Computer navigation and revision causes in knee arthroplasty

Gro Sævik Dyrhovden

Thesis for the Degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
2019

UNIVERSITY OF BERGEN

Computer navigation and revision causes in knee arthroplasty

Gro Sævik Dyrhovden

Thesis for the Degree of Philosophiae Doctor (PhD)
at the University of Bergen

Date of defence: 19.12.2019

Year: 2019

Title: Computer navigation and revision causes in knee arthroplasty

Name: Gro Sævik Dyrhovden

Print: Skipnes Kommunikasjon / University of Bergen

Contents

Scientific environment

This work was done at the Norwegian Arthroplasty Register, Department of Orthopedic Surgery, Haukeland University Hospital, Bergen, Norway.

Øystein Gøthesen (UiB) was the main supervisor while Ove Furnes, Geir Hallan and Anne Marie Fenstad were co-supervisors. Scientific support was also given by the staff at the Norwegian Arthroplasty Register and the Department of Orthopedic Surgery, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway.

The project was financed by the Western Norway Regional Health Authority (Helse-Vest) by a 3-year PhD fellowship.

This thesis is a part of the PhD program at the Department of Clinical Medicine (K1), Faculty of medicine and dentistry, University of Bergen. It was connected to the Postgraduate School of Clinical Medical Research, University of Bergen.

Acknowledgements

I am truly grateful for having the opportunity to write this thesis. Many people have worked together with me on this project, and I am grateful to have so many clever and helpful people around during my time as a PhD candidate.

To my main supervisor Øystein Gøthesen: Working with you has been a pleasure! You have taught me a lot about knee arthroplasty and research, and you managed to keep a good balance between support and challenges. A number of times, you widened my horizon by seeing things from different perspectives and we have had many good discussions. I hope that our discussions will continue in future projects!

Co-supervisor Ove Furnes: Your sky-high knowledge, optimism and passion for arthroplasty research inspires me to put some extra effort in my work. You are generous with positive feedback and your time, even when your schedule is overloaded. I am thankful for having the opportunity to work with you!

Co-supervisor Geir Hallan: I have enjoyed your reflections and constructive comments, which always stimulates to further improvement. Your research competence and thoroughness is admirable. You have my deepest respects!

Co-supervisor Anne Marie Fenstad: You have taught me so much about practical use of statistics and how to critically evaluate my own and other's research. You have patiently answered my endless questions and thanks to you, I have a deeper understanding of numbers in research. I really hope that we can continue working together in the years to come!

To my co-authors Stein Håkon Låstad Lygre, Mona Badawy, Gunnar Petursson, Kristin Haugan and Kjell G Nilsson: Thank you for your important contributions and valuable comments during the studies included in this thesis. This work would not have been possible without you.

To my colleagues at the Norwegian Arthroplasty Register: From the first time I showed up at the register as a student, you made me feel welcome. You are all very

clever at your work and you have helped me with countless practical issues. I also appreciate your high tolerance for the babies and the large pram I have brought to the office repeatedly during my maternity leaves. Your smiles and warmth can clearly cheer up a rough day, and it has been a great joy to get to know all of you. A special thanks to my fellow PhD candidate Tone Nystad for our many good discussions, hours of statistics colloquium (often combined with babysitting), and for reading my thesis.

I would like to thank the Western Norway Regional Health Authority for my 3-year PhD fellowship grant.

I am thankful for having a family that supported and encouraged through this project. I specially thank my parents and role models Margaret and Inge for always believing in me and for encouraging me to find a research project already when I was a student. Most importantly, you also taught me to put my faith and trust in Jesus Christ through all of life's joys and difficulties.

The greatest thanks go to my dear husband and best friend Ruben; your patience, love and respect means more than words can express. Last, but not least, I thank our beloved children Samuel (6), Rebekka Sofine (2) and Maria (10 months) for your catching laughter, long-lasting hugs and unconditional love. You complete my life.

Bergen, 03.09.2019

Gro Sævik Dyrhovden

Abbreviations

ADL	Activities of Daily Living
AOANJRR	Australian Orthopaedic Association National Joint Replacement Registry
ASA	The American Society of Anesthesiologists (ASA) Physical Status classification system
BMI	Body Mass Index
CAS	Computer Assisted Surgery
CI	95% Confidence Interval
CN	Condition Number
CON	Conventional technique
CT	Computed Tomography
DAG	Directed Acyclic Graph
EQ-5D	Health questionnaire developed by the EuroQol group
KOOS	Knee injury and Osteoarthritis Outcome Score
KSS	Knee Society Score
ME	Mean error of rigid body fitting
MIC	Minimal Important Change
MRI	Magnetic Resonance Imaging
MTPM	Maximum total point motion
NAR	Norwegian Arthroplasty Register
NNT	Number needed to treat
NPR	Norwegian Patient Registry
NZJR	New Zealand Joint Registry
OMERACT-OARSI	Outcome Measures in Rheumatology – Osteoarthritis Research Society International
PASS	Patient acceptable symptom state
PH	The proportional hazard assumption
PRO	Patient Reported Outcome

PROM	Patient Reported Outcome Measure
QOL	knee-related Quality of Life
RCT	Randomized Controlled Trial
RR	Relative Risk
RSA	Radiostereometric Analysis
SD	Standard deviation
SKAR	Swedish Knee Arthroplasty Register
SportRec	Function in sport and recreation
TKA	Total Knee Arthroplasty
UKA	Unicompartmental knee arthroplasty
VAS	Visual Analogue Scale
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

Abstract

Introduction

There is an increasing demand for total knee arthroplasty (TKA) and unicompartmental knee arthroplasty (UKA), and there is also an increasing number of revisions. To increase quality and patient satisfaction, new implants and techniques are developed. Computer assisted surgery (CAS) was introduced to TKA to improve implant position and alignment of the leg, which theoretically improves knee function and implant survival. The objective of this thesis was to compare CAS to conventional knee arthroplasty (CON) in implant survival, radiological and patient-reported outcomes (PROs). It also analyzes time trends in implant survival and revision causes for TKA and UKA, to evaluate the success of previous developments and to assess the need for further improvement.

Methods

The thesis is based on two registry studies and one follow-up study from a randomized controlled trial (RCT).

Paper I used the Norwegian Arthroplasty Register (NAR) to compare CAS and CON in TKA with respect to implant survival, relative risk of revision and revision causes at up to 8 years of follow-up. In paper II, two 11-year periods of TKAs and UKAs (period 1: 1994-2004; period 2: 2005-2015) from the NAR were compared regarding survivorship and risk of revision due to different revision causes in the latest time period relative to the first. Paper III is a 5-year follow-up from an RCT with 192 patients undergoing TKA with either CAS or CON. The outcomes were migration of the tibial component measured by radiostereometric analysis (RSA) in addition to radiolucent lines, PROs and the proportion of responders.

Results

Paper I showed no significant difference in survival or Cox relative risk of revision (RR) for CAS relative to CON (RR=0.8, CI: 0.7-1.0), but CAS had significantly fewer revisions due to malalignment (RR=0.5, CI: 0.3-0.9). Paper II showed that 10 years implant survival was improved for TKA from 91% in period 1 to 94% in period

2 ($p<0.001$), and there was an increasing risk of early revisions for infection. For UKA, 10 years survival was 80% in period 1 and 81% in period 2 ($p=0.3$), and the risk of revision caused by progression of osteoarthritis was increased. In paper III, CAS and CON did not differ in implant migration or the occurrence of radiolucent lines. Patients operated with CAS and CON had similar improvement in PROs from preoperative to 5 years. The CAS group had significantly more patients with a high improvement in pain scores ($p=0.04$).

Conclusions

The last two decades, implant survival has improved for TKA, but not for UKA. Patients operated with CAS and CON had similar migration of the tibial component, but CAS had better pain relief 5 years postoperatively. There was no statistically significant difference in survival for CAS compared to CON at 8 years.

List of publications

This thesis is based on the following papers:

Paper I

Dyrhovden GS, Fenstad AM, Furnes O, Gøthesen Ø. *Survivorship and relative risk of revision in computer-navigated versus conventional total knee replacement at 8-year follow-up.* Acta Orthop 2016; 87(6): 592-599.

URL: https://www.tandfonline.com/doi/full/10.1080/17453674.2016.1244884

Paper II

Dyrhovden GS, Lygre SHL, Badawy M, Gøthesen Ø, Furnes O. *Have the Causes of Revision for Total and Unicompartmental Knee Arthroplasties Changed During the Past Two Decades?* Clin Orthop Relat Res 2017; 475(7): 1874-1886.

URL:
https://journals.lww.com/clinorthop/Fulltext/2017/07000/Have_the_Causes_of_Revision_for_Total_and.24.aspx

Paper III

Dyrhovden GS, Furnes O, Petursson G, Fenstad AM, Lygre SHL, Nilsson KG, Haugan K, Hallan G, Gøthesen Ø. *Radiostereometric analysis and patient-reported outcomes for computer assisted and conventional total knee arthroplasty – 5 years follow-up from a randomized trial.*

Submitted 2019.

Introduction

1. Background

Knee osteoarthritis is a common disease in Norway and worldwide [1-4]. Osteoarthritis is a degenerative disease of the knee joint in which the cartilage of the knee is damaged. This leads to loss of cartilage, a narrow joint space and bone spurs. In end-stage osteoarthritis, there is a complete loss of cartilage in one or more compartments of the knee joint. In these cases, the patient often experiences severe knee pain, stiffness and reduced knee function. The treatment of osteoarthritis depends on patient age and the severity of the osteoarthritis. At an early stage, osteoarthritis is treated by non-surgical treatment, such as education, exercise, weight reduction, physiotherapy, and analgesic drugs. Patients with severe knee osteoarthritis can be assessed for surgical treatment with osteotomy or knee arthroplasty, which is a common and effective treatment against end-stage osteoarthritis [4, 5].

In 2018, 6905 primary knee arthroplasties were performed in Norway, which has increased from around 1000 annual procedures in 1994. The proportion of unicompartmental knee arthroplasty (UKA) has increased to 14.5% in 2018, from 9.4% in 2010 [3]. The lifetime risk of having a total knee arthroplasty in Norway in 2013 was 9.7% for females and 5.8% for males, and this risk has increased from 6.6% and 2.8% respectively in 2003 [6]. In some other developed countries (i.e. Finland and Australia) the lifetime risk for receiving a total knee arthroplasty (TKA) is twice as high as in Norway [6]. The rate of UKAs in the United States increased during 2002 to 2011, and a high proportion of the operations were performed in patients <65 years [7].

Using implant revision as the end point, TKA is a successful treatment against end stage knee osteoarthritis. The NAR reports in 2019 that 10 years survival is 94.6% for TKA. The most common unicompartmental implant in 1994-2013, the Oxford Uni (III), had a 10 years survival of 84.2% [3]. A Norwegian study found 95.5% 10 years survival for fixed bearing TKAs operated in Norway in 2003-2014 [8]. In Australia,

the cumulative revision rate is 5.3% at 10 years for patients with osteoarthritis [9], whereas the rate is around 4% in the UK and Sweden [10, 11]. For UKAs, 10 years cumulative revision rate is 15% in Australia [9], 11% in England and Wales [10].

In the United States and in England and Wales, the need for knee arthroplasties and revision knee arthroplasties is expected to increase further in the future [12, 13]. Revision knee arthroplasties are costly to patients, hospitals and society [13-15]. Compared to primary procedures, the patient satisfaction is lower and the rates of complications and re-revisions are higher [3, 16, 17]. To meet the increasing demand for knee arthroplasties, implants and surgical techniques are continuously developing. The effects of new implants and technology on survival, revision causes and the patient's pain and function should be studied, and a close follow-up on trends over time is needed.

Despite a high rate of revision-free primary TKAs, many patients experience dissatisfaction, pain or poor function following knee arthroplasty. In a study by Bourne at al., 72-86% of the patients were satisfied with their pain relief and 70-84% were satisfied with their function 1 year after TKA. Lindberg et al. found that 1 in 5 patients had no improvement in pain-related interference with walking 12 months after TKA [18]. Additional studies report high proportions of patients with significant pain or dissatisfaction after TKA [19-22]. These studies show that there is still a need for improvement in knee arthroplasty.

2. Alignment in total knee arthroplasty

One of the key factors for a successful TKA is to achieve a good alignment of the implant and hence the limb. Implant malalignment is a frequent reason for revision [23]. Previous studies have found that malaligned implants have inferior implant survival [24-26] and poorer outcomes for pain and function [27, 28]. Many of these studies use a neutral mechanical axis ±3° as target for optimal alignment of the extremity. In a mechanically aligned TKA, the femoral and tibial components are positioned perpendicular to the mechanical axis of each bone. This leads to a neutral

hip-knee-ankle angle of the limb in static weight-bearing conditions. In a knee with a neutral mechanical axis, a straight line from the center of the femoral head to the center of talus passes through the center of the knee. A neutral mechanical axis has been considered by most surgeons as the optimal alignment and is often referred to as *mechanical alignment*. Implants with more than ±3° of malalignment (varus or valgus, see figure 1) are often termed as outliers.

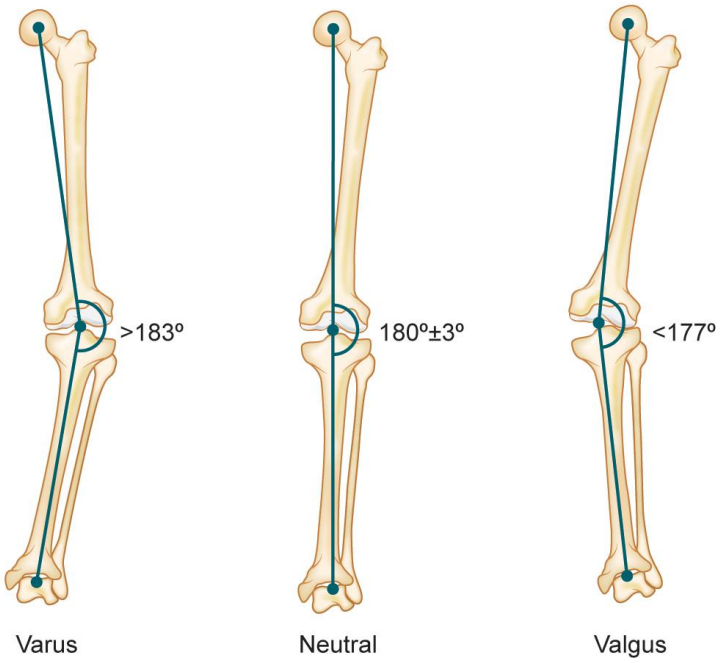


Figure 1. Illustration of knees with varus, neutral and valgus alignments (Elsevier illustration services, all rights reserved).

In the general population, it is not unusual to have a malaligned knee, despite the lack of symptoms. Bellemans et al. found that 32% of men and 17% of women aged 20 to 27 had varus alignment [29]. Others may have developed malalignment due to many years of osteoarthritis. A study of patients with preoperative varus deformity showed that these patients had a higher improvement in Knee Society Score after TKA if the postoperative alignment was left in mild varus (3-6°) compared to patients with postoperative neutral alignment or severe valgus (>6°) [30]. These studies indicate

that correction to a neutral mechanical axis is not necessarily the optimal situation for all patients.

During the last decade, it has been debated whether a neutral mechanical axis is the correct alignment for all patients, and some researchers claim that *kinematic alignment* is a better alternative for reducing pain, stiffness and instability [31-33]. With kinematic alignment, the surgeon attempts to restore the patient's pre-arthritic alignment in order to improve functional outcomes. In contrast to the mechanically aligned TKA, the native knee has an articular surface with the tibia in 3° varus and the femur in 2-3° valgus relative to the mechanical axis [29]. In patients with deformity, soft tissues and ligaments are adapted to the alignment of the patient's knee. If the mechanical axis is corrected in a TKA procedure, soft tissue releases are often needed, and some surgeons and researchers worry that a full correction of the original deformity may lead to instability and poor function [31, 34, 35]. A randomized controlled trial by Dosset et al. showed superior flexion, Knee Society score and patient-reported outcomes for kinematically aligned TKA compared to mechanically aligned TKA [36]. However, Young et al. found no difference in patient-reported outcomes between kinematically and mechanically aligned TKAs at two years [37]. The issue of alignment is continuously debated, but mechanical axis is still the gold standard for most surgeons [38, 39].

3. Computer navigation in total knee arthroplasty

Navigation in surgery was developed for neurosurgery in the 1990s using computed tomography (CT) and magnetic resonance imaging (MRI) based methods ("image-based" navigation). The goal was to allow the surgeon to perform surgical procedures safer and less invasive [40]. Later, computer navigation was introduced in orthopedic surgery to make joint replacement more accurate and reproducible. In TKA, the main purpose of navigation was to improve positioning of the prosthesis components and the mechanical axis of the knee [41]. Development of image free navigation ("model-based" navigation) made the procedure simpler and the patients did not need additional radiation exposure from CT imaging. The first *in vitro* image-free

navigated TKA was performed in 1997 by Saragaglia and Picard, and an early study by the same surgeons showed that the method had reliable results [42, 43]. The following years, Computer Assisted Surgery (CAS) was further developed, and many studies had promising results regarding improvement in implant alignment [44-47].

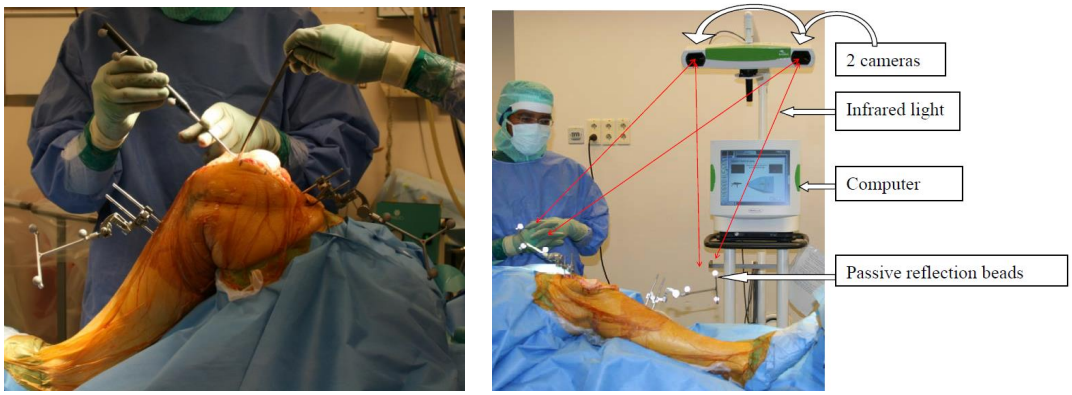


Figure 2. Photos from a CAS operation where markers with reflective beads are fixed to the femur and tibia (left). The computer is shown to the right. Photo: Øystein Gøthesen

The CAS technology uses computer software and specific anatomical landmarks to create a three-dimensional system that is used to guide the surgeon to the optimal component positioning. During the operation, two cameras emit and register infrared light, which is reflected by passive reflective beads that are fixed to the femur and tibia (rigid bodies). A marker, also with reflective beads, is used to mark specific anatomical landmarks. Marks on the tibial plateau and on the ankle are used to calculate the center of talus and to create the tibial axis. To find the femoral axis, the leg with reflection beads is rotated in circles. The computer software then calculates the center of the femoral head by using the formula of a cone. Information of the patient's anatomy is used by the computer to determine the position of the cutting blocks, the size and rotation of the prosthesis components and ligament balancing. The accuracy of the system is within 1 mm and ±1° of target for frontal and sagittal alignment [48, 49].

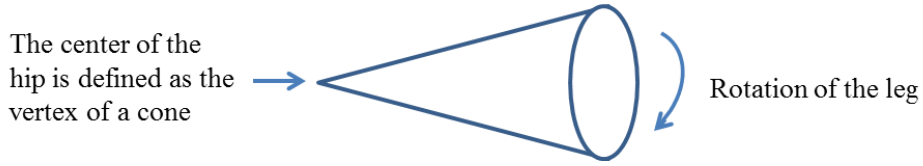


Figure 3. By rotating the leg, the femur forms a cone. The computer uses this information to calculate the center of the hip.

In Norway, the use of CAS has been registered in the Norwegian Arthroplasty Register since 2005. During 2008-2010, the use of CAS increased to almost 20% of the procedures. Since 2011, CAS has been used in approximately 10% of TKAs [3]. This is a high proportion compared to the use of CAS in Sweden (0.1% in 2015) [11]. In Australia, however, 30.8% of primary TKAs were inserted using CAS in 2016, which is an increase from 2.3% in 2003 [9]. The variation of its use illustrates that the effect of this tool is still inconclusive.

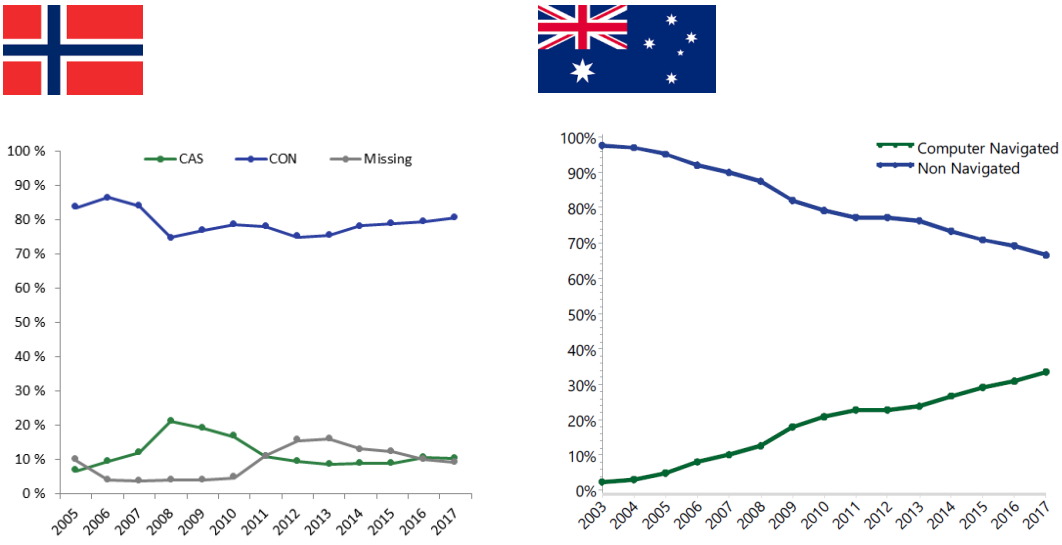


Figure 4. The use of CAS in Norway (left) [3] and in Australia (right). The curve to the right is from the AOANJRR annual report 2018 [9].

The role of CAS has been debated [42, 50]. Randomized trials and meta-analyses have concluded that CAS leads to a more accurate alignment, but the results are inconclusive regarding differences in PROs or implant survivorship [51-56]. Although mechanical alignment is preferred by many surgeons, it is not clear if CAS is the best method for achieving that target. Patient-specific instruments and patient-specific implants based on CT or MRI scans have also been used to improve alignment and kinematics in TKA [57-59]. However, there is no evidence to suggest that one of these methods is superior to the other in this respect [60-65].

CAS leads to higher costs for the clinics and a prolonged operative time for most surgeons. The effects on PROs and implant survivorship are also uncertain. This may be the reason that CAS is not widely used today, two decades after its introduction. This PhD project contributes to an increase in the knowledge on radiological outcomes, longevity of the implant and the patient's pain, function and quality of life in TKAs operated with CAS compared to conventional technique (CON).

4. Revision causes

Furthermore, this thesis addresses the causes of revisions in knee arthroplasties as reported to the NAR. Theoretically, a more accurate positioning of the knee implant, as with CAS, may result in a better longevity of the knee arthroplasty. It is not known what reasons for revision are lowered by an improved positioning. Consequently, a registry study investigating the most common revision causes of knee replacements was advocated. The reasons for revision may be different for TKAs and UKAs, and to address the failure mechanisms in order to avoid them, a comparative analysis was performed.

According to reports from large joint registries worldwide, infection and aseptic loosening are the most common revision causes for TKA [3, 9-11, 66, 67]. For UKA, most revisions are caused by aseptic loosening, progression of osteoarthritis or unexplained pain [3, 9, 11, 66]. Additional single- or multicentre studies have shown a high and increasing number of early revisions for TKA and UKA, and infection was

one of the major causes of early TKA revisions [23, 68, 69]. Infection is a serious complication after knee arthroplasty that often requires multiple revision procedures, and the costs are high [70].

A previous study from the NAR showed that the risk of aseptic loosening varied among different prosthesis brands, and that the risk of loosening was highest for the tibial component for most of the included implant models [71]. In a study by Lee et al., tibial loosening was also more common than femoral loosening, and >3° malalignment of the femoral component was associated with tibial loosening [72]. Instability is a common cause of both early and late revisions [73, 74]. Instability can arise from various reasons, such as aseptic loosening, malalignment of components, inaccurate size of components and polyethylene wear. Female gender or a great preoperative malalignment may have an increased risk of instability [75, 76], but surgical technique, ligament balancing and implant selection also play an important role. Polyethylene wear is most often seen in late revisions, accounting for up to 48% of revisions >15 years after primary TKA [23]. It is also found a decline in revisions caused by polyethylene wear compared to previous studies [69, 74].

Over the last decades, implants and surgical techniques have developed, and new technologies like CAS and patient-specific instruments and implants are introduced to improve results of knee arthroplasty. It is interesting to explore whether these changes over time affect the causes of revision and the occurrence of early and late revisions. Due to the increasing risk of revisions in general and the tendency of increasing early infections, it is important to investigate the reasons for revision in large joint registers, that have a wide range of surgeon experience and large volumes, leading to a high external validity.

5. Unicompartmental knee arthroplasty (UKA)

UKA can be used if the patient has an isolated medial or lateral osteoarthritis. In addition, the medial collateral ligament and the anterior and posterior cruciate ligaments must be intact and functional. Compared to TKA, patients with UKA have

a lower risk of postoperative complications, better forgotten joint score and marginally better patient-reported functional outcomes, but a higher revision rate [77-80]. A systematic review comparing UKA and TKA found that the two implant types had similar outcomes in PROMs regarding pain, but UKA had better functional PROM scores than TKA [78]. A different study found that patient satisfaction is not remarkably different for TKA and UKA [81]. Selecting appropriate patients is difficult and operating UKA is a technically demanding procedure, and a low hospital volume is associated with higher risk of revision [82-84].

6. Radiostereometric analysis (RSA) and implant loosening

Radiostereometric analysis is a precise method for the measurement of three-dimensional migration of an implant relative to the bone and polyethylene wear. It was introduced in 1974 by Gunnar Selvik and a Swedish research group [85] and has been widely used in research for the assessment of orthopedic joint replacements. It has been shown, also for TKA, that early implant migration corresponds to the risk of loosening at mid-term [86, 87]. The method can determine a relative motion of approximately 0.2 mm and 0.2-1.2° [87]. Thus, few patients are needed to achieve a high statistical power. In 2005, Valstar et al. published guidelines for standardization of RSA studies, including a checklist for presentation of RSA data [88].

In the existing literature, few RSA studies are linking migration to alignment. In a study by van Hamersveld et al., varus malalignment of the limb led to higher tibial migration at 5 years follow-up [89]. Teeter et al. found no correlation between leg alignment and migration at 10 years, but increasing varus alignment of the tibial component was associated with increasing migration [90]. Van Strien et al. compared RSA in CT-free and CT-based CAS compared to conventional TKA. This study found a higher caudal-cranial migration in the conventional group compared to CT-free and CT-based CAS, but there was no difference in the number of outliers among the groups [91].

A systematic review of RSA in TKA found an association between migration at 6 months and late revision [92]. On the other hand, Molt et al. claimed that long-term RSA is needed to avoid overestimation of late revisions [93]. To confirm the association between migration and revision, studies with repeated RSA over time is needed.

7. Patient reported outcomes (PROs)

Definition

A patient reported outcome (PRO) is defined by the U.S. Food and Drug Administration: "*A PRO is any report of the status of a patient's health condition that comes directly from the patient. The outcome can be measured in absolute terms (…) or as a change from a previous measure.*" [94].

Why use PROs?

Survivorship and alignment are important end points in the evaluation of knee arthroplasty, as a measure of success or failure of the implant. However, these outcomes give no information about the patient's function, level of pain or symptoms, which is highly important for the patients that undergo knee arthroplasty. The patient's opinion is important in a patient-centered approach to health care [95]. Patients and surgeons may have different expectations to outcomes of the operation, and the patient's subjective experience is important when considering whether the treatment was successful or not.

Different scoring systems are used to evaluate functional outcomes and symptoms after TKA. The scores can be filled out by health workers or by the patient. Health personnel administered scores give a more objective view of the patient's health condition, but are not suitable for assessing the patient's subjective experience of the disease/treatment, such as pain, satisfaction and health related quality of life. For this purpose, the score must be filled out by the patient, without influence of health workers, caregivers or others.

