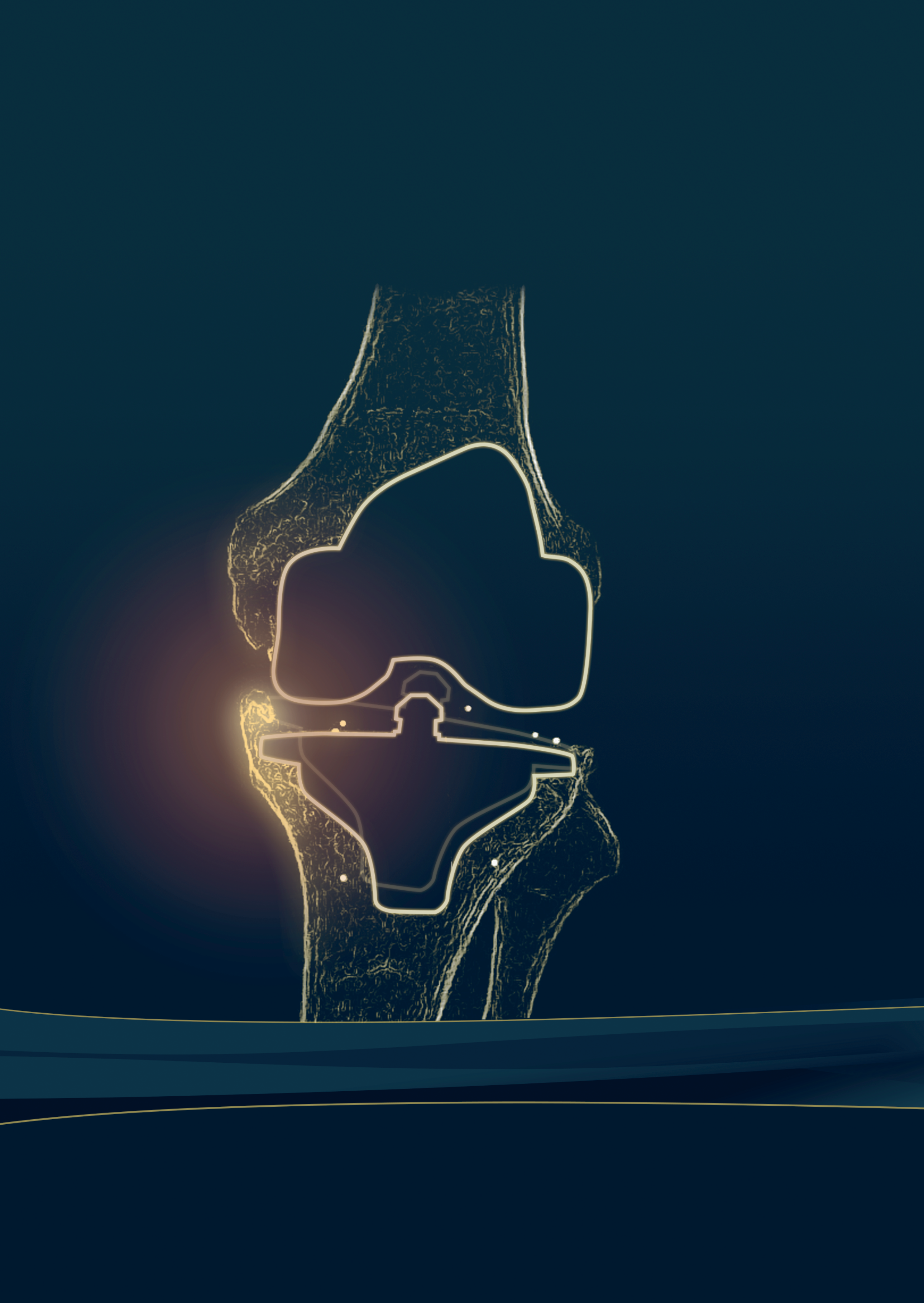
Risk factors for long-term failure of orthopaedic medical devices: taking advantage of RSA as an early detection tool

Hamersveld, K.T. van



9 Summary and general discussion

Summary

The aims of this thesis were to evaluate the effect of different implant design aspects on tibial component migration on a group level as measured with radiostereometric analysis (RSA). Furthermore, after exploring whether it is justified to pool outcomes from studies using different RSA techniques, we determined risk factors for loosening in such pooled data sets including implant design aspects, surgical alignment and patient characteristics.

The effect of implant design on tibial component migration

The first design aspect that was studied is the tibial component material. In **chapter 2**, we present the two-year results of a randomized controlled trial comparing cemented condylar-stabilizing total knee prostheses with either monoblock all-polyethylene tibial components (n = 29) or modular metal-backed tibial components (n = 30). The surgeries were performed by two experienced surgeons using a standardized technique. Tantalum markers were placed into the proximal tibial metaphysis and within the polyethylene to facilitate marker-based RSA measurements. Besides RSA, clinical scores including the Knee Society Score, the Forgotten Joint Score and the Knee Osteoarthritis and Injury Outcome Score were also evaluated throughout follow-up. After two years, a small but statistically significantly difference was found in favor of the all-polyethylene design, with a mean maximum total point motion (MTPM) of 0.61 mm (95% CI 0.49 to 0.74) for the all-polyethylene group *versus* 0.81 mm (95% CI 0.68 to 0.96) for the metal-backed group (p = 0.03). This difference was smaller and not statistically significant when adjusting for the operating surgeon in a *post hoc* analysis. Comparable improvements on all clinical outcome scores were found between groups. We concluded that the risk of aseptic loosening of all-polyethylene tibial components of this design is at least comparable with, if not less than, that of its metal-backed counterpart.

The second design aspect that was studied is the bearing concept. We performed a randomized clinical trial comparing migration and clinical outcomes of an otherwise similarly designed cemented fixed-bearing and (rotating-platform) mobile-bearing total knee arthroplasty (TKA) design, for which the results are presented in **chapter 3**. Although migration and clinical outcomes were similar between designs, several complications occurred which were inherent to the mobile-bearing design. In five cases, the surgeon experienced difficulties with gap balancing during mobile-bearing surgery, which led to the decision to deviate from the randomized treatment allocation and implant fixed-bearing components instead. Especially in patients with compromised (peri-)articular tissue (e.g., due to rheumatoid arthritis or previous surgery such as high tibial osteotomy), bone resections and soft-tissue releases are performed conservatively which may result in difficulties to place the mobile bearing onto the central post of the baseplate without forcing and thus potentially damaging the locking mechanism. In one procedure, damage of the locking mechanism instigated an insert dislocation, for which the revision surgery was sadly the onset of many adverse sequalae. Patient inclusion was prematurely terminated for patient safety reasons, awaiting investigation of the insert dislocation. After analyzing the final results of this study, we concluded that there was no clear benefit of this mobile-bearing design with respect to implant migration and clinical outcome scores, whilst this design posed a more challenging procedure to some surgeons with risks to patients.

