Revision Knee Arthroplasty in Norway 1994-2011

A register-based study with focus on implant survival, causes and risk of re-revision, pain relief, functional outcome, patient satisfaction, and health related quality of life

Tesfaye Hordofa Leta

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SCIENTIFIC ENVIRONMENT

This PhD study was performed as on a part-time basis in the period between April 2012 and December 2016 while the author was working as an authorized nurse at the Department of Orthopaedic Surgery, Haukeland University Hospital. During the study period, the author received three short full-time study grants from the Health Research Unit at Haukeland University Hospital for a total of 15 months (6+6+3 months).

This thesis is based on knee arthroplasty data from the Norwegian Arthroplasty Register (NAR) (1994-2011). Since its initiation as hip arthroplasty register in 1987, 21 candidates have accomplished their PhD based on data from the NAR. The author of this thesis has carried out his PhD study in this environment.

This PhD study is a part of the PhD program at the Department of Clinical Medicine, Faculty of Medicine and Dentistry, University of Bergen. Supervision has been given by the staff of: the NAR at the Department of Orthopedic Surgery, the Department of Occupational Medicine, and the Department of Research and Development, all at Haukeland University Hospital. Supervision has also been given by the staff of the Department of Clinical Medicine, and the Department of Global Public Health and Primary Care, both at the Faculty of Medicine and Dentistry, University of Bergen, Norway.

To Oromo people!

In the memory of those who have fallen for the liberty, equality, and freedom of Oromo and Oromia!

"Honor and glory for the fallen heroines and heroes,
and
'Nagaa' and 'Araaraa' for the 'Ayyaanaa' of our foreparents!

ACKNOWLEDGEMENTS

Contents

LIST OF ABBREVIATIONS

ADL	Activities of Daily Living
ASA	American Society of Anesthesiologists
CCK	Constrained Condylar Knee (Fully stabilized knee)
CI	Confidence Interval
CR	Cruciate-retaining
DMARD	Disease Modifying Anti-rheumatic Drug
EQ-5D	European Quality of Life (EuroQol) 5 Dimensions
ΔEQ-5D index score	Postoperative- minus Preoperative- EQ-5D index score
HRQOL	Health Related Quality of Life
ISAR	International Society of Arthroplasty Register
KOOS	Knee Injury and Osteoarthritis Outcome Score
MID	Minimum Important Difference
MCID	Minimum Clinical Important Difference
MPCD	Minimal Perceptible Clinical Difference
NAR	Norwegian Arthroplasty Register
NPR	Norwegian Patient Register
OA	Osteoarthritis
OKS	Oxford Knee Score
PCS	Posterior Cruciate Stabilizing
PRO	Patient Reported Outcome
PROM	Patient Reported Outcome Measure
QoL	Quality of Life
RA	Rheumatoid Arthritis
RCT	Randomized Controlled Trial
Rev-TKA*	Revision of a failed primary TKA to a TKA
Rev-UKA	Revision of a failed primary UKA to a TKA
RR	Relative Risk
SD	Standard Deviation

SF-36	Medical Outcome Study Short Form-36
SPR	Secondary Patella Resurfacing
TKA	Total Knee Arthroplasty
UKA	Unicompartmental Knee Arthroplasty
VAS	Visual Analogue Scale
WHO	World Health Organization
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

*In 2012, when we started planning the research project, and in the first paper included in this thesis, revision TKA referred to the aseptic revision of any part of failed primary TKAs to TKAs. In the third paper, revision-TKA refers only to the aseptic revision of failed primary TKAs to TKAs that had involved an exchange of the femoral and/or the tibial component and abbreviated as rev-TKA. In this thesis, however, rev-TKA was used referring to any primary TKA revised to TKA.

GLOSSARY/DEFINITIONS

Functional outcome (status): Ability of the individual to perform activities of daily living.

Health related quality of life (HRQOL): is "the value assigned to duration of life as modified by the impairment, functional states, perception, and social opportunities that are influenced by disease, injury, treatment or policy".

Isolated secondary patella resurfacing (SPR): A conversion of a non-resurfaced primary TKA into a resurfaced TKA with the isolated addition of a patella component and retention of the existing implant.

Primary knee arthroplasty: Replacing knee joint by a prosthetic implant for the first time.

Patient reported outcome (PRO): "is any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else".

Patient Reported Outcome Measures (PROMs) : are standardized instruments (questionnaires) designed to measure PROs.

Revision arthroplasty: Removal, addition or exchange of part or the whole implant for first time (first time revision).

Re-revision arthroplasty: Second time revision arthroplasty.

Unicompartmental Knee Arthroplasty (UKA): is knee arthroplasty surgery in which either the medial or lateral compartment of the knee joint is replaced by a prosthetic implant.

