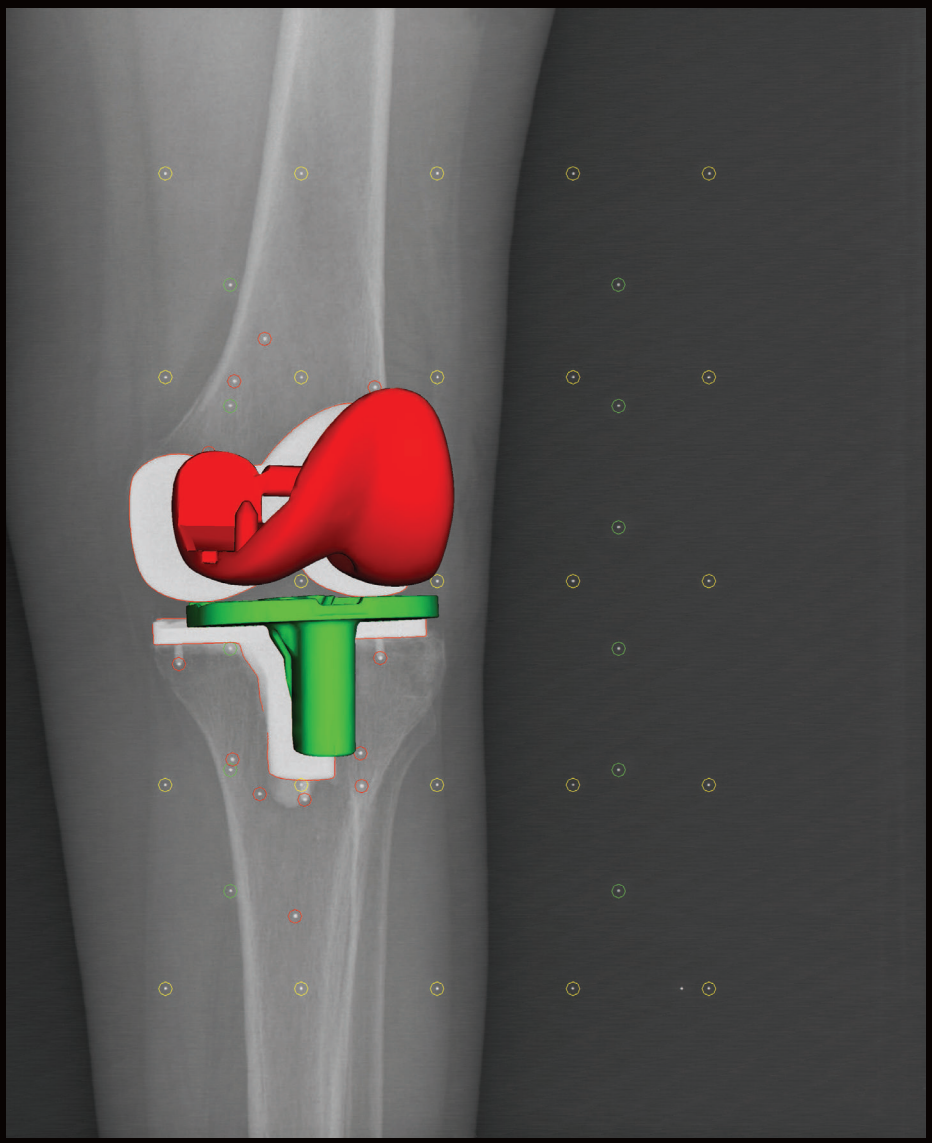
Evidence based introduction of orthopaedic implants

RSA, implant quality and patient safety



Bart Pijls

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	Prof. dr. F.R. Rosendaal

"Cui dono lepidum novum libellum ..." *(Catullus; Carmen I)*

... parentibus meis

... aan mijn ouders

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Chapter 1

General Introduction

One in four people will develop symptomatic hip osteoarthritis during their lifetime and one in two symptomatic knee osteoarthritis.[1,2] End stage osteoarthritis can be successfully treated surgically with Total Knee Arthroplasty and Total Hip Arthroplasty. Pain reduction as well as the vast improvement in health related quality-of-life have resulted in a widespread application of these procedures.[3] Worldwide several hundred thousands Total Knee Prostheses (TKP) and Total hip Prostheses (THP) are implanted each year and this number is expected to increase by a factor two to six within the next decades.[4,5]

Although TKP and THP are generally very successful[6], on average 5 to 10 percent of the patients require revision surgery 10 years after their TKP or THP.[7-10] Revision surgery is an extensive procedure with more blood loss than primary TKP and THP and increased risk of a re-revision.[9] Additionally, increased age, hypovolemia during surgery and administration of large amounts of fluids intra- and post-operatively are risk factors for multiorgan failure in these patients.[11] Considering this perioperatieve morbidity and mortality rates, it is paramount to monitor the safety and quality of TKP and THP before they are freely implanted in patients in order to prevent not only unneeded harm to patients but also increased costs to society (i.e. increase of the future revision burden).

At present, most new TKP and THP designs are approved and distributed on the market without extensive safety and effectiveness testing via the 510(k) pathway in the US and regulation via notified bodies in Europe (Directive 93/42/EEC) .[12,13] In 2007 the European Union reclassified total hip, total knee and total shoulder prostheses to "class III medical devices" (Directive 2005/50/EC). Class III medical devices are high risk devices that require pre-marketing testing in patients.[14] Nevertheless, the 510(k) pathway in the US and the reviews of device reliability via notified bodies in Europe have created an environment in which unsafe TKP and THP can reach the market.[15] This lack of adequate regulation has lead to the widespread use of potentially unsafe TKP and THP with failure rates 2 to 10 times the standard of national joint registries (5% failures at 10 years follow-up), see Figure 1.1.[13,16-22] Furthermore problems with fixation methods such as Boneloc cement have resulted in revision rates that were 14 times higher than normal.[23]

To ensure quality of orthopaedic implants and thus patient safety a phased evidence-based introduction, as is common for pharmaceuticals, is needed to regulate the introduction of new TKP and THP to the market.[24-26] This should include systematic assessment and early detection of the major cause of TKP and THP failure, which is aseptic loosening necessitating revision surgery.[7-10] Loosening starts with sub-millimeter (mm) migration of the prosthesis components relative to the bone and gradually evolves into gross movement accompanied by clinical symptoms such as pain.[27,28] It may take as long as 10 years before the final stages of gross loosening are visible on conventional X-rays.[27,28] However, it is possible to detect this loosening process as early

as one to two year postoperatively with Roentgen Stereophotogrammetric Analysis (RSA), an X-ray technique.[27-29]

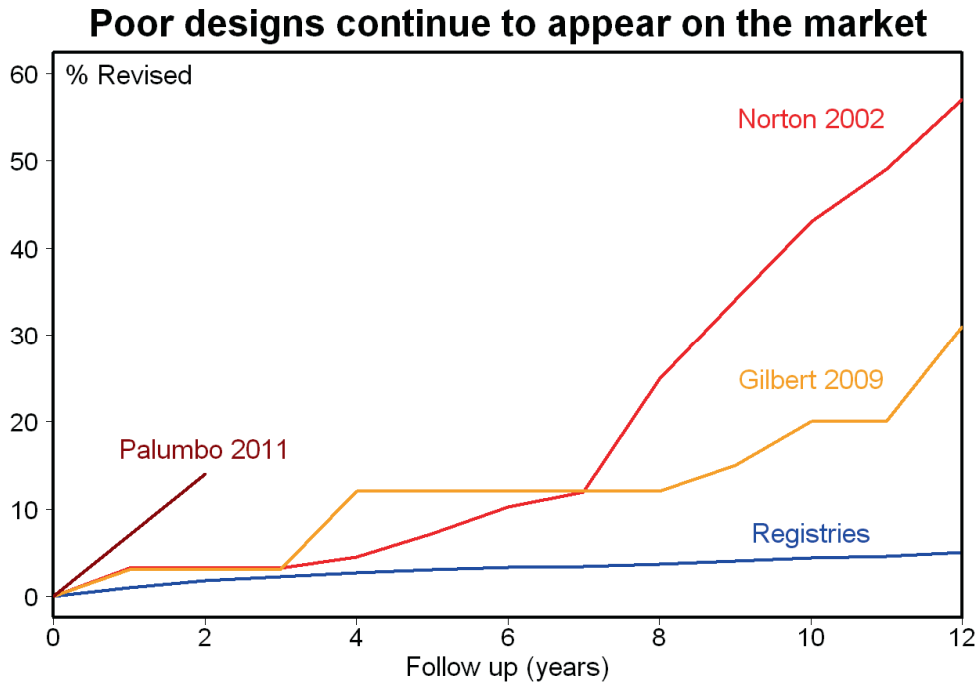

Figure 1.1: Graph showing the revision rate of TKP in percentage for registries (national average) and three unsafe TKP.

RSA

The history of roentgen stereophotogrammetry (RSA) dates back to the time when X-rays were discovered, when Davidson and Hedley determined the 3-D position of a pin that was radiographed on the same radiograph by two separate x-ray sources.[30] In 1972 Selvik, a Swedish mathematician and anatomist, developed a roentgen stereophotogrammetry system, which he later called roentgen stereophotogrammetric analysis (RSA).[29] Modern RSA systems are based on this RSA system from Selvik.[31] At the same time Kees Spoor, a biomechanical engineer developed RSA at the anatomy department (section Biomechanics) at the Leiden University.[32]

RSA is a highly accurate stereo X-ray technique for assessing three-dimensional (3-D) movement between two rigid bodies, i.e. migration of prostheses relative to the bone.[29]

The accuracy for measuring prosthetic translations (along the x,y,z axes) is between 0.2 and 0.3 mm and for rotations (along the x,y,z axes) between 0.2 and 1.2 degrees.[33-38] Compared to

conventional radiographs, which have an accuracy between 5 and 12 mm for translations, the accuracy of RSA is 10-20 fold better.[39]

In order to measure the migration markers are needed on the prostheses and in the bone. These markers have to be visible on radiographs. Furthermore they need to be both chemically and biologically inert. For these reasons they are made of tantalum (a metal with atomic number 73).[40,41] The bone markers are inserted into the bone during surgery. The prostheses markers are attached to the prosthesis by the manufacturer. This is referred to as marker-based RSA. However, marking prostheses creates problems with the planning and execution of the study: increased cost of implants, prolonged start-up period and over projection of markers by the implant itself.[42] Furthermore marking the prosthesis may jeopardize its strength and the markers could also act as local stress raisers in the bone cement resulting in cement cracks, which could lead to loosening. In order to overcome these problems caused by prosthesis markers, a method was developed that does not require any markers on the prostheses: model-based RSA (MB-RSA).[42,43] MB-RSA uses CAD models or models from reversed engineering instead of markers on the prosthesis. These 3-D surface models are "matched" on the radiographs by minimizing the difference between the virtual projection of the model with the actual projection of the prosthesis as is appears in a radiograph.[42,43]

The RSA set-up consists of two synchronized X-ray tubes, angled 20 degrees to the vertical and positioned approximately 1.5 meters above the X-ray sensor, see Figure 1.2. Generally, the first RSA radiograph is made direct post-operatively, because it serves as a baseline reference for the migration measurements.

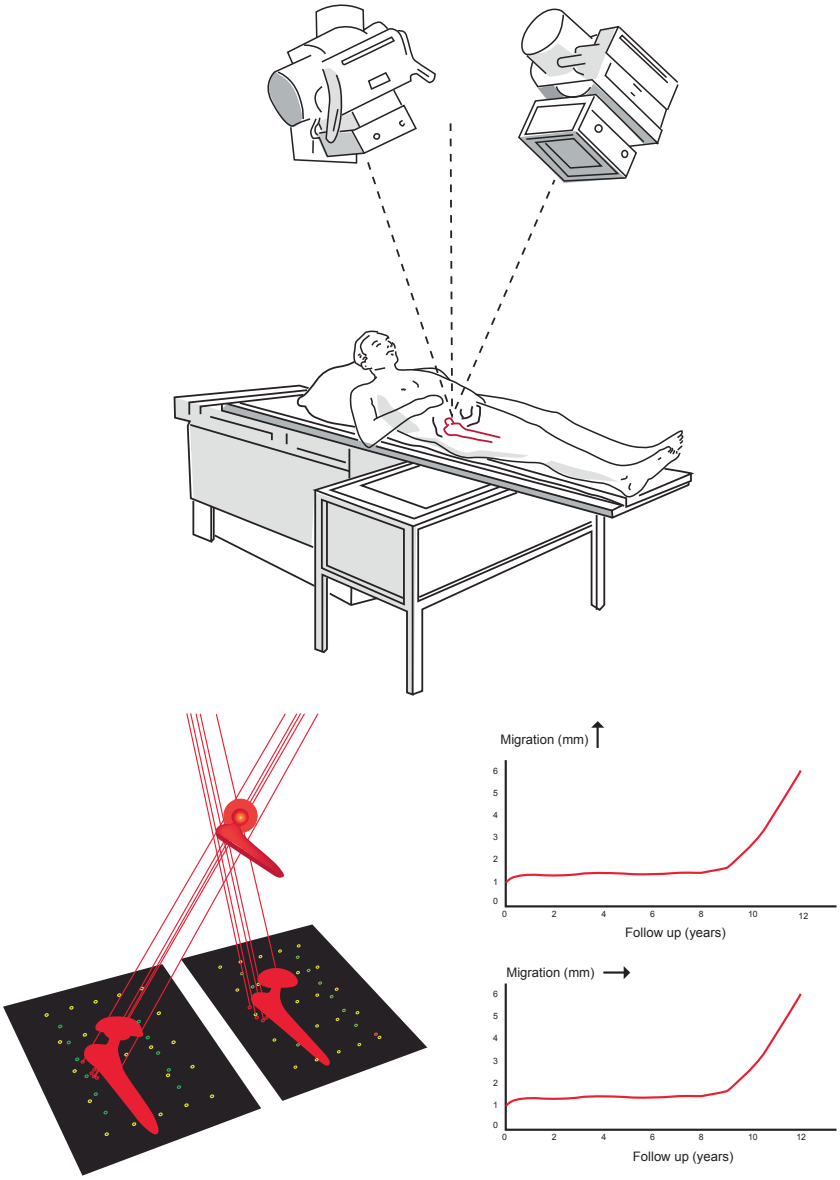

Figure 1.2 (designed by Bin Zhang): Top image: schematic drawing of the RSA set-up including patient position, table, calibration and the rontgen foci. The radiographic film/detector (not shown) are positioned under the calibration box. At the lower surface of the calibration box fiducial markers are attached and at the upper surface control markers are attached. These markers are positioned with a computer controlled device and the position of these markers is known within a few micrometers allowing an in vivo accuracy of the entire system of 0.2mm for translations and 0.5 degrees for rotations. **Lower left image:** (model based) RSA analysis with fiducial markers (yellow), control markers (green), bone markers (red) and prosthesis visisble on the left and right rontgen image. **Lower right image**: final 3-D migration results presented in graphs for the x and y-axis.

Early migration and late revision for aseptic loosening

The relation between short-term RSA results and future loosening of TKP and THP has been described in detail by Grewal[44], Ryd[27], Kärrholm[28], Nieuwenhuijse[45] and Hauptfleisch[22]. Grewal et al. studied three types of TKP and found that increased migration of the tibial component at 1 year was associated with increased revision rates for aseptic loosening at 5 years.[44] Ryd et al. studied 158 tibial components in TKA with a maximum follow-up of 10 years. Fifteen implants were revised for mechanical loosening. After one year follow-up, these implants had a significantly larger migration rate than the non-revised implants but were asymptomatic at that time.[27]

Kärrholm et al. found the same correlation in a study of 84 hip stems. After a period of five to eight years, 62 stems were still in situ while nine had been revised. The revised components exhibited significantly higher migration after two year.[28] Nieuwenhuijse et al. demonstrated the predictive value of RSA for future aseptic loosening in a study of 41 Exeter cups.[45] Hauptfleisch et al. confirmed the high revision rate of the Charnley Elite femoral stem.[22] This was predicted in their previous RSA study in which the Charnley Elite stem showed more rapid posterior head migration in the 1st year and the 2nd year than the Exeter stem.[22,46]

Although very promising, the evidence for the relation between early migration and late failure of TKP and THP by aseptic loosening, is limited to the TKP and THP used in the small number of studies mentioned above.[22,27,28,44] To ensure wide applicability of migration results further studies are needed that reflect the diversity in TKP and THP designs and fixation methods.

Aim of this thesis

The aim of this thesis is to evaluate the clinical value of migration measured with RSA for future aseptic loosening of new total knee (TKP) and total hip prostheses (THP) in the context of a phased introduction and as part of post-marketing surveillance.

Chapter 2 explores the proof of concept that early identification of potentially unsafe TKP and THP with RSA results in lower overall revision rates in the National Joint Registers.

Chapter 3 is a systematic review on the prediction of early migration of one type of TKP, based on the results of a the previous RSA trial at our institution and whether the results are applicable to the same TKP at different institutions (i.e. do the RSA results of one institution apply to other institutions).

Chapter 4 evaluates the effect of three types of fixation (uncoated, hydroxyapatite coated and cemented) on the long term migration of tibial components.

Chapter 5 compares the long term migration of tibial components between mobile bearing TKP and fixed bearing TKP and measures the wear underneath the mobile bearing in vivo.

Chapter 6 reports on the development of a quality assessment checklist for articles, the AQUILA checklists for reporting quality, methodological quality and generalizability for case series and cohorts in total hip and total knee arthroplasty. These checklists are used in chapters 7 and 8.

Chapter 7 is a systematic review on the association between early migration and late aseptic revision for the tibial component in TKP.

Chapter 8 is a systematic review on the association between early migration and late aseptic revision for the acetabular component in THP.

Chapter 9 elaborates on the methodological considerations of chapter 7 and 8 and also provides a worked example of the analyses of chapter 7 and 8.

Finally, a summary of the results and conclusions and a general discussion are presented in **chapter 10**.

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Chapter 2

RSA and Registries:

The Quest for Phased Introduction of New Implants

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J Bone Joint Surg Am. 2011 Dec 21;93 Suppl 3:62-5

Abstract

Although the overall survival of knee and hip prostheses at ten years averages 90%, recent problems with several hip and knee prostheses have illustrated that the orthopaedic community, industry, and regulators can still further improve patient safety. Given the early predictive properties of roentgen stereophotogrammetric analysis (RSA) and the meticulous follow-up of national joint registries, these two methods are ideal tools for such a phased clinical introduction. In this paper, we elaborate on the predictive power of RSA within a two-year follow-up after arthroplasty and its relationship to national joint registries. The association between RSA prosthesis-migration data and registry data is evaluated.

The five-year rate of revision of RSA-tested total knee replacements was compared with that of non-RSA-tested total knee replacements. Data were extracted from the published results of the national joint registries of Sweden, Australia, and New Zealand.

There was a 22% to 35% reduction in the number of revisions of RSA-tested total knee replacements as compared with non-RSA-tested total knee replacements in the national joint registries. Assuming that the total cost of total knee arthroplasty is $37,000 in the United States, a 22% to 35% reduction in the number of revisions (currently close to 55,000 annually) could lead to an estimated annual savings of over $400 million to the health-care system.

The phased clinical introduction of new prostheses with two-year RSA results as a qualitative tool could lead to better patient care and could reduce the costs associated with revision total knee arthroplasty. Follow-up in registries is necessary to substantiate these results and to improve post-market surveillance.

Introduction

The clinical introduction of new prosthetic designs by the orthopaedic industry has been compared with the introduction of new clothing designs by the fashion industry[1,2]. New prostheses with fashionable design features, such as a matte instead of a polished surface on the Exeter hip stem (Exeter, Exeter, United Kingdom), have been launched to the market without extensive clinical testing. Under the promise of theoretically superior clinical performance, such prostheses were chosen over very satisfactory standard prostheses with outstanding long-term implant survival records[3,4].

In 1991, the Capital hip (3M Health Care Ltd, Londonborough, United Kingdom) was introduced in the United Kingdom as a low-cost total hip replacement. Within six years, almost 5000 patients in ninety-five different centers were managed with a Capital hip. With a failure rate of 20% at five years, the use of this implant turned out to be disastrous[2,5].

However, such disasters do not stop at implant design features. Another disaster was the introduction of Boneloc cement (Polymers Reconstructive, Farum, Denmark) in the early 1990s. The cement was designed to have a lower curing temperature and a decreased release of toxic monomers. Theoretically, this would lead to a decrease in the incidence of aseptic loosening of prostheses. However, quite the opposite happened: the incidence of loosening of hip prostheses that were fixed with Boneloc cement was up to fourteen times higher in comparison with conventional cement[6]. After the first signs of clinical failure emerged, a small-scale randomized clinical roentgen stereophotogrammetric analysis (RSA) study involving fourteen patients who were managed with Boneloc cement and fifteen patients who were managed with Palacos cement was initiated[7]. Within one-half year, the migration of both the femoral and acetabular components was substantially increased in the patients managed with Boneloc cement. Furthermore, no tendency toward stabilization was seen and progressive continuous implant migration was present.

One would expect that these disasters could not happen today. However, in general, the introduction of new prostheses is still done in almost the same way as it was twenty years ago. Although Malchau proposed a much more controlled introduction of new prostheses in 1995[8], recent problems with the ProxiLock hip (Stratec Medical, Oberdorf, Switzerland)[9], ASR hip (DePuy, Warsaw, Indiana)[10,11], Accord knee (DePuy International Ltd., Leeds, United Kingdom)[12], and St. Leger knee (Covision, Carlton in Lindrick, United Kingdom)[13] are examples of situations in which the orthopaedic community, industry, and regulators can further improve patient safety.

There has been an upgrade in regulatory classification of hip, knee, and shoulder joint replacement prostheses by the European Union (EU) (2007) and by the United States Food and

Drug Administration (US FDA). This was important but, as hip and knee prostheses generally have a long survival, a difference between a ten-year survival of 95% and one of 80% will be detected only after years of follow-up involving a considerable number of patients[14]. Early detection might expose far fewer patients within a period of one or two years.

Most orthopaedic surgeons and decision-makers with a clinical background know and understand the concept of preclinical tests, randomized clinical studies, and registries. But what is the concept of RSA, and why can it play an important role in the phased introduction of new prostheses or related developments?

RSA is a highly accurate stereoradiographic technique for assessing the three-dimensional migration of prostheses. The accuracy of RSA for the measurement of prosthetic translations is between 0.2 and 0.3 mm, and the accuracy for the measurement of rotations is between 0.2° and 1.2°. The accuracy of RSA is ten to twenty times better than that of conventional radiographs. RSA provides highly detailed insight into the migration behavior of prostheses in the short term (i.e., one to two years) and with relatively small patient cohorts (i.e., thirty to forty patients)[15].

As the turnover of new prostheses is high, such a fast measurement technique would be beneficial. But the question is: are the early migration measurements indicative of future loosening?

Association of RSA Migration Results and Registry Data

It is no coincidence that several research groups that have initiated or are highly active in national registries of joint replacement prostheses are also involved in clinical RSA studies as both methods prove invaluable in different stages of the quality control of prostheses. For instance, clinical RSA originated in Sweden, which was also one of the first countries with a national joint registry. Sweden has the lowest national revision rates in the world for both total knee arthroplasty and total hip arthroplasty. The performance of RSA studies with follow-up in a national joint registry has proved to be highly successful.

Evidence supporting the assumption that early migration is indicative of late failure due to aseptic loosening is increasing. The relationship between short-term RSA results and future loosening of prostheses was described in detail by Ryd et al.[16] and Kärrholm et al.[17]. Ryd et al. studied 158 tibial components that were used for total knee arthroplasty and were followed for a maximum of ten years[16]. Fifteen implants were revised because of mechanical loosening. After six months of follow-up, these implants had a significantly larger migration rate than the nonrevised implants but were asymptomatic at that time. Kärrholm et al. found the same correlation in a study of eighty-four hip stems[17]. After a period of five to eight years, eight stems had been revised. The revised components exhibited significantly higher migration after six months as demonstrated with RSA.

In 1998, Nelissen et al. demonstrated in a randomized controlled trial that the uncoated, uncemented Interax Total Knee (Stryker-Howmedica, Rutherford, New Jersey) migrated excessively[18]. Therefore, this total knee replacement was considered to be at risk for a high rate of failure due to aseptic loosening. Recently, this prediction was confirmed in a systematic review, which demonstrates that the revision rate for the uncoated Interax total knee replacement was more than three times higher than that for the cemented Interax total knee replacement, underlining the early predictive value of RSA[19].

In a clinical RSA study of the ProxiLock hip stem (Zimmer, Warsaw, Indiana), six of forty-one stems showed nonstabilizing migration of up to 4.7 mm of translation and 12.2° of retroversion[9]. Early migration is associated with an increased risk of possible future loosening and revision, and therefore the use of this prosthesis was stopped and the manufacturer discontinued its production.

These observations on the clinical effect of RSA echo through several of the national joint registries. When an RSA study has been performed for a particular total knee replacement, there has been a 22% to 35% reduction in the number of revisions compared with that after total knee arthroplasty without RSA testing, as shown by data from the registries of Sweden, Australia, and New Zealand (Fig. 1)[20-22]. This phenomenon can be at least partially explained by the fact that RSA allows early identification of implants with poor performance. Once identified, such high-risk implants may be taken off the market in an early stage, preventing widespread introduction and large numbers of subsequent revisions.

Thus, the RSA-tested total knee replacements that are recorded in the registries represent a selection of the total knee replacements. They have low expected revision rates for aseptic loosening due to good early RSA results. Concomitantly, the use of RSA-tested total knee replacements with excessive early migration is discontinued early on and, as such, these prostheses will not be recorded in the registries. At the same time, this selection process is amplified by the transparent nature of the registries: poor hospital performance and subsequent low hospital ranking due to usage of inferiorly performing prostheses can be avoided by usage of prostheses with either excellent long-term results in registries or by usage of prostheses introduced after good RSA results.

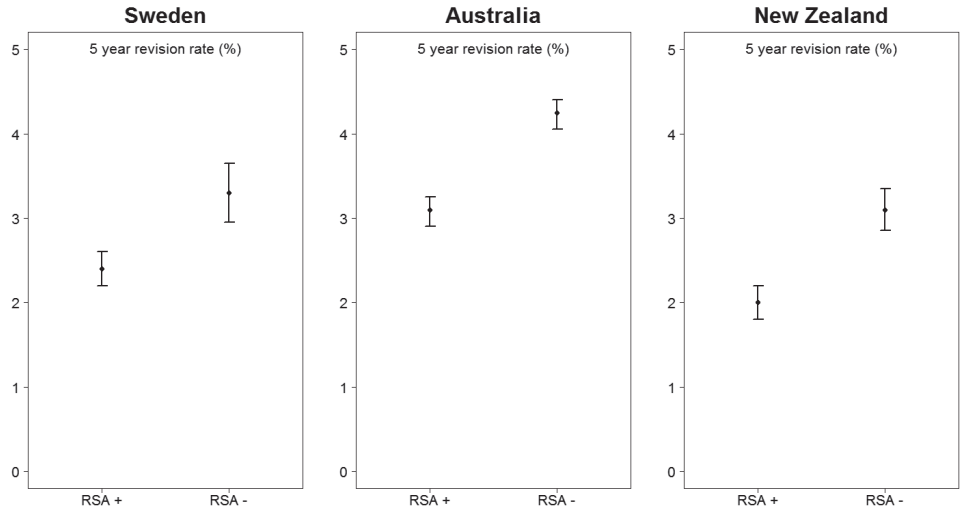

Figure 2.1 Revision rates for the national joint registries of Sweden, Australia, and New Zealand for RSA-tested total knee replacement (RSA +) compared with non-RSA-tested total knee replacement (RSA –), expressed in mean five-year revision rates with 95% confidence intervals. The revision rate for RSA-tested total knee replacement is significantly lower in all registries.

Cost-Effectiveness of RSA

The 22% to 35% reduction in the number of revision total knee arthroplasties associated with the use of with RSA can translate into considerable annual savings. While we did not perform any formal cost-effectiveness analyses, even modest reductions in revision arthroplasties can lead to substantial cost savings. For example, assuming that the total cost of revision total knee arthroplasty in the US is $37,000[23], a 22% to 35% reduction in the number of revisions (currently approximately 55,000 for total knee arthroplasty[24]) could lead to an estimated savings of over $400 million for the US health-care system. These savings could be even more substantial if RSA is used for each new total knee replacement prior to marketing. Future work will clarify the percent reduction in revision that can be attributed to RSA alone, but there is good evidence that the reduction is substantial. With these crude estimates of reduction in revision, such impressive savings will outweigh any concerns that RSA studies may be too expensive to conduct, even without taking into account the ethical issue of exposing patients to new, and as such potentially inferior, designs without optimal testing[25,26].

Standardization of RSA

Mandatory RSA studies require that the results of different RSA studies can be compared. Therefore, an international RSA group published RSA standardization guidelines in *Acta Orthopaedica* in 2005[27] and a larger consortium with RSA experts from all over the world is now establishing an actual ISO (International Organization for Standardization) standard for RSA. This draft of the standard is labeled Committee Draft and is currently being reviewed by all member countries. The standard is expected to be finalized in 2012. In addition, an international RSA network is being established currently. This network is intended to be a platform for improving the quality of clinical RSA research by sharing knowledge between research groups with different levels of RSA expertise and RSA-related developments.

The Era of Phased Introduction of New Prostheses

As outlined above, the potential of using RSA as a method of early (premarketing) assessment of implant performance is substantial. This potential is currently being recognized by various regulatory organs on different levels. The NICE (National Institute for Health and Clinical Excellence) guidelines of 2000 (United Kingdom) require adequate long-term clinical data for hip prostheses and indicate that RSA is a promising technique that may be an alternative for long-term follow-up studies[28]. However, additional proof of its predictive value for future loosening is demanded. The Dutch Orthopaedic Association has adopted in its new guidelines for hip prostheses—published in the beginning of 2011[29]—that any new hip prosthesis that is being considered for (commercial) introduction to the Dutch market has to pass a phased introduction. This phased introduction includes mandatory RSA studies even before larger clinical trials can be initiated.

A phased introduction of new implants or related developments has been proposed by several authors[8,30-32]. The stepwise introduction described by Malchau may be the most widely known proposal[8]. This phased introduction consists of the following three steps: (1) preclinical tests, (2) large clinical trials (ideally multicenter and randomized), and (3) postmarket surveillance in national registries. In this proposal, Malchau acknowledged the potential of RSA and recommended the application of RSA follow-up in both Step 1 and Step 2[8].

In this position statement, we propose to modify this stepwise introduction of new implants or related developments by introducing an additional, intermediary step that explicitly requires RSA studies after the initial first step of preclinical testing: (1) preclinical tests, (2) two-year clinical RSA trials, (3) larger multicenter clinical studies, and (4) postmarket surveillance in national registries. In this way, advantage is taken of the great potential of RSA regarding patient protection in the introduction of new implants.

Implementation of this phased introduction of new prostheses, with RSA as an early qualitative tool, will establish safer and more effective patient care.

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Chapter 3

RSA prediction of high failure rate for the uncoated Interax TKA confirmed by meta-analysis

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Abstract

In a previous radiostereometric (RSA) trial the uncoated Interax tibial components had shown excessive migration compared to HA-coated and cemented tibial components. It was predicted that this type of fixation would have a high failure rate. The purpose of this systematic review and meta-analysis is to investigate whether the RSA prediction is correct.

We performed a systematic review and meta-analysis to determine the revision rate for aseptic loosening of the uncoated and cemented Interax tibial components.