The third design aspect that was studied is the mode of fixation. In **chapter 4**, we randomized 60 patients to either a cemented TKA or an uncemented TKA coated with hydroxyapatite via a solution deposition technique called peri-apatite (PA). After five years of follow-up, we found higher initial migration for the uncemented PA coated TKAs, resulting in statistically significantly more overall migration of 0.97 mm (95% CI 0.81 to 1.11) as compared with 0.62 mm (95% CI 0.49 to 0.76) for the cemented group ($p = 0.003$). However, we also performed a *post hoc* analysis to compare migration after the initial settling phase by assessing the between-group differences in migration with three months as a baseline. Between three months and five years of follow-up, we found statistically significantly less migration in favor of the uncemented PA group, showing 0.13 mm (95% CI 0.01 to 0.25) of migration *versus* 0.27 mm (95% CI 0.19 to 0.36) for the cemented group ($p = 0.02$). Continuous migration between two and five years was seen in one implant in each group, with the cemented implant showing a more ominous migration pattern as compared with the uncemented implant.

In **chapter 5**, we evaluated whether the observed beneficial effect of PA-coating on uncemented total knee implants is sustained over time and, more importantly, whether continuous migration (i.e., >0.2 mm of migration) in the second postoperative year proves predictive for mechanical loosening after uncemented TKA. Sixty patients were randomized to either a PA-coated or uncoated (porous only) implant. In the short-term report of this study, continuous migration in the second postoperative year was observed in one PA-coated and seven uncoated implants. After ten years of follow-up, the PA-coated implants had a statistically significantly lower mean migration of 0.94 mm (95% CI 0.72 to 1.2) as compared with 1.72 mm (95% CI 1.4 to 1.2) for the uncoated group ($p < 0.001$). There was also a significant difference in migration between groups when analyzing migration with three months as baseline, but not with one year as baseline as both groups showed hardly any mean migration from that point onwards. Stabilization of continuous migration of the uncoated implants occurred between three months and one year of follow-up, whereas this was within the first three postoperative months for the PA-coated group. The individual implants showing continuous migration in the second postoperative year all stabilized between two years and final follow-up, except for two implants in the uncoated group. Both tibial components showed radiolucent lines and subsidence of the tibial component on conventional radiographs at final follow-up. Given the late stabilization, beyond the two years mark, observed in six implants, short-term RSA cut-off values to determine the risk of failure seem might be of limited value in these uncemented implants. The latter seems to be more prominent for knee implants without a biological mediator to enhance bone ingrowth. In these uncemented implants, three- to five-year follow-up is probably needed to predict its bone-fixation properties at the long-term.

Surgical and patient risk factors for tibial component migration

In the second part of this thesis, we pooled individual participant data of multiple RSA studies in order to increase statistical power and be able to find risk factors for loosening for the individual patient. However, we first had to confirm whether it is justified to pool data from studies using different RSA methods. As marker-based and model-based RSA both introduce different types of measurement error and may even introduce systematic bias due to methodological differences, we reanalyzed a marker-based RSA study with model-based RSA as described in **chapter 6**. The original study was a comparison between cemented all-polyethylene and cemented modular metal-backed tibial components. By reanalyzing the latter group with model-based RSA, we were able to find systematic differences in translations but not rotations and MTPM between both methods. These differences were caused by a difference in reference origin that is being used for migration calculation by each method. As a result, the marker-based method overestimated the transverse, longitudinal, and sagittal translations by 29%, 7% and 26%, respectively. When correcting for this proportional bias by using the same reference coordinate system, nearly identical translations were found. We also found slightly larger limits of agreement for the rotations and MTPM values between both RSA methods, which is caused by some imprecision of the model-based measurements due to relatively round, symmetrical shape of the tibial component in the transverse plane[1]. However, the limits of agreement were still considered precise enough. We were also able to demonstrate that there was no insert micromotion with respect to the metal tray affecting the migration results, a phenomenon that was found in older fixed-bearing designs[2, 3]. However, results of some individual patients differed substantially at some follow-up examinations due to different types of measurement error (e.g., marker occlusion in marker-based RSA and model-fit inaccuracies in model-based RSA). We therefore concluded that although both methods produced comparable results on a group level, one must not put too much weight on strict migration thresholds in individual patients as a sudden increase in migration may also be the result of measurement error.

Orthopaedic surgeons traditionally aim for a neutral coronal alignment of the lower limb during total knee arthroplasty, regardless of the patients' anatomy. Several short- to midterm studies have claimed improved clinical outcomes when constitutional (i.e., pre-morbid) joint kinematics are restored[4-10], e.g., with use of kinematic alignment techniques in which the lower limb is aligned according to its pre-arthritic varus or valgus state. However, such novel alignment techniques may impair the long-term survival of the implants as asymmetric loading in varus or valgus may result in mechanical loosening. We therefore specifically analyzed the effect of coronal alignment on tibial component migration with use of pooled long-term RSA data (**chapter 7**). Coronal alignment parameters were measured on pre- and postoperative full-leg radiographs in 85 patients that underwent cemented TKA. The patients' constitutional leg alignment was determined with use of the preoperative full-leg radiographs. The effect of the postoperative hip-knee-ankle angle on migration was determined relative to both the mechanical axis and the patients' constitutional alignment. After 5 years of follow-up, knees aligned in mechanical varus showed the highest mean migration of 1.55 mm (95% CI, 1.16 to 2.01 mm), compared with 1.07 mm (95% CI, 0.63 to 1.64 mm) and 0.77 mm (95% CI, 0.53 to 1.06 mm) for valgus and in-range knees, respectively ($p < 0.001$). In contrast, no significant differences in migration were seen across constitutional alignment categories. Furthermore, matching the patients' constitutional alignment did not preclude high migration, especially in mechanically varus-aligned TKAs. Given these results, the (adverse) effects of component alignment should be further investigated before alternative alignment techniques become widely adopted.