Patient-administered questionnaires are often referred to as a PRO instrument or Patient Reported Outcome Measure (PROM) [94]. Different PROMs are used for measuring general health status (generic PROMs) or the status of function or symptoms regarding a certain condition (disease-specific PROMs). Generic PROMs focus on the global health status of the patient, like self-care and mobility. It can be used across different populations and diagnoses, and thus compare the health status of a knee arthroplasty patient to patients with multiple sclerosis, depression or the general population in a certain age group. Disease-specific PROMs contain more detailed questions that are relevant for a certain condition. Compared to generic PROMs, these measures are often more sensitive to small changes that may be important to patients and clinicians [96]. For example, the Knee injury and Osteoarthritis Outcome Score (KOOS) questionnaire contains questions relevant to patients with osteoarthritis or patients with knee arthroplasty; most attention is given to the knee pain, stiffness and tasks that challenge the knee (i.e. ascending and descending stairs).

Interpretation of PROs

Interpretation of PROs can be challenging. Different PROM scores may display results on different scales, and it is not straightforward to find out what level of improvement that represents a good outcome or a clinically relevant change. The clinically relevant change is often termed the Minimal Important Change (MIC). The Patient acceptable symptom state (PASS) is the threshold value that indicates when the patients feel that their condition is satisfactory after the treatment, or "*the value beyond which patients consider themselves well*" [97]. The MIC and PASS values are not consistent across patient populations or diagnoses. For example, a young and active patient that is treated for anterior cruciate ligament rupture may have higher demands to postoperative knee function than a 70-year old moderately active patient after TKA. Therefore, it is important that the level and changes of scores are interpreted according to the patient population in question.

Different types of bias may influence the interpretation of PRO data. Sometimes patients are reluctant to select answers in the lower or upper extremes of the scale.

This phenomenon is referred to as *end-aversion bias* [98]. *Ceiling and floor effects* may occur when patients predominantly answer in the upper or lower extreme of the scale, indicating that the PRO instrument has limited validity for the area of interest in the target population [99]. *Recall bias* occurs when patients remember their former health state as better or as worse than it actually was. This can cause problems in cross-sectional studies when patients are asked about their current health status and their health status before treatment. Patients can also change their report of health status over time, despite that there is no change in objective circumstances. There may be a discrepancy in the patient's report of PROs and their degree of satisfaction [100]. This phenomenon is called *response shift*, and could be caused by subjective changes in the patient's perception of health status over time [98]. Despite the difficulties in interpretation of PROs, it is important to bring the patient's perspective into evaluation of TKA. When researchers are aware of possible sources of bias and limitations, PROs represent an important contribution to increased knowledge and improved outcome of arthroplasty surgery.

Aim of the thesis

The main objective of the thesis was to evaluate the mid-term effects of computer navigation in total knee arthroplasties in Norway, in terms of implant survival, causes of revision, implant migration and patient-reported outcomes. The thesis also aims to look at the results of computer navigation in light of the last decades' changes in survival and revision causes in knee arthroplasty in Norway.

The specific aims of each paper:

Paper I

- To assess the mid-term survivorship in CAS compared to CON in patients operated in Norway in 2005-2014.
- To compare the risk of revision and causes of revision in CAS and CON.

Paper II

The aim of this paper was to answer the following questions:

- Were there improvements in survival for TKA and UKA when comparing two consecutive 11-year periods with similar follow-ups in a national registry?
- Were there changes in the causes of revision in the two time periods?
- Could the changes in revision causes be attributed to patient or implant characteristics?

Paper III

- To compare the migration of the TKA tibial component measured by radiostereometric analysis (RSA) for CAS and CON at 5 years follow-up from a randomized controlled trial.
- To compare the number of responders to treatment for CAS and CON based on patient-reported outcomes at 5 years follow-up.
- To evaluate the improvement in patient-reported pain, function and quality of life for CAS compared to CON from preoperative to 5 years follow-up.

Methods

1. Data sources

The Norwegian Arthroplasty Register

The Norwegian Arthroplasty Register (NAR) was established in 1987 as a hip arthroplasty register [101]. Since 1994, the registration of knee arthroplasty and other joint replacements were included [102]. Information about the patient and the procedure is filled in a 1-page registration form by the surgeon immediately after operation and the information is stored in the NAR database. Registrations of revisions are linked to the primary operation by the unique 11-digit Norwegian personal identification number [103]. To update information on deaths and emigrations, the same identification number is used to link the NAR to the National Registry, which is Norway's largest register of personal information [104]. The NAR covers a population of approximately 5.2 million, and the number of annually registered knee implants has increased from around 1000 in 1994 to more than 7500 in 2018 (6905 primary operations and 648 revisions). The registration completeness is 97% for primary TKA and 91% for revision TKA [3, 105].

Since 2005, the NAR has registered the use of CAS in TKA. In the registration form, the surgeon marks «No» or «Yes» to register the use of computer navigation. If no box is checked, the information on computer navigation is registered as "missing". The type of navigation system is written by hand in a text-field.

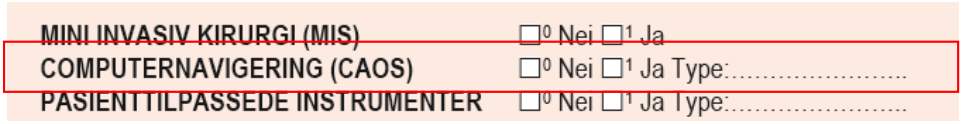


Figure 5. This detail from the NAR registration form shows registration of computer navigation and type of navigation system.

2. Outcomes and outcome measures

2.1. Implant longevity

Revision is a common outcome in arthroplasty register research. In the NAR, revision is defined as the removal, exchange, or addition of one or more prosthesis components (including exchange of a polyethylene insert or addition of a patellar component in patella non-resurfaced TKA). In arthroplasty register research, prosthesis survival and risk of revision is commonly calculated by the Kaplan-Meier method and Cox regression.

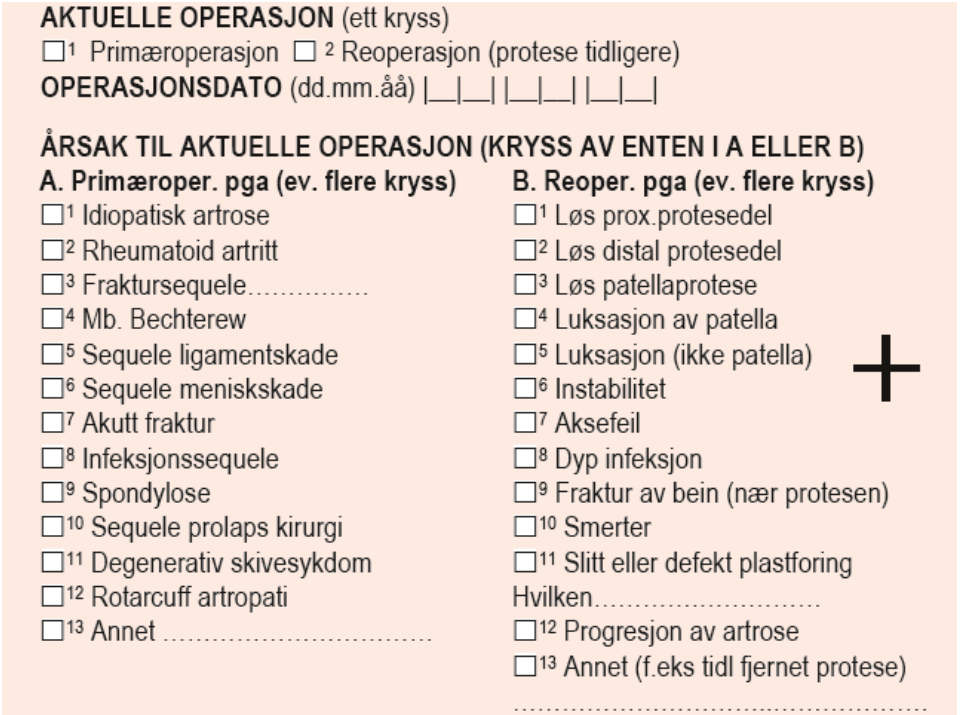
Some patients have pain or poor function after TKA, but do not undergo revision for various reasons, for instance severe comorbidity or surgeon reluctance. These TKAs are clinical failures, but are not presented as failures in the implant survival analyses. A combination of different outcomes (implant survival and PROs) gives a more complete view on the number of failures after TKA.

2.2. Revision causes

Causes of revision was an important outcome in paper II and also one of the secondary outcomes in paper I.

In the registration form, the surgeon marks whether the operation is a primary knee arthroplasty or a revision and the causes of revision. For each revision, several revision causes can be registered. However, if a patient had more than one revision, only the first revision was included in the analyses. The main cause of revision was determined by the hierarchy from the Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR) [9]. Some adjustments were made to make the hierarchy more appropriate for revision causes registered in the NAR. In example, the AOANJRR uses the term “aseptic loosening” for all components whereas the NAR registers loosening of proximal, distal or patellar component separately (figure 6). To be classified as a revision caused by pain, no other reason for revision could be registered. These revisions were termed “pain only” in paper I and “unexplained

pain" in paper II. Only the main cause of revision was included in the analyses of revision causes in paper I and II.


AKTUELLE OPERASJON (ett kryss)
☐1 Primæroperasjon ☐ 2 Reoperasjon (protese tidligere)
OPERASJONSDATO (dd.mm.åå) |__|__| |__|__| |__|__|

ÅRSAK TIL AKTUELLE OPERASJON (KRYSS AV ENTEN I A ELLER B)

A. Primæroper. pga (ev. flere kryss)
☐1 Idiopatisk artrose
☐2 Rheumatoid artritt
☐3 Fraktursequele.....
☐4 Mb. Bechterew
☐5 Sequele ligamentskade
☐6 Sequele meniskskade
☐7 Akutt fraktur
☐8 Infeksjonssequele
☐9 Spondylose
☐10 Sequele prolaps kirurgi
☐11 Degenerativ skivesykdom
☐12 Rotarcuff artropati
☐13 Annet .....

B. Reoper. pga (ev. flere kryss)
☐1 Løs prox.protesedel
☐2 Løs distal protesedel
☐3 Løs patellaprotese
☐4 Luksasjon av patella
☐5 Luksasjon (ikke patella)
☐6 Instabilitet
☐7 Aksefeil
☐8 Dyp infeksjon
☐9 Fraktur av bein (nær protesen)
☐10 Smerter
☐11 Slitt eller defekt plastforing
Hvilken.....
☐12 Progresjon av artrose
☐13 Annet (f.eks tidl fjernet protese)
.....

Figure 6. This detail from the NAR registration form shows how the surgeon registers whether the operation is a primary operation or revision and the cause of the operation.

The hierarchy from AOANJRR and the hierarchy used in paper I and II are provided in the appendix.

2.3. Radiological evaluation

Radiostereometric analysis (RSA)

During the TKA implantation, 9 tantalum markers (1.0 mm in diameter) were inserted into the proximal tibia and 6 markers (0.8 and 1.0 mm) were inserted into the polyethylene component in a specific manner. The markers in each segment (bone or polyethylene) defined a three-dimensional rigid body. The RSA examinations were done with the knee in a biplane calibration cage (cage 10; RSA Biomedical, Umeå, Sweden). Tantalum beads in the calibration cage make out a coordinate system as a reference to the markers in the patient. Radiographs from the repeated RSA examinations are uploaded to the software used to determine the coordinates of the markers (UmRSA Digital Measure version 6.0, RSA Biomedical).

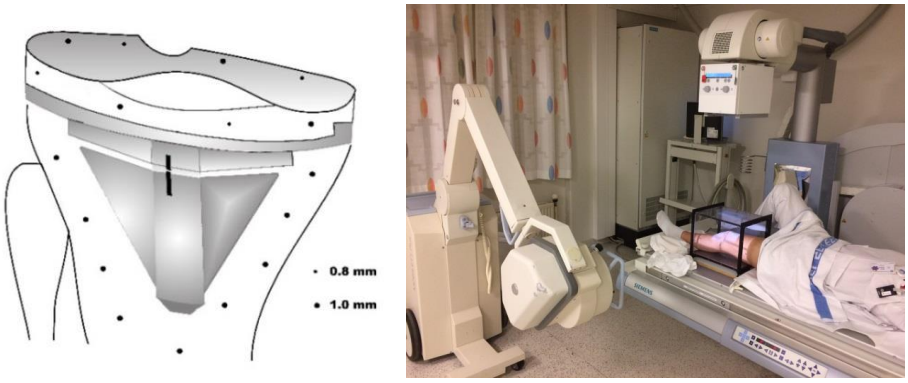


Figure 7. Left: Tantalum markers with diameter 0.8 mm and 1.0 mm were inserted into the tibial metaphysis and the polyethylene component during the operation. Illustration by The Department of Photo and Illustration, University of Bergen. Right: A patient with the knee inside an RSA calibration cage. Photo: Gunnar Petursson.

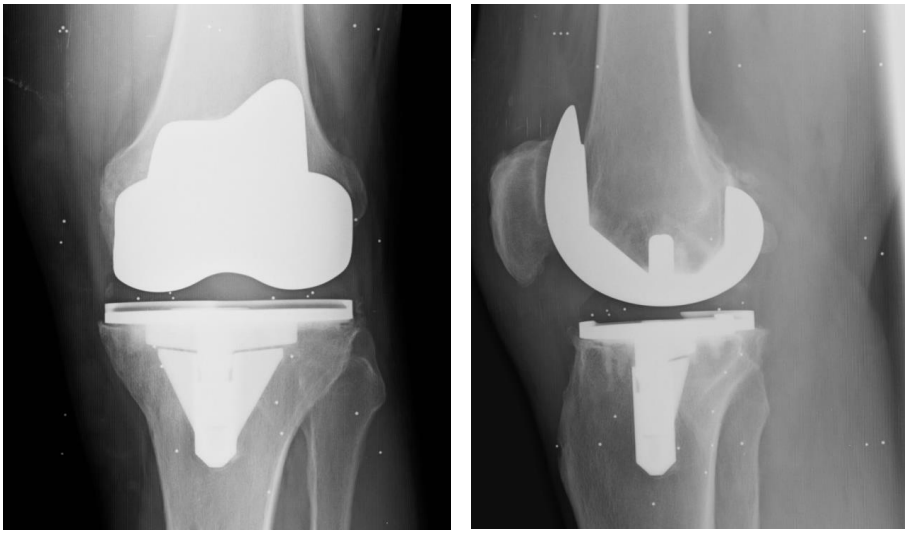


Figure 8. Postoperative radiographs of a knee with RSA markers.

The movements of the rigid bodies between the different examinations are used to calculate translation and rotation of the tibial component relative to the tibial bone. The three-dimensional movements of the implant were described as translation and rotation along and around the x-axis (medial-lateral; anterior-posterior rotation), y-axis (distal-proximal; internal-external rotation) and z-axis (posterior-anterior; varus-valgus rotation). Further, the maximum total point motion (MTPM) represents the length of the translation vector of the point in a rigid body that has the greatest motion [88].

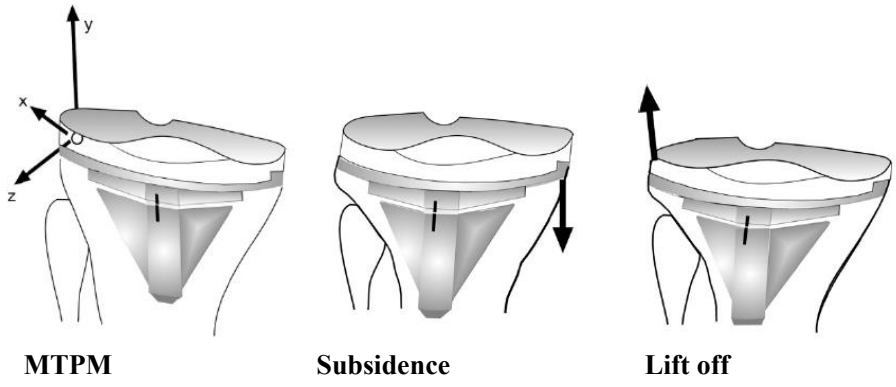


Figure 9. Possible translation of the tibia; Maximum total point motion (MTPM), subsidence and lift off.

The condition number (CN) and mean error of rigid body fitting (ME) were used to evaluate the quality of RSA measurements. The CN is determined by the number and three-dimensional spread of the markers, indicating the three-dimensional quality of the segment. If a segment has few markers, the markers are close to each other or on a straight line, the CN will increase. The ME describes the stability of the markers, expressed by the mean difference between the relative distances of markers in repeated examinations. Guidelines for RSA suggest 150 as a maximum value for CN and 0.35 mm as upper limit for ME [88], but in paper III the stricter limit of 130 for CN was used, as this indicate more reliable measurements.

The repeatability of the measurements was evaluated by double examinations of the same patient. After one examination, the patient walks a few steps in the room while the RSA setup is rearranged, before an immediate repetition of the same examination. The expected migration of the implant between these two examinations is zero, and the measured migration expresses the error of the method. Limits for significant translations and rotations (the precision) are calculated as the 99% confidence intervals of the absolute mean values from analyses of the double examinations.

Conventional radiographs

For the measurement of radiolucent lines, we used the Knee Society Total Knee Arthroplasty Roentgenographic Evaluation and Scoring System as described by Ewald in 1989 [106]. Radiolucent lines were measured on radiographs in frontal and sagittal view at 3 months and 5 years after the operation (figure 10).

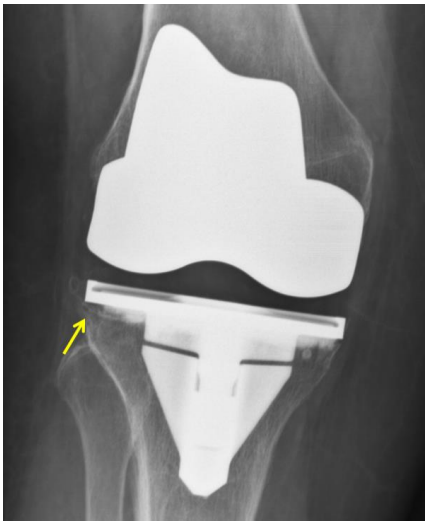


Figure 10. Postoperative radiographs with radiolucent lines (marked by a yellow arrow) in frontal view.

2.4. Patient reported outcomes (PROs)

Paper III included PROs as outcomes. The questionnaires consisted of validated, widely used scores, to make the results comparable to other studies. The EuroQol EQ-5D and the visual analogue scale (VAS) are generic scores, whereas the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), KOOS, Charnley category and Knee Society Score (KSS) are disease-specific scores for knee injury and osteoarthritis. We also used responder analysis that combines the results of different scores to divide patients in groups with high, moderate or no response to the treatment.

EQ-5D – general health status

EQ-5D is a self-administered, standardized measure of health, developed by the EuroQol Group [107]. The EQ-5D has 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Each dimension is divided into 3 levels/possible responses (no problem, some problems or extreme problems). Reference scores are generated through a large European study [108].

Visual Analogue Scale (VAS)

A Visual Analogue Scale is used for issues that are more suitable to measure on a continuous scale rather than in categories and is considered a reliable tool for the estimation of the intensity of pain [109]. The scale is a horizontal line (100 mm) where the left end (score 0) indicates total absence of pain or complete satisfaction, and the right end (score 100) indicates the worst possible pain or dissatisfaction. The patients mark a point on the line that corresponds to their situation. The distance from the left end to the mark determines the VAS score.

The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

The WOMAC score has 24 questions for assessment of pain, disability and joint stiffness in patients with hip or knee osteoarthritis [110]. It is widely used in the US., and recommended by the Journal of Bone and Joint Surgery (Am) for use in knee arthroplasty studies [111]. The questionnaire has 24 items and is considered valid, reliable and responsive to osteoarthritis outcomes [112]. Use of the WOMAC score requires licensing.

The Knee Injury and Osteoarthritis Outcome Score (KOOS)

KOOS is a knee-specific questionnaire that was developed by a Swedish research group in 1995 to evaluate the patient's opinion about their knee problems and treatment [113]. All questions in WOMAC are identically repeated in the KOOS score. Thus, WOMAC scores can be calculated from the KOOS score. In addition, KOOS contains questions to detect early and late disease-specific symptoms. The 42 questions are divided into 5 subscales: Pain (9 items), Symptoms (7 items), Activities

of Daily Living (ADL) (17 items), Sport and Recreation Function (SportRec) (5 items) and knee-related Quality of Life (QOL) (4 items). All items have 5 possible answers with scores from 0 to 4. The total score is summarized and transformed to a 0-100 scale, with 0 indicating extreme knee problems and 100 indicating no knee problems. In 40 of the 42 questions, only the knee related problems during the last week should be considered. The two remaining questions refer to the last month. KOOS is validated in several populations [113, 114]. A Norwegian version has been approved and used in studies [115], and a description of the validation process is available at "http://www.koos.nu".

Responder analysis

The responder analysis uses a set of criteria to determine if the patient is responding to the treatment. The Outcome Measures in Rheumatology – Osteoarthritis Research Society International (OMERACT-OARSI) set of responder criteria defines the patient as a responder or a non-responder according to the absolute and relative change of scores within three domains: pain, function and the patient's global assessment [116, 117]. The patient is considered a responder if he has an improvement in pain or function of ≥50% and an absolute change ≥20 points. The patient is considered a moderate responder if he has an improvement in at least two of the three following criteria: 1. Pain ≥20% and absolute change ≥10; 2. Function ≥20% and absolute change ≥10; 3. Patient's global assessment of the disease ≥20% and absolute change ≥10. Patients not meeting these criteria are defined as non-responders.

2.5. Other knee scores

Charnley category

This simple classification was developed by Sir John Charnley for hip arthroplasty patients to facilitate assessment of the function of walking, and was later modified for patients with knee arthroplasty [118, 119]. The score groups patients in 3 categories to classify knee-specific comorbidity that may affect outcome. Category A refers to a unilateral knee problem, with no other conditions interfering with walking. Patients in

category B have problems with both knees, whereas patients in category C have an additional medical condition interfering with walking, such as cardiovascular or respiratory disability, chronic back pain or *claudicatio intermittens*.

American Knee Society Score

The Knee Society Score was developed in 1989 as a health personnel administered, objective scoring system for the patient's functional abilities before and after TKA [120]. This scoring system is divided into a knee score (including clinical tests) and a function score with a maximum of 100 points each (0 worst, 200 best score). In 2012, a revised Knee Society Knee Scoring System was developed [121, 122].

3. Methodology description for each paper

3.1. Paper I

Study design

Paper I is a prospective, observational registry study. The level of evidence for this study is III.

Data sources

All data in this study was collected from the NAR. Since registration of CAS started in 2005, we included TKAs operated from 01.01.2005 to 31.12.2014. Hinged, bi-compartmental and patella resurfaced TKAs were excluded due to low numbers. A study from the NAR in 2011 compared CAS and CON at short-term follow-up with patients receiving a TKA in 2005-2008 [123]. In this time period, 10 different implants and 4 different navigation systems were used in CAS operations. Implants and navigation systems that were used in less than 25 procedures were excluded. Thus, the 5 most used prosthesis brands (AGC, Biomet; Duracon, Stryker; e.motion, Aesculap; LCS Complete, DePuy; Profix, Smith & Nephew) and the 3 most used navigation systems (Brainlab, Orthopilot and Stryker) were included. In paper I, we wanted to compare the results from the study by Gøthesen et al. [123], thus we included the same 5 prosthesis brands and the same 3 navigation systems. The same

prosthesis brands were also included in the CON group, leaving 3665 computer navigated and 20,019 conventionally operated knees that were eligible for evaluation.

Statistics

The null hypothesis for this study was that there was no difference in survival or relative risk of revision (RR) in TKAs operated with CAS or CON. Also, we wanted to study the relative risk of revision for CAS compared to CON in subgroups of the different prosthesis brands, fixation methods and in patients more or less than 65 years of age. We also wanted to study whether the groups differed in the risk of revision due to each of the registered revision causes and if there was a learning curve on hospital level.

Differences in baseline characteristics of the groups were calculated by Pearson's Chi square test and Student's t-test. Reverse Kaplan-Meier was used to calculate median follow-up [124]. The relative risk of revision for CAS relative to CON was tested in a Cox regression model, adjusted for age (continuous), sex (male/female), prosthesis brand (Profix as reference), The American Society of Anesthesiologists (ASA) category (1/2/3+), fixation method (cemented/uncemented/hybrid (uncemented femur, cemented tibia)), diagnosis (osteoarthritis/other) and previous surgery of the knee (yes/no). The proportional hazard assumption was assessed by visual inspection of log-log-plots. To ensure that deaths and emigrations did not affect the results, this was tested in a competing risk model [125]. The robustness of the analysis was investigated by a simpler Cox regression model adjusted for age, sex and diagnosis. We also did a Cox regression analysis with adjustment for a propensity score, in order to add more covariates to the model. The propensity score included the same covariates as the Cox regression model above, in addition to side (left/right), peroperative complications (yes/no), deficiency of anterior cruciate ligament preoperative (yes/no) and deficiency of posterior cruciate ligament preoperatively and postoperatively (yes/no).

Implant survival was defined as the time from the primary operation to the first revision. Implant survival was estimated by Kaplan-Meier analysis at 5 and 8 years

postoperative, with censoring at time of death, emigration or at the end of the study period (31.12.2014). The NAR was linked to the National Registry to obtain information about deaths and emigrations.

Possible effects of a learning curve were investigated by analyzing the first 30 procedures that were done in each hospital, since the learning curve was shown to stabilize after 30 procedures [126, 127]. Differences in operation time were tested by Mann-Whitney tests because the operation time was not normally distributed.

All tests were 2-sided and the significance level was 0.05.

3.2. Paper II

Study design

This paper is a prospective, observational registry study. The level of evidence is III.

The study was designed to answer the following research questions: (1) Were there improvements in survival for TKA and UKA when comparing two consecutive 11-year periods with similar follow-ups in a national registry? (2) Were there changes in the causes of revision in the two time periods? (3) Could the changes in revision causes be attributed to patient or implant characteristics?

Data sources

The NAR was the only data source for this study and primary knee arthroplasties reported between 01.01.1994 and 31.12.2015 were included. Hinged, bicompartmental and patellofemoral joint replacements were excluded due to low numbers and to ensure a more homogenous study population. For patients that were revised during the time of follow-up, only the first revision was accounted for in this study. If multiple revision causes were reported, the main cause of revision was determined based on the hierarchy from the AOANJRR [9]. In total, 60,623 TKAs (2426 revisions) and 7648 UKAs (725 revisions) were selected for analysis. 99.6% of the patients were accounted for at the time of analysis, whereas 0.4% had moved abroad. The included patients were divided into two time periods, based on the time

of the primary operation; from 1994 to 2004 (Period 1) and 2005 to 2015 (Period 2). In period 1, there were 17,404 TKAs and 2297 UKAs. Period 2 had 43,219 TKAs and 5351 UKAs.

Statistics

TKAs and UKAs were analyzed separately, but the same methods were used for both prosthesis types. To ensure that both periods had a maximum follow-up of 11 years, the arthroplasties in period 1 were censored 13.12.2004, whereas the arthroplasties in period 2 were censored 31.12.2015. Median follow-up was estimated by the reversed Kaplan-Meier method.

Overall implant survival was found by a Kaplan-Meier analysis with 10 years follow-up in each group, with censoring at time of death, emigration or at the end of follow-up. Differences in survival between period 1 and period 2 was calculated by the log-rank test, and an unadjusted Cox regression model was used to find a risk estimate. For each revision cause, a Cox regression model was used to calculate the relative risk of revision in period 2 relative to period 1, adjusted for age (continuous), sex, diagnosis (osteoarthritis/other), fixation (cemented/uncemented/hybrid), and use of patellar component for TKA (yes/no).

The proportional hazard assumption (PH) was tested for overall survivorship and for each revision cause for TKA and UKA by statistical tests and visual inspection of Schoenfeld residuals [128]. If PH failed, the follow-up was divided into time intervals individually for each revision cause until PH was fulfilled. The cut-off points for each time interval was decided based on inspection of the Schoenfeld residuals and statistical tests [129].

All tests were two-sided and the statistical significance level was 0.05. The statistical analyses were performed by IBM Statistics Version 22.0 (IBM Corporation, Armonk, NY, USA) and R Version 3.3.0 (The R Foundation, Vienna, Austria).

3.3. Paper III

Study design

Paper III is a 5-year follow-up from a multicenter, randomized controlled trial that was conducted in 2009-2011. The level of evidence is I for this study.

Intervention

192 patients were randomly parallel-group assigned to undergo TKA with either CAS or CON (allocation ratio 1:1). To ensure an equal number of patients in the two treatment groups, a computer generated block randomization for each of the involved surgeons was used, with randomly varying block sizes of two and four. The patients were included and operated at four different hospitals in Norway; Haukeland University Hospital (public, Bergen), Lovisenberg Diakonal Hospital (private non-profit, Oslo), Haugesund Hospital (public, Haugesund) and Haugesund Sanitetsforening's Hospital (private non-profit, Haugesund) and eight surgeons performed the knee arthroplasties. Before start-up of the study, all the surgeons had done at least 100 TKAs with CON and 10 TKAs with CAS. All patients received a cruciate retaining Profix knee prosthesis (Smith & Nephew, Memphis, Tennessee), cemented with Palacos R+G (Heraeus, Hanau, Germany). The navigation system used in the CAS group was the VectorVision knee software version 1.6.93616 with the Kolibri system from BrainLab (Munich, Germany). To ensure blinding of the patients, two sham incisions were made over midshaft tibia for the CON patients to mimic the stab incisions for the CAS patients.