Three studies were included with a total of 349 Interax total knee arthroplasties (TKA) for the comparison of uncoated fixation with cement. There were a total of 30 revisions: 27 uncoated and 3 cemented components. There was a 3 times higher revision rate of the uncoated Interax components compared to cemented Interax components; OR 3 [95% CI 1.4 to 7.2].

The meta-analysis confirms the prediction of a previous RSA trial. The uncoated Interax components showed the highest migration and turned out to have the highest revision rate for aseptic loosening. RSA appears to enable efficient detection of an inferior design as early as 2 year post-operatively in a small group of patients.

Introduction

Aseptic loosening remains a major reason for revision surgery in Total Knee Arthroplasty (TKA).[1,2] Since revision rates are generally low it is necessary to follow up hundreds if not thousands of patients for a long period of time (10 years) to be able to detect inferior designs.[3]

A method for early detection of aseptic loosening exposing as few patients as possible is therefore of value. Radiostereometric analysis (RSA) enables accurate measurement of migration of prosthetic components relative to the bone[4], which has been shown to be associated with late aseptic loosening.[5-7]

Although these findings are promising and the number for RSA studies is increasing, few studies have actually researched whether the RSA predictions are correct.[5-8] In TKA the question thus remains: Do TKA with increased early migration have higher revision rates for aseptic loosening? We have already shown in a randomized RSA trial that uncoated Interax tibial components have increased early migration compared to HA-coated and cemented tibial components.[9] We predicted that the uncoated components would have a high failure rate. The aim of the present study was therefore to investigate whether this prediction of the previous RSA trial is correct. We performed a meta-analysis to evaluate the failure rate of these components.

Methods

Design of the meta-analysis, and rationale

The design is based on the Cochrane standards and reporting of this meta-analysis is according to the PRISMA guidelines.[10] In order to exclude confounding due to differences in prosthesis design, the meta-analysis is restricted to studies comprising exactly the same implant as the previously published RSA-trial[9]: the cruciate retaining (CR) Interax TKA tibial component, (Howmedica / Stryker, Rutherford New Jersey) with two polyethylene halfbearings. The fixation of the components is either by cement or by bone ingrowth on uncoated or hydroxy-apatite (HA) coated prosthetic surfaces. The cemented components had a diamond surface on the side that was within bone, whereas the uncemented components had a mesh-wire surface (2.25 square millimetres corresponding to circular pore diameter of 1690 micrometers) with or without a HA coating.

The outcome of interest is the number of revisions or recommended revisions for aseptic loosening of the tibial component, for each fixation separately. This outcome will be compared to the early migration results of the RSA-trial [9] which showed increased early migration of the uncoated

tibial component compared to the cemented and HA coated tibial components (Figure 3.1). Uncemented components show high initial migration followed by stabilisation.[11-16] Thus, we also present the migration rate of MTPM (mm/year) determined on the migration measured with the post-operative RSA examination as reference (Table 3.1).

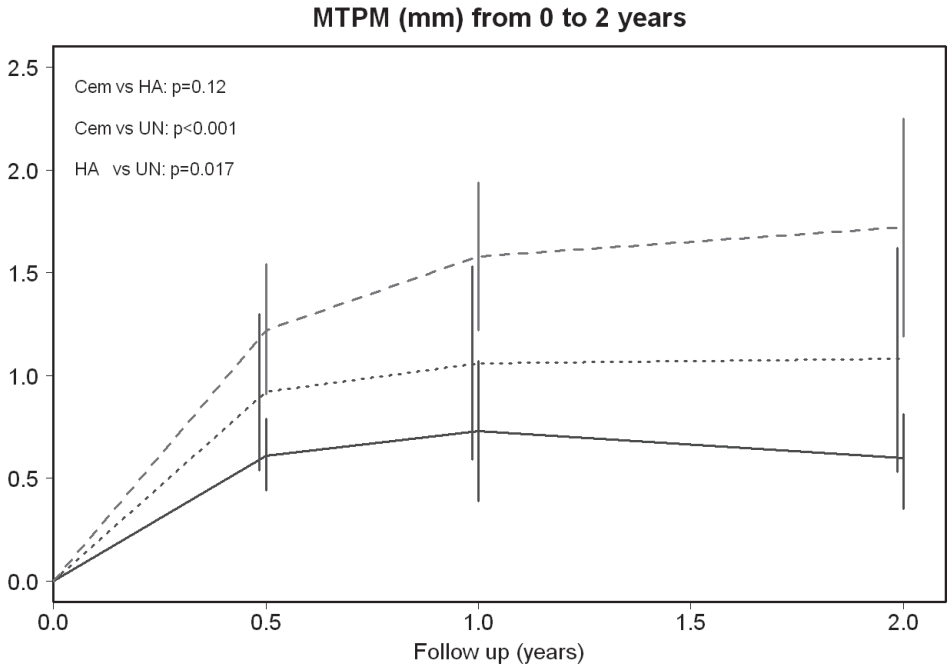

Figure 3.1 Summary of the migration results of the previous RSA trial.[9] The plot shows the mean migration – expressed as Maximal Total Point Motion (MTPM) - with 95% CI for each type of fixation of the tibial components: red dashed line for uncoated; green dotted line for HA-coated and blue solid line for cement. The uncoated tibial components showed the most migration. * mm = millimetre

Literature search

The literature search is the foundation on which a systematic review and meta-analysis is built. Inadequate search strategies have been shown to give biased results.[17] We therefore adopted a thorough search strategy in collaboration with a medical librarian, JWS. The following bibliographies were searched up to and including March 2011: PubMed, EMBASE (OVID version), Web of Science, Cochrane Library, Current Contents Connect, CINAHL (Ebscohost-version), Academic Search Premier (Ebscohost-version). Additionally, the websites of the following medical journal publishers were searched: Elsevier ScienceDirect, WileyBlackwell, Lippincott-Williams & Wilkins, Highwire, Informaworld/ Informahealth, and Springer. To reduce the effect of any publication bias the "gray literature" was searched up to and including March 2011: WHO

International Clinical Trials Registry Platform, clincialtrial.gov and the proceedings of the major conferences (NOF, AAOS, EFORT, ESSKA, ISTA). Furthermore, the bibliographies of included studies were hand searched for relevant publications. Also, various lesser known databases were searched, e.g. ScienceGov and OAIster. Finally, Google Scholar was searched.

The search involved among others the all fields- and fulltext-options to screen if the following component was mentioned anywhere in a manuscript: *"Interax"* and relevant abbreviations and extensions. Since "Interax" is a registered brand name of a particular TKA model, it was assumed to be spelled out the same way in the text of a manuscript irrespective of the language used. We did not use any language restrictions

Table 3.1: Mean migration rate of MTPM expressed in mm / year.

	Cemented		HA-coated		Uncoated	
Migration Rate*	Mean	95%CI	Mean	95%CI	Mean	95%CI
0 to 6 months	1.22	0.88 - 1.57	1.84	1.07 - 2.61	2.45	1.82 - 3.10
6 to 12 months	0.24	-0.34 - 0.82	0.27	-0.02 - 0.57	0.60	0.06 - 1.15
12 to 24 months	-0.12	-0.31 - 0.07	0.03	-0.12 - 0.18	0.19	0.02 - 0.35

* The uncoated components showed the highest migration rate. The migration rate was determined on the migration measured with the post-operative RSA examination as reference.
0 to 6 months: Cem vs HA p= 0.16; Cem vs UN p = 0.01; HA vs UN p= 0.15 (GLMM)

Study selection

All studies were subjected to the following inclusion criteria:

1) The study comprises an original patient cohort treated with the Interax TKA (Howmedica, Rutherford, New Jersey).
2) The cruciate retaining Interax prosthesis with halfbearings is used (Posterior stabilised Interax and Interax ISA versions are excluded).
3) The type of fixation of the tibial component and the number of knees receiving this type of fixation is adequately reported.
4) Number of revisions or recommended revision for aseptic loosening of the tibial component is reported for each fixation separately.
5) At least two fixation types are compared.

Two reviewers, BGP and MJN, independently subjected all studies to these five inclusion criteria. In cases where the title and abstract were inconclusive, the full text article was obtained. Any disagreement between the reviewers was resolved by re-examination and subsequent discussion

to reach a consensus. Randomized Controlled Trials (RCT) as well as observational studies were considered for inclusion.

Quality Assessment and Data extraction

The quality of each included study was independently appraised by two reviewers, BGP and MJN, using the Jadad Scale.[18] The same reviewers independently extracted relevant data for each included study using a standardized form including demographic data, number of TKA in each fixation group, number of revisions for aseptic loosening in each fixation group, and loss to follow up. Any disagreement between the reviewers was resolved by re-examination and subsequent discussion for consensus.

Statistical analysis

Before considering a meta-analysis (pooling of data), we investigated whether it was appropriate to pool the data. Studies should be similar in design and patient population. In addition, the variability in effect size between studies should not exceed those expected from sampling error: low heterogeneity is desirable. Heterogeneity was assessed by calculating the I^2-statistic, which is appropriate in case of a small number of studies.[19] Publication bias was assessed with a funnel plot.[20] Meta-analysis was performed with Peto Odds Ratio (OR) fixed effect pooling and Mantel-Haenszel random effects pooling for the risk difference (RD) and number needed to treat (NNT).[21] The NNT was defined as the number of cemented tibial components that would have to be implanted in order to prevent 1 revision as compared to when uncoated components were implanted. We used RevMan software.

Results

Study selection & study characteristics

The search strategy resulted in 268 unique hits of which 4 studies could be included (Figure 3.2).[22-25] Two papers were published in the English language[23,25], one in German[24] and one in French[22] (Table 3.2). Three studies compared the cemented component to the uncoated one.[22,24,25] One of these studies [24] was part of a thesis [26], which we used for more details. One of these studies[25] was the long term follow-up of the RSA-trial[9] and reported 3 revisions (2 uncoated and 1 cemented) for aseptic loosening of the tibial component.

Since only one study with 18 TKA [23] compared the HA-coated tibial component to the uncoated one, no pooling was performed for this comparison. The funnel plot did not show any publication bias.

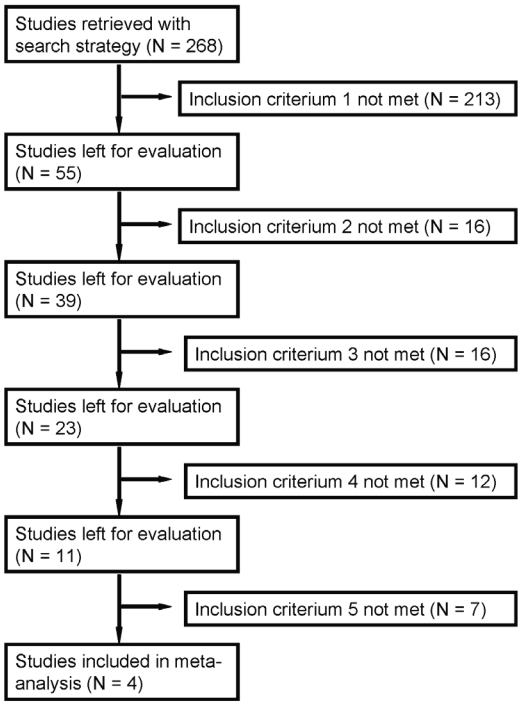

Figure 3.2 Flow diagram providing details on study selection. In case the title and abstract were insufficiently conclusive, the full text article was obtained.

Table 3.2 Characteristics of included studies

	Cemented vs uncoated			HA-coated vs uncoated
Study	Pijls 2011	Gicquel 2000	Stukenborg 2000	Petersen 2005§
Type	RCT	RCT	OBS	RCT
Number TKA	68	96	209	18
females (%)	55 (81)	NS (75)	166 (79)	15 (83)
OA (%)	18 (26)	NS (97)	NS (67)	18 (100)
RA (%)	49 (72)	NS (3)	NS (26)	0 (0)
Mean age at operation (years)	66	73	68	76
Mean FU (years)	7.6	2.3	6.8	2
Operation period	1993-1998	1993-1995	1991-1994	-
Deaths (%)	28 (42)	6 (6)	39 (19)	1 (5.5)
Lost to FU (%)	1 (1.5)	20* (20)	3 (1.4)	1 (5.5)
Jadad Quality Score**	3	3	1	2

*20 cases were lost to follow-up: 8 cemented cases and 12 uncoated cases
** Maximal attainable score is 3 because the evaluation of revision on the x-ray cannot be blinded.
§ Since Petersen et al is the only study evaluating HA-coated versus uncoated and includes only 18 patients, no meta-analysis could be performed for the HA-coated versus uncoated comparison.
RCT = Randomized Controlled Trial
OBS = Observational Study
NS = Not Stated

Uncoated versus cemented tibial component

349 TKA compose the meta-analysis of uncoated versus cemented components. There were 30 revisions of the tibial component for aseptic loosening of which 27 were for the uncoated components compared to 3 for the cemented component.

The odds of revision due to aseptic loosening of the uncoated tibial component was 3.1 times higher as compared to the cemented tibial component: pooled Odds Ratio (OR) 3.1 [95% CI 1.4 to 7.2] (Figure 3.3). The pooled risk difference was 7% [95% CI 3% to 12%] in favour of the cemented component. The number needed to treat (NNT) was 14 in favour of the cemented components [95% CI to 8 to 33]. This means that for every 14 patients treated with a cemented Interax tibial component, 1 revision for aseptic loosening is prevented compared to the uncoated component.

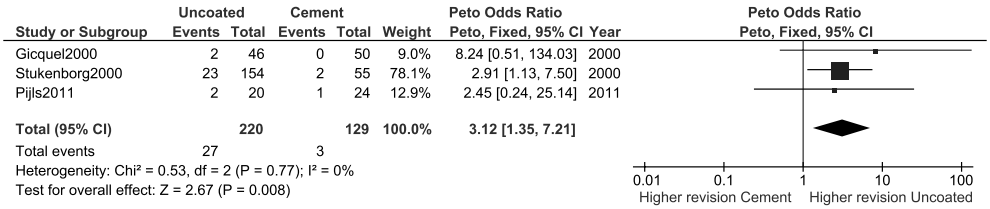

Figure 3.3 Forest plot summarising the pooled effect size of cemented versus uncoated tibial components. As shown there was a significantly 3.1 times higher revision rate for the uncoated Interax tibial components compared to the cemented ones.

Risk of bias within studies

The sequence of randomization as well as concealment of allocation was described and appropriate in two studies.[22,25] In one study [23] randomization was performed but the method and concealment not adequately described and in another study [24] no randomization was performed. In the non-randomized study the decision for implanting either a cemented or an uncoated uncemented tibial component was made by the surgeon during the operation leading to confounding by indication-because cemented components were used for cases with reduced bone quality.[24] This confounding would lead to a possible underestimation of the revision rate of the uncoated uncemented tibial component. Thus, the higher revision rate for the uncoated components compared to the cemented ones may have been an underestimation of the true revision rate.

In all studies blinding was a potential source of bias. Since evaluation of X-rays is essential for the indication of a revision and the presence or absence of cement cannot be masked on the X-ray, blinding – if possible at all– was not performed in any of the studies.

The number of withdrawals and dropouts was adequately described in all studies. The number of lost to follow-up (8 cemented and 12 uncoated) was high in study by Gicquel et al(Table 3.2).[22] All three studies which compared cemented versus uncoated components included all patients consecutively during study inclusion period and thus reduced the possibility of selection bias.[22,24,25]

Discussion

Uncoated versus Cemented Components

Our aim was to investigate whether the predictions of a previous Radiostereometric Analysis (RSA)-trial were correct. Since the uncoated Interax components had shown the highest migration, it was predicted that this type of fixation would have a high failure rate.[9] The results of the meta-analysis show a significant 3 times higher revision rate for the uncoated uncemented component compared to the cemented tibial component. Thus the prediction of the previous RSA-trial was correct: the uncoated tibial components showed the highest migration and had the highest revision rate for aseptic loosening. The uncoated tibial components also continued to migrate after 1 year, whereas the HA-coated components stabilized after 1 year. This is in accordance with a recent report by Wilson et al, who showed that tibial components can give solid fixation despite high levels of initial migration.[27]

In the RSA trial, the high degree of migration of the uncoated uncemented tibial components was identified within 2 years in a small group of 44 patients (24 in the cemented group and 20 in the non-coated group) compared to the 349 in the meta-analysis. This emphasizes the value of RSA for the early detection of inferior TKA designs in a small series of patients.[5-7]

It is noteworthy that none of the individual traditional clinical studies with large numbers of patients and medium term or long term follow-up reported a significant difference in revision rates between the uncoated uncemented and cemented Interax tibial component.[22,24] Only when the results of these studies were combined in a meta-analysis setting did the high revision rate in the uncoated components became clearly visible.

Uncoated versus HA-coated

One of the selected studies compared the uncoated tibial component to the HA-coated component.[23] This study involved only 18 patients followed for 2 years. Because of the short follow-up and small patient cohort it was not appropriate to perform a meta-analysis for the uncoated versus HA-coated components. The uncoated Interax tibial component has been withdrawn from the market after the results of the RSA trial were published. Since the HA-coating migrates less than the uncoated tibial component, a beneficial effect of the HA coating

is expected. Less migration of a HA component compared to the non-coated component for the Interax CR has also been demonstrated by Østgaard et al.[28] Their migration results were similar to those of our RSA trial, despite differences in patient characteristics: all their patients were suffering from osteoarthritis, compared to 30% osteoarthritis and 70% rheumatoid arthritis in our RSA trial.

Strengths and limitations

Our search strategy was thorough and complete. This is underscored by the fact that we found two studies that have been published in non-English literature. Although our research question was highly specialized, i.e. fixation of a single type of TKA, we were still able to include three studies. This is not uncommon for orthopaedic meta-analysis even in Cochrane reviews.[29]

The included studies were of moderate quality mostly due to issues with blinding for the fixation method, which is a general problem of any study comparing cemented with uncemented components and not specific to the present meta-analysis.

Publication bias generally favours the newly introduced treatment[30]: the uncoated uncemented fixation in this case. Since the studies included in this meta-analysis did not find a positive effect for the uncoated components, publication bias was probably not a major factor here. Thus, we are confident that our conclusion is correct: the uncoated tibial component of the Interax has a higher revision rate for aseptic loosening.

The I-statistic was 0%, so there was no indication for statistical heterogeneity. Despite differences in patient demographics, surgical technique or study design all OR's are on the same side, i.e. showed higher –although not individually significantly – revision rates for the uncoated component and this confirms the predictions of the RSA trial.

Future Perspectives

More than a decade ago Liow and Murray [31] and Muirhead-Allwood [32] called for a more evidence-based evaluation and clinical introduction of (new) prosthetic designs and fixations. Malchau [33] proposed a phased evidence based introduction of new designs. Recently, a renewed call for concrete steps has been made towards such a evidence-based clinical introduction.[34,35] A disastrous design can be detected early post-operatively in a small group of patients by RSA, which therefore has the potential to play an important role in the clinical introduction of new models and fixation methods in total knee arthroplasty. For example, in vitro testing machine studies, should be followed by two year RSA studies in small cohorts in different institutions worldwide, followed by larger comparative studies after which introduction to the market can be started.[33] The latter also involving follow-up in national registries. In this way a more phased prosthesis introduction to the market is guarantied, as is currently the standard for pharmacological agents.

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Authors Contributions

The following authors designed the study (SM, BGP, RGN, ERV), designed the search strategy for the literature search (JWS), performed the study selection (BGP, MJN), appraised the quality of the literature (BGP, MJN) analyzed the data (BGP, SM), wrote the initial draft manuscript (ERV, BGP, JWS, MJN) and ensured accuracy of data and analysis (SM, RGN). Critical revision of the manuscript was performed by all authors.

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Chapter 4

The beneficial effect of hydroxyapatite lasts: a randomized radiostereometric trial comparing hydroxyapatite-coated, uncoated, and cemented tibial components for up to 16 years

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Abstract

In contrast to early migration, the long-term migration of hydroxyapatite- (HA-) coated tibial components in TKA has been scantily reported. This randomized controlled trial investigated the long-term migration measured by radiostereometric analysis (RSA) of HA-coated, uncoated, and cemented tibial components in TKA.

68 knees were randomized to HA-coated (n = 24), uncoated (n = 20), and cemented (n = 24) components. All knees were prospectively followed for 11–16 years, or until death or revision. RSA was used to evaluate migration at yearly intervals. Clinical and radiographic evaluation was according to the Knee Society system. A generalized linear mixed model (GLMM, adjusted for age, sex, diagnosis, revisions, and BMI) was used to take into account the repeated-measurement design.

The present study involved 742 RSA analyses. The mean migration at 10 years was 1.66 mm for HA, 2.25 mm for uncoated and 0.79 mm for the cemented group ($p < 0.001$). The reduction of migration by HA as compared to uncoated components was most pronounced for subsidence and external rotation. 3 tibial components were revised for aseptic loosening (2 uncoated and 1 cemented), 3 for septic loosening (2 uncoated and 1 cemented), and 1 for instability (HA-coated). 2 of these cases were revised for secondary loosening after a period of stability: 1 case of osteolysis and 1 case of late infection. There were no statistically significant differences between the fixation groups regarding clinical or radiographic scores.

HA reduces migration of uncemented tibial components. This beneficial effect lasts for more than 10 years. Cemented components showed the lowest migration. Longitudinal follow-up of TKA with RSA allows early detection of secondary loosening.

Introduction

The early fixation properties of hydroxyapatite (HA) coatings on prostheses have been extensively studied [1]. Animal studies have shown that HA may convert fibrous tissue into bone, and that even under unstable mechanical conditions HA is capable of inducing bone growth across peri-implant gaps [2-4]. Additionally, radiostereometric (RSA) studies have shown reduced early migration of HA-coated tibial components compared to porous coated or non-coated tibial components in total knee arthroplasty (TKA) [5-8].

In contrast to early migration, the long-term migration of HA-coated tibial components has been scantily reported—as shown by a recent systematic review [9,10]. Thus, it is not clear whether the early biological fixation of HA-coated tibial components will endure and how the long-term migration compares to that of uncoated or cemented tibial components. Moreover, HA-specific complications such as delamination of the HA layer and third-body wear caused by HA particles have been reported in total hip arthroplasty and are potential problems in the long run [11,12].

We have already shown in a randomized radiostereometric trial of HA-coated, uncoated, and cemented tibial fixation that HA significantly reduces early migration compared to uncoated components [5]. Here, we investigated the long-term (11- to 16-year) migration in these patients.

Methods

Study design and patient demographics

68 consecutive posterior cruciate retaining TKAs (Interax; Howmedica, Rutherford, NJ) performed in 48 patients because of osteoarthritis or rheumatoid arthritis, were included in a randomized, controlled trial in an academic hospital between 1993 and 1998. The study was done in compliance with the Helsinki Declaration and was approved by the institutional ethics committee (pp 166/93; November 30, 1993), and patients gave informed consent. 24 TKAs were performed with cemented tibial components, 24 with HA-coated tibial components, and 20 with uncoated tibial components (Table 4.1).

Table 4.1. Baseline characteristics

	Cement (n = 24) Mean (SD)	HA (n = 24) Mean (SD)	Uncoated (n = 20) Mean (SD)
Age	69 (8.6)	63 (11)	65 (15)
Sex (F:M)	18:6	21:3	16:4
Diagnosis (RA:OA:SA)	15:9:0	17:6:1	17:3:0
BMI	26 (3.8)	27 (4.9)	24 (3.3)
Preoperative FTA angle	176 (8.1)	174 (8.7)	171 (12)
Preoperative KSS	27 (11)	22 (17)	25 (21)
Preoperative KSS (function)	14 (18)	14 (21)	5 (11)

RA: rheumatoid arthritis; OA: osteoarthritis; SA: sequelae after septic arthritis.

Reporting was in accordance with the CONSORT guidelines and the RSA guidelines [13,14]. 2-year migration results and details of patients and methods have been reported previously[5].

Fixation of the tibial component with HA was compared to uncoated fixation and to fixation with cement. The inserts were made of ultra-high-molecular-weight polyethylene (UHMWPE), sterilized by gamma radiation in air, and machined from ram-extruded GUR 415 resin containing calcium stearate.

In the present study, patients were followed for 11–16 years, or until death or revision of the tibial component (Figure 4.1). To account for the learning curve with this—at the time—new TKA at our institution (1992) and to gain experience with the RSA equipment, the first 12 TKAs were not randomized and received cemented fixation. These 12 TKAs were not included as part of the study. Nevertheless, RSA analysis was performed in order to exclude potential selection bias for the consecutive study. The migration was similar to that of the randomized cemented cases ($p = 0.3$), as analyzed with a generalized linear mixed model. During the study, patients remained blind regarding the fixation method. Observers were blinded during the RSA analysis regarding the presence or absence of HA coating, so the study was double-blind regarding the type of uncemented fixation (HA-coated or uncoated). Since cement is visible on (RSA) radiographs, the study was single-blind regarding the comparison with cement.

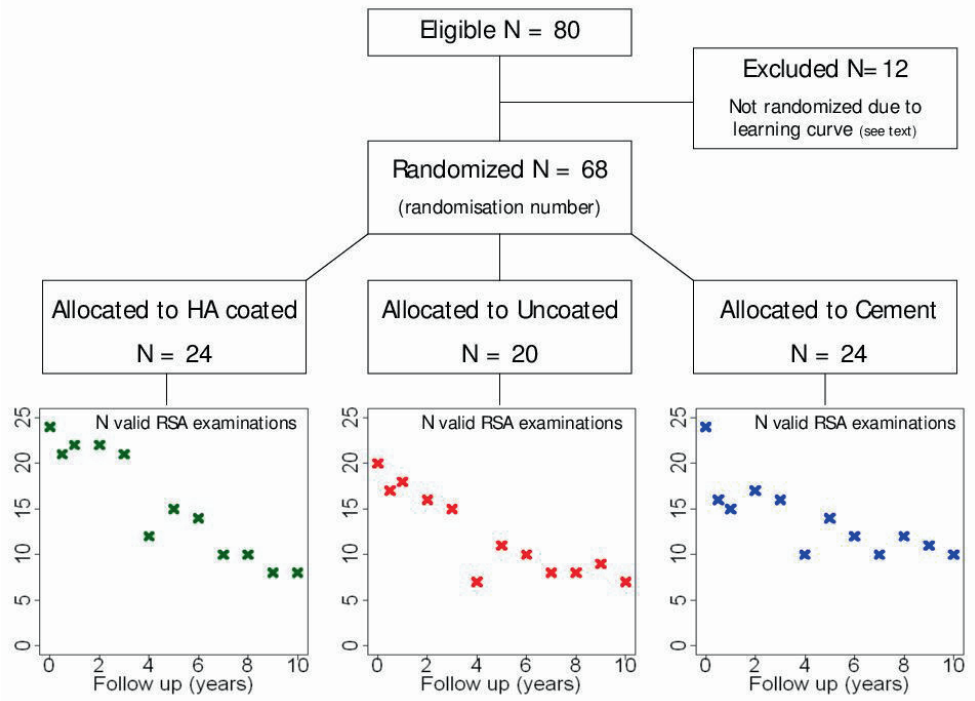

Figure 4.1. CONSORT flow chart.
* This patient moved out of the region at 3 years post-operatively, when the tibial component had stabilized at 0.64mm MTPM and there were no signs of loosening on the last radiograph.

Surgical technique

All TKAs were performed by two experienced knee surgeons or under their direct supervision, and implanted through a standard midline incision and medial parapatellar arthrotomy. 6–8 tantalum markers were inserted into the tibial metaphysic bone before final implantation of the tibial component.

In the cemented group, Palacos bone cement (Schering, Kenilworth, NJ) was used after mechanical pulse-lavage of the cut bone surfaces. To allow migration measurements by marker-based RSA, three 2-mm Vitallium markers had been attached to the tibial component by the manufacturer.

RSA technique

The RSA technique has been described previously [5]. Analysis of the RSA examinations was performed with MBRSA 3.2 software (Medis Specials, Leiden, the Netherlands). The marker configuration model RSA technique was used for measurement of the pose of a rigid body in situations where less than 3 markers could be detected in both images of an RSA radiograph [15]. In

2002, the calibration cage was replaced. Accuracy of the RSA set-up prior to 2002, as determined by double examination analysis (n = 40), was as follows for the translations expressed in means: x-axis 0.00 mm (SD 0.07 mm), y-axis 0.01 mm (SD 0.06 mm), and z-axis –0.02 mm (SD 0.13 mm) [5,14]. From 2002 onwards (n = 44), the accuracy was: x-axis 0.00 mm (SD 0.03 mm), y-axis 0.01 mm (SD 0.06 mm), and z-axis –0.01 mm (SD 0.08 mm) according to Kaptein et al. [16]. These values indicate a high level of precision for the measurement of migration of the tibial component relative to the bone and absence of any systematic bias.

Weight-bearing and flexion exercises were postponed until after the first RSA radiograph (1–5 days postoperatively). The patients were evaluated both clinically and by RSA examinations at predefined follow-up times (3 weeks, 6 weeks, 3 months, 6 months, and 1 year postoperatively) and then on an annual basis.

Primary outcome: measurement of migration with RSA

The first RSA radiograph served as a baseline reference for the migration measurements.

Maximal total point motion (MTPM)—migration of the point on the prosthesis that has moved the most—was used to determine whether the groups were different regarding migration. When MTPM was different between the groups, translations and rotations along the x-, y-, and z-axis were evaluated to determine how they differed.

Most migration occurs in the first postoperative year, followed by either stabilization or continuous migration of the tibial components [17]. Since MTPM represents the length of a vector, which cannot be subjected to regular addition or subtraction, an additional RSA analysis was carried out with the 1-year postoperative RSA radiograph as a reference.

Secondary outcome: clinical evaluation

Clinical evaluation was performed according to the Knee Society score (KSS) and Hospital for Special Surgery score (HSS) at each follow-up [18].

Secondary outcome: radiographic evaluation

In addition to the RSA radiographs, conventional weight-bearing radiographs were acquired at 2-, 5-, 10-, and 15-year follow-up and graded according to the Knee Society roentgenographic evaluation: femoral-tibial aligment (FTA angle) and also alfa angle (frontal angle of the femoral component), beta angle (frontal angle of the tibial component), and delta angle (sagittal angle of the tibial component) [19].

Statistics

Due to the high degree of accuracy of RSA, 20 TKAs were required for each trial arm—as was standard for RSA studies at the time the present study was designed (1992), [20,21]. The results were analyzed according to the intention-to-treat principle. To take into account the repeated-measures design of the study, any missing follow-up occasion, variation in duration of follow-up, and bilaterality, and also to allow for confounder correction [22], a generalized linear mixed model (GLMM) was used (R software version 2.12.0), which is considered to be the primary analysis method for this type of clinical study [23]. In accordance with recent studies, a log-transformation was used for maximal total point motion (MTPM)—migration of the point on the prosthesis that has moved the most—because it is not normally distributed [24]. Due to multiple primary outcomes (translations, rotations), a Holm-Bonferroni correction for multiple testing was performed [25]. Means are presented until 10 years of follow-up. Afterwards, cases are presented individually. 95% confidence intervals (CIs) were calculated.