Chapter 8 describes the results of a large meta-analysis of 630 patients collected from 11 RSA studies with long-term data available. By doing so, we were able to determine the effect of patient, implant and alignment characteristics on tibial component migration over time. By pooling such a large group of patients, statistical power increases as compared with the individual studies in which subgroup analyses on patient characteristics are underpowered and may produce false positive results due to multiple comparisons[11]. We found early mechanical loosening to occur in 2.9% of the implants, late loosening in 2.1%, septic loosening in 0.3% and stabilization of high initial migration in 2.7%. All other implants showed a stable migration pattern over time. In cemented prostheses, increased migration was found in females, in patients with rheumatoid arthritis and when a posterior-stabilized design was implanted. These differences were smaller and not significant when analyzing migration from three months onwards. We hypothesized that the initial increase in migration may be due to a lower bone mineral density in females and in patients with rheumatoid arthritis, and due to increased contact stresses on the post-cam mechanism in cases where a more constrained posterior-stabilized design was implanted. As a result, subsidence of the prosthesis is likely to occur within the first three months upon weight bearing. In uncemented prostheses, postoperative varus limb alignment increased migration and this became more evident with time. Furthermore, uncemented implants without an osseointegration promoting surface (i.e., porous coating only without additional hydroxyapatite coatings, nor made of highly porous metal) showed delayed stabilization and increased risk for failed ingrowth as compared with uncemented implants with a surface promoting osseointegration. The use of these biological mediators thus minimizes both initial and continuous migration. The found migration profiles reflect different failure mechanisms with early, progressive loosening being the result of subsidence of the tibial tray into the tibial plateau due to failed ingrowth or tibial collapse. Late loosening may be the result of progressive bone resorption at the cement-bone or prosthesis-bone interface[12]. Lastly, high initial migration may also be merely physiological, especially in uncemented prostheses without an osseointegration promoting surface. These implants may thus require longer follow-up with radiographic surveillance to ensure stabilization of migration.

General discussion

In the past five decades, total knee arthroplasty (TKA), and particularly its surgical procedure, has changed in many aspects. The first designs were reserved for highly disabled patients with extensive degeneration and deformities[13]. With improvements in design, functional results and implant longevity, the indication for arthroplasty changed and broadened to high demand patients. Some of the changes in implant design were minor, others fundamentally altered the design rationale, fixation techniques and implant materials in continuous attempts to improve function while minimizing the risk of loosening, the leading cause of revision[14, 15]. Registry data show that the majority of surgeons performing TKA today use a modular metal-backed, fixed-bearing design with cement fixation. Through three randomized controlled trials (RCTs), we contribute to the evidence base by examining whether changes in different design aspects improve migration patterns in comparison with a modern modular metal-backed fixed-bearing cemented TKA design (Triathlon, Stryker). A fourth RCT was conducted to determine the long-term effect on migration of an additional surface coating after an uncemented modular metal-backed fixed-bearing TKA.

All-polyethylene tibial components

Before the introduction of metal-backed tibial components in TKA in the late 1970s, almost all designs had an all-polyethylene tibial component[16]. As the metal-backed designs proved superior in several aspects including the risk of aseptic loosening, first-generation all-polyethylene designs were abandoned. However, there is a growing body of evidence that modern all-polyethylene designs perform at least equally well[17-19]. In **chapter 2**, we confirmed our hypothesis that the studied condylar stabilizing (CS) all-polyethylene components showed comparable (in the *post hoc* sensitivity analysis) or even less migration (in the primary analysis) after two years of follow-up than its metal-backed counterpart. The results of our study are in line with other RSA studies showing comparable implant migration[20-27]. Hyldahl *et al.*[24] hypothesized that the all-polyethylene components may partly absorb eccentric forces as they are more elastic than the rigid metal-backed components. The all-polyethylene tibial component designs may thus be slightly more resistant to adverse tensile forces upon peripheral compressive loading. Despite the comparable outcomes between all-polyethylene and metal-backed designs described in the abovementioned studies, all-polyethylene components are still rarely used. Given the reduced costs of manufacturing these implants, surgeons should consider using them more often now that the demand for TKA is growing substantially[16, 28].

An interesting finding in **chapter 2** was the surgeon effect in the *post hoc* sensitivity analysis, showing a statistically significant difference in migration between the implants operated by surgeon 1 and surgeon 2. This may indicate that meticulous performance of each surgical step can improve the outcome, at least on a subclinical level. A later study evaluating a posterior-stabilized (PS) all-polyethylene design with a PS metal-backed design, again performed by the same two surgeons, found no surgeon effect on migration[27]. Given that the same two surgeons performed the surgeries, it seems likely that it is not the surgeon experience per se, but rather the combination with the CS design which may be less forgiving. This stresses the importance for future new designs or changes in designs, to not only investigate their performance in ideal circumstances by very experienced surgeons, but also in routine practice.

Mobile-bearing insert

Mobile-bearing TKA designs were introduced to deal with two major problems affecting implant longevity: loosening and wear. The mobile-bearing design has an additional flat non-constrained articulation with the tibial component, thereby allowing a more congruent articulation with the femoral component which theoretically reduces both contact stresses at the implant-bone interface and polyethylene wear[29, 30]. However, previous RSA trials found no superiority of either design on tibial component migration[2, 31-33], and even questioned whether mobility is present in vivo due to (among other reasons) formation of fibrous tissue and a mismatch in pivot point of the rotating platform and the actual tibiofemoral rotation point[34]. Furthermore, mobile-bearing arthroplasty is technically more challenging with additional risks including insert dislocations[35-37]. In our study (**chapter 3**), no differences were found in migration between the single-radius mobile-bearing and fixed-bearing TKA design after six years of follow-up. We did experience a great number of adverse events in the mobile-bearing group which could likely be attributed to difficulty of intra-operative assembly of the mobile bearing insert of this design. In line with the conclusions of an earlier report on a subset of our study population[38], we believe that there is no clear benefit of this type of mobile-bearing design. For that matter, the manufacturer of this prosthesis decided to discontinue the mobile-bearing variant because of the observed complications. Moreover, the fixed-bearing single-radius design allows for some axial rotation during deep flexion with minimal constraint forces, which effectively eliminates the theoretical advantages of the mobile-bearing design.

Cementless fixation

The optimal fixation method of TKA is an ongoing debate. Cement has historically been considered the gold standard, producing reliable results. In contrast, early uncemented prostheses often failed miserably due to experimentation in design[39]. The high failure rates resulted in near abandonment of uncemented components, but the desire to achieve a more durable, biologic fixation in younger, heavier and more active patients undergoing TKA has caused a resurgence of interest in cementless fixation techniques[12, 40-42]. With the introduction of new implant materials and coating techniques, innovations in porous ingrowth technology may further improve osseointegration and thus the fixation of uncemented implants. We evaluated the effect of one of those new coatings called peri-apatite (PA), which is a solution deposition technique to increase the coverage of hydroxyapatite onto the 3D implant surface (**chapter 4**)[43]. We found higher initial migration in the first three months for the uncemented PA-coated tibial components as compared with cemented components. However, a stable migration pattern was found between three months and five years of follow-up while the cemented components showed slightly more migration from three months onwards. As found in previous long-term RSA studies[44, 45], the initial migration found after uncemented TKA is often benign and merely part of a typical biphasic migration pattern. After three months, full stabilization of migration of the PA-coated components suggests a durable biological fixation has been achieved which, in contrast with cement fixation, may not be subjected to loss of cement-bone interlock due to continuous trabecular resorption as well as deformation and degradation of the cement mantle over the years[46-48]. In **chapter 5**, the long-term results of an additional study showed that the early stabilization of the PA-coated tibial components is sustained over time, resulting in low mean migration values and the absence of components with continuous migration after ten years of follow-up as compared with 'uncoated' uncemented components (i.e., porous coated only with cobalt-chromium sintered beads without the additional PA-coating). In this study, the mean initial migration of the PA-coated components was comparable with the migration values found in **chapter 4**, with a mean MTPM of 0.9 mm. In contrast, the uncoated components had a much higher mean MTPM of 1.5 mm, time to stabilization was observed to take longer and several individual components with continuous migration did not stabilize over time resulting in radiolucent lines and subsidence of the tibial components visible on conventional radiographs at final follow-up.

