AARHUS
UNIVERSITY

Unicompartmental knee arthroplasty
Patient selection, treatment, and outcome

PhD thesis

Daan Koppens

Faculty of Health Sciences
University of Aarhus
2019

PhD Thesis by Daan Koppens
The Graduate School of Health, Aarhus University
Public defence: 10^{th} of January 2020

Unicompartmental knee arthroplasty
Patient selection, treatment, and outcome

PhD thesis

Daan Koppens

Faculty of Health Sciences
University of Aarhus

and

University Clinic for Hand, Hip and Knee Surgery,
Department of Orthopedic Surgery,
Regional Hospital West Jutland

Supervisors

Torben Bæk Hansen, Professor, MD, PhD
Head of Department, University Clinic for Hand, Hip and Knee Surgery, Department of Orthopaedic Surgery, Regional Hospital West Jutland, Denmark
Department of Clinical Medicine, Aarhus University, Denmark

Maiken Stilling, Professor, MD, PhD
Department of Orthopaedic Surgery, Aarhus University Hospital, Denmark
Department of Clinical Medicine, Aarhus University, Denmark

Søren Rytter, MD, PhD
Department of Orthopaedic Surgery, Aarhus University Hospital, Denmark

Ole Gade Sørensen, MD, PhD
Department of Orthopaedic Surgery, Aarhus University Hospital, Denmark

Evaluation committee

Stig Storgaard Jakobsen, Associate Professor, MD, PhD (Chairman)
Department of Orthopaedic Surgery, Aarhus University Hospital, Denmark
Department of Clinical Medicine, Aarhus University, Denmark

Leif Ryd, Professor, MD, PhD
Episurf Medical AB, Stockholm, Sweden
Karolinska Institute, Stockholm, Sweden

Bart L. Kaptein, Biomechanical Engineer, MSc, PhD
Biomechanics and Imaging Group, Department of Orthopaedic Surgery,
Leiden University Medical Center, Leiden, the Netherlands

Correspondence

Daan Koppens, MSc, MD

University Clinic for Hand, Hip and Knee Surgery

Hospital West Jutland

Lægårdvej 12, Entrance N

DK - 7500 Holstebro

E-mail: dkoppens@gmail.com

Phone: +45 31481429

Acknowledgements

This thesis is based on the scientific work conducted during my enrollment as a PhD student at the graduate school of health at the University of Aarhus from 2012 to 2019. All studies were performed at the University Clinic for Hand, Hip and Knee Surgery in the Regional Hospital of Holstebro.
Several people need mentioning in helping me get this far.
Off course, my main supervisor Torben Bæk Hansen. Torben has not only been my supervisor. He has influenced my life significantly since 2010. He offered me a position as a resident in orthopedic surgery in Holstebro and thereby enabled us to move to Denmark. I am truly grateful for the opportunity Torben has given me, combining my training as an orthopedic surgeon with performing research. He has been a generous boss & supervisor, giving me a lot of freedom, and always keeping the main objectives in mind, when I sometimes got lost in detail.
I am also indebted to my co-supervisors. Maiken Stilling, world champion in RSA in Denmark and beyond. Although Maiken is extremely busy, she always finds time to enlighten me in the world of RSA and DXA. Due to her experience in this field, she has been of major importance in performing the studies as well as interpreting the results. I am also indebted to Søren Rytter, who has always given valuable and positive feedback and has been very helpful connecting research with the clinic.
Although from a distance, Ole Gade Sørensen has been a valuable part of the team. Coming with new insights and perspectives, giving extra value to the studies.
Stig Munk and Jesper Dalsgaard, although not officially supervisors on my PhD, have been invaluable. Stig has been a driving force getting the PhD started. Stig and Jesper included and performed the surgeries on all of the patients. They have given their clinical insights throughout the process and taught me how to be a knee surgeon.
Again, thank you so much. I am looking forward to continuing working with all of you!

To all the colleagues at the orthopedic department and operating department, thank you for putting up with the extra work I provided. Special thanks to Helene Kjær Bredtoft, Liselotte Højriis Jeppesen, and Conny Sinkjær Pedersen, who have performed all the DXA scans during my project. Also, a special thanks to Conni Abildgaard Lisbjerg and Pia Toft Pedersen, for booking all appointments for follow-up, which I know has been a challenge.
I would like to thank the radiographic department, taking all the stereoradiographs and stress-radiographs. Also, the physical therapy department, especially Lis Møller Kristensen and Lene Kristiansen, for testing all patients with the leg rig.

I also need to mention Anne Dorthe Riedel, who has the neurotic need to keep order on all of our projects and analyzed all stereoradiographs and DXA scans. A big thank you, AD!

Doing a PhD does not only require good supervisors and colleagues. My family and friends have always been very supportive and interested in my scientific endeavours. And not unimportantly, have made sure that there was time to relax and take some distance now and then from work.

Finally, my own small family. Anke who took a big leap of faith and moved her entire life for me to Denmark. No-one is indispensable, they say. Well, Anke is indispensable for me. We have created a home and a life together in Denmark and of course Rune and Fie, who give joy (and sometimes headaches) to our life!

Thank you!

Daan

List of Studies

This thesis is based on the following 4 studies:

I. The lateral joint space width can be measured reliably with Telos valgus-stress radiography in medial knee osteoarthritis.
Koppens D, Sørensen OG, Munk S, Rytter S, Larsen SKA, Stilling M, Hansen TB.
Skeletal Radiology. 2019 Jul; 48(7): 1069-1077.
DOI: 10.1007/s00256-018-3111-5

II. Low implant migration of the Sigma medial unicompartmental knee arthroplasty.
Koppens D, Stilling M, Munk S, Dalsgaard J, Rytter S, Sørensen OG, Hansen TB.
Knee Surgery, Sports Traumatology, Arthroscopy. 2018; 26 (6): 1776-1785.
DOI: 10.1007/s00167-017-4782-5

III. Equal tibial component fixation of a mobile-bearing and fixed-bearing medial unicompartmental knee arthroplasty. A randomized controlled RSA study with 2-year follow-up.
Koppens D, Rytter S, Munk S, Dalsgaard J, Sørensen OG, Hansen TB, Stilling M.
Acta Orthopaedica. 2019; 90 (6): 575-581.
DOI: 10.1080/17453674.2019.1639965

IV. The effect of bone quality on migration in unicompartmental knee arthroplasty. A prospective cohort study using dual x-ray absorptiometry and radiostereometric analysis.
Koppens D, Rytter S, Dalsgaard J, Sørensen OG, Hansen TB, Stilling M.
Journal of Arthroplasty, 2019. Published online November 2019.
DOI: 10.1016/j.arth.2019.10.027

The papers that form the basis of this thesis will be referred to in the text by their Roman numerals (I–IV). Those currently in print have been reprinted by permission of the copyright holder.

Contents

Abbreviations

Abbreviations	**Definition**
ASA score	American Society of Anesthesiologists score
BMD	Bone mineral density
BMI	Body mass index
CI	95% confidence interval
DXA	Dual-energy X-ray absorptiometry
FB	Fixed bearing
GLA:D	Good Life with osteoarthritis in Denmark
ICC	Intra-class correlation coefficient
JSN	Joint space narrowing
JSW	Joint space width
κ	Weighted kappa
KL	Kellgren and Lawrence
LEP	Leg extension power
MB	Mobile bearing
MMA	Mixed model analysis
MTPM	Maximal total point motion
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
OKS	Oxford knee score
PI	Prediction interval
PROM	Patient-reported outcome measure
RSA	Radiostereometric analysis
SD	Standard deviation
TF	Tibiofemoral
THA	Total hip arthroplasty
TKA	Total knee arthroplasty
TR	Total rotation
TT	Total translation
UKA	Unicompartmental knee arthroplasty

1. English summary

Medial osteoarthritis (OA) of the knee can be treated with a medial unicompartmental knee arthroplasty (UKA). UKA offers a good clinical outcome and compared to total knee arthroplasty (TKA) fewer complications. Nevertheless, the survival rate of UKA is lower than the survival rate of TKA. The overall aim of this dissertation was therefore to identify aspects that have an influence on the selection, treatment, and outcome of patients with medial tibiofemoral (TF) OA treated with a medial UKA.

One of the selection criteria for a medial UKA is that there is full-cartilage thickness in the lateral TF joint. On regular weight-bearing radiographs, the lateral TF compartment is unloaded, and cartilage thickness cannot be sufficiently evaluated. As a supplement to weight-bearing radiographs, valgus-stress radiographs can be taken to evaluate the lateral TF compartment.

In *Study I*, we evaluated the reproducibility of valgus-stress radiography with the Telos stress device for assessment of lateral TF OA. We found that the assessment of OA in the lateral TF compartment was most reliable when based on measurement of the joint space width (JSW), showing an almost perfect intra-rater reliability and a substantial inter-rater reliability.

Early implant migration is a predictor for late implant loosening, which is the primary cause for revision surgery. Migration can be measured with radiostereometric analysis (RSA).

In *Studies II and III*, we evaluated migration of a fixed-bearing (FB) UKA and a mobile-bearing (MB) UKA with RSA. Due to design features of the tibial component and the polyethylene bearing, the loading and bone-implant fixation of FB and MB UKAs may be different, and the implants may migrate differently. We showed that fixation was similar and good with both the FB UKA and the MB UKA.

A low mid- to long-term (5- to 10-year) revision rate can therefore be expected for both implants. However, in *Study II*, continuous migration of the tibial component of the FB UKA was found in 30% of cases. Continuous migration poses a risk for loosening and consequently revision. This was not found in *Study III*. Patients in the FB UKA and the MB UKA group showed similar improvements in clinical outcome scores.

Bone mineral density (BMD) may be of importance in fixation of orthopedic implants and implant survival. There are only a few studies comparing tibial component migration and peri-prosthetic BMD, and they show contradictory results.

In *Study IV*, we investigated the influence of systemic and peri-prosthetic BMD on migration of the tibial component of a cemented medial UKA. During the first 12 months after surgery, a similar reduction of the peri-prosthetic BMD was seen in both the operated and the non-

operated knee. This suggests that a natural reduction in BMD due to aging is partly responsible for the BMD loss. Tibial component migration (MTPM) was associated with neither pre-operative systemic BMD nor with post-operative change in peri-prosthetic BMD, suggesting that long-term fixation is not influenced by BMD.

The findings of this thesis add new knowledge in the treatment of patients with medial OA of the knee. The thesis emphasizes on aspects of influence in patient selection, treatment, and outcome of treatment with a medial UKA.

2. Danish summary

Knæledsartrose i det mediale (indvendige) tibiofemorale (TF) ledkammer kan behandles med en medial unikompartmentel alloplastik (UKA). UKA giver gode kliniske resultater, og i forhold til total knæalloplastik (TKA), mindre komplikationer. Overlevelsen af UKA er dog lavere end overlevelsen af TKA.

Målet med denne afhandling har derfor været at identificere aspekter der kan have indflydelse på selektion, behandling og effekt hos patienter med knæledsartrose i det mediale TF ledkammer som er behandlet med medial UKA.

Et forbehold for at kunne få en medial UKA er, at der skal være normale brusk forhold i det laterale (udvendige) TF ledkammer. Det laterale TF ledkammer bliver normalt ikke belastet på vægtbærende røntgenbilleder, og dette ledkammer kan derfor ikke vurderes tilstrækkeligt. Som supplement kan der tages valgus-stress røntgenbilleder. I *Studie I*, har vi evalueret reproducerbarheden af valgus-stress røntgenbilleder, taget med Telos udstyr, for at vurdere artrosegraden i det laterale ledkammer. Vi fandt at artrose i det laterale TF ledkammer bedst vurderes ved at måle ledspalten, som giver en næsten perfekt intra-rater reliability og en substantielt inter-rater reliability.

Tidlig migration af et implantat er en prædiktor for senere løsning af implantatet, som er den hyppigste årsag til revisionskirurgi. Migration kan måles ved radiostereometrisk analyse (RSA).

I *Studie II og III*, har vi evalueret migrationen af en fixed-bearing (FB) UKA og en mobile-bearing (MB) UKA ved hjælp af RSA. På grund af forskellige designs af tibia komponenten samt polyethylen indsats mellem FB UKA og MB UKA kan der være en forskel i belastning og fiksering mellem knogle og implantat. Dette kunne teoretisk resultere i, at implantaterne migrerer forskelligt. Vi fandt dog en sammenlignelig og god fiksation for både FB UKA og MB UKA. Risikoen for revision på grund af løsning af implantaterne må derfor forventes at være lav indenfor en tidsramme på 5-10 år. I *Studie II*, fandt vi dog, at 30 % af tibia komponenterne blandt FB UKA viste kontinuerlig migration. Kontinuerlig migration er en risiko for senere løsning af implantaterne med efterfølgende revision. Dette blev ikke fundet i *Studie III*, og patienterne i både FB og MB gruppen viste den samme kliniske forbedring (Oxford Knee Score).

Knoglemineraltæthed (BMD) kan have en betydning i forhold til fiksering af implantater samt implantatoverlevelse. Der er kun få studier, der har sammenlignet migration af tibia komponenten og peri-prostetisk BMD, og de viser modstridende resultater.

I *Studie IV*, har vi undersøgt om systemisk og peri-prostetisk BMD har en indflydelse på migration af tibia komponenten i en cementeret medial UKA. I de første 12 måneder efter indsættelse af implantatet, var der en sammenlignelig reducering af peri-prostetisk BMD i det opererede og ikke-opererede knæ. Det kan tyde på, at der sker en naturlig reduktion i BMD på grund af naturlig aldring. Tibia komponent migration (MTPM) var hverken associeret med præ-operativt systemisk BMD eller med den post-operative forandring i peri-prostetisk BMD, hvilket tyder på at BMD ikke påvirker langtidsfikseringen af tibia komponenten.

Fundende i denne afhandling bidrager nyt viden om behandlingen af patienter med knæledsartrose i det mediale TF ledkammer. Denne afhandling fokuserer på aspekter der har indflydelse på patient selektion, behandling samt resultatet af behandlingen med en medial UKA.

3. Introduction

3.1. Osteoarthritis of the knee

Osteoarthritis (OA) of the knee is a frequently occurring disease. The lifetime risk of developing symptomatic knee OA is approximately 45%. With increasing age and more active elderly, the prevalence of OA is expected to increase in the coming years. In people over 60 years of age, approximately 10% (men) to 20% (women) have symptomatic knee OA, which is the most important cause of reduced mobility in elderly patients (W. N. Scott, 2017). In Denmark, 60,000 patients with symptomatic knee OA are seen in the primary sector each year, and 50% of these patients will be referred to an orthopedic surgeon. In approximately 25% of the referred patients with knee OA, a knee arthroplasty is carried out (DanishHealthAuthority, 2012). Annually, OA is estimated to cost 11.5 billion Danish kroner in treatment, sick leave, and disability retirement (Johnsen, Koch, Davidsen, & Juel, 2014).

OA of the knee can be defined as a gradual destruction of joint cartilage together with secondary changes of the underlying subchondral bone and the intra- and periarticular soft tissue (Englund et al., 2008). Inflammation of the joint with synovitis and increased synovial fluid production can also occur. The medial and lateral tibiofemoral (TF) compartments of a neutrally aligned knee are not evenly loaded, as 60–70% of the forces across the knee joint go through the medial TF compartment. (W. N. Scott, 2017). Therefore, OA of the knee most often affects the medial TF compartment. Risk factors for developing OA are age, female sex, and predisposing genetic inheritance as well as obesity and previous trauma of the knee (for example hard physical labor, meniscal and/or anterior cruciate ligament tear) (DanishHealthAuthority, 2012; W. N. Scott, 2017).

As knee OA progresses, it can lead to pain, stiffness, crepitus, swelling and effusion, decreased range of motion, atrophic quadriceps musculature, instability, and varus/valgus malalignment. This leads to reduced functional ability, inactivity, and immobility. Knee OA is diagnosed based on an evaluation of the medical history, physical examination, and weight-bearing radiographs of the knee (R. Altman et al., 1986).

3.2. Radiography

Severity of knee OA can be determined with weight-bearing radiographs, although it should be noted that radiological OA does not always correlate well with the clinical symptoms (Bedson & Croft, 2008). Usually posterior-anterior and lateral images as well as a patella-skyline image are obtained. Typical radiographic signs of OA are a reduced joint space width (JSW), sclerosis of the subchondral bone, osteophytes, bone cysts, and sometimes attrition (Figure 1) (Kellgren & Lawrence, 1957).

Figure 1 Posterior-anterior and lateral weight-bearing and patella-skyline radiographs of a knee with severe knee osteoarthritis.

In patients with medial TF OA, the lateral TF compartment is unloaded, and the lateral joint space may not be optimally evaluated. Therefore, as a supplement to the standard images, stress radiographs can be taken. Valgus-stress radiographs evaluate the cartilage thickness of the lateral compartment. Also, the function of the medial collateral ligament can be evaluated (Mukherjee, Pandit, Dodd, Ostlere, & Murray, 2008). This can be done manually, which has the disadvantages of radiation exposure to the examiner and a subjective amount of force applied to the knee. An alternative method is to use a stress device that enables use of a standardized position and applied force (Eriksson, Sadr-Azodi, Singh, Osti, & Bartlett, 2010).
Several classification systems are available for evaluating radiographic OA. The Kellgren-Lawrence (KL) classification and Ahlbäck classification are well known and routinely used in clinical and research settings (Ahlback, 1968; Kellgren & Lawrence, 1957). However, the Ahlbäck classification has shown a low reliability (Galli, De Santis, & Tafuro, 2003; Weidow, Cederlund, Ranstam, & Karrholm, 2006). The KL classification has the disadvantage that the score can be defined in different ways, making it difficult to compare results between observers and between studies (Schiphof, de Klerk, Koes, & Bierma-Zeinstra, 2008). Also, the KL classification is not as sensitive to change over time, especially in mild OA (R. D. Altman & Gold, 2007; Culvenor, Engen, Oiestad, Engebretsen, & Risberg, 2015).
The OARSI score has been developed to enable reliable scoring of OA from mild to severe grades and allows scoring of the medial and lateral compartment separately (R. D. Altman & Gold, 2007).

3.3. Non-operative treatment of knee OA

Conservative treatment of knee OA is warranted in patients with mild to moderate OA, as well as in patients with severe OA who have mild symptoms, are relatively young, or have severe comorbidities. The 3 most recommended treatment modalities are pharmacological treatment, exercise, and weight loss (McAlindon et al., 2014). These treatments may be combined in self-management programs to educate patients. In Denmark, the GLA:D (Good Life with osteoArthritis in Denmark) program has been shown to improve OA symptoms and physical function and to reduce the use of analgesics and sick leave (Skou & Roos, 2017). Primary pharmacological treatment consists of acetaminophen, which can be supplemented with opioids such as tramadol. If there is inflammation (effusion, synovitis) of the knee, oral or topical non-steroid anti-inflammatory drug (NSAID) and intra-articular injection with glucocorticoids can be used (DanishHealthAuthority, 2012; McAlindon et al., 2014). Exercise gives a reduction in pain, an improvement of function, and a reduction of the use of pain medication. It consists of cardiac training with low load and muscle strengthening exercises (McAlindon et al., 2014; Skou & Roos, 2017). Overweight is an important factor in both the development and treatment of OA. Weight management (reduction) has been shown to give pain reduction and improved function in overweight patients. To obtain a clinical improvement, a loss of more than 5% of body weight should be achieved (DanishHealthAuthority, 2012; McAlindon et al., 2014). Other treatment modalities that might be useful are a knee brace, a foot orthosis, and a walking cane (McAlindon et al., 2014).

3.4. Operative treatment of knee OA

Arthroscopic debridement and partial meniscectomy in patients with OA and degenerative meniscal tears were routinely performed in the past. These procedures are not as commonly performed anymore, as several studies have shown that there is no benefit with regard to pain or function after debridement or meniscectomy compared to sham surgery/conservative treatment (DanishHealthAuthority, 2016; Katz et al., 2013; Khan, Evaniew, Bedi, Ayeni, & Bhandari, 2014; Kirkley et al., 2008; Moseley et al., 2002; Sihvonen et al., 2013). However, arthroscopy can be indicated in patients with mechanical symptoms like catching or locking, implicating a symptomatic meniscal tear or a loose body, who do not have severe OA of the knee.

3.4.1. Correction osteotomy

In mild to moderate unicompartmental OA with varus or valgus malalignment, a correction osteotomy may be an option. Most often, the medial compartment is affected, with the patient having a varus alignment, indicating a valgus (open wedge) high tibial osteotomy. A correction osteotomy transfers the mechanical axis to the non-affected compartment and unloads the affected compartment. This results in pain relief and improved function. However, no comparison has been made with non-operative treatment, and approximately 30–50% of these patients will need knee replacement surgery within 10 years after their osteotomy (Brouwer et al., 2014; DanishHealthAuthority, 2012).

3.4.2. Total knee arthroplasty

In severe OA where non-operative treatment is no longer effective, knee replacement surgery has shown good clinical results, with improvement in both pain and function.

Total knee arthroplasty (TKA) consists of a resurfacing of the worn articulating parts of the distal femur and proximal tibia. In cases of patellofemoral OA, the patella can also be resurfaced. It is used in patients with severe OA of more than 1 compartment of the knee. TKA shows a good functional outcome and a good long-term survival in both studies and national registries. Ten-year survival of TKAs in national registries is approximately 95% (Figure 3) (DKAR, 2018; NJR, 2018).

3.4.3. Medial unicompartmental knee arthroplasty

In 20–30% of patients with knee OA, there is isolated medial OA, and a medial unicompartmental knee arthroplasty (UKA) can be indicated (Liddle, Judge, Pandit, & Murray, 2014). UKA is based on a different philosophy than TKA. TKA changes the axis of the joint line. To balance the knee in TKA, it is sometimes necessary to release the medial or lateral collateral ligament. This changes the kinematics of the knee. UKA restores the pre-OA alignment and kinematics of the joint by resurfacing the worn surfaces. To be able to do this, there must be a functioning anterior cruciate ligament (ACL) and medial collateral ligament (MCL), as these ligaments provide the main stability in the medial compartment. Ligament releases are not performed with UKA. Also, there should be full-thickness cartilage in the lateral TF compartment and the varus deformity should be correctable (Murray, Liddle, Dodd, & Pandit, 2015; White, Ludkowski, & Goodfellow, 1991). Overcorrection of the varus deformity leads to an increased load on the lateral compartment, thereby risking development of OA of the lateral TF compartment.