Results

Long-term migration

The migration analysis was composed of 742 RSA analyses using the direct postoperative RSA radiograph as reference. Figure 4.1 shows the number of valid RSA examinations for each follow-up occasion. Figure 4.2 shows the mean migration expressed in MTPM for each fixation group up to 10 years postoperatively. Throughout the follow-up period, the uncoated tibial components showed mean 0.39 mm (95% CI: 0.16–0.62) more migration than the HA-coated tibial components and mean 1.0 mm (CI: 0.82–1.18) more than the cemented tibial components, while the HA-coated components migrated mean 0.61 mm (CI: 0.42–0.80) more than the cemented components (unadjusted: $p < 0.001$, GLMM; and adjusted for age, sex, diagnosis, revisions, and BMI: $p < 0.001$, GLMM). The mean migration at 10 years was 1.61 mm for the osteoarthritis patients and 1.52 mm for the rheumatoid arthritis patients ($p = 0.2$, GLMM adjusted for fixation, age, sex, revision, and BMI).

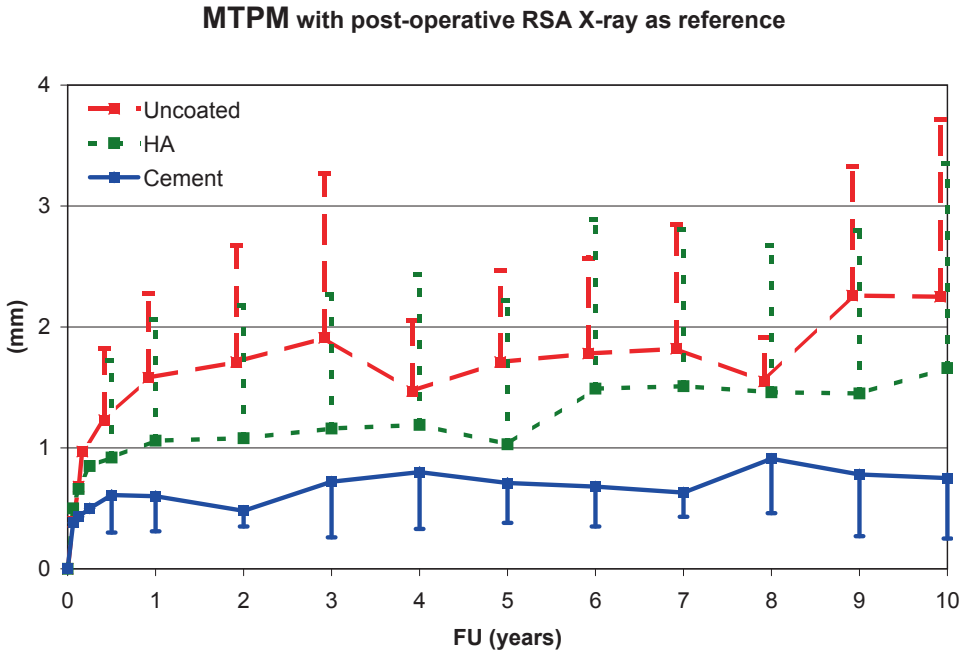

Figure 4.2. Migration in maximum total point motion (MTPM) (mean and standard deviation) according to the duration of follow-up in the hydroxyapatite (HA) group (green dotted line), the uncoated group (red dashed line), and the cemented group (blue solid line). The direct postoperative RSA radiograph is the reference. The groups differed significantly in migration ($p < 0.001$, GLMM). Missing values at 4-year follow-up were estimated as the mean of the 3-year and 5-year follow-up.

To determine whether migration patterns varied between the groups, the mean translations and rotations were determined. The uncoated tibial components showed statistically significantly increased subsidence, external rotation, and lateral and anterior translation (in the order of clinical relevance). The addition of HA affected migration by decreasing subsidence by mean 0.26 mm (CI: 0.10–0.42) and external rotation by mean 0.47 degrees (CI: 0.27–0.67) compared to uncoated components.

463 RSA analyses composed the migration analysis relative to the first postoperative year (Figure 4.3). There was a statistically significant difference between the fixation groups regarding migration from 1 to 10 years (unadjusted: $p < 0.001$, GLMM; and $p < 0.001$, GLMM adjusted for age, sex, diagnosis, revisions, and BMI). After 1 year, the cemented tibial components migrated 0.043 mm/year, the HA-coated tibial components migrated 0.057mm/year, and the uncoated tibial components migrated 0.067 mm/year ($p = 0.003$, GLMM adjusted for age, sex, diagnosis, revisions, and BMI).

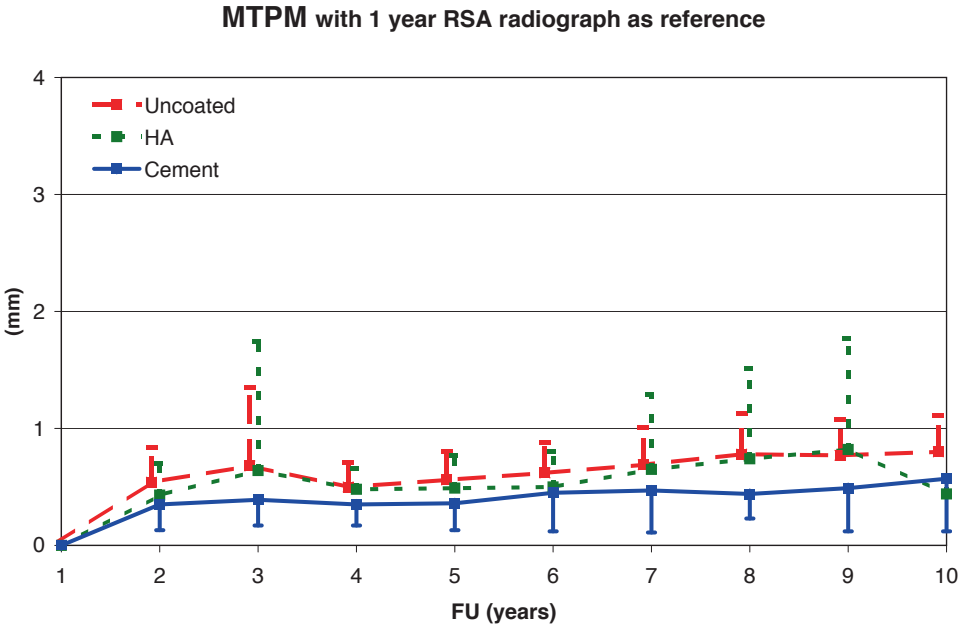

Figure 4.3. Migration from 1 to 10 years in maximum total point motion (MTPM) (mean and standard deviation) according to the duration of follow-up in the hydroxyapatite (HA) group (green dotted line), the uncoated group (red dashed line), and the cemented group (blue solid line). The 1-year postoperative RSA radiograph is the reference. The groups differed significantly in migration ($p < 0.001$, GLMM). Missing values at 4-year follow-up were estimated as the mean of the 3-year and 5-year follow-up.

Migration from 1 to 16 years for individual cases with 10 years or more of RSA follow-up is presented in Figure 4.4 according to fixation type: HA-coated (8 cases), uncoated (9 cases), and cemented (9 cases). There was 1 knee in the HA-coated group and 1 knee in the uncoated group and 1 knee in the cemented group with continuous migration. The patient in the HA-coated group and cemented group died with the TKA in situ. The patient in the uncoated group is still alive and is considered to be at risk of aseptic loosening.

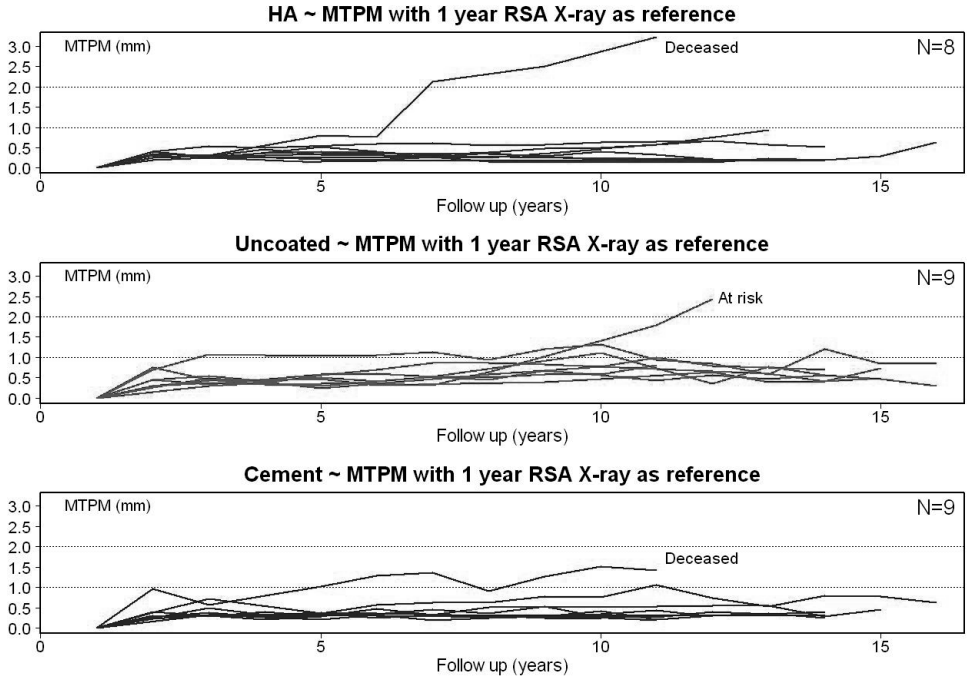

Figure 4.4. Migration from 1 to 16 years in maximum total point motion (MTPM) of individual cases with 10 years of RSA follow-up or more according to the duration of follow-up in the hydroxyapatite (HA) group (upper row), the uncoated group (middle row), and cemented group (lower row). The 1-year postoperative RSA radiograph was the reference.

Clinical evaluation

At 10 years postoperatively, there was a mean increase in KSS compared to preoperatively (59 (CI: 54–66)). There were no statistically significant or clinically relevant differences in KSS between the fixation types (p = 0.9, GLMM adjusted for age, sex, diagnosis, revisions, and BMI) (Table 4.2).

At 10 years postoperatively, there was a mean increase in KSS function compared to preoperatively (33 (CI: 21–46)). There were no statistically significant or clinically relevant differences in KSS function between the fixation types (p = 0.4, GLMM adjusted for age, gender, diagnosis, revisions, and BMI) (Table 4.2). There were no significant differences in HSS or flexion between the fixation types.

Table 4.2. Clinical and radiographic results

		Cement Mean; SD; (95% CI)	HA Mean; SD; (95% CI)	Uncoated Mean; SD; (95% CI)
Knee score[a]	5-year	81; 11; [75-88]	81; 13; [74-88]	83; 5; [80-86]
	10-year	81; 15; [71-91]	85; 7; [80-90]	87; 7; [81-92]
	Last FUf	76; 18; [68-84]	86; 10; [81-90]	81; 14; [74-87]
Knee function score[b]	5-year	69; 21; [55-82]	38; 30; [20-55]	52; 35; [30-75]
	10-year	45; 29; [25-65]	46; 33; [23-69]	42; 32; [18-67]
	Last FU[f]	29; 34; [14-44]	29; 32; [15-43]	23; 31; [8-38]
HSS[c]	5-year	48; 8; [44-53]	46; 11; [40-51]	49; 5; [47-52]
	10-year	48; 4; [45-50]	49; 7; [44-53]	47; 5; [43-51]
	Last FU[f]	41; 17; [33-48]	51; 14; [45-57]	41; 14; [33-47]
Flexion[d]	5-year	109; 16; [100-118]	100; 15; [92-108]	101; 14; [93-110]
	10-year	110; 16; [100-120]	103; 13; [93-113]	106; 12; [95-110]
	Last FU[f]	105; 13; [99-111]	106; 12; [101-111]	101; 17; [93-108]
FTA angle[e]	1-year	176; 2.8; [175-177]	177; 3.4; [176-178]	176; 2.4; [175-177]
	5-year	177; 2.3; [175-178]	177; 4.1 [175-179]	177; 2.9; [175;178]
	10-year	177; 2.2; [175-178]	178; 4.4; [175-181]	176; 2.8; [174-178]
Alfa angle	1-year	93; 2.6; [92-95]	94; 2.7; [93-95]	94; 3.0; [93-96]
Beta angle	1-year	90; 1.7; [89-90]	88; 3.0; [87-89]	89; 2.0; [88-90]
Delta angle	1-year	88; 3.1; [86-89]	88; 2.8; [87-89]	87; 3.5; [86-89]

[a] p =0.86, GLMM.
[b] p = 0.43, GLMM.
[c] p = 0.64, GLMM.
[d] p = 0.15, GLMM.
[e] p = 0.28, GLMM.
[f] Last FU at mean 9.0 years (range 3 months to 16 years) was calculated using the clinical score at the last available FU for each patient.
HSS: Hospital for Special Surgery score; FTA angle: femoral-tibial alignment; alfa angle: frontal angle of the femoral component; beta angle: frontal angle of the tibial component; delta angle: sagittal angle of the tibial component.

Radiographic evaluation

The FTA angles were similar between the fixation types (p = 0.3, GLMM adjusted for age, sex, diagnosis, revisions, and BMI) (Table 4.2). There were no statistically significant or clinically relevant differences in alfa, beta, or delta angles between the fixation types. Ten years postoperatively, there were 2 partial 2-mm radiolucent lines in the HA group, 1 partial 2-mm radiolucent line in the uncoated group, and no radiolucent lines of 2 mm or more in the cemented group.

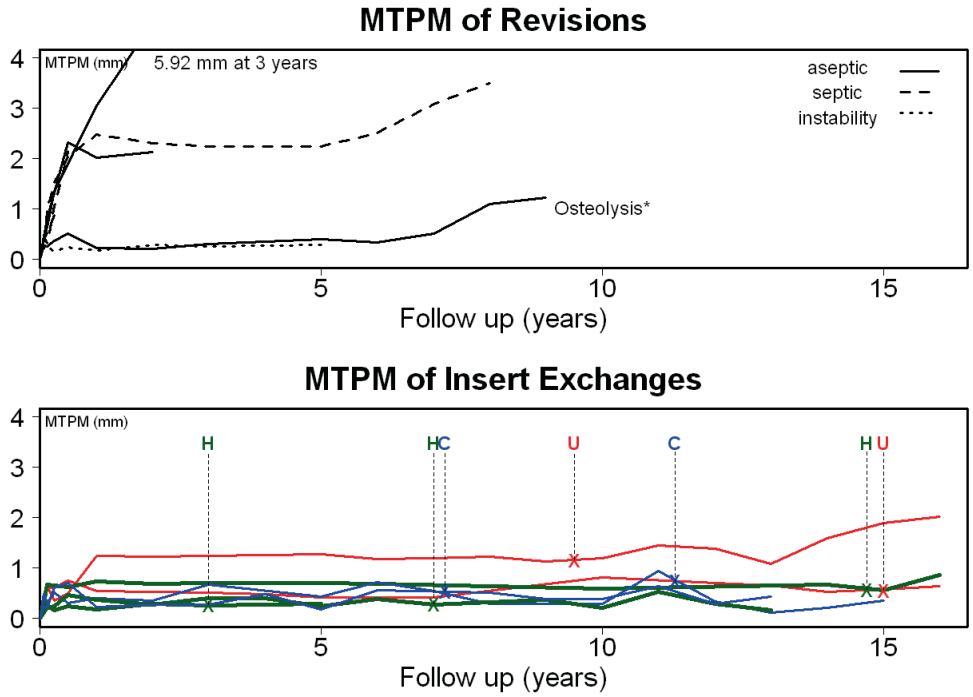

Figure 4.5. Individual migration patterns of the liner exchange and revised cases (with the postoperative radiograph as reference). For the insert exchanges, the letters at the top indicate the time of insert exchange with blue C for cemented tibial components, green H for HA-coated tibial components, and red U for uncoated tibial components. The tibial components remained securely fixed after the exchange of insert.
* Secondary loosening due to osteolysis. Extensive antero-lateral osteolysis was seen on the CT-scan. This was confirmed at the revision procedure.

Revisions and exchanges of insert

7 knees were revised: 3 tibial components for aseptic loosening (2 uncoated and 1 cemented), 3 for septic loosening (2 uncoated and 1 cemented), and 1 for instability (HA-coated). The individual migration patterns are shown in Figure 4.5. Of note is 1 case that was revised for secondary aseptic loosening after a period of stability. This secondary loosening was due to scalloping osteolysis at the tibial component located anterolaterally as identified on CT-scan and during the revision procedure. There was 1 case that was revised after late infection. This case also showed increasing migration after a stable period. There was 1 case of wound necrosis (cemented tibial component) early postoperatively that was treated successfully with surgical debridement and antibiotics, so the prosthesis was preserved.

There were 7 PE insert exchanges for wear: 2 in the cemented group, 3 in the HA group, and 2 in the uncoated group. There was no statistically difference between the groups in the rate of insert

exchange (with the numbers available; HA-coated vs. cemented, HR = 1.0, CI: 0.2–6.9; p = 1.0; and HA-coated vs. uncoated, HR = 0.6, CI: 0.1–5.6; p = 0.6).

Discussion

We found different long-term migration between the 3 fixation types, with cemented components showing the lowest migration. For the uncemented components, HA reduces migration compared to the uncoated components and this clinically relevant effect endures beyond 10 years. The positive effect of HA was most noticeable in reducing subsidence and external rotation compared to the uncoated tibial components.

Negative effects of HA are the risk of HA delamination and third-body wear due to HA particles, as demonstrated in total hip arthroplasty [11,12]. In the present study, the migration patterns of the HA-tibial components were stable at the long-term follow-up, so delamination of the HA coating was unlikely for the HA applied which was 60 µm thick and had a crystallinity of more than 90%. Crystallinity of more than 75% has been shown to provide adequate fixation and bone ingrowth [26]. The rate of insert exchange in the HA group was comparable to that of the cemented and uncoated groups, thus no indication for accelerated third-body wear due to HA particles was anticipated. However, larger comparative studies are needed to fully address the potential influence of third-body wear by HA particles in TKA.

Early migration appears to predict long-term migration [17,21]. Indeed, the increased (early) migration in the uncoated group compared to the cemented and HA group has been associated with an increased revision rate for the uncoated components [27]. There were 2 cases of secondary loosening after a period of stability. Since these patterns have not been described before, there is a need for long-term RSA studies to further investigate these interesting migration patterns. The HA-coated components in our study also showed the well-described migration pattern for uncemented tibial components: substantial initial migration followed by stabilization [28-30].

Compared to the HA-coated tibial components, the uncoated components showed more initial migration, which took more time to stabilize. Other RSA studies with follow-up ranging from 1 to 5 years have found similar results regarding the effect of HA on migration compared to porous coated and uncoated tibial components [5-8,30-32]. In addition, recent clinical cohort series have illustrated that good long-term survival (with any reason for revision as endpoint) of 99% at 10 years and 98% at 10–15 years of follow-up can be achieved with similar HA-coated, posterior cruciate retaining tibial components [33,34].

The magnitude of difference in migration from 1 to 10 years was less pronounced than the magnitude of difference in migration in the early postoperative period. It is not clear whether the differences in migration from 1 to 10 years are clinically relevant.

Knee Society scores and radiolographical outcome were similar in all groups. The high rate of insert exchange due to wear for the Interax TKA has been described in the literature and was judged to be caused by the type of sterilization of the polyethylene (gamma in air) and inappropriate shift of the load center on the tibial component, particularly in the smaller sized non-conforming inserts, causing excessive stress on the posteromedial and posterolateral surfaces [35].

The strengths of our study are the long-term follow-up and the blinding for the presence or absence of the HA coating for both the patient and the observers. In surgical trials, blinding is often an issue [36]. An HA coating, however, is ideal for a double-blind design, since it cannot be seen on radiographs, so the RSA analyzers and patients were blinded. On the other hand, cement is visible on (RSA) radiographs, so the study was only single-blind (patient) regarding the comparisons with cement. Nonetheless, migration analysis with RSA is a standardized and objective method with low susceptibility to different interpretations [14]. The risk of biased results for the cemented components is therefore negligible.

We should also note some limitations. Three-quarters of our patients suffered from end-stage rheumatoid arthritis. One could question whether the conclusions apply to osteoarthritis. However, the migration at 10 years was very similar between OA patients and RA patients (1.61 mm and 1.52 mm). The long-term migration of HA-coated tibial components compared to cemented components has been scantily reported [10]. The early migration in our study is comparable to that found by Önsten et al. [37], who included only OA patients. At 2 years, their cemented components migrated (MTPM) approximately 0.6 mm and their HA components migrated approximately 1.0 mm. These migrations are similar to our results; OA or RA did not influence the effect of HA on long-term migration of the tibial components.

In conclusion, HA reduces migration of uncemented tibial components, which was most pronounced in the first postoperative years. The beneficial effect of HA endures beyond 10 years and there is no evidence for delamination of the HA layer. Since cemented components showed the lowest migration throughout the follow-up and have excellent survival in the registries, cement is a safe choice for fixation of the tibial component. Longitudinal follow-up of TKA with RSA allows early detection of secondary loosening.

Contributions of authors

The following authors designed the study (RGN, ERV), gathered the clinical data (RGN, BGP), gathered the RSA data (BLK, ERV), performed the RSA analysis (BGP, BLK) analyzed the data (BGP, MF) and wrote the initial draft manuscript (BGP, ERV, MF). Critical revision of the manuscript was performed by all authors.

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Chapter 5

Differences in long-term fixation between mobile-bearing and fixed-bearing knee prostheses at ten to 12 years' follow-up: a single-blinded randomised controlled radiostereometric trial

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Abstract

This single-blinded randomised controlled trial investigated whether one design of mobile-bearing (MB) total knee replacement (TKR) has any advantage over a fixed-bearing (FB) design on long-term fixation as measured by radiostereometry. The amount of wear underneath the mobile bearing was also evaluated. A series of 42 knees was randomised to MB or FB tibial components with appropriate polyethylene inserts and followed for between ten and 12 years, or until the death of the patient. The polyethylene in the MB group was superior in that it was gamma-irradiated in inert gas and was calcium-stearate free; the polyethylene in the FB group was gamma-irradiated in air and contained calcium stearate. In theory this should be advantageous to the wear rate of the MB group. At final follow-up the overall mean migration was 0.75 mm (sd 0.76) in the MB group and 0.66 mm (sd 0.4) in the FB group, with the FB group demonstrating more posterior tilt and the MB group more internal rotation. In the FB group there was one revision for aseptic loosening, but none in the MB group. There were no significant differences in clinical or radiological scores.

For the MB group, the mean linear wear rate on the under-surface was 0.026 mm/year (sd 0.014). This was significantly smaller than the wear rate of 0.11 mm/year (sd 0.06) in the MB between femur and polyethylene ($p < 0.001$). Nevertheless, even in a best-case setting the mobile bearings of this TKR design had no apparent advantage in terms of fixation over the FB knee prosthesis at ten to 12 years. The wear underneath the mobile bearing was small and is unlikely to be clinically relevant.

Introduction

Mobile-bearing (MB) total knee replacements (TKRs) have greater conformity of the femorotibial articulation than fixed-bearing (FB) prostheses. This increase in femorotibial contact area should reduce contact stresses at both polyethylene (PE) surfaces and theoretically lead to less PE wear.[1,2] The mobility of the PE liner should at least partially transfer shear forces to the ligaments and other soft tissues,[3] which would tend to reduce the stress at the bone–cement interface, thereby reducing the likelihood of component loosening.[1,2]

However, the advantages described above remain strictly theoretical. Several recent meta-analyses could not demonstrate any clinical or radiological advantage for MB TKRs in short- to medium-term follow-up.[4-7] There are only a few randomised controlled trials with long-term -follow-up comparing MB with FB TKR.[8-10] Although the advantages of the MB TKR remain to be proved, reports on bearing dislocation in some designs and third-body wear underneath the mobile insert where it is in contact with the tibial base plate raise some concerns.[11]

In this study we evaluated the potential long-term advantages of MB TKRs using objective outcomes measures, including PE wear and migration measured by radiostereometric analysis (RSA). RSA is a radiological technique that can be used to accurately measure three-dimensional (3D) migration of the knee prosthesis relative to the bone, with resolutions of 0.2 mm.[12]

Methods

A total of 33 patients with 42 consecutive primary cemented TKRs were included in a randomised, controlled trial at the Leiden University Medical Center, which commenced in 1998. The intention was to compare MB and FB TKRs in terms of survival and wear, measured by RSA. All patients gave informed consent. We used the CONSORT guidelines and RSA guidelines for reporting of the ten- to 12-year results.[13,14] Patients were allocated based on a random number table to receive either an FB TKR (Interax PS; Stryker-Howmedica, Rutherford, New Jersey) or an MB TKR -(Interax Integrated Secure Asymmetric (ISA); Stryker-Howmedica). Bilateral cases were performed simultaneously, and randomisation always started with the right knee. The femoral components from both designs had identical geometric shapes. The MB design had a greater contact area than the FB design owing to higher congruency between the bearing surfaces, both between the PE surface and the tibia and between the PE and the femoral component.

Implant and surgical techniques were identical to those described in the two-year results.[15] The PE in the FB group was different from that in the MB group. This difference was previously

unknown until the final evaluation of this study. By this time four liners in the FB group had failed at 1.6, 6.5, 8.2 and 11.6 years post-operatively, whereas none in the MB group had failed. As the liner failures did not require revision of the tibial or femoral components they remained in the migration analyses. The PE in the FB group was GUR 415 gamma sterilised in air and contained calcium stearate. It had a mean shelf-life (i.e., interval between time of manufacture (data provided by manufacturer) and implantation) of 3.0 years. The PE in the MB group was GUR 1050 gamma sterilised in inert gas and free of calcium stearate. The mean shelf-life of the MB inserts was 0.9 years. This randomised trial therefore compared a best-case (superior PE) MB design with a worst-case (inferior PE) FB design.

The study was a single-blinded design during the course of which patients remained blinded to the type of prosthesis they had received. Surgeons and observers were not blinded, as the type of bearing is obvious on radiographs. Inclusion criteria were primary TKR for end-stage osteo-arthritis (OA) or rheumatoid arthritis (RA). Exclusion criteria were revision TKR and a deformity of > 20° in any plane. The two-year results of this trial have been previously reported.[15]

After randomisation there were 21 prostheses in each group. The groups were similar with regard to age, gender, diagnosis, body mass index (BMI), pre-operative limb alignment and function (Table 5.1).[16]

Table 5.1: Baseline pre-operative characteristics

	Mobile (N=21)	Fixed (N=21)
Age (yrs)	64 (SD 11)	66 (SD 14)
Female:Male	18:3	16:5
OA:RA	7:14	6:15
BMI	27 (SD 3.1)	27 (SD 5.4)
FTA angle* (degrees)	178 (SD 8.5)	175 (SD 9.2)
KSS (points)	20 (SD 15)	19 (SD 12)
KSS function (points)	24 (SD 19)	17 (SD 19)

* < 175 degrees is valgus, >175 degrees is varus; OA = Osteoarthritis; RA = Rheumatoid Arthritis; KSS = Knee Society Score

Patients were followed prospectively at three and six weeks, three and six months, and then annually for ten to 12 years post-operatively. During the course of the study eight patients (11 TKRs: three MB, eight FB) died of causes unrelated to surgery. For all patients who died it was known whether they had undergone a revision or not, and their follow-up has been used until time of death at a mean of 5.0 years (2.0 to 8.5). Details of the study flow are depicted according to the CONSORT guidelines in Figure 5.1.

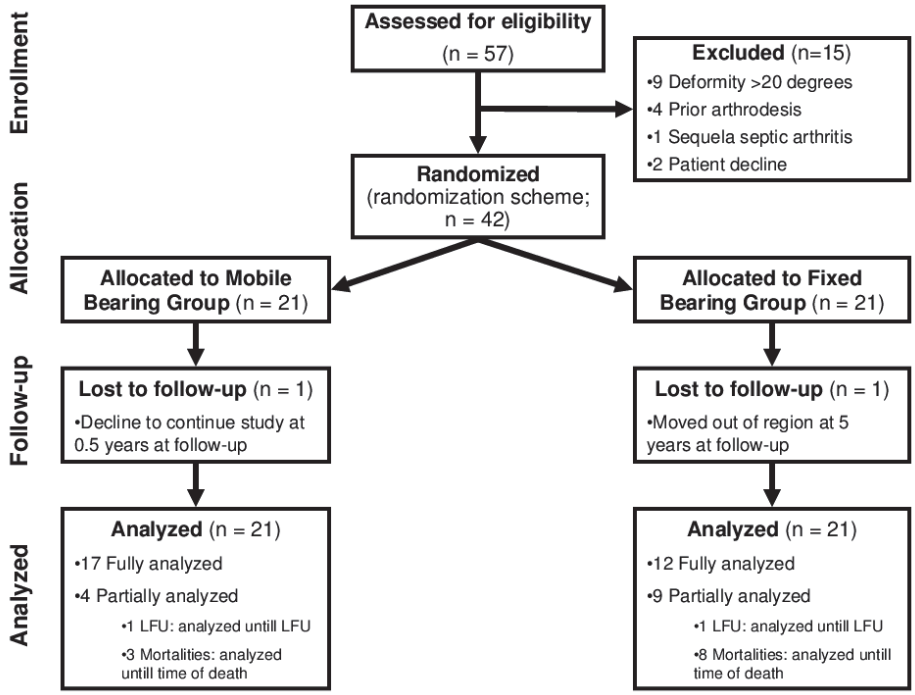

Figure 5.1: CONSORT flow chart of progression through the trial (LFU, lost to -follow-up).

Clinical and radiological evaluation

Clinical evaluation was performed according to the Knee Society score (KSS)[17] at each follow-up. In addition to the RSA radiographs, conventional weight-bearing radiographs were acquired at six weeks, five years and ten years and graded according to the Knee Society roentgenographic evaluation: femorotibial aligment (FTA) angle, as well as α (frontal angle of the femoral component), β (frontal angle of the tibial component) and δ angles (sagittal angle of the tibial component).[18]

Measurement of 3D migration

The first RSA radiograph served as a baseline reference for the measurement of migration, which was performed to a high degree of accuracy throughout the follow-up period.[14] It was determined whether the groups were different with regard to long-term migration expressed in maximal total point motion (MTPM), which is the length of the translation vector of the point on the prosthesis that has moved the most.[14] The three-dimensional migration (translations and rotations) of the tibial components along the *x-*, *y-* and *z*-axes was also assessed.

The RSA setup consists of two synchronised x-ray tubes angled 20° from the vertical and positioned 1.5 m above the x-ray sensor. The RSA was analysed using MBRSA 3.2 software (Medis Specials, Leiden, Netherlands). This enables determination of the relative 3D position of the markers of the prosthesis in relation to the bone markers. In situations where fewer than three markers could be detected in both images of the RSA radiograph, the Marker Configuration Model RSA technique was used to measure the position of a rigid body.[19] This technique was used in six TKRs (two FB and four MB) to save 23 extra follow-up events.

As determined by double examination analysis (n = 33), the bias in the system was very small for translations (*x*-axis -0.01 mm, *y*-axis 0.01 mm and *z*-axis 0.01 mm) and rotations (*x*-axis -0.07°, *y*-axis -0.03° and *z*-axis 0.00°). Accuracy at the 95% confidence level for translations was *x*-axis 0.14 mm, *y*-axis 0.12 mm and *z*-axis 0.28 mm. For rotations the accuracy was *x*-axis 0.50°, *y*-axis 0.46° and *z*-axis 0.12°. These values indicate a high level of precision for the measurement of migration of the tibial component relative to the bone and the absence of any systematic bias. In 2002 the calibration cage of our RSA unit was replaced, but this had no effect on the accuracy of the measurements (p = 0.72, linear regression).