Especially in young patients, uncemented fixation techniques may be preferred due to the long-lasting biological fixation of the implant. Uncemented implants relying on ingrowth are well suited to hip arthroplasty as the forces acting on the interface are largely compressive, the knee differs however[39]. In the knee, compression alternates with adverse tensile forces. Therefore, bone ingrowth needs to occur fast after an initial rigid (press-fit) stability. Peri-apatite proves to be a valuable mediator for such a long-term biological fixation of tibial components, although migration in the first weeks after implantation is still larger than after cemented TKA. New component designs and biomaterials may be able to further improve the fixation of cementless implants. These must be carefully evaluated however, as some new designs clearly do not suffice. For example, Nivbrant *et al.* (2020)[49] recently published the two-year results of an RCT evaluating the ACS knee (Implantcast), which has an additional ceramic coating of titanium nitride. The uncemented tibial components in this study displayed high initial migration which did not stabilize in a large number of patients. The authors raised their concerns about the risk of loosening given the observed late ongoing subsidence and high MTPM values, and advised to only use the cemented version of this TKA design. This particular implant has also been identified to have a much higher than anticipated revision rate in the Australian registry[14]. On the other hand, more promising are the 3D printed highly porous metal implants matching the pore size and elasticity of the surrounding trabecular bone, which may further improve osseointegration and should prevent a mismatch in stiffness and shear forces at the implant-bone interface[50]. Hasan *et al.* (2020)[51] recently showed that the initial migration of such a 3D printed implant is indeed slightly less than that of the PA-coated implants studied in this thesis. Hence, it appears that this design and biomaterial may further improve the fixation of cementless implants.

The value of short-term RSA outcomes in randomized controlled trials

The introduction of new orthopaedic implants and surgical techniques has been disastrous at times. For example, hip prostheses that were fixed with a new type of cement called Boneloc showed a remarkable increase in revision risk for aseptic loosening of up to fourteen times[52, 53]. This is just one example of many other introductions that have failed miserably. New implants should therefore have been rigorously tested in a stepwise manner, including preclinical studies and small, randomized clinical trials prior to market introduction[54, 55]. Clinical RSA studies play an important role. If the manufacturer of Boneloc cement, for example, performed such a study, widespread introduction into the international market would have been prevented. The results of a randomized RSA study including only 30 patients, performed after market introduction by an independent research group, were unambiguous; a substantially higher initial migration within six months and no signs of stabilization at one year follow-up was found for the patients that received Boneloc cement as compared with conventional cement[56]. The authors therefore did not recommend the use of this new type of cement. A later study showed similar results with increased migration and clinical failure after TKA with Boneloc cement[57].

Earlier evaluation of prostheses using RSA could play an important role in lowering the total revision burden. A recent study showed that RSA-tested knee implants on average have a lower 10-year revision rate than implants that have not been tested with RSA[58]. Possible explanations for this difference are (1) the early warning function of poor performance (i.e., high migration values) leading to subsequent discontinuation of the given implant and continued use of well-fixed implants; (2) RSA testing may be a proxy for rigorous clinical testing by the manufacturer; and (3) prudent surgeons may choose to only use thoroughly tested implants[58]. However, although excessive implant migration may correctly predict a high failure rate[59], the short-term cut-off values that have been proposed in earlier studies may not be applicable to all implants or fixation techniques. The cut-off values reported by Ryd *et al.*[60] and Pijls *et al.*[61] suggest that one only needs two-year data to determine whether an increased risk of loosening at ten years is likely or not. Many RSA studies therefore terminate after two years. Indeed, when analyzing the migration of a certain prosthesis in a randomized setting, two-year data can be sufficient if both prostheses are comparable in many aspects, especially if the same cement is used for fixation. We performed such randomized controlled trials (RCTs) in **chapters 2 and 3**. The results of these trials show no major differences in terms of early migration, which allows for subsequent clinical and registry studies to evaluate other outcomes in larger groups of patients. In c**hapter 4**, we compared the migration of a cemented implant with an uncemented implant. As the uncemented implants showed clear stabilization of migration, here too the short-term migration values are sufficient to conclude that there are no major concerns regarding the expected long-term survival of the investigated implants. Conversely, the uncoated implants in **chapter 5** showed much higher initial migration and several individual implants showed continuous migration in the second postoperative year. Given the known biphasic migration pattern of uncemented components, two-year data were too short to make any succinct statements on whether delayed stabilization will occur or that a high incidence of aseptic loosening is likely. Hence, the known and much used cut-off values at one to two years are too short to be applied for uncemented knee implants, whilst three- to five-year data might suffice. Although the long-term outcomes presented in **chapter 5** showed delayed stabilization of the majority of the uncoated implants, we advise against the widespread use of the uncoated version of this specific implant given the magnitude of the mean migration and the number of implants showing progressive migration with subsequent radiographic signs of loosening on conventional radiographs.

Longer follow-up is also needed to assess whether continuous migration observed in the second postoperative year is the result of marker instability or model-fit inaccuracies in the marker-based or model-based RSA examinations, respectively. Even though we demonstrated in **chapter 6** that mean migration values are comparable between marker-based and model-based measurements, measurement errors related to the used RSA method may produce falsely high migration measurements for individual patients (as confirmed by the results of the alternative RSA method not subjected to this type of measurement error). We thus advise to avoid making strong statements regarding the occurrence of continuous migration based on the final available RSA examination.

Predisposing factors for loosening

National arthroplasty registries provide important analyses on patient- and implant-related factors for revision arthroplasty. Likewise, large cohort studies evaluating risk factors for revision often rely on implant revision as the main outcome measure. When analyzing the effect of certain factors on the risk of loosening, however, revision data have its limitations. The decision to revise is subjective to major competing risk factors such as death and the willingness of the patient or surgeon to revise. As loosening of an implant is asymptomatic at first, the onset of symptoms that gradually progress years after implantation are often present in a patient that is now at a higher age with increasing comorbidities and lower functional demands. Even if the diagnosis of loosening is made, the orthopaedic surgeon may be in doubt of when to offer a revision arthroplasty. How many complaints should the patient have? The experience of the surgeon in revision arthroplasty may result in hesitance given the uncertainties whether the, often complex, procedure will have a beneficial effect on the patients' complaints or make it worse. As revisions are publicly marked as failure of the center in which they are performed in some national arthroplasty registries, it may even promote reluctance to revise, subsequently denying patients with inferior results an opportunity to gain improved outcomes of a well performed revision arthroplasty.