There are both MB and FB UKAs (Figure 2). Both designs have theoretical differences and advantages. The MB UKA is congruent throughout the entire range of motion and converts stress/strains evenly as compressive forces over the tibial implant, resulting in good fixation of the tibial component (Simpson, Price, Gulati, Murray, & Gill, 2009). The MB design is designed to reduce polyethylene wear, as the fully congruent polyethylene bearing reduces contact stress. Wear can, however, occur on both the articular side and the backside of the bearing. Also, there is a 1–2% risk of bearing dislocation with MB UKA, which is a reason for revision surgery, although often only to replacement of the bearing (AOANJRR, 2018; NJR, 2018). The FB UKA is not congruent and stress/strains are not evenly distributed over the tibial component, resulting in oblique forces at the interface between the tibial component and the bone, which theoretically could influence implant fixation (J. Goodfellow, O'Connor, Pandit, Dodd, & Murray, 2015). Alternatively, the decreased constraint articulation allows for anatomical knee movement, reducing torsional and shear forces and thereby reducing the risk of loosening (Engh, Zimmerman, Parks, & Engh, 2009). The FB design may also result in high point contact on the polyethylene insert, causing increased wear compared to MB designs. Risk of dislocation is minimized in FB UKA and only occurs in relation to surgical mistakes.

Differences in polyethylene wear between the 2 designs have been discussed in the literature. Wear particles can cause osteolysis and lead to aseptic loosening. Several retrieval studies have been performed. Normally functioning MB UKAs showed low rates of polyethylene wear, but increased wear rates were shown if the bearings showed signs of impingement or incongruous articulation (B. J. Kendrick et al., 2010; B. J. L. Kendrick et al., 2011; Price et al., 2005). These studies, however, were based on small samples and on a single cross-sectional measurement 10 or 20 years after surgery. A clinical study, using radiostereometric analysis (RSA), has recently shown that the polyethylene wear rate of a cemented and cementless MB UKA is low (Horsager et al., 2018). FB UKAs showed excavation of the polyethylene, although at a slower rate than anticipated (Ashraf, Newman, Desai, Beard, & Nevelos, 2004). A retrieval study comparing MB UKA and FB UKA produced with the exact same polyethylene showed no difference in wear (Engh et al., 2009). Mechanical studies comparing volumetric wear between a MB and FB UKA (including the UKAs used in our study) do, however, show reduced wear for the medial FB UKA compared to the medial MB UKA (Brockett, Jennings, & Fisher, 2011; Kretzer et al., 2011). This difference might be explained by a difference in polyethylene used (Brockett et al., 2011). Another possible explanation could be the design of the MB UKA, which does not allow rotation, and which may result in cross-shear on both surfaces (Brockett et al., 2011). Again, the results in these studies should be interpreted with caution because both studies were based on small samples.

Figure 2 *Sigma fixed-bearing medial UKA* *Oxford mobile-bearing medial UKA*

UKA offers several advantages over TKA. UKA gives less surgical trauma in general and less damage to the extensor apparatus, and it preserves the ACL and the lateral TF compartment. During rehabilitation after UKA, patients experience less pain, have a quicker rehabilitation, and have a more natural feeling of their knee than patients that have received a TKA (Murray et al., 2015). Also, the incidence of severe complications like deep venous thrombosis, pulmonary embolus, myocardial infarct, and death is significantly lower in UKA compared to TKA (Liddle et al., 2014; Murray et al., 2015).

In general, medial UKA offers good clinical outcome and a good survival rate (J. W. Goodfellow, O'Connor, & Murray, 2010; Murray et al., 2015). However, the survival rate is lower than that of TKA, with national registries showing twice as a high revision rate for UKAs as for TKAs (Figure 3) (DKAR, 2018; J. W. Goodfellow et al., 2010; Liddle et al., 2014; NJR, 2018). A registry study showed that this difference remained after adjustment for age, sex, ethnic origin, comorbidities, American Society of Anesthesiologists (ASA) score, implant fixation, thromboprophylaxis, or surgical caseload (Liddle et al., 2014).

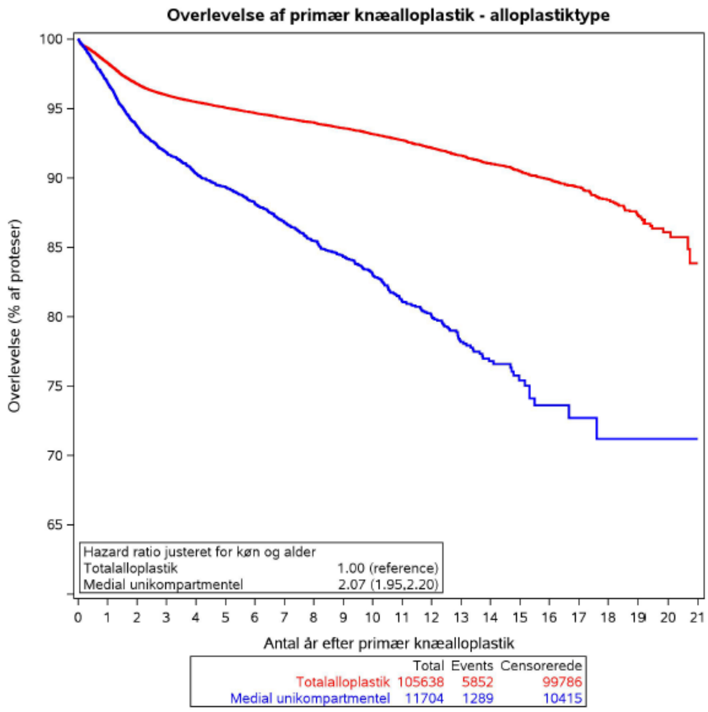

Figure 3 Kaplan-Meier survival curve of TKA and UKA from The Danish Knee Arthroplasty Register - Annual report 2018 (DKAR, 2018).

Several explanations for this difference in survival rate are possible. Firstly, a revision of a UKA is technically less demanding, and can often be revised to a primary TKA. This may lower the threshold for revising an UKA. Also, there are other modes of failure compared to TKA. Progression of OA in the lateral TF compartment or the patellofemoral compartment after medial UKA can cause pain and be an indication for revision surgery. The polyethylene bearing in MB UKAs can dislocate. Often this particular problem can be solved by exchange of the polyethylene bearing, although in recurrent dislocations, a revision to a TKA can be indicated. The New Zealand joint registry reports both survival rates and clinical outcome scores (Rothwell, Hooper, Hobbs, & Frampton, 2010). A poor clinical outcome at 6 months correlates with a higher risk of revision for both TKA and UKA. Interestingly, the risk of revision for a UKA with poor clinical outcome is about 60%, whereas it is only 10% for a TKA with poor clinical outcome (J. W. Goodfellow et al., 2010), possibly reflecting a difference in the threshold for revision. Surgical experience and routine with UKA are also of importance. Surgeons who use UKA in 20% or more of their cases have a lower revision rate compared to surgeons with a lower usage of UKAs (Liddle, Pandit, Judge, & Murray, 2016; Murray et al., 2015).

3.5. Outcome

The outcome after joint arthroplasty may be influenced by patient factors, implant design, and the treatment.

Outcome after knee replacement can be measured in several ways. Historically, the survival rate of an implant has been used to monitor implant performance.

Nowadays, clinical outcome that includes patient-reported outcome measures (PROM) is becoming more important. There are general health outcome scores like the RAND-36 and EQ-5D, and disease-specific outcome scores like the Oxford Knee Score (OKS). Disease-specific outcome scores have been widely used in research to monitor changes after treatment, for example, after knee replacement surgery. Several studies have been performed to determine a minimal clinical improvement or a clinically relevant difference. This means that if there is a change in outcome score, it should not only be significant, but also clinically meaningful (Beard et al., 2015; Clement, MacDonald, & Simpson, 2014). The patient/group of patients should perceive this change as a relevant improvement. In a comparison, a difference between 2 treatments should also be clinically relevant. New Zealand, Sweden, and the Netherlands have implemented PROMs in their national registries, not only to focus on survival data but also on clinical outcome.

Knee replacement has in general a good outcome, although 15–20% of patients are not completely satisfied with the result (Ingelsrud et al., 2018). A good outcome after surgery depends on several aspects related to the patient, pre-operative selection, surgery, and type of implant.

Patient characteristics are of importance (Birch, Stilling, Mechlenburg, & Hansen, 2019). Although the decision to operate is a shared between surgeon and patient, the eligibility for surgery is determined by the surgeon. The criteria for UKA have been discussed previously, and they should be strictly adhered to.

The most reliable result is obtained in patients with symptomatic, severe OA of the knee in whom conservative treatment is insufficient. More specifically, there should be full-thickness cartilage loss in the medial TF compartment, sufficient function of the ACL and the MCL, as well as full-cartilage thickness in the lateral TF compartment. In partial-thickness cartilage loss, the results are less reliable: the outcome is less optimal, the rehabilitation period is prolonged, and there is a higher re-operation rate (Hamilton, Pandit, et al., 2017; Pandit, Gulati, et al., 2011).

It is important that there is full-cartilage thickness in the lateral TF compartment if a medial UKA is considered. Due to the varus malalignment in the medial OA, the lateral compartment is unloaded on regular weight-bearing radiographs of the knee. It is therefore recommended to obtain supplementary valgus-stress radiographs.

The mechanical loading of bone is altered during surgery, and the implant-bone interface is expected to last for many years (Soininvaara, Harju, Miettinen, & Kroger, 2013). Bone quality is therefore considered to be of importance with regard to implant fixation (Li & Nilsson, 2000). Other patient factors, such as gender, age, and obesity, also influence the risk of revision (DKAR, 2018; Gottsche et al., 2019).

The surgeon and the operative technique influence the outcome. It has been shown that a certain caseload/volume is necessary to ensure a good outcome. Surgeons performing less than 10 UKAs annually have a higher risk of complications/revisions (Hamilton, Rizkalla, et al., 2017). Type of implant can also influence outcome. Although MB and FB UKAs have shown similar clinical outcomes and survivals, the modes of failure differ (Parratte, Pauly, Aubaniac, & Argenson, 2012).

3.6. Radiostereometric analysis

RSA was first introduced in 1974 by Selvik (Selvik, 1989) and is used to assess micromotion. Early implant migration has been related to late implant loosening (Pijls, Plevier, & Nelissen, 2018; Pijls, Valstar, Nouta, et al., 2012; Ryd et al., 1995). RSA has been used to study implant fixation, joint kinematics, fracture stability, skeletal growth, and spinal fusion (Valstar et al., 2005). Migration on regular radiographs cannot be observed accurately (Selvik, 1989). With RSA, migration can be measured with an accuracy of at least 0.2 mm (Ryd et al., 1995). This makes it possible to identify implants that migrate at an early stage of follow-up in a limited number of patients.

More recently, dynamic RSA has been introduced, which allows for measuring real-time 3D-movement of implants during motion (Horsager, Kaptein, Romer, Jorgensen, & Stilling, 2017). It can be used to study implant kinematics, induced displacement, stability, and migration under loaded and functional conditions.

3.6.1. RSA set-up

During surgery, tantalum beads are introduced in the periprosthetic bone. After surgery and during follow-up, stereo radiographs are taken. Two synchronized radiographs are taken of a knee at different angles. A calibration box with tantalum beads is used during radiography (Figure 4).

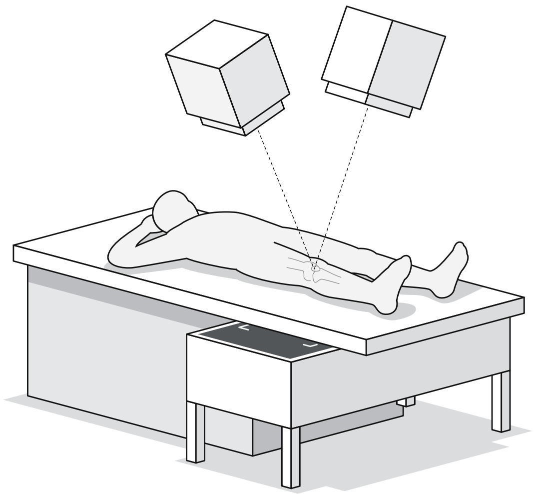

Figure 4 RSA set-up with 2 synchronized x-ray tubes and a calibration box placed underneath the patient. The radiographic detectors were placed underneath the calibration box.

To analyze the radiographs (Figure 5), both radiographs are first calibrated using the tantalum beads from the calibration box. Then the tantalum beads in the bone are identified in both radiographs and a bone model is created. The implants can be defined in 2 ways, marker-based or model-based. Originally, RSA was marker-based, meaning that markers attached to the implant served as the implant model. This technique is slightly more accurate than model-based RSA, but the markers need to be attached to the implant. This gives additional costs and requires CE marking. Theoretically the markers could alter the fixation and performance of the implant. Model-based RSA does not require manipulation of the implant. It is based on a 3D model of the implant created either with CAD models or by reversed engineering, where actual implants are optical or laser scanned into a 3D model. Both techniques offer clinically acceptable accuracy (Kaptein, Valstar, Stoel, Reiber, & Nelissen, 2007; Valstar, de Jong, Vrooman, Rozing, & Reiber, 2001). The contours of the implant are outlined in both radiographs, and the model of the implant is matched with the contours. The position of the implant can now be determined in relation to the bone model. Comparing the position of the model relative to the bone model at different points in time gives migration in 3 translations and 3 rotations. The reference origin for migration calculation was the geometric center of the model (van Hamersveld et al., 2019).

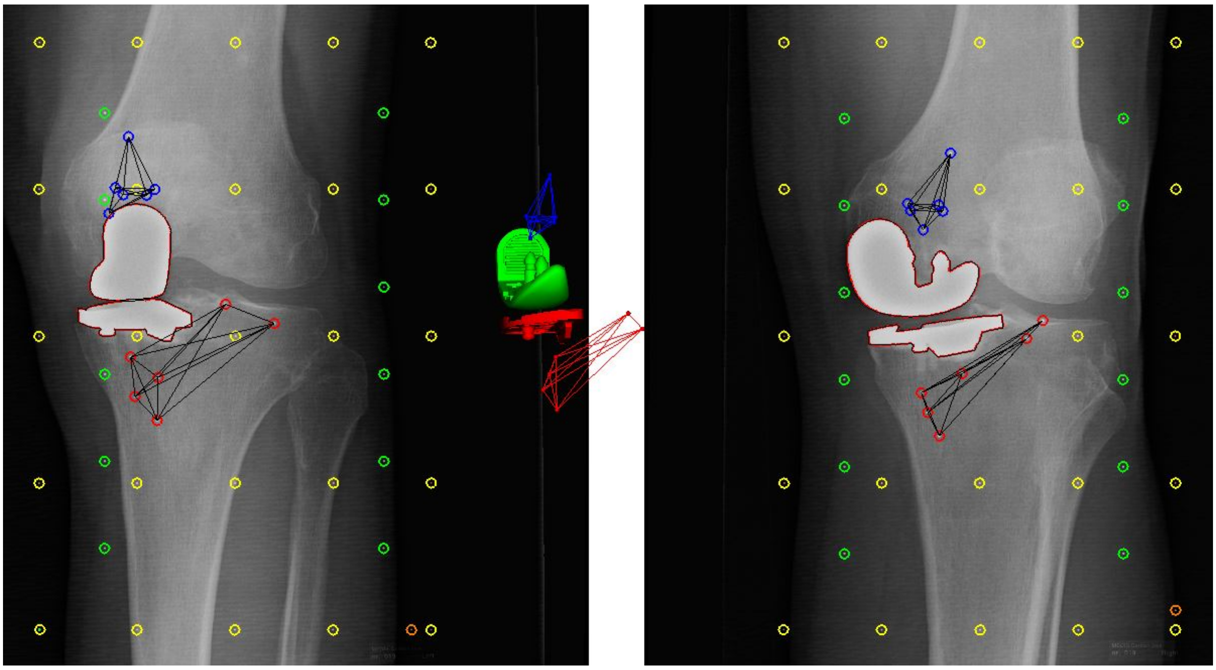

Figure 5 RSA radiographs showing detected fiducial (yellow), control (green), femoral bone (blue), and tibial bone (red) markers, as well as the 3D models of the femoral (green) and tibial (red) component.

3.6.2. RSA thresholds

Several thresholds have been proposed for acceptable migration of an implant. Ryd et al. defined continuous migration as migration (MTPM) between 1 and 2 years of more than 0.2 mm (Ryd et al., 1995). A total of 158 cemented/cementless UKAs/TKAs were followed with use of RSA. Sixty knees showed continuous migration, 12 (20%) of which were revised because of aseptic loosening. Mid- to long-term revision for aseptic loosening is associated with early migration of the tibial component of TKAs in national registries (Pijls, Valstar, Nouta, et al., 2012). The acceptable revision rates used in the national registries were used as reference: < 3% at 5 years and < 5% at 10 years. This resulted in the following thresholds for migration: acceptable: implants with a MTPM at 1 year lower than 0.50 mm; at risk: implants with a MTPM at 1 year between 0.5 and 1.6 mm; unacceptable: implants with a MTPM at 1 year over 1.6 mm. These thresholds were recently revised and divided into early migration, stabilization 1, and stabilization 2 (Figure 6) (Pijls et al., 2018).

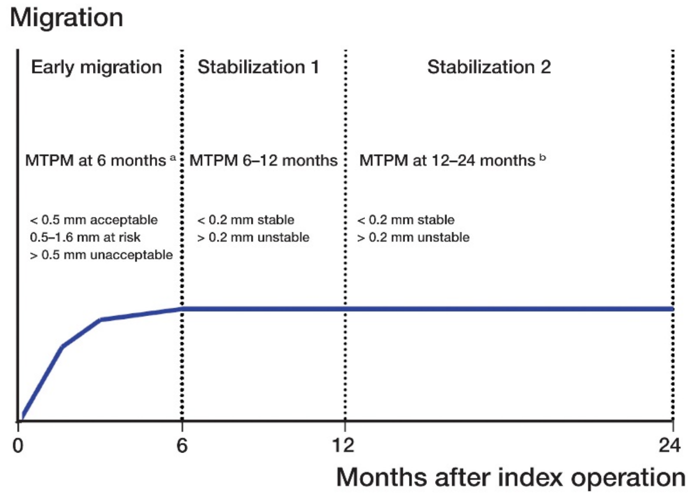

Figure 6 Thresholds of migration for knee replacements (Pijls et al., 2018)

Other thresholds have been proposed. Thresholds based on translations and rotations may have an advantage over MTPM, as translation along or rotation about a single axis not only describe a magnitude of migration but also the direction. Gudnason (Gudnason, Adalberth, Nilsson, & Hailer, 2017) followed-up on a pooled cohort of 116 TKAs studied with use of RSA for 2 years, at a median of 16 years after surgery. Five TKAs were revised due to aseptic loosening of the tibial component. These revisions showed a different migration pattern than the other TKAs. Posterior rotation was the best predictor of loosening, as well as subsidence/lift-off at the periphery of the tibial component. These results need to be interpreted with caution, however, as they are based on only 5 revisions, 4 of which were of the same prosthesis type. It has also been suggested to distinguish thresholds according to method of fixation (Laende et al., 2019). Cementless TKAs show higher migration at 1 year compared to cemented TKAs, indicating a longer stabilization phase for the cementless TKAs. This would place all cementless TKAs in the "at risk" group defined by Pijls (Pijls, Valstar, Nouta, et al., 2012). Between 1 and 2 years, however, similar migration was found for cemented and cementless TKAs.

Instead of using an indirect technique of correlating clinical RSA studies to national registries, large RSA databases (cemented/cementless implants, TKA/UKA) would allow for differentiating the migration pattern of both well-fixated implants and the migration pattern of implants with aseptic loosening. This would enable the RSA community to further specify migration thresholds/patterns, and possibly develop RSA into a clinical tool. Besides static RSA thresholds, inducible displacement may be developed into a clinical tool.

3.7. Introduction of new implants

New developments in implant design continue to emerge, with the intent to improve the longevity of an implant and the satisfaction of the patient. For example, cementless implants are being introduced, as well as implants that aim to resemble normal knee kinematics and provide a more natural feeling for the patient. These new implants need to perform at least as well as the implants used to date. In the past, some implants have been introduced because of theoretical benefits that in practice did not meet up to their expectations. To prevent under-performing implants to be released to the global marked, a stepwise introduction of new implants and other products has been suggested (Malchau, 2000; Nelissen et al., 2011; Pijls & Nelissen, 2016). A stepwise introduction (Figure 7) consists of preclinical studies including RSA studies, larger multicenter clinical studies, and postmarked surveillance in national registries (Nelissen et al., 2011; Pijls, Valstar, Nouta, et al., 2012). By introducing a product stepwise, a limited number of patients is exposed. As aseptic loosening is the most common cause of late revision (DKAR, 2018), RSA is a good method to use to evaluate new products in this stepwise introduction.