Total Knee Arthroplasty (TKA): is knee arthroplasty surgery in which both the medial, lateral and patellofemoral compartments of the knee joint are replaced with a prostetic implant. If TKA surgery also involves replacement of the patella we call it TKA with resurfaced patella (resurfaced TKA).

Type of revision operation: In this thesis we classified revision operations into three categories defined as: (1) **Complete revision operation** is a revision of the whole

prosthesis, i.e. revision procedures that involve an exchange, removal or addition of all components. (2) **Partial revision operation** is a revision of one or more components and retantion of others. (3) **Isolated SPR** is a conversion of a non-resurfaced primary TKA into a resurfaced TKA with the isolated addition of a patella component and retention of the existing implant.

ABSTRACT

Background and purpose: Globally, the number of both primary and revision knee arthroplasty surgeries performed each year is increasing. Revision knee arthroplasty surgery is more expensive, technically more difficult and complicated, and consumes more time and supplies than the primary knee arthroplasty surgery. Consequently, a reduced number of revisions would mean significant cost saving for society as well as reduced risk of pain, loss of function, and risk of complications for the patients. The overall aim of this thesis was to evaluate the outcomes of aseptic revision knee arthroplasties in Norway in terms of implant survival rate, causes and risk of re-revision, pain relief, functional outcome, patient satisfaction, and health related quality of life (HRQOL).

Materials and Methods: All studies included in this thesis were based on aseptic revision knee arthroplasties reported to the Norwegian Arthroplasty Register (NAR) in the period 1994-2011 (Paper I-III) and additional information on patient reported outcomes (PROs) data in the period 1994-2005 (Paper II and III). The PROs data were on HRQOL (using EQ-5D), functional outcome, pain, and knee related quality of life (using the Knee Injury and Osteoarthritis Outcome Score (KOOS)), postoperative pain and satisfaction (using Visual Analogue Scale (VAS)), and on musculoskeletal comorbidity (using Charnley Category A, B, C)**.** Kaplan-Meier and Cox-regression were used to analyze prostheses survival rate and the risk of re-revision, whereas t-test and multiple linear regression were used to evaluate mean differences in the patient reported outcome measures (PROMs) scores between different revision procedures or treatment groups.

Results: Paper I was based on 1016 primary Total Knee Arthroplasties (TKAs) revised to TKAs (rev-TKAs). The 10 years survival percentage was 78 %. Deep infection (28 %) and instability (26 %) were found to be the two most frequent causes of re-revision. Rev-TKAs with an exchange of the femoral or tibial component exclusively had a higher risk of re-revision (Relative Risk (RR) =1.7; p=0.02) compared to those with an exchange of the whole prosthesis. The risk of re-revision was double for men as compared to women (RR=2.0; p<0.001), and also increased for patients aged < 60 years compared to patients aged >70 years (RR=1.6; p=0.03). The use of bone impac-

tion grafting had a positive effect on the survival rate whereas the use of long stem extensions, stabilization, bone cement, and patella resurfacing had no significant effect on the risk of re-revision. Survival rates were similar among prosthesis brands.

In Paper II, the survival rate of TKAs revised with isolated secondary patella re-surfacing (SPR) was assessed based on 308 knees (301 patients) of which 114 patient had PRO data. The 10 years survival of these revisions was 87 %. Pain alone (10 knees) was the most frequent cause of re-revision. The risk of re-revision was nearly 9 times higher for patients aged <60 years compared to patients aged >70 years (RR=8.6; p<0.001). The mean EQ-5D index score had significantly improved by 0.15 points following the revision TKA with isolated SPR. Nearly 70 % of patients who had preoperative severe pain in the EQ-5D pain/discomfort domain reported an im-provement postoperatively. Overall, 63 % of patients that had reported PROs were satisfied with the SPR procedure. Males had a better result in mean ΔEQ-5D index score (i.e. postoperative minus preoperative EQ-5D index score). Older patients (>70 years) had better mean scores in the KOOS subscales compared to younger patients (≤ 70 years). Patients with unilateral knee joint problem (Charnley category 'A') had sig-nificantly better mean score in the KOOS subscales than patients with bilateral or mul-tiple joint or general health problems.