Patients with excessive early tibial component migration measured with RSA can be identified long before symptoms occur. As RSA is a highly accurate and objective outcome measure, the data presented in this thesis are less subjective to competing risk factors than revision as an outcome measure in registry data and cohort studies. The downside of RSA is that it is only a proxy for clinical failure associated with micromotion of the implant. Some patients remain asymptomatic despite excessive migration measured with RSA, which may be partly due to lower functional demands of the given patient. These limitations notwithstanding, pooling long-term RSA data as performed in **chapter 7** and **chapter 8** have given insight into factors associated with increased migration and thus the risk of loosening of the implant. Knowing these risk factors can aid the surgeon in choosing the optimal implant design and surgical technique for each patient, as well as to decide on the timing and duration of postoperative radiographic surveillance.

A remarkable difference with revision data is that we did not find age to be associated with increased migration. In national arthroplasty registries, younger patients have a much higher revision rate than older patients[42, 62]. Possible explanations include a higher physical activity, a "higher expectancy of pain relief" and "a health condition that better allows for revision surgery"[63]. Thus, the willingness of the patient and surgeon to revise plays an important role in the effect of age in revision data. The higher physical activity at younger age on the other hand, appears to play a minor role in the onset of loosening when migration is analyzed as a proxy for failure (**chapter 8**). In our study, the mean migration of both cemented and uncemented components did not differ between three different age groups. However, it is possible that the occurrence of late loosening in 13 prostheses is the result of cement debonding and osteolysis in physically active patients, which could not be further evaluated due to the small number of events.

There is conflicting evidence on the effect of body mass index (BMI) on revision for loosening of the implant. Ritter *et al.*[64] found increasing BMI to be associated with an increasing risk for failure (other than infection), although patients with a BMI below 23 kg/m^2 also had an increased risk of failure as compared with the 23-26 kg/m^2 group. They concluded to "intuitively believe that poor implant alignment combined with a high BMI represents a much greater risk to implant survival than either risk factor alone"[64]. Abdel *et al.*[65] also found BMI to be inversely related to 20-year implant survivorship (excluding infection). Other authors did not find such an association[66]. National arthroplasty registry data primarily show BMI to be associated with an increased risk of infection and not aseptic loosening[14]. In **chapter 8**, BMI was not found to be associated with an increase in migration despite what is often intuitively thought. The association of BMI and migration may be very small and therefore clinically irrelevant after TKA with a neutral mechanical alignment. Future studies analyzing specific cohorts of patients with a varus or valgus implant alignment may show more relevant associations, as indeed one expects implant survival to be especially impaired by asymmetric loading conditions in the presence of a high BMI.

Coronal alignment of the lower limb has attracted much attention as new alignment techniques are being popularized in search of improving the patients' satisfaction after TKA. The goal of these new techniques, such as kinematic alignment, are to restore the patients' native anatomy rather than aligning the limb in standard neutral position as in mechanical alignment. By doing so, the three kinematic axes of the knee are respected and all bone resections, corrected for wear, are equal in thickness to the implanted components[67]. By resurfacing the knee in this manner, the components will be intentionally placed in varus or valgus in a large proportion of patients given the normal distribution of native lower limb alignment[68, 69]. The upside of this method is that the tension of the soft-tissue envelope is restored, hence releases of the collateral, posterior cruciate and retinacular ligaments are rarely needed[8, 69]. However, there are concerns about the risk of aseptic loosening in components subjected to asymmetric loading conditions when a neutral mechanical alignment has not been achieved. Short-term outcomes of kinematically aligned knees have not shown 'catastrophic' failure in knees aligned in varus or valgus, but these outcomes cannot be extrapolated to the long-term[8, 70]. The ten-year results of one study are promising with only 3 revisions for aseptic loosening (1.5% in 198 kinematically aligned TKAs), but these single-surgeon outcomes have yet to be reproduced by other authors[71]. For mechanically aligned TKA, conflicting evidence has been reported on surgical imprecision potentially leading to malalignment and its impact on long-term outcomes. Some authors have found increased failure rates[64, 72-75], while others did not find such an association[65, 76]. RSA may contribute to this discussion by its ability to measure migration long before a prosthesis will fail, and less dependent on surgeon and patient factors influencing a decision for revision surgery. In **chapter 7**, we found mechanical varus alignment to have the highest tibial component migration after cemented TKA. Furthermore, mean migration values were higher in mechanical varus as compared with neutral and valgus even in patients that were aligned in range with their constitutional alignment. Therefore, we advise to further investigate the effect of alternative alignment techniques on implant survival before implementing new alignment techniques on a large scale that do not aim for neutral mechanical alignment. It must be stressed however that the patients in this study were all treated with the intent to achieve a neutral mechanical alignment, but in some cases ended up with an unintended varus or valgus alignment, rather than with such a new technique actually intending to achieve the patients' constitutional alignment which is often in varus or valgus. In **chapter 8**, a similar effect of coronal alignment on migration was only found after uncemented TKA. The absence of an effect of alignment on migration after cemented TKA may be related to the fact that a much larger group of patients (> 400) was included in the analysis, resulting in relatively fewer cases with high migration. Furthermore, the aetiology of loosening is complex. High migration seems to occur more often in a group of patients with the lower limb aligned in varus, but varus alignment is tolerated for in the majority of these cases suggesting other factors play a crucial part in the onset of loosening such as the patient activity level, BMI, bone mineral density, ligament balancing, quality of the fixation technique, other alignment parameters such as the posterior slope of the tibial component, the magnitude of alignment correction and the presence of residual fixed flexion deformity[77-79].

We found three factors to be associated with higher initial migration after cemented TKA in **chapter 8**: female gender, rheumatoid arthritis and a posterior stabilized design. From three months onwards, no association was found for these factors. We hypothesized that slight tibial collapse upon weightbearing as a result of either decreased bone mineral density (in postmenopausal women and patients with rheumatoid arthritis) or increased contact stresses in the more constrained posterior-stabilized design occurs in the first weeks after implantation, after which a stable situation is achieved. Two other RSA studies have shown a relationship between migration and a lower bone mineral density, which besides patient-related factors is affected by the prosthesis design that can induce periprosthetic stress shielding (bone loss) and subsequent migration[77, 80].