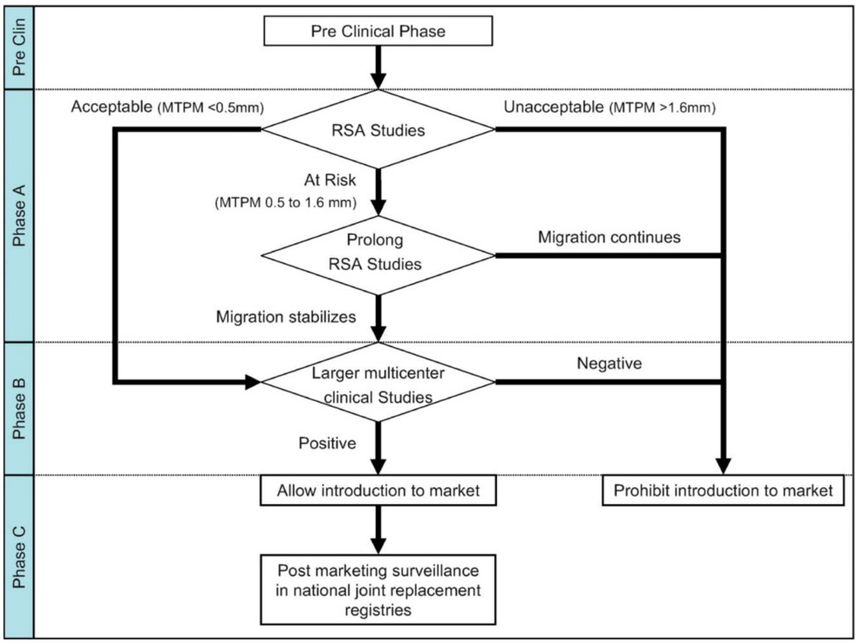

Figure 7 Stepwise introduction of new knee implants (Pijls, Valstar, Nouta, et al., 2012).

In Denmark, the best-known example of a failed product is Boneloc bone cement, which was introduced in the 1990s. Total hip arthroplasties (THA) implanted with Boneloc cement required more and earlier revision than THAs implanted with other bone cements. After suspicion of inferior results with Boneloc cement arose, a small RSA study was initiated comparing migration of a Spectron hip stem (Smith & Nephew) fixated with either Boneloc cement or Palacos cement with gentamicin (Schering-Plough) (Thanner, Freij-larsson, Kärrholm, Malchau, & Wesslén, 1995). This clearly showed increased migration of both the acetabular and femoral component fixed with Boneloc cement compared to the control group. Similar results were shown in an RSA study in which a TKA was performed (Nilsson & Dalen, 1998). If these studies had been performed before the introduction of Boneloc bone cement to the global marked, the use of this product and thereby unnecessary revisions could have been prevented. Other examples of failed orthopedic implants can be given, for example, the Accord knee and the St. Leger knee (Nelissen et al., 2011). National joint registries can be used as a quality control regarding how implants are performing. A 22–35% reduction in revisions has been shown in RSA-tested TKAs compared to non-RSA-tested TKAs in the national registries (Nelissen et al., 2011).

3.8. Bone mineral density

Bone mineral density (BMD) is used to assess the areal mineral content of the bone and is a surrogate marker of bone quality and strength. It is used to diagnose osteoporosis, characterized as low bone mass, disruption of bone architecture, and compromised bone strength. Using the WHO classification of osteoporosis (Table 1), BMD assessment of the lumbar spine and both hips (proximal femurs) is referenced to the mean BMD of a young adult reference population, expressed as a T-score (Cosman et al., 2014).

Table 1 WHO classification of osteoporosis

	T-score
Normal	$T \geq -1.0$
Osteopenia	$-2.5 < T < -1.0$
Osteoporosis	$T \leq -2.5$

BMD diminishes during a lifetime, leading to osteoporosis, and is most pronounced in postmenopausal women. Osteoporosis can, for example, lead to an increased fracture risk.

BMD is also thought to be of importance in fixation of orthopedic implants (Li & Nilsson, 2000), and thereby influence implant survival. Several studies have shown a decrease in BMD in the periprosthetic tibia bone after TKA (Jaroma, Soininvaara, & Kroger, 2016; Soininvaara et al., 2013; Winther et al., 2016). This decrease is not as pronounced in UKA (Hooper et al., 2013; Richmond, Hadlow, Lynskey, Walker, & Munro, 2013). Different theories exist regarding the reason for this decrease. Possibly, it occurs right after surgery due to protective weight bearing, causing disuse osteoporosis of the proximal tibia. Alternatively, it may be caused by stress shielding due to a different load distribution on the proximal tibia resulting in local bone loss. In UKA, it has been proposed that the medial proximal tibia is overloaded pre-operatively. By restoring the original leg axis, the medial part of the proximal tibia is offloaded, and bone loss occurs. However, it has not been clearly shown that this change in bone density influences implant migration.

BMD can be measured in different ways, such as grayscale values on standard radiographs, quantitative ultrasound, peripheral quantitative computed tomography (CT) assisted osteodensitometry, but the gold standard method to measure BMD is dual-energy X-ray absorptiometry (DXA). DXA uses dual energies by generating high- and low-energy X-ray photons. The detectors measure the amount of energy absorbed and thereby measure the density of a particular tissue, for example, bone (Dasher, Newton, & Lenchik, 2010). DXA has been shown to accurately measure bone density around orthopedic implants (Stilling, Soballe, Larsen, Andersen, & Rahbek, 2010).

3.8. Summary

Medial osteoarthritis of the knee can be treated successfully with a medial UKA, although it can be further optimized. In selecting a patient for medial UKA, weight-bearing radiographs might not be optimal to assess cartilage in the lateral TF compartment. Valgus-stress radiographs can therefore be obtained using a stress device. The reliability of these valgus-stress radiographs has not been studied.

Another possibility to optimize is the development of new implants. New implants should be introduced stepwise. The first step being an RSA study, as early implant migration is related to late implant loosening.

A patient-related factor that may be of influence on implant fixation and subsequent loosening, is bone quality. Although bone density reduces after knee arthroplasty, it has not been shown that this is of influence on the risk of revision.

4. Designs, aims, and hypotheses

The overall aim of this dissertation was to identify aspects in patient selection, implant design, and treatment that have an influence on the outcome of patients with medial TF OA treated with a medial UKA.

The specific designs, aims, and hypotheses were as follows:

I. *Design:* Prospective reliability study of valgus-stress radiography.
Aim: To examine the reproducibility of valgus-stress radiography with the Telos stress device for assessment of lateral compartment degenerative changes in patients with medial OA of the knee.
Hypothesis: A substantial reliability (weighted kappa 0.61 – 0.80) can be obtained with stress radiographs taken with the help of the Telos stress device.

II. *Design:* Prospective cohort RSA study.
Aim: To investigate early implant migration of the medial FB Sigma UKA with RSA with a follow-up of 2 years. Clinical outcome was evaluated using PROMs.
Hypothesis: The Sigma UKA will show low implant migration.

III. *Design:* Prospective, randomized, patient-blinded clinical trial.
Aim: To compare early implant migration of a MB UKA and a FB UKA with RSA with a follow-up of 2 years and to assess clinical outcome with PROMS and leg extension power (LEP).
Hypotheses: Equal tibial component migration (difference in MTPM <0.20 mm) of the MB UKA and FB UKA.
Similar clinical outcome for MB UKA and FM UKA.

IV. *Design:* Prospective cohort DXA and RSA study.
Aim: To study the influence of systemic and peri-prosthetic BMD on migration of the tibial component of a cemented medial UKA with 2 years' follow-up.
Hypotheses: Patients with normal systemic BMD in comparison to patients with low systemic BMD have:
1. higher pre-operative BMD in the proximal tibia (10% difference)
2. similar post-operative BMD loss in proximity of cemented UKA tibial components until 2 years' follow-up

3. similar tibial component migration (difference in MTPM < 0.20 mm) until 2 years' follow-up

Furthermore, we hypothesized that there was no association between migration and peri-prosthetic BMD over time

5. Materials & methods

5.1. Ethical issues

Central Denmark Region Committees on Health Research Ethics

Study I: journal no. 91/2017

Study II: journal no. 1-10-72-99-14

Study III/IV: journal no. 1-10-72-591-12

Danish Data Protection Agency

Study I: accepted as a quality assurance surveillance study

Study II: journal no. 1-16-02-709-14

Study III/IV: journal no. 1-16-02-82-13

ClinicalTrials.gov

Study III/IV: NCT03434600

All patients in studies I, II, and IV gave written informed consent.

All studies were conducted in accordance with the Helsinki Declaration.

5.2. Patients

Study I: All patients with medial OA on weight-bearing, fixed-flexion posterior-anterior radiographs on referral to the outpatient clinic of the orthopedic department of the Regional Hospital of Holstebro, Holstebro, Denmark (Table 2). Medial OA was defined as joint space narrowing (JSN) of the medial compartment. Patients were included between January 2015 and January 2016.

Studies II, III, and IV: All patients above 18 years of age with severe medial OA of the knee, who were eligible for medial UKA (Table 2). Patients were eligible for medial UKA if there were severe (bone on bone) OA in the medial compartment, retained full-thickness cartilage in the lateral compartment, a functionally normal medial collateral ligament (MCL), a functionally normal anterior cruciate ligament (ACL), and no severe OA of the lateral facet of the patellofemoral joint and no lateral subluxation of the patella (Hamilton et al., 2016). Exclusion criteria for studies III/IV were inflammatory arthritis, contralateral knee prosthesis at time of inclusion, disseminated malignant disease, serious systemic disease, female patients in reproductive age, and patients unable to give written informed consent. Flow diagrams of studies II and III are shown in Figures 8 and 9. As studies III and IV were set up as 1 study, study IV contained the same patient population (Figure 10). Instead of randomizing patients into 2 groups, patients were studied as a cohort. Patients in study II were included between December 2012 and December 2013. Patients in studies III/IV were included between January 2014 and November 2015.

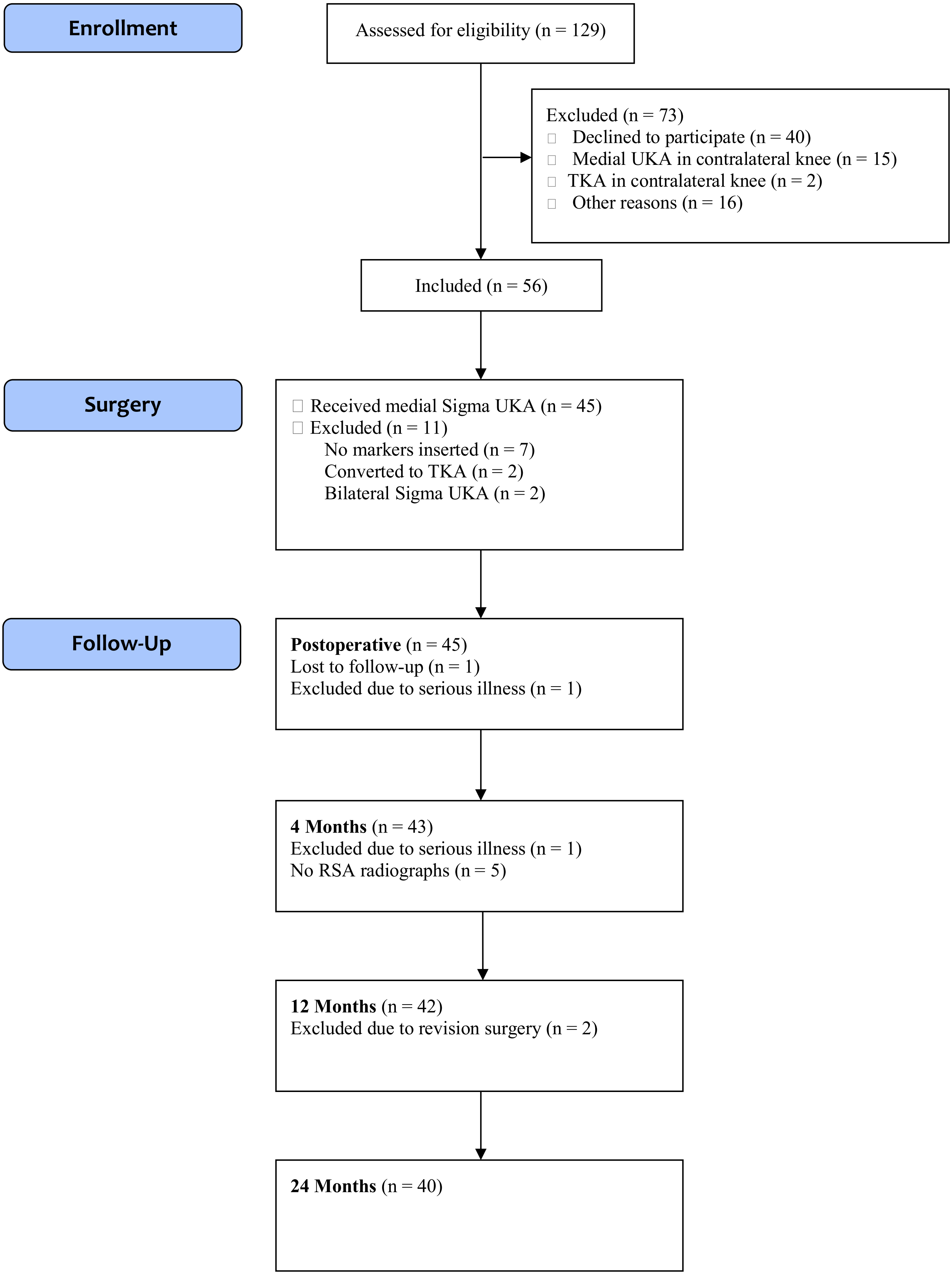

Figure 8 Flow diagram of study II. Adapted from Paper II

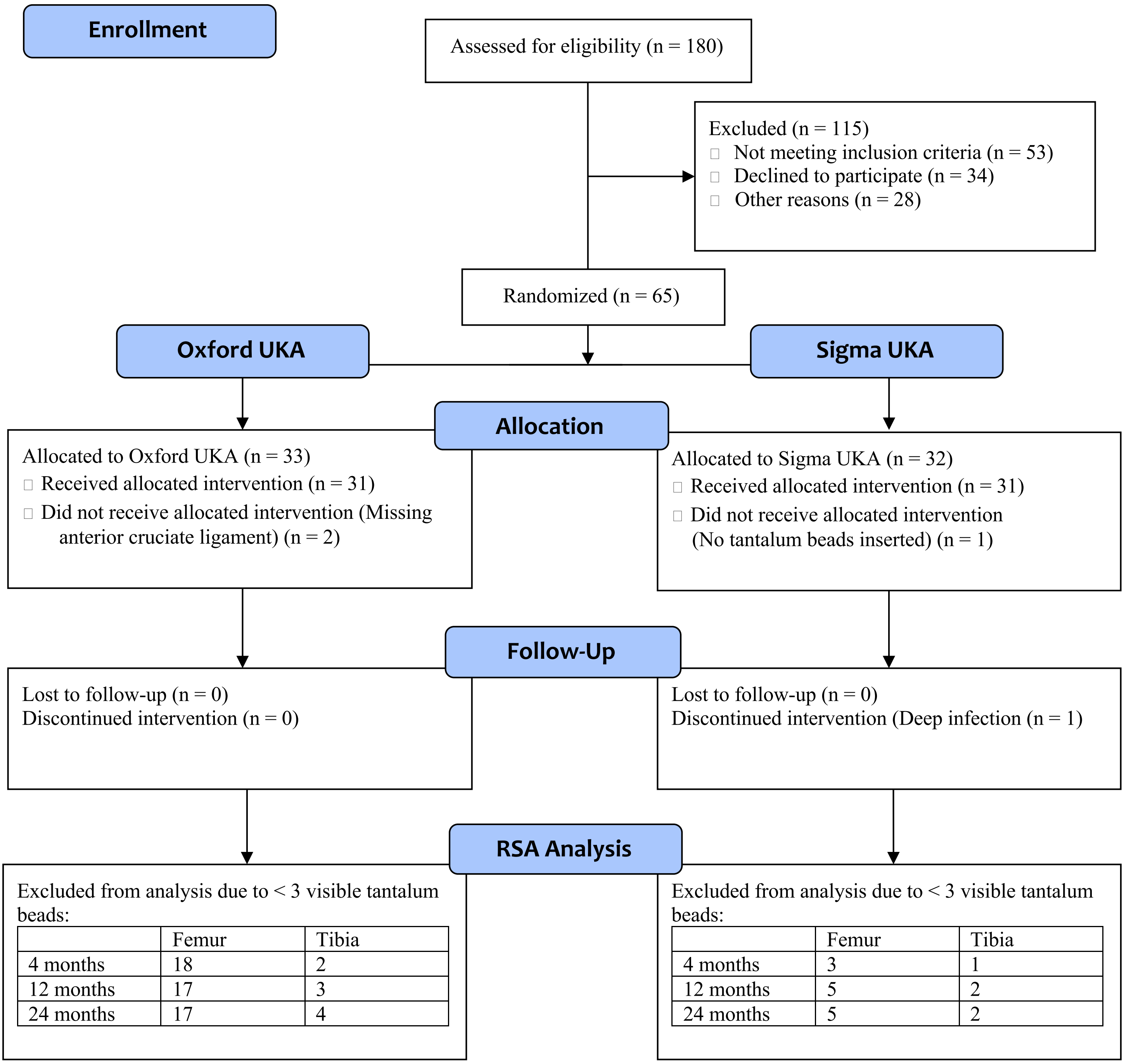

Figure 9 Flow diagram of study III. Adapted from Paper III

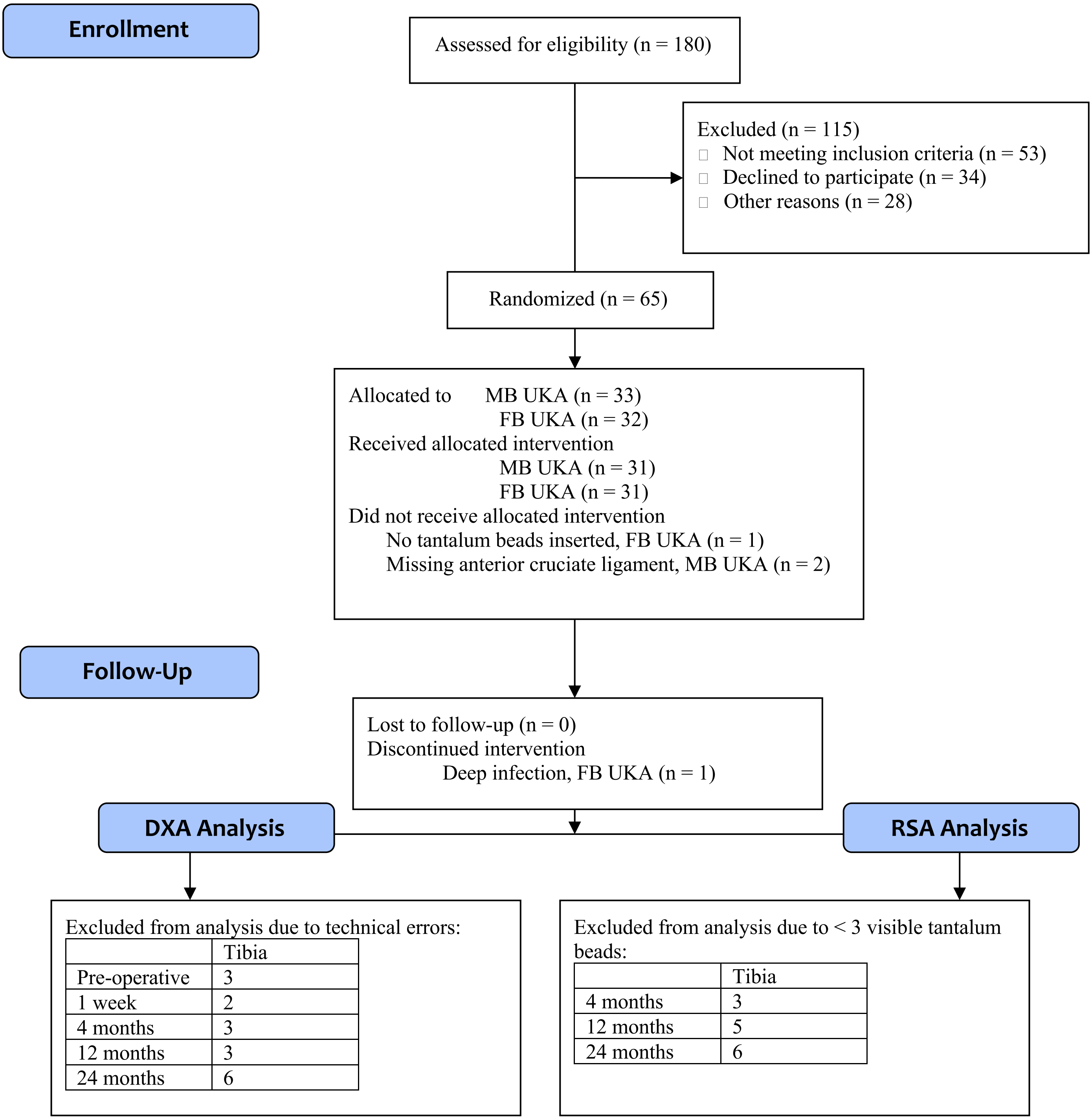

Figure 10 Flow diagram of study IV. Adapted from Paper IV.

Table 2 Demographics of studies I–IV. Adapted from Papers I–IV.

Study I		
Number of patients (knees)	79 (80)	
Mean age, year (range)	66 (39–90)	
Gender, male/female	32/47	
Study II	MB UKA	FB UKA
Number of patients	56	
Median age, years (range)	64 (45–88)	
Gender, male/female	22/34	
Median height, cm (range)	173 (152–191)	
Median weight, kg (range)	85 (63–120)	
Mean BMI**, kg/m^2 (SD*)	30 (3.7)	
Studies III/IV	MB UKA	FB UKA
Number of patients	33	32
Mean age, years (range)	64 (50–78)	61 (47–79)
Gender, male/female	16/17	17/15
Mean height, cm (SD*)	171 (10.1)	173 (8.9)
Mean weight, kg (SD*)	87 (15.3)	89 (13.0)
Mean BMI**, kg/m^2 (SD*)	29 (4.1)	30 (4.0)

* SD = standard deviation

** BMI = Body mass index

5.3. Randomization

In **study III**, patients were randomized to receive a MB UKA or a FB UKA. Block randomization was used; via www.random.org/lists, blocks of 10 patients were generated. Opaque envelopes were drawn 1 day before surgery for logistic purposes. If a patient was excluded during the inclusion period of the study, an extra patient was included to maintain the power of the study. Reason for exclusion could, for example, be conversion to a TKA during surgery due to lateral OA.