The first 54 included patients were operated with RSA markers. During the operation, six tantalum-sphere markers (diameter 0.8 mm and 1.0 mm) were inserted into the polyethylene component, whereas nine markers (diameter 1.0 mm) were inserted in the tibial metaphysis before cementing. The index RSA examination was taken within one week after insertion. The RSA examinations were sent to the RSA-lab at the Orthopedic Research Center at Trondheim University Hospital for analysis. All patients received the same antithrombotic and antibiotic medication and a standardized exercise program was carried out for the patients postoperatively.

Scheduled follow-up examinations for all included patients were at 3, 12, 24 months and 5 years after operation. The follow-up consisted of radiographs (front and side view) of the operated knee (patients with RSA markers had RSA examinations according to the RSA protocol), a clinical examination including KSS and a self-administered questionnaire (KOOS, VAS-pain and EQ-5D). The clinical examinations were done by trained physiotherapists who were blinded to treatment group.

Inclusion

The age criterion was initially 60-80 years, but was expanded to 50-85 years 6 months after the start of inclusion due to a slow recruitment rate. Eligible patients for inclusion were men and women aged 50-85 years in need of a total knee replacement due to osteoarthritis or arthritic disease of the knee, within ASA category 1-3. Exclusion criteria were severe systemic disease, severe neurological disorder, a history of cancer, dementia, body mass index (BMI) > 35 kg/m^2, previous fractures of the shaft of tibia or femur, severe valgus position of the knee (>15° from the mechanical axis of the knee), previous osteotomy of the tibia or femur, recent knee injury (less than one year pre-operatively), severe stiffness of the ipsilateral hip, ipsilateral hip replacement and allergy to metals. If a patient needed two knee replacements, only the first knee evaluated in the recruitment period was included in the trial.

Statistics

The study was divided in two parts; all the included patients were assessed on PROs and postoperative alignment. A sub-group of patients also received RSA markers for the evaluation of implant migration. The 1-year follow-up of the patients was published in 2014 by Gøthesen et al., with KOOS pain score as primary outcome and additional PROs and postoperative alignment as secondary outcomes [53]. At 2 years follow-up, migration of the implant was the primary outcome, whereas PROs were secondary outcomes [130, 131].

The primary outcome in this study was migration of the implant 5 years after primary TKA, measured by RSA. Secondary outcomes were mean changes of PROs from preoperative to 5 years (KSS, KOOS, EQ-5D and VAS for pain), the proportion of responders according to the OMERACT-OARSI criteria and the occurrence of radiolucent lines. To calculate sample size, we used the minimal important change of KOOS, which is 8-10 units [113]. With a standard deviation of 20, a statistical power of 80% and significance level of 0.05, we needed 64 patients in each group. To account for deaths and lost to follow-up, we included a total of 192 patients (97 CAS, 95 CON). For the RSA part of the trial, we assumed that 0.1 mm was a clinically relevant difference between the groups. The repeatability of the RSA measurements is 0.1 mm, measured from double examinations. To achieve a power of 80% and significance level 0.05, we needed 17 patients in each group. Due to the risk of drop-outs or technical difficulties during measurements we included 54 patients in the RSA study (26 CAS, 28 CON).

The groups were analyzed as intention to treat. The normality assumption was controlled by the Kolmogorov-Smirnov test and Shapiro-Wilk test. Differences in demographic variables between CAS and CON were calculated by Pearson's chi-square test for proportions and Student's independent sample t-test for mean values. RSA data for migration were not normally distributed. The median difference in migration and corresponding 95% CI for the median difference in migration was calculated according to Campbell and Gardner [132]. Amongst the 24 measured PRO dimensions, 9 were not normally distributed. Due to the high number of patients ($n \geq 70$ for all measurements), we used the Student's t-test in the tables presented in the article. The differences in PRO measures were also done by Mann-Whitney U test, and the results from parametric and non-parametric tests were comparable.

All tests were two-sided and the significance level was 0.05. For the statistical analyses, SPSS Statistics software (version 23; Armonk, NY: IBM Corp) was used.

4. Ethical approval

Paper I and paper II used data from the NAR, which has concession from the Norwegian Data Inspectorate to collect patient data, based on a written consent from the patient (last issued 15 September 2014, ref.no: 03/00058-20/CGN).

Paper III was approved by the Regional committee for medical and health research ethics (REK Vest), Bergen September 29, 2007 (ref.no: 2007/12587-ARS). It was registered in the trial database ClinicalTrials.gov, which is a service from the United States National Institutes of Health (date of registration 30 October 2008, ref.no: NCT00782444).

Results

Paper I

Patient characteristics

Median time of follow-up was 5.3 years for CAS and 5.0 years for CON. The CAS group had a higher proportion of men, the mean age was 1 year younger and the patients had a lower mean ASA score compared to the CON group. The CAS group had a higher frequency of uncemented prostheses, previous surgery of the knee and preoperative deficiency of the anterior cruciate ligament. Of the 65 hospitals included, three hospitals had a total CAS volume of >200 TKAs from 2005 to 2014 and 33 hospitals had a total CON volume of >200 TKAs.

Survivorship

The 8 years Kaplan-Meier survival rate was 94.8% (CI: 93.8-95.8) for CAS and 94.9% (CI: 94.5-95.3) for CON. There was no statistically significant difference in the risk of revision for CAS relative to CON (table 1). The simple Cox regression model, the propensity score adjusted Cox regression model and the competing risk model showed small variations in the RR estimate, but there was no statistically significant change between CAS and CON.

Test	Overall RR (95% CI)	RR <65 years (95% CI)
Cox with many covariates*	0.8 (0.7-1.0)	0.8 (0.6-1.1)
Simple Cox model**	0.9 (0.8-1.1)	0.9 (0.8-1.2)
Propensity score adjusted	0.8 (0.7-1.1)	0.8 (0.6-1.1)
Competing risk	0.9 (0.8-1.2)	0.9 (0.8-1.2)

Table 1. This table shows the relative risk of revision (RR) for CAS relative to CON for all the included patients and for patients <65 years of age, calculated in different statistical models. *Adjusted for age, sex, prosthesis brand, ASA classification, fixation method, diagnosis and previous surgery of the knee. **Adjusted for age, sex and diagnosis.

Secondary outcomes

For patients older or younger than 65 years of age, there was no statistically significant difference in the risk of revision for CAS relative to CON. Further analyses showed no significant difference between CAS and CON in subgroups of cemented, uncemented and hybrid implants or for each of the included prosthesis brands. When we compared the 30 first CAS procedures (learning group) to the entire CON group, there was no statistically significant difference in risk of revision for CAS relative to CON (RR=1.1; CI: 0.7-1.5).

Median operating time was 11 minutes ($p<0.001$) longer for CAS when all implants were included and 21 minutes ($p<0.001$) longer for cemented implants. Deep infection and aseptic loosening was the most common revision causes. For CAS patients <65 years, instability was the most common revision cause. Patients in the CAS group had significantly fewer revisions due to malalignment with RR=0.5 (CI: 0.3-0.9) for the entire group and RR=0.3 (CI: 0.1-0.8) for age <65 years.

Paper II

Survivorship free from revision

For TKAs, the 10-year Kaplan-Meier survival free from revision improved from Period 1 to Period 2 from 91% (CI: 90%–92%) to 94% (CI: 94%–95%; p< 0.001). To fulfill the proportional hazard assumption, the follow-up was split into four intervals and a risk estimate between the two time periods was calculated for each time interval: The first 1.5 months after the operation, there was a higher risk of revision in period 2 relative to period 1 (RR=2.8, CI: 1.9-4.0). At more than 6 months postoperatively, period 2 had significantly lower risk of revision with RR=0.6 (CI: 0.6-0.7) from 0.5-6 years and RR=0.3 (CI: 0.2-0.4) from 6-11 years.

With UKAs, the 10-year survival free from revision was 80% (CI: 76%–84%) in Period 1 and 81% (CI: 79%–83%; p = 0.261) in Period 2. The relative risk of revision in period 2 relative to period 1 was 0.9 (CI: 0.8-1.1).

Changes in revision causes

For TKA, revisions resulting from aseptic loosening of the femoral component, polyethylene wear/breakage, patellar dislocation, and unexplained pain decreased from period 1 to period 2. There was an increase in revisions resulting from infection within the first 6 months, with the highest risk the first 6 weeks (RR=5.1; CI: 2.9-8.9). At more than one year postoperatively, the risk of revision due to infection was decreased in period 2 (RR=0.6; CI: 0.4-0.8).

UKA had a decrease in revisions resulting from aseptic loosening, polyethylene wear/breakage, and periprosthetic fractures, but there were more revisions resulting from progression of osteoarthritis (RR=5.0; CI: 1.8-13.7).

Changes in patient and implant characteristics

Patients receiving TKA were younger and more often men in period 2 compared with patients in Period 1. A higher risk of revision was found for male sex (RR=1.1; CI: 1.0–1.2) and age younger than 65 years (RR=1.7; CI: 1.6–1.9). From period 1 to

period 2, there was an increase in patella non-resurfaced implants, uncemented and hybrid fixation and the use of mobile bearing implants.

For UKAs, period 2 had more men and the average age was younger than for patients in Period 1. Patients with age younger than 65 years had a higher risk of revision (RR=1.7, CI: 1.5–2.0), whereas sex did not affect the risk of revision. Only 66 implants were uncemented, and all were operated in period 2. The Oxford® Phase 3 was the most used implant in both periods (61% in period 1, 70% in period 2).

Paper III

Description of the study groups

160 patients participated in the 5 years follow-up (82 CAS, 78 CON). 42 of these patients had RSA markers, 21 in each group. The groups were similar in mean sex, mean age, BMI, diagnosis and side of the operation.

RSA and radiolucent lines

From 3 months to 5 years, CAS and CON did not differ significantly in rotation, MTPM, subsidence or lift-off. Median difference in MTPM between CAS and CON from 3 to 60 months was 0.13, but the difference was not statistically significant ($p=0.14$). The CAS had higher migration than the CON group from 24 to 60 months, but this difference was not statistically significant. Five patients had MTPM of more than 1.0 mm, four of these were in the CAS group.

More than 95% of the 160 patients had less than 4 mm total width of radiolucent lines at 3 months and 5 years. No patients in either group had more than 10 mm total width of radiolucent lines in any measurement, and the groups did not differ significantly in the number of patients with radiolucent lines more than 4 mm.

Patient-reported outcomes

The mean improvement from preoperative to 5 years was higher in the CAS group for all PRO subscales, but the differences were not statistically or clinically significant. The CAS group had more patients achieving highest possible score than the CON group for all PRO subscales, except from the WOMAC stiffness score.

Of the included patients, 150 (79 CAS, 71 CON) had completed enough questions in the questionnaire to calculate WOMAC scores, and were thus included in the responder analysis, according to the OMERACT-OARSI criteria. The CAS group had a higher proportion of high responders (n=66, 83%) compared to the CON group (n=52, 73%), but the difference was not statistically significant ($p=0.3$). The CAS group had statistically significant more patients meeting the criteria for high

responders in pain score compared to the CON group (p=0.04). The number needed to treat was 7.

Discussion

5. Methodological considerations

1.1. Study design

The papers in this thesis have two different study designs; paper I and II are registry studies (cohort studies), whereas paper III is a randomized controlled trial.

Registry study (paper I and II)

The patients in paper I and paper II were included from the NAR; a nation-wide arthroplasty register. The data represents patients from all parts of the country and include many different surgeons and hospitals, varying in tradition and experience. Consequently, the external validity of registry studies is high, and the results represent the outcome for an average surgeon in Norway. Compared to RCTs, the level of evidence is lower. The data from a registry study can be used to find associations between exposure and outcome, but not to claim causality [133].

Patients included in the NAR are diverse and have a large number of different diagnoses and prostheses. When designing a registry study, some groups of patients need to be excluded to make the results relevant for the group of patients that we want to study. In paper I and II, we excluded patients with hinged, bicompartmental and patellofemoral prostheses. These patients represent a sub-group with different indications and prognosis (i.e. cancer), and exclusion of these patients will make the results more relevant to the average knee arthroplasty patient. On the other hand, exclusion of too many patients decreases the external validity. In example, a study from the New Zealand joint registry (NZJR) compared CAS and CON, only including Triathlon prostheses [56]. These results are not necessarily transferable to other prosthesis brands, as different revision rates and revision causes are observed for different implants [71].

In paper I, we wanted to compare the results to the short-term follow-up of CAS from 2011 [123]. For this reason, we included the same prosthesis brands, which were the

5 most used brands from 2005-2009. The use of prosthesis brands has changed over time, and some of the included prosthesis brands are no longer in use in Norway [3]. Thus, the results are not necessarily valid for the prostheses that are used today. Still, we wanted to study the longest possible follow-up in our data. By including the most frequently used prosthesis brands, we avoided that results from low-volume brands (or brands that had a low CAS volume) influenced the results.

Paper II compared two consecutive time periods, focusing on time trends in survival and causes of revision. The patients operated in period 1 had time of follow-up up to 22 years in the registry (from 01.01.1994 to 31.12.2015), and we censored the patients in period 1 at 31.12.2004 to make the time of follow-up more similar. A similar follow-up is especially important in a study comparing revision causes, since early and late revisions differ in type of revision cause [23, 69, 134]. In paper II, median follow-up for TKA was 3.5 in period 1 and 4.2 in period 2. For UKA, median follow-up was 2.7 years in period 1 and 4.6 years in period 2. The incidence of TKA and UKA has increased remarkably since 1994, and the early portion of period 1 had few TKAs and UKAs compared to the early portion of period 2. Consequently, median follow-up was longer in period 2 for both TKA and UKA.

Randomized, controlled trial (paper III)

Paper III is a 5 years follow-up from an RCT. The study was conducted in 2009-2011 as a large project evaluating the short- and long-term effects of CAS compared to CON, with angle measurements on radiographs and CT-scans, RSA analyses and PROs. Results from 3 months, 1 year and 2 years follow-up are previously published [53, 130, 131]. The outcomes, inclusion- and exclusion criteria were registered in ClinicalTrials.gov before start of inclusion.

An RCT is considered the best study design to find causal relations between exposure and outcome. The patients are randomly assigned to treatment group, and the risk of bias and confounding factors is low. An important limitation of RCTs is that the study often includes a limited subgroup of patients that receive a treatment in clinics with a close follow-up by highly engaged doctors. In that case, the external validity is

low compared to larger studies that include a more diverse patient group. In addition, RCTs are often underpowered to study rare events like revision.

1.2. Data quality

Strengths and limitations of the NAR

The NAR started the individual registration of knee implantations in 1994, and has a long follow-up compared to other joint registries worldwide. The high registration completeness increases the applicability and external validity of the data. If a study has a high external validity, the results of the study can be generalized to other patient groups or situations [135]. Applicability means that the effects observed in a study is reflecting the expected results if the intervention or treatment was used in a large population under "real-world" conditions [136].

Patients in NAR are identified by the Norwegian personal 11-digit identification number, which ensures a correct registration of age and sex, and also a correct linkage between primary operation and revision. The same identification number is used to link the NAR to the National Registry, to get a complete follow-up of deaths and emigrations. The NAR is also linked to the Norwegian Patient Registry (NPR) for validation of registered operative procedures, which is used to calculate registration completeness of primary operations and revisions. However, the codes for inclusion in NPR and the NAR are not identical. This complicates the calculation of registration completeness, (especially for revisions, which include many different procedures and codes). A previous validation study showed that infections often are underreported to the NAR [137]. One explanation could be that infections are more frequently revised out of scheduled operating hours and thus are more easily forgotten by the operating surgeon.

Code	Description
NGC0*	Secondary implantation of partial prosthesis in knee joint not using cement
NGC1*	Secondary implantation of partial prosthesis in knee joint using cement
NGC2*	Secondary implantation of total prosthesis in knee joint not using cement
NGC3*	Secondary implantation of total prosthesis in knee joint using hybrid technique
NGC4*	Secondary implantation of total prosthesis in knee joint using cement
NGC99	Other secondary prosthetic replacement in knee joint
NGU0*	Removal of partial prosthesis from knee joint
NGU1*	Removal of total prosthesis from knee joint

Table 2. This table shows NCSP procedure codes for combining data from NPR hospital stays and the NAR. The table is provided from the NAR annual report [3].

Stickers from the implant packaging are attached to the registration form and punched into the NAR database to ensure a correct registration of implants with specific catalogue numbers. Separate studies are done to validate data on operation date, diagnoses and registration completeness [137, 138]. Validation of registration completeness of hip and knee arthroplasties in NAR was done for the period 1999-2002 by Espehaug et al., with linkage to the NPR [105]. Since 2008, validation of registration completeness has been updated every second year and the results are published in the annual report [3]. Most validation studies from NAR include data from hip arthroplasties. The registration form for hip and knee arthroplasties are quite similar, and the routine for registration of data by specially trained secretaries at the NAR is the same for hip and knee arthroplasties. Thus, we assume that the results from validation of hip arthroplasties are, to some extent, transferrable to knee arthroplasties.

Revision is a common outcome in studies using data from arthroplasty registers, and revision of any cause was also the main outcome in paper II. Due to the high registration completeness of revisions in NAR, revision is considered as a valid outcome. Revision as an outcome is successfully used to calculate longevity of an implant. Still, revision does not tell the whole truth; a patient with an unrevised TKA does not necessarily have a good clinical outcome or satisfactory radiographs. Patients with poor knee function or pain after TKA may remain unrevised due to concomitant diseases, a high risk of complications or reluctance by the surgeon towards revision surgery. A study by Murray et al. found that survival was 72% at 7 years with moderate pain as the end point for the AGC implant. This compared to 97.5% with revision as the end point [139]. If pain and dissatisfaction of the knee implant is defined as a failure, the true number of failures in Norway is unknown. Collection of PROs in the NAR will hopefully increase knowledge about the patients' pain and satisfaction in the future.

There may also be patients that are unnecessarily revised. In example, a patient with unexplained knee pain may undergo revision although the pain is caused by other reasons than the knee arthroplasty. In paper II, unexplained pain was a common cause of revision for both TKA and UKA. Previous studies have pointed out that patients with painful TKAs should be evaluated systematically using diagnostic algorithms, and conservative treatment is recommended if there is no specific manageable explanation for the knee pain [140-142].

Although the NAR has high registration completeness for primary operations and revisions, the registration completeness and accuracy of some other variables are unknown. Registration of prosthesis components and cement is done by punching the catalogue numbers from the stickers from the manufacturer. The stickers are attached to the registration form by the surgeon. All prosthesis components that are in use in Norway are pre-registered in the database, and unknown numbers are declined by the system to control for punching errors. Hence, we assume that the registration of components is correct.

Causes of revision are registered by the surgeon performing the revision procedure. Each surgeon may classify revision causes differently, based on subjective assessments, personal awareness to a specific revision cause or local traditions (misclassification bias). In example, a loose implant in a malaligned knee may be classified as aseptic loosening by one surgeon and malalignment by another. Misclassification of revision causes is more likely to occur for revision causes that have an unclear definition, like instability or arthrofibrosis. Awareness of these revision causes typically fluctuates over time. Changes in the number of revisions from one time period to another, like in paper II, could be influenced by different classification rather than a change in patients or implants. A more accurate definition of the different revision causes will reduce the error of misclassification.

Register studies use the registered patient information to adjust for possible confounding from age, sex and other relevant variables. Still, some important confounding factors like BMI, diabetes, smoking status, degree of knee stability or radiologic measures are not registered in the NAR and cannot be accounted for in the statistical analyses.

Radiological outcomes

RSA is the most precise method for the measurement of migration of implants *in situ*. This means that a low number of patients in each treatment arm is needed. Within our defined limits of significant migration, there was no difference between the groups. The predictive value of migration with respect to survival of the implant, will depend on the extent of migration. There is no hard evidence to define a predictive cut-off value for any migration vector. However, there are suggestions that MTPM at 1 year of 0.54 mm-1.6 mm is considered “at risk”, whereas MTPM above 1.6 mm is “unacceptable” [143]. The migration pattern applies to a group of patients with similar implants, and is not applicable to individual patients. Individual patients vary with respect to bone quality, weight, size and fit of the implant, activity, comorbidity etc., hence the migration patterns will differ within the group.

Further, RSA is believed to be a proxy for loosening at mid-term follow-up; this has been shown in a small number of papers on TKA [87, 92, 143]. The literature on this point is not overwhelming, and the real risk of loosening can only be found by long term follow-up in register studies.

PROs

To measure PROs in paper III, we used validated and widely used scores that also had been used in previous Norwegian studies [115, 144]. We used the KOOS guidelines and KOOS scoring instructions in order to make a correct calculation and presentation of the KOOS results [145]. A limitation with the questionnaire is that we did not include any anchoring questions for determination of the proportion of patients that were satisfied with the treatment and the proportion of patients that considered their treatment as a failure. In the literature, patient satisfaction is often termed "Patient acceptable symptom state" (PASS) [117, 146]. Ingelsrud et al. collected this information from patients with anterior cruciate ligament reconstruction [147]. In addition to the KOOS questionnaire, the authors asked: "Considering your knee function, do you feel that your current state is satisfactory?" This could be answered by "yes" or "no". If this question was answered by "no", the patient was also asked "If you answered NO to the former question, would you consider your current state as being so unsatisfactory that you think the treatment has failed?"; also to be answered by "yes" or "no". If we had this information, we could have identified the proportion of patients that were satisfied with the treatment and how patient satisfaction corresponded to the different PRO scores included in the studies.

A recent study by Connelly et al. has suggested PASS for KOOS in patients undergoing TKA, with patient-reported satisfaction as anchor [148]. The authors suggested PASS thresholds at 1 year and at 3 years for each KOOS subscale, except from KOOS SportRec (because it was considered less applicable to TKA patients). This study was not available when paper III was submitted, but the numbers of patients above PASS for CAS and CON are compared in table 3. The table shows that CAS has more patients above PASS in all KOOS subscales, but the difference is not statistically significant from CON. However, a box plot in the article by Connelly et

al. shows that there is a large overlap in KOOS scores for patients that are categorized as satisfied or dissatisfied. This illustrates that the interpretation of PROMs is complex, and it is difficult to predict satisfaction from scores in pain and function. As pointed out by Nilsdotter et al., satisfaction is also influenced by the patient's expectations, which can change over time [149].

KOOS subscale	PASS threshold at 3 years (Connelly et al.)	CAS % of patients above threshold	CON % of patients above threshold	P value* CAS vs CON
Pain	87.5	70%	59%	0.1
Symptoms	84.0	57%	47%	0.2
Activities of daily living	87.5	67%	57%	0.2
Quality of life	66.0	49%	42%	0.3
*Pearson's Chi square test				

Table 3. This table presents the PASS thresholds at 3 years for each KOOS subscale [148]. The proportion of patients with score above threshold at 5 years for CAS and CON is compared for each KOOS subscale.

We used responder analysis to measure treatment success in paper III. We calculated the number of responders by the OMERACT-OARSI criteria, based on improvements in WOMAC scores for pain and function and EQ-5D quality of life. The responder analysis does not directly measure the patient's level of satisfaction, but uses a certain improvement in pain and functional scores to define treatment response. Consequently, a patient with a high treatment response is not necessarily satisfied, and a patient with a low treatment response could still be satisfied. A responder analysis was not included in the 1-year follow-up of the RCT, published by Gøthesen et al. [53]. This study compared PROs by mean differences in each

category. The minimal important change (MIC) for KOOS is considered to be 8-10 units [113, 145]. If the mean change between CAS and CON exceeded this difference, it was considered a clinically significant difference among the groups. The last years, it has been clearer to researchers that the MIC value should be used to measure differences before and after a treatment in the individual patient, and that the MIC value is not applicable to group comparisons [146, 150, 151]. MIC values also vary between different patient groups and treatments, and the MIC for KOOS in young patients after anterior cruciate ligament reconstruction is not similar to MIC for KOOS in patients undergoing TKA [152].

As recommended by Ewa Roos [151], we considered responder analyses to be more appropriate to compare the difference in PROs with CAS and CON. This was done at two-year follow up [130] and also in paper III. The use of responder analysis could be challenging, because the power of the study could be reduced and the cutoff value for a responder may be unclear [153]. In paper III, we used the terms “high responder”, “moderate responder” and “non-responder” to divide treatment response into three groups. The issue of cutoff values and power should be considered when interpreting the results.

1.3. Statistical methods

Survival and competing risk

In paper I and II, we used Kaplan-Meier curves and log-rank test to find differences in survival. Kaplan-Meier is a non-parametric method that illustrates the unadjusted implant survival in the two groups. In other words, it shows the *net failure*, which is the number of revisions assuming that no patients die or emigrate during follow-up [154]. To account for non-informative censoring, we used a competing risk model [125]. The competing risk model estimates the *crude failure*, which is the number of revisions in practice (since dead patients do not undergo revision) [154]. Estimates of the Cox regression model and the competing risk model are quite similar if the rate of death is low.

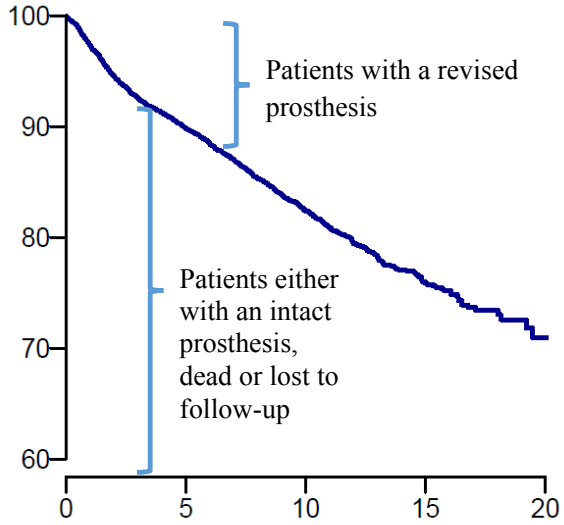


Figure 11. Example of Kaplan-Meier survival curve, illustrating survivorship of unicondylar knee arthroplasties from the Norwegian Arthroplasty Register, annual report 2018.

In paper I, the rate of deaths was 8.5 % in the CAS group and 10.4 % in the CON group and the rate of emigrations was 0.4 % in both groups (table 4). The difference in rate of deaths was statistically significant and the survival rates was further investigated in a competing risk model. However, the risk estimates of the competing risk model and the adjusted Cox regression models did not differ significantly, and we therefore assume that the number of deaths had a minor effect on the risk estimates.

	CAS, n (%)	CON, n (%)	P value
Alive at censoring	3338	17861	
Dead	311	2084	<0.001
Emigrated	16	74	0.6

Table 4. The number of deaths and emigrations for paper I is shown. P-values represent comparison with the number of patients alive at censoring (Pearson's Chi-Square test).

A similar competing risk model including deaths and emigrations was also used in paper II in estimation of changes in survival from period 1 to period 2. The estimated RR of revision was similar in the competing risk model and the Cox regression model both for TKA and UKA.

We presented the Kaplan-Meier survival and the Cox estimates as the main findings, because it presents the risk of revision assuming that the patient is still alive. This is the most relevant risk estimate for orthopedic surgeons and patients, and is considered preferable in arthroplasty register research [128, 155, 156]. A competing risk model could be appropriate in long-term follow-up or in cohorts of elderly or frail patients (such as hip fracture cohorts), which is not the case in our studies.

Factors that affect the survival rate

In paper I, the relative risk of revision for CAS relative to CON was calculated in a Cox regression model adjusted for age, sex, ASA category, prosthesis brand, fixation method, previous surgery and diagnosis. These covariates were included in the model because they were considered clinically relevant. With a high number of covariates, there is a risk of overadjustment bias. Overadjustment bias is defined as "*control for an intermediate variable (or a descending proxy for an intermediate variable) on a causal path from exposure to outcome*" [157]. We know from previous studies and reports that prosthesis brand and fixation method affect the revision rate [3, 71]. Table 1 in paper I showed that CAS had more prostheses with uncemented fixation

and the distribution of prosthesis brands was different in CAS and CON. Thus, the use of CAS (exposure) affected the choice of fixation method and prosthesis brand, which secondly affected the revision rate, as shown in the directed acyclic graph (DAG) 1 (figure 12).

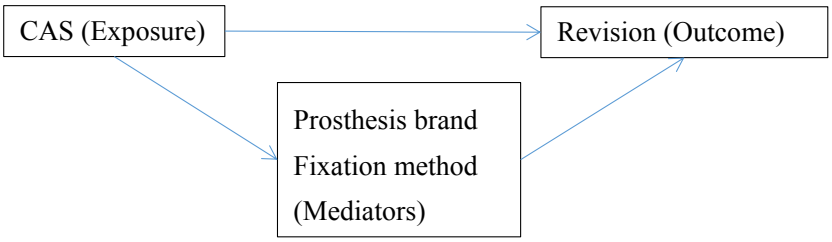


Figure 12. DAG 1.

In paper II, both TKA and UKA had more men in period 2, and the mean age was lower compared to period 1. The covariates age and sex are known to affect revision rate [158, 159]. In addition, the age and sex of the patient may affect the choice of prosthesis brand and fixation method. In this case, age and sex are confounders that have an effect on both the mediator and the outcome, illustrated in DAG 2 (figure 13). By adjusting for only age and sex in DAG 2, we find the total effect of having a TKA or UKA in period 2 compared to period 1. If we only adjust for the mediators, we open the pathway through the confounders and the effect of CAS on revision cannot be separated from the effect of the confounders.