In Paper III, the survival rates of Unicompartmental Knee Arthroplasties (UKAs) to TKA (rev-UKAs) vs rev-TKA were assessed based on 768 rev-TKAs and 578 rev-UKAs, and clinical outcome was assessed based on PROs data from 150 of the 768 rev-TKAs and 127 of the 578 rev-UKAs. The technical difficulty of the surgical pro-cedure for these two revision groups were assessed as a proxies of the length of opera-tive time, and the need for bone impaction grafting, stem extensions, and/ or stabiliza-tion. The 10 years survival percentage of rev-UKAs vs rev-TKAs was 82 vs 81 %, re-spectively. The overall risk of a re-revision for rev-UKAs vs rev-TKAs was similar (RR= 1.3; p=0.2), nor did we find any differences in the mean PROM scores. For the elderly (> 70 years), however, the risk of a re-revision was double for rev-TKAs com-pared to the rev-UKAs (RR= 2.1; p=0.05). Loose tibia (28 vs 17 %), pain alone (21 vs 12 %), instability (19 vs 19 %), and deep infection (16 vs 31 %) were main causes of re-revision for rev-UKAs vs rev-TKAs, respectively. The observed differences in the

proportion of reasons for re-revision were statistically significant only for the deep infection where the rev-TKAs were 2.2 times more frequently re-revised due to deep infection than the rev-UKAs (RR=2.2; p=0.03). The surgical procedure for rev-TKAs took longer time (mean=150 vs 114 minutes) and needed more stems (58 vs 19 %), bone impaction (24 vs 19 %), and stabilizing (27 vs 9 %) compared to rev-UKAs.

Conclusions: The overall conclusion of this PhD study is that the long-term implant survival following aseptic revision knee arthroplasty in Norway in the period between 1994 and 2011 was satisfactory (range 78-87 % at 10 years), and a number of points were noted. Specifically:

i)   Complete TKA revisions had better implant survival rate than partial revisions. Thus, partial revisions should only be done after careful consideration in specific instances. Male gender and younger age (<60 years) were risk factors for re-revision. Patellar resurfacing, prosthesis brands, constrained implants, the use of stem extensions, and/or fixation method had no effect on the survival of rev-TKAs, whereas cases with bone impaction grafting had better results in terms of survival. Deep infection and instability were the most frequent causes of failure of rev-TKAs (Paper I).

ii)   For isolated SPR procedures pain and loosening were the main causes for re-revision. Young age (<60 years) was a risk factor for re-revision after these procedures. The mean HRQOL significantly improved following SPR. Isolated SPR procedure can provide a solution to patients with severe preoperative pain. Still, more than one-third of patients were dissatisfied with the outcomes of the SPR procedure. Male patients had a better post-revision improvement in mean EQ-5D index score, and patients with a unilateral joint problem (Charnley category 'A') had significantly better mean score in KOOS subscales than the other categories following revision TKA with isolated SPR (Paper II).

iii)   The overall outcomes of rev-UKAs and rev-TKAs in terms of implant survival rates, functional outcome, level of postoperative pain, patient satisfaction, and change on HRQOL status were similar. However, rev-TKAs seemed to be a technically more difficult surgical procedure, were re-revised more frequently due to deep infection, and had a double risk of re-revision for patient older than 70 years compared to that of rev-UKAs (Paper III).

LIST OF PUBLICATIONS

This thesis is based on the following three scientific papers.

Paper I

Leta TH, Lygre SHL, Skredderstuen A, Hallan G, and Furnes O. Failure of aseptic revision total knee arthroplasties. 145 revision failures from the Norwegian Arthroplasty Register, 1994–2011. *Acta Orthopaedica 2015; 86 (1): 48-57.*

Paper II

Leta TH, Lygre SHL, Skredderstuen A, Hallan G, Gjertsen JE, Rokne B, and Furnes O. Secondary patella resurfacing in painful non-resurfaced total knee arthroplasties. A study of survival and clinical outcome from the Norwegian Arthroplasty Register (1994-2011). *International Orthopaedics 2015; 40(4):715-22.*

Paper III

Leta TH, Lygre SHL, Skredderstuen A, Hallan G, Gjertsen JE, Rokne B, and Furnes O. Outcomes of unicompartmental knee arthroplasty after aseptic revision to total knee arthroplasty. A comparative study of 768 TKAs and 578 UKAs revised to TKAs from the Norwegian Arthroplasty Register (1994 to 2011). *Journal of Bone & Joint Surgery (Am) 2016; 98 (6):431-40.*