Future perspectives

The studies presented in this thesis highlight the need for more research on risk factors for implant loosening and have pointed to some avenues that may be particularly relevant. It would be helpful to further expand the pooled RSA database to be able to perform subgroup analyses within various alignment categories and enable some of the questions raised above to be answered. Also, the addition of other relevant factors such as bone mineral density measurements, sagittal alignment parameters (posterior slope) and magnitude of alignment correction could give more insight into the mechanisms leading to aseptic loosening. Perhaps the most interesting field to further explore is the effect of different alignment strategies on implant migration. Until recently, not a single study evaluating kinematically aligned TKA has used RSA as an outcome measure. Laende *et al.*[81] have published the first randomized controlled trial analyzing migration with RSA, randomizing between kinematically aligned versus mechanically aligned TKA. After two years of follow-up, they found similar migration patterns between groups and no significant relationship between postoperative limb alignment and migration. They concluded that their findings support continued investigation of alternative alignment techniques. This is indeed what should be done; continued investigation of the effect of alternative alignment strategies with different implants and fixation techniques, monitored with RSA to enable early detection of any problem in a continuous cycle of improvements, to be able to provide patients the best possible short- and long-term clinical outcomes.

References

1. Kaptein BL, Valstar ER, Stoel BC, Reiber HC, Nelissen RG. Clinical validation of model-based RSA for a total knee prosthesis. *Clinical orthopaedics and related research* 2007; 464: 205-9.
2. Hansson U, Toksvig-Larsen S, Jorn LP, Ryd L. Mobile vs. fixed meniscal bearing in total knee replacement: a randomised radiostereometric study. *The Knee* 2005; 12: 414-8.
3. Nilsson KG, Henricson A, Dalen T. In vivo determination of modular tibial insert micromotion. *Trans Orthop Res Soc* 2003; 28: 1402.
4. Magnussen RA, Weppe F, Demey G, Servien E, Lustig S. Residual varus alignment does not compromise results of TKAs in patients with preoperative varus. *Clinical orthopaedics and related research* 2011; 469: 3443-50.
5. Matziolis G, Adam J, Perka C. Varus malalignment has no influence on clinical outcome in midterm follow-up after total knee replacement. *Archives of orthopaedic and trauma surgery* 2010; 130: 1487-91.
6. Vanlommel L, Vanlommel J, Claes S, Bellemans J. Slight undercorrection following total knee arthroplasty results in superior clinical outcomes in varus knees. *Knee Surg Sports Traumatol Arthrosc* 2013; 21: 2325-30.
7. Dossett HG, Estrada NA, Swartz GJ, LeFevre GW, Kwasman BG. A randomised controlled trial of kinematically and mechanically aligned total knee replacements: two-year clinical results. *The bone & joint journal* 2014; 96-b: 907-13.
8. Howell SM, Papadopoulos S, Kuznik K, Ghaly LR, Hull ML. Does varus alignment adversely affect implant survival and function six years after kinematically aligned total knee arthroplasty? *Int Orthop* 2015; 39: 2117-24.
9. Calliess T, Bauer K, Stukenborg-Colsman C, Windhagen H, Budde S, Ettinger M. PSI kinematic versus non-PSI mechanical alignment in total knee arthroplasty: a prospective, randomized study. *Knee Surg Sports Traumatol Arthrosc* 2017; 25: 1743-8.
10. Young SW, Walker ML, Bayan A, Briant-Evans T, Pavlou P, Farrington B. The Chitranjan S. Ranawat Award : No Difference in 2-year Functional Outcomes Using Kinematic versus Mechanical Alignment in TKA: A Randomized Controlled Clinical Trial. *Clinical orthopaedics and related research* 2017; 475: 9-20.
11. Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. *BMJ (Clinical research ed)* 2010; 340: c221.
12. Nilsson KG, Henricson A, Norgren B, Dalen T. Uncemented HA-coated implant is the optimum fixation for TKA in the young patient. *Clinical orthopaedics and related research* 2006; 448: 129-39.
13. Oussedik S, Abdel MP, Cross MB, Haddad FS. Alignment and fixation in total knee arthroplasty: changing paradigms. *The bone & joint journal* 2015; 97-b: 16-9.
14. Australian Orthopaedic Association National Joint Replacement Registry. Annual Report 2019. *Adelaide: AOA* 2019.
15. Dutch Arthroplasty Register (LROI). Annual Report 2019. *'s-Hertogenbosch: NOV* 2019.
16. Gioe TJ, Maheshwari AV. The all-polyethylene tibial component in primary total knee arthroplasty. *The Journal of bone and joint surgery American volume* 2010; 92: 478-87.
17. Voigt J, Mosier M. Cemented all-polyethylene and metal-backed polyethylene tibial components used for primary total knee arthroplasty: a systematic review of the literature and meta-analysis of randomized controlled trials involving 1798 primary total knee implants. *The Journal of bone and joint surgery American volume* 2011; 93: 1790-8.

18. Nouta KA, Verra WC, Pijls BG, Schoones JW, Nelissen RG. All-polyethylene tibial components are equal to metal-backed components: systematic review and meta-regression. *Clinical orthopaedics and related research* 2012; 470: 3549-59.
19. Voss B, El-Othmani MM, Schnur AK, Botchway A, Mihalko WM, Saleh KJ. A Meta-Analysis Comparing All-Polyethylene Tibial Component to Metal-Backed Tibial Component in Total Knee Arthroplasty: Assessing Survivorship and Functional Outcomes. *J Arthroplasty* 2016; 31: 2628-36.
20. Adalberth G, Nilsson KG, Bystrom S, Kolstad K, Mallmin H, Milbrink J. Stability assessment of a moderately conforming all-polyethylene tibial component in total knee arthroplasty: a prospective RSA study with 2 years of follow-up of the Kinemax Plus design. *The American journal of knee surgery* 1999; 12: 233-40.
21. Adalberth G, Nilsson KG, Bystrom S, Kolstad K, Milbrink J. Low-conforming all-polyethylene tibial component not inferior to metal-backed component in cemented total knee arthroplasty: prospective, randomized radiostereometric analysis study of the AGC total knee prosthesis. *J Arthroplasty* 2000; 15: 783-92.
22. Adalberth G, Nilsson KG, Bystrom S, Kolstad K, Milbrink J. All-polyethylene versus metal-backed and stemmed tibial components in cemented total knee arthroplasty. A prospective, randomised RSA study. *J Bone Joint Surg Br* 2001; 83: 825-31.
23. Norgren B, Dalen T, Nilsson KG. All-poly tibial component better than metal-backed: a randomized RSA study. *The Knee* 2004; 11: 189-96.
24. Hyldahl H, Regner L, Carlsson L, Karrholm J, Weidenhielm L. All-polyethylene vs. metal-backed tibial component in total knee arthroplasty-a randomized RSA study comparing early fixation of horizontally and completely cemented tibial components: part 1. Horizontally cemented components: AP better fixated than MB. *Acta orthopaedica* 2005; 76: 769-77.
25. Hyldahl H, Regner L, Carlsson L, Karrholm J, Weidenhielm L. All-polyethylene vs. metal-backed tibial component in total knee arthroplasty-a randomized RSA study comparing early fixation of horizontally and completely cemented tibial components: part 2. Completely cemented components: MB not superior to AP components. *Acta orthopaedica* 2005; 76: 778-84.
26. Muller SD, Deehan DJ, Holland JP, Outterside SE, Kirk LM, Gregg PJ, et al. Should we reconsider all-polyethylene tibial implants in total knee replacement? *J Bone Joint Surg Br* 2006; 88: 1596-602.
27. Hasan S, Marang-Van De Mheen PJ, Kaptein BL, Nelissen R, Toksvig-Larsen S. All-polyethylene versus metal-backed posterior stabilized total knee arthroplasty: similar 2-year results of a randomized radiostereometric analysis study. *Acta orthopaedica* 2019; 90: 590-5.
28. Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. *The Journal of bone and joint surgery American volume* 2007; 89: 780-5.
29. Callaghan JJ, Insall JN, Greenwald AS, Dennis DA, Komistek RD, Murray DW, et al. Mobile-bearing knee replacement: concepts and results. *Instructional course lectures* 2001; 50: 431-49.
30. Mahoney OM, Kinsey TL, D'Errico TJ, Shen J. The John Insall Award: no functional advantage of a mobile bearing posterior stabilized TKA. *Clinical orthopaedics and related research* 2012; 470: 33-44.
31. Henricson A, Dalen T, Nilsson KG. Mobile bearings do not improve fixation in cemented total knee arthroplasty. *Clinical orthopaedics and related research* 2006; 448: 114-21.
32. Pijls BG, Valstar ER, Kaptein BL, Nelissen RG. 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. *J Bone Joint Surg Br* 2012; 94: 1366-71.
33. Tjornild M, Soballe K, Hansen PM, Holm C, Stilling M. Mobile- vs. fixed-bearing total knee replacement. *Acta orthopaedica* 2015; 86: 208-14.