Measurement of wear on the undersurface of the mobile bearings

The amount of wear on the under-surface of the mobile PE inserts at follow-up was measured using RSA. Wear was defined as a change in distance in the proximal–distal direction between tantalum markers in the PE insert and those in the tibial component. Markers (3) on the tibial component provide a reference for migration of the marker model of the PE insert in the proximal and distal directions. The markers were inserted from the periphery of the PE in order to prevent them becoming detached, a situation that could imitate wear. In order to allow reproducible insertion, the tantalum markers were inserted during surgery with drill guides at predefined angles and depths.[15]

Because the PE insert is designed to move only in the transverse plane and not proximally or distally, it is possible to define wear as the migration of the PE markers in the distal direction. In every case wear followed a linear pattern over time.

As the MB and FB groups were different regarding the quality of the PE, it is not possible to study whether the MB reduces PE wear more than the FB. For this reason it was decided that it was not appropriate to determine the linear wear rate in the FB group.

In the MB group the total linear wear of the PE insert was measured on conventional anteroposterior (AP) radiographs as described by Collier et al,[20] while using the size of the central stem to correct for the magnification caused by diverging X-ray beams. Hide et al[21] have shown that this method allows repeatable and precise measurement of insert thickness. The wear at the femorotibial

articulation was defined as the total linear wear minus wear between the PE insert and the tibial surface.

Statistical analysis

Owing to the high degree of accuracy of RSA, 20 TKRs were required for each arm of the trial, as was standard for RSA studies at the time this study was designed.[22] The results were analysed according to the intention-to-treat principle. To take into account the repeated measures design of the study, bilateral cases (n = 9), any missing follow-up moments and variations in follow-up duration, a generalised linear mixed model (GLMM) was used, which is considered the analytical method of choice for this type of clinical study.[23] A p-value < 0.05 was considered statistically significant.

Results

Clinical and radiological evaluation

The clinical results are presented in Table 5.2. Post-operatively there was a mean 68 points (63 to 74) increase in KSS compared with the pre-operative scores. There was no statistically significant or clinically relevant difference in the KSS knee score between the two groups (p = 0.85, GLMM). Death had no effect on KSS score (p = 0.24, GLMM). Post-operatively there was a mean 44 points (34 to 54) increase in KSS function score compared with pre-operatively. There was no statistically significant or clinically relevant difference in KSS function between the groups (p = 0.14, GLMM). There were also no significant differences in flexion between the groups.

Table 5.2: Clinical Results presented as means, standard deviation (SD) and 95% confidence interval [95%CI]

		Mobile Mean; SD; [95%CI]	Fixed Mean; SD; [95%CI]
KSS* (points)	5 yr	91; 5; [88-94]	85; 15; [76-94]
	10 yr	84; 13; [76-92]	90; 6; [86-95]
	Last FU^	81; 15; [74-88]	82; 17; [75-90]
KSS Function** (points)	5 yr	73; 30; [59-88]	55; 34; [36-75]
	10 yr	63; 28; [46-80]	63; 33; [39-86]
	Last FU^	52; 33; [36-67]	33; 36; [16-50]
Flexion (degrees)	Last FU^	110; 11; [104-115]	109; 14; [103-115]

* p = 0.85 GLMM
** p = 0.14 GLMM
^mean 8 years follow-up (range 6 months to 12 years)

The radiological results are presented in Table 5.3. There was no statistically significant or clinically relevant difference in FTA angle between the MB and FB groups (p = 0.94, GLMM), and no statistically significant or clinically relevant differences in α, β or δ angles. The groups were comparable with regard to the incidence of radiolucent lines at ten years' radiological follow-up. Two partial 2 mm radiolucent lines in the MB group, both at the lateral side of the tibial tray, were noted and one partial 2 mm radiolucent line in the FB group was observed at the medial side of the tibial tray.

Table 5.3: Radiological Results presented as means, standard deviation (SD) and 95% confidence interval [95%CI]

			Mobile Mean; SD; [95%CI]	Fixed Mean; SD; [95%CI]
FTA angle* (degrees)		PO	178; 2.7; [177-179]	178; 2.7; [177-179]
		5 yr	178; 2.0; [177-179]	179; 3.3 [177-181]
		10 yr	179; 2.7; [177-180]	181; 3.9; [179-184]
Alpha angle (degrees)	PO		94; 2.3; [93-95]	94; 2.8; [93-95]
Beta angle (degrees	PO		87; 2.9; [86-89]	87; 2.5; [86-88]
Delta angle (degrees)	PO		88; 2.2; [87-89]	88; 2.1; [87-89]

* p = 0.94GLMM; < 175 degrees is valgus, >175 degrees is varus
PO = post-operatively
FTA angle = Femoral-Tibial Aligment
Alpha angle = Frontal angle of the femoral component
Beta angle = Frontal angle of the tibial component
Delta angle = Saggital angle of the tibial component

3D migration

A total of 447 RSA analyses form the migration analysis. At ten years' follow-up the mean MTPM was 0.75 mm (sd 0.76) in the MB group and 0.66 mm (sd 0.4) in the FB group (p = 0.42, GLMM) (Figure 5.2). Throughout the follow-up the difference in MTPM between the two groups was neither statistically significant nor clinically relevant: MTPM MB – MTPM FB = 0.05 mm (95% confidence interval (CI) -0.07 to 0.17). When restricted to patients with OA the difference in MTPM was 0.02 mm (95% CI -0.13 to 0.16), and when restricted to RA patients the difference was 0.11 mm (95% CI -0.08 to 0.30). In the FB group there were two tibial components with continuous migration and none in the MB group. The rates of migration were not different in the group of patients who died. The mean translations and rotations are presented in Figure 5.3. The FB tibial components showed slightly more lateral translation, subsidence and posterior tilt, whereas the MB tibial components showed more internal rotation (p < 0.001 in all cases, GLMM).

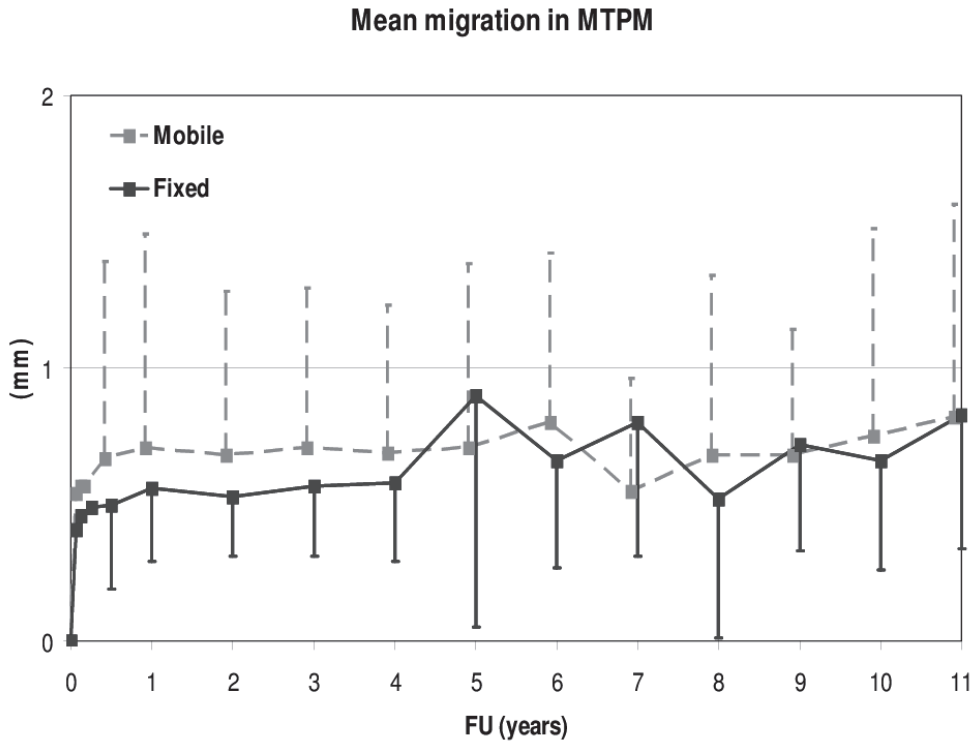

Figure 5.2. Graph showing the mean migration in maximum total point motion (MTPM) according to the duration of follow-up in the mobile- and fixed-bearing groups. The groups do not differ significantly in MTPM ($p = 0.42$, GLMM). The error bars represent the standard deviation.

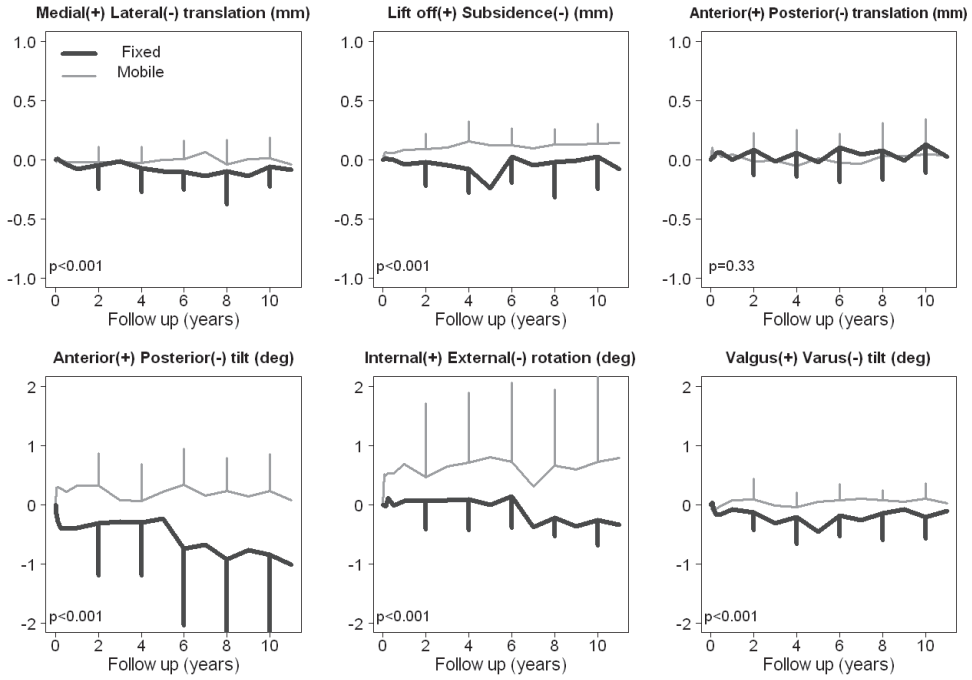

Figure 5.3. Graphs showing the mean translations (upper row) and rotations (lower row) according to the duration of follow-up in the mobile- (MB) and fixed-bearing (FB) groups. For reasons of clarity the standard deviation (vertical bars) is only presented for two, four, six, eight and ten years' follow-up. The FB tibial components showed statistically significantly more lateral translation, subsidence and posterior tilt. The MB tibial components showed statistically significantly more internal rotation. All analyses using generalised linear mixed model statistics.

Wear of the mobile bearings

The mean linear wear on the tibial bearing surface of the PE component for the MB group was 0.026 mm/year (0.019 to 0.033) (Fig. 5.4). The mean total linear wear rate was 0.14 mm/year in the MB group (0.11 to 0.17). The mean wear of the PE at the femoral bearing surface was 0.11 mm/year (0.08 to 0.14). The mean tibial surface PE wear rate of 0.026 mm/year was significantly smaller than the mean wear rate of 0.11 mm/year at the femoral bearing surface ($p < 0.001$).

Complications

In the MB group there was one case that required revision of all components because of septic loosening. None of the bearings dislocated. In the FB group there were two cases that required revision of all components, one for aseptic loosening and one for septic loosening. There were four cases in the FB group that required exchange of the PE insert. The reason was wear and

subsequent instability in three cases and fracture of the posterior stabilising central post of the insert after a fall in one case. Including these four liner failures, there was a total of six revisions in the FB group during almost 12 years of follow-up, compared with one revision in the MB group.

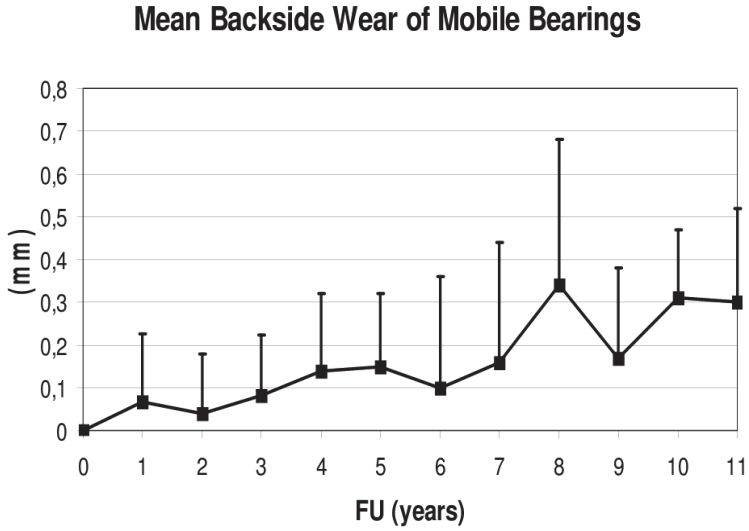

Figure 5.4. Graph showing the mean linear underside wear of the polyethylene mobile-bearing according to the duration of follow-up, measured with radio-stereometric analysis. The error bars represent the standard deviation

Discussion

The results of this randomised controlled trial using RSA show that the MB had comparable migration to the FB during ten to 12 years' follow-up. Therefore, even in a best-case scenario (superior PE in the MB group), the MB design did not yield any apparent advantages in terms of long-term fixation compared with the FB design with femoral components of the same geometrical shape. A mean difference in MTPM < 0.2 mm is not considered clinically relevant.[12,14] There are no studies with long-term RSA follow-up available in the literature for comparison. However, studies with two years' RSA follow-up by Hansson et al[24] and Henricson et al[25] also found no difference in MTPM between mobile and fixed bearings. In comparison to the previous report by Garling et al,[15] who presented the two-year results of this trial, there was higher variability in subsidence and AP tilting in the FB group. However, at that time no-one was aware of the confounding manufacturing and sterilisation differences in the PE, used in the two versions. Therefore the MB design was considered more predictable and forgiving with respect to

migration of the tibial component. This conclusion can no longer be supported. In this updated study the FB group showed statistically more posterior tilting than the MB group, but the clinical relevance of this finding is unclear. One explanation might be the posterior-stabilised design of the FB insert compared with the MB insert. Strain on the post in the FB prosthesis due to contact with the femoral component during flexion may have caused posterior tilting.

In addition, there was statistically more internal rotation of the MB group relative to the bone, whereas there was little rotation in the FB group. This finding is surprising, considering that MB TKRs are designed to, and indeed have been shown to reduce strain on the proximal tibia.[26] However, not all MB designs are the same. This particular MB design accommodates only guided rotation through a curved slot on the underside of the liner with respect to the polished tibial tray, and not full freedom to rotate around a central or eccentric tibial tray post. Therefore, the seemingly paradoxical outwards rotation in this MB TKR might be due to the friction between the curved slot and the metal tibial pivot post.

The number of revisions in this series was small. These results are in accordance with other trials where no difference was found in revision rate at long-term follow-up.[8-10] With regard to medium-term follow-up, several meta--analyses could not demonstrate a difference in revision rates.[4-7] Therefore, additional trials of long-term follow-up are needed to investigate whether mobile bearings have any advantage over the fixed bearings regarding revision rates.

The additional articulating surface for MB TKRs may itself be a source of problems. In particular, Engh et al[27] found pitting, scratching and burnishing on the underside of the PE to be greater in mobile than in fixed bearings. However, *in vivo* we found only a small amount of wear under the mobile bearing of 0.3 mm at 11 years' follow-up, which corresponds to a rate of wear of 0.026 mm/year. This backside wear rate was significantly smaller than the wear rate of the PE between the mobile insert and the femur of 0.11 mm/year ($p < 0.001$), and is unlikely to be of clinical relevance.

Although this was a small series there were no differences between the MB and FB groups with regard to clinical outcomes and radiological parameters. These findings confirm the results of several meta-analyses.[4-7]

The strengths of this study are the randomised design, the objective outcome measures (RSA, linear wear), the long-term follow-up, blinding of the patients, and the fact that the femoral components of both the mobile- and the fixed-bearing group were identical in geometric shape. We were also able to demonstrate that even in a best-case scenario the MB knee prostheses have no apparent advantage for long-term fixation or wear over the FB prostheses.

This study has some limitations. Because the type of bearing is recognisable on radiographs the observers were not blinded during the RSA analysis. However, RSA is a standardised and objective

method with low susceptibility to individual interpretation, so the risk of bias can be considered negligible.[14]

It should be accepted that although the study has sufficient power to delineate RSA differences, this is unlikely to be true for the clinical scores. The possibility that the results were affected by differences in migration between RA and OA patients should also be considered. A separate analysis on the difference in migration between MB and FB restricted to either RA or OA patients was carried out and no difference in migration rates between the two cohorts was demonstrable. Finally it is accepted there was a serious confounder as the MB inserts were produced in superior quality PE that was sterilised in inert gas, unlike the material used in the FB TKRs.

In conclusion, even in a best-case setting the AP sliding, rotating mobile bearings of the studied TKR have no clinically relevant advantage on long term fixation over the studied FB knee prosthesis. The backside wear underneath the mobile bearing was small and may not be of clinical relevance.

Acknowledgement

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Chapter 6

AQUILA: assessment of quality in lower limb arthroplasty. An expert Delphi consensus for total knee and total hip arthroplasty

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Abstract

In the light of both the importance and large numbers of case series and cohort studies (observational studies) in orthopaedic literature, it is remarkable that there is currently no validated measurement tool to appraise their quality. A Delphi approach was used to develop a checklist for reporting quality, methodological quality and generalizability of case series and cohorts in total hip and total knee arthroplasty with a focus on aseptic loosening.

A web-based Delphi was conducted consisting of two internal rounds and three external rounds in order to achieve expert consensus on items considered relevant for reporting quality, methodological quality and generalizability.

The internal rounds were used to construct a master list. The first external round was completed by 44 experts, 35 of them completed the second external round and 33 of them completed the third external round. Consensus was reached on an 8-item reporting quality checklist, a 6-item methodological checklist and a 22-item generalizability checklist.

Checklist for reporting quality, methodological quality and generalizability for case series and cohorts in total hip and total knee arthroplasty were successfully created through this Delphi. These checklists should improve the accuracy, completeness and quality of case series and cohorts regarding total hip and total knee arthroplasty.

Introduction

Observational studies (case series and cohorts) provide an important source of knowledge on total hip arthroplasty (THA) and total knee arthroplasty (TKA). In addition to personal experience, they are the most common type of evidence used by orthopaedic surgeons for clinical decision making according to a survey of the participants at the 2007 Annual Meeting of the American Orthopaedic Association [1].

Nevertheless, their rank in the hierarchy of scientific evidence is lower than evidence obtained from randomised experiments, and they often suffer from lack of a control group, incomplete data collection, selection bias and confounding by indication [2]. Despite these issues, case series and cohorts are important in signalling inferior prosthesis designs, particularly those prone to aseptic loosening, which accounts for 60% of THA revisions. They are therefore a valuable addition to clinical trials and implant registries [3-6]. Further advantages are great detail, relatively low costs, short study completion time and a potentially high external validity due to the inclusion of a wide range of patients [2].

Considering the substantial value and large volume of case series and cohorts in orthopaedic literature as well as the methodological issues mentioned above, it is remarkable that there is currently no validated measurement tool to appraise their quality [7]. A validated measurement tool could contribute to more accurate, transparent and complete case series and cohorts, resulting in higher quality [8]. Although STROBE is available as a guideline for reporting in observational studies it lacks details that are important for TKA and THA such as details on type of implant and surgical technique. Additionally, the STROBE-group has recently emphasized that STROBE is a reporting guideline and that it should not be misused for the appraisal of methodological quality [9].

The aim of this study was therefore to develop a tool to appraise the reporting quality and methodological quality of case series and cohorts of lower limb arthroplasty with emphasis on revision for aseptic prosthesis loosening by means of a Delphi approach. The second aim was to construct a checklist of items that are important for the generalizability of the results of case series and cohorts.

Methods

A Delphi approach was used for the development of a checklist for reporting quality, a checklist for methodological quality and a generalizability tool. The Delphi approach is a well recognized research method for consensus formation amongst a group of experts through several iterations

of questionnaires [10,11]. The advantages are anonymity of the participants, so avoiding dominance, expression of consensus by summary measures and several iterations with controlled feedback, which allows individuals to change their opinion in light of the group's response. A Delphi takes full advantage of both the research and clinical experience of the involved experts while imposing no geographical limitations on participation [10].

Design of Delphi

An internet-based Delphi design was adapted from Graham et al. and the reporting was according to the CHERRIES guidelines for reporting results of internet E-surveys [12,13]. The focus of the Delphi was on the revision rate for aseptic loosening in TKA and THA. During the conceptual phase we determined that the checklists should require quality items (internal validity) and generalizability items (external validity) specific for TKA and TKA. Furthermore the quality items should include items for the appraisal of selection bias, confounding by indication and competing events [2,14]. Additionally, the checklists had to be easy to use, be able to be completed in an acceptable amount of time and had to allow for the possibility that items be scored as "unknown" in cases with insufficient information.

A master list of relevant items was created as a pre-checklist to allow external experts to asses the face validity and to further develop the final checklist through a Delphi method in an efficient fashion with the desire to optimize the construct validity. This kind of approach is common for consensus development through a Delphi [15-17]. The master list was generated from items of a recent systematic review of the literature and from the Equator Network website http://www.equator-network.org/ webcite [18,19]. The authors of the manuscript, the internal working group, achieved consensus after evaluating and revising this master list in two internal rounds. The actions of the internal working group consisted of the rephrasing of selected items, so that these items met the requirements described above. Since item generation for the master list is an important initial step that may determine the course of the Delphi, we ensured that the members of the internal working group covered all fields (TKA, THA and epidemiology) of the Delphi, that no items were discarded during the internal rounds and that the master list was as comprehensive as possible. Additional aims of the internal rounds were completion of the master list and further testing and fine tuning of the web-based Delphi survey form. During the external rounds of the Delphi survey the internal working group analyzed and discussed the external experts' answers after each round, modified the list of items accordingly and rephrased, merged and clarified individual items to optimize their clarity and conciseness.

The Delphi survey consisted of three external rounds and the external experts consulted were not involved in the internal rounds and did not take part in the development of the survey [16]. In

accordance with the principles of a Delphi survey each expert remained blind to the identity of other experts. The experts who completed the first external round were invited to participate in the second and third external rounds. During the second and third round the experts received a newly created checklist which was modified according to the results of the preceding round. Each item of the newly created checklist was presented with a summary of the groups' response to allow the experts change their answer in view of the groups' response [13].

Invited experts were identified via Pubmed and were required to have had at least one international peer-reviewed publication in the last three years in the field of TKA, THA or evidence based medicine in more general terms (expertise in musculoskeletal field or reporting guidelines or advised by one of the authors). One reminder was sent to those experts who did not respond during the first external round. Four reminders were sent to non responders during the second and third external rounds. The reminders consisted of a personal e-mail message sent by the internal experts when applicable, in order to maximize the response rate [20]. The first internal round commenced in July 2009 and the last external round was concluded in June 2011.

Design and handling of the E-survey

An electronic form was created in Google documents comprising 50 items in the first internal round, 42 items in the second internal round, 45 items in the first external round, 48 items in the second external round and 22 items in the third external round (only generalizability). The survey consisted of general items (e.g. expert name; remarks boxes), quality items and generalizability items.

External experts were invited by e-mail to complete the online survey. This e-mail contained a link to the survey, information regarding the purpose of the Delphi and an estimate of the duration of the survey as derived from the internal rounds. Experts were informed that they would be invited for further rounds before opening the survey. The only incentive used was an offer to the external experts of a mention in the acknowledgements on the condition of completion of two rounds.

All items of the survey, except the remarks boxes, were required items. Omitted questions were highlighted in cases with an incomplete submission. The survey consisted of a mixture of multiple-choice and open questions and included text boxes for remarks in order to take full advantage of the knowledge of the expert panel and to ensure creativity of the items. Furthermore all the multiple-choice questions in the first external round had the "other" option with a free text field, so that no restrictions were placed on the answers of the experts. Additionally, opportunity was given to the experts to add items, to modify wording of items and to give explanations and reasons for their answers. Text boxes for remarks ensured that experts could make additions, suggestions and remarks in an unrestricted manner.

Each expert had to answer all questions. Since the survey comprised multiple areas of expertise the experts could choose the option "*no opinion*" when necessary. Experts were able to view and change their answers before submission.
Experts were also asked for their names and e-mail addresses in order to prevent duplicate entries from the same individual.

Domains of the Delphi

The three domains of the Delphi checklist were reporting quality, methodological quality and generalizibility.

Reporting quality and methodological quality

The Delphi distinguished between reporting quality and methodological quality, because while reporting quality is particularly important for transparency, methodological quality is helpful in appraising and understanding the sources and magnitude of bias in a study [9]. Accordingly, a study with a high level of reporting quality may be methodologically unsound (low methodological quality) and vice versa.

Generalizability

The fact that two studies will never be completely identical poses difficulties for the comparability and generalizability of their results [21]. Since patient demographics, component positioning, post operative functioning (activity level) and regional influences may all affect revision rates for aseptic loosening, so it is important to investigate to what extent each factor may differ between two studies [5,22-24]. For example, are the results of a study with 60% female patients comparable to those of a study with 90% female patients when all other factors are the same? Does each factor need to be exactly the same or are small differences acceptable and if so, to what extend? In order to identify relevant items, the experts were asked to select items that are important for case series and cohorts with aseptic loosening in TKA and THA. When an item was chosen they were then asked to specify the extent of the allowable difference, for each relevant factor, that would be acceptable when comparing different studies in terms of generalizibility.

Statistical analysis

Standard descriptive statistics were used. For an item to be included in the final checklists it must have been selected by at least two thirds of the experts [25].
For generalizibility items the mode was determined, which is the value that was chosen most frequently (e.g. 5 years). The preference for the mode value was calculated by dividing the

number of experts who chose the mode value by the total number of experts who considered the generilizability item relevant (N_{Mode}/N_{Total}) The preference was considered high in case 80% or more of the experts chose the mode value. The preference was considered moderate in case 67% to 80% of the experts chose the mode value and the preference was considered low in case fewer than 67% of the experts chose the same value.
The "*no opinion*" answers were not used for the calculation of agreement, because this option could be used by experts when faced with a question outside the scope of their expertise.

Results

Delphi flow

An overview of the Delphi flow and the number of experts involved in each round is depicted in Figure 6.1. Of the 272 experts contacted, 44 agreed to participate and completed the first external round. 37 of them also completed the second (n = 35) or third (n = 33) external round. These 37 external experts form the basis of this Delphi and had a mean experience of 16 years (range 3 to 30 years; S D7.5), see Table 6.1 for the area of expertise. The professional background of the experts was as follows: 30 orthopaedic surgeons or residents, 5 epidemiologists, 1 biomedical engineer and 1 physical therapist. The mean number of publications for all expert was 80 (range 2 to 445). The experts were of the following 17 nationalities covering 5 continents: American, Argentinean, Australian, Austrian, Belgian, British, Danish, Dutch, Finish, French, German, Indian, Israelian, Italian, Spanish, Swedish and New Zealander. Additional characteristics of the experts are presented in Table 6.1. The mean total completion time for all external rounds was 32 minutes SD 13 (range 17 to 65 minutes). There were no apparent differences in ratings and answers between the experts who completed both external rounds and those who only participated in the first external round.

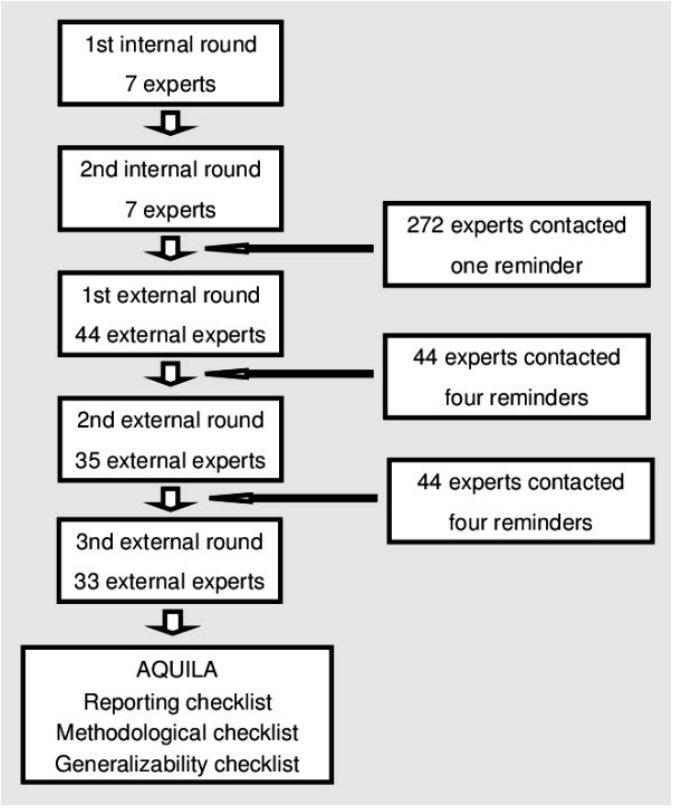

Figure 6.1 Flowchart. Overview of the Delphi flow and the number of experts involved in each round.

Table 6.1: Characteristics of experts (N =-37) who completed both external rounds

	Count
Area of expertise[a]	
• Hip surgery	24
• Knee surgery	20
• Evidence Based Medicine	11
• Other[b]	7
Background*	
• Academic	27
• Public	9
• Private	6
• Other[c]	2

[a] Multiple answers for each expert are possible. Therefore the total is more than 35.

[b] One expert indicated "Implant Biology" in the other field. The remaining 6 answers in the other field were in addition to either "Hip surgery", "Knee surgery" or "EBM"

[c] One expert indicated "Private Research Center" in the other field. The remaining answer in the other field was in addition to "Private Hospital".

Reporting quality and methodological quality

At the beginning of round 1 the Delphi consisted of two domains as determined by the internal working group: quality (internal validity) and generalizability (external validity) After round 1 a clear distinction between reporting items and methodological items was made, as suggested by one of the external experts. The quality items were therefore allocated to either the reporting quality checklist or methodological quality checklist. Furthermore, the FU-quotient has been added to methodological quality item nr 3, as suggested by one of the external experts [26]. Additional modifications after round 1 consisted mainly of rephrasing. Some items were divided into two separate items (5 years post-operatively and 10 years post-operatively). Following round 1 these items were compiled into one item without a time specification.

By the second external round, agreement was reached on eight items relating to reporting quality as well as on six items on methodological quality. Additionally, 21 of the 35 experts indicated that a case series or cohort should include at least 100 arthroplasties at baseline in order to accurately determine the number of revisions or revision rate. The answers ranged from a minimum of 40 to a minimum of 300 arthroplasties. The final list of items covering reporting quality and methodological quality can be found in Table 6.2.

Table 6.2: The final AQUILA checklist for use by authors

Reporting Quality Item
1. Are the in- and exclusion criteria clearly reported?
2. Is information adequately reported regarding the number of patients who did not gave informed consent and who were not willing to participate?
3. Are the baseline characteristics of included patients reported?
4. Is the surgical technique adequately reported?
5. Are the prosthesis brand and fixation reported with enough detail?
6. Are the reasons or definitions for revision adequately reported?
7. Are the number of revisions (N) and revision rates regarding aseptic loosening (either Kaplan-Meier or life table or revisions per 100 observed component years) adequately reported?
8. Are the number of deaths, lost-to-follow up (e.g. no show at clinic or emigration), amputations, and revisions other than the primary endpoint adequately reported?