5.4. Intervention

5.4.1. Intervention Study I

Valgus-stress radiographs were obtained for all patients in a standard manner. The patient was positioned supine with the patella in the midline of the knee. A wedge placed under the knee ascertained approximately 20° of knee flexion. The Telos stress device (Metax GmhH, Hungen-Obbornhofen) was applied according to the manufacturer's guidelines (Figure 11) (Ware, Snow, Kosinski, & Barbara, 1993). The pressure pad was placed in line with the lateral joint line, and 2 counter supports were placed medially on the femur and tibia. A pressure of 150 N was applied on the pressure pad.

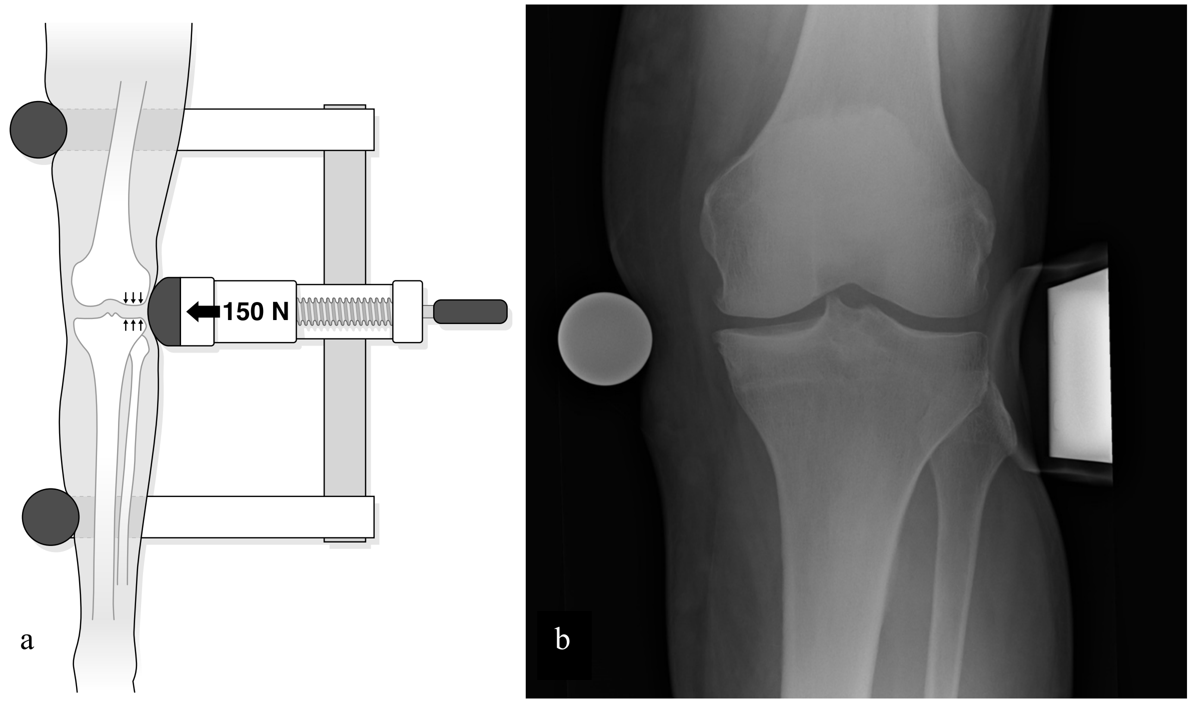

Figure 11 a. Illustration of the knee placed in the Telos stress device. b. Valgus-stress radiograph of the knee. Adapted from Paper I.

The radiograph was aligned with the lateral joint line. For calibration purposes, a marker (30 mm diameter) was placed medial of the medial joint line. Radiographs were stored in DICOM format (4096 pixels). Double measurement radiographs were taken after repositioning of the patient and reapplication of the stress device (Koppens, Sorensen, et al., 2019).

5.4.2. Intervention Study II

All patients received the medial FB Sigma UKA (DePuy International Ltd, Leeds, UK). It consists of a 2-pegged femoral component with a large posterior condyle radius, the articular surface is highly polished. The tibial component has a keel and a peg at the non-articulating surface. A concave fixed moderately cross-linked (4MRAD irradiated and remelted GUR 1020

polyethylene) polyethylene bearing is mechanically locked on the tibial component (Figure 2). Both components were implanted with Palacos bone cement (Heraeus Holding GmbH, Hanau, Germany).
After initial bone preparation, 4–6 1-mm tantalum beads were inserted in both the femoral and tibial bones.

5.4.3. Intervention Studies III/IV

Patients received either an Oxford MB UKA or a Sigma FB UKA after randomization.
The MB phase 3 Oxford medial UKA (Zimmer Biomet, Bridgend, UK) consists of a 2-pegged femoral component with a spherical articulation, a fully congruous mobile Arcom ultra-high-molecular-weight polyethylene (UHMWPE) bearing (3.3 MRAD irradiated Argon packaged, compression moulded 1900H polyethylene), and a tibial component with a flat articulation surface and a keel at the non-articulating surface (Figure 2). The Sigma UKA was described under Study II. All components were implanted with Palacos bone cement with gentamicin (Heraeus Holding GmbH, Hanau, Germany).
Tantalum beads were inserted as previously described.

5.5. Outcomes

5.5.1. Outcome in Study I

Radiographs were assessed for osteophytes and JSN according to the Osteoarthritis Research Society International (OARSI) classification. The "Atlas of individual radiographic features in osteoarthritis, revised" by Altman et al. (R. D. Altman & Gold, 2007) was used during grading of the radiographs.
After correction for magnification with the use of the calibration marker, JSW was measured in millimeters using a digital caliper. JSW was measured from the midpoint of the femoral condyle to the midpoint of the corresponding tibial plateau. The first radiographs were examined twice by each observer, the double examination once. There was a minimum period of 2 weeks between each assessment, to ensure nondependent assessments. All observers were blinded for clinical data.
Before the start of the study, a plenary session was held to discuss grading with the OARSI atlas as well as the method of measuring JSW. Otherwise, no further education was received by the observers.

All assessment of the radiographs was done by 2 orthopedic surgeons and a radiologist on a picture and archiving and communication system (PACS) (Impax system; AGFA Healthcare N.V., Ghent, Belgium).

5.5.2. Outcome in Study II

Primary outcome – RSA

Stereoradiographs were obtained on the first post-operative day, and at 4, 12, and 24 months after surgery (Figure 12). A standardized RSA set up was used (Koppens et al., 2018). The patient was supine and parallel with a uniplanar calibration box underneath the examination table (Carbon box 19, Medis Specials, Leiden, the Netherlands). The lower leg was positioned in a foam positioner, and the anatomical axis of the leg was parallel to the y-axis of the calibration box. The position and orientation of the global coordination system in the reference examination defined the direction of implant migration in the follow-up examinations. Two ceiling-fixed, synchronized roentgen tubes (Arco-Ceil/Medira; Santax Medico, Aarhus, Denmark) were positioned in a 40° angle to each other, at 100 cm from the calibration box. The analog images were digitized (FCR Profect CS; Fujifil, Vedbaek, Denmark) (1760 x 2140 pixels). The upper limit for mean error rigid body fitting was 0.35 mm. A minimum of 3 bone markers was required. If a condition number was above 120, the analysis was excluded, as suggested by Valstar et al. (Valstar et al., 2005).

Implant migration was evaluated using all radiographs, the post-operative radiographs serving as reference. Signed translations were expressed as x-translation (lateral/medial), y-translation (distal/proximal), and z-translation (posterior/anterior). Signed rotations were expressed as x-rotation (anterior tilt/posterior tilt), y-rotation (internal rotation/external rotation), and z-translation (adduction/abduction) (Valstar et al., 2005).

Maximal total point motion (MTPM) is defined as the translational vector of the point in the CAD model that had the greatest motion. Tibial implants were classified as stable if the difference in MTPM between 12 and 24 months was < 0.20 mm, and as continuously migration if the difference was ≥ 0.20 mm (Ryd et al., 1995).

Stereoradiographs were analyzed with Model-Based RSA software, version 4.10 (Medis Specials, Leiden, the Netherlands). Computer-aided design (CAD) models of the implant were provided by the manufacturer (DePuy International LTD, Leeds, UK).

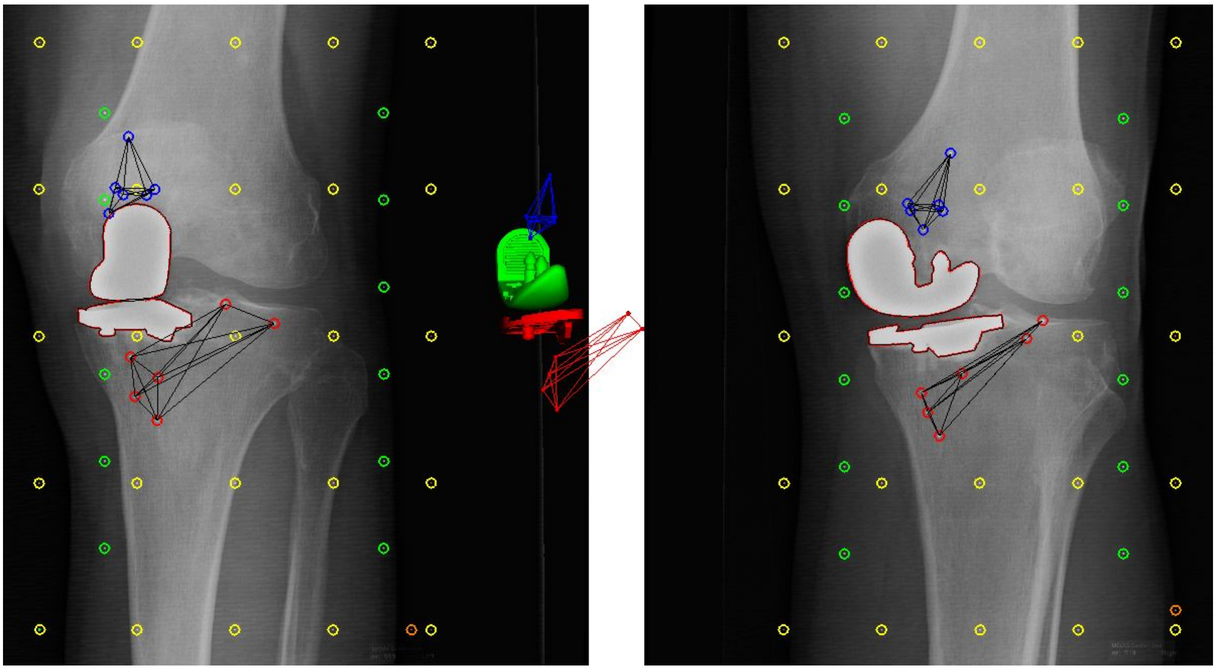

Figure 12 RSA analysis displaying the calibration markers (yellow and green), the bone markers (red and blue), and the CAD model (green and red) fitted to the implant.

Precision

The measurement precision was determined with double determinations taken at 4 and 12 months. The post-operative stereoradiograph served as a reference in the migration analysis. The bias was defined as the mean difference between the double determinations in translation along and rotation about the 3 axes. The precision was defined as the SD of this difference. The prediction interval (PI) (1.96 x SD) represented the expected clinical precision (Table 3). Comparable precision results have been shown in TKA studies (Ejaz et al., 2015; Molt, Ljung, & Toksvig-Larsen, 2012; Pijls, Valstar, Kaptein, & Nelissen, 2012; Stilling et al., 2011; Tjornild, Soballe, Hansen, Holm, & Stilling, 2015).

Table 3 Precision of RSA measurements for the femoral and tibial components. Adapted from paper II.

	Translation (mm)			Rotation (°)		
	x	y	z	x	y	z
Femoral component						
Mean	0.01	−0.01	−0.05	0.00	0.01	0.02
SD	0.03	0.04	0.15	0.23	0.16	0.23
PI	0.05	0.08	0.29	0.45	0.31	0.45
Tibial component						
Mean	−0.00	−0.01	0.00	0.02	−0.04	0.06
SD	0.06	0.05	0.14	0.18	0.29	0.08

PI	0.12	0.09	0.27	0.36	0.56	0.15

Secondary outcome – Oxford Knee Score (OKS)

Patient-reported knee pain and function was evaluated with the OKS. This is a 12-item questionnaire, with an outcome score that ranges from 0 (worst) to 48 (best) (Dawson, Fitzpatrick, Murray, & Carr, 1998; Judge et al., 2012). Outcomes can be categorized: < 27 = poor, 27–33 = fair, 34–41 = good, > 41 = excellent (NZJR, 2016). If there were 1 or 2 missing values in a questionnaire, the mean value of the remaining responses was used. If more than 2 values were missing in a questionnaire, it was discarded (Murray et al., 2007). The OKS was obtained pre-operatively and at 4, 12, and 24 months after surgery.

5.5.3. Outcome in Study III

Primary outcome – RSA

The same set-up was used as described in *Study II*, with the exception that a new auto-positioning, direct-digital roentgen system (AdoraRSA suite, NRT, Aarhus, Denmark) was used. Two ceiling-fixed, synchronized roentgen tubes (Varian Medical Systems, USA) were positioned 100 cm above the calibration box at an angle of 40° to each other. Digital image detectors (Canon, CXDi-701C Wireless) were placed behind the calibration box. Digital radiographs were stored in DICOM-format at a resolution of 160 µm pixel pitch and a 16-bit grey-scale resolution in a picture archiving and communication system (PACS) (Impax system (AGFA Healthcare N.V., Ghent, Belgium)).

If migration analysis was not possible due to occluded markers or primary analysis showed a high condition number (>80), a patient-specific marker configuration model (MC model) of the bone markers was constructed if possible and applied in the analysis (Kaptein, Valstar, Stoel, Rozing, & Reiber, 2005). An MC model for the tibia bone was used to analyze 3 tibial components in the MB group and 4 tibial components in the FB group. An MC model for the femoral bone was used to analyze 6 femoral components in the MB group and 7 femoral components in the FB group. Precision was comparable to Study II (Table 4).

Table 4 Precision of RSA measurements for the femoral and tibial components. Adapted from paper III.

	Translation (mm)			Rotation (°)		
	x	y	z	x	y	z
Femoral component						
Mean	0.03	0.00	0.02	0.00	0.05	0.12

SD	0.11	0.05	0.19	0.29	0.28	0.39
PI	0.21	0.09	0.37	0.57	0.54	0.77
Tibial component						
Mean	0.01	0.00	0.01	0.00	0.03	0.03
SD	0.05	0.03	0.09	0.18	0.16	0.14
PI	0.01	0.07	0.18	0.36	0.32	0.27

Secondary outcome

OKS – As described in Study II.

Leg-extension power (LEP) is a functional outcome measured using the leg-extensor power-rig (Bio-Med International, Nottingham, UK) (Barker, Jenkins, Pandit, & Murray, 2012; Munk et al., 2012). Both legs were tested before surgery and at 24 months after surgery, and the operated leg was further tested at 1 and 12 months after surgery. The patient was seated on the power rig with his/her back positioned against the back support and with the foot on the footplate. Seat position was adjusted to allow comfortable knee and hip flexion. The patient was then instructed to extend the leg as forcefully and quickly as possible. Two warm-up attempts were allowed. Patients performed a minimum of 5 repetitions and a maximum 10 repetitions, with a 15 seconds recovery period between attempts. The session was stopped if the patient had reached his or her maximum, defined as 2 attempts with lower score than the previous or if the patient reported pain in the knee (Aalund, Larsen, Hansen, & Bandholm, 2013). The maximum recorded measurement was used in the analysis. LEP is expressed as power per kg of body weight (W/kg).

5.5.4. Outcome in Study IV

Bone Mineral Density

A standardized set-up was used to measure BMD with a DXA scanner (GE Lunar iDXA, General Electric, Chicago, IL). EnCORE version 16.1 software was used to scan the knee. An anteroposterior DXA scan of the knee was obtained with the patient supine, and the leg placed in a soft foam positioner (Stilling et al., 2010).

DXA scans of the knee were performed before surgery (both knees), and at 7 days, 4, 12, and 24 (both knees) months post-operatvely. Before surgery, standard DXA scans of both hips and the lumbar spine were performed to determine the systemic BMD. Systemic BMD (T-score) was categorized in 3 groups: normal (T-score ≥ -1.0), osteopenia ($-1.0 >$ T-score > -2.5), osteoporosis (T-score ≤ -2.5) according to WHO criteria (Abu-Rajab et al., 2006). The cohort was dichotomized in a normal systemic BMD group and a low systemic BMD group (osteopenia and osteoporosis).

EnCORE version 16.1 software was used for analysis. Automatic dynamic threshold detection was used to define bone, tissue, artefact, air, or neutral. Manual corrections were made after automatic detection to ensure correct point typing of the implant/cement mantle and bone edges. Regions of Interest (ROI) were determined for the tibial bone and left/right specific ROI templates were developed for analyses (Figure 13). A patient-specific template was created with the first scan, using the ROI template locked in its position according to the bone edge. In subsequent scans, this patient-specific template was aligned with the bone edge to assure a similar placement of ROIs during follow-up. For each ROI, BMD is presented as g/cm^2 as well as percent difference with the pre-operative measurement as reference. All DXA analysis was performed by 1 analyst at the end of the study.

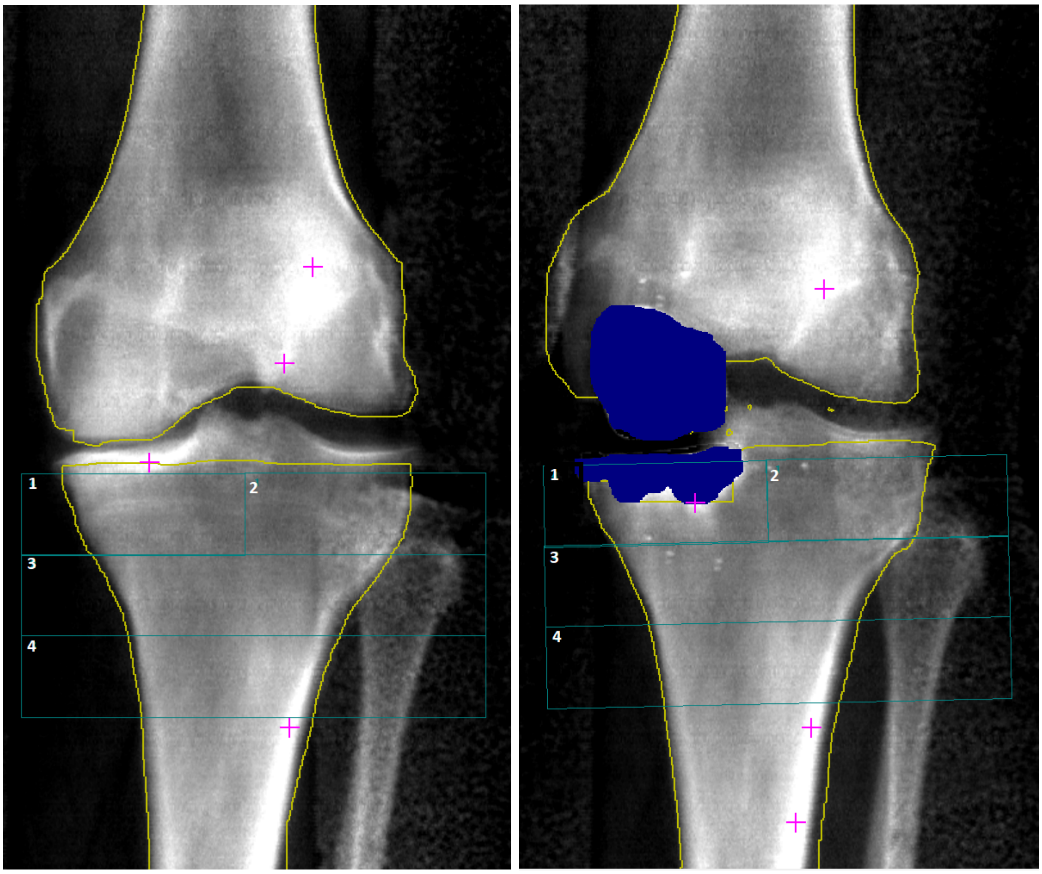

Figure 13 ROI-template for the tibial bone, left image shows pre-operative radiograph, right image shows the same knee 4 months post-operative. ROI1 and 2 are directly adjacent to the joint line, separated at the middle of the joint. ROI3 and 4 are in the metaphyseal part of the proximal tibia. Adapted from Paper IV.

Precision of DXA

The precision of the measurements was determined by double-examinations of the operated knee at 4 months and for both knees at 24 months. Precision error (PE) is expressed as root mean square standard deviation (RMS SD (g/cm^2)) and least significant change (LSC) as $1.96 \times \sqrt{2} \times RMS\,SD$ (g/cm^2). The percent coefficient of variation (%CV (%)) is also reported (Gluer et al., 1995; ISCD) (Table 5).

Table 5 Precision of DXA measurements. Adapted from Paper IV.

			PE (g/cm^2)	LSC (g/cm^2)	%CV (%)
Operated knee	4 months	ROI 1	0.04	0.11	4.2
	(n = 56)	ROI 2	0.04	0.10	4.0
		ROI 3	0.02	0.06	2.1
		ROI 4	0.03	0.08	2.3
	24 months	ROI 1	0.04	0.12	4.4
	(n = 48)	ROI 2	0.03	0.10	3.9
		ROI 3	0.02	0.06	2.2
		ROI 4	0.03	0.07	2.1
Non-operated knee	24 Months (n = 50)	ROI 1	0.04	0.10	3.8
		ROI 2	0.02	0.05	2.1
		ROI 3	0.02	0.06	2.2
		ROI 4	0.04	0.11	3.1

PE = Precision Error

LSC = Least Significant Change

%CV = Percent coefficient of variation

RSA

As described under study III.

5.6. Statistics

For all studies, statistical significance was assumed at $p > 0.05$. Intercooled Stata version 13.1 (StataCorp, College Station, TX, USA) was used for statistical analysis.