34. Garling EH, Kaptein BL, Nelissen RG, Valstar ER. Limited rotation of the mobile-bearing in a rotating platform total knee prosthesis. *Journal of biomechanics* 2007; 40 Suppl 1: S25-30.
35. Cho WS, Youm YS, Ahn SC, Sohn DW. What have we learned from LCS mobile-bearing knee system? *Knee Surg Sports Traumatol Arthrosc* 2010; 18: 1345-51.
36. Fisher DA, Bernasek TL, Puri RD, Burgess ML. Rotating platform spinouts with cruciate-retaining mobile-bearing knees. *J Arthroplasty* 2011; 26: 877-82.
37. Namba RS, Inacio MC, Paxton EW, Ake CF, Wang C, Gross TP, et al. Risk of revision for fixed versus mobile-bearing primary total knee replacements. *The Journal of bone and joint surgery American volume* 2012; 94: 1929-35.
38. Wolterbeek N, Garling EH, Mertens BJ, Nelissen RG, Valstar ER. Kinematics and early migration in single-radius mobile- and fixed-bearing total knee prostheses. *Clin Biomech (Bristol, Avon)* 2012; 27: 398-402.
39. Vince KG, Whiteside LA. Point-counterpoint. Fixation for primary total knee arthroplasty: cemented versus cementless. *Journal of Arthroplasty* 1996; 11: 123-9.
40. Voigt JD, Mosier M. Hydroxyapatite (HA) coating appears to be of benefit for implant durability of tibial components in primary total knee arthroplasty. *Acta orthopaedica* 2011; 82: 448-59.
41. Meneghini RM, Hanssen AD. Cementless fixation in total knee arthroplasty: past, present, and future. *J Knee Surg* 2008; 21: 307-14.
42. Bayliss LE, Culliford D, Monk AP, Glyn-Jones S, Prieto-Alhambra D, Judge A, et al. The effect of patient age at intervention on risk of implant revision after total replacement of the hip or knee: a population-based cohort study. *Lancet* 2017; 389: 1424-30.
43. Serekian P. Hydroxyapatite: from plasma spray to electrochemical deposition. In: Epinette J, Manley MT, editors. Fifteen years of clinical experience with hydroxyapatite coatings in joint arthroplasty: Springer, France; 2004. p. 29-33.
44. Henricson A, Nilsson KG. Trabecular metal tibial knee component still stable at 10 years. *Acta orthopaedica* 2016; 1-7.
45. Pijls BG, Valstar ER, Kaptein BL, Fiocco M, Nelissen RG. The beneficial effect of hydroxyapatite lasts: a randomized radiostereometric trial comparing hydroxyapatite-coated, uncoated, and cemented tibial components for up to 16 years. *Acta orthopaedica* 2012; 83: 135-41.
46. Freeman MA, Tennant R. The scientific basis of cement versus cementless fixation. *Clinical orthopaedics and related research* 1992; 19-25.
47. Gandhi R, Tsvetkov D, Davey JR, Mahomed NN. Survival and clinical function of cemented and uncemented prostheses in total knee replacement: a meta-analysis. *J Bone Joint Surg Br* 2009; 91: 889-95.
48. Miller MA, Terbush MJ, Goodheart JR, Izant TH, Mann KA. Increased initial cement-bone interlock correlates with reduced total knee arthroplasty micro-motion following in vivo service. *Journal of biomechanics* 2014; 47: 2460-6.
49. Nivbrant NO, Khan RJK, Fick DP, Haebich S, Smith E. Cementless Versus Cemented Tibial Fixation in Posterior Stabilized Total Knee Replacement: A Randomized Trial. *The Journal of bone and joint surgery American volume* 2020; 102: 1075-82.
50. Haddad FS, Plastow R. Is it time to revisit cementless total knee arthroplasty? *The bone & joint journal* 2020; 102-b: 965-6.
51. Hasan S, van Hamersveld KT, Marang-van de Mheen PJ, Kaptein BL, Nelissen RGHH, Toksvig-Larsen S. Migration of a novel 3D-printed cementless versus a cemented total knee arthroplasty: two-year results of a randomized controlled trial using radiostereometric analysis. *The bone & joint journal* 2020; 102-b: 1016-24.