Methodological Quality Item
1. Is there a clear primary research question / hypothesis?*
2. How were the cohorts constructed?
a. Consecutively[a]
b. Non-consecutively
c. Unknown
3. How was the adequacy of follow-up (FU)?
a. Fully completed FU
b. 5% or less lost-to-FU or FU quotient[b] is 1 or less
c. More than 5% lost-to-FU or FU quotient is more than 1
d. Unknown
4. How as the FU performed?
a. Predefined e.g. yearly
b. When patient had complaints or chart review (of non-predefined FU)
c. Unknown
5. How many arthroplasties are at risk at the FU of interest?
a. 20 or more
b. Less than 20
c. Unknown
6. Is a worst case analysis or competing risk analysis for competing endpoints[28] performed?

* In case of aseptic loosening: Does the research question or hypothesis include revision of the component due to aseptic loosening?

[a] Consecutively is defined as all patients receiving an arthroplasty (TKA or THA) in a defined period of time have also received the arthroplasty of interest. The following situation is therefore non-consecutive: all patients receiving prosthesis X while prosthesis Y has also been used for the same indication during that period of time.

[b] FU quotient = Number of lost to follow up / Number of failures [26]

Generalizibility

After round 1 the following items were dropped from the checklist, because less than two thirds of the external experts found them relevant: Hospital for Special Surgery Score (TKA), Merle D'Aubigné Score (THA) and Range of Motion (THA). After the second round the following items

were added to the checklists, as suggested by one of the experts: KOOS (TKA), WOMAC (TKA), Oxford Knee Score (TKA), HOOS (THA), WOMAC (THA) and Oxford Hip Score (THA). All these six items were considered relevant in the third round and thus remained in the final checklist.

Twenty-two items, related to the comparison of revision rates between studies, were agreed upon by the third external round. These items comprised domains of patient demographics, component positioning, post-operative functioning and regional influences. The final list of these generalizability items can be found in Table 6.3.

Table 6.3: Expert agreement to allowed difference of generalizability items between two studies

Generalizability item		Mode [a]	N_{Mode} of N_{Total} (%)[b]	Preference for mode value[c]
Patient demographics				
Age		5 years	22 of 31 (71)	M
Gender		10%	20 of 30 (67)	M
Diagnosis		10%	17 of 31(55)	P
BMI		5 points	16 of 29 (55)	P
Component positioning				
TKA	Hip Knee Angle	5 degrees	13 of 24 (54)	P
	Varus/valgus tibial component	3 degrees	17 of 25 (68)	M
	Slope of tibial component	3 degrees	15 of 24 (63)	P
THA	Inclination of acetabular cup	10 degrees	19 of 28 (68)	M
	Varus/valgus femoral stem	5 degrees	16 of 27 (60)	P
Post-operative functioning				
TKA	Knee Society Score	10 points	18 of 23 (78)	M
	Knee Society Function Score	10 points	20 of 24 (83)	G
	Range of Motion	10 degrees	18 of 24 (75)	M
	KOOS	10 points	11 of 17 (65)	P
	WOMAC Knee	10 points	11 of 19 (58)	P
	Oxford Knee Score	5 points	18 of 24 (82)	G
THA	Harris Hip Score	10 points	17 of 21 (81)	G
	HOOS	10 points	12 of 17 (71)	M
	WOMAC Hip	10 points	12 of 20 (60)	M
	Oxford Hip Score	5 points	16 of 22 (73)	M
Regional influences				
Are the studies from the same region (developing country or western countries // continents)?				
Are the studies similar in type en experience of the surgeon (academic; high volume; consultant; trainee)?				
Are two studies similar regarding hospital type (developer hospital/ special institute/ regular hospital)?				

[A] Mode: the value that was chosen most frequently (e.g. 5 years)
[b] N_{Mode} = the number of experts who chose the mode value
N_{Total} = the total number of experts who considered the generalizability item relevant
[c] H = High preference, 80% or more of the experts chose the mode value
M = Moderate preference, between 67% and 80% of experts chose the mode value
L = Low preference, less than 67% of experts chose the mode value
Example: the preference for the mode value "5 years" is moderate.

Discussion

The AQUILA initiative resulted in a checklist for reporting quality, methodological quality and generalizability for case series and cohorts of total hip and total knee arthroplasty. The STROBE guidelines are already available for use in reporting original patient research in TKA and THA. The AQUILA checklist now adds to these guidelines, as a treatment specific extension of STROBE, addressing items that are specific for TKA and THA in observational studies. Additionally, the AQUILA checklist addresses both methodological quality and generalizability, while STROBE is strictly a reporting guideline [9]. Since there are currently no specific checklists available for the assessment of case series or descriptive cohorts in lower limb arthroplasty, nor in orthopaedics in general, the AQUILA checklists should have an important role in improving the accuracy, completeness and quality of TKA-and THA-related case series and cohorts [8].

In terms of generalizability, there was consensus on the items that are relevant when comparing revision rates between studies, although in round 3 most of the included postoperative functioning items only just reached the cut off point of two thirds. However, the preference for the mode values (e.g. 5 years) was mostly moderate and even low for some items. This was most notable for component positioning and some functional outcome scores and may be a reflection of the ongoing research into the development of a core set of outcome measures and the current controversy in literature regarding neutral alignment of prostheses [27,28].

We should also note some limitations. As mentioned above, although consensus was achieved on the relevance of the generalizability items, the preference for the mode value (e.g. 5 years) was mostly moderate and even low for some items. The latter should therefore be interpreted with some caution. Furthermore, the application of a pre-checklist may have dampened the creativity of the external experts. However, this approach has been successfully used in the development of other checklists [15-17].

The possibility that the results were affected by non-responder bias should also be considered. As is the case for all surveys, the responders may have different opinions to those of the non-responders. However, experts who participate in a survey can be very similar to those who decline, as demonstrated by a study from McKee et al [29]. Indeed, the final expert panel in our study consisted of a balanced sample representative of the international musculoskeletal scientific community involving 17 nationalities on five different continents and included experts with a wide range of experience (mean 16 years range 3 to 30 years). Furthermore, the face validity of the checklists was good and at least 88% of the experts with an opinion consider the reporting quality and methodological quality items relevant. Moreover, the experts were unanimous in 8 out of 14 items.

The participation rate was 44/272 (16%). This is towards the lower end of participation rates commonly achieved in this type of survey [20,30]. The number of experts who completed at least two external rounds (n = 37) is respectable, considering that some Delphi's are based on as few as 12 experts [11,13]. Our aim was to obtain a balanced and representative sample of experts thus minimizing bias due to the selection of a small group of experts with a particular opinion. This highly sensitive approach could therefore have resulted in a dilution of available and interested experts. Accordingly, the response rate of the first external round is the trade off for the representative and balanced sample of experts obtained in our study. Furthermore, as only complete responses were recorded, incomplete responses could have been missed. Nevertheless 44 experts responded to the first external round and the response rate in the second (80%) and third (75%) external rounds was high.

It is not uncommon that studies of the same type of TKA or THA report rather different revision rates [31]. What factors have caused this difference? Are dissimilarities in patient demographics the cause, or component positioning, or post-operative functioning or perhaps regional influences (including skill and experience of the surgeon)? The generalizabity checklist provides a tool to help address this issue. For example: if the difference in mean age between two study populations is lager than 5 years, age is considered an important factor according to the results of the AQUILA.

Although the name *Assessment of Quality in Lower limb Arthroplasty* may suggest otherwise, the AQUILA was developed specifically for THA and TKA, and does not include Total Ankle Arthroplasty (TAA) or other types of lower limb arthroplasty. However, some of the reporting and methodological quality items may also be useful for the appraisal of these types of lower limb arthroplasty studies, since the mechanisms of bias (e.g. selection bias and competing risks) are the same [2,14]. On the other hand, the recommended minimal number of arthroplasties at baseline (100) may not be realistic for TAA Studies. Some of the generalizibility items, especially regarding component positioning and post-operative functioning may also not be applicable to TAA studies.

While the AQUILA checklist was specifically developed for revision rates for aseptic loosening, it may also be useful for other endpoints in lower limb arthroplasty, such as revision rates for septic loosening or revision for other reasons, since the mechanisms of bias are the same [2,14].

In conclusion, the AQUILA checklist is the first tool that can be used to assess the quality of reporting, methodology and generalizibility in case series and cohorts in lower limb arthroplasty. Use of the checklist will lead to more accurate, transparent and complete case series and cohorts in this field [8].

Authors' contributions

The following authors designed the study BP, EV, HH, RN, SM, analyzed the data BP, HH, wrote the manuscript BP, HH, OD and ensured accuracy of data and analysis HL, RN, OD, SM. All authors were involved as internal experts for the creation of the master list, completed both two internal rounds and assisted during the external rounds. Critical revision of the manuscript was performed by all authors. All authors read and approved the final manuscript.

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Note that their participation in this study does not imply full agreement with the final checklist of items.

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Chapter 7

Early migration of tibial components is associated with late revision

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Abstract

We performed two parallel systematic reviews and meta-analyses to determine the association between early migration of tibial components and late aseptic revision.

One review comprised early migration data from Radiostereometric analysis (RSA) studies, while the other focused on revision rates for aseptic loosening from long term survival studies. Thresholds for acceptable and unacceptable migration were determined according to that of several national joint registries: <5% revision at 10 years.

Following an elaborate literature search 50 studies (847 Total Knee Prostheses(TKP)) were included in the RSA-review and 56 studies (20,599 TKP) were included in the survival-review. The results showed that for every mm increase in migration there was an 8% increase in revision rate, which remained after correction for age, sex, diagnosis, hospital type, continent, and study quality. Consequently, migration up to 0.5 mm was considered acceptable during the first post-operative year, while migration of 1.6 mm or more was unacceptable. TKP with migration between 0.5 and 1.6 mm were considered at risk for revision rates higher than 5% at 10 years.

There was a clinically relevant association between early migration of TKP and late revision for loosening. The proposed migration thresholds can be implemented in a phased evidence-based introduction of new types of knee prostheses, since they allow early detection of high risk TKP while exposing only a small number of patients.

Introduction

Worldwide several hundred thousand Total Knee Prostheses (TKP) are implanted each year and this number is expected to increase by a factor 6 within the next 2 decades [1,2]. Most of the new TKP designs have been introduced on the market without demonstrating safety or effectiveness [3]. This has resulted in the widespread use of TKP with failure rates exceeding 10 times the standard of national joint registries (5% failures at 10 years follow-up), such as the Accord, St Leger and Journey-Deuce [3-6]. As a response several countries have developed guidelines to guarantee patient safety e.g. the NICE guidelines for total hip prostheses [7]. Furthermore, it has become increasingly evident that a phased evidence-based introduction, as is common for pharmaceuticals, is needed to regulate the introduction of new TKP to the market [8-10]. This should include systematic assessment and early detection of the major cause of TKP failure, which is aseptic loosening of the tibial component necessitating revision surgery [7,11].

Although it may take 10 years before loosening may cause symptoms, it is possible to detect loosening early post-operatively with Radiostereometric analysis (RSA) [12-15]. Since, RSA allows in vivo, three-dimensional measurement of the migration of TKP with an accuracy of 0.2mm for translations and 0.5 degrees for rotations, only a small number of patients have to be exposed to potentially unsafe TKP [13,14,16]. RSA could therefore play an important role in the phased evidence-based introduction of new TKP [12,13,15]. However, the evidence for the relation between early migration and TKP revision for aseptic loosening is limited to a few studies from the 1990s [13,14]. Furthermore, the applicability of these studies is restricted, because both surgical technique, fixation methods, implant design and polyethylene have evolved since their publication.

We hypothesize that early migration of the tibial component, measured through RSA, is associated with late revision for aseptic loosening in TKP. Therefore, we set out to systematically review the association between early migration and late aseptic revision for the tibial component in TKP. Ultimately, this could lead to clinical guidelines to be used in a phased introduction of new TKP.

Methods

We performed two parallel systematic reviews (international registration number NTR2417; www.trialregister.nl) on studies of patients treated with TKP for end stage osteoarthritis (OA) and rheumatoid arthritis (RA). One review comprises early migration data of TKP from RSA studies. In the other we determined the long term revision rates for aseptic loosening of TKP from survival studies. Figure 7.1 shows the flow of the systematic reviews. During all phases of the review, a referee – RN – with over 20 years of experience in both RSA and TKP was available for consultation.

Systematic review of RSA studies

Literature search

A thorough literature search was performed together with a medical librarian, JP, to reduce bias by increasing the likelihood of retrieving all relevant studies [17]. The following bibliographies were searched up to 2009: PubMed, Embase, Web-of-Science and the Cochrane library. Relevant articles were screened for additional references. Additionally, a separate search was conducted within nine leading orthopaedic and biomechanical journals (Acta Orthop, Clin Orthop Rel Res, J Arthroplasty, J Bone Joint Surg (Am and Br) Knee Surg Sports Traumatol Arthrosc, J Orthop Res, J Biomec and Clin Biomech). Finally, Google Scholar was used. Articles in English, French, Italian, Spanish, Dutch and German were considered. The search strategy consisted of the following components, each defined by a combination of controlled vocabulary and free text terms: 1) RSA; and 2) Joint replacement.

Inclusion and exclusion analysis

Initial screening on title and abstract of RSA studies was performed by BP to identify studies on patients treated with TKP for end stage OA or RA. In case the information in the abstract did not suffice or in case of any doubt, the studies remained eligible. The full text of eligible studies was independently evaluated in duplicate by two reviewers, BP and EV. The inclusion criteria for RSA studies were 1) primary TKP and 2) minimal RSA follow-up of 1 year, measuring tibial component migration. Non-clinical studies (animal, phantom) were excluded.

Data extraction

BP and KN independently extracted migration data in duplicate from the RSA studies. Migration data comprised translations, rotations and Maximal Total Point Motion (MTPM) of the tibial component in the 1st post-operative year. MTPM is the unit of measurement for the largest 3D-migration of any point on the prosthesis' surface [13]. Data concerning patient demographics and regional influences were also extracted to allow for confounder correction.

Quality Assessment

The quality of the RSA studies was independently appraised in duplicate by BP and KN at the level of outcome using the AQUILA methodological score [18]. For the RSA studies we modified the AQUILA by removing items not considered relevant for early migration: long term follow-up and the revision assessment.

Systematic review of survival studies

Literature search

The search strategy and bibliographies are the same as those in the RSA review with the exception of the components of the search strategy. The search strategy of the survival studies consisted of the following components, each defined by a combination of controlled vocabulary and free text terms: 1) Joint replacement; 2) Implant failure; and 3) Survival analysis. In the search strategy no distinction was made between total knee and total hip prostheses (THP), because some studies report on TKP as well as THP [19].

Inclusion and exclusion analysis

The procedure of screening the survival studies for eligibility and subsequent inclusion and exclusion analysis was identical to the procedures of the RSA studies with the exception of inclusion and exclusion criteria. The inclusion criteria for survival studies were 1) primary TKP; 2) follow up of 5, 10, 15, 20 or 25 years; 3) endpoint revision surgery for aseptic loosening of the tibial component, or indication for revision surgery in case of poor general health or patient decline; and 4) survival or percentage revised must be available for specific follow-up (see point 2). Studies with less than 75 TKP at baseline were excluded.

Data extraction

BP and KN independently determined the revision rates in duplicate for aseptic loosening of the tibial component at 5 year intervals from the survival studies. Data concerning patient demographics and regional influences were extracted to allow for confounder correction.

Quality assessment

The quality of the survival studies was independently appraised in duplicate by BP and KN at the level of outcome using the AQUILA methodological score [18].

Analysis

A detailed description of the analysis, methodology and a worked example is available in Chapter 9. To determine the association between early migration and late revision we matched the results from the RSA review to the results of the survival review on type of Prosthesis, Fixation method (e.g. cement or bone ingrowth) and articulating Insert (e.g. modular or non-modular). The combination was termed PFI. Since PFI are technical factors known to be associated with both migration and the likelihood of revision for aseptic loosening, matching on PFI prevents confounding by PFI.[11,20-22] Depending on the available studies, it is possible that there is more than

one combination of matching RSA and survival studies for a particular PFI. For instance, if there are 3 RSA studies and 2 survival studies of the same PFI, then there are 6 possible combinations (3 times 2). All combinations were considered in the analysis. A meta-analysis for the revision rate at 5 years was performed. A model for the censoring mechanism was employed to reconstruct the data and then a generalized linear mixed model with study as a random effect has been applied to estimate the survival at 5 years and its confidence interval [23-25]. Regarding the RSA studies pooling of migration results at the level of PFI was based on weights according to study size (N). The 10 year results of TKP with high revision rates may not be published once the 5 year results have been published. Since 10 year revision rates in the registries are on average 1.7 times higher than 5 year revision rates, any missing 10 year results were estimated on 5 year results by applying a factor of 1.7. This method was validated by comparing the estimated 10 year results with the known 10 year results, for the complete cases [11,20-22].

Adjustment for confounding

Since migration data and revision rate data were extracted from different studies, it is possible that differences between study populations may confound the observed association. In order to address this issue we determined the degree of similarity of the population from RSA and survival study combinations, expressed by a match score, for age, gender, diagnosis, hospital type, and continent. The match score is constructed according to the results of a recent Delphi among an international group of 37 independent experts and can vary between 5 (excellent) and 0 (poor) [18]. The RSA study and survival study combination score 1 point for each of the following criteria (up to a maximum of 5 points):

- the difference in the mean age between the patients from RSA study and those from the survival study was 5 years or less.
- the difference in percentage females between the RSA study and survival study was 10% or less.
- the difference in percentage patients diagnosed with osteoarthritis between the RSA study and survival study was 10% or less.
- the RSA study and survival study were performed in the similar hospital type (e.g. both university medical centers).
- the RSA study and survival study were performed on the same continent.

All other cases score zero points.

We used a weighted regression model to assess on the association between early migration and late aseptic revision corrected for match score, RSA study quality, survival study quality, number of TKP in the RSA studies and number of TKP in the survival studies.

Migration thresholds

According to the principle of "primum non nocere" (first do no harm), new implant designs should perform at least as well as the revision standard of national registries: 3% revision at 5 years and 5% revision at 10 years according to the Swedish Knee Arthroplasty Registry [20]. Based on this revision standard the following three categories were constructed for the phased introduction of new TKP: acceptable, at risk and unacceptable. The acceptable category was defined as the level of migration up to which all survival studies have lower revision rates than the standard. The unacceptable category was defined as the level of migration from which all revision rates are higher than the standard. The category at risk is defined as the migration interval between the acceptable and unacceptable thresholds, in which studies with revision rates lower and higher than the standard were observed.

Appraisal of publication bias

We assessed the potential effect of publication bias by comparing the results from the meta-analysis to the results from national joint registries, since they do not suffer from publication bias [11,20-22]. Accordingly, the PFI that perform better than average in the meta-analysis should also perform better than average in the national joint registries. The same principle also applies to PFI that perform worse than average. For this purpose the migration pooled by PFI was sorted according to revision rate pooled by PFI and visualized in a dot chart [26].

Results

RSA studies

The literature search yielded 629 hits for the RSA review and 50 studies were included with a total of 847 patients [16,27-68]. Details on study selection and flow of the review are shown in Figure 7.1. The mean quality score of the RSA studies was 3.8 (SD 1.7) on a 7-point scale. MTPM at 1 year was the most frequently and most consistently reported migration value: 44 out of 50 RSA studies reported it. Translations and rotations of the tibial component were reported infrequently and inconsistently and did not allow a meaningful analysis. All analyses will therefore focus on MTPM at 1 year.

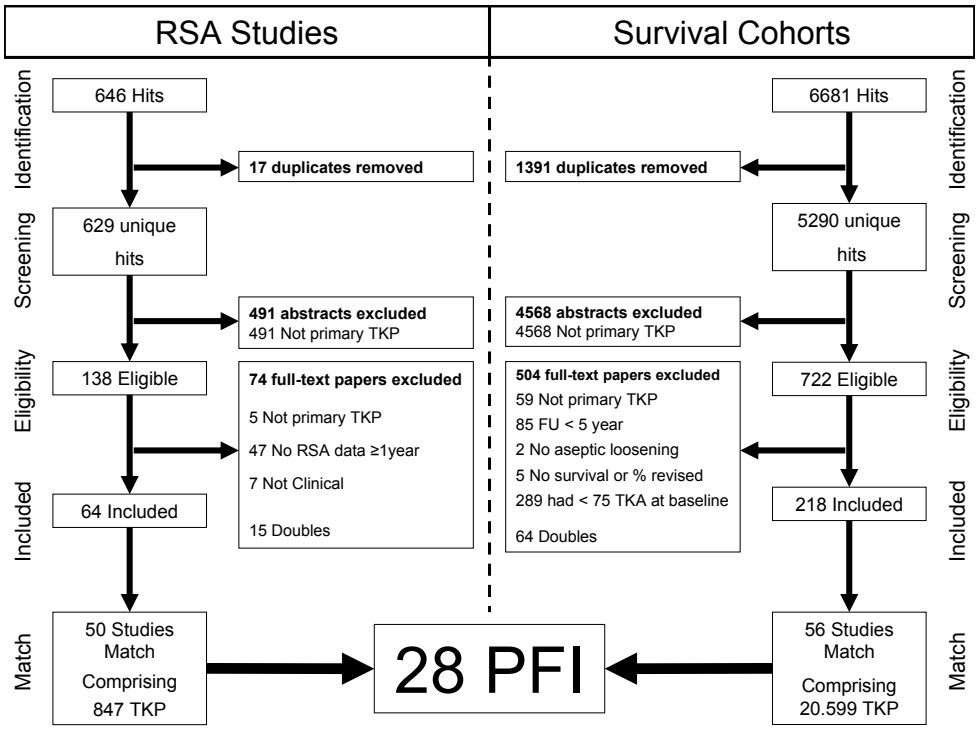

Figure 7.1: PRISMA flowchart of both reviews. Details of the 28 PFI can be found in Table 7.1.
RSA = radiostereometric analysis; TKP = total knee prosthesis; FU = follow-up; PFI = Prosthesis Fixation Insert

Survival studies

After the literature search there were 5,290 hits for the survival review and 56 studies were included with a total of 20.599 patients, see Figure 7.1 [14,69-118]. The mean quality score of the survival studies was 6.0 (SD 1.8) on an 11-point scale.

Early migration and late revision

The matching procedure resulted in 28 different PFI and 89 combinations of RSA and survival studies, see Table 7.1. There was a clear association between early migration, expressed as MTPM at 1 year and the 5 year revision rate as expressed as prosthesis survival, as shown in Figure 7.2. For every millimeter increase in migration 7.6% [95% CI 5.7% to 9.5%], p<0.05, was added to the 5 year revision rate. The influences of RSA study quality, survival study quality, number of TKP in the RSA study, number of TKP in the survival study and match score were small relative to the overall effect of migration on revision rate, see Table 7.2. For TKP that rely on primary fixation (cemented and uncemented with screws) 7.1% [95%CI 4.7 to 9.5], p<0.001 was added to the

5 year revision rate for every 1mm increase in MTPM. For TKP that rely on secondary fixation (uncemented without screws) 10.1% [95%CI 2.7 to 17.4], p=0.018, was added to the 5 year revision rate for every 1mm increase in MTPM.

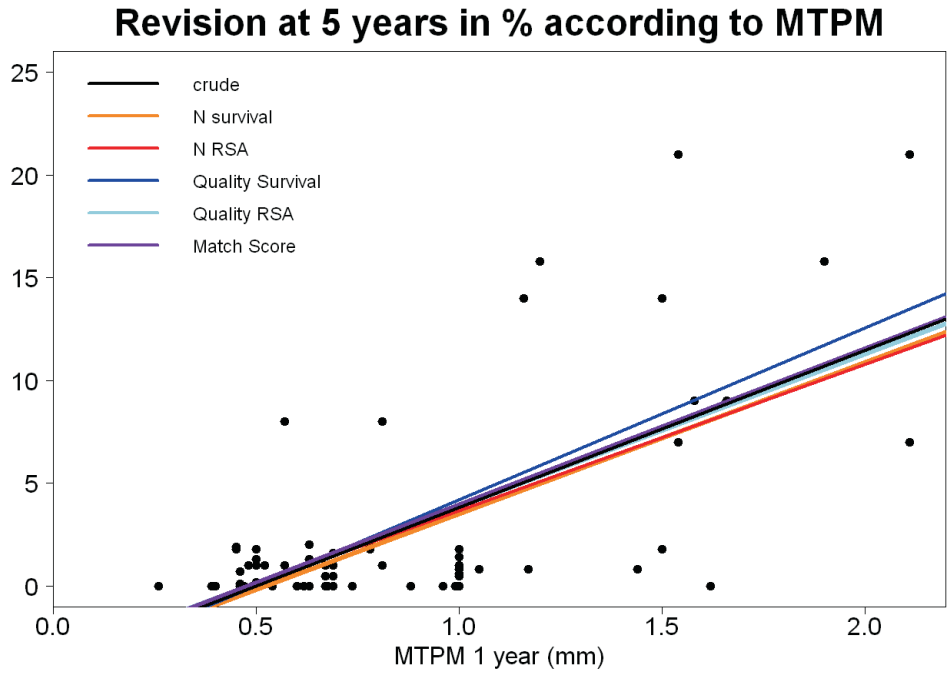

Figure 7.2 Scatterplot showing association between migration in the 1st post-operative year expressed as Maximal Total Point Motion (MTPM) in mm and revision rate for aseptic loosening of the tibial component at 5 years in percentages. The dotted lines are derived from weighted regression according to match quality, survival study quality and RSA study quality (the coeffcients and 95%CI are presented in Table 7.2).

Table 7.1: Prosthesis, Fixation and Insert (PFI) characteristics.

PFI	Prosthesis	Fixation	Insert	Number of RSA studies	Number of Survival studies	Number of combinations
1	Anatomic Modular Knee, CR, MB	Cement	Fixed, Modular	2	2	4
2	Tricon M, PE pegs, MB	Porous coated, no stem, no screws	Fixed	3	1	3
3	Duracon, CR, MB	Cement	Fixed, Modular	1	1	1
4	Total Condylar, no CR	Cement	All PE	1	5	5
5	Freeman-Samuelson	Uncoated	All PE (HDP)	2	2	4
6	Freeman-Samuelson, PE pegs, MB	Uncoated	Fixed	1	2	2
7	Anatomic Graduated Component 2000, CR, MB	Porous coated	Fixed, Non-modular	1	1	1
8	Miller-Galante I, 4 pegs, CR, MB	Cement	Fixed, Modular	2	1	2
9	Miller-Galante II, 4pegs, CR, MB	Cement	Fixed, Modular	2	1	2
10	Optetrak, PS, MB, finned stem	Cement	Fixed	1	1	1
11	Kinemax Plus, no PS	Cement	All PE	1	1	1
12	Profix, stemmed, CR, MB	Cement	Fixed, Modular	1	3	3
13	Porous Coated Anatomic, cruciform stem, CR, MB	Cement	Fixed, Modular	1	1	1
14	Kinematic Condylar, CR, MB	Cement	Fixed, Non-modular	6	1	6
15	Miller-Galante I, 4 pegs, CR, MB	Porous coated, 4 screws	Fixed, Modular	2	2	4
16	Anatomic Graduated Component, CR, MB	Cement	Fixed, Non-Modular	3	3	9
17	Press Fit Condylar, CR, MB	Porous coated	Fixed, Modular	1	1	1
18	Duracon, CR, MB	HA/PA coated	Fixed, Modular	1	5	5
19	Press Fit Condylar, CR, MB	Cement	Fixed, Modular	9	1	9
20	Press Fit Condylar Sigma, CR, MB	Cement	Fixed, Modular	3	2	6
21	NexGen Legacy, PS, MB	Cement	Fixed, Modular	2	2	4
22	Freeman-Samuelson, PE pegs, MB	Cement	Fixed	2	1	2
23	Freeman-Samuelson, metal pegs, MB	Cement	Fixed, Modular	2	2	4
24	NexGen, CR, MB, stem	Cement	Fixed, Modular	1	2	2
25	NexGen, 4 pegs, CR, MB	Cement	Fixed, Modular	1	2	2
26	Miller-Galante II, 4 pegs, CR, MB	Porous coated, 4 screws	Fixed, Modular	1	2	2
27	Porous Coated Anatomic, no PS, MB, no stem	Porous coated, 1 screw	Fixed	1	2	2
28	Interax, CR, MB	Uncoated	Fixed, two halfbearings	2	1	2

CR = cruciate retaining
PS = posterior stabilized
MB = metal backed
HDP = High Density Poly-Ethylene
PE = Poly-Ethylene
HA/PA = Hydroxyapatite/Periapatite

Table 7.2: Association between MTPM at 1 year and revision rate for aseptic loosening at 5 years.

	Increase in revision (%) / mm MTPM	95% CI
Crude	7.6	5.7 – 9.5
Adjusted for*:		
N survival**	7.4	5.6 – 9.2
N RSA**	7.1	5.4 – 8.8
Survival study quality	8.4	6.5 – 10.3
RSA study quality	7.4	5.4 – 9.4
Total Match Score	7.6	5.6 – 9.4
Range of values:		
	7.1 – 8.4	5.4 – 10.3

Table 7.2 shows the increase in the 5-year revision (%) for each mm increase in MTPM at 1 year.
In the crude analysis (unadjusted) 7.6% [95%CI 5.7% to 9.5%], p<0.05, is added to the 5-year revision rate for every mm increase in MTPM at 1 year.
* When adjusted for e.g. the number of TKP in survival studies (N survival) 7.4% [95%CI 5.6% to 9.2%], p>0.05, is added to the 5-year revision rate for every mm increase in MTPM at 1 year.
The association between MTPM1 and revision rate for aseptic loosening remains significant, when adjusting for confounders(all p-values <0.05).
** The square rote of N was used for the weighted regression, so larger studies weigh heavier.
N survival = number of TKP in survival studies
N RSA = number of TKP in RSA studies

Migration thresholds

Figure 7.3 shows the three categories for the TKP migration. For MTPM at 1 year between 0 and 0.54mm there was no tibial component with more than 3% revision for aseptic loosening at 5 years. In case of 1 year MTPM of more than 1.6mm there was no tibial component with less than 3% revision for aseptic loosening at 5 years. This implies that accepting 3% revision at 5 year resulted in a threshold of 0.54mm or acceptable MTPM at 1 year and a threshold of 1.6mm for unacceptable MTPM at 1 year. For the 10 year revision rates, the thresholds for acceptable and unacceptable migration were 0·45 mm and 1·6mm respectively, see Figure 7.4.

The mean difference between the estimated 10 year revision rate and known 10 year revision rate is 0.17% (SD 2.1%) indicating absence of any systematic error. The 5 year revision rates of the studies with missing 10 year revision rates were already higher than the 5% ten-year revision rate that is considered to be acceptable. Therefore, the 10 years thresholds are not influenced by any missing values.