Mixed model analysis (MMA) was used to analyze data in studies II - IV. MMA is an extension of a cross-sectional linear regression analysis, introducing random slopes and random intercept in the model. This enables for analysis of longitudinal data with repeated measurements within 1 subject. MMA also takes into account missing values (Twisk, 2003). Assumptions about the data distribution were ensured, using mixed model residual QQ-plots, fitted vs. residuals plots and histograms. To test for interactions, different models were tested using a likelihood-ratio test. Differences within the model were tested using a Wald test. If a difference was found, pairwise comparisons were used to specify the differences.
All available data gathered up to the time of eventual study exclusion were used in the analyses.

5.6.1. Statistics in Study I

Intra- and inter-rater reliability and test-retest reliability for the OARSI scores on osteophytes and JSN were determined as weighted kappa (κ) and 95% confidence intervals (CI) , as these are categorical data (Landis & Koch, 1977). The percent of agreement is given besides weighted kappa for interpretational reasons (Gisev, Bell, & Chen, 2013).
Reliability for JSW of the medial and lateral compartment was determined as the intra-class correlation coefficient (ICC), as these are continuous data (Gisev et al., 2013).
Weighted κ and the ICC were defined as followed: ≤ 0 = poor, 0.01 – 0.20 = slight, 0.21 – 0.40 = fair, 0.41 – 0.60 = moderate, 0.61 – 0.80 = substantial, 0.81 – 1 = almost perfect (Fleiss & Cohen, 1973; Gisev et al., 2013; Landis & Koch, 1977). To detect a difference between 0.40 to 0.60 using κ and 3 observers, a sample size of 51.5 was sufficient (Walter, Eliasziw, & Donner, 1998).

5.6.2. Statistics in Studies II/III

MMA was used to assess RSA data. Bias concerning independence between observations occurred in 2 patients in Study II, who were included with both knees. To reduce bias in bilateral cases, 1 knee was randomly excluded from the study (Bryant, Havey, Roberts, & Guyatt, 2006). Translations and rotations were expressed as mean and 95% CI. MTPM was not normally distributed and therefore transformed and analyzed on a logarithmic scale. MTPM was expressed as median and 95% CI. To accommodate comparison to the literature, mean and 95% CI were also presented.

In *Study II*, the OKS was expressed as mean and 95% CI. Subgroup analysis were performed between the stable and continuously migrating group for OKS and migration (MTPM).

In *Study III*, a difference in OKS between the MB and FB group was analyzed using MMA. The minimal clinically important difference (MCID) was defined as 8–9 points within groups, and 5 points between groups (Beard et al., 2015; Ingelsrud et al., 2018).

LEP data of the operated leg were analyzed using MMA. LEP data of the operated leg and the contralateral leg pre-operatively and at 24 months were analyzed using paired t-tests (Barker et al., 2012; Bassey & Short, 1990; Frost, Lamb, & Robertson, 2002; Munk et al., 2012).
In *Study III*, to detect a 0.2 mm difference in MTPM, 22 patients per group were required (power 90%, alpha 0.05, SD 0.2 mm). To anticipate dropouts, 30 patients per group were included (B. J. Kendrick et al., 2015).

5.6.3. Statistics in Study IV

Mixed models were fitted with peri-prosthetic BMD of each ROI as dependent variable and systemic BMD (normal BMD/low BMD) as independent variable.
Differences in pre-operative and 2-year post-operative peri-prosthetic BMD between the operated and the non-operated knee were tested; a supplementary variable (operated leg/non-operated leg) was introduced in the random-effects equation to allow for analysis of both legs of the patient.
Mixed models were fitted with migration (MTPM) as dependent variable and systemic BMD (normal BMD/low BMD) as independent variable. Also, MMAs were fitted for each ROI with migration as dependent variable and change in peri-prosthetic BMD (with the pre-operative BMD as reference) and time as independent variables. As MTPM was not normally distributed, it was analyzed on a logarithmic scale and presented as median and 95% CI.
Primary sample size was calculated in relation to *Study III*. In order to detect a 10% difference in BMD (reference 1.15 g/cm^2) (power 80%, alpha 0.05, SD 0.15), 25 patients in each group were required (Soininvaara et al., 2013).

6. Results

6.1. Results of Study I

Table 6 shows intra- and inter-rater reliability, as well as the test-retest reliability for the lateral TF compartment.

6.1.1. Intra-rater reliability

Assessment of the femoral and tibial osteophytes showed substantial to almost perfect agreement. Assessment of JSN showed fair to moderate agreement laterally. JSW measurement showed almost perfect agreement.

6.1.2. Inter-rater reliability

Assessment of the tibial osteophytes showed substantial agreement. JSN and JSW showed moderate to substantial agreement.

6.1.3. Test-retest reliability

Assessment of the tibial osteophytes showed substantial agreement. Assessment of femoral osteophytes showed slight to substantial agreement. Assessment of JSN showed fair to moderate agreement. JSW measurement showed substantial to almost perfect agreement.

Table 6 Intra- and inter-observer reliability as well as test-retest reliability of the assessment of the lateral TF compartment. Osteophytes and JSN are shown as weighted kappa (95% CI), as well as percent of agreement. JSW is shown as ICC (95% CI). Adapted from paper I.

	Osteophytes		JSN	JSW
	Femoral condyle	Tibial condyle		
Intra-rater 1	0.55 (0.14 – 0.80) 96.0%	0.82 (0.78 – 0.87) 96.7%	0.32 (0.10 – 0.37) 94.7%	0.81 (0.68 – 0.88)
Intra-rater 2	0.69 (0.58 – 0.77) 92.9%	0.76 (0.73 – 0.84) 96.5%	0.59 (0.51 – 0.79) 96.9%	0.81 (0.69 – 0.88)
Intra-rater 3	0.87 (0.82 – 0.94) 98.2%	0.85 (0.81 – 0.87) 98.2%	0.65 (0.44 – 0.87) 97.2%	0.89 (0.81– 0.93)
Inter-rater 1-2	0.39 (0.26 – 0.44) 88.8%	0.76 (0.71 – 0.81) 96.0%	0.52 (0.28 – 0.80) 95.9%	0.59 (0.33 – 0.75)
Inter-rater 1-3	0.55 (0.36 – 0.67) 94.7%	0.73 (0.62 – 0.77) 95.8%	0.62 (0.61 – 0.70) 96.6%	0.69 (0.49 – 0.81)
Inter-rater 2-3	0.67 (0.54 – 0.75) 93.8%	0.75 (0.65 – 0.79) 96.5%	0.45 (0.28 – 0.60) 95.6%	0.79 (0.66 – 0.87)
Test-retest 1	0.07 (-0.07 – 0.30) 93.1%	0.67 (0.62 – 0.82) 94.2%	0.36 (0.25 – 0.52) 95.6%	0.69 (0.50 – 0.81)
Test-retest 2	0.48 (0.31 – 0.51) 86.5%	0.77 (0.65 – 0.88) 97.1%	0.54 (0.38 – 0.61) 96.3%	0.82 (0.70 – 0.89)
Test-retest 3	0.76 (0.51 – 0.84) 96.8%	0.74 (0.71 – 0.80) 97.1%	0.37 (0.11 – 0.63) 93.8%	0.90 (0.83 – 0.94)

6.2. Results of Study II

6.2.1. Radiostereometric analysis

Translations and rotations (mean and 95% CI) and MTPM (mean, median, and 95% CI) for the femoral and tibial components are given in Table 7.

MTPM of the tibial components for a stable group (n = 26) and a continuously migrating group (n = 11) is shown in Figure 14. After initial migration in the first 4 months, the stable group stabilized. The continuously migrating group migrated 0.52 mm (95% CI 0.33 – 0.76) between 4 and 24 months.

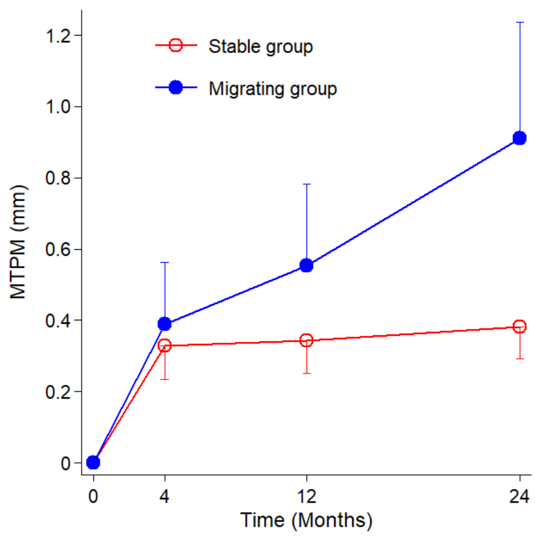

Figure 14 MTPM of the tibial component for the stable and continuously migration group (median and 95% CI). Adjusted from paper II.

Table 7 Translations, rotations and MTPM for the femoral and tibial component. Adjusted from paper II.

		Femoral Component		Tibial component	
		Mean (95% CI)	Median (95% CI)	Mean (95% CI)	Median (95% CI)
Tx (mm)	4 months	0.01 (−0.05 – 0.07)		0.03 (−0.02 – 0.08)	
	12 months	0.02 (−0.04 – 0.08)		0.08 (0.03 – 0.13)	
	24 months	0.06 (0.03 – 0.14)		0.08 (0.03 – 0.13)	
Ty (mm)	4 months	0.03 (−0.01 – 0.06)		−0.04 (−0.07 to −0.00)	
	12 months	0.06 (0.00 – 0.11)		−0.04 (−0.08 to −0.01)	
	24 months	0.11 (−0.01 – 0.23)		−0.04 (−0.09 – 0.01)	
Tz (mm)	4 months	0.05 (−0.05 – 0.15)		0.02 (−0.03 – 0.08)	
	12 months	0.02 (−0.11 – 0.15)		0.01 (−0.03 – 0.06)	
	24 months	0.00 (−0.14 – 0.14)		0.04 (−0.02 – 0.10)	
Rx (°)	4 months	0.08 (−0.14 – 0.29)		−0.05 (−0.39 – 0.29)	
	12 months	0.12 (−0.12 – 0.37)		−0.28 (−0.66 – 0.10)	
	24 months	0.47 (−0.14 – 0.80)		−0.56 (−0.96 to −0.15)	
Ry (°)	4 months	0.07 (−0.07 – 0.20)		−0.19 (−0.35 to −0.04)	
	12 months	0.07 (−0.11 – 0.25)		−0.16 (−0.32 to −0.01)	
	24 months	0.07 (−0.16 – 0.30)		−0.08 (−0.24 – 0.08)	
Rz (°)	4 months	−0.04 (−0.18 – 0.09)		0.17 (−0.07 – 0.41)	
	12 months	−0.08 (−0.22 – 0.07)		0.06 (−0.19 – 0.31)	
	24 months	0.11 (−0.15 – 0.36)		0.05 (−0.19 – 0.28)	
MTPM (mm)	4 months	0.51 (0.43 – 0.60)	0.45 (0.37 – 0.54)	0.47 (0.32 – 0.63)	0.34 (0.27 – 0.42)

	12 months	0.59 (0.45 – 0.73)	0.50 (0.40 – 0.60)	0.53 (0.36 – 0.70)	0.39 (0.31 – 0.48)
	24 months	0.75 (0.49 – 1.01)	0.56 (0.41 – 0.71)	0.65 (0.47 – 0.84)	0.50 (0.39 – 0.60)

6.2.2. Clinical outcome

Results of the OKS are shown in Table 8. An improvement of 15 (95% CI 12–17) was seen after surgery, which was maintained throughout follow-up.

Table 8 Oxford Knee Score (mean and 95% CI) during follow-up. Adjusted from paper II.

	Mean OKS	95% CI
Pre-operatively	23	21 – 25
4 months	38	35 – 40
12 months	40	38 – 42
24 months	41	39 – 43

6.3. Results of Study III

6.3.1. Radiostereometric analysis

Tibial component

Migration of the tibial components was similar between groups throughout follow-up (Table 9). Between 4 and 24 months, the tibial components showed lift-off of mean 0.05 mm (95% CI 0.02 – 0.08) in the MB group and mean 0.04 mm (95% CI 0.01 – 0.07) in the FB group. Between 4 and 12 months, the tibial components showed posterior rotation of mean 0.18° (95% CI −0.29 to −0.08) in the MB group and mean −0.21° (95% CI −0.31 to −0.11) in the FB group. Continuous migration was found for 1 MB UKA and 2 FB UKAs.

Table 9 Translations, rotations and MTPM for the tibial component for the MB and FB UKA. Adjusted from paper III

		MB UKA		FB UKA	
		Mean (95% CI)	Median (95% CI)	Mean (95% CI)	Median (95% CI)
Tx (mm)	4 months	0.06 (0.02 – 0.11)		0.03 (−0.01 – 0.08)	
	12 months	0.09 (0.03 – 0.15)		0.04 (−0.02 – 0.10)	
	24 months	0.08 (0.03 – 0.13)		0.05 (−0.00 – 0.10)	
Ty (mm)	4 months	0.01 (−0.02 – 0.04)		0.00 (−0.03 – 0.03)	
	12 months	0.03 (−0.01 – 0.06)		0.04 (−0.00 – 0.08)	
	24 months	0.06 (0.02 – 0.10)		0.04 (−0.00 – 0.08)	
Tz (mm)	4 months	−0.08 (−0.16 to −0.01)		0.00 (−0.07 – 0.08)	
	12 months	−0.11 (−0.20 to −0.01)		0.03 (−0.07 – 0.12)	
	24 months	−0.08 (−0.16 to −0.01)		0.03 (−0.04 – 0.11)	
Rx (°)	4 months	−0.19 (−0.36 to −0.01)		0.02 (−0.15 – 0.20)	
	12 months	−0.37 (−0.59 to −0.16)		−0.19 (−0.40 – 0.03)	

	24 months	−0.49		−0.28	
		(−0.67 to −0.31)		(−0.46 to −0.11)	
Ry (°)	4 months	0.04		−0.17	
		(−0.17 – 0.24)		(−0.38 – 0.04)	
	12 months	0.02		−0.28	
		(−0.19 – 0.24)		(−0.50 to −0.07)	
	24 months	0.02		−0.25	
		(−0.20 – 0.24)		(−0.47 to −0.03)	
Rz (°)	4 months	−0.10		−0.03	
		(−0.22 – 0.02)		(−015 – 0.09)	
	12 months	−0.18		0.06	
		(−0.36 to −0.00)		(−0.12 – 0.25)	
	24 months	−0.18		0.01	
		(−0.38 – 0.01)		(−0.18 – 0.21)	
MTPM (mm)	4 months	0.42	0.35	0.44	0.36
		(0.31 – 0.53)	(0.27 – 0.43)	(0.33 – 0.55)	(0.28 – 0.44)
	12 months	0.54	0.44	0.51	0.40
		(0.40 – 0.69)	(0.34 – 0.55)	(0.37 – 0.66)	(0.31 – 0.50)
	24 months	0.55	0.47	0.50	0.43
		(0.43 – 0.67)	(0.37 – 0.56)	(0.38 – 0.62)	(0.34 – 0.51)

Femoral component

Translations and rotations of the femoral components were similar between groups throughout follow-up (Table 10). The FB group showed a median 0.20 mm (95% CI 0.04 – 0.30) higher MTPM than the MB group at 4 months, which remained throughout follow-up (Figure 15).

Table 10 Translations, rotations and MTPM of the femoral component for the MB and FB UKA. Adjusted from paper III

		MB UKA		FB UKA	
		Mean (95% CI)	Median (95% CI)	Mean (95% CI)	Median (95% CI)
Tx (mm)	4 months	0.02 (−0.07 – 0.12)		−0.05 (−0.12 – 0.02)	
	12 months	0.05 (−0.06 – 0.15)		−0.05 (−0.13 – 0.02)	
	24 months	−0.02 (−0.12 – 0.07)		−0.06 (−0.13 – 0.00)	
Ty (mm)	4 months	0.03 (−0.04 – 0.09)		0.07 (0.02 – 0.11)	
	12 months	0.02 (−0.04 – 0.09)		0.06 (0.01 – 0.11)	
	24 months	0.01 (−0.07 – 0.09)		0.07 (0.02 – 0.13)	
Tz (mm)	4 months	0.12 (−0.00 – 0.25)		0.05 (−0.04 – 0.14)	
	12 months	0.15 (0.02 – 0.27)		0.02 (−0.07 – 0.11)	
	24 months	0.15 (0.02 – 0.27)		0.01 (−0.08 – 0.11)	
Rx (°)	4 months	−0.04 (−0.37 – 0.28)		0.21 (−0.02 – 0.45)	
	12 months	0.08 (−0.23 – 0.40)		0.27 (0.04 – 0.50)	
	24 months	0.17 (−0.13 – 0.47)		0.40 (0.18 – 0.62)	
Ry (°)	4 months	0.19 (−0.12 – 0.49)		0.38 (0.16 – 0.60)	
	12 months	0.28 (−0.03 – 0.59)		0.42 (0.19 – 0.64)	
	24 months	0.38 (0.07 – 0.69)		0.53 (0.30 – 0.75)	
Rz (°)	4 months	−0.11 (−0.43 – 0.21)		−0.26 (−0.49 to −0.03)	
	12 months	−0.06 (−0.41 – 0.29)		−0.10 (−0.36 – 0.16)	
	24 months	−0.22 (−0.56 – 0.12)		−0.14 (−0.39 – 0.11)	

MTPM (mm)	4 months	0.43 (0.27 – 0.59)	0.38 (0.28 – 0.49)	0.66 (0.54 – 0.78)	0.58 (0.47 – 0.68)
	12 months	0.50 (0.34 –0.65)	0.45 (0.32 – 0.59)	0.66 (0.54 – 0.77)	0.55 (0.43 – 0.67)
	24 months	0.46 (0.29 – 0.62)	0.42 (0.30 – 0.53)	0.72 (0.59 – 0.84)	0.61 (0.49 – 0.74)

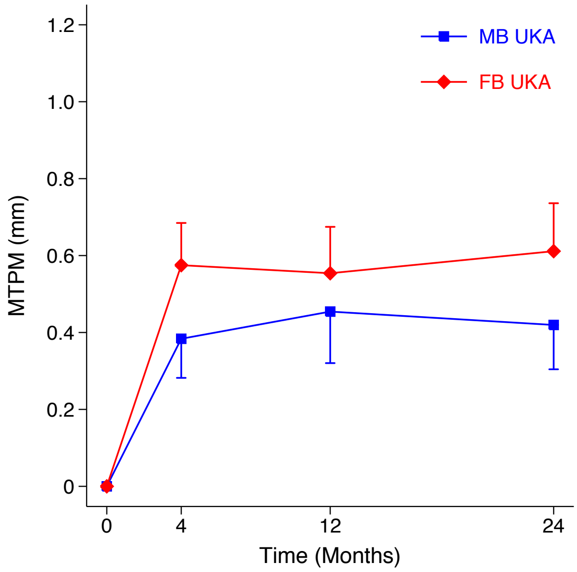

Figure 15 MTPM (median and 95% CI) of the femoral component. Adjusted from paper III

6.3.2. Clinical outcome

Overall, the MB and FB UKA had an equally good clinical outcome, with an improvement in both OKS as well as in LEP (Table 11).

Table 11 Clinical outcomes for the MB and FB UKA. OKS and LEP are shown as mean and 95% CI. Adjusted from paper III

		MB UKA	FB UKA
OKS			
	Pre-operative	26 (24 – 28)	28 (26 – 30)
	4 months	38 (35 – 40)	37 (34 – 39)
	12 months	42 (40 – 44)	41 (39 – 43)
	24 months	40 (37 – 43)	41 (38 – 44)
LEP			
Operated leg (W/kg)	Pre-operative	1.5 (1.3 – 1.7)	1.7 (1.5 – 1.8)
	4 months	1.4 (1.2 – 1.6)	1.5 (1.3 – 1.7)
	12 months	2.0 (1.8 – 2.2)	1.9 (1.6 – 2.1)
	24 months	1.8 (1.6 – 2.0)	1.9 (1.7 – 2.1)
	Pre-operative	1.9 (1.7 – 2.2)	2.1 (1.8 – 2.4)

Non-operated leg (W/kg)	24 months	1.8 (1.6 – 2.0)	1.9 (1.6 – 2.1)

6.4. Results of Study IV

6.4.1. BMD of the operated knee

Patients with normal systemic BMD had a 11-15% higher BMD in all ROIs compared to patients with low systemic BMD (Figure 16). These differences in peri-prosthetic BMD remained throughout follow-up.

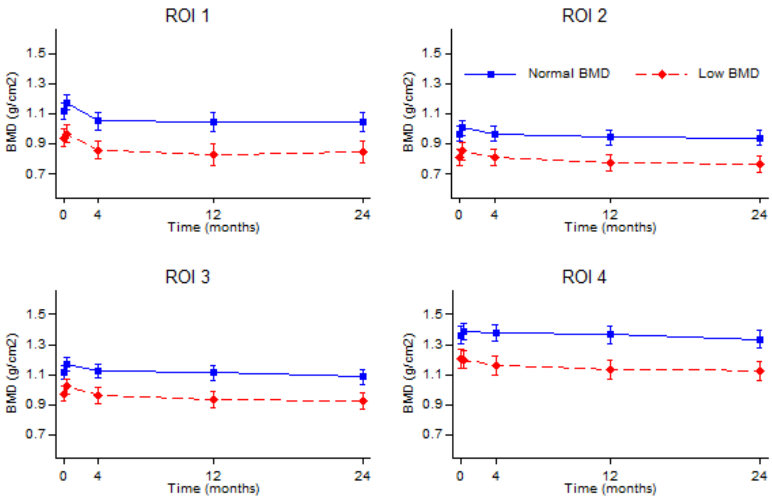

Figure 16 Difference in BMD over time for the normal BMD group and the low BMD group for the 4 ROIs. Adapted from Paper IV.

6.4.2. BMD changes of the non-operated knee

BMD of the tibial bone was similar between the operated knee and the non-operated knee both pre-operatively and at 24 months in ROIs 1, 3, and 4. In ROI 2, the non-operated knee had a higher BMD compared to the operated knee for both time points. Patient's operated knees and contralateral knees showed a similar reduction in BMD in all ROIs between pre-operative and 24 months (Table 12).

Table 12 BMD (g/cm²) (mean and 95% CI) and percent difference in BMD (% and 95% CI) of the operated knee and the non-operated knee between pre-operative and 24-month follow-up. Adapted from Paper IV.