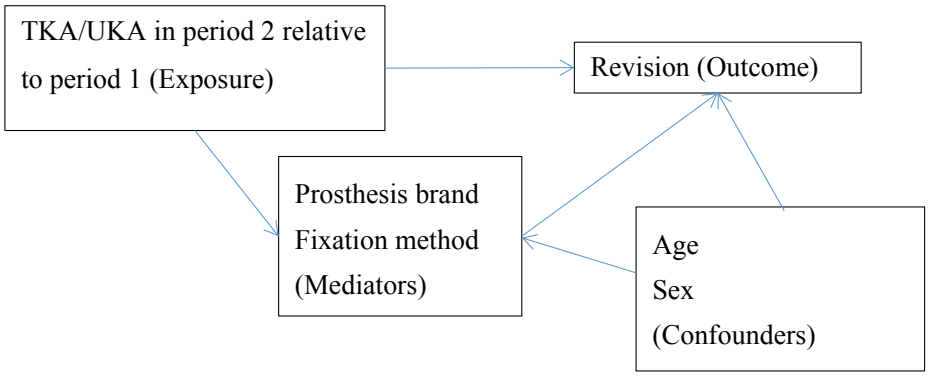


Figure 13. DAG 2.

To address the issue of overadjustment, we made an unadjusted survival estimate by Kaplan-Meier and Log-rank test (paper I and II). In paper I, we also performed simple Cox regression analyses adjusted only for age, sex and diagnosis; factors that were unlikely to have a mediating effect. In addition, we used a Cox regression model adjusted for a propensity score including more covariates. Propensity score is "*the probability of receiving one of the treatments being compared, given the measured covariates*" [160]. The use of propensity score is recommended for studies with a large number of confounders and a low number of events [160]. We used propensity score in paper I to investigate if inclusion of additional covariates would change the estimated effect of CAS. All four models showed that there was no statistically significant difference between CAS and CON, and the estimated treatment effect of CAS was similar for the three Cox regression models. However, there may be unmeasured covariates in all models that could affect the results.

Schoenfeld analysis

When the proportional hazard assumption (PH) is fulfilled, the relative risk of revision between two groups is constant over time [128]. The TKA cohort in paper II did not fulfill PH, and this was also an issue for some revision causes for TKA (infection, polyethylene wear/breakage and unexplained pain) and UKA (polyethylene wear/breakage). For survival of TKA, the Kaplan-Meier survival was

highest for period 1 at early follow-up, but the survival curves for period 1 and 2 were crossing at approximately 1 year. We investigated this further by Schoenfeld residuals, also known as partial residual plots [161]. These plots show the relative risk of revision for period 2 relative to period 1, as a function of time. Inspecting the Schoenfeld residuals makes it easier to understand how the proportion of early and late revisions changed during the two time periods for a certain cause of revision.

To address the non-PH assumption, the Cox regression model was stratified to follow-up intervals, where PH was fulfilled. The cut-points for these intervals were set individually for each revision cause, based on visual inspection of the Schoenfeld residuals and confirmed by statistical tests [129].

Sample size and statistical power

During the planning phase of paper III, power analyses were performed to calculate sample size for the two parts of the trial; RSA and PROs. We used 80% power and significance level 0.05 in all the following sample size calculations. For RSA, 0.1 mm was considered a clinically relevant difference between the groups. With a standard deviation of 0.1, 17 patients in each group was required. Due to the risk of drop-outs, 26 CAS and 28 CON were included. The MIC for KOOS was used to calculate the sample size for comparisons of PROs. As suggested from the developers of KOOS, a difference of 10 units was considered clinically relevant [113], and a standard deviation (SD) of 20 was used to calculate sample size. We needed 64 patients in each group, and 192 patients (97 CAS, 95 CON) were initially enrolled in the study. At 5 years, 21 patients in each group had valid RSA measures and 160 patients (82 CAS, 78 CON) participated at 5 years follow-up. All PRO subscales had at least 70 patients in each group. With this number of patients, we consider the power of the analyses as adequate.

As discussed in section 1.2, MIC should not be used to find between-group differences. In paper III, we used responder analyses as a secondary outcome. The responder criteria are based on changes in scores in the individual patient; an increase in absolute score of ≥20 points in pain or function, or ≥10 points in two out of three

of pain, function and global assessment of the disease defined a responder. The number of patients in paper III was based on differences in KOOS and the number was not necessarily high enough to prove a difference in the proportion of responders.

6. Discussion on the results

2.1. Survival of computer navigated implants

The main purpose of paper I was to compare CAS and CON with respect to implant survival and relative risk of revision. We found an almost identical implant survival at 8 years with 94.8% for CAS and 94.9% for CON. The AOANJRR did a study comparing CAS and CON in primary TKAs performed in Australia from 2003 to 2012. They found that the 9 years survival was 95.4% for CAS and 94.8% for CON, and this was not a significant difference. However, a subgroup of patients <65 years of age had a higher cumulative revision rate for CON compared to CAS, and the hazard ratio was 1.13 (CI: 1.03-1.25, p=0.01) [162]. In paper I, the relative risk of revision for patients of all ages and for patients <65 years was 0.8 (CI: 0.6-1.1, p=0.1) for CAS compared to CON, and the differences were not statistically significant. Knee prostheses have a low rate of revision, thus a large sample size and long follow-up is required to identify if one implant or method is beneficial compared to another. A power calculation (not published) showed that 8158 patients is needed in each group to detect an increase in survival from 94% to 95% (power 80%, significance level 0.05) [163]. Our study did not have enough CAS patients to detect a difference between the groups according to this calculation. Thus, there is a risk of type II error, which means failing to reject a false null hypothesis. Australia has a larger population than Norway and a higher life time risk of knee arthroplasty [6]. In addition, a higher proportion of knee arthroplasties in Australia are performed with CAS [9]. Consequently, the Norwegian cohort needs a longer period of inclusion and a longer follow-up to achieve a similar statistical power. The 13% increased risk of revision for the Australian below 65 cohort is not necessarily clinically significant, and can be caused by a number of factors others than the use of CAS and CON; surgeon factors, patient factors and selection bias to mention some. Low power may also explain why

RCTs with a long follow-up do not find difference in survival between CAS and CON [55, 164, 165].

Study	Number of patients	Number of patients <65 years	Survival all ages (%)*	Survival <65 years (%)*	RR all ages (CI)**	RR patients <65 years
Paper I – Dyrhovden et al. 2016 (NAR)						
CAS	3665	1292	94.8	93.6	0.8 (0.7-1.0)	0.8 (0.6-1.1)
CON	20019	6481	94.9	92.4	1	1
de Steiger et al. 2015 (AOANJRR)						
CAS	44573	16020	95.4	93.7	0.95 (0.9-1.0)**	0.88 (0.8-0.97)
CON	270545	87984	94.8	92.2	1	1
*** 8 years survival for NAR, 9 years survival for AOANJRR** **** HRs are inverted for easier comparison (presented as CON relative to CAS in the article)**						

Table 5. Comparison of the number of patients and results of paper I and de Steiger et al. 2015 [162].

We included five prosthesis brands in the paper I; AGC (Biomet, Warsaw, IN, USA), Duracon (Stryker, Kalamazoo, MI, USA), e.motion (B. Braun, Melsungen, Germany), LCS complete (DePuy, Warsaw, IN, USA) and Profix (Smith & Nephew, Memphis, TN, USA). We compared CAS and CON in subgroups of each prosthesis brand, but found no significant difference in relative risk of revision in the adjusted Cox regression model. This result differs from the short-term follow-up from 2011 by Gøthesen et al. [123]. In the short-term follow-up, the mobile bearing LCS complete had a significantly higher risk of revision in CAS compared to CON (RR=2.1, CI:

1.3-3.4), whereas the other prosthesis brands had no difference in risk of revision for CAS versus CON [123]. There is no clear reason why the LCS complete had a higher risk of revision at short-term, but the authors suggested that the inferior survival may result from technical difficulties with navigation of the implant. In addition, LCS complete had a high risk of revision compared to Profix implants in a study of non-navigated TKAs from the NAR, primarily due to an increased risk of loosening of the tibial component (RR=7.7, CI: 4.1-14.4) [71]. However, the use of CAS did not affect the risk of revision for LCS complete in paper I. This could result from a learning curve at the hospitals using CAS for LCS complete or due to updated versions of the navigation system used with LCS complete. Unfortunately, the software version of the navigation system is not reported to the NAR, and we were therefore not able to control for this.

The arthroplasty register in New Zealand compared CAS and CON using the Triathlon TKA system at 5 years follow-up [56]. According to their findings, CAS and CON had similar risk of revision for all implants and a non-significant tendency of higher risk of revision for CAS in patients <65 years. This indicates that survival of CAS may be implant-specific and illustrates that introduction of new technology could increase the risk of revision, despite promising results in small-scale studies.

Another important question is whether the rate of improvement is clinically and economically relevant. Gøthesen et al. used a Markov model to calculate the percentage improvement in implant survival that is needed to be cost-effective [166]. The cost-benefit calculation was based on the Norwegian health care sector's threshold value for acceptable added cost per quality-adjusted life year gained [167]. The result depended on the hospital's annual TKA volume and the average age of the patients. In a cohort of patients aged 60 years and an annual hospital volume of 25 TKAs, an improvement in 10 years survival from 89.8% to 90.6% is cost-effective. If the age of the patients increase to 75 years and the hospital volume is 250 TKAs annually, cost-effectiveness is achieved with an improvement in 10 years survival from 95.4% to 95.7%. A study by Slover et al. suggested that the annual revision rate should be reduced with 2% in a center with 250 CAS procedures annually and 13% in

a center with 25 annual procedures [168]. Both studies indicate that CAS is cost-effective in high-volume centers, but is less likely to be cost-effective in centers with a low annual CAS volume. Based on the results from paper I, introducing CAS in a large scale is so far not cost-effective in Norway.

2.2. Learning curve

In the NAR paper on short-term follow-up of CAS and CON, 2 years survival was 96% for CAS and 98% for CON [123]. One possible explanation for the difference is that there was a learning curve in each hospital during introduction of CAS. Smith et al. and Jenny et al. studied the learning curve of CAS, comparing TKA patients operated by experienced CAS surgeons compared to surgeons unexperienced with CAS [126, 169]. The experienced and unexperienced surgeons had similar results regarding post-operative alignment, functional outcomes (Oxford knee score, Knee Society score and range of motion) and complications. In both studies, the operating time was longer for unexperienced surgeons, but this difference was not found after 20-30 operations for all included centers.

To explore the learning curve in paper I, we divided the CAS patients in two groups; one group including the 30 first CAS TKAs at each hospital (unexperienced group) and the rest of the CAS TKAs in the second group (experienced group). Comparing CAS patients in the unexperienced group to all CON patients, we found no difference in relative risk of revision (RR=1.1, CI: 0.7-1.5). In the unexperienced group, median operating time was 31 minutes longer than for the CON group ($p<0.001$). In contrast to the studies by Smith et al. and Jenny et al., the operating time in the experienced CAS group was still 17 minutes longer than for the CON group ($p<0.001$). One explanation could be that many hospitals have more than one surgeon performing CAS, and the learning curve for one hospital would be more than 30 procedures if the operations are dispersed on a number of surgeons. In a previous Norwegian study, one experienced surgeon performed all operations in the CAS and CON group, using 11 minutes longer for CON in average ($p<0.001$) [170]. This study exemplifies that an experienced surgeon can use CAS without adding time compared to CON.

2.3. Time trends in survival free from revision for TKA and UKA

The 10 years survival rate for TKA improved from 91% in period 1 to 94% in period 2. A similar improvement is reported from the Swedish Knee Arthroplasty Register (SKAR) [11], which showed an improved 10 years survival from 92% for TKAs performed during 1987 to 1996 to 96% during 2007-2016. The survival for TKA in NAR is comparable to what other joint registries found from the same time period, shown in table 6. UKA had a non-significant improved 10 years survival rate from 80% in period 1 to 81% in period 2. This survival rate is dramatically lower than for TKA, but also lower than the UKA survival rates that are reported from some other large joint registries (table 6). The differences between countries could be explained by various reasons, like differences in implants, fixation, selection of patients, surgeon/hospital volumes, thresholds for revision, and completeness of reporting of revisions. Improvement of implant survival is multifactorial, and correlations found in registry studies must be confirmed by RCTs.

Joint registry	TKA 10 years survival rate (%)	UKA 10 years survival rate (%)	Year of operation
NAR (Norway, paper II)	94	81	2005-2015
SKAR (Sweden) [11]	96	86	2007-2016
AOANJRR (Australia) [9]	95	85	2003-2017
NZJR (New Zealand) [66]	96	90	2000-2017
NJR England & Wales [10]	96	89	2003-2017

Table 6. Overview of 10 years survival rates of TKA and UKA from paper II compared to other large joint registries.

Previous registry studies from NAR have shown a correlation between a high hospital volume and a lower risk of revision for TKA and UKA [82, 83]. Since 2000, there was an increase in hospitals with a high UKA volume (more than 21 per year), but

also an increase in the number of hospitals with an annual UKA volume less than 10. The type of implants changed extensively from period 1 to period 2 for TKA, whereas the Oxford® Phase 3 was the dominant UKA implant in both periods, indicating that improvement in design was less extensive for UKA as for TKA. Since its introduction in 2011, the use of Oxford Partial Knee has increased to >90% of UKAs in Norway in 2016-2018 [3]. A high use of one implant could be an advantage in a country with a low number of UKAs annually, but it is also vulnerable since long-term results of this specific implant is unclear, and continuous surveillance of UKA survival is necessary.

2.4. Causes of revision

Revision causes for computer navigated TKAs (paper I)

In paper II, deep infection and malalignment were the most common revision causes. The rate of deep infection was similar for CAS and CON, but the CAS group had a lower risk of revision due to malalignment. This indicates that CAS leads to fewer patients with severe malalignment and need for a subsequent revision. This finding fits with the results from previous studies, in which CAS patients had fewer outliers on postoperative radiographs [27, 44, 50, 53, 170-173]. In the survivorship study from AOANJRR, the CAS group had a significantly lower risk of revision due to loosening in patients <65 years. Loosening was the most common revision cause for both CAS and CON in this age group [162]. Differences between the two registry studies could be explained by differences in patient demographics or the use of implants. The Australian study included adjustments for age and sex only, whereas factors like implant, fixation method or diagnosis were not taken into account. If important demographic variables differed among the study groups, it could skew the results, as shown in previous studies and reports from arthroplasty registers [3, 9, 71].

Time trends in revision causes for TKA and UKA (paper II)

In paper II, patients are included in the registry over a long period of time, and changes over time in registration procedures may affect the results. This type of bias is difficult to detect, because the bias and the change in revision cause are trends that

change over time. One example is the inclusion of the revision cause “progression of osteoarthritis”, that was introduced in the NAR registration form in 2011. Before this change, the surgeon would have to tick the box “other” and then write “progression of osteoarthritis” in a text-field in hand writing. Possibly, many surgeons classified these patients with “pain” or “other” with no further specification. Consequently, there was a dramatic increase of revisions due to progression of osteoarthritis from 1 TKA and 4 UKA in period 1 to 21 TKA and 83 UKA in period 2.

Unexplained pain was a common revision cause for TKA and UKA in both periods. This high number could be caused by misclassification, but it is still worrying that many patients are revised without a clear diagnosis. From our data, it is impossible to distinguish between a real change in revisions for unexplained pain and a change in registration procedures. In addition to this example, there may also be other less obvious changes in the classification of revisions that influence the results. If surgeon awareness for a specific revision cause is changed, i.e. infections, the registered number of revisions for infection will increase regardless of the real number of infections.

From period 1 to period 2, there was a decline in revisions caused by polyethylene wear/breakage. In 2013-2015, highly crosslinked polyethylene was only used in 8% of TKAs [174], indicating that locking mechanisms, sterilizing and polishing has also played a role in improving the quality of polyethylene components [175-177]. Improvements in implant design, like improved patella tracking, may have contributed to the reduction of revisions resulting from aseptic loosening of the femoral component and patella dislocation. It is also shown that pressurizing and bi-surface cementing technique reduces loosening of the femoral component [178]. The same change was not found for the tibial component, and tibial loosening was the third most common revision cause in period 2.

The most commonly used implant in period 2 was LCS complete, which has previously shown an increased risk of tibial aseptic loosening (RR=7.7, CI: 4.1-14.4) in a Norwegian registry study [71]. The high use of this implant probably contributed

to the lack of improvement in tibial loosening in period 2. A Norwegian retrieval study of revised LCS complete tibial components found that 12 of 22 components loosened at the implant-cement interface, and only 3 at the bone-cement interface [179]. A low surface roughness, non-keeled stem and a thin cement layer were suggested as possible reasons for mechanical loosening. Although this study only included one implant design, the results illustrate that improvement in design and cementing technique for the tibial component is needed.

Arthrofibrosis was not a common revision cause. This diagnosis is not well defined and reoperations for this reason often includes soft tissue procedures without component removal or exchange, which are not included in the NAR. For this reason, a consensus statement from 2016 suggested that joint registries are not suitable to identify patients with post-surgical joint fibrosis [180]. Thus, the true number of patients with arthrofibrosis in paper II is unknown.

The risk of early postoperative revisions for infection was increased in period 2, with a fivefold increase the first 1.5 months. A similar increase is also observed in Scandinavian studies of hip arthroplasties [181, 182]. One explanation could be a new approach to prosthetic infections, with higher awareness and earlier removal of the components (rather than protracted antibiotic treatment) [183]. Higher awareness to infections could also lead to an improved reporting rate of low-grade infections. These patients may have been classified as “aseptic loosening” or “pain” in period 1. Since the registration form is completed immediately after surgery, the diagnosis is not confirmed by microbiological samples. Over-reporting of uncertain infections, such as prolonged wound drainage, could have contributed to a high number of reported infections in period 2. Early revision of infection can be one explanation to the lower risk of late revision (>1 year) for infection in period 2, but this cannot be concluded from a registry study.

Instability and malalignment are still important causes of failure for TKA, which was also found by Thiele et al. [74]. This illustrates the importance of optimizing alignment and soft tissue balancing in knee arthroplasty, in which CAS could be an

important tool. In paper I, fewer revisions for malalignment was observed in the CAS group. A more extensive use of CAS may contribute to address the problem of malalignment and instability, but this should be explored in future studies with a higher number of patients than in paper I.

In paper II, UKA was not divided into medial and lateral UKA. Lateral UKA is far less common than medial UKA and the procedure is considered different regarding surgical technique and outcome [184]. Previous studies of lateral UKA failure include a small number of patients and the causes of revision are not shown to be different from medial UKA revisions [185]. Survival of lateral UKA was similar to medial UKA in a review by van der List et al. [186]. Registration of medial and lateral UKA started in 1999 in NAR, and the variable has many missing values. We did no separate analyses of medial and lateral UKA in paper II due to this uncertainty. There are few lateral UKA in Norway and the results from paper II are most relevant for medial UKA.

	Medial	Lateral	Missing data
Period 1	929	17	1351
Period 2	4369	63	919

Table 7. The number of medial UKA, lateral UKA and missing data (UKAs not classified as medial or lateral) in period 1 (1994-2004) and period 2 (2005-2015).

2.5. Radiological outcomes

RSA

5 years postoperative, there was no statistically significant difference in rotation or migration of the tibial component for CAS and CON; the same result as Petursson et al. found at 2 years follow-up [131]. This also correlates with a systematic review by Pijls et al., where cemented TKAs had little migration from 6 months to 5 years [92]. Teeter et al. found that varus alignment of the tibial component after TKA was

associated with increased migration and lateral liftoff at 10 years follow-up [90]. In our study, only 5 patients had postoperative tibial varus alignment, and the study was underpowered to correlate alignment to migration. We found no other studies comparing migration for CAS and CON after TKA. There was a tendency of more migration (MTPM) in the CAS group. Possibly the difference would have proven significant if we had more patients (type II error). Due to a low number of patients in the RSA study however; a couple of outliers can significantly skew the results, as discussed earlier.

Radiolucent lines

A comparison of radiolucent lines around the components was one of the secondary outcomes in paper III. Results from 3 months and 5 years postoperative radiographs showed that only 9 patients had radiolucent lines of >4mm at 5 years, and there was no significant difference between CAS and CON. Napier et al. found radiolucent lines of >1mm in 12 out of 240 knees 10 years after TKA with LCS complete, supporting that radiolucent lines are not very common after TKA, even at long-term follow-up [187]. To our knowledge, no other studies have compared radiolucent lines for CAS and CON. The correlation between radiolucent lines and loosening of the implant is uncertain and has not been confirmed in contemporary studies [188]. Only 7 of the patients included in paper III were revised within 5 years (3 infection <2 months, 1 instability, 1 periprosthetic fracture, 1 arthrofibrosis, 1 unexplained pain), and this number is too low to associate revisions to radiolucent lines.

2.6. Patient reported outcomes (PROs)

In paper III, CAS had more high responders for pain score, and the number needed to treat (NNT) was 7. There was no significant difference in the number of patients classified as high responders in function or the proportion of high, moderate or non-responders according to the OMERACT-OARSI criteria. At 2 years follow-up from the same trial, the CAS group had more high responders for both pain and function [130]. Compared to the CON group, CAS also had more patients classified as high responders and fewer patients classified as moderate responders at 2 years [130]. At 2

years, 3 of 11 PRO subscales were significantly in favor of CAS, whereas none of the subscales differed statistically or clinically significant between CAS and CON at 5 years (paper III). To our knowledge, no other clinical trials have used responder analyses in comparing CAS and CON over time. Kim et al. presented a randomized trial with 15 years follow-up of 282 patients younger than 65 years old, operated by the same surgeon with bilateral TKA; one knee operated with CAS and one knee operated with CON [55]. They found no difference in alignment, Kaplan-Meier survivorship, KSS, WOMAC score, UCLA activity score or patient satisfaction at final follow-up. The study had a high proportion of female patients (74%) and a lower age (59 (SD 5) years) compared to the patients in paper III (60% women, age 69 (SD 7) years, so the results are not directly comparable. Still, it shows similar long-term results for CAS and CON, which is comparable to the 5 years follow-up in paper III. Comparing the results at 2 and 5 years from the same patients, it seems like the differences in PROMs are equalized within 5 years. This may indicate that the long-term clinical benefit of CAS is small. Similar results at 5 years could also be a result of response shift, which means that the patients adapt to their new situation over time [98].

Both CAS and CON had a high improvement in PRO scores from preoperative to 5 years. In 10 of the 12 included PRO dimensions, CAS had a higher number of patients achieving the highest possible score (ceiling effect). A similar pattern was found in the 2-years follow up of the same patients; all PRO dimensions had higher ceiling effect in the CAS group, and the difference was statistically significant in 4 PRO dimensions. The lowest ceiling effect was found for KSS knee score and KOOS SportRec [130]. A study by Aunan et al. comparing patella resurfaced and non-resurfaced TKA found a high ceiling effect for KSS function score, VAS-satisfaction and KOOS (19-40%). KSS knee score and Oxford knee score had 16% ceiling effect, and KOOS SportRec had the lowest ceiling effect (6%) [189].

When a high number of patients reach a ceiling effect, it indicates that the scoring system is not capable of detecting the size of the improvement from the treatment. A high ceiling effect increases the risk of type II error; to overlook a true difference

between the groups. Ceiling effect is an important limitation, and a maximum ceiling effect of 15% is a quality criterion for health status questionnaires [99]. In paper III, the ceiling effect was above 15% in 10 out of 12 PROs for CAS and 6 out of 12 categories for CON. KOOS SportRec had the lowest ceiling effect with 9% for CAS and 4% for CON. The average improvement from preoperative to 5 years for KOOS SportRec was 7.6 points (CI: -1.9-17, p=0.1) higher in the CAS group compared to CON, which was the category with the largest difference in improvement among the treatment groups. We do not know how high the patients would score on a scale with no ceiling effect or whether there would be a difference in scores between CAS and CON. Higher ceiling effect for CAS patients could indicate that CAS would have the highest scores in a different scale, but this cannot be confirmed by the data in paper III.

Due to the increasing demand of TKAs in the future and patient's high expectations, there is a need for further improvement in the outcome of TKA. Although the PROs in paper III did not show a difference between CAS and CON, the available scoring systems are not sensitive enough to separate "good" from "very good" results. The Forgotten Joint Score is shown to be more responsive to change compared to WOMAC and EQ-5D, and it has a low ceiling effect compared to WOMAC, EQ-5D, KSS and Oxford Knee Score (Still, the ceiling effect is 16-33% at 1-4 years follow-up after TKA, which is higher than recommended) [190, 191]. If CAS is a method that can improve the result of an average patient from good to very good, the method could be beneficial regardless of improvement in survival rates. To answer this question, future studies should use scoring systems for knee-specific health status with minimal ceiling effects.

Conclusions

Paper I

- In the Norwegian cohort, CAS and CON did not differ significantly in 8 years overall survivorship.
- Patients operated with CAS had a lower risk of revision due to malalignment.

Paper II

- There was an improvement in overall survivorship for TKA in the last time period, but similar improvement was not found for UKA, and the survivorship for UKA remains remarkably lower than for TKA.
- TKA had an increasing risk of early revisions due to infection and a decrease in risk of revision due to aseptic loosening of the femoral component, patella dislocation, polyethylene wear/breakage and unexplained pain. UKA had more revisions resulting from progression of osteoarthritis in period 2, but a decrease in revisions resulting from aseptic loosening, polyethylene wear/breakage and periprosthetic fractures.
- For TKAs and UKAs, age younger than 65 years was associated with a higher risk of revision. For TKAs, a higher risk of revision was found for male sex, but sex did not affect the risk of revision for UKAs.

Paper III

- There was no statistically significant difference in implant migration or the occurrence of radiolucent lines between CAS and CON at 5 years follow-up.
- The CAS group had a higher number of patients with a high pain reduction compared to the CON group, but there was no difference in the number of responders based on mean pain, function and quality of life.
- There were no differences in the amount of improvement of patient-reported pain, function and quality of life from preoperative to 5 years follow-up between CAS and CON.

Future research

Long term survivorship with at least 15 years follow-up of CAS versus CON should be evaluated, including patient characteristics that are associated with a higher or lower risk of revisions in the CAS group. This is especially important since CAS is claimed to improve survivorship in young patients, with a long life expectancy. To find the best selection of patients for CAS, it is also important to identify subgroups of patients that have the highest benefits of CAS (i.e. age groups, comorbidities, preoperative PROs).

Despite the improvement of TKA survival the last decade, it is concerning that survival of UKA is unchanged. Future studies should focus on factors that can improve UKA survival, i.e. patient selection and implant design. New technologies should be developed to simplify this technically demanding procedure, and CAS and robotic technology may be a tool worth studying for UKA as well.

A large, population-based randomized trial that compares survivorship and PROs in CAS compared to CON is needed. A registry-based randomized trial is a suitable design, because a large patient sample could be included at low costs compared to traditional RCTs. To perform this type of study, a knee arthroplasty register that collects data on revisions and PROs pre- and postoperatively is needed.

It is still uncertain whether malalignment leads to poor implant survival. To address this issue, a study that correlates alignment to migration by RSA or long term survival should be performed. Malalignment and instability are still common revision causes. Further development of implants and technologies is important to reduce the number of these revisions. However, this should be introduced in a small scale, under control of RCTs and registry studies to control the effects in short and long term.

For most patients the clinical outcome after TKA is very good. There is a need of knee-specific scoring systems with a low ceiling effect in order to separate *good* from *very good* results. Such a scoring system would be useful in studies of CAS and also generally for patient groups with high demands of knee function.