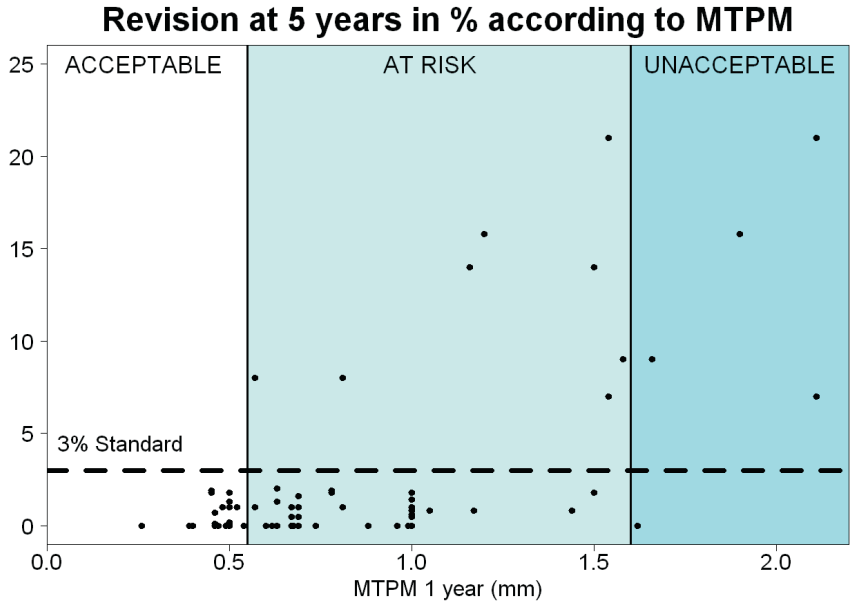

Figure 7.3. Scatter plot showing the relation between MTPM at 1 year and revision of the tibial component for aseptic loosening at 5 years. The thresholds of 0.54 and 1.6mm for the three categories – acceptable; at risk; unacceptable - are shown. MTPM = Maximal Total Point Motion

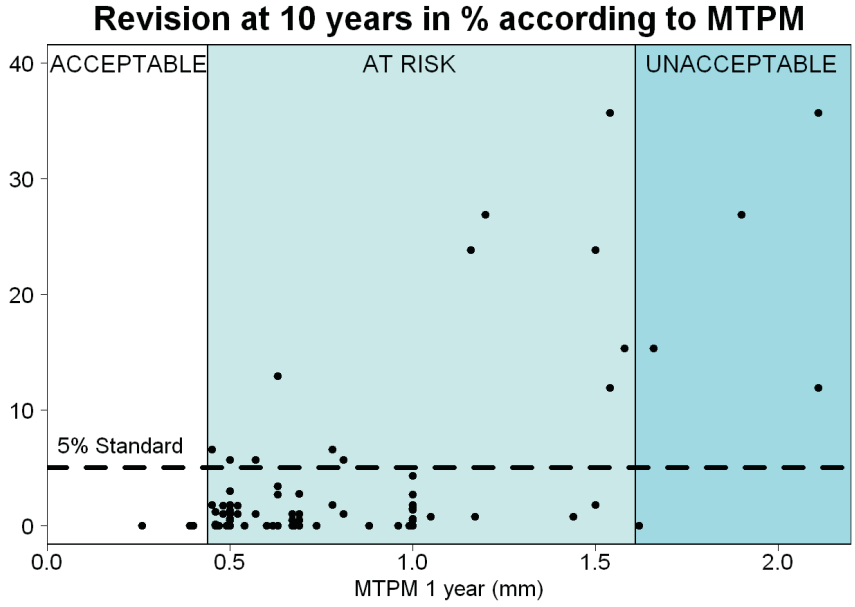

Figure 7.4. Scatter plot showing the relation between MTPM at 1 year and revision of the tibial component for aseptic loosening at 10 years. The thresholds of 0.45 and 1.6mm for the three categories – acceptable; at risk; unacceptable - are shown. MTPM = Maximal Total Point Motion

Publication bias

The pooled MTPM ranked by the pooled revision rate for each PFI is presented in Figure 7.5. The PFI that migrate significantly less than the acceptable threshold -classified as acceptable - have excellent track records and low revision rates in several national joint registries [11,20-22]. Conversely, the PFI that are classified as unacceptable on basis of their pooled migration have been abandoned and are no longer used. The potential influence of publication bias on the results is therefore small.

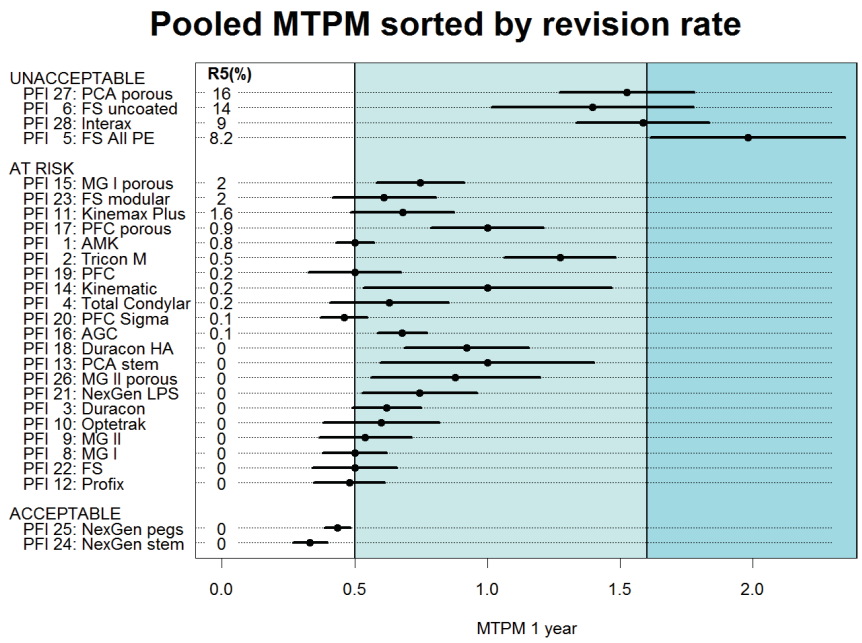

Figure 7.5: Dotchart showing the pooled MTPM ranked by the pooled revision rate for each PFI. The acceptable PFI (based on migration) have excellent track records and low revision rates in several national registries, whereas the unacceptable PFI (based on migration) have been abandoned. Therefore the potential influence of publication bias on the results is small. A detailed description for each PFI is available in Table 1. R5(%) = pooled revision rate at 5 years follow-up in percentage.

Discussion

Results of this systematic review demonstrate a clinically relevant association between early migration, as measured with RSA, and long term clinical failure resulting in revision for aseptic loosening. Each millimeter migration increases the 5 year revision rate by 8%, which remained

after correction for age, gender, diagnosis, hospital type, continent and study quality. This is more than twice the standard revision rate of several national joint registries [11,20-22]. The results of this systematic review show that RSA studies can identify unsafe TKP (in terms of aseptic loosening) as early as 1 year post-operatively. Early identification of unsafe TKP with RSA prevents their widespread use. Compared to the present system this safeguards numerous patients from extensive revision surgery with potential postoperative complications.

Some strengths of this systematic review are the large number of included studies (>100) and patients (>27,000) which resulted in 28 different PFI. This large variation in PFI, which reflects the diversity in TKP designs and fixation methods, ensures wide applicability of the results. Since migration and revision rates are from different studies, there is no migration data available in survival studies to be incorporated into the decision to perform a revision. Consequently there is no incorporation bias in our results. The risk of publication bias in this systematic review was considered to be small, since the results from the meta-analysis are similar to those from the national joint registries, which do not suffer from publication bias. Confounders had only a small influence on the association between early migration and long term aseptic revision.

We should also consider some limitations. The quality of the survival and RSA studies showed large variation. High methodological quality of all included studies is desirable. Nevertheless survival study quality and RSA study quality showed only very small effects on the association between migration and revision rates.

We focused on MTPM at 1 year post-operatively, while other migration parameters and follow-up beyond 1 year are also of interest [13]. Unfortunately, these parameters were reported too infrequently and inconsistently to allow a meaningful analysis. Future RSA studies could therefore benefit from further standardization particularly regarding the reporting of the results [119].

We also recognize that RSA only evaluates aseptic loosening while other failure mechanisms (e.g. infection, pain and instability or pseudotumors in metal-on-metal total arthroplasty) are not evaluated by RSA. As a consequence RSA studies are only the first step in the phased evidence-based introduction as proposed by Malchau, see Figure 7.6 [8].

During phase A, multiple single center RSA studies should be performed to determine the safety of the TKP with regard to the risk of revision for aseptic loosening. If the TKP is considered safe, phase B studies have to be conducted to evaluate the clinical performance of the TKP regarding pain relief and functioning (clinical scores and patient reported outcome measures (PROMS)) and to determine the rate of expected or unexpected complications. Since RSA studies have already evaluated the risk of aseptic loosening, follow-up of 2 years instead of 10 years will be sufficient. This reduces the follow-up needed for a successful phased introduction with almost a decade compared to traditional cohort studies. It therefore becomes possible to safely introduce

new TKP to the market before their patent has expired. After release to the market, phase C, the performance of the TKP has to be monitored by post-marketing surveillance in national joint replacement registries [10]. This includes both the revision rate and patient evaluations using patient reported outcome measures (PROMS).

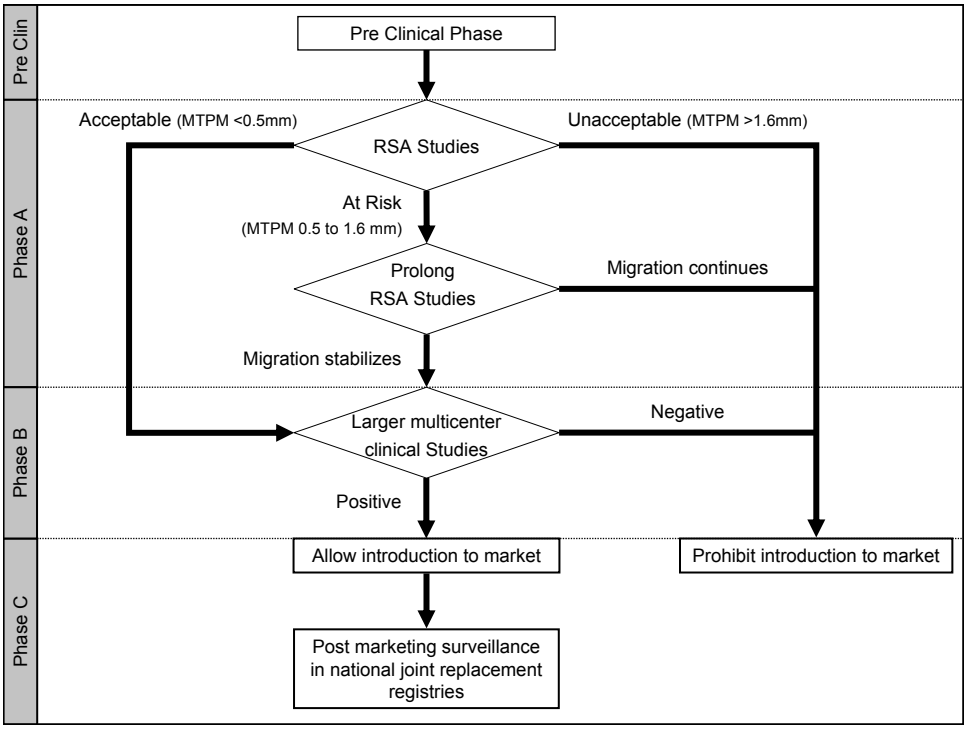

Figure 7.6 Flowchart showing the role of RSA studies in the phased evidence-based introduction of new TKP modified according the Malchau proposal. Stabilization is defined as migration of less than 0.2mm in the second post-operative year (MTPM from year 1 to year 2) as described by Ryd et al (1995) See discussion for details on each phase.

In this systematic review, RSA studies of 20 to 60 patients followed for 1 year led to the same conclusion as national joint registries with thousands of patients followed for 5 to10 years. A recent publication has shown a 22% to 35% reduction in the number of revisions of RSA-tested total knee replacements as compared with non-RSA-tested total knee replacements in the national joint registries [120]. Because inferior designs can already be detected early post-operatively exposing only a small group of patients to potentially unsafe TKP, RSA provides the necessary efficiency to effectuate phased evidence-based introduction. Already more than a decade ago several authors placed a call for phased evidence-based evaluation and clinical introduction of

new prostheses [8,121-123]. Now the observed association between early migration and long term revision translates into practical thresholds that can lead to clinical guidelines for phased evidence-based introduction of new TKP.

Various authors and regulatory agencies recognize the potential of RSA [8,13-15,124,125]. The NICE guidelines of 2003 (United Kingdom) require adequate long-term clinical data for hip prostheses and indicate RSA as a promising technique that may be an alternative for long-term follow-up studies. The Dutch Orthopaedic Society now requires a phased introduction with mandatory RSA-studies before any new hip prosthesis is considered for introduction to the Dutch market. Official guidelines for knee prosthesis are expected to follow.

In the light of the recent disasters with introducing new orthopaedic implants to the market, a phased clinical introduction for new TKP is mandatory to prevent patients from receiving potentially unsafe TKP when standard TKP with excellent long term track records are available. In conclusion there was a clinically relevant association between early migration of TKP and late revision for loosening. The proposed migration thresholds can be implemented in a phased evidence-based introduction, since they allow early detection of TKP with a high risk of aseptic loosening while exposing a small number of patients.

Authors' contributions

RN, BP and EV had the idea of the study. SM provided methodological input and MF statistical input during the conceptual phase of the study. JP designed the search strategy for the literature search. BP and EV performed the study selection and matching procedure. KN and BP appraised the quality of the literature and performed the data extraction. MF and BP analyzed the data. BP, KN, EV and RN wrote the initial draft manuscript. MF and SM ensured accuracy of data and analysis. BP and MF wrote the appendix. Critical revision of the manuscript was performed by all authors. All authors read and approved the final manuscript.

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Data sharing

Statistical code and dataset are available upon request from the corresponding author at b.g.c.w.pijls@lumc.nl. R code for the analysis described in the Appendix is available from one of the author: m.fiocco@lumc.nl

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Chapter 8

Early proximal migration of cups is associated with late revision in THA

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Abstract

We performed 2 parallel systematic reviews and meta-analyses to determine the association between early migration of acetabular cups and late aseptic revision.

One review comprised early migration data from Radiostereometric analysis (RSA) studies, while the other focused on revision rates for aseptic loosening from long term survival studies. Thresholds for acceptable and unacceptable migration were determined according the national joint registries: 5% revision at 10 years.

Following an elaborate literature search 26 studies (700 cups) were included in the RSA-review and 49 studies (38,013 cups) in the survival-review. The results showed that for every millimeter increase in 2-year proximal migration there was an increase of 10% in revision rate, which remained after correction for age, gender, diagnosis, hospital type, continent and study quality. Consequently, proximal migration up to 0.2mm was considered acceptable, while proximal migration of 1.0mm or more was unacceptable. Cups with proximal migration between 0.2 and 1.0mm were considered at risk for revision rates higher than 5% at 10 years.

There was a clinically relevant association between early migration of acetabular cups and late revision for loosening. The proposed migration thresholds can be implemented in a phased evidence-based introduction, since they allow early detection of high risk cups while exposing a small number of patients.

Introduction

Worldwide several hundred thousand Total Hip Prostheses (THP) are implanted each year and this number is expected to double within the next decades [1,2]. It is crucial to monitor the safety and quality of THP to prevent unneeded harm to patients and costs to society (i.e. reduction of the future revision burden). Most of the new THP designs are on the market without demonstrating safety or effectiveness [3]. This has resulted in the use of several THP with high failure rates, such as the Wagner cup, the Link V cup and the Mecron cup [4-6]. In response to these problems, several countries have developed guidelines to guarantee patient safety e.g. the NICE guidelines [7]. Furthermore, it has become increasingly evident that a phased evidence-based introduction, as is common for pharmaceuticals, is needed to regulate the introduction of new THP to the market [8-10]. This should include systematic assessment and early detection of the major cause of THP failure, which is aseptic loosening necessitating revision surgery[11,12]

Although it may take 10 years before the final stages of loosening are visible on conventional radiographs, it is possible to detect loosening early post-operatively with Radiostereometric analysis (RSA). Since, RSA allows in vivo, 3-dimensional measurement of the migration of THP with an accuracy of 0.2mm for translations and 0.5 degrees for rotations, only a small number of patients have to be exposed to potentially unsafe THP [13,14]. RSA could therefore play an important role in the phased evidence-based introduction of new THP.

In this systematic review and meta-analysis we concentrated on the acetabular cup. We hypothesize that early migration of the acetabular cup, measured through RSA, is associated with late revision for aseptic loosening. Therefore, we systematically reviewed the association between early migration and late aseptic revision for the acetabular cup in primary THP. Eventually, this could lead to clinical guidelines to be used in a phased introduction of new THP.

Methods

We performed 2 parallel systematic reviews (international registration number NTR3128; www.trialregister.nl) on studies of patients treated with THP for primary osteoarthritis (OA), secondary osteoarthritis (SA) and fractures of the proximal femur (FF). One review comprises early migration data of acetabular cups from RSA studies. In the other we determined the long term revision rates for aseptic loosening of acetabular cups from survival studies. Figure 8.1 shows the flow of the systematic reviews. During all phases of the review process, a referee – RN – with over 20 years of experience in both RSA and THP was available for consultancy.

Systematic review of RSA studies

Literature search

A thorough literature search was performed together with a medical librarian, JP, to reduce bias by increasing the likelihood of retrieving all relevant studies [15]. The following bibliographies were searched up to 2009: PubMed, Embase, Web-of-Science and the Cochrane library. Relevant articles were screened for additional references. Additionally, a separate search was conducted within nine leading orthopaedic and biomechanical journals (Acta Orthop, Clin Orthop Rel Res, J Arthroplasty, J Bone Joint Surg (Am and Br), Knee Surg Sports Traumatol Arthrosc, J Orthop Res, J Biomech, Clin Biomech). Finally, Google Scholar was used. Articles in English, French, Italian, Spanish, Dutch and German were considered. The search strategy consisted of the following components, each defined by a combination of controlled vocabulary and free text terms: 1) RSA; and 2) Joint replacement.

Inclusion and exclusion analysis

Initial screening on title and abstract of RSA studies was performed by BP to identify studies on patients treated with THP for OA, SA or FF. In cases where the information in the abstract did not suffice or where there was any doubt, studies remained eligible. The full text of eligible studies was independently evaluated in duplicate by 2 reviewers, BP and MN. The inclusion criteria for RSA studies were 1) primary THP and 2) minimal RSA follow-up of 1 year, measuring acetabular cup migration. Non-clinical studies (animal, phantom) were excluded.

Data extraction

BP and MN independently extracted migration data in duplicate from the RSA studies. Since the failure mechanism of acetabular cups consist of increasing proximal migration and increasing inclination the data extraction of RSA studies comprised proximal migration and inclination of the acetabular cup until the second post-operative year [16]. Data concerning patient demographics and regional influences were also extracted to allow for confounder correction [17].

Quality Assessment

The quality of the RSA studies was independently appraised in duplicate by BP and MN at the level of outcome using the AQUILA methodological score [17]. For the RSA studies we modified the AQUILA score by removing items that were not considered relevant for early migration, such as long term follow-up and revision assessment.

Systematic review of survival studies

Literature search

The search strategy and bibliographies are the same as those in the RSA review with the exception of the components of the search strategy. The search strategy of the survival studies consisted of the following components, each defined by a combination of controlled vocabulary and free text terms: 1) Joint replacement; 2) Implant failure; and 3) Survival analysis. In the search strategy no distinction was made between total knee and total hip prostheses (THP), because some studies report on TKP as well as THP [18].

Inclusion and exclusion analysis

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

Data extraction

BP and MN independently determined the revision rates in duplicate for aseptic loosening of the acetabular cups at 5 year intervals from the survival studies. Data concerning patient demographics and regional influences were extracted to allow for confounder correction.

Quality assessment

The quality of the survival studies was independently evaluated by BP and MN at the level of outcome using the AQUILA methodological score [17].

Analysis

A detailed description of the analysis, methodology and a worked example is available in Chapter 9. To determine the association between early migration and late revision we matched the results from the RSA review to the results of the survival review on type of Prosthesis and Fixation method (e.g. cement or bone ingrowth) here abbreviated to PF. Since PF is determined by technical factors known to be associated with both migration and a high likelihood for revision for aseptic loosening, matching on PF prevents confounding by PF [11,12,19]. Depending on the

available studies, it is possible that there is more than one combination of matching RSA and survival studies for a particular PF. For instance, if there are 3 RSA studies and 2 survival studies of the same PF, then there are 6 possible combinations (3 times 2). All combinations were considered in the analysis. A meta-analysis for the revision rate at 10 years was performed. A model for the censoring mechanism was employed to reconstruct the data and then a generalized linear mixed model with study as a random effect has been applied to estimate the survival at 10 years and its confidence interval [20-23]. Regarding the RSA studies pooling of migration results at the level of PF was based on weights according to study size (N).

Adjustment for confounding

Since migration data and revision rate data were extracted from different studies, it is possible that differences between study populations may confound the observed association. In order to address this issue we determined the degree of similarity of the population from RSA and survival study combinations, expressed by a match score, for age, gender, diagnosis, hospital type, and continent. The match score is constructed according to the results of a recent Delphi among an international group of 37 independent experts and can vary between 0 (poor) and 5 (excellent) [17]. The RSA study and survival study combination score 1 point for each of the following criteria (up to a maximum of 5 points):

- the difference in the mean age between the patients from RSA study and those from the survival study was 5 years or less.
- the difference in percentage of females between the RSA study and survival study was 10% or less.
- the difference in percentage of patients diagnosed with primary osteoarthritis between the RSA study and survival study was 10% or less.
- the RSA study and survival study were performed in the similar type of hospital (e.g. both university medical centers).
- the RSA study and survival study were performed on the same continent.

All other cases score zero points.

We used a weighted regression model to assess the association between early migration and late aseptic revision corrected for the influence of match score, RSA study quality, survival study quality, number of THP in the RSA studies and number of THP in the survival studies.

Migration thresholds

According to the principle of "primum non nocere" (first do no harm), new implant designs should perform at least as well as the revision standard of national registries: 3% revision at 5 years and 5% revision at 10 years according to the Swedish Hip Arthroplasty Registry and Australian National Joint Replacement Registry [11,12]. Based on this revision standard the following three categories were constructed for the phased introduction of new THP: acceptable, at risk and unacceptable. The category "acceptable" was defined as the level of migration up to which all survival studies have lower revision rates than the standard. The category " unacceptable" was defined as the level of migration from which all revision rates are higher than the standard. The category "at risk" is defined as the migration interval between the acceptable and unacceptable thresholds, in which studies with revision rates lower and higher than the standard were observed.

Appraisal of publication bias

We assessed the potential effect of publication bias by comparing the results from the meta-analysis to the results from national joint registries since they do not suffer from publication bias [11,12,19]. Accordingly, the PF that perform better than average in the meta-analysis should also perform better than average in the national joint registries. The same principle also applies to PF that perform worse than average. For this purpose the migration pooled by PF was sorted according to revision rate pooled by PF and visualized in a dot chart [24].

Results

RSA studies

The literature search yielded 629 hits for the RSA review and 26 studies were included with a total of 700 acetabular cups [5,6,25-42]. Details on study selection and flow of the review are shown in Figure 8.1. The mean AQUILA methodological quality score of the RSA studies was 4.9 (SD 0.8) on a 7-point scale. Proximal migration at 2 year was the most frequently and most consistently reported migration value: 23 out of 26 RSA studies reported it. Change in inclination (rotation around the z-axis) was reported infrequently and inconsistently and did not allow a meaningful analysis. All analyses will therefore focus on proximal migration at 2 year.

Survival studies

After the literature search there were 5,290 hits for the survival review and 49 studies were included with a total of 38,013 acetabular cups, see Figure 8.1 [43-85]. The mean AQUILA methodological quality score of the survival studies was 7.3 (SD 1.1) on an 11-point scale.

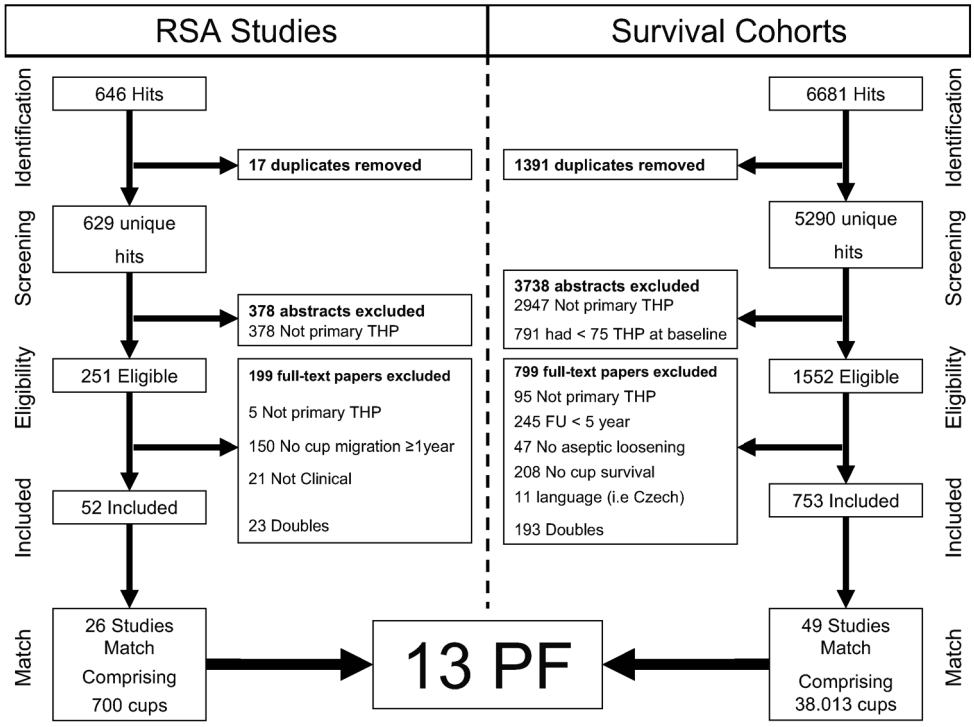

Figure 8.1 PRISMA flowchart of both reviews. Details of the 13 PF can be found in Table 8.1.
RSA = radiostereometric analysis
THP = total hip prosthesis
FU = follow-up
PF = Prosthesis Fixation

Early migration and late revision

The matching procedure resulted in 13 different PF and 94 combinations of RSA and survival studies, see Table 8.1. There was a clear association between 2 year proximal migration and the 10 year revision rate as expressed as prosthesis survival, as shown in Figure 8.2. For every millimeter increase in proximal migration (at 2 years) 10% [95% CI 5.5% to 14.2%], $p < 0.05$, is added to the 10-year revision rate. Although there was some influence on the results of RSA study quality, survival study quality, number of acetabular cups in the RSA study, number of acetabular cups in the survival study and match score, the association remained significant (all p-values <0.05), see Table 8.2.

There was no clear association between proximal migration rate (= 2 year proximal migration minus 1 year proximal migration) and the 10 year revision rate.

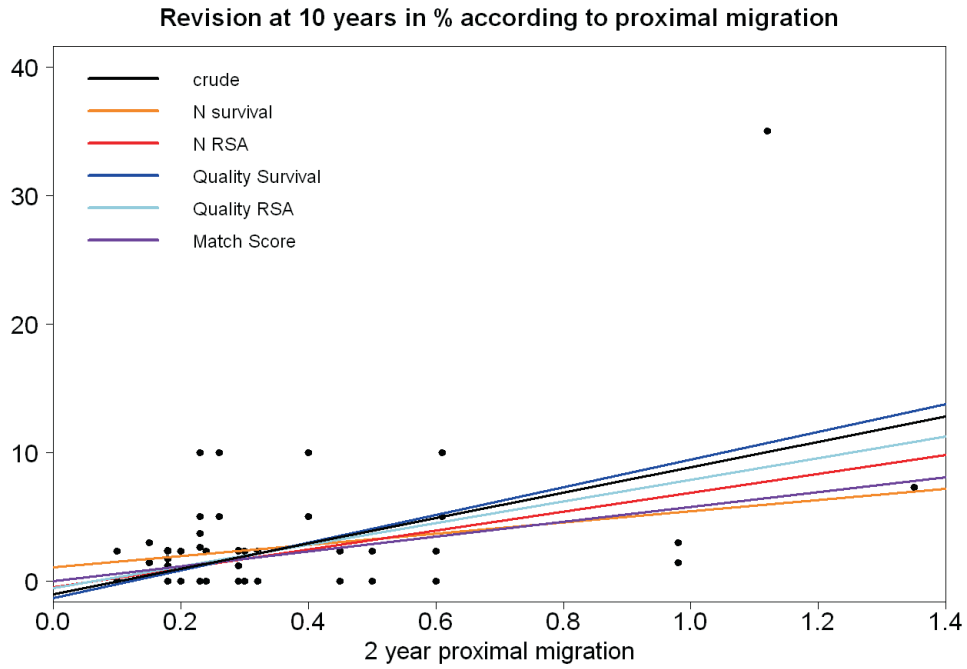

Figure 8.2 Scatterplot showing association between 2 year proximal migration in mm and revision rate for aseptic loosening of the acetabular cup at 10 years in percentages. The colored lines are derived from weighted regression according to match quality, survival study quality and RSA study quality (the coeffcients and 95%CI are presented in Table 8.2).

Table 8.1: Prosthesis and Fixation (PF) characteristics.

PFI	Prosthesis (cups)	Fixation	Number of RSA studies	Number of Survival studies	Number of combinations
1	ABG I	HA coated	1	8	8
2	Birmingham Hip Resurfacing	HA coated	1	4	4
3	Exeter all PE	Cement (high viscosity)	2	3	6
4	Harris Galante I	Porous coated, screws	2	14	28
5	Harris Galante II	Porous coated, screws	1	7	7
6	Link V, threaded	Uncoated	1	1	1
7	Omnifit dual radius	HA coated	2	1	2
8	Scanhip all PE	Cement (high viscosity)	1	3	3
9	Wagner (double) cup	Cement	1	1	1
10	Charnley Ogee	Cement (high viscosity)	8	3	24
11	Spectron all PE	Cement (high viscosity)	1	1	1
12	Lubinus eccentric	Cement (high viscosity)	4	2	8
13	Reflection all PE	Cement (high viscosity)	1	1	1
Total			26	49	94

PE = Poly-Ethylene; HA = Hydroxyapatite; ABG = Anatomique Benoist Giraud

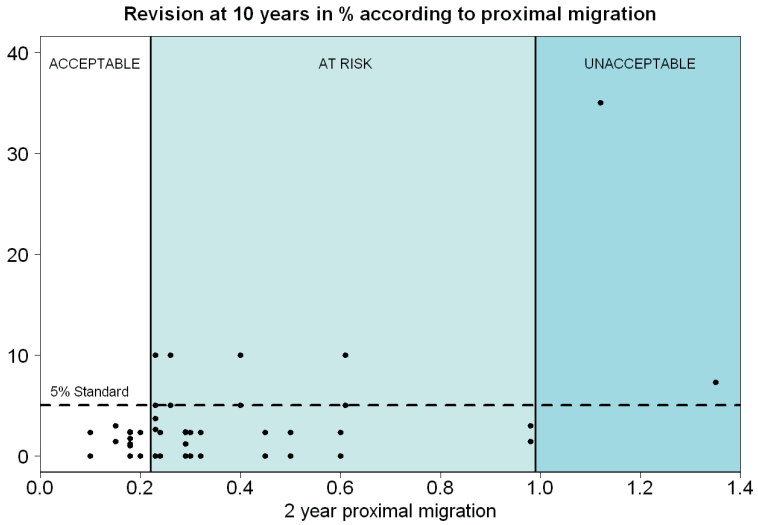

Figure 8.3 Scatter plot showing the relation between 2 year proximal migration and revision of the acetabular cup for aseptic loosening at 10 years. The thresholds of 0.2 and 1.0mm for the three categories – acceptable; at risk; unacceptable - are shown.