		Pre-operatively	24 months	% Difference
ROI 1	Operated knee	1.04 (0.99 – 1.09)	0.96 (0.91 – 1.01)	−7.7% (−10.8 to −4.3)
	Non-operated knee	1.02 (0.97 – 1.07)	0.95 (0.90 – 1.01)	−6.9% (−9.6 to −2.8)
ROI 2	Operated knee	0.90 (0.85 – 0.94)	0.86 (0.81 – 0.90)	−4.4% (−7.2 to −2.2)
	Non-operated knee	0.94 (0.89 – 0.98)	0.90 (0.85 – 0.94)	−4.3% (−6.9 to −2.0)
ROI 3	Operated knee	1.05 (1.01 – 1.09)	1.01 (0.97 – 1.05)	−3.8% (−6.0 to −2.0)
	Non-operated knee	1.06 (1.02 – 1.10)	1.03 (0.99 – 1.07)	−2.8% (−5.2 to −1.1)
ROI 4	Operated knee	1.29 (1.24 – 1.34)	1.24 (1.19 – 1.29)	−3.9% (−6.7 to −1.9)
	Non-operated knee	1.29 (1.25 – 1.34)	1.26 (1.21 – 1.31)	−2.3% (−4.7 – 0.2)

6.4.3. Migration of the tibial component in patients with normal BMD vs low BMD

MTPM of the normal BMD group was similar to the MTPM of the low BMD group throughout follow-up (Figure 17).

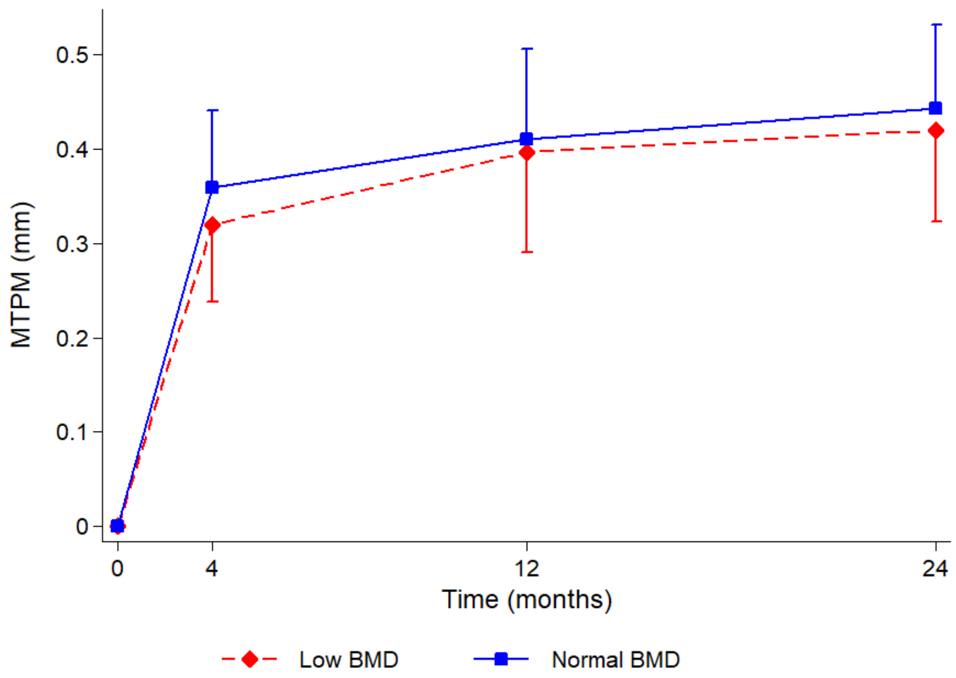

Figure 17 MTPM (mm) for the normal BMD group and the low BMD group, error bars show 95% CI. Adapted from Paper IV.

Migration over time was not influenced by peri-prosthetic BMD in any ROI (Figure 18).

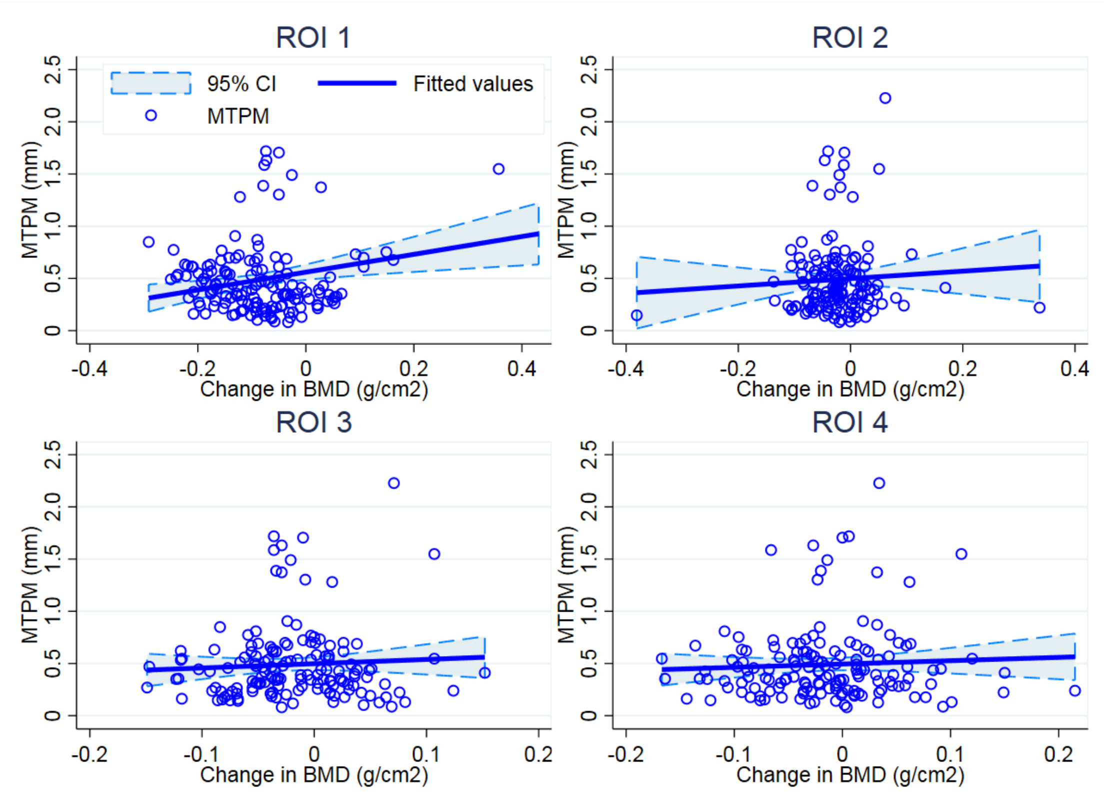

Figure 18 Scatterplots and fitted regression lines with 95% CI of the change of BMD of the proximal tibia (with pre-operative BMD as reference) and MTPM for all time points. Adapted from Paper IV.

7. Discussion

7.1.1. Discussion Study I

The most important finding concerned the assessment of OA in the lateral compartment. JSW of the lateral compartment showed an almost perfect intra-rater reliability and a substantial inter-rater reliability. More variation in both intra- and inter-rater reliability was seen for the OARSI criteria, the assessment of osteophytes ranging from fair to almost perfect, and the assessment of lateral JSN ranging from fair to substantial. The suggested minimum that should be obtained in a reliability study is substantial reliability (McHugh, 2012).

This is the first study to evaluate the reliability of valgus stress radiographs. Eriksson et al. compared joint space width in standard weight-bearing radiographs with stress radiographs (Eriksson et al., 2010). Stress radiographs were taken with a self-manufactured stress device. One observer assessed all radiographs and 10 radiographs were assessed twice, giving an almost perfect intra-rater reliability. Waldstein et al. compared valgus stress radiographs with intra-operative grading of OA (Waldstein, Monsef, Buckup, & Boettner, 2013). Reliability was assessed using 20 radiographs. This resulted in an almost perfect intra- and inter-rater reliability for the assessment of lateral JSW. These results are comparable or slightly better (inter-rater reliability) than our results.

Gossec et al. compared 3 radiographic scoring methods, the KL classification, the OARSI JSN score, and measurement of the JSW using 50 radiographs (Gossec et al., 2008). A substantial intra-rater reliability and a moderate inter-rater reliability was obtained for JSN. A similar study showed substantial to almost perfect intra- and inter-rater reliability for ORASI JSN and osteophyte scores (Culvenor et al., 2015). Two studies evaluated the intra- and inter-rater reliability of experienced and inexperienced observers of KL classification and OARSI classification with weight-bearing radiographs (Klara et al., 2016; Riddle, Jiranek, & Hull, 2013). They found a fair to almost perfect intra-rater reliability and a moderate to substantial inter-rater reliability for JSN. These results are comparable or somewhat better than our results, which may be explained by the difference in severity of OA. Most studies included patients with severe OA, whereas our study included patients with mild to severe OA. Mild OA is more difficult to grade and results in greater variability (Riddle et al., 2013). Also, most other studies did not have reliability as main outcome and had only a small sample size.

7.1.2. Discussion Studies II/III

RSA

Migration of the tibial component was similar for the MB and FB UKA. Migration occurred primarily in the first 12 months, after which the tibial components stabilized. Analogous migration patterns were seen in other RSA studies (B. J. Kendrick et al., 2015; Ryd et al., 1995; Tjornild, Soballe, Hansen, Holm, & Stilling, 2014). A higher strain at the bone-interface in the FB tibial component could pose a potential risk of higher migration. However, a wider keel and an additional peg on the medial side of the keel might provide extra stability for the FB tibial component.

In both the MB UKA and FB UKA, the tibial component showed posterior rotation (rotation around the x-axis) of tibial components between 4 and 12 months. However, the posterior rotation was less than 0.8° at 24 months, which has been suggested as an acceptable threshold (Gudnason et al., 2017). Compared to other thresholds for tibial component migration (Pijls et al., 2018; Pijls, Valstar, Nouta, et al., 2012), the FB UKA and MB UKA showed acceptable migration. In general, tibial component migration in Studies II and III was similar or better to migration shown in the literature. A higher migration (mean 0.6 mm MTPM at 1 year after surgery) of a tibial component of 2 all-polyethylene FB UKAs was shown compared to our results (Ensini, Barbadoro, Leardini, Catani, & Giannini, 2013; Lindstrand, Stenstrom, Ryd, & Toksvig-Larsen, 2000). In a randomized controlled trial (B. J. Kendrick et al., 2015), a significantly higher subsidence was shown in the first year for an uncemented MB UKA (mean 0.28 mm) compared to a cemented MB UKA (mean 0.09mm). This stabilized in the second year, showing no difference between components. Translations and rotations of the cemented MB UKA were similar to both the MB UKA and the FB UKA in our study.

For the femoral component, the FB UKA and the MB UKA showed similar translations and rotations. However, MTPM was higher in the FB UKA at 4 months after surgery. Although the migration stabilized after 4 months, the difference in MTPM between the FB UKA and the MB UKA remained.

The low migration for the MB UKA and the FB UKA, suggesting a good long-term survival, is in line with data from national registries (AOANJRR, 2018; NJR, 2018) that report low mid-term revision rates, 6–8% for MB UKA and 5–6% for FB UKA at 5 years' follow-up.

In study II, however, 30% of FB UKAs migrated continuously between 12 and 24 months, putting them at risk for revision (Ryd et al., 1995). Subgroup analysis for this group showed migration between all follow-ups and a statistic significant difference was found at 24 months compared to the stable group. It is shown that 20% of continuously migrating implants develop into clinical loosening (Ryd et al., 1995). In our cohort, this would result in approximately 2 clinically loose implants, which is still acceptable according to revision thresholds (<5%) of national registries at 10 year (Pijls, Valstar, Nouta, et al., 2012). An explanation for the continuous migration might be the learning curve with the introduction of the FB UKA in our department at the start of Study II. Introducing a new arthroplasty has a learning curve, which is associated with a higher risk of early revision (Lindstrand et al., 2000; Peltola, Malmivaara, & Paavola, 2013). At the start of study III, the 2 surgeons were familiar with both the FB UKA and the MB UKA, indication for UKA and surgical procedures remained unchanged between Studies II and III. Only 3 continuously migrating tibial components occurred in study III (1 MB and 2 FB tibial components). The caseload of UKAs in the department, which has been stable around 30% of knee arthroplasties, is not expected to have influenced the difference in continuous migration between Study II and Study III (Liddle, Pandit, Judge, & Murray, 2015).

Clinical outcome

Patients of both the FB UKA and the MB UKA group showed equal and clinically relevant improvements from poor before surgery to good/excellent 1 year after surgery (Beard et al., 2015; Clement et al., 2014; Ingelsrud et al., 2018), which were maintained throughout follow-up. Similar clinical improvements after medial UKA have been reported in the literature (Baker et al., 2012; B. J. Kendrick et al., 2015; Pandit, Jenkins, et al., 2011).

LEP of the operated leg showed a statistic significant improvement over time for patients in both the FB and MB UKA groups and reached the same level as that of the non-operated leg 24 months after surgery. Similar improvements in LEP have been described in the literature in patients with MB UKA and TKA (Barker et al., 2012; Frost et al., 2002; Jorgensen et al., 2017).

7.1.3. Discussion Study IV

Patients with normal systemic pre-operative BMD showed a 11-15% higher peri-prosthetic BMD than patients with low systemic BMD (osteopenia/osteoporosis). However, migration of cemented tibial components of a UKA was neither associated with pre-operative systemic and proximal tibial BMD, nor with change in peri-prosthetic BMD.

After an initial increase in peri-prosthetic BMD directly after surgery, a reduction in peri-prosthetic BMD occurred, especially directly adjacent to the medial joint line. UKA restores the natural alignment of the knee, resulting in off-loading of the medial tibial condyle, with bone remodeling and a reduction in BMD over time (C. E. Scott et al., 2016; Simpson et al., 2009). Protected weight-bearing and reduced activity levels may also contribute to peri-prosthetic BMD loss. It may also be explained by the natural reduction in BMD due to aging (Warming, Hassager, & Christiansen, 2002), as BMD loss was the same in both the operated knee and the non-operated knee.

Other studies have shown a similar decrease in peri-prosthetic BMD after surgery in both cemented and cementless MB and FB UKAs (C. E. Scott et al., 2016; Tuncer, Patel, Cobb, Hansen, & Amis, 2015). In contrast to our findings, one study showed an increase in BMD in the medial periprosthetic proximal tibial bone 3 months after cemented UKA (Soininvaara et al., 2013), and another study found preservation of the periprosthetic BMD of the tibia 2 years after surgery with a cemented MB UKA and an all-polyethylene FB UKA (Richmond et al., 2013). These differences may be explained by the use of other ROIs and the method for point typing bone, implant and cement interface as well as differences in software used for scanning and analyzing. Also, all studies measured BMD after surgery, whereas our reference BMD was measured before surgery. Besides DXA, digital radiographic densitometry and CT-assisted osteodensitometry has been used to measure BMD in 2 reported studies (Richmond et al., 2013; C. E. Scott et al., 2016)

Tibial component migration between 12 and 24 months was equally low for patients with normal BMD and patients with low BMD. Both groups showed acceptable migration at 12 months according to Pijls' thresholds, indicating good long-term survival (Pijls et al., 2018). There was no association between the change in BMD of the proximal tibia and the migration of the tibial component (Koppens, Rytter, Dalsgaard, et al., 2019; Koppens, Rytter, Munk, et al., 2019).

In accordance with our study, no association was found between post-operative change in BMD of the proximal tibia and tibial component migration of cemented and cementless TKAs (Li & Nilsson, 2001; Regner et al., 1999; Saari, Uvehammer, Carlsson, Regner, & Karrholm, 2007). In a study of cementless TKAs, less migration of the tibial component was reported between 1 and 3 years for patients with a high pre-operative BMD in the proximal tibia (Petersen, Nielsen, Lebech, Toksvig-Larsen, & Lund, 1999). Also, a low pre-operative BMD of the proximal tibia was shown to be associated with high migration for cementless TKAs. This association was not shown for cemented TKAs, suggesting that cemented fixation is less dependent on BMD of the proximal tibia (Li & Nilsson, 2000). However, a recent study could not show an association between pre-operative BMD and migration in either cemented/cementless TKAs nor cemented UKAs (Linde et al., 2019). However, TKAs have a different post-operative change in BMD than UKAs (Hooper et al., 2013; Richmond et al., 2013), making it difficult to compare with our results.

7.2. Limitations and methodological considerations

7.2.1. Limitations of Study I

Selection bias was present as only referred patients with mild to severe medial OA were included in the study. We do not believe this has influenced our results because we aimed to evaluate the reliability of grading of OA on valgus-stress radiographs.

The grading of OA with valgus-stress radiographs was not tested against a gold standard. Our intention was to test the reliability of the stress radiographs and not the validity. A validity study would require additional assessment of the OA grade with, for example, MRI or arthroscopy.

Approximately 20% of radiographs had incomplete calibration and could not be used for measuring JSW. The reason for this was suboptimal placement of the calibration marker. There were, however, 65 radiographs available for assessment, which was enough according to the power calculation.

In instances of low prevalence, kappa is skewed to lower outcomes. Kappa accounts for the agreement beyond the expected agreement by chance. For example, for lateral femoral osteophytes there was a high agreement, which could be explained by chance therefore resulting in a low kappa (Gisev et al., 2013; Sim & Wright, 2005).

OARSI classification was chosen because it enables grading of the medial and lateral compartment separately, which was required for Study I. The OARSI score is a more recently developed grading system, compared to the Kellgren-Lawrence system or the Albeck's classification. The disadvantages with these latter systems are that they are primarily based on severe cases of OA and the assumption that radiographic progression of OA is linear, and they do not allow classification of the separate knee compartments, and grading is inconsistent between studies (Kohn, Sassoon, & Fernando, 2016)

Weighted kappa was chosen because it adds weight to the amount of difference between, for example, the first and second grading of a radiograph. If 2 observations only differ with 1 point, there is a higher agreement as when 2 observations differ 2 points. This nuance is not possible when using kappa (Landis & Koch, 1977).

7.2.2. Limitations of study II/III

The main limitation of study II was that there was no control group for comparison. This was accounted for in study III, which was designed as an RCT study comparing a FB UKA and a MB UKA.

Selection bias could have occurred, as a large part of eligible patients declined to participate in both studies. This is, however, not unusual in clinical trials (Thoma, Farrokhyar, McKnight, &

Bhandari, 2010). Our inclusion criteria were, however, similar to the normal indications for UKA. Therefore, we believe that our results should be generalizable to other, similar clinical settings.

The reference origin for migration calculation was the geometric center of the 3-dimensional implant model. As the MB and FB UKA have different designs, the reference origin may differ. This might have an influence on translations, although this is expected to be very small. No influence on rotations or MTPM is to be expected (van Hamersveld et al., 2019).

Missing values were common for RSA radiographs in both studies due to occluded bone markers and poor marker distribution. In study III, this issue was partly solved by using an MC model (Kaptein et al., 2005). Missing values were completely at random (Bhaskaran & Smeeth, 2014). The statistical method used for analysis, MMA with likelihood-ratio testing, is, however, robust for missing values and enables the use all the data available.

Thresholds for migration are based on TKAs (Gudnason et al., 2017; Pijls et al., 2018; Pijls, Valstar, Nouta, et al., 2012; Ryd et al., 1995), and may therefore not be appropriate for migration of UKAs. However, the low migration of the MB UKA and the FB UKA is in line with the low mid-term revision rates seen in the national registries (AOANJRR, 2018; NJR, 2018).

7.2.3. Limitations of study IV

The normal BMD group and low BMD group were sufficiently large for analysis of tibial component migration. However, there were too few patients with osteoporosis (n = 2) to divide the cohort into 3 groups (normal/osteopenia/osteoporosis). We can therefore not conclude whether there is an association between osteoporosis and migration.

The design of the UKA (MB/FB) could have influenced changes in BMD of the proximal tibia as well as migration. We have, however, shown that the 2 UKA designs had similar change in periprosthetic BMD and migration of the tibial component during follow-up (Studies III and IV), making it unlikely that the design has had an influence on our results.

We did not use a knee-specific DXA software, which could have influenced the DXA measurements. A validated method (Stilling et al., 2010) was, however, utilized showing a high reproducibility comparable to other studies in which UKAs were used (Soininvaara et al., 2013; Tuncer et al., 2015). No analysis was made of peri-prosthetic BMD and continuous migration as defined by Ryd et al. (Ryd et al., 1995). Although relevant, only 3 knees showed continuous migration.

8. Conclusion

The overall aim of this dissertation was to identify aspects in patient selection, implant design, and treatment that have an influence on the outcome of patients with medial TF OA treated with a medial UKA.

8.1. Patient selection

Valgus-stress radiographs are a good supplement in the clinical evaluation of patients with medial OA. The assessment of OA in the lateral TF compartment was most reliable when based on measurement of the joint space width (JSW).

We performed our study in a typical clinical setting, and results are therefore generalizable to similar departments.

8.2. Treatment

We evaluated migration of a new FB UKA and compared it to a well-documented MB UKA. We showed similar good fixation of the FB UKA compared to the MB UKA and equal clinical improvements until 2 years. An acceptable mid- (<3%) to long-term (<5%) (5- to 10-year) revision rate can be expected for both implants (Pijls, Valstar, Nouta, et al., 2012).

In study II, 30% of tibial components of the FB UKA showed continuous migration and were at risk of loosening and consequently revision. This was not found in study III.

8.3. Outcome

Patients of both the FB UKA and the MB UKA group showed equal and clinically relevant improvement after surgery.

Also, we evaluated the association between (peri-prosthetic and systemic) BMD and migration of the tibial component of cemented medial UKAs.

A reduction of the peri-prosthetic BMD was seen during the first 12 months after surgery. This reduction was similar in the non-operated knee, suggesting that a natural decrease in BMD due to aging is partly responsible. Tibial component migration was associated with neither pre-operative systemic BMD nor with post-operative change in peri-prosthetic BMD, suggesting that long-term fixation is not influenced by BMD.