Source of data

1. Arden N, Nevitt MC. *Osteoarthritis: epidemiology. Best practice & research Clinical rheumatology.* 2006;20(1):3-25.
2. Michael JW, Schluter-Brust KU, Eysel P. *The epidemiology, etiology, diagnosis, and treatment of osteoarthritis of the knee.* Deutsches Arzteblatt international. 2010;107(9):152-62.
3. No authors listed. *Norwegian Arthroplasty Register Annual Report*. 2019: Bergen, Norway.
4. Carr AJ, Robertsson O, Graves S, Price AJ, Arden NK, Judge A, Beard DJ. *Knee replacement.* Lancet. 2012;379(9823):1331-40.
5. Skou ST, Roos EM, Laursen MB, Rathleff MS, Arendt-Nielsen L, Simonsen O, Rasmussen S. *A Randomized, Controlled Trial of Total Knee Replacement.* The New England journal of medicine. 2015;373(17):1597-606.
6. Ackerman IN, Bohensky MA, de Steiger R, Brand CA, Eskelinen A, Fenstad AM, Furnes O, Garellick G, Graves SE, Haapakoski J, Havelin LI, Makela K, Mehnert F, Pedersen AB, Robertsson O. *Substantial rise in the lifetime risk of primary total knee replacement surgery for osteoarthritis from 2003 to 2013: an international, population-level analysis.* Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society. 2017;25(4):455-61.
7. Hansen EN, Ong KL, Lau E, Kurtz SM, Lonner JH. *Unicondylar Knee Arthroplasty in the U.S. Patient Population: Prevalence and Epidemiology.* American journal of orthopedics (Belle Mead, NJ). 2018;47(12).
8. Gothesen O, Lygre SHL, Lorimer M, Graves S, Furnes O. *Increased risk of aseptic loosening for 43,525 rotating-platform vs. fixed-bearing total knee replacements.* Acta orthopaedica. 2017;88(6):649-56.
9. No authors listed. *Australian Orthopaedic Association National Joint Replacement Registry. Annual Report.* 2018: Adelaide, Australia. p. 230.
10. No authors listed. *National Joint Registry for England, Wales, Northern Ireland and the Isle of Man. Annual report 2018.* 2018: Hemel Hempstead, England.
11. No authors listed. *Swedish Knee Arthroplasty Register. 2017 Annual Report.* 2017: Lund, Sweden.
12. Patel A, Pavlou G, Mujica-Mota RE, Toms AD. *The epidemiology of revision total knee and hip arthroplasty in England and Wales: a comparative analysis with projections for the United States. A study using the National Joint Registry dataset.* The bone & joint journal. 2015;97-b(8):1076-81.
13. Kurtz SM, Ong KL, Schmier J, Mowat F, Saleh K, Dybvik E, Karrholm J, Garellick G, Havelin LI, Furnes O, Malchau H, Lau E. *Future clinical and economic impact of revision total hip and knee arthroplasty.* The Journal of bone and joint surgery American volume. 2007;89 Suppl 3:144-51.

14. Bozic KJ, Lau E, Kurtz S, Ong K, Berry DJ. *Patient-related risk factors for postoperative mortality and periprosthetic joint infection in medicare patients undergoing TKA.* Clinical orthopaedics and related research. 2012;470(1):130-7.

15. Bozic KJ, Kamath AF, Ong K, Lau E, Kurtz S, Chan V, Vail TP, Rubash H, Berry DJ. *Comparative Epidemiology of Revision Arthroplasty: Failed THA Poses Greater Clinical and Economic Burdens Than Failed TKA.* Clinical orthopaedics and related research. 2015;473(6):2131-8.

16. Greidanus NV, Peterson RC, Masri BA, Garbuz DS. *Quality of life outcomes in revision versus primary total knee arthroplasty.* The Journal of arthroplasty. 2011;26(4):615-20.

17. Pearse AJ, Hooper GJ, Rothwell A, Frampton C. *Survival and functional outcome after revision of a unicompartmental to a total knee replacement: the New Zealand National Joint Registry.* The Journal of bone and joint surgery British volume. 2010;92(4):508-12.

18. Lindberg MF, Miaskowski C, RustoEn T, Rosseland LA, Cooper BA, Lerdal A. *Factors that can predict pain with walking, 12 months after total knee arthroplasty.* Acta orthopaedica. 2016;87(6):600-6.

19. Brander VA, Stulberg SD, Adams AD, Harden RN, Bruehl S, Stanos SP, Houle T. *Predicting total knee replacement pain: a prospective, observational study.* Clinical orthopaedics and related research. 2003(416):27-36.

20. Hawker G, Wright J, Coyte P, Paul J, Dittus R, Croxford R, Katz B, Bombardier C, Heck D, Freund D. *Health-related quality of life after knee replacement.* The Journal of bone and joint surgery American volume. 1998;80(2):163-73.

21. Beswick AD, Wylde V, Gooberman-Hill R, Blom A, Dieppe P. *What proportion of patients report long-term pain after total hip or knee replacement for osteoarthritis?* A systematic review of prospective studies in unselected patients. BMJ open. 2012;2(1):e000435.

22. Dunbar MJ, Richardson G, Robertsson O. *I can't get no satisfaction after my total knee replacement: rhymes and reasons.* The bone & joint journal. 2013;95-b(11 Suppl A):148-52.

23. Schroer WC, Berend KR, Lombardi AV, Barnes CL, Bolognesi MP, Berend ME, Ritter MA, Nunley RM. *Why are total knees failing today? Etiology of total knee revision in 2010 and 2011.* The Journal of arthroplasty. 2013;28(8 Suppl):116-9.

24. Jeffery RS, Morris RW, Denham RA. *Coronal alignment after total knee replacement.* J Bone Joint Surg (Br). 1991;73(5):709-14.

25. Ritter MA, Davis KE, Meding JB, Pierson JL, Berend ME, Malinzak RA. *The effect of alignment and BMI on failure of total knee replacement.* J Bone Joint Surg (Am). 2011;93(17):1588-96.

26. Rand JA, Coventry MB. *Ten-year evaluation of geometric total knee arthroplasty.* Clinical orthopaedics and related research. 1988(232):168-73.

27. Choong PF, Dowsey MM, Stoney JD. *Does accurate anatomical alignment result in better function and quality of life? Comparing conventional and computer-assisted total knee arthroplasty.* The Journal of arthroplasty. 2009;24(4):560-9.

28. Longstaff LM, Sloan K, Stamp N, Scaddan M, Beaver R. *Good alignment after total knee arthroplasty leads to faster rehabilitation and better function.* The Journal of arthroplasty. 2009;24(4):570-8.

29. Bellemans J, Colyn W, Vandenneucker H, Victor J. *The Chitranjan Ranawat award: is neutral mechanical alignment normal for all patients? The concept of constitutional varus.* Clinical orthopaedics and related research. 2012;470(1):45-53.

30. Vanlommel L, Vanlommel J, Claes S, Bellemans J. *Slight undercorrection following total knee arthroplasty results in superior clinical outcomes in varus knees.* Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA. 2013;21(10):2325-30.

31. Bellemans J. *Neutral mechanical alignment: a requirement for successful TKA: opposes.* Orthopedics. 2011;34(9):e507-9.

32. Lombardi AV, Jr., Berend KR, Ng VY. *Neutral mechanical alignment: a requirement for successful TKA: affirms.* Orthopedics. 2011;34(9):e504-6.

33. Howell SM, Howell SJ, Kuznik KT, Cohen J, Hull ML. *Does a kinematically aligned total knee arthroplasty restore function without failure regardless of alignment category?* Clinical orthopaedics and related research. 2013;471(3):1000-7.

34. Howell SM, Papadopoulos S, Kuznik KT, Hull ML. *Accurate alignment and high function after kinematically aligned TKA performed with generic instruments.* Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA. 2013;21(10):2271-80.

35. Victor J. *Optimising position and stability in total knee arthroplasty.* EFORT open reviews. 2017;2(5):215-20.

36. Dossett HG, Estrada NA, Swartz GJ, LeFevre GW, Kwasman BG. *A randomised controlled trial of kinematically and mechanically aligned total knee replacements: two-year clinical results.* The bone & joint journal. 2014;96-b(7):907-13.

37. Young SW, Walker ML, Bayan A, Briant-Evans T, Pavlou P, Farrington B. The Chitranjan S. Ranawat Award : *No Difference in 2-year Functional Outcomes Using Kinematic versus Mechanical Alignment in TKA: A Randomized Controlled Clinical Trial.* Clinical orthopaedics and related research. 2017;475(1):9-20.

38. Allen MM, Pagnano MW. *Neutral mechanical alignment: Is it Necessary?* The bone & joint journal. 2016;98-b(1 Suppl A):81-3.

39. Gromov K, Korchi M, Thomsen MG, Husted H, Troelsen A. *What is the optimal alignment of the tibial and femoral components in knee arthroplasty?* Acta orthopaedica. 2014;85(5):480-7.

40. Mezger U, Jendrewski C, Bartels M. *Navigation in surgery.* Langenbeck's archives of surgery. 2013;398(4):501-14.

41. Krackow KA, Bayers-Thering M, Phillips MJ, Mihalko WM. *A new technique for determining proper mechanical axis alignment during total knee arthroplasty: progress toward computer-assisted TKA.* Orthopedics. 1999;22(7):698-702.

42. Deep K, Shankar S, Mahendra A. *Computer assisted navigation in total knee and hip arthroplasty.* Sicot-j. 2017;3:50.

43. Saragaglia D, Picard F, Chaussard C, Montbarbon E, Leitner F, Cinquin P. [*Computer-assisted knee arthroplasty: comparison with a conventional procedure. Results of 50 cases in a prospective randomized stud*y]. Revue de chirurgie orthopedique et reparatrice de l'appareil moteur. 2001;87(1):18-28.

44. Bathis H, Perlick L, Tingart M, Luring C, Zurakowski D, Grifka J. *Alignment in total knee arthroplasty. A comparison of computer-assisted surgery with the conventional technique.* The Journal of bone and joint surgery British volume. 2004;86(5):682-7.

45. Chauhan SK, Scott RG, Breidahl W, Beaver RJ. *Computer-assisted knee arthroplasty versus a conventional jig-based technique. A randomised, prospective trial.* The Journal of bone and joint surgery British volume. 2004;86(3):372-7.

46. Matziolis G, Krocker D, Weiss U, Tohtz S, Perka C. *A prospective, randomized study of computer-assisted and conventional total knee arthroplasty. Three-dimensional evaluation of implant alignment and rotation.* The Journal of bone and joint surgery American volume. 2007;89(2):236-43.

47. Chin PL, Yang KY, Yeo SJ, Lo NN. *Randomized control trial comparing radiographic total knee arthroplasty implant placement using computer navigation versus conventional technique.* The Journal of arthroplasty. 2005;20(5):618-26.

48. Lionberger DR, Weise J, Ho DM, Haddad JL. *How does electromagnetic navigation stack up against infrared navigation in minimally invasive total knee arthroplasties?* The Journal of arthroplasty. 2008;23(4):573-80.

49. Lustig S, Fleury C, Goy D, Neyret P, Donell ST. *The accuracy of acquisition of an imageless computer-assisted system and its implication for knee arthroplasty.* The Knee. 2011;18(1):15-20.

50. Jones CW, Jerabek SA. *Current Role of Computer Navigation in Total Knee Arthroplasty.* The Journal of arthroplasty. 2018.

51. Cheng T, Zhao S, Peng X, Zhang X. *Does computer-assisted surgery improve postoperative leg alignment and implant positioning following total knee arthroplasty? A meta-analysis of randomized controlled trials?* Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA. 2012;20(7):1307-22.

52. Shi J, Wei Y, Wang S, Chen F, Wu J, Huang G, Chen J, Wei L, Xia J. *Computer navigation and total knee arthroplasty.* Orthopedics. 2014;37(1):e39-43.

53. Gothesen O, Espehaug B, Havelin LI, Petursson G, Hallan G, Strom E, Dyrhovden G, Furnes O. *Functional outcome and alignment in computer-assisted and conventionally operated total knee replacements: a multicentre parallel-group randomised controlled trial.* The bone & joint journal. 2014;96-B(5):609-18.

54. Burnett RS, Barrack RL. *Computer-assisted total knee arthroplasty is currently of no proven clinical benefit: a systematic review.* Clinical orthopaedics and related research. 2013;471(1):264-76.

55. Kim YH, Park JW, Kim JS. 2017 *Chitranjan S. Ranawat Award: Does Computer Navigation in Knee Arthroplasty Improve Functional Outcomes in Young Patients? A Randomized Study.* Clinical orthopaedics and related research. 2018;476(1):6-15.

56. Roberts TD, Clatworthy MG, Frampton CM, Young SW. *Does Computer Assisted Navigation Improve Functional Outcomes and Implant Survivability after Total Knee Arthroplasty?* The Journal of arthroplasty. 2015;30(9 Suppl):59-63.

57. Ast MP, Nam D, Haas SB. *Patient-specific instrumentation for total knee arthroplasty: a review.* The Orthopedic clinics of North America. 2012;43(5):e17-22.

58. Nam D, McArthur BA, Cross MB, Pearle AD, Mayman DJ, Haas SB. *Patient-specific instrumentation in total knee arthroplasty: a review. The journal of knee surgery.* 2012;25(3):213-9.

59. Patil S, Bunn A, Bugbee WD, Colwell CW, Jr., D'Lima DD. *Patient-specific implants with custom cutting blocks better approximate natural knee kinematics than standard TKA without custom cutting blocks.* The Knee. 2015;22(6):624-9.

60. Pfitzner T, Abdel MP, von Roth P, Perka C, Hommel H. *Small improvements in mechanical axis alignment achieved with MRI versus CT-based patient-specific instruments in TKA: a randomized clinical trial.* Clinical orthopaedics and related research. 2014;472(10):2913-22.

61. Suero EM, Lueke U, Stuebig T, Hawi N, Krettek C, Liodakis E. *Computer navigation for total knee arthroplasty achieves better postoperative alignment compared to conventional and patient-specific instrumentation in a low-*

volume setting. Orthopaedics & traumatology, surgery & research : OTSR. 2018.

62. Ollivier M, Tribot-Laspiere Q, Amzallag J, Boisrenoult P, Pujol N, Beaufils P. *Abnormal rate of intraoperative and postoperative implant positioning outliers using "MRI-based patient-specific" compared to "computer assisted" instrumentation in total knee replacement.* Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA. 2016;24(11):3441-7.

63. Van Leeuwen J, Snorrason F, Rohrl SM. *No radiological and clinical advantages with patient-specific positioning guides in total knee replacement.* Acta orthopaedica. 2018;89(1):89-94.

64. Leeuwen JA, Grogaard B, Nordsletten L, Rohrl SM. *Comparison of planned and achieved implant position in total knee arthroplasty with patient-specific positioning guides.* Acta orthopaedica. 2015;86(2):201-7.

65. Victor J, Dujardin J, Vandenneucker H, Arnout N, Bellemans J. *Patient-specific guides do not improve accuracy in total knee arthroplasty: a prospective randomized controlled trial.* Clinical orthopaedics and related research. 2014;472(1):263-71.

66. No authors listed. *The New Zealand Joint Registry. Sixteen Year Report January 1999 to December 2014*. 2015: Wellington, New Zealand.

67. No authors listed. *Hip and Knee Replacements in Canada: Canadian Joint Replacement Registry 2015 Annual Report*. 2015: Toronto, Canada.

68. Fehring TK, Odum SM, Masonis JL, Springer BD. *Early failures in unicondylar arthroplasty.* Orthopedics. 2010;33(1):11.

69. Sharkey PF, Lichstein PM, Shen C, Tokarski AT, Parvizi J. *Why are total knee arthroplasties failing today--has anything changed after 10 years?* The Journal of arthroplasty. 2014;29(9):1774-8.

70. Shepard J, Ward W, Milstone A, Carlson T, Frederick J, Hadhazy E, Perl T. *Financial impact of surgical site infections on hospitals: the hospital management perspective.* JAMA surgery. 2013;148(10):907-14.

71. Gothesen O, Espehaug B, Havelin LI, Petursson G, Lygre S, Ellison P, Hallan G, Furnes O. *Survival rates and causes of revision in cemented primary total knee replacement: a report from the Norwegian Arthroplasty Register 1994-2009.* The bone & joint journal. 2013;95-B(5):636-42.

72. Lee BS, Cho HI, Bin SI, Kim JM, Jo BK. *Femoral Component Varus Malposition is Associated with Tibial Aseptic Loosening After TKA.* Clinical orthopaedics and related research. 2018;476(2):400-7.

73. Fehring TK, Odum S, Griffin WL, Mason JB, Nadaud M. *Early failures in total knee arthroplasty.* Clinical orthopaedics and related research. 2001(392):315-8.

74. Thiele K, Perka C, Matziolis G, Mayr HO, Sostheim M, Hube R. *Current failure mechanisms after knee arthroplasty have changed: polyethylene wear*

is less common in revision surgery. The Journal of bone and joint surgery American volume. 2015;97(9):715-20.

75. Wilson CJ, Theodoulou A, Damarell RA, Krishnan J. *Knee instability as the primary cause of failure following Total Knee Arthroplasty (TKA): A systematic review on the patient, surgical and implant characteristics of revised TKA patients.* The Knee. 2017;24(6):1271-81.

76. Vince KG, Abdeen A, Sugimori T. *The unstable total knee arthroplasty: causes and cures.* The Journal of arthroplasty. 2006;21(4 Suppl 1):44-9.

77. Arirachakaran A, Choowit P, Putananon C, Muangsiri S, Kongtharvonskul J. *Is unicompartmental knee arthroplasty (UKA) superior to total knee arthroplasty (TKA)? A systematic review and meta-analysis of randomized controlled trial.* European journal of orthopaedic surgery & traumatology : orthopedie traumatologie. 2015;25(5):799-806.

78. Wilson HA, Middleton R, Abram SGF, Smith S, Alvand A, Jackson WF, Bottomley N, Hopewell S, Price AJ. *Patient relevant outcomes of unicompartmental versus total knee replacement: systematic review and meta-analysis.* BMJ (Clinical research ed). 2019;364:l352.

79. Hansen EN, Ong KL, Lau E, Kurtz SM, Lonner JH. *Unicondylar Knee Arthroplasty Has Fewer Complications but Higher Revision Rates Than Total Knee Arthroplasty in a Study of Large United States Databases.* The Journal of arthroplasty. 2019.

80. Zuiderbaan HA, van der List JP, Khamaisy S, Nawabi DH, Thein R, Ishmael C, Paul S, Pearle AD. *Unicompartmental knee arthroplasty versus total knee arthroplasty: Which type of artificial joint do patients forget?* Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA. 2017;25(3):681-6.

81. Casper DS, Fleischman AN, Papas PV, Grossman J, Scuderi GR, Lonner JH. *Unicompartmental Knee Arthroplasty Provides Significantly Greater Improvement in Function than Total Knee Arthroplasty Despite Equivalent Satisfaction for Isolated Medial Compartment Osteoarthritis.* The Journal of arthroplasty. 2019;34(8):1611-6.

82. Badawy M, Espehaug B, Indrekvam K, Engesaeter LB, Havelin LI, Furnes O. *Influence of hospital volume on revision rate after total knee arthroplasty with cement.* The Journal of bone and joint surgery American volume. 2013;95(18):e131.

83. Badawy M, Espehaug B, Indrekvam K, Havelin LI, Furnes O. *Higher revision risk for unicompartmental knee arthroplasty in low-volume hospitals.* Acta orthopaedica. 2014;85(4):342-7.

84. Arias-de la Torre J, Valderas JM, Evans JP, Martin V, Molina AJ, Munoz L, Pons-Cabrafiga M, Espallargues M. *Differences in Risk of Revision and Mortality Between Total and Unicompartmental Knee Arthroplasty. The Influence of Hospital Volume.* The Journal of arthroplasty. 2019;34(5):865-71.

85. Selvik G. Roentgen stereophotogrammetry. *A method for the study of the kinematics of the skeletal system.* Acta orthopaedica Scandinavica Supplementum. 1989;232:1-51.

86. Karrholm J, Borssen B, Lowenhielm G, Snorrason F. *Does early micromotion of femoral stem prostheses matter? 4-7-year stereoradiographic follow-up of 84 cemented prostheses.* The Journal of bone and joint surgery British volume. 1994;76(6):912-7.

87. Ryd L, Albrektsson BE, Carlsson L, Dansgard F, Herberts P, Lindstrand A, Regner L, Toksvig-Larsen S. *Roentgen stereophotogrammetric analysis as a predictor of mechanical loosening of knee prostheses.* J Bone Joint Surg (Br). 1995;77(3):377-83.

88. Valstar ER, Gill R, Ryd L, Flivik G, Börlin N, Kärrholm J. *Guidelines for standardization of radiostereometry (RSA) of implants.* Acta orthopaedica. 2005;76(4):563-72.

89. van Hamersveld KT, Marang-van de Mheen PJ, Nelissen R. The Effect of *Coronal Alignment on Tibial Component Migration Following Total Knee Arthroplasty: A Cohort Study with Long-Term Radiostereometric Analysis Results.* The Journal of bone and joint surgery American volume. 2019;101(13):1203-12.

90. Teeter MG, Naudie DD, McCalden RW, Yuan X, Holdsworth DW, MacDonald SJ, Lanting BA. *Varus tibial alignment is associated with greater tibial baseplate migration at 10 years following total knee arthroplasty.* Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA. 2018;26(6):1610-7.

91. van Strien T, van der Linden-van der Zwaag E, Kaptein B, van Erkel A, Valstar E, Nelissen R. *Computer assisted versus conventional cemented total knee prostheses alignment accuracy and micromotion of the tibial component.* International orthopaedics. 2009;33(5):1255-61.

92. Pijls BG, Plevier JWM, Nelissen R. *RSA migration of total knee replacements.* Acta orthopaedica. 2018:1-9.

93. Molt M, Ryd L, Toksvig-Larsen S. *A randomized RSA study concentrating especially on continuous migration.* Acta orthopaedica. 2016;87(3):262-7.

94. (FDA) UFaDA. *Guidance for industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims.* New Hampshire, Silver Spring, US: Department of Health and Human Services (US), Food and Drug Administration, Center for Drug Evaluation and Research (CDER); 2009 Available from: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf.

95. Refolo P, Minacori R, Mele V, Sacchini D, Spagnolo AG. *Patient-reported outcomes (PROs): the significance of using humanistic measures in clinical*

trial and clinical practice. European review for medical and pharmacological sciences. 2012;16(10):1319-23.

96. Patrick DL, Deyo RA. *Generic and disease-specific measures in assessing health status and quality of life.* Medical care. 1989;27(3 Suppl):S217-32.

97. Tubach F, Ravaud P, Baron G, Falissard B, Logeart I, Bellamy N, Bombardier C, Felson D, Hochberg M, van der Heijde D, Dougados M. *Evaluation of clinically relevant states in patient reported outcomes in knee and hip osteoarthritis: the patient acceptable symptom state.* Annals of the rheumatic diseases. 2005;64(1):34-7.

98. Blome C, Augustin M. *Measuring change in quality of life: bias in prospective and retrospective evaluation.* Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2015;18(1):110-5.

99. Terwee CB, Bot SD, de Boer MR, van der Windt DA, Knol DL, Dekker J, Bouter LM, de Vet HC. *Quality criteria were proposed for measurement properties of health status questionnaires.* Journal of clinical epidemiology. 2007;60(1):34-42.

100. Schwartz CE, Powell VE, Rapkin BD. *When global rating of change contradicts observed change: Examining appraisal processes underlying paradoxical responses over time.* Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. 2017;26(4):847-57.

101. Havelin LI, Engesaeter LB, Espehaug B, Furnes O, Lie SA, Vollset SE. *The Norwegian Arthroplasty Register: 11 years and 73,000 arthroplasties.* Acta orthopaedica Scandinavica. 2000;71(4):337-53.

102. Furnes O, Espehaug B, Lie SA, Vollset SE, Engesaeter LB, Havelin LI. *Early failures among 7,174 primary total knee replacements: a follow-up study from the Norwegian Arthroplasty Register 1994-2000.* Acta orthopaedica Scandinavica. 2002;73(2):117-29.

103. Selmer ES. *Personnummerering i Norge: Litt anvendt tallteori og psykologi.* Nordisk matematisk tidsskrift. 1964;12(1):36-44.

104. Administration TNT. *This is the National Registry 2018.* Available from: https://www.skatteetaten.no/en/person/national-registry/om/this-is-the-national-registry/.

105. Espehaug B, Furnes O, Havelin LI, Engesæter LB, Vollset SE, Kindseth O. *Registration completeness in the Norwegian Arthroplasty Register.* Acta orthopaedica. 2006;77(1):49-56.

106. Ewald FC. *The Knee Society total knee arthroplasty roentgenographic evaluation and scoring system.* Clinical orthopaedics and related research. 1989(248):9-12.

107. Brooks R. *EuroQol: the current state of play.* Health Policy. 1996;37(1):53-72.

108. Greiner W, Weijnen T, Nieuwenhuizen M, Oppe S, Badia X, Busschbach J, Buxton M, Dolan P, Kind P, Krabbe P, Ohinmaa A, Parkin D, Roset M, Sintonen H, Tsuchiya A, de Charro F. *A single European currency for EQ-5D health states. Results from a six-country study.* Eur J Health Econ. 2003;4(3):222-31.

109. Scott J, Huskisson EC. *Graphic representation of pain.* Pain. 1976;2(2):175-84.

110. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. *Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee.* The Journal of rheumatology. 1988;15(12):1833-40.

111. Poss R, Clark CR, Heckman JD. *A concise format for reporting the longer-term follow-up status of patients managed with total hip arthroplasty.* The Journal of bone and joint surgery American volume. 2001;83-a(12):1779-81.

112. Rolfson O, Bohm E, Franklin P, Lyman S, Denissen G, Dawson J, Dunn J, Eresian Chenok K, Dunbar M, Overgaard S, Garellick G, Lubbeke A. *Patient-reported outcome measures in arthroplasty registries Report of the Patient-Reported Outcome Measures Working Group of the International Society of Arthroplasty Registries Part II. Recommendations for selection, administration, and analysis.* Acta orthopaedica. 2016;87 Suppl 1:9-23.

113. Roos EM, Lohmander LS. *The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis.* Health and quality of life outcomes. 2003;1:64.

114. Roos EM, Toksvig-Larsen S. *Knee injury and Osteoarthritis Outcome Score (KOOS) - validation and comparison to the WOMAC in total knee replacement.* Health and quality of life outcomes. 2003;1:17.

115. Lygre SH, Espehaug B, Havelin LI, Vollset SE, Furnes O. *Does patella resurfacing really matter? Pain and function in 972 patients after primary total knee arthroplasty.* Acta orthopaedica. 2010;81(1):99-107.

116. Pham T, van der Heijde D, Altman RD, Anderson JJ, Bellamy N, Hochberg M, Simon L, Strand V, Woodworth T, Dougados M. *OMERACT-OARSI initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited.* Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society. 2004;12(5):389-99.

117. Escobar A, Gonzalez M, Quintana JM, Vrotsou K, Bilbao A, Herrera-Espineira C, Garcia-Perez L, Aizpuru F, Sarasqueta C. *Patient acceptable symptom state and OMERACT-OARSI set of responder criteria in joint replacement. Identification of cut-off values.* Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society. 2012;20(2):87-92.

118. Charnley J. *The long-term results of low-friction arthroplasty of the hip performed as a primary intervention.* The Journal of bone and joint surgery British volume. 1972;54(1):61-76.

119. Dunbar MJ, Robertsson O, Ryd L. *What's all that noise? The effect of co-morbidity on health outcome questionnaire results after knee arthroplasty.* Acta orthopaedica Scandinavica. 2004;75(2):119-26.

120. Insall JN, Dorr LD, Scott RD, Scott WN. *Rationale of the Knee Society clinical rating system.* Clinical orthopaedics and related research. 1989(248):13-4.

121. Scuderi GR, Bourne RB, Noble PC, Benjamin JB, Lonner JH, Scott WN. *The new Knee Society Knee Scoring System. Clinical orthopaedics and related research.* 2012;470(1):3-19.

122. Noble PC, Scuderi GR, Brekke AC, Sikorskii A, Benjamin JB, Lonner JH, Chadha P, Daylamani DA, Scott WN, Bourne RB. *Development of a new Knee Society scoring system.* Clinical orthopaedics and related research. 2012;470(1):20-32.

123. Gothesen O, Espehaug B, Havelin L, Petursson G, Furnes O. *Short-term outcome of 1,465 computer-navigated primary total knee replacements 2005-2008.* Acta orthopaedica. 2011;82(3):293-300.

124. Schemper M, Smith TL. *A note on quantifying follow-up in studies of failure time.* Controlled clinical trials. 1996;17(4):343-6.

125. Fine JP, Gray RJ. *A Proportional Hazards Model for the Subdistribution of a Competing Risk.* Journal of the American Statistical Association. 1999;94(446):496-509.

126. Jenny JY, Miehlke RK, Giurea A. *Learning curve in navigated total knee replacement. A multi-centre study comparing experienced and beginner centres.* The Knee. 2008;15(2):80-4.

127. Nizard RS, Porcher R, Ravaud P, Vangaver E, Hannouche D, Bizot P, Sedel L. *Use of the Cusum technique for evaluation of a CT-based navigation system for total knee replacement.* Clinical orthopaedics and related research. 2004(425):180-8.

128. Ranstam J, Karrholm J, Pulkkinen P, Makela K, Espehaug B, Pedersen AB, Mehnert F, Furnes O. *Statistical analysis of arthroplasty data. II. Guidelines.* Acta orthopaedica. 2011;82(3):258-67.

129. Grambsch PM, Therneau TM. *Proportional hazards tests and diagnostics based on weighted residuals.* Biometrica. 1994;81(3):515-26.

130. Petursson G, Fenstad AM, Gothesen O, Dyrhovden GS, Hallan G, Rohrl SM, Aamodt A, Furnes O. *Computer-Assisted Compared with Conventional Total Knee Replacement: A Multicenter Parallel-Group Randomized Controlled Trial.* The Journal of bone and joint surgery American volume. 2018;100(15):1265-74.

131. Petursson G, Fenstad AM, Gothesen O, Haugan K, Dyrhovden GS, Hallan G, Rohrl SM, Aamodt A, Nilsson KG, Furnes O. *Similar migration in computer-assisted and conventional total knee arthroplasty.* Acta orthopaedica. 2017;88(2):166-72.

132. Campbell MJ, Gardner MJ. *Calculating confidence intervals for some non-parametric analyses.* British medical journal (Clinical research ed). 1988;296(6634):1454-6.