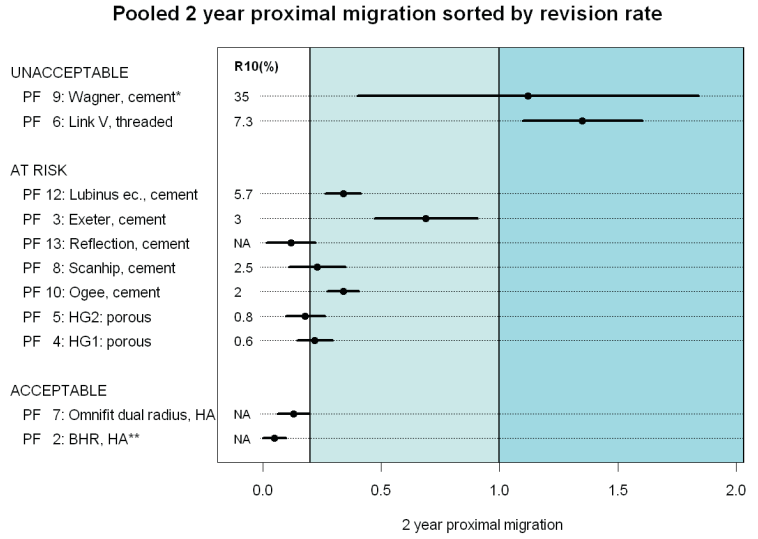

Figure 8.4 Dotchart showing the pooled 2 year proximal migration ranked by the pooled 10 year revision rate for each PF. The unacceptable PF (based on their migration pattern) have been abandoned with the Wagner cup having the worst recorded survival in the Swedish Register [86]. A detailed description for each PF is available in Table 8.1. R10(%) = pooled revision rate at 10 years follow-up in percentage. NA = not available

* This a best-case scenario for the Wagner cup, since the reference scene was not made direct postoperatively. Hence, the actual 2 year proximal migration is more than the observed value presented here.
** The Birmingham Hip Resurface (BHR) prostheses of the RSA study were implanted by the developer, so the migration results (and "acceptable" classification) may not apply to non-developers.

Table 8.2: Association between 2-year proximal migration and revision rate for aseptic loosening at 10 years.

	Increase in revision (%) / mm proximal migration	95% CI
Crude	10	5.5 – 14.2
Adjusted for*:		
N survival**	4.4	1.1 – 7.7
N RSA**	7.4	3.4 – 11.4
Survival study quality	10.8	6.2 – 15.4
RSA study quality	8.4	4.2 – 12.6
Total Match Score	5.8	2.2 – 9.4

Table 8.2 shows the increase in the 10 year revision (%) for each mm increase in 2-year proximal migration. In the crude analysis (unadjusted) 10% [95% CI 5.5% to 14.2%], p <0.05, is added to the 10-year revision rate for every mm increase in 2-year proximal migration.
* When adjusted for e.g. the number of hips in survival studies (N survival) 4.4% [95% CI 1.1% to 7.7%], p <0.05, is added to the 10-year revision rate for every mm increase in 2-year proximal migration.
The associated between 2 year proximal migration and revision rate for aseptic loosening remains significant, when adjusting for confounders (all p-values <0.05).
**The square rote of N was used for the weighted regression, so larger studies weigh heavier.
N survival = number of cups in survival studies (survival study size).
N RSA = number of cups in RSA studies (RSA study size).

Migration thresholds

Figure 8.3 shows the three categories for the THP. For proximal migration at 2 years between 0 to 0.2mm, there was no cup with more than 5% revision for aseptic loosening at 10 years. In case of 2-year proximal migration of more than 1.0mm, there was no cup with less than 5% revision for aseptic loosening at 10 years. This implies that accepting 5% revision at 10 years resulted in a threshold of 0.2mm for acceptable proximal migration at 2 years and a threshold of 1.0mm for unacceptable migration proximal migration at 2 years.

Publication bias

The pooled 2-year migration ranked by the pooled 10-year revision rate for each PF is presented in Figure 8.4. The Wagner cup and threaded Link V cup were classified as unacceptable based of their pooled migration. These cups have been abandoned and are no longer used in today's orthopaedic practice. Moreover, the Wagner cup, has the worst (overall) survival ever recorded in the history of the Swedish Register: 28% at 10 years [86]. The potential influence of publication bias on the unacceptable threshold is therefore small. The 10-year revision rate for the acceptable PF were lacking (NA), so longer FU of these PF is necessary to investigate if their 10 year revision rate for aseptic loosening of the cup is lower than 5%.

Discussion

Results of this systematic review show a clinically relevant association between early proximal migration of acetabular cups, as measured with RSA, and clinical failure (i,e, revision surgery) at mid term and long term follow-up corrected for, age, gender, diagnosis, type of hospital, region, study size and study quality. Each millimeter proximal migration increases the 10 year revision rate on average by 10%, which is more than twice the standard revision rate of several national joint registries [11,12,19].

We also found that RSA studies can identify unsafe acetabular cups as early as 2 year post-operatively. Early identification of these less optimal performing THP with RSA prevents their widespread use. Compared to the present policy of introduction of new prostheses, such a policy would safeguard numerous patients from potential (extensive) revision surgery with potential postoperative comorbidities.

Strengths of this systematic review are the large number of included studies (75) and patients (>38,000), which resulted in 13 different PF. This large variation in PF, which reflects the diversity in THP designs and fixation methods, ensures wide applicability of the results. Since migration and revision rates are from different studies, the RSA data could not have been used (incorporated) for the decision to perform a revision, this means that there is no incorporation bias.

One limitation is that the migration of the BHR and Omnifit acetabular cups were classified as "acceptable". This means that we expect their 10 year revision rate for aseptic loosening to be lower than 5%. However, since their 10-year revision rate was not available in this review, longer FU of the BHR and Omnifit is required. Regarding the BHR, it should also be noted that the surgery in the RSA study was performed by the developer [27]. Thus, the observed migration (and "acceptable" classification) does not necessarily apply to non-developers. Regarding the Omnifit dual radius cup, it should be noted that although the early migration (primary fixation) is classified "acceptable" the problem is secondary loosening due to excessive wear and osteolysis [34]. A phased introduction should therefore also focus on wear measurements, in which RSA could play an important role.

We are also aware that RSA only evaluates aseptic loosening while other failure mechanisms (e.g. osteolysis and pseudotumors in BHR resurfacing) are not evaluated by RSA. Therefore RSA studies are only the first step in the phased introduction as proposed by Malchau [8,87].

Already more than a decade ago several authors pleaded for a phased evidence-based introduction of new prostheses [8,88-90]. The observed association between early migration and long term revision of acetabular cups translates into practical thresholds values of migration (i.e. RSA) for such a phased evidence-based introduction policy of new THP [8]. During phase A, multiple single

center RSA studies should be performed to determine the safety of the THP with regard to the risk of revision for aseptic loosening and wear. Once the THP is considered safe, phase B studies have to be conducted to evaluate the clinical performance of the THP regarding pain relief and functioning (clinical scores and patient reported outcome measures (PROMS)) and to determine the rate of other complications (e.g. pseudotumors) [87]. After release to the market, phase C starts where the performance of the THP has to be monitored by post-marketing surveillance in national joint replacement registries [10]. This includes both the revision rate and patient evaluations using patient reported outcome measures (PROMS).

In this systematic review, RSA studies of 10 to 60 patients followed for only 2 year had the same conclusion as national joint registries where thousands of patients were followed for 10 years. A recent publication has shown a 22% to 35% reduction in the number of revisions of RSA-tested total knee replacements as compared with non-RSA-tested total knee replacements in the national joint registries [91].

Of special interest is the Wagner cup, which has the worst survival ever recorded in the history of the Swedish Register: 28% at 10 years [86]. If the threshold of unacceptable migration (1.0 mm) had been known at the time the Wagner cup was introduced, it would have been classified as "unacceptable" after 2 years of RSA follow-up with only eleven patients. The latter would have urged a more close follow-up of this prosthesis. The Link V cup would also have been classified as "unacceptable" after only 2 years of follow-up with RSA. Both examples illustrate the clinical value of the migration thresholds for the early identification of THP with a high likelihood of failure at long-term follow-up.

Various authors and regulatory agencies recognize the potential of RSA [8,13,14,92,93]. The NICE guidelines of 2003 (United Kingdom) require adequate long-term clinical data for hip prostheses and indicate RSA as a promising technique that may be an early warning indicator of expected poor long term revision rates [7]. The Dutch Orthopaedic Society now requires a phased introduction with mandatory RSA-studies before any new hip prosthesis is considered for introduction to the Dutch market.

In conclusion there was a clinically relevant association between early migration of THP and late revision for loosening. The proposed migration thresholds can be implemented in a phased evidence-based introduction, since they allow early detection of high risk THP while exposing a small number of patients.

Authors' contributions

RGN, BGP and ERV had the idea of the study. SM provided methodological input and MF statistical input during the conceptual phase of the study. JWP designed the search strategy for the literature search. BGP and MJN performed the study selection and matching procedure, appraised the quality of the literature and performed the data extraction. MF and BGP analyzed the data. BGP, MJN, ERV and RGN wrote the initial draft manuscript. MF and SM ensured accuracy of data and analysis. BGP and MF wrote the appendix. Critical revision of the manuscript was performed by all authors. All authors read and approved the final manuscript.

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Data sharing

Statistical code and dataset are available upon request from the corresponding author at b.g.c.w.pijls@lumc.nl. R code for the analysis described in the Appendix is available from one of the author: m.fiocco@lumc.nl

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Chapter 9

Methodological considerations on the systematic reviews of chapter 7 and 8

Published as online supplementary article data to:

Early migration of tibial components is associated with late revision.
Pijls BG, Valstar ER, Nouta KA, Plevier JW, Fiocco M, Middeldorp S, Nelissen RG.
Acta orthop 2012; 83 (Id.no 5477)

AND

Early proximal migration of cups is associated with late revision in THA.
Pijls BG, Nieuwenhuijse MJ, Fiocco M, Plevier JW, Middeldorp S, Nelissen RG, Valstar ER.
Acta Orthop 2012; 83 (Id.no 5482)

Methodological concept

To determine the association between early migration and late revision it is necessary to match the results from the RSA review to the results of the survival review, because migration data and revision rate data are commonly reported in different studies. In other words, since there are very few studies directly addressing the relation between early migration of tibial components and late revision, it is only possible to study this relation indirectly.

In medicine, treatment effects can be studied indirectly in so called meta-analyses of indirect comparison by comparing two different treatments against a common control[1]. Results of such meta-analyses are usually, but not always, similar to those of meta-analyses of direct comparison trials. This mostly depends on whether underlying assumptions are met or not. This will be elaborated on further below. The concept of indirect comparison is illustrated in appendix figure 9.1. Suppose we are interested in the comparison of treatment A versus treatment C yet no studies are available that directly compare these two treatments. However, there are studies that directly compare treatment A with treatment B (study 1) and treatment C with treatment B (study 2). Then the estimate of the indirect comparison of treatment A versus C (Tac) is calculated by:

Tac = Tstudy1 - Tstudy 2

or

Tac = Tab - Tbc

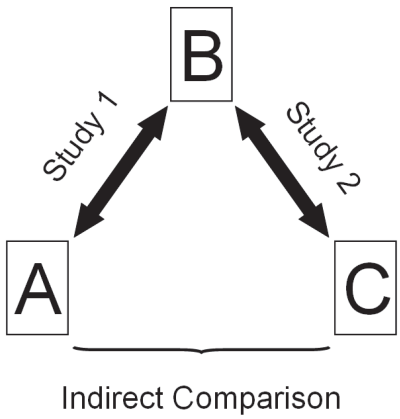

Figure 9.1 Indirect comparison of A versus C

Regarding the association between early migration and late revision, the concept is the same as that for indirect meta-analyses. However, since we are dealing with an association rather than a treatment effect, there is no common control group. Instead, we use the type of Prosthesis, Fixation method (e.g. cement or bone ingrowth) and articulating Insert (e.g. modular or non-modular):, PFI, to match migration with revision rates, as illustrated in appendix figure 9.2.

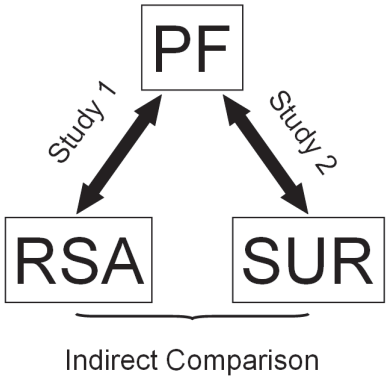

Figure 9.2 Indirect comparison of RSA and SUR (survival)

Migration and revision rates are assumed to be a characteristic of a particular type of prosthesis, fixation method and articulating insert (PFI). Therefore prosthesis, fixation method and articulating insert (PFI) acts similar to the common control group (B) in indirect meta-analyses.

PFI is defined as an uniquely identifiable tibial component with uniquely identifiable fixation method and uniquely identifiable articulating insert. It should be noted that uniquely identifiable tibial component is not equal to brand name, as there are multiple tibial components with the same brand name. For instance the Miller Galante (MG) was available in at least the following different versions:

P	F	I
MG I, CR, metal backed, 4 pegs, no stem	no screws, cemented	fixed, modular
MG I, CR, metal backed, 4 pegs, no stem	4 screws, porous-coated	fixed, modular
MG II, CR, metal backed, 4 pegs, no stem	no screws, cemented	fixed, modular
MG II, CR, metal backed, 4 pegs, no stem	4 screws, porous-coated	fixed, modular
MG II, CR, metal backed, 4 pegs, no stem	4 screws, HA-coated	fixed, modular
MG II, CR, metal backed, 4 pegs, stemmed	4 screws, porous-coated	fixed, modular

Each of the above versions is considered as a separate PFI. The Miller Galante example also clearly illustrates the variation in fixation methods. We distinguished the following fixation methods:

cemented (Boneloc was considered separately as a special case)
HA-coated
porous-coated
uncoated
any other type of coating, e.g. HA + tricalcium phosphate (TCP)
Additionally we considered whether screws were used or not.

We distinguished the following articulating inserts:

Fixed bearing modular
Fixed bearing non-modular
Fixed half bearings
Fixed All poly-ethylene
Mobile bearing

Assumption for the indirect method

The validity of the indirect comparison depends on the internal validity (methodological quality) and similarity of the included studies[1].

Internal validity

Regarding the internal validity we determined the methodological quality of the RSA studies and survival studies according to the AQUILA methodological score[2]. This score was used as a weight in a weighted regression model to assess how it influenced the association between early migration and late aseptic revision: studies with higher scores weighed heavier in the analyses.
Table 7.2 from chapter 7 shows that in the crude analysis the 5 year revision rate increases by 7.6% for every mm increase in 1-year MTPM. When survival study quality was used as a weight, the 7.6% increase/mm 1-year MTPM of the crude analysis changed to 7.4%. So, with survival study quality as a weight 7.4% is added to the revision rate for every mm increase in 1-year MTPM. When RSA study quality was used as a weight, the 7.6% increase/mm in 1-year MTPM of the crude analysis changed to 7.1%. So, with RSA study quality as a weight 7.1% is added to the revision rate for every mm increase in 1-year MTPM.

In conclusion internal validity expressed as survival study quality and RSA study quality had a small effect on the association between early migration and late aseptic revision and together with on average good methodological score for the RSA and survival studies, the requirement of adequate internal validity is met.

Similarity

Regarding the similarity (external validity) of the matched RSA and survival studies we determined the match score based on similarity in age, gender, diagnosis, hospital type and continent. These items and cut off values are based on the results of a recent Delphi among an international group of 37 independent experts and were hence determined before the analyses were performed[2]. The match score thus resembles similarity between matching RSA and survival studies and varies between 0 and 5 points. A worked example of the calculation of match scores is available further below. A higher score indicates greater similarity of the matched RSA and survival study. The match score is calculated as follows:

Age

When the difference in mean age between matching RSA and survival study is less than 5 years they receive 1 point. When the difference is more than 5 years or unknown (mean age is not reported), they receive 0 points.

Gender

When the difference in percentage females between matching RSA and survival study is less than 10% they receive 1 point. When the difference is more than 10% or unknown (percentage females is not reported), they receive 0 points.

Diagnosis

When the difference in percentage patients with osteoarthritis between matching RSA and survival study is less than 10% they receive 1 point. When the difference is more than 10% or unknown (percentage patients with osteoarthritis is not reported), they receive 0 points.

Hospital type

The following hospital types were considered: Academic, Developer, Special institute, High volume, Public. When the matching RSA and survival study were performed in the same type of hospital they received 1 point. When they were performed in different types of hospital or the type of hospital was unknown, they received 0 points.

Continent

When the matching RSA and survival study were performed on the same continent they received 1 point. When they were performed on different continents or the continent was unknown, they received 0 points.

The match score was used as a weight in a weighted regression model to assess how it influenced the association between early migration and late aseptic revision: studies with higher scores weighed heavier in the analyses.

Table 7.2 from chapter 7 shows that in the crude analysis the 5 year revision rate increases by 7.6% for every mm increase in 1-year MTPM. When match score was used as a weight, the 7.6% increase/mm 1-year migration of the crude analysis remained 7.6%.

In conclusion similarity expressed as match score had almost no effect on the association between early migration and late aseptic revision. Therefore the requirement of similarity is met.

Pooling of migration data and survival data

Pooling of migration data and survival data was performed for the appraisal of publication bias: the pooled results from the literature were compared with those from the national joint registries, since they do not suffer from publication bias.

Pooling of migration data

Regarding the RSA studies pooling of migration results at the level of PFI was weighed by number of tibial components in the RSA study according to the following formula:

$$\text{Pooled mean}_{1\text{-}x} = (\text{mean}_1 * N_1 + \text{mean}_2 * N_2 + \ldots + \text{mean}_x * N_x) / (N_1 + N_{2+\ldots} + N_x)$$

The standard deviation (SD) was pooled according to weighted variation according to the following formula:

$$\text{Pooled SD}_{1\text{-}x} = \text{sqrt}((SD_1 * SD_1 * (N_1\text{-}1) + SD_2 * SD_2 * (N_2\text{-}1) + \ldots. + SD_x * SD_x * (N_x\text{-}1)..) / (N_1 + N_2 + \ldots + N_x - x))$$

sqrt = square root of

Pooling of survival data

Starting point for the meta-analysis are the revision rates at 5 years reported in each manuscript and the minimum and the maximum follow-up (min_{FUP}, max_{FUP}) of patients. These quantities may be given directly but most often they will need to be estimated from the manuscript by looking at dates of accrual (if given) and from the date of submission, or perhaps publication of the manuscript. A model for the censoring mechanism based on the minimum and the maximum follow-up is assumed here for computing the number at risk and person years for each time. Let C(t) be the function that models the censoring mechanism. Based on the available information we choose the function C(t) as follows

$$C(t) = \begin{cases} 1 & \text{if } t \leq \min_{\text{FUP}} \\ 1 - \frac{t - \min_{\text{FUP}}}{\max_{\text{FUP}} - \min_{\text{FUP}}} & \text{if } \min_{\text{FUP}} < t < \max_{\text{FUP}} \\ 0 & \text{if } t \geq \max_{\text{FUP}}. \end{cases} \quad (1)$$

This function expresses the proportion of patients at time t that have at least t time units of follow-up. Given the number of eligible patients (n), the effective number at risk, the number of revisions at time j and the number of censored are estimated, respectively, as

$$\tilde{r}_j = nS_jC_j \ , \quad (2)$$

$$d_j = n(S_{j-1} - S_j)\frac{C_{j-1} + C_j}{2}, \quad (3)$$

and

$$c_j = n(C_{j-1} - C_j)\frac{S_{j-1} + S_j}{2}. \quad (4)$$

S_j: survival at time j
C_j: value of the function C(t) defined in (1) at a specific time j
r_j: number at risk at time j
d_j: number of deaths at time j
c_j: number of censored at time j

This assumes that the censored observations are distributed uniformly over the interval. Under the same assumption, from the number of patients at risk $\sim r_j$, we can define the number of person-years over interval I_j , as $r_j = \Delta_j(\sim r_j - c_j/2)$, where $\Delta_j = t_j - t_{j-1}$is the length of I_j . Following the methodology described the data for each study involved in the meta-analysis have been

reconstructed. A Poisson mixed model with study as random effects has been fitted to the reconstructed data, to estimate the pooled revision probability and the confidence interval at 5 years.

Worked example

For this worked example will use the Freeman-Samuelson, metal backed, metal pegs, cemented, fixed, modular.

Matching procedure

2 RSA studies met the inclusion criteria[3,4] both of them report migration of the Freeman-Samuelson, metal backed, metal pegs, cemented, fixed, modular.

2 survival studies met the inclusion criteria [5,6] both of them report revision rate of the Freeman-Samuelson, metal backed, metal pegs, cemented, fixed, modular.

When matching the RSA studies to the survival study we get the following 4 (2 * 2) combinations.

Combi	Survival study	RSA study
1	Arora 2005 JBJSBr	Adalberth 2001 JBJSBr
2	"	Uvehammer 2007 JKneeSurg
3	Robertsson 2000 JBJSBr	Adalberth 2001 JBJSBr
4	"	Uvehammer 2007 JKneeSurg

These combinations provide the x-coordinate (migration) and y-coordinate (revision) for the figures 7.2 and 7.3 of chapter 7.

Combi	1 year MTPM (mm)	5 year revision (%)
1	0.78	1.9
2	0.45	1.9
3	0.78	2
4	0.45	2

Match score

Regarding the similarity (external validity) of the matched RSA and survival studies we determined the match score based on similarity in age, gender, diagnosis, hospital type and continent (see above).

For example regarding Adalberth 2001 and Arora 2005 the match score is calculated as follows:

age (1 point), because the difference in mean is less than 5 years
gender (0 point), because the difference in % females is more than 10 percent
diagnosis (0 points), because the difference in % OA is more than 10 percent
hospital (1 point), because patients were operated in similar hospital types
continent (1point), both studies are from the same continent

Thus the match score for combi 1 (Adalberth 2001 and Arora 2005) is 1+0+0+1+1 = 3. The match scores of combi 1 through 4 are shown below.

Combi	age	gender	Diagnosis	Hospital	Continent	Match score
1	1	0	0	1	1	3
2	1	0	0	1	1	3
3	1	0	0	0	1	2
4	0	0	0	0	1	1

A higher score indicates greater similarity of the matched RSA and survival study. The match score was used as a weight in a weighted regression model to assess how it influenced the association between early migration and late aseptic revision (see above): therefore in this example combi 1 and 2 weighed the heaviest, while combi 4 had the lowest weight.

Pooling of migration data

We will continue with the cemented fixed bearing FS modular to illustrate the pooling of migration data.

The data for the 1 year MTPM are:

		mean	SD	N
Adalberth 2001	:	0.78	0.77	18
Uvehammer 2007	:	0.45	0.38	19

The pooled mean is calculated according to the following formula:

Pooled $mean_{1-x} = (mean_1 * N_1 + mean_2 * N_2 + \ldots + mean_x * N_x) / (N_1 + N_{2+\ldots} + N_x)$

Pooled mean = (0.78 * 18 + 0.45 * 19) / (18 + 19) = 22.6/37 = 0.61 mm

The standard deviation (SD) was pooled according to weighted variation according to the following formula:

Pooled SD_{1-x} = sqrt((SD_1*SD_1*(N_1-1) + SD_2*SD_2* (N_2-1) + ….+ SD_x*SD_x*(N_x-1)..) / (N_1+N_2+… + N_x – x))

Pooled SD = sqrt ((0.77*0.77*(18-1) + 0.38*0.38*(19-1)) / (18 +19 -2)) = sqrt ((10.1 + 2.60) / 35) = sqrt (0.362) = 0.60

With a pooled mean of 0.61mm a pooled SD of 0.60 and N_{total} of 37 the 95% confidence interval becomes:

0.42mm to 0.80mm

Pooling of survival data
The pooled 5 year revision of the cemented fixed bearing FS modular uses the revision rates from the 2 included studies (see above). The pooled 5 year revision aseptic loosening was 2% for the cemented fixed bearing FS modular as is shown in figure 7.5 of chapter 7.

Details of the literature search strategy

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

Survival cohort studies
PubMed: ("Joint Prosthesis"[Mesh] OR hip prosthesis OR knee prosthesis OR TKA OR THA OR THR OR TKR OR "joint replacement" OR Arthroplasty, Replacement[mesh] OR "total knee replacement" OR "total hip replacement")
AND
("Prosthesis Failure"[Mesh] OR "prosthetic loosening" OR "aseptic loosening" OR "implant loosening" OR "implant failure")

AND

("survival analysis"[MeSH Terms] OR ("survival"[All Fields] AND "analysis"[All Fields]) OR "survival analysis"[All Fields] OR cohort studies[mesh] OR "follow up" OR "follow-up" OR experience OR outcome)

These strings were adapted to fit the vocabulary of the other databases mentioned above.

The results were limited to humans

References

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Chapter 10

Summary and General discussion

General Discussion

The aim of this thesis is to evaluate the clinical value of migration measured with RSA in TKP and THP. The first aim was on the association of short term (two year) migration and the likelihood for long term (10 year) revision for aseptic loosening. The latter is important in the context of a phased introduction of new TKP and THP. The second aim was on the long term migration patterns of different types of fixation (i.e. cemented and cementless) of different types of TKP as part of a post-marketing surveillance with RSA. In this general discussion of my thesis I will address the strengths and limitations of the clinical value of RSA as well as future perspectives.

10.1 Proof of concept

The association between short-term RSA results and future loosening of TKP and THP has been previously studied, but the effect of pre-market testing with RSA on the revision burden remains unknown.[1-4] A phased evidence based introduction of new TKP and THP does not yet exist. At present, most new TKP and THP designs are approved and distributed on the market without extensive safety and effectiveness testing via the 510(k) pathway in the US and regulation via notified bodies in Europe (Directive 93/42/EEC) .[5,6] Both the 510(k) pathway in the US and the reviews of device reliability via notified bodies in Europe have created an environment in which unsafe TKP and THP can reach the market.[7]

Nevertheless, even in the absence of a formal phased introduction RSA studies that show high migration for a particular TKP or THP may result in discontinuing the implantation and production of that TKP and THP. This was for instance the case with the uncoated uncemented Interax TKP.[8] Once identified such high risk implants could be taken off the market in an early stage preventing widespread introduction and subsequent large numbers of revisions. This effect should be detectable in the national joint registries given there has been sufficient time to make decisions based upon the results of RSA studies. Considering that clinical RSA studies have been conducted for over 35 years, there has indeed been sufficient time to draw conclusions and make those decisions.[9] In **chapter 2** the revision rates of TKP with RSA testing and without RSA testing were determined in the national joint registries of Sweden, Australia and New Zealand. In case an RSA study was performed for a particular TKP there was a 22% to 35% reduction in the number of revisions (any reason) compared to TKP without RSA testing. It should be noted, however, that RSA testing focuses on the risk of revision for aseptic loosening, while the registries reported revision for any reason. Another limitation to be considered is the notion that registries do not always provide detailed information on small modifications to an implant design (e.g. use

pegs or stem; cruciate retaining or posterior stabilized). Nevertheless the phenomenon that TKP with RSA testing have lower revision rates than TKP without RSA testing is a proof of concept to demonstrate the feasibility of pre-market RSA testing of new TKP and THP in the context of a phased evidence-based introduction.

10.2 Generalizability

When the phased evidence based introduction of new TKP and THP would come into effect, the decision whether to allow a prosthesis onto the market or not, will ideally depend on a small number of studies with as few patients as possible.[10,11] Small study size (n= 20 to n= 60)[12] will minimize the patients put at risk and a small number of studies will reduce the time needed to make a decision for market approval, because consecutive studies would postpone the final decision. The question could then be raised whether the results from this small number of studies can be generalized.[13] In other words, do the results from those studies apply to other institutions with different patient populations (e.g different. age or pre-operative diagnosis) and different regional influences (e.g. differences in experience of the surgeon or type of hospital) ? And do they apply to the rest of the world? **Chapter 3 and 6** dealt with this external validity. **Chapter 3** was a systematic review that evaluated whether the prediction of implant performance as studied in a previous RSA trial, published in 1998, was correct.[8] The results of that RSA trial by Nelissen et al. showed that the uncoated Interax tibial components had increased early migration compared to HA-coated and cemented tibial components.[8] Since these uncoated components had shown the highest migration, it was predicted that this type of fixation would have a high failure rate.[2,3] In the systematic review two studies were included from other institutions (one German and one French) with patient populations that were rather different from the RSA trial by Nelissen et al.[14,15] When the results of these studies were combined in a meta-analysis, the high revision rate in the uncoated components became clearly visible. Furthermore, high migration of the uncoated Interax tibial components has also been demonstrated by Østgaard et al.[16] Their migration results were very similar to those of Nelissen et al despite differences in patient characteristics: all their patients were suffering from osteoarthritis, compared to 30% osteoarthritis and 70% rheumatoid arthritis in the study by Nelissen et al.[8,16] Although these findings plead strongly in favour of generalizability of RSA results beyond the study they were investigated in, it should be noted that the number of studies that actually confirm this at the level of prosthesis design is still limited.[4]
Even though the results from RSA studies appear to be applicable beyond the study they were studied in, it would still be helpful to identify what factors are relevant for generalizing the results. Identification of these factors would help answering the question if and to what extend the results from studies performed during the phased evidence based introduction of

new TKP and THP would apply to other institutions (i.e. the rest of the world). In **chapter 6** factors relevant for generalizability were identified by a group of 37 international experts through a Delphi procedure: AQUILA initiative. Consensus was reached on factors comprising patient demographics, component positioning, post-operative functioning and regional influences including type of institution (e.g. developer, academic or regional hospital). It would therefore be prudent that studies performed during a phased evidence based introduction of a new TKP and THP include a wide range of these generalizability factors to ensure wide applicability of the results. Since the majority of TKP and THP, if approved for the market, will be implanted by non-developer surgeons it is equally important that those pre-marketing studies are performed by the non-developer surgeons.