9. Perspectives and future research

9.1. Patient selection

The logical next step is to perform a validity study, to evaluate whether radiographic OA on valgus-stress radiographs correlates with the grade of OA measured with use of a gold standard, for example, MRI or arthroscopy.

9.2. Treatment

Polyethylene wear of a FB UKA may be different than that of a MB UKA. This difference might be explained by the different types of wear between a FB UKA and a MB UKA, and by the difference in polyethylene production. Wear particles can cause osteolysis and loosening of the implant.

As part of our RCT comparing the FB UKA and the MB UKA, weight-bearing stereoradiographs were obtained and will enable us to study the polyethylene wear of these implants. Due to the very low polyethylene wear rate reported on the MB UKA (0.02 mm/year) (B. J. L. Kendrick et al., 2011) in relation to the accuracy of RSA (0.1 mm) based on Studies II and III, patients will be followed up for 5 years with weight-bearing RSA in addition to supine RSA.

At 5 years, we will be able to evaluate polyethylene wear as well as mid-term migration of the 2 UKA designs.

Continuous migration was found in 30% of the tibial components in the cohort study. Implants with continuous migration have an increased risk of loosening. Therefore, prolonged clinical and radiological follow-up of this group is warranted.

In general, RSA could be developed further by defining more implant-specific thresholds, for example for TKA/UKA, or cemented/cementless. This would be possible with large RSA databases with long-time follow-up (>10 years). Furthermore, migration patterns (both static and dynamic) could be more specified, to allow for differentiation between well-performing and failing implants, which might be used in individual cases.

9.3. Outcome

Although Study IV was powered to detect a difference between the normal and low systemic BMD group, there were not enough patients with osteoporosis to divide the cohort into 3 groups and differentiate between osteopenia and osteoporosis. No conclusions can therefore be drawn on the association between migration and osteoporosis. Future studies should include larger numbers of patients to assure that there are an adequate number of patients with osteoporosis to be able to study the association between osteoporosis and migration.

Outcome after knee arthroplasty is dependent on multiple physical and psychological aspects. Large registry studies have differentiated outcome for gender, age, etc. Larger research databases, encompassing both implant/surgery-related factors (type of implant, fixation method, RSA) and patient-related factors (DXA, gender, age, co-morbidities), would make it possible to identify aspects of influence on implant migration and thereby implant survival.

10. References

Aalund, P. K., Larsen, K., Hansen, T. B., & Bandholm, T. (2013). Normalized knee-extension strength or leg-press power after fast-track total knee arthroplasty: which measure is most closely associated with performance-based and self-reported function? *Arch Phys Med Rehabil, 94*(2), 384-390. doi:10.1016/j.apmr.2012.09.031

Abu-Rajab, R. B., Watson, W. S., Walker, B., Roberts, J., Gallacher, S. J., & Meek, R. M. (2006). Peri-prosthetic bone mineral density after total knee arthroplasty. Cemented versus cementless fixation. *J Bone Joint Surg Br, 88*(5), 606-613. doi:10.1302/0301-620x.88b5.16893

Ahlback, S. (1968). Osteoarthrosis of the knee. A radiographic investigation. *Acta Radiol Diagn (Stockh)*, Suppl 277:277-272.

Altman, R., Asch, E., Bloch, D., Bole, G., Borenstein, D., Brandt, K., . . . et al. (1986). Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. *Arthritis Rheum, 29*(8), 1039-1049.

Altman, R. D., & Gold, G. E. (2007). Atlas of individual radiographic features in osteoarthritis, revised. *Osteoarthritis Cartilage, 15 Suppl A*(1063-4584 (Print)), A1-56. doi:10.1016/j.joca.2006.11.009

AOANJRR. (2018). *Australian Orthopaedic Association National Joint Replacement Registry: Annual Report 2018*. Retrieved from Adelaide, Australia: https://aoanjrr.sahmri.com/documents/10180/576950/Hip%2C%20Knee%20%26%20Shoulder%20Arthroplasty

Ashraf, T., Newman, J. H., Desai, V. V., Beard, D., & Nevelos, J. E. (2004). Polyethylene wear in a non-congruous unicompartmental knee replacement: a retrieval analysis. *Knee, 11*(3), 177-181. doi:10.1016/j.knee.2004.03.004
9002-88-4 (Polyethylene)

Baker, P. N., Petheram, T., Jameson, S. S., Avery, P. J., Reed, M. R., Gregg, P. J., & Deehan, D. J. (2012). Comparison of patient-reported outcome measures following total and unicondylar knee replacement. *J Bone Joint Surg Br, 94*(7), 919-927. doi:10.1302/0301-620X.94B7.28436

Barker, K. L., Jenkins, C., Pandit, H., & Murray, D. (2012). Muscle power and function two years after unicompartmental knee replacement. *Knee, 19*(4), 360-364. doi:10.1016/j.knee.2011.05.006

Bassey, E. J., & Short, A. H. (1990). A new method for measuring power output in a single leg extension: feasibility, reliability and validity. *Eur J Appl Physiol Occup Physiol, 60*(5), 385-390.

Beard, D. J., Harris, K., Dawson, J., Doll, H., Murray, D. W., Carr, A. J., & Price, A. J. (2015). Meaningful changes for the Oxford hip and knee scores after joint replacement surgery. *J Clin Epidemiol, 68*(1), 73-79. doi:10.1016/j.jclinepi.2014.08.009

Bedson, J., & Croft, P. R. (2008). The discordance between clinical and radiographic knee osteoarthritis: a systematic search and summary of the literature. *BMC Musculoskelet Disord, 9*, 116. doi:10.1186/1471-2474-9-116

Bhaskaran, K., & Smeeth, L. (2014). What is the difference between missing completely at random and missing at random? *Int J Epidemiol, 43*(4), 1336-1339. doi:10.1093/ije/dyu080

Birch, S., Stilling, M., Mechlenburg, I., & Hansen, T. B. (2019). The association between pain catastrophizing, physical function and pain in a cohort of patients undergoing knee arthroplasty. *BMC Musculoskelet Disord, 20*(1), 421. doi:10.1186/s12891-019-2787-6

Brockett, C. L., Jennings, L. M., & Fisher, J. (2011). The wear of fixed and mobile bearing unicompartmental knee replacements. *Proc Inst Mech Eng H, 225*(5), 511-519. doi:10.1177/2041303310393824

Brouwer, R. W., Huizinga, M. R., Duivenvoorden, T., van Raaij, T. M., Verhagen, A. P., Bierma-Zeinstra, S. M., & Verhaar, J. A. (2014). Osteotomy for treating knee osteoarthritis. *Cochrane Database Syst Rev*(12), Cd004019. doi:10.1002/14651858.CD004019.pub4

Bryant, D., Havey, T. C., Roberts, R., & Guyatt, G. (2006). How many patients? How many limbs? Analysis of patients or limbs in the orthopaedic literature: a systematic review. *J Bone Joint Surg Am, 88*(1), 41-45. doi:10.2106/jbjs.e.00272

Clement, N. D., MacDonald, D., & Simpson, A. H. (2014). The minimal clinically important difference in the Oxford knee score and Short Form 12 score after total knee arthroplasty. *Knee Surg Sports Traumatol Arthrosc, 22*(8), 1933-1939. doi:10.1007/s00167-013-2776-5

Cosman, F., de Beur, S. J., LeBoff, M. S., Lewiecki, E. M., Tanner, B., Randall, S., & Lindsay, R. (2014). Clinician's Guide to Prevention and Treatment of Osteoporosis. *Osteoporos Int, 25*(10), 2359-2381. doi:10.1007/s00198-014-2794-2

Culvenor, A. G., Engen, C. N., Oiestad, B. E., Engebretsen, L., & Risberg, M. A. (2015). Defining the presence of radiographic knee osteoarthritis: a comparison between the Kellgren and Lawrence system and OARSI atlas criteria. *Knee Surg Sports Traumatol Arthrosc, 23*(12), 3532-3539. doi:10.1007/s00167-014-3205-0

DanishHealthAuthority. (2012). *Knæartrose - Nationale kliniske retningslinjer og faglige visitationsretningslinjer*. Retrieved from http://www.sst.dk

DanishHealthAuthority. (2016). *National klinisk retningslinje for meniskpatologi i knæet*. Retrieved from http://sst.dk

Dasher, L. G., Newton, C. D., & Lenchik, L. (2010). Dual X-ray absorptiometry in today's clinical practice. *Radiol Clin North Am, 48*(3), 541-560. doi:10.1016/j.rcl.2010.02.019

Dawson, J., Fitzpatrick, R., Murray, D., & Carr, A. (1998). Questionnaire on the perceptions of patients about total knee replacement. *J Bone Joint Surg Br, 80*(1), 63-69.

DKAR. (2018). *Danish Knee Arthroplasty Register - Annual report 2018*. Retrieved from

Ejaz, A., Laursen, A. C., Jakobsen, T., Rasmussen, S., Nielsen, P. T., & Laursen, M. B. (2015). Absence of a Tourniquet Does Not Affect Fixation of Cemented TKA: A Randomized RSA Study of 70 Patients. *J Arthroplasty, 30*(12), 2128-2132. doi:10.1016/j.arth.2015.05.058

Engh, G. A., Zimmerman, R. L., Parks, N. L., & Engh, C. A. (2009). Analysis of wear in retrieved mobile and fixed bearing knee inserts. *J Arthroplasty, 24*(6 Suppl), 28-32. doi:10.1016/j.arth.2009.03.010

Englund, M., Guermazi, A., Gale, D., Hunter, D. J., Aliabadi, P., Clancy, M., & Felson, D. T. (2008). Incidental meniscal findings on knee MRI in middle-aged and elderly persons. *N Engl J Med, 359*(11), 1108-1115. doi:10.1056/NEJMoa0800777

Ensini, A., Barbadoro, P., Leardini, A., Catani, F., & Giannini, S. (2013). Early migration of the cemented tibial component of unicompartmental knee arthroplasty: a radiostereometry study. *Knee Surg Sports Traumatol Arthrosc, 21*(11), 2474-2479. doi:10.1007/s00167-012-2068-5

Eriksson, K., Sadr-Azodi, O., Singh, C., Osti, L., & Bartlett, J. (2010). Stress radiography for osteoarthritis of the knee: a new technique. *Knee Surg Sports Traumatol Arthrosc, 18*(10), 1356-1359. doi:10.1007/s00167-010-1169-2

Fleiss, J. L., & Cohen, J. (1973). The Equivalence of Weighted Kappa and the Intraclass Correlation Coefficient as Measures of Reliability. *Educational and Psychological Measurement, 33*(3), 613-619. doi:10.1177/001316447303300309

Frost, H., Lamb, S. E., & Robertson, S. (2002). A randomized controlled trial of exercise to improve mobility and function after elective knee arthroplasty. Feasibility, results and methodological difficulties. *Clin Rehabil, 16*(2), 200-209. doi:10.1191/0269215502cr483oa

Galli, M., De Santis, V., & Tafuro, L. (2003). Reliability of the Ahlback classification of knee osteoarthritis. *Osteoarthritis Cartilage, 11*(8), 580-584. doi:http://dx.doi.org/10.1016/S1063-4584(03)00095-5

Gisev, N., Bell, J. S., & Chen, T. F. (2013). Interrater agreement and interrater reliability: Key concepts, approaches, and applications. *Research in Social and Administrative Pharmacy, 9*(3), 330-338. doi:https://doi.org/10.1016/j.sapharm.2012.04.004

Gluer, C. C., Blake, G., Lu, Y., Blunt, B. A., Jergas, M., & Genant, H. K. (1995). Accurate assessment of precision errors: how to measure the reproducibility of bone densitometry techniques. *Osteoporos Int*, *5*(4), 262-270.

Goodfellow, J., O'Connor, J., Pandit, H., Dodd, C., & Murray, D. (2015). *Unicompartmental arthroplasty with the Oxford knee* (Second edition ed.). Wolvercote, Oxford: Goodfellow Publishers Limited.

Goodfellow, J. W., O'Connor, J. J., & Murray, D. W. (2010). A critique of revision rate as an outcome measure: re-interpretation of knee joint registry data. *J Bone Joint Surg Br, 92*(12), 1628-1631. doi:10.1302/0301-620X.92B12.25193

Gossec, L., Jordan, J. M., Mazzuca, S. A., Lam, M. A., Suarez-Almazor, M. E., Renner, J. B., . . . Maillefert, J. F. (2008). Comparative evaluation of three semi-quantitative radiographic grading techniques for knee osteoarthritis in terms of validity and reproducibility in 1759 X-rays: report of the OARSI-OMERACT task force. *Osteoarthritis Cartilage, 16*(7), 742-748. doi:10.1016/j.joca.2008.02.021

Gottsche, D., Gromov, K., Viborg, P. H., Brauner, E. V., Pedersen, A. B., & Troelsen, A. (2019). Weight affects survival of primary total knee arthroplasty: study based on the Danish Knee Arthroplasty Register with 67,810 patients and a median follow-up time of 5 years. *Acta Orthop, 90*(1), 60-66. doi:10.1080/17453674.2018.1540091

Gudnason, A., Adalberth, G., Nilsson, K. G., & Hailer, N. P. (2017). Tibial component rotation around the transverse axis measured by radiostereometry predicts aseptic loosening better than maximal total point motion. *Acta Orthop*, *88*(3), 282-287. doi:10.1080/17453674.2017.1297001

Hamilton, T. W., Pandit, H. G., Inabathula, A., Ostlere, S. J., Jenkins, C., Mellon, S. J., . . . Murray, D. W. (2017). Unsatisfactory outcomes following unicompartmental knee arthroplasty in patients with partial thickness cartilage loss: a medium-term follow-up. *Bone Joint J, 99-b*(4), 475-482. doi:10.1302/0301-620x.99b4.bjj-2016-1061.r1

Hamilton, T. W., Pandit, H. G., Lombardi, A. V., Adams, J. B., Oosthuizen, C. R., Clave, A., . . . Murray, D. W. (2016). Radiological Decision Aid to determine suitability for medial unicompartmental knee arthroplasty: development and preliminary validation. *Bone Joint J, 98-b*(10 Supple B), 3-10. doi:10.1302/0301-620x.98b10.bjj-2016-0432.r1

Hamilton, T. W., Rizkalla, J. M., Kontochristos, L., Marks, B. E., Mellon, S. J., Dodd, C. A. F., . . . Murray, D. W. (2017). The Interaction of Caseload and Usage in Determining Outcomes of Unicompartmental Knee Arthroplasty: A Meta-Analysis. *J Arthroplasty*, *32*(10), 3228-3237 e3222. doi:10.1016/j.arth.2017.04.063

Hooper, G. J., Gilchrist, N., Maxwell, R., March, R., Heard, A., & Frampton, C. (2013). The effect of the Oxford uncemented medial compartment arthroplasty on the bone mineral density and content of the proximal tibia. *Bone Joint J, 95-B*(11), 1480-1483. doi:10.1302/0301-620x.95b11.31509

Horsager, K., Kaptein, B. L., Romer, L., Jorgensen, P. B., & Stilling, M. (2017). Dynamic RSA for the evaluation of inducible micromotion of Oxford UKA during step-up and step-down motion. *Acta Orthop*, 1-7. doi:10.1080/17453674.2016.1274592

Horsager, K., Madsen, F., Odgaard, A., Fink Jepsen, C., Romer, L., Kristensen, P. W., . . . Stilling, M. (2018). Similar polyethylene wear between cemented and cementless Oxford medial UKA: a 5-year follow-up randomized controlled trial on 79 patients using radiostereometry. *Acta Orthop*, 1-12. doi:10.1080/17453674.2018.1543757

Ingelsrud, L. H., Roos, E. M., Terluin, B., Gromov, K., Husted, H., & Troelsen, A. (2018). Minimal important change values for the Oxford Knee Score and the Forgotten Joint Score at 1 year after total knee replacement. *Acta Orthop*, 1-7. doi:10.1080/17453674.2018.1480739

ISCD. The International Society For Clinical Densitometry. Retrieved from https://www.iscd.org/resources/calculators/

Jaroma, A., Soininvaara, T., & Kroger, H. (2016). Periprosthetic tibial bone mineral density changes after total knee arthroplasty. *Acta Orthop, 87*(3), 268-273. doi:10.3109/17453674.2016.1173982

Johnsen, N. F., Koch, M. B., Davidsen, M., & Juel, K. (2014). *De samfundsmæssige omkostninger ved artrose*. Retrieved from http://www.si-folkesundhed.dk

Jorgensen, P. B., Bogh, S. B., Kierkegaard, S., Sorensen, H., Odgaard, A., Soballe, K., & Mechlenburg, I. (2017). The efficacy of early initiated, supervised, progressive resistance training compared to unsupervised, home-based exercise after unicompartmental knee arthroplasty: a single-blinded randomized controlled trial. *Clin Rehabil, 31*(1), 61-70. doi:10.1177/0269215516640035

Judge, A., Arden, N. K., Kiran, A., Price, A., Javaid, M. K., Beard, D., . . . Field, R. E. (2012). Interpretation of patient-reported outcomes for hip and knee replacement surgery: identification of thresholds associated with satisfaction with surgery. *J Bone Joint Surg Br, 94*(3), 412-418. doi:10.1302/0301-620x.94b3.27425

Kaptein, B. L., Valstar, E. R., Stoel, B. C., Reiber, H. C., & Nelissen, R. G. (2007). Clinical validation of model-based RSA for a total knee prosthesis. *Clin Orthop Relat Res, 464*, 205-209.

Kaptein, B. L., Valstar, E. R., Stoel, B. C., Rozing, P. M., & Reiber, J. H. (2005). A new type of model-based Roentgen stereophotogrammetric analysis for solving the occluded marker problem. *J Biomech, 38*(11), 2330-2334. doi:10.1016/j.jbiomech.2004.09.018

Katz, J. N., Brophy, R. H., Chaisson, C. E., de Chaves, L., Cole, B. J., Dahm, D. L., . . . Losina, E. (2013). Surgery versus physical therapy for a meniscal tear and osteoarthritis. *N Engl J Med, 368*(18), 1675-1684. doi:10.1056/NEJMoa1301408

Kellgren, J. H., & Lawrence, J. S. (1957). Radiological assessment of osteo-arthrosis. *Annals of the rheuamtic diseases, 16*(0003-4967 (Print)), 8. doi:D - CLML: 5833:41706:366
D - NLM: PMC1006995 OTO - NLM

Kendrick, B. J., Kaptein, B. L., Valstar, E. R., Gill, H. S., Jackson, W. F., Dodd, C. A., . . . Murray, D. W. (2015). Cemented versus cementless Oxford unicompartmental knee arthroplasty using radiostereometric analysis: A randomised controlled trial. *Bone Joint J, 97-B*(2), 185-191. doi:10.1302/0301-620x.97b2.34331

Kendrick, B. J., Longino, D., Pandit, H., Svard, U., Gill, H. S., Dodd, C. A., . . . Price, A. J. (2010). Polyethylene wear in Oxford unicompartmental knee replacement: a retrieval study of 47 bearings. *J Bone Joint Surg Br, 92*(3), 367-373. doi:10.1302/0301-620X.92B3.22491
9002-88-4 (Polyethylene)

Kendrick, B. J. L., Simpson, D. J., Kaptein, B. L., Valstar, E. R., Gill, H. S., Murray, D. W., & Price, A. J. (2011). Polyethylene wear of mobile-bearing unicompartmental knee replacement at 20 years. *Journal of Bone and Joint Surgery-British Volume, 93B*(4), 470-475. doi:Doi 10.1302/0301-620x.93b4.25605

Khan, M., Evaniew, N., Bedi, A., Ayeni, O. R., & Bhandari, M. (2014). Arthroscopic surgery for degenerative tears of the meniscus: a systematic review and meta-analysis. *Cmaj, 186*(14), 1057-1064. doi:10.1503/cmaj.140433

Kirkley, A., Birmingham, T. B., Litchfield, R. B., Giffin, J. R., Willits, K. R., Wong, C. J., . . . Fowler, P. J. (2008). A randomized trial of arthroscopic surgery for osteoarthritis of the knee. *N Engl J Med, 359*(11), 1097-1107. doi:10.1056/NEJMoa0708333

Klara, K., Collins, J. E., Gurary, E., Elman, S. A., Stenquist, D. S., Losina, E., & Katz, J. N. (2016). Reliability and Accuracy of Cross-sectional Radiographic Assessment of Severe Knee Osteoarthritis: Role of Training and Experience. *J Rheumatol, 43*(7), 1421-1426. doi:10.3899/jrheum.151300

Kohn, M. D., Sassoon, A. A., & Fernando, N. D. (2016). Classifications in Brief: Kellgren-Lawrence Classification of Osteoarthritis. *Clin Orthop Relat Res, 474*(8), 1886-1893. doi:10.1007/s11999-016-4732-4

Koppens, D., Rytter, S., Dalsgaard, J., Sorensen, O. G., Hansen, T. B., & Stilling, M. (2019). The Effect of Bone Quality on Tibial Component Migration in Medial Cemented Unicompartmental Knee Arthroplasty. A Prospective Cohort Study Using Dual X-Ray Absorptiometry and Radiostereometric Analysis. *J Arthroplasty*. doi:10.1016/j.arth.2019.10.027

Koppens, D., Rytter, S., Munk, S., Dalsgaard, J., Sorensen, O. G., Hansen, T. B., & Stilling, M. (2019). Equal tibial component fixation of a mobile-bearing and fixed-bearing medial unicompartmental knee arthroplasty: a randomized controlled RSA study with 2-year follow-up. *Acta Orthop, 90*(6), 575-581. doi:10.1080/17453674.2019.1639965

Koppens, D., Sorensen, O. G., Munk, S., Rytter, S., Larsen, S. K. A., Stilling, M., & Hansen, T. B. (2019). The lateral joint space width can be measured reliably with Telos valgus stress radiography in medial knee osteoarthritis. *Skeletal Radiol, 48*(7), 1069-1077. doi:10.1007/s00256-018-3111-5

Koppens, D., Stilling, M., Munk, S., Dalsgaard, J., Rytter, S., Sorensen, O. G., & Hansen, T. B. (2018). Low implant migration of the SIGMA((R)) medial unicompartmental knee arthroplasty. *Knee Surg Sports Traumatol Arthrosc, 26*(6), 1776-1785. doi:10.1007/s00167-017-4782-5

Kretzer, J. P., Jakubowitz, E., Reinders, J., Lietz, E., Moradi, B., Hofmann, K., & Sonntag, R. (2011). Wear analysis of unicondylar mobile bearing and fixed bearing knee systems: a knee simulator study. *Acta Biomater, 7*(2), 710-715. doi:10.1016/j.actbio.2010.09.031

Laende, E. K., Astephen Wilson, J. L., Mills Flemming, J., Valstar, E. R., Richardson, C. G., & Dunbar, M. J. (2019). Equivalent 2-year stabilization of uncemented tibial component migration despite higher early migration compared with cemented fixation: an RSA study on 360 total knee arthroplasties. *Acta Orthop*, 1-11. doi:10.1080/17453674.2018.1562633

Landis, J. R., & Koch, G. G. (1977). The measurement of observer agreement for categorical data. *Biometrics, 33*(1), 159-174. doi:10.2307/2529310

Li, M. G., & Nilsson, K. G. (2000). The effect of the preoperative bone quality on the fixation of the tibial component in total knee arthroplasty. *J Arthroplasty, 15*(6), 744-753. doi:10.1054/arth.2000.6617

Li, M. G., & Nilsson, K. G. (2001). No relationship between postoperative changes in bone density at the proximal tibia and the migration of the tibial component 2 years after total knee arthroplasty. *J Arthroplasty, 16*(7), 893-900. doi:10.1054/arth.2001.24376

Liddle, A. D., Judge, A., Pandit, H., & Murray, D. W. (2014). Adverse outcomes after total and unicompartmental knee replacement in 101,330 matched patients: a study of data from the National Joint Registry for England and Wales. *Lancet, 384*(9952), 1437-1445. doi:10.1016/s0140-6736(14)60419-0

Liddle, A. D., Pandit, H., Judge, A., & Murray, D. W. (2015). Optimal usage of unicompartmental knee arthroplasty: a study of 41 986 cases from the National Joint Registry for England and Wales. *Bone Joint J, 97-b*(11), 1506-1511. doi:10.1302/0301-620x.97b11.35551

Liddle, A. D., Pandit, H., Judge, A., & Murray, D. W. (2016). Effect of Surgical Caseload on Revision Rate Following Total and Unicompartmental Knee Replacement. *J Bone Joint Surg Am, 98*(1), 1-8. doi:10.2106/jbjs.n.00487

Linde, K. N., Madsen, F., Puhakka, K. B., Langdahl, B. L., Soballe, K., Krog-Mikkelsen, I., & Stilling, M. (2019). Preoperative Systemic Bone Quality Does Not Affect Tibial Component Migration in Knee Arthroplasty: A 2-Year Radiostereometric Analysis of a Hundred Consecutive Patients. *J Arthroplasty, 34*(10), 2351-2359. doi:10.1016/j.arth.2019.05.019

Lindstrand, A., Stenstrom, A., Ryd, L., & Toksvig-Larsen, S. (2000). The introduction period of unicompartmental knee arthroplasty is critical: a clinical, clinical multicentered, and radiostereometric study of 251 Duracon unicompartmental knee arthroplasties. *J Arthroplasty, 15*(5), 608-616.