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1. INTRODUCTION

1.1. BACKGROUND

Painful destruction and stiffness of the knee joint caused by severe disease (i.e. primary osteoarthritis or rheumatoid arthritis) or injury are increasingly treated with knee arthroplasty. Globally, the number of knee arthroplasty surgeries performed each year is increasing [1]. It is expected that as the need for primary knee arthroplasties increases so will the need for revision knee arthroplasties [2, 3]. It has been projected that the number of revision knee arthroplasties performed in the USA will increase from 38300 in 2005 to 268000 by the year 2030 [3]. In Norway, the number of primary knee arthroplasties has increased from 995 knees in 1994 to 6093 knees in 2015 and the number of revisions also increased from 74 knees in 1994 to 545 knees in 2015 (Fig.1) [4].
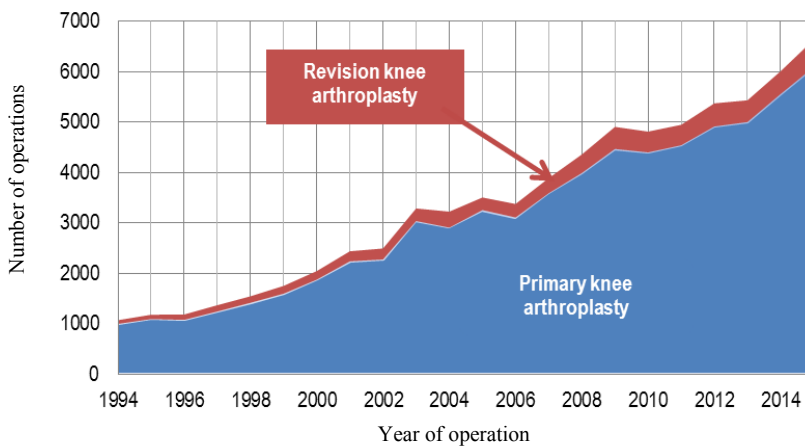
Fig.1. *Number of knee arthroplasty operations annually performed in Norway between 1994 and 2015.*

Up to the end of December 2014, 21 studies related to knee arthroplasty surgeries have been published based on data from the Norwegian Arthroplasty Register (NAR). All of these studies were related to issues on primary knee arthroplasties [4]. Although the revision of joint arthroplasties is becoming a challenge both medically and economically [5], to our knowledge, no study on the results of revision knee arthroplasties has been conducted in Norway prior to this PhD study project. Moreover, in orthopaedic literature, different surgical techniques and procedures have been described on how to approach revision knee arthroplasties with respect to fixation techniques such as

using long stems, stabilization, bone impaction and/or bone cement [6-11], whether to resurface the patella or not [12-17], and on the issue of revising failed primary Unicompartmental Knee Arthroplasties (UKAs) into Total Knee Arthroplasties (TKAs) [18-25]. However, the findings reported were varying and inconclusive.

Some authors have reported that patients with patella non-resurfaced primary TKAs are at higher risk of anterior knee pain and a need for revision with patella resurfacing than those patients with patella-resurfaced primary TKAs [14, 26-29]. In Norway, about 20 % of revisions done to patella non-resurfaced primary TKAs due to pain alone were isolated secondary patella resurfacing (SPR) [30]. However, it is not clear whether the pain after patella non-resurfaced primary TKAs is resolved with isolated SPR procedure. Several studies have been published addressing the results of SPR, but the number of reported cases was small. None of these studies reported implants survival rate and clinical outcomes in terms of functional outcome, level of pain relief, satisfaction, and changes in health-related quality of life (HRQOL) as combined outcome measures [15, 17, 31-36].

UKA is an alternative to TKA for patients with unicompartmental knee osteoarthritis [37-39]. Some earlier studies have reported that the functional outcome after primary UKA is somewhat better than primary TKA [40, 41] but the risk of revision is higher for primary UKAs than for primary TKAs [22, 24, 39, 42, 43]. The general recommendation for failed primary UKA is revision to a TKA [39, 43]. Many surgeons prefer to use primary UKAs in younger patients claiming that a revision of a primary UKA to a TKA (rev-UKA) yields the same results as a primary TKA [20-22, 24] and better than the results of a primary TKA revised to a TKA (rev-TKA) [21, 25]. For this to be true, the outcomes of rev-UKA should outperform that of rev-TKA. However, few comparative studies of rev-UKAs and rev-TKAs have been reported, and results have varied [21, 25, 39, 44, 45].

Furthermore, joint arthroplasty outcomes are traditionally assessed based on implant survival using revision as an endpoint. From a patient's perspective, however, the survival of implants alone may not give us the whole truth about the success or failure of the surgery [46]; and pain, physical functions, satisfaction and quality of life is of more importance. Earlier studies have, for instance, reported that up to 20 % of un-

revised [16, 47] and 41 % of revised [16] primary TKA patients were not satisfied with the outcomes. The use of patient-reported outcomes (PROs) in evaluating the quality of joint arthroplasty has not traditionally been given a significant role, however, PROs have gained increased acceptance recently [48]. Yet, comprehensive studies on outcome of revision knee arthroplasty using PROs data are scarce.