10.3 Early migration and late revision for aseptic loosening

The evidence for the relation between early (two year) migration and late (10 year) failure of TKP and THP by aseptic loosening, has been studied by Grewal, Ryd,, Kärrholm, Nieuwenhuijse and Hauptfleish.[1-4,17] The systematic reviews in **chapter 7 and 8** confirm the results of these studies. **Chapter 7** was a systematic review that demonstrated a clear and clinically relevant association between early migration (expressed as MTPM at 1 year) of tibial components, as measured with RSA, and clinical failure (i,e, revision surgery) at mid term and long term follow-up, which remained after correction for, age, gender, diagnosis, type of hospital, region, study size and study quality. Equally, **chapter 8** showed that 2 year proximal migration of acetabular components was associated with revision surgery for aseptic loosening at long term follow-up. This association also remained after correction for age gender, diagnosis, type of hospital, region, study size and study quality. MTPM at 1 year and proximal migration at 2 year were chosen because they were reported most often and most consistently. However this does not imply that these migration parameters and follow-up are optimal. Further research is needed to determine the optimal migration parameter and follow-up. Such research would consist of large RSA cohorts followed for 10 years or more to determine the optimal migration parameters to predict loosening. For the present MTPM at 1 year can be used for early detection of unsafe TKP (tibial components) that are at risk for high revision rates and proximal migration at 2 year can be used for the early detection of unsafe acetabular cups. These migration parameters for a new to be introduced TKP or THP can be determined in multiple centers worldwide to substantiate the evidence. However, when these migration parameters are used in the context of a phased evidence based introduction one should recognize the fact that RSA only evaluates aseptic loosening. Futhermore, new TKP and THP may introduce new failure mechanisms (e.g. pseudotumors in hip resurfacing).[18] These failure mechanisms are not detected by RSA and require additional steps in the phased introduction as proposed by Malchau.[10]

10.4 Standardization of outcome reporting

It is generally accepted that reporting guidelines such as CONSORT, STARD en STROBE (including the diseases specific extension AQUILA) have an important role in improving the accuracy, completeness and quality of clinical studies.[19-23] For RSA studies an additional guideline has been developed for terminology, description, use of RSA arrangement including radiographic set-up and techniques and among others describing of prosthetic migration.[24] However, in **chapters 7 and 8** it became apparent that RSA studies could benefit from further improvement in the reporting of migration results. Future updates of the systematic reviews from **chapter 7 and 8** in particular would greatly benefit from standardized and complete reporting of prosthetic migration: mean migration (minimum requirements MTPM for TKP and proximal migration and change in inclination for cups), the number of RSA examinations and standard deviation for each type of prosthesis at each follow-up moment and detailed description of the type of prosthesis and fixation method.

10.5 Post-market surveillance

After release to the market the performance of the TKP and THP should be monitored by post-marketing surveillance in national joint replacement registries.[10,11,25] This includes both the revision rate and patient evaluations using patient reported outcome measures (PROMS). In addition to the registries, post-marketing studies as well as long term follow up of the pre-marketing studies could prove valuable similar to post-marketing surveillance in pharmaceuticals[10,11,25-27] Since the pre-marketing studies have the longest available follow-up, these studies would be the first to detect long term problems and complications. On the other hand they could also provide further evidence for the conclusions made on the early results. For instance the study by Nelissen et al demonstrated that hydroxyapatite (HA) significantly reduced the early migration of uncemented tibial components in TKA.[8] **Chapter 4** evaluated the long term result of the Nelissen trial. The study results indicated that HA significantly reduces migration compared to the uncoated components and that this effect endured beyond 10 years. Moreover, any negative effects of HA, such as delamination of the HA layer and third body wear due to HA-particles, were not observed.[28,29] Furthermore there were two cases among the revisions that were of particular interest, because of their migration pattern. The tibial components of these cases started to migrate after a period of stability. Such failure mechanism has not yet been observed with RSA and is different from that described by Ryd consisting of continuous migration that eventually requires revision.[2]

In **Chapter 5** the 10 to 12 year fixation of mobile bearing (MB) TKP was compared to fixed bearing (FB) TKP in a best case setting. The results showed that even in a best case setting (better quality of the polyethylene insert in the MB group) the MB had no clinically or statistically significant

advantage over the FB in terms of long term migration. These results are in accordance with the conclusions from several recent meta-analyses that found no difference in clinical and radiological scores between MB and FB.[30-33] In **chapter 5** it was also possible to determine the backside wear rate of the mobile bearings with RSA: 0.026 mm/ year. The backside wear underneath the mobile bearing was small and may not be of clinical relevance.

10.6 Future perspectives

A phased evidence based introduction of new TKP and THP does not yet exist, see Table 10.1. At present, most new TKP and THP designs are approved and distributed on the market without extensive safety and effectiveness testing via the 510(k) pathway in the US and via notified bodies in Europe (Directive 93/42/EEC) .[5,6] Future phases of a phased clinical introduction of new total knee and total hip implants include RSA studies and larger multicenter studies as indicated in Table 10.1.

Table 10.1: Present and future phases of a phased clinical introduction of new total knee and total hip implants. Note that after successful introduction to the market, the implant needs post-market surveillance in national implant registries.

1	Pre clinical (bench) testing (501k pathway)[36]	
2	Mandatory clinical studies (CE class III, Directive 93/42/EEC and Directive 2005/50/EC; Premarket approval application (PMA))[5,7,37,38]	**Present**
3	RSA studies for evaluation of migration and wear	
4	Larger multicenter studies to evaluate pain relief, functioning (clinical scores and patient-reported outcome measures (PROMS)) and the rate of expected or unexpected complications by labaratory studies (Co Cr levels), osteolysis and pseudotumours by CT or MRI	**Future**

It is already possible to measure measurement of polyethylene wear in TKP and THP with great accuracy.[34] The accuracy of this technique has been reported by Ijsseldijk et al to be 0.1mm with a precision of 0.2mm for the linear wear measurements in TKP.[34] However there are no clear thresholds of wear at 1 or 2 years follow-up that predict long term polyethylene (PE) failure and wear related revisions. Therefore further research is needed to evaluate how these high precision early wear measurements relate to long term polyethylene (PE) wear and related revisions before such measurements can be implemented in the phased evidence introduction of new TKP and THP. Nevertheless, eventual implementation of this technique would mean that both early migration and PE wear can be measured in the same patient group maximizing efficiency and minimizing the patient at risk of receiving an unsafe prosthesis.

In the light of a phased clinical introduction of new implants it is of paramount importance to register RSA studies (including case series and cohorts) e.g. at clinicaltrials.gov before start of the study and data-analysis, as is common practice for randomized controlled trials. Although study registration is not yet compulsory for RSA cohorts and case-series, proper study registration of such studies would ensure assessment of publication bias especially when the migration of new prostheses exceed the unacceptable thresholds. Future RSA research will greatly benefit from further standardisation by ISO standards and reporting guidelines for outcomes.

Early detection of migration allows early (re)fixation of loosened implants, which hold great promise for the future.[35]

Finally, a future RSA data network (i.e. registry) would be extremely useful to exchange knowledge and to combine data, so that research questions that require greater diversity or a larger sample size can be answered.

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Summary

The aim of this thesis is to evaluate the clinical value of migration measured with RSA in TKP and THP. The first aim was on the association of short term (two year) migration and the likelihood for long term (10 year) revision for aseptic loosening. The latter is important in the context of a phased introduction of new TKP and THP. The second aim was on the long term migration patterns of different types of fixation (i.e. cemented and cementless) of different types of TKP as part of a post-marketing surveillance with RSA.

Chapter 2 RSA and registries: the quest for phased introduction of new implants
In this chapter the predictive power of RSA was evaluated within a two-year follow-up after arthroplasty and its relationship to national joint registries. For this purpose the association between RSA prosthesis-migration data and registry data was studied. The five-year rate of revision of RSA-tested total knee replacements was compared with that of non-RSA-tested total knee replacements. Data were extracted from the published results of the national joint registries of Sweden, Australia, and New Zealand. There was a 22% to 35% reduction in the number of revisions of RSA-tested total knee replacements as compared with non-RSA-tested total knee replacements in the national joint registries. Assuming that the total cost of revision total knee arthroplasty is $37,000 in the United States, a 22% to 35% reduction in the number of revisions (currently close to 55,000 annually) could lead to an estimated annual savings of over $400 million to the health-care system. The phased clinical introduction of new prostheses with two-year RSA results as a qualitative tool could lead to better patient care and could reduce the costs associated with revision total knee arthroplasty. Follow-up in registries is necessary to substantiate these results and to improve post-market surveillance.

Chapter 3 RSA prediction of high failure rate for the uncoated Interax TKA confirmed by meta-analysis
In a previous radiostereometric (RSA) trial the uncoated, uncemented, Interax tibial components showed excessive migration within 2 years compared to HA-coated and cemented tibial components. It was predicted that this type of fixation would have a high failure rate. The purpose of the systematic review and meta-analysis in chapter 3 was to investigate whether this RSA prediction was correct. A systematic review and meta-analysis was performed to determine the revision rate for aseptic loosening of the uncoated and cemented Interax tibial components. 3 studies were included, involving 349 Interax total knee arthroplasties (TKAs) for the comparison of uncoated and cemented fixation. There were 30 revisions: 27 uncoated and 3 cemented

components. There was a 3-times higher revision rate for the uncoated Interax components than that for cemented Interax components (OR = 3; 95% CI: 1.4-7.2). This meta-analysis confirmed the prediction of a previous RSA trial. The uncoated Interax components showed the highest migration and turned out to have the highest revision rate for aseptic loosening. RSA appeared to enable efficient detection of an inferior design as early as 2 years postoperatively in a small group of patients.

Chapter 4 The beneficial effect of hydroxyapatite lasts: a randomized radiostereometric trial comparing hydroxyapatite-coated, uncoated, and cemented tibial components for up to 16 years

In contrast to early migration, the long-term migration of hydroxyapatite- (HA-) coated tibial components in TKA has been scantily reported. The randomized controlled trial in chapter 4 investigated the long-term migration measured by radiostereometric analysis (RSA) of HA-coated, uncoated, and cemented tibial components in TKA. 68 knees were randomized to HA-coated (n = 24), uncoated (n = 20), and cemented (n = 24) components. All knees were prospectively followed for 11-16 years, or until death or revision. RSA was used to evaluate migration at yearly intervals. Clinical and radiographic evaluation was according to the Knee Society system. A generalized linear mixed model (GLMM, adjusted for age, sex, diagnosis, revisions, and BMI) was used to take into account the repeated-measurement design. The present study involved 742 RSA analyses. The mean migration at 10 years was 1.66 mm for HA, 2.25 mm for uncoated and 0.79 mm for the cemented group ($p < 0.001$). The reduction of migration by HA as compared to uncoated components was most pronounced for subsidence and external rotation. 3 tibial components were revised for aseptic loosening (2 uncoated and 1 cemented), 3 for septic loosening (2 uncoated and 1 cemented), and 1 for instability (HA-coated). 2 of these cases were revised for secondary loosening after a period of stability: 1 case of osteolysis and 1 case of late infection. There were no statistically significant differences between the fixation groups regarding clinical or radiographic scores. HA reduced migration of uncemented tibial components. This beneficial effect lasted for more than 10 years. Cemented components showed the lowest migration. Longitudinal follow-up of TKA with RSA allows early detection of secondary loosening.

Chapter 5 Differences in long-term fixation between mobile-bearing and fixed-bearing knee prostheses at ten to 12 years' follow-up: A single-blinded randomised controlled radiostereometric trial

The single-blinded randomised controlled trial in chapter 5 investigated whether one design of mobile-bearing (MB) total knee replacement (TKR) has any advantage over a fixed-bearing (FB)

design on long-term fixation as measured by radiostereometry. The amount of wear underneath the mobile bearing was also evaluated. A series of 42 knees was randomised to MB or FB tibial components with appropriate polyethylene inserts and followed for between ten and 12 years, or until the death of the patient. The polyethylene in the MB group was superior in that it was gamma-irradiated in inert gas and was calcium-stearate free; the polyethylene in the FB group was gamma-irradiated in air and contained calcium stearate. In theory this should be advantageous to the wear rate of the MB group. At final follow-up the overall mean migration was 0.75 mm (sd 0.76) in the MB group and 0.66 mm (sd 0.4) in the FB group, with the FB group demonstrating more posterior tilt and the MB group more internal rotation. In the FB group there was one revision for aseptic loosening, but none in the MB group. There were no significant differences in clinical or radiological scores. For the MB group, the mean linear wear rate on the under-surface was 0.026 mm/year (sd 0.014). This was significantly smaller than the wear rate of 0.11 mm/year (sd 0.06) in the MB between femur and polyethylene ($p < 0.001$). Nevertheless, even in a best-case setting the mobile bearings of this TKR design had no apparent advantage in terms of fixation over the FB knee prosthesis at ten to 12 years. The wear underneath the mobile bearing was small and is unlikely to be clinically relevant.

Chapter 6 AQUILA: assessment of quality in lower limb arthroplasty. An expert Delphi consensus for total knee and total hip arthroplasty

In this chapter a Delphi approach was used to develop a checklist for reporting quality, methodological quality and generalizability of case series and cohorts in total hip and total knee arthroplasty with a focus on aseptic loosening. The web-based Delphi consisted of two internal rounds and three external rounds. The internal rounds were used to construct a master list. The first external round was completed by 44 external experts, 35 of them completed the second external round and 33 of them completed the third external round. Consensus was reached on an 8-item reporting quality checklist, a 6-item methodological checklist and a 22-item generalizability checklist. Checklist for reporting quality, methodological quality and generalizability for case series and cohorts in total hip and total knee arthroplasty were successfully created through this Delphi. These checklists should improve the accuracy, completeness and quality of case series and cohorts regarding total hip and total knee arthroplasty.

Chapter 7 Early migration of tibial components is associated with late revision
A systematic review and meta-analysis of 21,000 knee arthroplasties

In this chapter two parallel systematic reviews and meta-analyses were performed to determine the association between early migration of tibial components and late aseptic revision. One

review comprised early migration data from radiostereometric analysis (RSA) studies, while the other focused on revision rates for aseptic loosening from long-term survival studies. Thresholds for acceptable and unacceptable migration were determined according to that of several national joint registries: < 5% revision at 10 years. Following an elaborate literature search, 50 studies (involving 847 total knee prostheses (TKPs)) were included in the RSA review and 56 studies (20,599 TKPs) were included in the survival review. The results showed that for every mm increase in migration there was an 8% increase in revision rate, which remained after correction for age, sex, diagnosis, hospital type, continent, and study quality. Consequently, migration up to 0.5 mm was considered acceptable during the first postoperative year, while migration of 1.6 mm or more was unacceptable. TKPs with migration of between 0.5 and 1.6 mm were considered to be at risk of having revision rates higher than 5% at 10 years. In conclusion, there was a clinically relevant association between early migration of TKPs and late revision for loosening. The proposed migration thresholds can be implemented in a phased, evidence-based introduction of new types of knee prostheses, since they allow early detection of high-risk TKPs while exposing only a small number of patients.

Chapter 8 Early proximal migration of cups is associated with late revision in THA
A systematic review and meta-analysis of 26 RSA studies and 49 survival studies

In this chapter two parallel systematic reviews and meta-analyses were performed to determine the association between early migration of acetabular cups and late aseptic revision. One review covered early migration data from radiostereometric analysis (RSA) studies, while the other focused on revision rates for aseptic loosening from long-term survival studies. Thresholds for acceptable and unacceptable migration were classified according the Swedish Hip Arthroplasty Register and the Australian National Joint Replacement Registry: < 5% revision at 10 years. Following an elaborate literature search, 26 studies (involving 700 cups) were included in the RSA review and 49 studies (involving 38,013 cups) were included in the survival review. For every mm increase in 2-year proximal migration, there was a 10% increase in revision rate, which remained after correction for age, sex, diagnosis, hospital type, continent, and study quality. Consequently, proximal migration of up to 0.2 mm was considered acceptable and proximal migration of 1.0 mm or more was considered unacceptable. Cups with proximal migration of between 0.2 and 1.0 mm were considered to be at risk of having revision rates higher than 5% at 10 years. In conclusion, there was a clinically relevant association between early migration of acetabular cups and late revision due to loosening. The proposed migration thresholds can be implemented in a phased evidence-based introduction, since they allow early detection of high-risk cups while exposing a small number of patients.

Discussion and Conclusion

At present, most new TKP and THP designs are approved and distributed on the market without extensive safety and effectiveness testing via the 510(k) pathway in the US and via notified bodies in Europe (Directive 93/42/EEC) .[1,2] This practice has created an environment in which unsafe TKP and THP can reach the market.[3]

It has become increasingly evident that a phased evidence-based introduction, which is common for pharmaceuticals, is needed to regulate the introduction of new TKP and THP to the market. This would allow monitoring of the safety and quality of TKP and THP to prevent harm to patients and to minimize costs to society (i.e. reduction of the future revision burden).

The studies in this thesis show that RSA studies can identify unsafe (i.e. high failure rates due to loosening) TKP and THP as early as 2 years postoperatively. Early identification of these less optimal performing TKP and THP with RSA prevents their widespread use.

The phased clinical introduction of new prostheses with two-year RSA results as a qualitative tool could lead to better patient care and could reduce the costs associated with revision surgery. Follow-up in registries is necessary to substantiate these results and to improve post-market surveillance.

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Nederlandse Samenvatting

Het doel van deze thesis is het onderzoeken van de klinische waarde van migratie van totale knie protheses (TKP) en totale heup protheses (THP) gemeten met Radiostereometrische Analyse (RSA). Het eerste doel is om de associatie te onderzoeken tussen vroege migratie en late revisie voor aseptische loslating in de context van een gefaseerde klinische introductie voor nieuwe TKP en THP. Het tweede doel is om de lange termijn migratie te bepalen van verschillende type TKP en verschillende fixaties in de context van post-markering surveillance met RSA.

Hoofdstuk 2 RSA en registers: de zoektocht naar gefaseerde introductie van nieuwe implantaten

In dit hoofdstuk werd de vroeg (2 jaar) voorspellende waarde van RSA voor revisie van gewrichtsimplantaten onderzocht. Hiervoor werd de associatie tussen migratie van de prothese, gemeten met RSA, en revisie percentages uit nationale implantaten registers bestudeerd. Het 5-jaar revisie percentage van RSA-geteste totale knie protheses (TKP) werd vergeleken met dat van niet-RSA-geteste TKP. De gegevens werden geëxtraheerd uit de gepubliceerde resultaten van de nationale implantaten registers van Zweden, Australië en Nieuw Zeeland. Uit de gegevens van de nationale implantaten registers bleek een reductie van 22% tot 35% in het aantal revisies voor RSA-geteste TKP vergeleken met de niet-RSA-geteste TKP. Aangenomen dat in de Verenigde Staten de totale kosten voor een revisie van een TKP $37,000 bedragen, kan een reductie in het aantal revisies van 22% tot 35% oplopen tot een besparing van $400 miljoen per jaar in de zorg in de VS. De gefaseerde klinische introductie van nieuwe implantaten op basis van RSA studies met 2 jaar follow-up kan leiden tot betere patiëntzorg en tot een reductie van de kosten in de zorg ten gevolge van revisie van TKP. Follow-up in nationale implantaten registers is noodzakelijk om de resultaten van de implantaten te blijven vervolgen, nadat deze op de markt zijn gekomen.

Hoofdstuk 3 Voorspelling van hoog revisie percentage voor de ongecoate Interax TKP bevestigd door meta-analyse

Uit eerder gerandomiseerd onderzoek bleek dat 2 jaar post-operatief de ongecoate, ongecementeerde Interax tibiale componenten excessief veel migreerden vergeleken met de hydroxyapatite (HA)-gecoate en gecementeerde tibiale componenten. Op basis van dit resultaat werd een hoog revisie percetage voor de ongecoated Interax TKP voorspeld. Het doel van de systematische review en meta-analyse in hoofdstuk 3 is om te onderzoeken of deze RSA voorspelling klopt. Er werd een systematische review en meta-analyse gedaan naar het revisie percentage voor aseptische loslating van de ongecoate en gecementeerde Interax tibiale componenten. Drie studies werden geincludeerd met in totaal 349 TKP van het Interax type. Er waren 30 revisies: 27 in de ongecoate groep en 3 in de gecementeerde groep. Dit resulteerde

in een 3 keer zo hoog revisie percentage voor de ongecoate Interax componenten vergeleken met de gecementeerde componenten (OR = 3; 95% CI: 1.4-7.2). Deze meta-analyse bevestigd de voorspelling van de RSA studie uit 1998: de ongecoate Interax componenten migreerden het meeste en hadden het hoogste revisie percentage voor aseptische loslating. Met RSA was het dus mogelijk om een inferieur type TKP vroeg post-operatief (2 jaar) te identificeren in een kleine groep patiënten.

Hoofdstuk 4 Het gunstige effect van hydroxyapatite (HA) persisteert: een gerandomiseerd radiostereometric onderzoek van HA-gecoate, ongecoate en gecementeerde tibiale componenten tot 16 jaar follow-up

In tegenstelling tot vroege migratie is de lange termijn migratie van HA-gecoate tibiale componenten van totale knie protheses nauwelijks gerapporteerd in de literatuur. Het doel van deze geblindeerde, gerandomiseerde studie was om te onderzoeken hoe drie verschillende type fixaties de lange termijn migratie van totale knie protheses beïnvloeden.

68 knieën werden gerandomiseerd tot hydroxyapatite (HA) gecoate, ongecoate of gecementeerde componenten en prospectief gevolgd voor 11-16 jaar, of tot revisie van de prothese of dood van de patiënt. Met behulp van Radiostereometrische Analyse (RSA) werd jaarlijks de migratie bepaald. Klinische en radiologische evaluatie vond plaats volgens het systeem van The Knee Society. Een lineair mixed effect model (GLMM) werd gebruikt voor de statistische analyse vanwege de herhaalde metingen en om voor leeftijd, geslacht, diagnose, revisies en BMI te corrigeren. In totaal werden er 759 RSA analyses verricht. De gemiddelde migratie op 10 jaar was 1.66mm voor HA-gecoate, 2.25mm voor ongecoate en 0.79mm voor de gecementeerde groep ($p < 0.001$). De afname in migratie door HA, vergeleken met de ongecoate componenten, was het meest uitgesproken voor inzakking en exorotatie van de componenten. Drie tibiale componenten waren gereviseerd voor aseptische loslating (2 ongecoate en 1 gecementeerde), 3 voor septische loslating (2 ongecoate en 1 gecementeerde) en 1 voor instabiliteit (HA-gecoate). Twee van deze componenten werden gereviseerd voor secundaire loslating na een periode van stabiliteit: 1 geval van osteolyse en 1 geval van late infectie. Wat betreft klinische en radiologische uitkomstmaten waren er geen klinisch relevante of statistisch significante verschillen tussen de fixatie groepen. HA bewerkstelligde een significante reductie op de migratie en dit gunstige effect was op 10 jaar nog steeds aanwezig. Gecementeerde componenten migreerden het minste. Het is mogelijk om secundaire loslating vroeg te detecteren met longitudinale follow-up van TKP met RSA

Hoofdstuk 5 Verschillen in lange termijn fixatie tussen totale knie prothesen met beweegbaar lager en vast lager 10 tot 12 jaar post-operatief: een enkel geblindeerd gerandomiseerd radiostereometrisch onderzoek

Het doel van dit hoofdstuk was om te onderzoeken of een bepaald type TKP met beweegbaar lager voordelen heeft ten opzichte van een vast lager wat betreft de lange termijn fixatie als gemeten met RSA. De mate van slijtage aan de onderkant van het beweegbaar lager werd ook gemeten. Een serie van 42 knieën werd gerandomiseerd tot een TKP met beweegbaar of vast lager en gevolgd voor 10-12 jaar of tot revisie van de prothese of dood van de patiënt. Het polyethylene van de beweegbare lagers (gamma-bestraald in inert gas en vrij van calcium-stearaat) was superior aan dat van de vaste lagers (gamma-bestraald in lucht en bevat calcium-stearaat). Dit zou theoretisch in het voordeel zijn voor de beweegbare lagers. Bij de laatste follow-up was de gemiddelde migratie 0.75mm (sd 0.76) voor de beweegbare lagers en 0.66mm (sd 0.4) voor de vaste lagers. Er was meer posterieure tilt bij de vaste lagers en meer interne rotatie bij de beweegbare lagers. In de vaste lager groep vond 1 revisie plaats voor aseptische loslating versus geen revisie voor aseptische loslating in de beweegbare lager groep. Wat betreft klinische en radiologische uitkomstmaten waren er geen klinisch relevante of statistisch significante verschillen tussen de groepen. De gemiddelde lineaire slijtage aan de onderkant van de beweegbare lager was 0,026mm per jaar (sd 0,014). Dit was significant kleiner dan de slijtage van 0,11mm per jaar (sd 0,06) aan de bovenkant van de beweegbare later ($p<0.001$). Zelfs met superior PE van de beweegbare lagers hadden deze geen evidente voordeel ten opzichte van de vaste lagers wat betreft lange termijn fixatie. De slijtage aan de onderkant van de beweegbare lagers was minimaal en waarschijnlijk niet klinisch relevant.

Hoofdstuk 6 AQUILA: assessment of quality in lower limb arthroplasty. Een Delphi concensus van experts van totale knie en totale heup protheses

In dit hoofdstuk werd door middel van een Delphi proces een checklist ontwikkeld voor rapportage kwaliteit, methodologische kwaliteit en generaliseerbaarheid van case series en cohorten in totale knie (TKP) en totale heup prothesiologie (THP) met focus op aseptische loslating.

De web-based Delphi bestond uit twee interne rondes en drie externe rondes. Tijdens de interne rondes werd een master lijst gecreëerd, welke de basis vormde voor de externe rondes. De eerste externe ronde werd voltooid door 44 externe experts, van wie 35 ook de tweede en 33 ook de derde ronden voltooiden. Er werd consensus bereikt op een 8-item rapportage kwaliteit checklist, een 6-item methodologische kwaliteit checklist en een 22-item checklist voor generaliseerbaarheid. Deze checklists dragen bij aan de verbetering van de nauwkeurigheid, volledigheid en kwaliteit van rapportage en methodologie van case series en cohorten in THK en THP.

Hoofdstuk 7 Vroege migratie van tibiale componenten is geassocieerd met late revisie. Een systematische review en meta-analyse van 21.000 totale knie protheses

In dit hoofdstuk werden de resultaten gepresenteerd van twee parallelle systematische reviews en meta-analyses naar de associatie tussen vroege migratie van tibiale componenten en late revisie. Een review omvatte vroege migratie waardes van RSA studies, terwijl de andere review revisie percentages aseptische loslating uit lange termijn survival studies betrof.

Uitgaande van verscheidene nationale implantaten registers waren revisie percentages van 5% op 10 jaar als standaard gekozen. Na de inclusie procedure bleven er 56 survival studies (20.559 TKPs) over en 50 RSA studies (847 TKPs). Er bleek een significante associatie tussen vroege migratie en late revisie percentage: voor elke millimeter migratie nam het revisie percentage toe met 8%, hetgeen significant bleef na correctie voor leeftijd, geslacht, diagnose, type ziekenhuis, continent en studie kwaliteit. Migratie van minder dan 0,5mm op 1 jaar was acceptabel. Een overschrijding van 1,6mm op 1 jaar was onacceptabel. Als de migratie tussen de 0,5 en 1,6mm lag was het type prothese "at risk" voor revisie hoger dan de 5% 10-jaars revisiestandaard. Concluderend, met de voorgestelde migratie drempelwaardes was het mogelijk om onveilige TKP vroeg te identificeren in een kleine groep patiënten. TKP surveillance met de drempelwaardes kan passen in een gefaseerde klinische introductie voor nieuwe totale knie prothesen.

Hoofdstuk 8 Vroege proximale migratie van cups is geassocieerd met late revisie in THP. Een systematische review en meta-analyse van 26 RSA studies en 49 survival studies

In dit hoofdstuk werden de resultaten gepresenteerd van twee parallelle systematische reviews en meta-analyses naar de associatie tussen vroege proximale migratie van acetabulaire cups en late revisie. Een review omvatte vroege migratie waardes van RSA studies, terwijl de andere review revisie percentages aseptische loslating uit lange termijn survival studies betrof. Uitgaande van het verscheidene nationale implantaten registers waren revisie percentages van 5% op 10 jaar als standaard gekozen. Na de inclusie procedure bleven er 49 survival studies met totaal 38.013 cups over en 26 RSA studies met totaal 700 cups. Er was een significante associatie tussen proximale migratie en revisie percentage: voor elke millimeter proximale migratie nam het revisie percentage toe met 10%, hetgeen significant bleef na correctie voor leeftijd, geslacht, diagnose, type ziekenhuis, continent en studie kwaliteit. Dit leidde tot de volgende drempelwaardes. Proximale migratie van minder dan 0,2mm op 2 jaar was acceptabel. Een overschrijding van 1,0mm op 2 jaar was onacceptabel. Als de migratie tussen de 0,2 en 1,0mm lag was het type prothese "at risk" voor revisie hoger dan de 5% 10-jaars revisiestandaard. Concluderend, met de voorgestelde migratie drempelwaardes was het mogelijk om onveilige cups vroeg te identificeren in een kleine groep patiënten. Cup surveillance met de drempelwaardes kan passen in een gefaseerde klinische introductie voor nieuwe totale heup prothesen.

Discussie and Conclusie

Via de "501(k) pathway" in de Verenigde Staten en via "notified bodies" in Europa (Directive 93/42/EEC) worden nieuwe TKP en THP nu toegelaten op de vrije markt en verder gedistribueerd zonder uitgebreide veiligheid- en effectiviteitonderzoeken. [1,2] Deze gang van zaken heeft een reguleringsklimaat gecreëerd waarin onveilige TKP en THP op de markt kunnen komen. [3]

De noodzaak van een gefaseerde klinische introductie voor nieuwe TKP en THP wordt steeds duidelijker. Zo'n gefaseerde klinische introductie bestaat al geruime tijd voor medicijnen en zou het mogelijk maken om de veiligheid en effectiviteit van nieuwe TKP en THP te monitoren om zo letsel aan patienten te voorkomen en kosten voor de maatschappij te beperken (anders gezegd de revisie last in de toekomst te reduceren).

De studies van deze thesis laten zien dat onveilige (hoog revisie percentage voor loslating) TKP en THP met RSA studies kunnen worden geïdentificeerd in slechts 2 jaar follow-up. Vroege identificatie met RSA van deze onveilige TKP en THP voorkomt wijdverbreide gebruik.

De gefaseerde klinische introductie van nieuwe implantaten op basis van RSA studies met 2 jaar follow-up kan leiden tot betere en veiligere patiëntzorg en tot een reductie van de kosten in de zorg ten gevolge van revisie van TKP en THP. Follow-up in nationale implantaten registers is noodzakelijk om de resultaten van de implantaten te blijven vervolgen, nadat deze op de markt zijn gekomen.

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Curriculum Vitae

Bart Pijls was born on the 16th of February 1983 in Roermond, the Netherlands. He graduated from secondary school in 2001 at the Scholengemeenschap Sint Ursula, Horn. In that same year he started to study medicine at the University of Maastricht. During his medical training he worked as a teaching assistant at the Department of Anatomy and Embryology at the University of Maastricht, he followed an internship Orthopaedics and Traumatology in St. Luke's Hospital in Malta and he performed a research project on navigation in total knee replacements at the Department of Orthopaedics at the Maastricht University Medical Center.

Part of his clinical training was performed at the Department of Orthopaedics and Traumatology of the Elkerliek Hospital, Helmond.

After obtaining his medical degree (cum laude) in July 2007 he returned to the Department of Orthopaedics and Traumatology of the Elkerliek Hospital in Helmond to work as an Orthopaedic Resident. In October 2008 he started to perform the research described in this thesis at the Biomechanics and Imaging Group at the Department of Orthopaedics at the Leiden University Medical Center under the supervision of prof. dr. R.G.H.H. Nelissen and prof. dr. ir. E.R. Valstar. This Ph.D.-project was part of the AIF-project (Atlantic Innovation Fund), a collaboration between the Departments of Orthopaedics of the Leiden University Medical Center and of the Dalhousie University, Halifax, Canada. The goal of the AIF-project is to explore and develop the clinical applicability of RSA in everyday orthopaedic practice.

Bart has been accepted to the University of Leiden Orthopaedic Residency Program and has completed the General Surgery Training at the Rijnland Ziekenhuis, Leiderdorp, under the supervision of dr. A.M. Zeillemaker. In July 2013 he started working as Orthopaedic Surgery Resident at the Leiden University Medical Center under the supervision of prof. dr. R.G.H.H. Nelissen.

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