Malchau, H. (2000). Introducing new technology: a stepwise algorithm. *Spine (Phila Pa 1976), 25*(3), 285.

McAlindon, T. E., Bannuru, R. R., Sullivan, M. C., Arden, N. K., Berenbaum, F., Bierma-Zeinstra, S. M., . . . Underwood, M. (2014). OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis Cartilage, 22*(3), 363-388. doi:10.1016/j.joca.2014.01.003

McHugh, M. L. (2012). Interrater reliability: the kappa statistic. *Biochem Med (Zagreb), 22*(3), 276-282.

Molt, M., Ljung, P., & Toksvig-Larsen, S. (2012). Does a new knee design perform as well as the design it replaces? *Bone Joint Res, 1*(12), 315-323. doi:10.1302/2046-3758.112.2000064

Moseley, J. B., O'Malley, K., Petersen, N. J., Menke, T. J., Brody, B. A., Kuykendall, D. H., . . . Wray, N. P. (2002). A controlled trial of arthroscopic surgery for osteoarthritis of the knee. *N Engl J Med, 347*(2), 81-88. doi:10.1056/NEJMoa013259

Mukherjee, K., Pandit, H., Dodd, C. A., Ostlere, S., & Murray, D. W. (2008). The Oxford unicompartmental knee arthroplasty: a radiological perspective. *Clin Radiol, 63*(10), 1169-1176. doi:10.1016/j.crad.2007.12.017

Munk, S., Dalsgaard, J., Bjerggaard, K., Andersen, I., Hansen, T. B., & Kehlet, H. (2012). Early recovery after fast-track Oxford unicompartmental knee arthroplasty. 35 patients with minimal invasive surgery. *Acta Orthop, 83*(1), 41-45. doi:10.3109/17453674.2012.657578

Murray, D. W., Fitzpatrick, R., Rogers, K., Pandit, H., Beard, D. J., Carr, A. J., & Dawson, J. (2007). The use of the Oxford hip and knee scores. *J Bone Joint Surg Br, 89*(8), 1010-1014. doi:10.1302/0301-620X.89B8.19424

Murray, D. W., Liddle, A. D., Dodd, C. A., & Pandit, H. (2015). Unicompartmental knee arthroplasty: is the glass half full or half empty? *Bone Joint J, 97-B*(10 Suppl A), 3-8. doi:10.1302/0301-620X.97B10.36542

Nelissen, R. G., Pijls, B. G., Karrholm, J., Malchau, H., Nieuwenhuijse, M. J., & Valstar, E. R. (2011). RSA and registries: the quest for phased introduction of new implants. *J Bone Joint Surg Am, 93 Suppl 3*, 62-65. doi:10.2106/JBJS.K.00907

Nilsson, K. G., & Dalen, T. (1998). 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 Orthop Scand, 69*(5), 479-483. doi:10.3109/17453679808997782

NJR. (2018). *National Joint Registry for England, Wales and Northern Ireland and the Isle of Man: 15th Annual Report 2018*. Retrieved from www.njrcentre.org.uk

NZJR. (2016). Seventeen year report, january 1999 to december 2015. from The New Zealand Joint Registry https://nzoa.org.nz/system/files/NZJR%2017%20year%20Report.pdf

Pandit, H., Gulati, A., Jenkins, C., Barker, K., Price, A. J., Dodd, C. A., & Murray, D. W. (2011). Unicompartmental knee replacement for patients with partial thickness cartilage loss in the affected compartment. *Knee, 18*(3), 168-171. doi:10.1016/j.knee.2010.05.003

Pandit, H., Jenkins, C., Gill, H. S., Barker, K., Dodd, C. A., & Murray, D. W. (2011). Minimally invasive Oxford phase 3 unicompartmental knee replacement: results of 1000 cases. *J Bone Joint Surg Br, 93*(2), 198-204. doi:10.1302/0301-620x.93b2.25767

Parratte, S., Pauly, V., Aubaniac, J. M., & Argenson, J. N. (2012). No long-term difference between fixed and mobile medial unicompartmental arthroplasty. *Clin Orthop Relat Res, 470*(1), 61-68. doi:10.1007/s11999-011-1961-4

Peltola, M., Malmivaara, A., & Paavola, M. (2013). Learning curve for new technology?: a nationwide register-based study of 46,363 total knee arthroplasties. *J Bone Joint Surg Am, 95*(23), 2097-2103. doi:10.2106/jbjs.L.01296

Petersen, M. M., Nielsen, P. T., Lebech, A., Toksvig-Larsen, S., & Lund, B. (1999). Preoperative bone mineral density of the proximal tibia and migration of the tibial component after uncemented total knee arthroplasty. *J Arthroplasty, 14*(1), 77-81.

Pijls, B. G., & Nelissen, R. G. (2016). The era of phased introduction of new implants. *Bone Joint Res, 5*(6), 215-217. doi:10.1302/2046-3758.56.2000653

Pijls, B. G., Plevier, J. W. M., & Nelissen, R. (2018). RSA migration of total knee replacements. *Acta Orthop, 89*(3), 320-328. doi:10.1080/17453674.2018.1443635

Pijls, B. G., Valstar, E. R., Kaptein, B. L., & Nelissen, R. G. (2012). 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, 94*(10), 1366-1371. doi:10.1302/0301-620x.94b10.28858

Pijls, B. G., Valstar, E. R., Nouta, K. A., Plevier, J. W., Fiocco, M., Middeldorp, S., & Nelissen, R. G. (2012). Early migration of tibial components is associated with late revision: a systematic review and meta-analysis of 21,000 knee arthroplasties. *Acta Orthop, 83*(6), 614-624. doi:10.3109/17453674.2012.747052

Price, A. J., Short, A., Kellett, C., Beard, D., Gill, H., Pandit, H., . . . Murray, D. W. (2005). Ten-year in vivo wear measurement of a fully congruent mobile bearing unicompartmental knee arthroplasty. *J Bone Joint Surg Br, 87*(11), 1493-1497. doi:10.1302/0301-620X.87B11.16325

Regner, L. R., Carlsson, L. V., Karrholm, J. N., Hansson, T. H., Herberts, P. G., & Swanpalmer, J. (1999). Bone mineral and migratory patterns in uncemented total knee arthroplasties: a randomized 5-year follow-up study of 38 knees. *Acta Orthop Scand, 70*(6), 603-608.

Richmond, B. I., Hadlow, S. V., Lynskey, T. G., Walker, C. G., & Munro, J. T. (2013). Proximal tibial bone density is preserved after unicompartmental knee arthroplasty. *Clin Orthop Relat Res, 471*(5), 1661-1669. doi:10.1007/s11999-013-2784-2

Riddle, D. L., Jiranek, W. A., & Hull, J. R. (2013). Validity and reliability of radiographic knee osteoarthritis measures by arthroplasty surgeons. *Orthopedics, 36*(1), 25-32. doi:10.3928/01477447-20121217-14

Rothwell, A. G., Hooper, G. J., Hobbs, A., & Frampton, C. M. (2010). An analysis of the Oxford hip and knee scores and their relationship to early joint revision in the New Zealand Joint Registry. *J Bone Joint Surg Br, 92*(3), 413-418. doi:10.1302/0301-620X.92B3.22913

Ryd, L., Albrektsson, B. E., Carlsson, L., Dansgard, F., Herberts, P., Lindstrand, A., . . . Toksvig-Larsen, S. (1995). Roentgen stereophotogrammetric analysis as a predictor of mechanical loosening of knee prostheses. *J Bone Joint Surg Br, 77*(3), 377-383.

Saari, T., Uvehammer, J., Carlsson, L., Regner, L., & Karrholm, J. (2007). Joint area constraint had no influence on bone loss in proximal tibia 5 years after total knee replacement. *J Orthop Res, 25*(6), 798-803. doi:10.1002/jor.20358

Schiphof, D., de Klerk, B. M., Koes, B. W., & Bierma-Zeinstra, S. (2008). Good reliability, questionable validity of 25 different classification criteria of knee osteoarthritis: a systematic appraisal. *J Clin Epidemiol, 61*(12), 1205-1215. doi:10.1016/j.jclinepi.2008.04.003

Scott, C. E., Wade, F. A., Bhattacharya, R., MacDonald, D., Pankaj, P., & Nutton, R. W. (2016). Changes in Bone Density in Metal-Backed and All-Polyethylene Medial Unicompartmental Knee Arthroplasty. *J Arthroplasty, 31*(3), 702-709. doi:10.1016/j.arth.2015.09.046

Scott, W. N. (2017). Insall & Scott Surgery of the Knee, Sixth Edition. In W. N. Scott (Ed.), (pp. 992-997): Elsevier. Retrieved from https://www.statsbiblioteket.dk/au/#/search?query=recordID%3A%22summon_FETCH-dawson_primary_97803234785403%22.

Selvik, G. (1989). Roentgen stereophotogrammetry. A method for the study of the kinematics of the skeletal system. *Acta Orthop Scand Suppl, 232*, 1-51.

Sihvonen, R., Paavola, M., Malmivaara, A., Itala, A., Joukainen, A., Nurmi, H., . . . Jarvinen, T. L. (2013). Arthroscopic partial meniscectomy versus sham surgery for a degenerative meniscal tear. *N Engl J Med, 369*(26), 2515-2524. doi:10.1056/NEJMoa1305189

Sim, J., & Wright, C. C. (2005). The kappa statistic in reliability studies: Use, interpretation, and sample size requirements. *Physical Therapy, 85*(3), 257-268.

Simpson, D. J., Price, A. J., Gulati, A., Murray, D. W., & Gill, H. S. (2009). Elevated proximal tibial strains following unicompartmental knee replacement--a possible cause of pain. *Med Eng Phys, 31*(7), 752-757. doi:10.1016/j.medengphy.2009.02.004

Skou, S. T., & Roos, E. M. (2017). Good Life with osteoArthritis in Denmark (GLA:D): evidence-based education and supervised neuromuscular exercise delivered by certified physiotherapists nationwide. *BMC Musculoskelet Disord, 18*(1), 72. doi:10.1186/s12891-017-1439-y

Soininvaara, T. A., Harju, K. A., Miettinen, H. J., & Kroger, H. P. (2013). Periprosthetic bone mineral density changes after unicondylar knee arthroplasty. *Knee, 20*(2), 120-127. doi:10.1016/j.knee.2012.10.004

Stilling, M., Madsen, F., Odgaard, A., Romer, L., Andersen, N. T., Rahbek, O., & Soballe, K. (2011). Superior fixation of pegged trabecular metal over screw-fixed pegged porous titanium fiber mesh: a randomized clinical RSA study on cementless tibial components. *Acta Orthop, 82*(2), 177-186. doi:10.3109/17453674.2011.566139

Stilling, M., Soballe, K., Larsen, K., Andersen, N. T., & Rahbek, O. (2010). Knee flexion influences periprosthetic BMD measurement in the tibia. Suggestions for a reproducible clinical scan protocol. *Acta Orthop, 81*(4), 463-470. doi:10.3109/17453674.2010.501746

Thanner, J., Freij-larsson, C., Kärrholm, J., Malchau, H., & Wesslén, B. (1995). Evaluation of Boneloc®: Chemical and mechanical properties, and a randomized clinical study of 30 total hip arthroplasties. *Acta Orthop Scand, 66*(3), 207-214. doi:10.3109/17453679508995525

Thoma, A., Farrokhyar, F., McKnight, L., & Bhandari, M. (2010). Practical tips for surgical research: how to optimize patient recruitment. *Canadian journal of surgery. Journal canadien de chirurgie, 53*(3), 205-210.

Tjornild, M., Soballe, K., Hansen, P. M., Holm, C., & Stilling, M. (2014). Mobile- vs. fixed-bearing total knee replacement. *Acta Orthop*, 1-7. doi:10.3109/17453674.2014.968476

Tjornild, M., Soballe, K., Hansen, P. M., Holm, C., & Stilling, M. (2015). Mobile- vs. fixed-bearing total knee replacement. *Acta Orthop, 86*(2), 208-214. doi:10.3109/17453674.2014.968476

Tuncer, M., Patel, R., Cobb, J. P., Hansen, U. N., & Amis, A. A. (2015). Variable bone mineral density reductions post-unicompartmental knee arthroplasty. *Knee Surg Sports Traumatol Arthrosc, 23*(8), 2230-2236. doi:10.1007/s00167-014-3014-5

Twisk, J. W. R. (2003). *Applied Longitudinal Data Analysis for Epidemiology, A pratical guide*. Cambridge, UK: Cambridge University Press.

Valstar, E. R., de Jong, F. W., Vrooman, H. A., Rozing, P. M., & Reiber, J. H. C. (2001). Model-based Roentgen stereophotogrammetry of orthopaedic implants. *J Biomech, 34*(6), 715-722. doi:http://dx.doi.org/10.1016/S0021-9290(01)00028-8

Valstar, E. R., Gill, R., Ryd, L., Flivik, G., Borlin, N., & Karrholm, J. (2005). Guidelines for standardization of radiostereometry (RSA) of implants. *Acta Orthop, 76*(4), 563-572. doi:10.1080/17453670510041574

van Hamersveld, K. T., Marang-van de Mheen, P. J., Koster, L. A., Nelissen, R., Toksvig-Larsen, S., & Kaptein, B. L. (2019). Marker-based versus model-based radiostereometric analysis of total knee arthroplasty migration: a reanalysis with comparable mean outcomes despite distinct types of measurement error. *Acta Orthop*, 1-9. doi:10.1080/17453674.2019.1605692

Waldstein, W., Monsef, J. B., Buckup, J., & Boettner, F. (2013). The value of valgus stress radiographs in the workup for medial unicompartmental arthritis. *Clin Orthop Relat Res, 471*(12), 3998-4003. doi:10.1007/s11999-013-3212-3

Walter, S. D., Eliasziw, M., & Donner, A. (1998). Sample size and optimal designs for reliability studies. *Stat Med, 17*(1), 101-110.

Ware, J., Snow, K., Kosinski, M., & Barbara, G. (1993). *SF36 Health Survey: Manual and Interpretation Guide* (Vol. 30).

Warming, L., Hassager, C., & Christiansen, C. (2002). Changes in bone mineral density with age in men and women: a longitudinal study. *Osteoporos Int, 13*(2), 105-112. doi:10.1007/s001980200001

Weidow, J., Cederlund, C. G., Ranstam, J., & Karrholm, J. (2006). Ahlback grading of osteoarthritis of the knee: poor reproducibility and validity based on visual inspection of the joint. *Acta Orthop, 77*(2), 262-266. doi:10.1080/17453670610046000

White, S. H., Ludkowski, P. F., & Goodfellow, J. W. (1991). Anteromedial osteoarthritis of the knee. *J Bone Joint Surg Br, 73*(4), 582-586.

Winther, N., Jensen, C., Petersen, M., Lind, T., Schroder, H., & Petersen, M. (2016). Changes in bone mineral density of the proximal tibia after uncemented total knee arthroplasty. A prospective randomized study. *Int Orthop, 40*(2), 285-294. doi:10.1007/s00264-015-2852-1

Appendices

Appendix 1 Copyright Agreement Paper I

SPRINGER NATURE LICENSE TERMS AND CONDITIONS

May 20, 2019

This Agreement between Egevænget 11 ("You") and Springer Nature ("Springer Nature") consists of your license details and the terms and conditions provided by Springer Nature and Copyright Clearance Center.

License Number	4534770704267
License date	Feb 23, 2019
Licensed Content Publisher	Springer Nature
Licensed Content Publication	Skeletal Radiology
Licensed Content Title	The lateral joint space width can be measured reliably with Telos valgus stress radiography in medial knee osteoarthritis
Licensed Content Author	Daan Koppens, Ole Gade Sørensen, Stig Munk et al
Licensed Content Date	Jan 1, 2018
Type of Use	Thesis/Dissertation
Requestor type	academic/university or research institute
Format	print and electronic
Portion	full article/chapter
Will you be translating?	no
Circulation/distribution	<501
Author of this Springer Nature content	yes
Title	PHD Thesis on medial unbicompartmental knee arthroplasty
Institution name	University of Aarhus
Expected presentation date	Oct 2019
Requestor Location	Egevænget 11 Egevænget 11 Hammerum, 7400 Denmark Attn: Egevænget 11
Billing Type	Invoice
Billing Address	Egevænget 11 Egevænget 11 Hammerum, Denmark 7400 Attn: Egevænget 11
Total	**0.00 USD**
Terms and Conditions	

Springer Nature Terms and Conditions for RightsLink Permissions

Springer Nature Customer Service Centre GmbH (the Licensor) hereby grants you a non-exclusive, world-wide licence to reproduce the material and for the purpose and requirements specified in the attached copy of your order form, and for no other use, subject to the conditions below:

1. The Licensor warrants that it has, to the best of its knowledge, the rights to license reuse of this material. However, you should ensure that the material you are requesting is original to the Licensor and does not carry the copyright of another entity (as credited in the published version).

   If the credit line on any part of the material you have requested indicates that it was reprinted or adapted with permission

Appendix 2 Copyright Agreement Paper II

SPRINGER NATURE LICENSE TERMS AND CONDITIONS

May 20, 2019

This Agreement between Egevænget 11 ("You") and Springer Nature ("Springer Nature") consists of your license details and the terms and conditions provided by Springer Nature and Copyright Clearance Center.

License Number	4534070932987
License date	Feb 22, 2019
Licensed Content Publisher	Springer Nature
Licensed Content Publication	Knee Surgery, Sports Traumatology, Arthroscopy
Licensed Content Title	Low implant migration of the SIGMA® medial unicompartmental knee arthroplasty
Licensed Content Author	Daan Koppens, Maiken Stilling, Stig Munk et al
Licensed Content Date	Jan 1, 2017
Licensed Content Volume	26
Licensed Content Issue	6
Type of Use	Thesis/Dissertation
Requestor type	academic/university or research institute
Format	print and electronic
Portion	full article/chapter
Will you be translating?	no
Circulation/distribution	<501
Author of this Springer Nature content	yes
Title	PHD Thesis on medial unbicompartmental knee arthroplasty
Institution name	University of Aarhus
Expected presentation date	Oct 2019
Requestor Location	Egevænget 11 Egevænget 11 Hammerum, 7400 Denmark Attn: Egevænget 11
Billing Type	Invoice
Billing Address	Egevænget 11 Egevænget 11 Hammerum, Denmark 7400 Attn: Egevænget 11
Total	**0.00 USD**
Terms and Conditions	

Springer Nature Terms and Conditions for RightsLink Permissions

Springer Nature Customer Service Centre GmbH (the Licensor) hereby grants you a non-exclusive, world-wide licence to reproduce the material and for the purpose and requirements specified in the attached copy of your order form, and for no other use, subject to the conditions below:

1. The Licensor warrants that it has, to the best of its knowledge, the rights to license reuse of this material. However, you should ensure that the material you are requesting is original to the Licensor and does not carry the copyright of another entity (as credited in the published version).

Appendix 3 Co-authorship declaration Paper I-IV