1.2. KNEE AND KNEE ARTHROPLASTY

1.2.1. Knee anatomy

The human knee (Fig. 2) is the largest synovial joint of our body, made of three compartments: the medial, lateral, and patellofemoral compartments. The knee constitutes four bones: the femur (thighbone), the tibia (shinbone), the fibula (outer shin bone), and the patella (kneecap) [49, 50]. The distal end of the femur has a medial and a lateral condyle each with a distinct shape that corresponds to the shape of the tibial plateau. The shape of these condyles is essential for the movement of the femur on the tibia [49]. The articular cartilage, menisci, ligaments, subchondral bone plates, and tendons are some of the essential internal parts of the knee which help in distributing the load and in providing some stability to the knee. Ligaments attached to the femur and tibia and several muscles/tendons also provide further stability to the knee. The main movements of the knee joint occur between the femur, patella, and tibia. The weight of the body is transferred through the femur, across the knee joint and into the tibia [50].
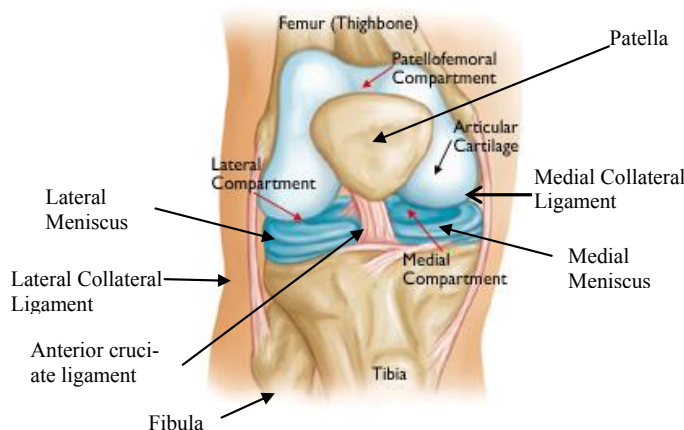
Fig. 2. *Natural anatomy of the human knee. The image was modified and reprinted with permission* [51].

1.2.2. Knee disease and treatment options

The most common disease affecting the knee joint is osteoarthritis (OA). OA is the most common form of arthritis, also known as a degenerative joint disease. OA causes pain, swelling, and reduced motion in joints (stiffness) (Fig. 3) [51]. According to a set of criteria defined by the American Rheumatism Association published by Altman et al. [52], OA is classified into two categories: (i) those with no presently known prior event or disease related to the OA (idiopathic or primary gonarthritis), and (ii) those with known events or disease associated with OA, for example, a trauma (secondary gonarthritis). Sequela of fractures, ligament and meniscal injuries are the most common causes of secondary gonarthritis [52].
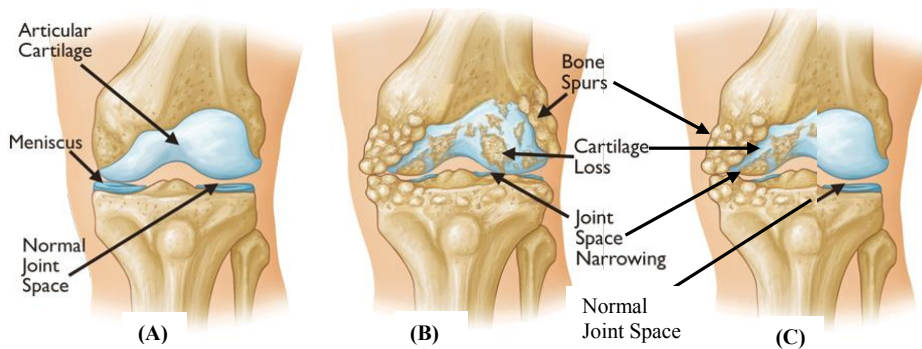
Fig. 3. *Knee joint space and effect of OA: (A) Normal joint space between the femur and the tibia. (B) Arthritis affects both the medial (inner) and lateral (outer) compartments. The joint space decreases due to damaged cartilage. Thus, it is a good candidate for TKA. (C) In this knee, the arthritis is limited to the medial compartment, and this may be a good candidate for UKA. The images were modified and reprinted with permission [51].*

OA breaks down the surface layer of cartilage in the knee joints and affects all the compartments of the knees, but to different degrees (Fig. 3). Healthy cartilage allows bones (bone ends) to glide over one another, and it also absorbs the shock of physical movement and weight bearing. In the knees with damaged cartilage, bones start to rub against each other (Fig. 3B, 3C, 4A, and 4C) [51]. With time, small deposits of bone called osteophytes may grow on the edges of the joint; and the joint may lose its normal shape and bits of bone or cartilage can float inside the joint space causing more pain and further damage to the joint [51].

OA is a complex disease and the etiology involves both biomechanics and biochemistry [53]. In most individual cases, the cause of OA is unknown [53-55]. However,

excessive body weight, joint injury, and advancing age [54-56] are reported as factors increasing the risk of developing OA. As per the year 2005, an estimated 9 million adults in the USA were affected by OA of the knees [55]. In Norway, 87 % of the patients who received primary TKAs and UKAs between 1994 and 2015 had OA as the diagnosis, followed by meniscal sequela (5.5 %), rheumatoid arthritis (RA) (4.9 %), fracture sequela (2.9 %), ligament injury sequela (2.7 %), and psoriatic arthritis (0.6 %) [4].