52. Nelissen RG, Pijls BG, Karrholm J, Malchau H, Nieuwenhuijse MJ, Valstar ER. RSA and registries: the quest for phased introduction of new implants. *The Journal of bone and joint surgery American volume* 2011; 93 Suppl 3: 62-5.
53. Furnes O, Lie SA, Havelin LI, Vollset SE, Engesaeter LB. Exeter and charnley arthroplasties with Boneloc or high viscosity cement. Comparison of 1,127 arthroplasties followed for 5 years in the Norwegian Arthroplasty Register. *Acta orthopaedica Scandinavica* 1997; 68: 515-20.
54. Malchau H. Introducing new technology: a stepwise algorithm. *Spine (Phila Pa 1976)* 2000; 25: 285.
55. McCulloch P, Altman DG, Campbell WB, Flum DR, Glasziou P, Marshall JC, et al. No surgical innovation without evaluation: the IDEAL recommendations. *Lancet (London, England)* 2009; 374: 1105-12.
56. Thanner J, Freij-Larsson C, Kärrholm J, Malchau H, Wesslén B. Evaluation of Boneloc. Chemical and mechanical properties, and a randomized clinical study of 30 total hip arthroplasties. *Acta orthopaedica Scandinavica* 1995; 66: 207-14.
57. Nilsson KG, Dalén T. Inferior performance of Boneloc bone cement in total knee arthroplasty: a prospective randomized study comparing Boneloc with Palacos using radiostereometry (RSA) in 19 patients. *Acta orthopaedica Scandinavica* 1998; 69: 479-83.
58. Hasan S, Marang-van de Mheen PJ, Kaptein BL, Nelissen R, Pijls BG. RSA-tested TKA Implants on Average Have Lower Mean 10-year Revision Rates Than Non-RSA-tested Designs. *Clinical orthopaedics and related research* 2020; 478: 1232-41.
59. Pijls BG, Nieuwenhuijse MJ, Schoones JW, Middeldorp S, Valstar ER, Nelissen RG. RSA prediction of high failure rate for the uncoated Interax TKA confirmed by meta-analysis. *Acta orthopaedica* 2012; 83: 142-7.
60. Ryd L, Albrektsson BE, Carlsson L, Dansgard F, Herberts P, Lindstrand A, et al. Roentgen stereophotogrammetric analysis as a predictor of mechanical loosening of knee prostheses. *J Bone Joint Surg Br* 1995; 77: 377-83.
61. Pijls BG, Plevier JWM, Nelissen R. RSA migration of total knee replacements. *Acta orthopaedica* 2018; 89: 320-8.
62. Gademan MGJ, Van Steenbergen LN, Cannegieter SC, Nelissen R, Marang-Van De Mheen PJ. Population-based 10-year cumulative revision risks after hip and knee arthroplasty for osteoarthritis to inform patients in clinical practice: a competing risk analysis from the Dutch Arthroplasty Register. *Acta orthopaedica* 2021; 1-5.
63. Swedish Knee Arthroplasty Register. Annual Report 2019. *Lund: SKAR* 2019.
64. Ritter MA, Davis KE, Meding JB, Pierson JL, Berend ME, Malinzak RA. The effect of alignment and BMI on failure of total knee replacement. *The Journal of bone and joint surgery American volume* 2011; 93: 1588-96.
65. Abdel MP, Ollivier M, Parratte S, Trousdale RT, Berry DJ, Pagnano MW. Effect of Postoperative Mechanical Axis Alignment on Survival and Functional Outcomes of Modern Total Knee Arthroplasties with Cement: A Concise Follow-up at 20 Years. *The Journal of bone and joint surgery American volume* 2018; 100: 472-8.
66. Pitta M, Esposito CI, Li Z, Lee YY, Wright TM, Padgett DE. Failure After Modern Total Knee Arthroplasty: A Prospective Study of 18,065 Knees. *J Arthroplasty* 2018; 33: 407-14.
67. Howell SM, Papadopoulos S, Kuznik KT, Hull ML. Accurate alignment and high function after kinematically aligned TKA performed with generic instruments. *Knee Surg Sports Traumatol Arthrosc* 2013; 21: 2271-80.

68. Bellemans J, Colyn W, Vandenneucker H, Victor J. The Chitranjan Ranawat award: is neutral mechanical alignment normal for all patients? The concept of constitutional varus. *Clinical orthopaedics and related research* 2012; 470: 45-53.
69. Almaawi AM, Hutt JRB, Masse V, Lavigne M, Vendittoli PA. The Impact of Mechanical and Restricted Kinematic Alignment on Knee Anatomy in Total Knee Arthroplasty. *J Arthroplasty* 2017; 32: 2133-40.
70. Abdel MP, Oussedik S, Parratte S, Lustig S, Haddad FS. Coronal alignment in total knee replacement: historical review, contemporary analysis, and future direction. *The bone & joint journal* 2014; 96-b: 857-62.
71. Howell SM, Shelton TJ, Hull ML. Implant Survival and Function Ten Years After Kinematically Aligned Total Knee Arthroplasty. *J Arthroplasty* 2018; 33: 3678-84.
72. Berend ME, Ritter MA, Meding JB, Faris PM, Keating EM, Redelman R, et al. Tibial component failure mechanisms in total knee arthroplasty. *Clinical orthopaedics and related research* 2004; 26-34.
73. Fang DM, Ritter MA, Davis KE. Coronal alignment in total knee arthroplasty: just how important is it? *J Arthroplasty* 2009; 24: 39-43.
74. Nakamura S, Tian Y, Tanaka Y, Kuriyama S, Ito H, Furu M, et al. The effects of kinematically aligned total knee arthroplasty on stress at the medial tibia: A case study for varus knee. *Bone & joint research* 2017; 6: 43-51.
75. Suh DS, Kang KT, Son J, Kwon OR, Baek C, Koh YG. Computational study on the effect of malalignment of the tibial component on the biomechanics of total knee arthroplasty: A Finite Element Analysis. *Bone & joint research* 2017; 6: 623-30.
76. Bonner TJ, Eardley WG, Patterson P, Gregg PJ. The effect of post-operative mechanical axis alignment on the survival of primary total knee replacements after a follow-up of 15 years. *J Bone Joint Surg Br* 2011; 93: 1217-22.
77. Stilling M, Mechlenburg I, Jepsen CF, Romer L, Rahbek O, Soballe K, et al. Superior fixation and less periprosthetic stress-shielding of tibial components with a finned stem versus an I-beam block stem: a randomized RSA and DXA study with minimum 5 years' follow-up. *Acta orthopaedica* 2019; 1-10.
78. Nedopil AJ, Howell SM, Hull ML. What mechanisms are associated with tibial component failure after kinematically-aligned total knee arthroplasty? *Int Orthop* 2017; 41: 1561-9.
79. Nisar S, Palan J, Rivière C, Emerton M, Pandit H. Kinematic alignment in total knee arthroplasty. *EFORT open reviews* 2020; 5: 380-90.
80. Andersen MR, Winther NS, Lind T, Schroder HM, Flivik G, Petersen MM. Low Preoperative BMD Is Related to High Migration of Tibia Components in Uncemented TKA-92 Patients in a Combined DEXA and RSA Study With 2-Year Follow-Up. *J Arthroplasty* 2017; 32: 2141-6.
81. Laende EK, Richardson CG, Dunbar MJ. A randomized controlled trial of tibial component migration with kinematic alignment using patient-specific instrumentation versus mechanical alignment using computer-assisted surgery in total knee arthroplasty. *The bone & joint journal* 2019; 101-b: 929-40.