133. Inacio MC, Paxton EW, Dillon MT. *Understanding Orthopaedic Registry Studies: A Comparison with Clinical Studies.* The Journal of bone and joint surgery American volume. 2016;98(1):e3.

134. Mozella Ade P, Borges Goncalves F, Osterno Vasconcelos J, de Araujo Barros Cobra HA. *Revision of unicompartmental knee arthroplasty: implants used and causes of failure.* Revista brasileira de ortopedia. 2014;49(2):154-9.

135. Shadish WR, Cook TD, Campbell DT. *Experimental and Quasi-Experimental Designs for Generalized Causal Interference.* Boston: Houghton Mifflin Company; 2002.

136. Atkins D, Chang SM, Gartlehner G, Buckley DI, Whitlock EP, Berliner E, Matchar D. *Assessing applicability when comparing medical interventions: AHRQ and the Effective Health Care Program.* Journal of clinical epidemiology. 2011;64(11):1198-207.

137. Arthursson AJ, Furnes O, Espehaug B, Havelin LI, Soreide JA. *Validation of data in the Norwegian Arthroplasty Register and the Norwegian Patient Register: 5,134 primary total hip arthroplasties and revisions operated at a single hospital between 1987 and 2003.* Acta orthopaedica. 2005;76(6):823-8.

138. Lehmann TG, Engesaeter IO, Laborie LB, Lie SA, Rosendahl K, Engesaeter LB. *Total hip arthroplasty in young adults, with focus on Perthes' disease and slipped capital femoral epiphysis: follow-up of 540 subjects reported to the Norwegian Arthroplasty Register during 1987-2007.* Acta orthopaedica. 2012;83(2):159-64.

139. Murray DW, Frost SJ. *Pain in the assessment of total knee replacement.* The Journal of bone and joint surgery British volume. 1998;80(3):426-31.

140. Djahani O, Rainer S, Pietsch M, Hofmann S. *Systematic analysis of painful total knee prosthesis, a diagnostic algorithm.* Archives of bone and joint surgery. 2013;1(2):48-52.

141. Hofmann S, Seitlinger G, Djahani O, Pietsch M. *The painful knee after TKA: a diagnostic algorithm for failure analysis.* Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA. 2011;19(9):1442-52.

142. Park CN, White PB, Meftah M, Ranawat AS, Ranawat CS. *Diagnostic Algorithm for Residual Pain After Total Knee Arthroplasty.* Orthopedics. 2016:1-7.

143. Pijls BG, Valstar ER, Nouta KA, Plevier JW, Fiocco M, Middeldorp S, Nelissen RG. *Early migration of tibial components is associated with late revision: a systematic review and meta-analysis of 21,000 knee arthroplasties.* Acta orthopaedica. 2012;83(6):614-24.

144. Lygre SH, Espehaug B, Havelin LI, Furnes O, Vollset SE. *Pain and function in patients after primary unicompartmental and total knee arthroplasty.* The Journal of bone and joint surgery American volume. 2010;92(18):2890-7.

145. No authors listed. *KOOS User's guide 2012.* Available from: http://www.koos.nu.

146. King MT. *A point of minimal important difference (MID): a critique of terminology and methods.* Expert review of pharmacoeconomics & outcomes research. 2011;11(2):171-84.

147. Ingelsrud LH, Granan LP, Terwee CB, Engebretsen L, Roos EM. *Proportion of Patients Reporting Acceptable Symptoms or Treatment Failure and Their Associated KOOS Values at 6 to 24 Months After Anterior Cruciate Ligament Reconstruction: A Study From the Norwegian Knee Ligament Registry.* The American journal of sports medicine. 2015;43(8):1902-7.

148. Connelly JW, Galea VP, Rojanasopondist P, Matuszak SJ, Ingelsrud LH, Nielsen CS, Bragdon CR, Huddleston JI, 3rd, Malchau H, Troelsen A. *Patient Acceptable Symptom State at 1 and 3 Years After Total Knee Arthroplasty: Thresholds for the Knee Injury and Osteoarthritis Outcome Score (KOOS).* The Journal of bone and joint surgery American volume. 2019;101(11):995-1003.

149. Nilsdotter AK, Toksvig-Larsen S, Roos EM. *Knee arthroplasty: are patients' expectations fulfilled? A prospective study of pain and function in 102 patients with 5-year follow-up.* Acta orthopaedica. 2009;80(1):55-61.

150. Katz NP, Paillard FC, Ekman E. *Determining the clinical importance of treatment benefits for interventions for painful orthopedic conditions.* Journal of orthopaedic surgery and research. 2015;10:24.

151. Roos EM. *3 steps to improve reporting and interpretation of patient-reported outcome scores in orthopedic studies.* Acta orthopaedica. 2017:1-2.

152. Ingelsrud LH. *Patient-reported outcome measurement threshold values in patients undergoing elective knee surgery.* Copenhagen, Denmark: University of Southern Denmark; 2018.

153. Lin Y. *Robust inference for responder analysis: Innovative clinical trial design using a minimum p-value approach.* Contemporary clinical trials communications. 2016;3:65-9.

154. Sayers A, Evans JT, Whitehouse MR, Blom AW. *Are competing risks models appropriate to describe implant failure?* Acta orthopaedica. 2018;89(3):256-8.

155. Ranstam J, Karrholm J, Pulkkinen P, Makela K, Espehaug B, Pedersen AB, Mehnert F, Furnes O. *Statistical analysis of arthroplasty data. I. Introduction and background.* Acta orthopaedica. 2011;82(3):253-7.

156. Ranstam J, Robertsson O. *The Cox model is better than the Fine and Gray model when estimating relative revision risks from arthroplasty register data.* Acta orthopaedica. 2017;88(6):578-80.

157. Schisterman EF, Cole SR, Platt RW. *Overadjustment bias and unnecessary adjustment in epidemiologic studies.* Epidemiology (Cambridge, Mass). 2009;20(4):488-95.

158. Paxton EW, Furnes O, Namba RS, Inacio MC, Fenstad AM, Havelin LI. *Comparison of the Norwegian knee arthroplasty register and a United States arthroplasty registry.* J Bone Joint Surg (Am). 2011;93 Suppl 3:20-30.

159. Santaguida PL, Hawker GA, Hudak PL, Glazier R, Mahomed NN, Kreder HJ, Coyte PC, Wright JG. *Patient characteristics affecting the prognosis of total hip and knee joint arthroplasty: a systematic review.* Canadian journal of surgery Journal canadien de chirurgie. 2008;51(6):428-36.

160. Inacio MC, Chen Y, Paxton EW, Namba RS, Kurtz SM, Cafri G. *Statistics in Brief: An Introduction to the Use of Propensity Scores.* Clinical orthopaedics and related research. 2015;473(8):2722-6.

161. Grambsch PM, Therneau TM, Fleming TR. *Diagnostic plots to reveal functional form for covariates in multiplicative intensity models.* Biometrics. 1995;51(4):1469-82.

162. de Steiger RN, Liu YL, Graves SE. *Computer navigation for total knee arthroplasty reduces revision rate for patients less than sixty-five years of age.* J Bone Joint Surg (Am). 2015;97(8):635-42.

163. No authors listed. *Power calculator for binary outcome superiority trial: Sealed Envelope Ltd; 2012* Available from: https://www.sealedenvelope.com/power/binary-superiority/

164. Cip J, Obwegeser F, Benesch T, Bach C, Ruckenstuhl P, Martin A. *Twelve-Year Follow-Up of Navigated Computer-Assisted Versus Conventional Total Knee Arthroplasty: A Prospective Randomized Comparative Trial.* The Journal of arthroplasty. 2017.

165. Ouanezar H, Franck F, Jacquel A, Pibarot V, Wegrzyn J. *Does computer-assisted surgery influence survivorship of cementless total knee arthroplasty in patients with primary osteoarthritis? A 10-year follow-up study.* Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA. 2016;24(11):3448-56.

166. Gothesen O, Slover J, Havelin L, Askildsen JE, Malchau H, Furnes O. *An economic model to evaluate cost-effectiveness of computer assisted knee replacement surgery in Norway.* BMC musculoskeletal disorders. 2013;14:202.

167. Sælensminde K. *Helseeffekter i samfunnsøkonomiske analyser Sosial- og helsedirektoratet.* Helseøkonomi og finansiering, Pb. 7000 St Olavs plass, 0130 Oslo2007 Available from: https://helsedirektoratet.no/Lists/Publikasjoner/Attachments/643/Helseeffekter-i-samfunnsokonomiske-analyser-IS-1435.pdf.

168. Slover JD, Tosteson AN, Bozic KJ, Rubash HE, Malchau H. *Impact of hospital volume on the economic value of computer navigation for total knee replacement.* The Journal of bone and joint surgery American volume. 2008;90(7):1492-500.

169. Smith BR, Deakin AH, Baines J, Picard F. *Computer navigated total knee arthroplasty: the learning curve.* Computer aided surgery : official journal of the International Society for Computer Aided Surgery. 2010;15(1-3):40-8.

170. Dyrhovden GS, Gothesen O, Lygre SH, Fenstad AM, Soras TE, Halvorsen S, Jellestad T, Furnes O. *Is the use of computer navigation in total knee arthroplasty improving implant positioning and function? A comparative study of 198 knees operated at a Norwegian district hospital.* BMC musculoskeletal disorders. 2013;14(1):321.

171. Hetaimish BM, Khan MM, Simunovic N, Al-Harbi HH, Bhandari M, Zalzal PK. *Meta-analysis of navigation vs conventional total knee arthroplasty.* The Journal of arthroplasty. 2012;27(6):1177-82.

172. Cip J, Widemschek M, Luegmair M, Sheinkop MB, Benesch T, Martin A. *Conventional versus computer-assisted technique for total knee arthroplasty: a minimum of 5-year follow-up of 200 patients in a prospective randomized comparative trial.* The Journal of arthroplasty. 2014;29(9):1795-802.

173. Todesca A, Garro L, Penna M, Bejui-Hugues J. *Conventional versus computer-navigated TKA: a prospective randomized study.* Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA. 2017;25(6):1778-83.

174. No authors listed. *Norwegian arthroplasty Register Annual Report*. 2016. p. 43-75.

175. Lapaj L, Mroz A, Kokoszka P, Markuszewski J, Wendland J, Helak-Lapaj C, Kruczynski J. *Peripheral snap-fit locking mechanisms and smooth surface finish of tibial trays reduce backside wear in fixed-bearing total knee arthroplasty.* Acta orthopaedica. 2016:1-8.

176. Levine RA, Lewicki KA, Currier JH, Mayor MB, Van Citters DW. *Contribution of micro-motion to backside wear in a fixed bearing total knee arthroplasty.* Journal of orthopaedic research : official publication of the Orthopaedic Research Society. 2016.

177. Teeter MG, Lanting BA, Shrestha KR, Howard JL, Vasarhelyi EM. *Contribution of Surface Polishing and Sterilization Method to Backside Wear in Total Knee Arthroplasty.* The Journal of arthroplasty. 2015;30(12):2320-2.

178. Han HS, Lee MC. *Cementing technique affects the rate of femoral component loosening after high flexion total knee arthroplasty.* The Knee. 2017;24(6):1435-41.

179. Kutzner I, Hallan G, Hol PJ, Furnes O, Gothesen O, Figved W, Ellison P. *Early aseptic loosening of a mobile-bearing total knee replacement.* Acta orthopaedica. 2018;89(1):77-83.

180. Kalson NS, Borthwick LA, Mann DA, Deehan DJ, Lewis P, Mann C, Mont MA, Morgan-Jones R, Oussedik S, Williams FM, Toms A, Argenson JN, Bellemans J, Bhave A, Furnes O, Gollwitzer H, Haddad FS, Hofmann S, Krenn V. *International consensus on the definition and classification of fibrosis of the knee joint.* The bone & joint journal. 2016;98-b(11):1479-88.

181. Dale H, Fenstad AM, Hallan G, Havelin LI, Furnes O, Overgaard S, Pedersen AB, Karrholm J, Garellick G, Pulkkinen P, Eskelinen A, Makela K, Engesaeter LB. *Increasing risk of prosthetic joint infection after total hip arthroplasty.* Acta orthopaedica. 2012;83(5):449-58.

182. Schrama JC, Fenstad AM, Dale H, Havelin L, Hallan G, Overgaard S, Pedersen AB, Karrholm J, Garellick G, Pulkkinen P, Eskelinen A, Makela K, Engesaeter LB, Fevang BT. *Increased risk of revision for infection in rheumatoid arthritis patients with total hip replacements.* Acta orthopaedica. 2015;86(4):469-76.

183. Gehrke T, Alijanipour P, Parvizi J. *The management of an infected total knee arthroplasty.* The bone & joint journal. 2015;97-b(10 Suppl A):20-9.

184. Fiocchi A, Condello V, Madonna V, Bonomo M, Zorzi C. *Medial vs lateral unicompartmental knee arthrroplasty: clinical results.* Acta bio-medica : Atenei Parmensis. 2017;88(2s):38-44.

185. Citak M, Cross MB, Gehrke T, Dersch K, Kendoff D. *Modes of failure and revision of failed lateral unicompartmental knee arthroplasties.* The Knee. 2015;22(4):338-40.

186. van der List JP, McDonald LS, Pearle AD. *Systematic review of medial versus lateral survivorship in unicompartmental knee arthroplasty.* The Knee. 2015;22(6):454-60.

187. Napier RJ, O'Neill C, O'Brien S, Doran E, Mockford B, Boldt J, Beverland DE. *A prospective evaluation of a largely cementless total knee arthroplasty cohort without patellar resurfacing: 10-year outcomes and survivorship.* BMC musculoskeletal disorders. 2018;19(1):205.

188. Ecker ML, Lotke PA, Windsor RE, Cella JP. *Long-term results after total condylar knee arthroplasty. Significance of radiolucent lines.* Clinical orthopaedics and related research. 1987(216):151-8.

189. Aunan E, Naess G, Clarke-Jenssen J, Sandvik L, Kibsgard TJ. *Patellar resurfacing in total knee arthroplasty: functional outcome differs with different outcome scores: A randomized, double-blind study of 129 knees with 3 years of follow-up.* Acta orthopaedica. 2016;87(2):158-64.

190. Giesinger K, Hamilton DF, Jost B, Holzner B, Giesinger JM. *Comparative responsiveness of outcome measures for total knee arthroplasty.* Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society. 2014;22(2):184-9.

191. Thomsen MG, Latifi R, Kallemose T, Barfod KW, Husted H, Troelsen A. *Good validity and reliability of the forgotten joint score in evaluating the outcome of total knee arthroplasty.* Acta orthopaedica. 2016;87(3):280-5.

Appendices

Appendix 1	NAR knee registration form
Appendix 2	Hierarchy for revision causes, paper I and II
Appendix 3	Hierarchy for revision causes, Australian Orthopaedic Association National Joint Replacement Registry
Appendix 4	Information letter, paper III
Appendix 5	Registration of patient information, paper III
Appendix 6	Knee Society Score, paper III
Appendix 7	Questionnaire, paper III

Nasjonalt Register for Leddproteser
Ortopedisk klinikk, Helse Bergen HF
Haukeland universitetssjukehus, Postboks 1400
Møllendalsbakken 11, 5021 BERGEN
Tlf 55973742/55973743

F.nr. (11 sifre).....
Navn:.....
(Skriv tydelig ev. pasientklistrelapp – **spesifiser sykehus**.)
Sykehus:.....

KNEPROTESER og andre leddproteser

Innsetting, skifting eller fjerning av protese eller protesedeler, samt bløtdelsrevisjoner for infisert protese og protesenære frakturer.

LOKALISASJON, AKTUELL OPERASJON
☐1 Kne ☐6 Håndledd
☐2 Ankel ☐7 Fingre (angi ledd) .....
☐3 Tær (angi ledd) ..... ☐8 Annet .....
☐4 Skulder ☐9 Rygg (angi nivå).....
☐5 Albue

AKTUELLE SIDE (ett kryss) (Bilateral opr. = 2 skjema)
☐1 Høyre ☐2 Venstre

TIDLIGERE OPERASJON I AKTUELLE LEDD (ev. flere kryss)
☐0 Nei
☐1 Osteosyntese for intraartikulær/leddnær fraktur
☐2 Osteotomi
☐3 Artrodese
☐4 Protese
☐5 Synovectomi
☐6 Annet (f.eks menisk og leddbåndsop.).....

AKTUELLE OPERASJON (ett kryss)
☐1 Primæroperasjon ☐2 Reoperasjon (protese tidligere)

OPERASJONSDATO (dd.mm.åå) |__|__| |__|__| |__|__|

ÅRSAK TIL AKTUELLE OPERASJON (KRYSS AV ENTEN I A ELLER B)

A. Primæroper. pga (ev. flere kryss)
☐1 Idiopatisk artrose
☐2 Rheumatoid artritt
☐3 Fraktursequele.....
☐4 Mb. Bechterew
☐5 Sequele ligamentskade
☐6 Sequele meniskskade
☐7 Akutt fraktur
☐8 Infeksjonssequele
☐9 Spondylose
☐10 Sequele prolaps kirurgi
☐11 Degenerativ skivesykdom
☐12 Rotarcuff artropati
☐13 Annet .....

B. Reoper. pga (ev. flere kryss)
☐1 Løs prox.protesedel
☐2 Løs distal protesedel
☐3 Løs patellaprotese
☐4 Luksasjon av patella
☐5 Luksasjon (ikke patella)
☐6 Instabilitet
☐7 Aksefeil
☐8 Dyp infeksjon
☐9 Fraktur av bein (nær protesen)
☐10 Smerter
☐11 Slitt eller defekt plastforing
Hvilken.....
☐12 Progresjon av artrose
☐13 Annet (f.eks tidl fjernet protese)
.....

REOPERASJONSTYPE (ev. flere kryss)
☐1 Bytte el. innsetting av distal komponent
☐2 Bytte el. innsetting av proximal protesedel
☐3 Bytte el. innsetting av hele protesen
☐4 Innsetting av patellakomp.
☐5 Bytte av patellaprotese
☐6 Bytte av plastforing
☐7 Artrodese
☐8 Amputasjon
☐9 Fjernet protesedeler (inkl. sementspacer)
Angi hvilke deler .....
.....
☐10 Bløtdelsdebridement for infisert protese
☐11 Osteosyntese av protesenær fraktur. Angi hvilket ben .....
☐12 Annet.....

BENTRANSPLANTASJON / BENERSTATNING (ev. flere kryss)

Proximalt	☐0 Nei	☐1 Ja	☐2 Benpakking	☐3 Kjegler (cones)
Distalt	☐0 Nei	☐1 Ja	☐2 Benpakking	☐3 Kjegler (cones)

ANTIBIOTIKAPROFYLAKSE ☐0 Nei ☐1 Ja

	Navn	*Dosering*	*Varighet i timer*
Medikament 1	.....	.....	.....timer
Medikament 2	.....	.....	.....timer

TROMBOSEPROFYLAKSE
☐0 Nei ☐1 Ja: Første dose ☐1 Preoperativt ☐2 Postoperativt
Medikament 1.....Dosering opr.dag.....
Dosering videre.....Varighet.....døgn
Medikament 2..... Dosering.....Varighet.....døgn

FAST TROMBOSEPROFYLAKSE
☐0 Nei ☐1 Ja, type: .....

FIBRINOLYSEHEMMER
☐0 Nei ☐1 Ja, medikament: ..... Dosering.....

DREN ☐0 Nei ☐1 Ja. Antatt varighet .....døgn

OPERASJONSTID (hud til hud) .....minutter

BLODTOMHET ☐0 Nei ☐1 Ja **BLODTOMHETSTID**..... minutter
BLODTOMHET UNDER SEMENTERING ☐0 Nei ☐1 Ja

PEROPERATIV KOMPLIKASJON
☐0 Nei ☐1 Ja,hvilke(n): .....

MINI INVASIV KIRURGI (MIS) ☐0 Nei ☐1 Ja
COMPUTERNAVIGERING (CAOS) ☐0 Nei ☐1 Ja Type:.....
PASIENTTILPASSEDE INSTRUMENTER ☐0 Nei ☐1 Ja Type:.....

ASA KLASSE (se baksiden for definisjon)
☐1 Frisk
☐2 Asymptomatisk tilstand som gir økt risiko
☐3 Symptomatisk sykdom
☐4 Livstruende sykdom
☐5 Moribund

PROTESE KNE (Bruk klistrelapper på baksiden, eller spesifiser nøyaktig)

PROTESETYPE
☐1 Totalprot. m/patella . ☐4 Patellofemoralledd prot.
☐2 Totalprot. u/patella ☐5 Bi-compartmental ☐6 Hengslet protese
☐3 Unicondylær prot ☐ Medial ☐ Lateral ☐7 Annet .....

FEMURKOMPONENT
Navn/Type/Str / evt. Katalognr.....
ev. katalognummer .....
Sentral stamme ☐0 Nei ☐1 Ja, ev. lengde .....mm
Sementert stamme ☐0 Nei ☐1 Ja
Metallforing (Wedge) ☐0 Nei ☐1 Ja
Stabilisering ☐0 Nei ☐1 Ja, bakre ☐2 Ja, annen
☐1 Sement med antibiotika – Navn .....
☐2 Sement uten antibiotika – Navn .....
☐3 Usementert

TIBIAKOMPONENT (metallplatå)
Navn/Type/Str / ev. katalognummer .....
Forlenget sentral stamme ☐0 Nei ☐1 Ja, ev. lengde .....mm
Sementert stamme ☐0 Nei ☐1 Ja
Metallforing (Wedge) ☐0 Nei ☐1 Ja
☐1 Sement med antibiotika – Navn .....
☐2 Sement uten antibiotika – Navn .....
☐3 Usementert

TIBIAKOMPONENT (plastkomponent)
Navn/Type/Str / ev. katalognummer.....
Tykkelse ..... mm
Stabilisering ☐0 Nei ☐1 Ja, bakre ☐2 Ja, annen

PATELLAKOMPONENT
Navn/Type/Str / ev. katalognummer.....
Metallrygg ☐0 Nei ☐1 Ja
☐1 Sement med antibiotika – Navn .....
☐2 Sement uten antibiotika – Navn .....
☐3 Usementert

KORSBÅND

Intakt fremre korsbånd før operasjon	☐0 Nei	☐1 Ja
Intakt fremre korsbånd etter operasjon	☐0 Nei	☐1 Ja
Intakt bakre korsbånd før operasjon	☐0 Nei	☐1 Ja
Intakt bakre korsbånd etter operasjon	☐0 Nei	☐1 Ja

PROTESE ANDRE LEDD (Bruk klistrelapper på baksiden, eller spesifiser nøyaktig)

PROTESETYPE
☐1 Totalprotese ☐2 Hemiprotese ☐3 Enkomponentprotese ☐4 Annet .....

PROKSIMAL KOMPONENT
Navn/Type/Str / ev. katalognummer.....
☐1 Sement med antibiotika – Navn .....
☐2 Sement uten antibiotika – Navn .....
☐3 Usementert

DISTAL KOMPONENT
Navn/Type/Str / ev. katalognummer.....
☐1 Sement med antibiotika – Navn .....
☐2 Sement uten antibiotika – Navn .....
☐3 Usementert

INTERMEDIÆR KOMPONENT (f.eks. caput humeri)
Navn/Type/Str/Diameter / ev. katalognummer.....

Lege .....
Legen som har fylt ut skjemaet (navnet registreres ikke i databasen).

RETTLEDNING KNEPROTESER og andre leddproteser

Registreringen gjelder innsetting, skifting eller fjerning av protese i kne, skuldre og andre ledd med unntak av hofter som har eget skjema. Ett skjema fylles ut for hver operasjon. Pasientens fødselsnummer (11 sifre) og sykehus må være påført. Aktuelle ruter markeres med kryss.
På eget Samtykkeskjema skal pasienten gi samtykke til rapportering til Leddregisteret.

Kommentarer til de enkelte punktene

AKTUELLE OPERASJON
Primæroperasjon: Dette er første totalproteseoperasjon.
Kryss av enten i A eller i B. Kryss av for alle årsakene til operasjonen. Bløtdelsrevisjon for infeksjon skal registreres selv om protesedeler ikke skiftes.

REOPERASJONSTYPE
Fjerning av protesedeler må spesifiseres og føres opp, også fjerning ved infeksjon.

BENTRANSPLANTASJON
Påsmøring av benvev rundt protesen regnes ikke som bentransplantat.

ANTIBIOTIKAPROFYLAKSE
Medikament, dose og varighet av profylaksen skal angis f.eks. slik: Medikament: Keflin, Dosering: 2g x 4, med varighet 4,5 timer.

TROMBOSEPROFYLAKSE
Medikament, dose og antatt varighet av profylaksen skal angis separat for operasjonsdagen og senere. Det skal også oppgis om pasienten står fast på tromboseprofylakse (AlbyIE, Marevan, Plavix ol).

FIBRINOLYSEHEMMER
Her føres det på om en benytter blødningsreduserende legemidler i forbindelse med operasjonen (f.eks. Cyklokapron).

PEROPERATIV KOMPLIKASJON
Dersom det foreligger komplikasjon i form av stor blødning, må mengden angis.
Dersom pasienten dør under eller like etter operasjonen, ønsker vi likevel melding om operasjonen.

ASA-KLASSE (ASA=American Society of Anesthesiologists)
ASA-klasse 1: Friske pasienter som røyker mindre enn 5 sigaretter daglig.
ASA-klasse 2: Pasienter med en asymptomatisk tilstand som behandles medikamentelt (f.eks. hypertensjon) eller med kost (f.eks. diabetes mellitus type 2) og ellers friske pasienter som røyker 5 sigaretter eller mer daglig.
ASA-klasse 3: Pasienter med en tilstand som kan gi symptomer, men som holdes under kontroll medikamentelt (f.eks. moderat angina pectoris og mild astma).
ASA-klasse 4: Pasienter med en tilstand som ikke er under kontroll (f.eks. hjertesvikt og astma).
ASA-klasse 5: Moribund/døende pasient

PROTESETYPE
Dersom det er gjort revisjon av totalprotese uten patellakomponent og REOPERASJONSTYPE er **innsetting av patellakomponent,** skal det krysses av for pkt. 1: Totalprotese med patellakomponent (dvs. protesen har nå blitt en totalprotese med patellakomponent). Ved revisjon av unicondylær protese til totalprotese brukes enten pkt. 1 eller 2.

PROTESEKOMPONENTER
Her anføres kommersielle navn, materiale, størrelse og design. Alternativt kan en føre opp protesenavn og katalognummer eller benytte klistrelapp som følger med de fleste protesene. **Denne kan limes på baksiden av skjemaet (vennligst ikke plasser klistrelapper på markeringskryss, som brukes ved scanning av skjema).**
Navnet på sementen som evt. brukes må anføres, f.eks. Palacos R+G. (Bruk helst klistrelapp)
Under femurkomponent skal evt. påsatt **femurstamme** anføres med lengde.
Med **metallforing** under femur- og tibiakomponent menes bruk av en eller flere separate metallkiler (wedges) som erstatning for manglende benstøtte.
Stabilisering er bruk av proteser med stabilisering som kompensasjon for sviktende båndapparat.
Forlenget sentral stamme under tibiakomponent (metallplatå) skal bare anføres ved bruk av en lengre påsatt stamme enn standardkomponenten.

ANDRE LEDD. PROTESETYPE
Ved bruk av hemiprotese med bare en komponent, f.eks. resurfacing i skulder, skrives dette på DISTAL KOMPONENT. Enkomponent-protese i finger/tå, skrives på PROKSIMAL KOMPONENT.

COMPUTERNAVIGERING (CAOS = Computer Aided Orthopaedic Surgery**)**
Angi firmanavn på computersystem.

MINIINVASIV KIRURGI (MIS = Minimally Invasive Surgery**)**
Her menes at kirurgen har brukt kort snitt og at det er brukt spesialinstrument laget for MIS.

PASIENTTILPASSEDE INSTRUMENTER
Her menes kutteblokker eller instrumenter som lages etter MR eller CT bilder tatt av pasienten før operasjonen. Oppgi navn på systemet.

Kopi beholdes til pasientjournalen, originalen sendes Haukeland universitetssjukehus.

Kontaktpersoner vedrørende registreringsskjema er
Seksjonsoverlege Ove Furnes, tlf. 55 97 56 90.
Overlege Randi Hole, kontaktperson (skulder), tlf. 55 97 56 79.
Overlege Yngvar Krukhaug, kontaktperson (albue/hånd), tlf. 55 97 56 88.
Ortopedisk klinikk, Haukeland universitetssjukehus. Besøksadresse: Møllendalsbakken 11.
Sekretærer i Nasjonalt Register for Leddproteser, Ortopedisk klinikk, Helse Bergen:
Randi Furnes, tlf. 55 97 37 42.
Epost: nrl@helse-bergen.no Internett: http://nrlweb.ihelse.net/
Skjema revidert i januar 2018.