Another joint disease affecting the knee joint is inflammatory arthritis. It is a condition in which the synovial membrane is inflamed. There are many forms of inflammatory arthritis including RA, lupus arthritis, ankylosing spondylitis, Reiter's syndrome, psoriatic arthritis, reactive arthritis, and juvenile idiopathic arthritis. They are auto-immune disorders in which the body's immune defense reacts against its own tissues [50, 57].

Knee disease including OA and RA can be treated with conservative therapies and/or surgery [58]. Conservative (non-surgical) treatment and therapies include change of physical activity and weight control, health education, pain relief with painkillers (e.g. paracetamol, non-steroid anti-inflammatory drugs and disease modifying anti-rheumatic drugs (DMARDs)), injections (such as corticosteroids, hyaluronic acid), acupuncture, strength exercise, and physiotherapy [50, 59, 60].

Such non-operative medical treatments may help to relieve the symptoms of arthritis but they do not, with the exception of modern DMARDs, address the root of the disease. Thus, to improve the quality of life of patients suffering from joint destruction and functional disability, surgical treatments may eventually be necessary [50]. Operative treatment includes osteotomy and arthroplasty [59, 60]. Operative treatment is usually reserved for patients with severe arthritis that do not respond to conservative treatments. Nowadays, excellent outcomes from joint arthroplasties (particularly hip, knee, and shoulder) are obtained in the majority of patients with arthritis, and they can be highly successful in reducing pain and improving joint function. However, joint arthroplasty surgery may also lead to surgical and medical complications.

1.2.3. Brief historical background of knee arthroplasty

It is claimed that joint arthroplasty was introduced by a German surgeon: The-mistocles Gluck. Gluck used prostheses made of ivory for hip and knee joint replacements as early as 1890 [60, 61]. The era of modern knee arthroplasty started in the 1940s. The use of an interposition knee arthroplasty made of cobalt chromium (VitalliumRT) was reported in 1940 [62]. The cobalt chromium prosthesis was well tolerated, but it did not produce sufficient pain relief [60].

One of the first encouraging results of total joint replacement was reported in 1957 by Walldius and Shiers from their Walldius hinge prostheses [60, 61]. The results of the cemented hinged Walldius knee arthroplasty were good regarding functional improvement but had a high failure rates (13 %) at 3 years of follow-up [63]. The real breakthrough of knee arthroplasty came in the 1970s [61]. In 1974, the unconstrained total condylar prosthesis with a metal femoral and ultra-high molecular weight poly-ethylene tibial component used with polymethyl methacrylate cement was successfully introduced [64].

1.2.4. Modern knee arthroplasty

The most common and modern knee arthroplasties are TKA in which both the medial and the lateral compartments of the knee are replaced with an artificial materi-al; and UKA where only one of the compartments is replaced [65]. TKA is the main treatment option for the majority of severe cases, but for disease isolated only to one compartment of the knee (Fig. 3-5), UKA can be used [42, 51]. With the development of TKAs in the early 1970's, attention was also given to the patellofemoral joint prob-lems and its treatment since several patients reported anterior knee pain after having a TKA [66] and thus, a patella resurfacing component was also designed [67].

Knee arthroplasty composes of 2, 3 or 4 parts. These parts are called components and made of either metal or hard plastic materials: (1) the femoral component, (2) the tibial component, (3) the patella component, and (4) the polyethylene tibial platform (Fig. 5). The femoral component is made of metal and curves around the end of the femur. The tibial platform (liner) is a flat polyethylene component fixed on the top of the metal tibial component. Some implant designs do not have the metal tibial compo-nent and fix the polyethylene directly to the bone. In most cases, the metal tibial com-

ponent has a stem that protrudes into the center of the tibia for additional stability. The patellar component is most often dome-shaped on its articular surface and made of high-density polyethylene that replaces the back surface of the patella and mimics the shape of the patella [51].

