique could potentially have a major impact on revision rates or functional outcomes after TKA. Therefore, **Chapter IV**, **Chapter V**, and **Chapter VI** assessed the effect of two different design changes on migration in a randomized controlled trial using RSA. First, a MBT and APT TKA were compared up to two years in **Chapter IV**. Second, a cemented TKA was compared to a 3D-printed, uncemented TKA in terms of migration in **Chapter V**. Although two-year migration is a commonly used follow-up duration for RSA studies, longer follow-up is needed to determine whether implants showing continuous migration in the second postoperative year continue to migrate or stabilize. The aim of **Chapter VI** was therefore to compare migration up to five years of metal-backed (MBT) and all-polyethylene tibial (APT) components in total knee arthroplasty using a cruciate-stabilising (CS) design in one study and a posterior-stabilising (PS) design in another study. In addition, migration profiles of continuously migrating implants in the second postoperative year were evaluated.

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

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

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