Diagnosis Hierarchy for Revision Knee Replacement in the Norwegian Arthroplasty Register

Rank	Diagnosis
1	Infection
2	Malalignment
3	Aseptic loosening femur and tibia
4	Aseptic loosening femur
5	Aseptic loosening tibia
6	Aseptic loosening patella
7	Polyethylene wear
8	Dislocation (not patella)
9	Patella dislocation
10	Instability
11	Periprosthetic fracture
12	Progression of osteoarthritis
13	Arthrofibrosis
14	Unexplained pain
15	Other

Diagnosis hierarchy for revision knee replacement, from the Australian Orthopaedic Association National Joint Replacement Registry, Annual report 2018 (p. 425)

Rank	Diagnosis	Category
1	Tumor	Dominant diagnosis independent of prosthesis/surgery
2	Infection	
3	Incorrect Side	Surgical procedure
4	Incorrect Sizing	
5	Malalignment	
6	Metal Related Pathology	Reaction to prosthesis
7	Loosening	
8	Lysis	
9	Wear Knee Insert	Wear and implant breakage
10	Wear Tibial Tray	
11	Wear Femoral	
12	Wear Patella	
13	Implant Breakage Femoral	
14	Implant Breakage Knee Insert	
15	Implant Breakage Tibial Tray	
16	Implant Breakage Patella	
17	Breakage Dislocation	Stability of prosthesis/knee
18	Patellar Dislocation	
19	Prosthesis Dislocation	
20	Instability	
21	Patellar Maltracking	
22	Fracture (Femur/tibia/Patella/Periprosthetic)	Fracture of bone
23	Progression of Disease	Progression of disease on non-operated part of joint
24	Patellar Erosion	
25	Synovitis	New diseases occurring in association with joint replacement
26	Arthrofibrosis	
27	Osteonecrosis/AVN	
28	Heterotropic bone	
29	Patellofemoral Pain	Pain
30	Pain	
31	Other	Remaining diagnoses

FORESPØRSEL OM DELTAKELSE I FORSKNINGSPROSJEKT
Profix kneprotese, konvensjonell vs computernavigert.

De skal opereres med en kneprotese. Dette er en etablert behandling med gode resultater for de aller fleste pasienter. Operasjonen innebærer at man setter inn et kunstig kneledd av plast og metall som festes med bensement. Som annen medisinsk behandling er også kneprotesekirurgien i stadig utvikling, og man forsøker hele tiden å finne løsninger som ytterligere vil bedre behandlingsresultatene. Som ledd i vår søken etter bedre løsninger vil vi nå sammenligne kneproteser operert med vanlig, standard metode og kneproteser operert ved hjelp av såkalt computernavigasjon.
Profix-protesen er den protesen som brukes som standard i Helse Vest og på Lovisenberg Diakonale Sykehus, og den har gode resultater.
Computernavigasjon har de siste 5-6 år kommet for fullt inn i protesekirurgien. I Norge er det få sykehus som tilbyr slik behandling. Man har foreløpig begrenset dokumentasjon på nytten av dette nye operasjonsverktøyet. Man bruker et infrarødt kamera som sender og mottar signaler under operasjonen. Signalene overføres fra kneet til en computer som lager en modell av kneet ditt. Ut ifra denne modellen foretas visse beregninger som hjelper kirurgen å plassere protesen riktig. Standardmetoden i dag er å beregne protesens plassering ved hjelp av en siktepinne som settes i marghulen og visse anatomiske landemerker. Vi vil undersøke hvilken metode som gir best resultat med tanke på riktig plassering av protesen, som igjen har betydning for hvor lenge protesen varer før den evt må skiftes ut. Vi vil også undersøke hvilken metode som gir minst sykelighet og komplikasjoner etter operasjonen. Funksjon og livskvalitet vil bli vurdert, også i et helseøkonomisk perspektiv.

De blir herved forespurt om De vil delta i en studie som har til hensikt å sammenligne behandlingsresultatet med disse to metodene.

Hva innebærer deltakelse i studien?

Studien innebærer at man ved loddtrekning velger hvilken metode pasienten skal opereres med. Plassering av reflektorkuler for computernavigering innebærer to små (1cm) hudsnitt på leggen. Kulene festes med pinner som skrues fast i benet. Begge grupper vil få dette hudsnittet. Oppfølgingen vil også være den samme uavhengig av metoden. Pasienter som deltar i studien, vil under operasjonen få satt inn små metallmarkører (0,8-1mm) av metallet tantal i benet rundt protesen og i plastkomponenten. Disse metallmarkørene har vært benyttet til dette formålet internasjonalt i flere tiår og har ingen påviste bivirkninger. Ved hjelp av markørene og helt spesielle røntgenbilder kan man påvise mikroskopisk bevegelse av protesedelene og slitasje av plasten. Grad av bevegelse og slitasje sier noe om protesens stabilitet og derved kvalitet. Pasienter som deltar i studien vil få en ekstra nøye oppfølging med røntgenundersøkelser etter 3, 12 og 24 måneder, samt vanlig rtg. kontroll og undersøkelse etter 5 og 10 år. Det vil dessuten bli foretatt en CT-kontroll av kneet 3 måneder etter operasjonen for å sjekke protesens plassering. Dette medfører en strålebelastning på 1 mSv som tilsvarer 3 røntgenbilder av bekkenet.

Håndtering av opplysninger og Personvern

Deltagelse er frivillig, og De kan trekke dem fra studien, også etter operasjon. Dersom De velger ikke å delta i studien, vil dette ikke ha noen innvirkning på Deres behandling ved sykehuset, og De vil bli operert på vanlig måte med en standard Profix kneprotese.

De opplysninger og data som framkommer gjennom studien vil samles og databehandles. Dataene tas fra din vanlige pasientjournal fra opphold ved innleggelse for operasjon, påfølgende rtg. og polikliniske kontroller hos lege og fysioterapeut. Vi registrerer plassering av protesen, bevegelse av protese, grad av smerte, funksjon, andre sykdommer, evt. bivirkninger og bruk av medikamenter. I tillegg vil fysioterapeuten evaluere opptreningsperioden med et eget spørreskjema. Studien er et samarbeidsprosjekt mellom Haugesund sjukehus, Haugesund sanitetsforenings revmatismesjukehus, Lovisenberg Diakonale Sykehus og Haukeland Universitetssykehus. Opplysninger om enkeltpasienters identitet vil bli oppbevart ved hvert behandlende sykehus, mens data samlet inn i prosjektet vil bli utvekslet mellom sykehusene i avidentifisert form. Alle opplysningene vil bli behandlet konfidensielt. Prosjektet avsluttes år 2017, etter 10 års oppfølging av alle pasienter, og alle innsamlede forskningsdata vil da anonymiseres. Vanlige journalopplysninger vil ikke slettes.

Studien er klarert av Regional komité for medisinsk forskningsetikk Vest-Norge og meldt til Personvernombudet for forskning, Norsk samfunnsvitenskapelig datatjeneste AS.

Studien ledes av Klinikkoverlege professor dr. med. Ove Furnes, ved Ortopedisk avd. Haukeland Universitetssykehus.

Spørsmål vedrørende studien kan rettes til din behandlende lege, eller til legen som er ansvarlig for studien ved det sykehuset hvor De behandles.

Vennlig hilsen

Klinikkoverlege professor dr. med. Ove Furnes
Haukeland Universitetssykehus

Overlege Øystein Gøthesen
Haugesund Sjukehus

Overlege Herman Luhr
Haugesund sanitetsforenings revmatismesjukehus

Avdelingsoverlege Øystein Høvik
Lovisenberg Diakonale Sykehus

INFORMERT SAMTYKKE

Undertegnede har lest den vedlagte informasjonen og har diskutert studien med ansvarlig lege. Jeg er villig til å delta i studien.

_____	_____
Pasientsignatur	**Dato:** **(Pasienten skriver selv dato)**

Som ansvarlig lege bekrefter jeg at pasienten har fått muntlig og skriftlig informasjon om studien, og at pasienten har signert samtykke før prosjektspesifikke undersøkelser eller prosedyrer er påbegynt.

_____	_____
Ansvarlig leges signatur	**Dato:**

Revidert 2.august, 2010

PASIENTSKJEMA;

Computernavigasjon vs konvensjonell metode v/TKA.

- **Pasientnummer:…….**
- **Fødselsdato:.....**
- **Kjønn: Mann____Kvinne___**(sett kryss)
- **Diagnose:**
  1. Primær gonartrose
  2. Sequele fraktur
  3. RA
  4. Psoriasis / Bechterev
  5. Annet. Presiser:…….
- **Side:** Hø
  Ve
- **Charnley klasse:**
  A -Unilateral knelidelse
  B -Bilateral knelidelse
  C -Multippel leddlidelse eller annen sykdom som nedsetter gangfunksjonen
- **Status i kontralaterale kne:**
  1. Normal funksjon
  2. Moderat nedsatt funksjon
  3. Alvorlig nedsatt funksjon
- **Tidligere inngrep i aktuelle kne:**
  1. Åpen/Artroskopisk meniskreseksjon/debridement
     a. 0-1 år siden
     b. >1 år siden
  2. Osteosyntese etter fraktur:
     a. Patella
     b. Femur
     c. Tibia
     d. Kombinasjon av ovennevnte
  3. Artroskopisk båndoperasjon
     a. ACL
     b. Annet (inkl pcl, mcl, lcl, menisksutur etc)
- **Tidligere sykdommer:**
  1. DVT i aktuelle underekstremitet
  2. DVT i kontralaterale underekstremitet
  3. Lungeemboli
  4. Hjerteinfarkt
  5. Atrieflimmer/flutter
  6. Annen hjerterytmeforstyrrelse
  7. Hjerteklaff-sykdom
  8. TIA
  9. Sequele etter hjerneslag/hjerneblødning
  10. Revmatoid artritt
  11. Psoriasis artritt
  12. Polyartritt

⇨ **Allergier: penicillinallergi: Ja___Nei___**

⇨ **Medikamenter:**

Medikament	Dose (vedlikeholds-)	Sluttdato preop	Gjenoppstarts -dato postop	Pågående (ikke seponert preop – sett kryss)
1. Marevan	mg pr uke			
2. Albyl-E	mg pr dag			
3. Plavix	mg pr dag			
4. Ticlid	mg pr dag			
5. Persantin	mg pr dag			
6. **Annet antitrombotikum**	mg pr dag			

⇨ **Høyde (cm):_____**

⇨ **Vekt (kg):_____**

⇨ **Blodprøver:**

Preoperativt: Hb_____
Hct____
Postoperativt dag 2-3: Hb_____
Hct____

⇨ **Transfusjoner (totalt antall enheter a 250ml):_____**

⇨ **Operasjonsdato:**

⇨ **Operatør:**

⇨ **Blodtomhetstid (min):_____**

⇨ **Knivtid (min):_____**

⇨ **Anestesitype/postop sm.regime:**

1. **Spinal/epidural**
2. **Narkose/annet**

⇨ **Komplikasjoner/bivirkninger:**

1. Dyp infeksjon
2. DVT
3. Lungeemboli
4. Hjerteinfarkt
5. Hjerneslag
6. Fraktur
7. Utstyrssvikt (spesifiser!)
8. Annet

Signatur, ansvarlig lege……

Dato:……

Pasientnummer:.....

American Knee Society Score (KSS)

Sett kryss ved svaret som best beskriver ditt kne

1.Hvor mye smerter har du fra kneet ditt når du går?	**2.Hvor mye smerter har du i kneet når du går opp eller ned trapper?**
☐ Ingen ☐ Lette/periodevise ☐ Moderate ☐ Svært store	☐ Ingen ☐ Lette/periodevise ☐ Moderate ☐ Svært store
3.Hvor mye smerter har du i kneet ditt når du er i ro?	**4.Hvordan påvirker kneet gangfunksjonen din?**
☐ Ingen ☐ Lette ☐ Moderate ☐ Svært store	☐ Jeg kan gå ubegrenset langt ☐ Jeg kan gå 1 – 2 km ☐ ½ til 1 km ☐ Jeg kan gå < 500 meter ☐ Jeg kan ikke gå utenfor huset ☐ Jeg kan ikke gå
5.Hvordan går du opp/ned trapper?	**6.Hvilken støtte bruker du når du går?**
☐ Jeg går normalt opp og ned trapper, med en fot foran den andre ☐ Jeg går normalt opp, men må bruke rekkverket ned ☐ Jeg bruker rekkverket både opp og ned ☐ Jeg bruker rekkverket opp, kan ikke gå ned ☐ Jeg kan ikke gå i trapper	☐ Ingen ☐ En stokk eller en krykke ☐ To stokker ☐ To krykker ☐ Rullator

Klinisk vurdering av kneet

7. **Grader bevegelse** (fra maksimal aktiv strekk til maksimal aktiv bøy) _____Grader
8. **Mangler på full aktiv strekk (extension lag)** _____Grader
9. **Mangler på passiv strekk (flexion contracture)** _____Grader

10.Medial/lateral stabilitet (20 grader fleksjon)	**11.Anterior/Posterior stabilitet (skuffetest)**
☐ 0-5 mm ☐ 5-10 mm ☐ >10 mm	☐ 0-5 mm ☐ 5-10 mm ☐ >10 mm

12.Akseavvik (Varus eller valgusfeilstilling i forhold til 0 grader mekanisk akse, klinisk bedømt)_____Grader

Pasientnummer..... Dato(dag/mnd/år...../ ...../ ...../

VAS – Visual analogue scale

Merk av på linjen nedenfor hvordan du opplever smertene i kneet. Angi verste smerte du har hatt siste uken.

Høyre kne:

Ingen smerte _____ Uutholdelige smerter

Venstre kne:

Ingen smerte _____ Uutholdelige smerter

Pasientnummer..... Dato(dag/mnd/år)...../...../.....

KOOS – Spørreskjema for knepasienter.

Veiledning: Dette spørreskjemaet inneholder spørsmål om hvordan du opplever kneet ditt. Informasjonen vil hjelpe oss til å følge med i hvordan du har det og fungerer i ditt daglige liv. Besvar spørsmålene ved å krysse av for det alternativ du synes passer best for deg (kun ett kryss ved hvert spørsmål). Hvis du er usikker, kryss likevel av for det alternativet som føles mest riktig.

Symptom

Tenk på de **symptomene** du har hatt fra kneet ditt den **siste uken** når du besvarer disse spørsmålene.

S1. Har kneet vært hovent?

Aldri	Sjelden	I blant	Ofte	Alltid
☐0	☐1	☐2	☐3	☐4

S2. Har du følt knirking, hørt klikking eller andre lyder fra kneet?

Aldri	Sjelden	I blant	Ofte	Alltid
☐0	☐1	☐2	☐3	☐4

S3. Har kneet haket seg opp eller låst seg?

Aldri	Sjelden	I blant	Ofte	Alltid
☐0	☐1	☐2	☐3	☐4

S4. Har du kunnet rette kneet helt ut?

Alltid	Ofte	I blant	Sjelden	Aldri
☐0	☐1	☐2	☐3	☐4

S5. Har du kunnet bøye kneet helt?

Alltid	Ofte	I blant	Sjelden	Aldri
☐0	☐1	☐2	☐3	☐4

Stivhet

De neste spørsmålene handler om **leddstivhet** . Leddstivhet innebærer vanskeligheter med å komme i gang eller økt motstand når du bøyer eller strekker kneet. Marker graden av leddstivhet du har opplevd i kneet ditt den **siste uken**

S6. Hvor stivt er kneet ditt når du nettopp har våknet om morgenen?

Ikke noe	Litt	Moderat	Betydelig	Ekstremt
☐0	☐1	☐2	☐3	☐4

S7. Hvor stivt er kneet ditt senere på dagen etter å ha sittet, ligget eller hvilt?

Ikke noe	Litt	Moderat	Betydelig	Ekstremt
☐0	☐1	☐2	☐3	☐4

Smerte

P1. Hvor ofte har du vondt i kneet?

Aldri	Månedlig	Ukentlig	Daglig	Hele tiden
☐0	☐1	☐2	☐3	☐4

Hvilken grad av smerte har du hatt i kneet ditt den **siste uken** ved følgende aktiviteter?

Pasientnummer..... Dato(dag/mnd/år)...../ ...../ .....

P2. Snu/vende på belastet kne

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

P3. Rette kneet helt ut

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

P4. Bøye kneet helt

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

P5. Gå på flatt underlag

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

P6. Gå opp eller ned trapper

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

P7. Om natten i sengen (smerter som forstyrrer søvnen)

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

P8. Sittende eller liggende

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

P9. Stående

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

Funksjon i hverdagen

De neste spørsmål handler om din fysiske funksjon. **Angi graden av vanskeligheter du har opplevd den siste uken ved følgende aktiviteter på grunn av dine kneproblemer.**

A1. Gå ned trapper

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

A2. Gå opp trapper

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

Angi graden av **vanskeligheter** du har opplevd ved hver aktivitet den **siste uken.**

A3. Reise deg fra sittende stilling

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

Pasientnummer..... Dato(dag/mnd/år...../ ...../ .....

A4. Stå stille

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

A5. Bøye deg, f.eks. for å plukke opp en gjenstand fra gulvet

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

A6. Gå på flatt underlag

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

A7. Gå inn/ut av bil

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

A8. Handle/gjøre innkjøp

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

A9. Ta på sokker/strømper

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

A10. Stå opp fra sengen

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

A11. Ta av sokker/strømper

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

A12. Ligge i sengen (snu deg, holde kneet i samme stilling i lengre tid)

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

A13. Gå inn og ut av badekar/dusj

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

A14. Sitte

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

A15. Sette deg og reise deg fra toalettet

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

Angi graden av **vanskeligheter** du har opplevd ved hver aktivitet den **siste uken.**

Pasientnummer..... Dato(dag/mnd/år)...../ ...../ .....

A16. Gjøre tungt husarbeid (måke snø, vaske gulv, støvsuge osv.)

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

A17. Gjøre lett husarbeid (lage mat, tørke støv osv.)

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

Funksjon, sport og fritid

De neste spørsmålene handler om din fysiske funksjon. **Angi graden av vanskeligheter du har opplevd den siste uken ved følgende aktiviteter på grunn av dine kneproblemer.**

SP1. Sitte på huk

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

SP2. Løpe

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

SP3. Hoppe

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

SP4. Snu/vende på belastet kne

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

SP5. Stå på kne

Ingen	Lett	Moderat	Betydelig	Svært stor
☐0	☐1	☐2	☐3	☐4

Livskvalitet

Q1. Hvor ofte gjør ditt kneproblem seg bemerket?

Aldri	Månedlig	Ukentlig	Daglig	Alltid
☐0	☐1	☐2	☐3	☐4

Q2. Har du forandret levesett for å unngå å overbelaste kneet?

Ingenting	Noe	Moderat	Betydelig	Fullstendig
☐0	☐1	☐2	☐3	☐4

Q3. I hvor stor grad kan du stole på kneet ditt?

Fullstendig	I stor grad	Moderat	Til en viss grad	Ikke i det hele tatt
☐0	☐1	☐2	☐3	☐4

Q4. Generelt sett, hvor store problemer har du med kneet ditt?

Ingen	Lette	Moderate	Betydelige	Svært store
☐0	☐1	☐2	☐3	☐4

Takk for at du tok deg tid og besvarte samtlige spørsmål!

Pasientnummer..... Dato(dag/mnd/år...../ ...../ .....

EQ-5D

I de 5 neste spørsmålene ønsker vi å vite hvordan livssituasjonen din er NÅ. Sett kryss ved det svaret som passer best:

1. **Hvordan opplever du gangevnen din?**
   - ☐ Jeg har ingen problemer med å gå omkring
   - ☐ Jeg har litt problemer med å gå omkring
   - ☐ Jeg er sengeliggende

2. **Hvordan klarer du personlig stell?**
   - ☐ Jeg har ingen problemer med personlig stell
   - ☐ Jeg har litt problemer med å vaske meg eller kle meg
   - ☐ Jeg klarer ikke å vaske meg eller kle meg

3. **Hvordan klarer du dine vanlige gjøremål (f.eks. arbeid, studier, husarbeid, familie- og fritidsaktiviteter)?**
   - ☐ Jeg har ingen problemer med å utføre mine vanlige gjøremål
   - ☐ Jeg har litt problemer med å utføre mine vanlige gjøremål
   - ☐ Jeg er ute av stand til å utføre mine vanlige gjøremål

4. **Smerter eller ubehag?**
   - ☐ Jeg har verken smerte eller ubehag
   - ☐ Jeg har moderat smerte eller ubehag
   - ☐ Jeg har sterk smerte eller ubehag

5. **Angst eller depresjon?**
   - ☐ Jeg er verken engstelig eller deprimert
   - ☐ Jeg er noe engstelig eller deprimert
   - ☐ Jeg er svært engstelig eller deprimert

Registrering ved 5 års kontroll

I

Survivorship and relative risk of revision in computer-navigated versus conventional total knee replacement at 8-year follow-up

A study of 23,684 cases reported to the Norwegian Arthroplasty Register, 2005–2014

Gro S DYRHOVDEN [1,2], Anne M FENSTAD [1], Ove FURNES [1,2], and Øystein GØTHESEN [1,2,3]

[1] Norwegian Arthroplasty Register, Department of Orthopaedic Surgery, Haukeland University Hospital, Bergen; [2] Department of Clinical Medicine (K1), Faculty of Medicine and Dentristy, University of Bergen, Bergen; [3] Orthopaedic Department, Haugesund Hospital, Haugesund, Norway.
Correspondence: gro.dyrhovden@helse-bergen.no
Submitted 2016-03-04. Accepted 2016-08-01.

Background and purpose — The long-term effects of computer-assisted surgery in total knee replacement (CAS) compared to conventionally operated knee replacement (CON) are still not clear. We compared survivorship and relative risk of revision in CAS and CON based on data from the Norwegian Arthroplasty Register.

Patients and methods — We assessed primary total knee replacements without patellar resurfacing reported to the Norwegian Arthroplasty Register from 2005 through 2014. The 5 most used implants and the 3 most common navigation systems were included. The groups (CAS, n = 3,665; CON, n = 20,019) were compared using a Cox regression analysis adjusted for age, sex, ASA category, prosthesis brand, fixation method, previous surgery, and diagnosis with the risk of revision for any reason as endpoint. Secondary outcomes were reasons for revision and effects of prosthesis brand, fixation method, age (± 65 years), and hospital volume.

Results — Prosthesis survival and risk of revision were similar for CAS and CON. CAS had significantly fewer revisions due to malalignment. Otherwise, no statistically significant difference was found between the groups in analyses of secondary outcomes. Mean operating time was 13 minutes longer in CAS.

Interpretation — At 8 years of follow-up, CAS and CON had similar rates of overall revision, but CAS had fewer revisions due to malalignment. According to our findings, the benefits of CAS at medium-term follow-up are limited. Further research may identify subgroups that benefit from CAS, and it should also emphasize patient-reported outcomes.

In total knee replacement (TKR), alignment of the implant is considered important to achieve a satisfactory outcome (Jeffery et al. 1991, Ritter et al. 2011, Huang et al. 2012). Computer-assisted surgery (CAS) is widely used to improve implant positioning, and several randomized trials and meta-analyses have concluded that CAS provides more accurate alignment of the implant (Choong et al. 2009, Hetaimish et al. 2012, Cip et al. 2014, Rebal et al. 2014, Shi et al. 2014). CAS has been shown to have a short learning curve and is claimed to be useful in training of inexperienced surgeons (Jenny et al. 2008, Smith et al. 2010). Still, the long-term effects on survival and causes of revision for CAS as opposed to conventionally operated TKR (CON) are not clear (Burnett and Barrack 2013).

A randomized, controlled trial in Norway found improved alignment and marginally better functional outcome with CAS 1 year after surgery (Gothesen et al. 2014). Nevertheless, a 2-year follow-up from the Norwegian Arthroplasty Register (NAR) in 2011 showed a higher revision rate with use of computer navigation (Gothesen et al. 2011). Data from the New Zealand National Joint Registry with 5 years of follow-up showed similar revision rates and functional outcomes between navigated and non-navigated TKR (Roberts et al. 2015). On the other hand, a recent study from the Australian Orthopaedic Association National Joint Replacement Registry found a lower cumulative revision rate for computer navigation in patients less than 65 years (de Steiger et al. 2015).

The purpose of this study was to use the large cohort from the nationwide Norwegian Arthroplasty Register to investigate medium-term effects of computer navigation in primary total knee replacement by comparing CAS and CON, with risk of

DOI 10.1080/17453674.2016.1244884

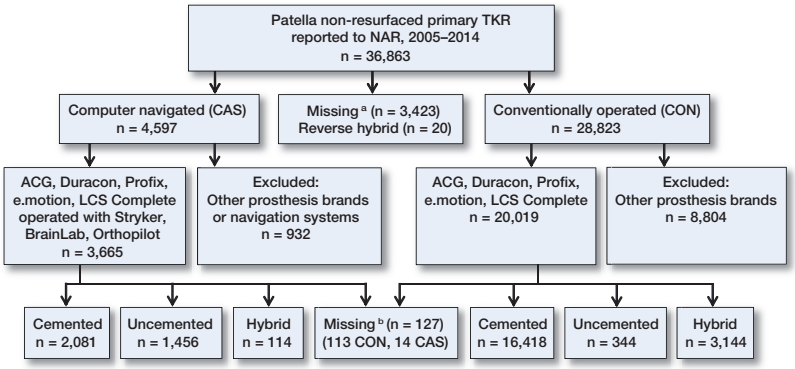


Figure 1. Selection of patients. TKR: total knee replacement; NAR: Norwegian Arthroplasty Register; CAS: computer-navigated knee replacement; CON: conventionally operated knee replacement. [a] No information on use of computer navigation. [b] No information on fixation method.

revision for any reason as endpoint. We also wanted to determine how CAS affected the rate and causes of revision in different prosthesis brands, fixation methods, and age groups, and to analyze the learning curve and the impact of hospital volume.

Patients and methods

Sources of data

This prospective observational study was based on data from the Norwegian Arthroplasty Register (NAR). The NAR was established in 1987 as a national hip registry (Havelin et al. 2000). From 1994, registration also included knee prostheses and other joint replacements (Furnes et al. 2002). The registry covers a population of approximately 5.2 million and the completeness of registration is 95% for primary TKR and 89% for revision TKR (Espehaug et al. 2006, Havelin et al. 2015). Registration of CAS started in 2005. In 2014, 8% of knee prostheses were implanted with CAS (Havelin et al. 2015).

36,863 primary total knee replacements without patellar resurfacing were reported to the NAR from January 1, 2005 through December 31, 2014. As only 2.5% of the knees were patella resurfaced during this period, prostheses with a patellar component were excluded. Hinged (n = 48), bi-compartmental (n = 3), and reverse hybrid implants (cemented femur and uncemented tibia, n = 10) were also excluded due to low numbers. The cohort was divided into 2 groups according to the surgical technique used for the implantation: either the CAS technique or CON (Figure 1).

In the short-term follow-up study from the NAR in 2011, the 5 most used prosthesis brands (AGC, Duracon, e.motion, LCS complete, and Profix) and the 3 most frequently used navigation systems (Brainlab, Orthopilot, and Stryker) were selected for analysis. We used the same selection criteria to compare the results with the study from 2011 (Gothesen et al. 2011).

Statistics

Baseline characteristics of the groups were investigated by descriptive analysis. Differences in demographic variables were calculated using chi-square test and Student's t-test, assuming equal variances. Median follow-up was calculated using reverse Kaplan-Meier (Schemper and Smith 1996). Implant survival (time from operation to first revision) was estimated by Kaplan-Meier analysis after 5 and 8 years of follow-up, with censoring at the time of death, emigration, or at the end of inclusion (December 31, 2014). Information about deaths and emigrations until December 31, 2014 was obtained from the National Population Register. To ensure that deaths and emigrations did not affect the results, this was tested in a competing-risk model (Fine and Gray 1999).

The null hypothesis was that there would be no difference in survival or relative risk of revision in total knee arthroplasty performed with CAS and with CON. The relative risk (RR) was calculated using a Cox multiple regression model, to make a statistical comparison of the survival rates of the groups, adjusted for age (continuous), sex, prosthesis brand, ASA category (1/2/3+), fixation method (cemented/uncemented/hybrid (uncemented femur, cemented tibia)), diagnosis (osteoarthritis/other), and previous surgery of the knee (yes/no). The Cox regression analyses were also performed with adjustments for a propensity score with the same covariates as above in addition to side (left/right), peroperative complications (yes/no), and deficiency of anterior cruciate ligament preoperatively and posterior cruciate ligaments preoperatively and postoperatively (yes/no). The proportional hazards assumption of the Cox regression model was assessed by visual inspection (log-minus-log plot).

Main causes of revision were determined based on the hierarchy from the Australian Orthopaedic Association National Joint Replacement Registry (2015), modified according to causes of revision registered in the NAR (Table 3). The adjusted RR estimates for CAS relative to CON are reported with 95% confidence intervals (CIs) and p-values. Survival curves were constructed by Cox regression with CAS as stratification factor, with the same adjustments as described above.