(A)   **(B)**   **(C)**   **(D)**
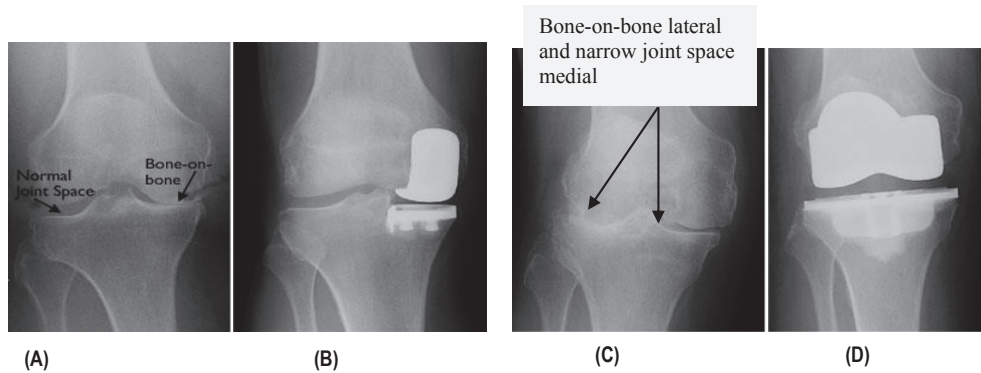
Fig. 4. *X-ray before and after knee arthroplasty surgery. (A) The lateral compartment has a normal joint space, and the medial compartment has severe arthritis with "bone-on-bone" degeneration. (B) The same knee as in (A) after UKA. (C) Severe arthritis in both the medial and lateral compartments. (D).The images were reprinted with permission [51].*

(A)   **(B)**
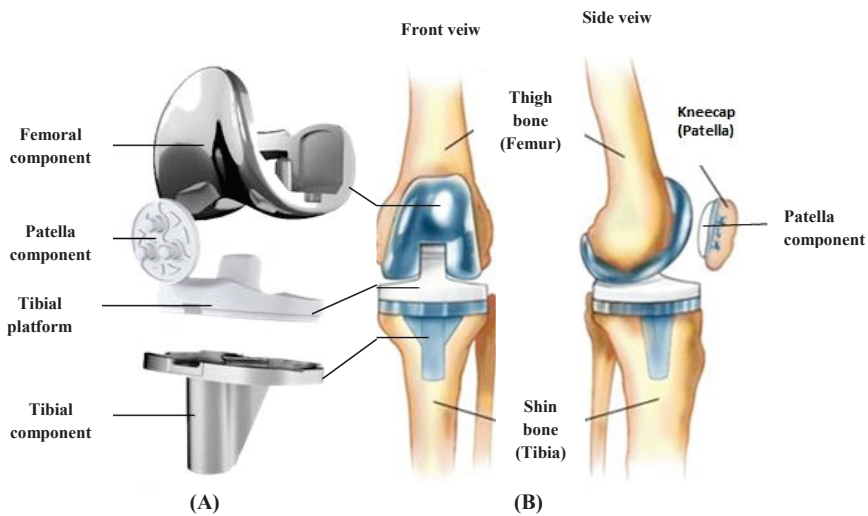
Fig. 5. *Total Knee Arthroplasty: (A) Individual implant components and (B) the implants assembled and placed in the knee joint. The images are modified and reprinted with permission.*
http://www.robodoc.com/patient_about_faqs.html.

1.2.5. Success or failure of knee arthroplasty

A success or a failure of joint arthroplasty surgery has traditionally been assessed using the survival of prosthesis with revision surgery as the endpoint. The use of survival analysis methods began in the 17th century to produce life tables and in the medical field, it was initially used in cancer studies [61]. The survival method was used for the first time as statistical methods for joint arthroplasties in 1980 by Dobbs for analyzing success or failure following hip arthroplasty and then by Tew and Waugh in 1982 and Knutson et al. in 1985 and 1986 for knee arthroplasty [61].

Evaluating a success or a failure of joint arthroplasty solely based on implant survivorship might, however, be inadequate and lack sensitivity [46]. Because, even if revision is used as endpoint indicating failure of the surgery, patients who have not been offered or elected to undergo revision surgery but with poor outcome will not be captured [46]. Probably, if 10 % of patients are revised after 10 year, at least another 10 % have clinical and/or radiographic failure of the implant [68]. Besides, there is a variation in the literature regarding whether all or only specific revisions should be used as the endpoint. Thus, judging the success or failure of joint replacement solely based on how long the implant remains in place is questionable from the patient's perspective [46]. Survival analyses with revision as the endpoint have used to evaluate the knee arthroplasty outcome in most papers from the NAR so far. To get a complete picture of the success or failure of joint arthroplasty, survival analyses should be supplemented with PROs.

1.2.6. Revision knee arthroplasty

Knee arthroplasty is an effective treatment for degenerative joint disease [58, 69, 70] and ranks among the most expensive but effective procedures both clinically and in terms of cost- effectiveness [70, 71]. The number of revisions of knee arthroplasty is, however, increasing both internationally [3] and in Norway (Fig. 1) [4]. Revision of joint arthroplasty is a serious burden for the individual patient and for the health-care provider and society.