In subanalyses, we investigated the effect of CAS on survival in different brands of prosthesis, in different fixation methods, and in patients younger or older than 65 years of age. To investigate possible effects of a learning curve, we split the data file in order to analyze the first 30 computer-navigated

Table 1. Demographic data for computer-navigated total knee replacement (CAS) and conventionally operated total knee replacement (CON)

	CAS	CON	p-value
Number	3,665	20,019	
Men, %	38	35	< 0.001
Age, years	68.4	69.2	< 0.001
95% CI	68.1–68.7	69.1–69.3	
Right knee, %	54	54	0.9
MIS [a], n (%)	21 (0.6)	65 (0.4)	0.02
ASA category [b], n (%)			0.01
1	602 (16)	3316 (17)	
2	2,378 (65)	12,506 (62)	
3+	640 (18)	3,944 (20)	
Missing	45 (1)	253 (1)	
Diagnosis preoperatively, %			0.02
Primary gonarthritis	82	84	
Other	18	16	
Missing	0.1	0.2	
Fixation method, n (%)			< 0.001
Cemented	2,081 (57)	16,418 (82)	
Uncemented	1,456 (40)	344 (2)	
Hybrid (uncemented femur)	114 (3)	3,144 (16)	
Missing	14 (0.4)	113 (0.6)	
Prosthesis brand, n (%)			< 0.001
AGC	94 (3)	2,054 (10)	
Duracon	629 (17)	1,368 (7)	
e.motion	352 (10)	8 (0)	
LCS complete	1,387 (38)	8,408 (42)	
Profix	1,203 (33)	8,181 (41)	
Previous operations of the knee, %	38	31	< 0.001
Osteosynthesis affecting the knee joint	2.7	1.9	< 0.001
Osteotomy	3.5	3.3	0.6
Synovectomy	1.3	1.9	0.02
Other	33	25	< 0.001
Peroperative complication, %	1.8	2.1	0.2
Intact ACL c preoperatively, %	76	81	< 0.001
Intact PCL [d] preoperatively, %	95	94	0.1
Intact PCL postoperatively, %	57	56	0.3
Hospital volume 2005–2014, n [e]			
1–30	6	12	
31–100	7	9	
101–200	6	11	
> 200	3	33	
Total number of hospitals	22	65	

[a] MIS: minimally invasive surgery.
[b] ASA category: American Society of Anesthesiologists physical status classification system.
[c] ACL: anterior cruciate ligament.
[d] PCL: posterior cruciate ligament.
[e] Number of hospitals.

procedures (learning group) at each center and the remaining procedures (experienced group) separately, since the learning curve for computer navigation in TKR has been shown to stabilize after 30 procedures (Nizard et al. 2004, Jenny et al. 2008). Operation time is presented as median and interquartile range (IQR) and differences in operation time were calculated using Mann-Whitney tests.

All tests were 2-sided, and the significance level was set at 0.05. Statistical analyses were performed using IBM SPSS Statistics version 22.

Ethics

The NAR has permission from the Norwegian Data Inspectorate to collect patient data, based on obtaining written consent from the patient. (Permission was last issued September 15, 2014; reference number 03/00058-20/CGN).

Results

In the CAS group, the patients were 1 year younger on average, with males predominating, and they had a lower mean ASA score than the CON group (Table 1). Use of uncemented prostheses, previous surgery of the knee, and preoperative deficiency of the ACL was more frequent in the CAS group. Median follow-up was 5.3 years in the CAS group and 5.0 years in the CON group. 65 different hospitals were represented. All 22 hospitals that used CAS performed both techniques. For the implants included, the number of CAS operations during the study period varied between > 200 TKRs in 3 hospitals and < 30 TKRs in 5 hospitals. In the CON group, 33 hospitals had a volume of > 200.

Overall survivorship (Table 2)

At 5-year follow-up, the survival rate in the CON group was 95.5% (CI: 95.1–95.9) and it was 95.7% (CI: 94.9–96.5) in the CAS group. At 8 years, the survival rate was 94.9% (CI: 94.5–95.3) in the CON group and 94.8% (CI: 93.8–95.8) in the CAS group (Figure 2). The Cox regression analysis did not show any statistically significant difference in risk of revision between the CAS group and the CON group (RR = 0.8, CI: 0.7–1.0; p = 0.1); nor did the propensity score-adjusted Cox regression analysis (RR = 0.8, CI: 0.7–1.1; p = 0.1). The robustness of the analysis was investigated further with a simpler Cox regression model adjusted for age, sex, and diagnosis, and this RR estimate was 0.95 (CI: 0.80–1.13; p = 0.6). The Cox-adjusted RR was also tested for 0–2 years and 2–8 years after surgery, separately, but there was still no statistically significant difference in relative risk of revision between the groups. The proportion of deaths was 8.0% in the CAS group and 10% in the CON group, and the proportion of emigrations was 0.4% in both groups. In the competing-risk model, the overall relative risk of revision for CAS versus CON was 0.9 (CI: 0.8–1.2; p = 0.7) and for patients < 65 years, the relative risk of revision was 0.9 (CI: 0.8–1.2, p = 0.8).

Secondary outcomes

We also performed Cox regression analyses comparing CAS and CON for each selected prosthesis brand. In analyses adjusted for age, sex, ASA category, fixation method, and diagnosis, there was no statistically significant difference in risk of revision for Profix, LCS complete, AGC, or Duracon. For the e.motion prosthesis (352 CAS, 8 CON), there were 6 revisions in the CAS group and no revisions in the CON group, so an RR could not be estimated.

Table 2. Kaplan-Meier survival (KM) and Cox-adjusted relative risk of revision for computer-navigated total knee replacement (CAS) and for conventionally operated total knee replacement (CON)

	MF [a], years (95 % CI)	5 years At risk	5 years KM survival (95 % CI)	8 years At risk	8 years KM survival (95 % CI)	Cox-adjusted RR [b] (95% CI)	p-value	Cox regression adjusted by PS [c] (95% CI)	p-value
All ages									
CAS	5.3 (5.2–5.4)	1,965	95.7 (94.9–96.5)	354	94.8 (93.8–95.8)	0.8 (0.7–1.0)	0.1	0.8 (0.7–1.1)	0.1
CON	5.0 (4.9–5.0)	9,509	95.5 (95.1–95.9)	2,836	94.9 (94.5–95.3)	1		1	
< 65 years									
CAS	6.1 (5.7–6.5)	695	93.6 (92.2–95.0)	126	93.6 (92.2–95.0)	0.8 (0.6–1.1)	0.1	0.8 (0.6–1.1)	0.1
CON	5.4 (5.2–5.5)	3,102	93.1 (92.5–93.7)	955	92.4 (91.6–93.2)	1		1	

[a] MF: median follow-up (reversed KM).
[b] RR: relative risk, CAS versus CON, adjusted for age, sex, ASA category, diagnosis, previous surgery of the knee, prosthesis brand, and fixation method.
[c] PS: propensity score. Covariates included in PS are the same as in the Cox-adjusted RR in addition to side, peroperative complications, and deficiency of anterior cruciate ligament preoperatively and posterior cruciate ligaments preoperatively and postoperatively.

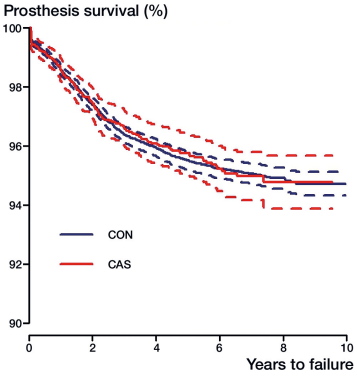


Figure 2. Kaplan-Meier survival curves with 95% confidence intervals (broken lines) for computer-navigated total knee replacement (CAS) and conventionally operated (CON) total knee replacement. Log-rank test: p = 0.9. 8 years at risk: CAS, n = 354; CON, n = 2,836.

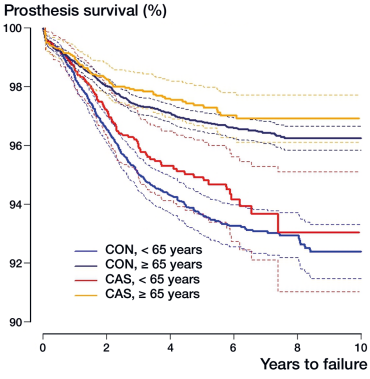


Figure 3 Cox regression survival curves with 95% confidence intervals (broken lines) for computer-navigated total knee replacement (CAS) and conventionally operated total knee replacement (CON) in patients who were more than or less than 65 years of age, adjusted for sex, ASA category, diagnosis, previous surgery, prosthesis brand, and fixation method. 8 years at risk: ≥ 65 years old: CAS, n = 228; CON, n = 1,881; < 65 years old: CAS, n = 126; CON, n = 955.

When selecting cemented prostheses only (2,080 CAS, 16,418 CON), there was still no significant difference in our Cox-adjusted estimates for risk of revision (RR = 0.9, CI: 0.7–1.1; p = 0.4). For hybrid implants (114 CAS, 3,143 CON), the Cox-adjusted relative risk was 1.2 (CI: 0.4–3.9; p = 0.7). Only Profix and LCS complete were used as uncemented implants. Uncemented Profix implants (836 CAS, 27 CON) had 6 revisions reported, all in the CAS group. For the uncemented LCS compete (619 CAS, 316 CON), no significant difference was found (RR = 0.8, CI: 0.5–1.3; p = 0.3).

We did not find any statistically significant difference in overall risk of revision between CAS and CON in patients who were older and younger than 65 years (Figure 3). Patients < 65 years of age had a lower risk of revision in the CAS group, with RR = 0.8, but this was not statistically significant (CI: 0.6–1.1; p = 0.1). For patients ≥ 65 years of age, the relative risk was 0.9 (CI: 0.7–1.2; p = 0.6). Analyses of fixation method in patients < 65 years of age did not indicate that CAS affected the revision risk differently for cemented, uncemented, or hybrid implants. The use of computer navigation did not affect the Kaplan-Meier survival rate after 5 or 8 years (Table 2).

3 hospitals were using both techniques (CAS and CON), and were regarded as high-volume centers with more than 300 computer-navigated TKRs. 1 hospital mainly used Profix (hospital A: 917 CAS, 137 CON), and the other 2 used LCS complete (hospital B: 342 CAS, 183 CON; hospital C: 578 CAS, 55 CON). We compared the 2 techniques in these hos-

Table 3. Reasons for revision in computer-navigated total knee replacement (CAS) and conventionally operated total knee replacement (CON) for all patients and for patients less than 65 years of age

No [a]		All ages CAS n	% [b]	CON n	% [b]	CAS vs. CON [c] RR (95% CI)	p-value	< 65 years old CAS n	% [b]	CON n	% [b]	CAS vs. CON [c] RR (95% CI)	p-value
1	Deep infection	40	26	202	24	1.0 (0.6–1.4)	0.8	17	20	81	20	0.7 (0.4–1.3)	0.3
2	Malalignment	15	10	90	11	0.5 (0.3–0.9)	0.02	5	6	49	12	0.3 (0.1–0.8)	0.01
3	Aseptic loosening	33	21	190	23	1.1 (0.7–1.6)	0.7	17	20	99	24	1.0 (0.6–1.8)	0.9
4	Instability	29	19	112	14	0.7 (0.4–1.2)	0.2	22	27	63	15	0.9 (0.5–1.7)	0.7
5	Periprosthetic fracture	4	3	14	1.7	0.5 (0.1–2.1)	0.4	1	1	4	1.0	0.6 (0.04–7.9)	0.7
6	Decreased range of motion [d]	5	3	34	4.1	0.8 (0.3–2.3)	0.7	5	6	22	5.4	1.4 (0.4–4.5)	0.6
7	Other [e]	6	4	56	6.8	0.6 (0.2–1.6)	0.3	1	1	26	6.3	0.1 (0.01–1.0)	0.05
8	Pain only	24	15	125	15	1.1 (0.6–1.9)	0.7	15	18	66	16	1.2 (0.6–2.5)	0.6
	Missing	0	0	4	0.5			0	0	1	0.2		
	No. of revisions	156		827				83		411			
	No. of total knee replacements	3,665		20,019				1,292		6,481			

[a] Listed in the same order as hierarchy for determination of main cause of revision.
[b] Percentage of number of revisions.
[c] Adjusted for age, sex, prosthesis brand, ASA category, fixation method (cemented, uncemented, hybrid), diagnosis (OA, other), and previous surgery of the knee (yes, no).
[d] Including arthrofibrosis and joint stiffness.
[e] Including dislocation (patella and other), polyethylene wear, and progression of arthrosis.

pitals separately. All 3 high-volume hospitals had small, statistically insignificant differences in the risk of revision when CAS and CON were compared.

Median operating time was 100 min (IQR: 35) in the CAS group and 89 min (IQR: 25) in the CON group ($p < 0.001$). When only cemented implants were selected, median operating time was 111 min (IQR: 31) for CAS and 90 min (IQR: 32) for CON ($p < 0.001$).

Learning curve

The learning group involved 533 computer-navigated (CAS) knee procedures in 22 different hospitals and the experienced group involved 3,140 CAS procedures in 15 different hospitals. Comparison of the learning group with the entire CON group did not reveal any difference in risk of revision (RR = 1.1, CI: 0.7–1.5; $p = 0.9$). Median operating time for the learning CAS group was 31 min longer than for CON ($p < 0.001$). In the experienced CAS group, the risk of revision relative to CON was 0.8 (CI: 0.7–1.0; $p = 0.09$). Median operation time was 17 min longer with CAS ($p < 0.001$) for all fixation methods and 19 minutes longer with CAS for cemented implants ($p < 0.001$).

Causes of revision (Table 3)

Deep infection and aseptic loosening were the most common causes of revision, except in CAS patients aged < 65 years, where revision due to instability was more frequent. When we adjusted for age, sex, ASA class, diagnosis, prosthesis brand, and fixation method, the CAS group had fewer revisions due to malalignment, with RR = 0.5 (CI: 0.3–0.9; $p = 0.02$) in all patients and RR = 0.3 (CI: 0.1–0.8; $p = 0.01$) in patients who were < 65 years old. Otherwise, there were no statistically significant differences in risk of revision for the causes reported.

Discussion

We used data from the Norwegian Arthroplasty Register to compare survival, relative risk of revision, and causes of revision in total knee replacements performed with conventional methods or computer navigation. After 8 years of follow-up, we did not find any statistically significant differences in survival between groups. In subanalyses, we could not detect any difference in RR of revision for CAS and CON, either for different prosthesis brands or hospital volumes. Computer navigation did not affect the outcome differently with certain fixation methods or in patients less than 65 years. Risk of revision was not elevated in the first 30 computer-navigated cases at each center compared to the risk for the later procedures. CAS had statistically significantly fewer revisions due to malalignment.

Strengths and limitations

This registry-based study involved a large number of patients from all surgical units that perform total knee replacements in Norway (Espehaug et al. 2006, Havelin et al. 2015). Selection of the 5 most frequently used prosthesis brands and the 3 most frequently used navigation systems strengthened the applicability and external validity. The high completeness of reporting led to good external validity and 8 years of follow-up enabled us to discover possible complications of computer navigation, such as higher rates of infection and fracture, or advantages.

Despite the high quality of the NAR database and the registry study design, there were some limitations. Because of the low revision rate of knee prostheses, a large cohort and a long follow-up time were required to uncover benefits or

small disadvantages in the study group. Serving a population of approximately 5.2 million citizens, the Norwegian registry has smaller numbers of operations than registries in larger countries, and is thus underpowered to detect small differences. This limitation was especially noticeable in some subanalyses with low numbers of revisions, and these results are less conclusive. Additionally, the different prosthesis brands and the use of computer navigation were unequally distributed among the hospitals. Consequently, the effect of single surgeons or differences in patient demographics between the hospitals may have affected the results, especially in the subanalyses where the number of patients was low. Complications that do not lead to revision of the prosthesis are not registered in the database. Thus, fractures or infections in pinholes after CAS are usually not registered. Common confounding factors were treated by adjustments in the statistical analyses, but we cannot account for unmeasured differences such as surgeon volume and postoperative treatment. In contrast to randomized trials, uncontrolled confounders might also have had a role. Adjustment for many different confounding factors increases the risk of overadjustment bias (Schisterman et al. 2009) and a Cox model only adjusted for age, sex, and diagnosis was performed to address this problem. However, inclusion of death in a competing risks model, and also the Cox model with fewer adjustments, did not alter the conclusions in our study.

Comparison with other studies

In a short-term follow-up from the NAR (Gothesen et al. 2011), the risk of revision was higher with CAS than with CON, and the LCS complete had inferior results than other prosthesis brands in the CAS group. At 8-year follow-up, we could no longer detect these differences. The short-term results might be caused by challenges during the introduction period of this new technology. Even so, we could not detect a learning curve, which supports previous findings that surgeons achieve satisfactory results with computer navigation shortly after introduction (Jenny et al. 2008, Chinnappa et al. 2015). There have been few studies comparing different implant designs in computer-aided navigation, but the LCS complete has also shown inferior results in registry-based studies both in Norway and in the USA (the Kaiser Permanente Total Joint Arthroplasty Registry) with conventional surgery (Paxton et al. 2011, Gothesen et al. 2013) and with mobile-bearing knee replacement in general (Namba et al. 2014). Baker et al. (2012) found that implant brand and hospital type affected patient-reported outcome. Thus, it is likely that the inferior results with the LCS complete in the short term were mainly caused by the prosthesis design and challenges during introduction of new technology, rather than by the use of CAS.

In 2015, arthroplasty registries in New Zealand and Australia published studies on computer navigation in TKA, with 5 and 9 years of follow-up (respectively). The Australian registry reported a reduced revision rate for computer-navigated procedures in patients less than 65 years of age, and there was a reduction in revision rate due to loosening (de Steiger et al. 2015), but only with adjustment for age and sex. In a group of equivalent age, the arthroplasty registry in New Zealand found a trend of a higher revision rate for Triathlon implants inserted with computer-assisted navigation (not statistically significant) (Roberts et al. 2015). We found a statistically insignificantly lower revision rate and also lower risk of loosening in patients who were less than 65 years in the CAS group, supporting the Australian results. The smaller number of cases in our registry may explain why we were unable to detect a significant difference.

Improved alignment with CAS is expected to give better resistance to aseptic loosening and lower wear of the implant, as well as better functional results. We found a lower risk of revision due to malalignment, but this did not affect the overall survival or the risk of revision. There is evidence that malalignment is associated with implant failure (Jeffery et al. 1991, Huang et al. 2012) and a recent review article by Gromov et al. (2014) recommended aiming for optimal alignment of the components in TKA. On the other hand, Parratte et al. (2010) found no difference in survivorship for knees with mechanical axis within 3° of neutral compared to malaligned knees in a retrospective study with 15 years of follow-up. Bellemans et al. (2012) emphasized the importance of recognizing patients with constitutional varus, and Vanlommel et al. (2013) showed that these patients had superior clinical outcomes when the alignment was left in mild varus. In these cases, computer navigation could in theory cause a poorer outcome by correcting the patient's natural alignment. As an alternative to mechanically aligned TKA, some surgeons prefer to have the prostheses kinematically aligned. A study by Howell et al. (2013) showed similar Oxford knee scores in kinematically aligned knees regardless of alignment, and a randomized, controlled trial by Dossett et al. (2014) found superior functional outcome and pain relief in kinematically aligned TKAs than in mechanically aligned TKAs. These different approaches might also play an important role in the success of TKA.

Analysis of registry data is limited to the information collected in the registry. The Norwegian Arthroplasty Register contains no information on radiological measurements or functional outcomes. In order to claim causality between alignment and survival, radiological measurements of the revised cases are required. Our results illustrate that computer-assisted navigation alone does not change large trends in survival of knee prostheses. The patient's health status has been suggested to be more important than surgical factors (Baker et al. 2012), and alignment may be of less importance than previously assumed.

Future research

Registry studies with a longer follow-up time will provide useful information in future assessment of computer naviga-

tion in TKR. However, to investigate correlations between malalignment and functional results, long-term follow-up of randomized trials should also be conducted. Radiostereometric analysis can be helpful in detecting early loosening as a predictor of implant failure (Ryd et al. 1995). Collection of revised implants for laboratory studies and radiographs for alignment measurements from revisions might be useful in addition to collection of patient-reported outcome measures in arthroplasty registries. These modalities would enable researchers to assess revision rates in the context of patient satisfaction and function, with a view to improving the quality of life of the patients.

Summary

This study has shown similar 8-year survivorship in computer-navigated TKR and conventionally operated TKR, but CAS had fewer revisions for malalignment. We were unable to find specific benefits of CAS in particular age groups or regarding particular prosthesis brands.

The study was planned and designed by OG, GSD, and OF. GSD and AMF performed the statistical analyses. GSD drafted the manuscript. All the authors took part in interpretation of the study findings and revision and final approval of the manuscript before submission.

We thank all the orthopedic surgeons in Norway for reporting data to the NAR, and the patients who gave their consent to be included to the NAR database.

The Norwegian Arthroplasty Register is financed by the Western Norway Regional Health Authority (Helse-Vest). During the study period, GSD received a study grant from the Western Norway Regional Health Authority (Helse-Vest). No competing interests declared.

Australian Orthopaedic Association National Joint Replacement Registry. Annual Report. Australian Orthopaedic Association National Joint Replacement Registry. Annual Report. AOA: Adelaide; 2015; 230.

Baker P N, Deehan D J, Lees D, Jameson S, Avery P J, Gregg P J, Reed M R. The effect of surgical factors on early patient-reported outcome measures (PROMS) following total knee replacement. J Bone Joint Surg (Br) 2012; 94 (8): 1058-66.

Bellemans J, Colyn W, Vandenneucker H, Victor J. The Chitranjan Ranawat award: is neutral mechanical alignment normal for all patients? The concept of constitutional varus. Clin Orthop Relat Res 2012; 470 (1): 45-53.

Burnett R S, Barrack R L. Computer-assisted total knee arthroplasty is currently of no proven clinical benefit: a systematic review. Clin Orthop Relat Res 2013; 471 (1): 264-76.

Chinnappa J, Chen D B, Harris I A, MacDessi S J. Total knee arthroplasty using patient-specific guides: Is there a learning curve? Knee 2015; 22(6): 613-7.

Choong P F, Dowsey M M, Stoney J D. Does accurate anatomical alignment result in better function and quality of life? Comparing conventional and computer-assisted total knee arthroplasty. J Arthroplasty 2009; 24 (4): 560-9.

Cip J, Widemschek M, Luegmair M, Sheinkop M B, Benesch T, Martin A. Conventional versus computer-assisted technique for total knee arthroplasty: a minimum of 5-year follow-up of 200 patients in a prospective randomized comparative trial. J Arthroplasty 2014; 29 (9): 1795-802.

de Steiger R N, Liu Y L, Graves S E. Computer navigation for total knee arthroplasty reduces revision rate for patients less than sixty-five years of age. J Bone Joint Surg (Am) 2015; 97 (8): 635-42.

Dossett H G, Estrada N A, Swartz G J, LeFevre G W, Kwasman B G. A randomised controlled trial of kinematically and mechanically aligned total knee replacements: two-year clinical results. Bone Joint J 2014; 96-b (7): 907-13.

Espehaug B, Furnes O, Havelin L I, Engesæter L B, Vollset S E, Kindseth O. Registration completeness in the Norwegian Arthroplasty Register. Acta Orthop 2006; 77 (1): 49-56.

Fine J P, Gray R J. A Proportional hazards model for the subdistribution of a competing risk. Journal of the American Statistical Association 1999; 94 (446): 496-509.

Furnes O, Espehaug B, Lie S A, Vollset S E, Engesaeter L B, Havelin L I. Early failures among 7,174 primary total knee replacements: a follow-up study from the Norwegian Arthroplasty Register 1994-2000. Acta Orthop Scand 2002; 73 (2): 117-29.

Gothesen O, Espehaug B, Havelin L, Petursson G, Furnes O. Short-term outcome of 1,465 computer-navigated primary total knee replacements 2005-2008. Acta Orthop 2011; 82 (3): 293-300.

Gothesen O, Espehaug B, Havelin L, Petursson G, Lygre S, Ellison P, Hallan G, Furnes O. Survival rates and causes of revision in cemented primary total knee replacement: a report from the Norwegian Arthroplasty Register 1994-2009. Bone Joint J 2013; 95-B (5): 636-42.

Gothesen O, Espehaug B, Havelin L I, Petursson G, Hallan G, Strom E, Dyrhovden G, Furnes O. Functional outcome and alignment in computer-assisted and conventionally operated total knee replacements: a multicentre parallel-group randomised controlled trial. Bone Joint J 2014; 96-B (5): 609-18.

Gromov K, Korchi M, Thomsen M G, Husted H, Troelsen A. What is the optimal alignment of the tibial and femoral components in knee arthroplasty? Acta Orthop 2014; 85 (5): 480-7.

Havelin L I, Engesaeter L B, Espehaug B, Furnes O, Lie S A, Vollset S E. The Norwegian Arthroplasty Register: 11 years and 73,000 arthroplasties. Acta Orthop Scand 2000; 71 (4): 337-53.

Havelin L I, Furnes O, Engesaeter L B, Fenstad A M, Bartz-Johannessen C, Fjeldsgaard K, Wiig O, Dybvik E. Norwegian Arthroplasty Register Annual Report. Norwegian Arthroplasty Register Annual Report. Norwegian Arthroplasty Register: Bergen; 2015.

Hetaimish B M, Khan M M, Simunovic N, Al-Harbi H H, Bhandari M, Zalzal P K. Meta-analysis of navigation vs conventional total knee arthroplasty. J Arthroplasty 2012; 27 (6): 1177-82.

Howell S M, Howell S J, Kuznik K T, Cohen J, Hull M L. Does a kinematically aligned total knee arthroplasty restore function without failure regardless of alignment category? Clin Orthop Relat Res 2013; 471 (3): 1000-7.

Huang N F, Dowsey M M, Ee E, Stoney J D, Babazadeh S, Choong P F. Coronal alignment correlates with outcome after total knee arthroplasty: five-year follow-up of a randomized controlled trial. J Arthroplasty 2012; 27 (9): 1737-41.

Jeffery R S, Morris R W, Denham R A. Coronal alignment after total knee replacement. J Bone Joint Surg (Br) 1991; 73 (5): 709-14.

Jenny J Y, Miehlke R K, Giurea A. Learning curve in navigated total knee replacement. A multi-centre study comparing experienced and beginner centres. Knee 2008; 15 (2): 80-4.

Namba R, Graves S, Robertsson O, Furnes O, Stea S, Puig-Verdie L, Hoeffel D, Cafri G, Paxton E, Sedrakyan A. International comparative evaluation of knee replacement with fixed or mobile non-posterior-stabilized implants. J Bone Joint Surg (Am) 2014; 96 Suppl 1: 52-8.

Nizard R S, Porcher R, Ravaud P, Vangaver E, Hannouche D, Bizot P, Sedel L. Use of the Cusum technique for evaluation of a CT-based navigation system for total knee replacement. Clin Orthop Relat Res 2004; (425): 180-8.

Parratte S, Pagnano M W, Trousdale R T, Berry D J. Effect of postoperative mechanical axis alignment on the fifteen-year survival of modern, cemented total knee replacements. J Bone Joint Surg (Am) 2010; 92 (12): 2143-9.

Paxton E W, Furnes O, Namba R S, Inacio M C, Fenstad A M, Havelin L I. Comparison of the Norwegian knee arthroplasty register and a United States arthroplasty registry. J Bone Joint Surg (Am) 2011; 93 Suppl 3: 20-30.

Rebal B A, Babatunde O M, Lee J H, Geller J A, Patrick D A, Jr., Macaulay W. Imageless computer navigation in total knee arthroplasty provides superior short term functional outcomes: a meta-analysis. J Arthroplasty 2014; 29 (5): 938-44.

Ritter M A, Davis K E, Meding J B, Pierson J L, Berend M E, Malinzak R A. The effect of alignment and BMI on failure of total knee replacement. J Bone Joint Surg (Am) 2011; 93 (17): 1588-96.

Roberts T D, Clatworthy M G, Frampton C M, Young S W. Does computer assisted navigation improve functional outcomes and implant survivability after total knee arthroplasty? J Arthroplasty 2015; 30 (9 Suppl): 59-63.

Ryd L, Albrektsson B E, Carlsson L, Dansgard F, Herberts P, Lindstrand A, Regner L, Toksvig-Larsen S. Roentgen stereophotogrammetric analysis as a predictor of mechanical loosening of knee prostheses. J Bone Joint Surg (Br) 1995; 77 (3): 377-83.

Schemper M, Smith T L. A note on quantifying follow-up in studies of failure time. Control Clin Trials 1996; 17 (4): 343-6.

Schisterman E F, Cole S R, Platt R W. Overadjustment bias and unnecessary adjustment in epidemiologic studies. Epidemiology 2009; 20 (4): 488-95.

Shi J, Wei Y, Wang S, Chen F, Wu J, Huang G, Chen J, Wei L, Xia J. Computer navigation and total knee arthroplasty. Orthopedics 2014; 37 (1): e39-43.

Smith B R, Deakin A H, Baines J, Picard F. Computer navigated total knee arthroplasty: the learning curve. Comput Aided Surg 2010; 15 (1-3): 40-8.

Vanlommel L, Vanlommel J, Claes S, Bellemans J. Slight undercorrection following total knee arthroplasty results in superior clinical outcomes in varus knees. Knee Surg Sports Traumatol Arthrosc 2013; 21 (10): 2325-30.

Graphic design: Communication Division, UiB / Print: Skipnes Kommunikasjon AS

uib.no

ISBN: 978-82-308-7084-6 (PRINT)
978-82-308-7173-7 (PDF)