1.2.6.1. Principles of revision knee arthroplasty

Restoring the original anatomy of the knee, regaining the function, and providing stability are some of the objectives (principles) of knee arthroplasty surgery. Thus, the principles of primary and revision knee arthroplasty surgery are more or less the same. However, revision knee arthroplasty is often a more technically demanding and complex procedure [50, 72]. Experts have summarized the goals and steps of revision knee arthroplasty: (1) identification of the failure mechanism, (2) good preoperative planning, (3) adequate surgical exposure, (4) removal of failed implant component with minimum bone loss, (5) bone defect management, (6) restoration of joint line, (7) ligamentous stability, (8) flexion-extension gaps balancing, (9) selection and implantation of an appropriate new implant component, (10) optimal rehabilitation, and (11) avoidance of complications [72-77].

Indications for revision

Determining mechanism of failure of the primary knee arthroplasty is essential so that the same failure is not repeated [73]. A careful assessment of patient history, physical examination, and radiological and laboratory investigation are important in determining failure mechanisms [50, 73, 78].

According to the findings from earlier studies and data from joint arthroplasty registries; aseptic loosening of implants component (3-55 %), deep infection (5-38 %), pain (9-36 %), instability (5-28 %), polyethylene wear (2-25 %), disease progression (5-29 %), joint stiffness (2-25 %), patella related complications (1-11%), periprosthetic fracture (0-10 %), and malalignment (<10 %) are some of the most common indications for revision of primary knee arthroplasty [79-84].

Although the cause(s) of implant loosening is not always clear, high-impact activities, excessive body weight, polyethylene wear, implant design, surgical technique with poor alignment and cementing technique, and osteolysis are common factors that may contribute to loosening [51, 85]. In some cases, the tiny particles that wear off the polyethylene accumulate around the knee joint and are attacked by the immune system of our body which can activate the osteoclasts that lead to resorption of the healthy bone around the implant (osteolysis). Thus, the bone mass and bone quality around the implant deteriorates, and the implant may loosen [51].

According to the NAR 2016 annual report the most frequent causes for revision knee arthroplasty surgery were pain (which could be in combination with other reasons) (24.6 %), loosening of implant component (21.1 %), deep infection (10.9 %), instability (10.1 %), malalignment (5.7 %), polyethylene wear (3.9 %), progression of arthrosis (3.5 %), dislocation (2.7 %), and/ or periprosthetic fracture (2.4 %) [4].

Preoperative assessment and planning

Taking an adequate history of the patient is essential before any patient examination. The goals of taking patient history are to determine if patient's symptoms are consistent with the objective clinical and radiographic findings, and to exclude conditions in which revision knee arthroplasty may need to be delayed [78]. In addition, having an adequate patient history will ensure that subsequent examinations such as physical examination, and radiological examination can be properly directed [50]. Patient's pain history is very important; pain with activity suggests a mechanical failure, and constant pain could indicate infection [78].

As a general principle, revision knee arthroplasty surgery should be performed as soon as the failure mechanism is diagnosed [86]. Delaying the revision surgery can result in progressive bone destruction and creation of larger defects. For example, if polyethylene wear of the tibia or the patella component with the metal backing exposed is diagnosed, delaying the revision surgery will produce a more massive metallic synovitis [86]. Thus, a more satisfactory result of the revision operation is achieved by early intervention [86]. However, before any knee surgery can be performed, the surgeon must assess whether the patient fits medically for the required surgery and the decision to operate are often made with the help of an internal medicine specialist and anesthesiologist [73].

Preoperatively, all cases must be reviewed carefully. Obtaining the preceding operative report and determining the size and manufacturer of the implant components is also necessary. Thought must also be given to the type of prosthesis that will be required for the revision [73, 78, 86]. Furthermore, the knee should be assessed for its range of motion, ligamentous stability, lower limb alignment, and patellofemoral tracking during the preoperative physical examination. The presence of any fixed contracture

identified during preoperative physical examination may alert the surgeon to potential surgical exposure difficulties [78].

An appropriate preoperative radiographic examination is vital to assess loosening of implant, bone stock and to decide whether bone graft or augments are needed as well as to determine implant position, alignment, and/or assessment of joint line height. Determination of joint line position preoperatively simplifies the actual surgery and facilitates balancing of the flexion-extension space [50, 78].

The other important preoperative assessment is routine blood tests including complete blood count, hemoglobin level, C-reactive protein, and sedimentation rate to help in the diagnosis of infection. The most important test for determining the presence of deep periprosthetic infection is an aspirate of synovial fluid from the joint [78, 86].

Surgical Exposure

Adequate surgical exposure is required to prevent excessive tension and /or rupture on the patellar tendon and the catastrophic complication of the tibial tubercle avulsion [73, 78, 86]. There are three important decisions to be made during the exposure in the revision surgery: (1) how to perform the skin incision, (2) how to perform the capsular incision, and (3) how to mobilize the extensor mechanism [78]. It is usually preferable to incorporate the previous incisions in the revision surgical approach whenever possible [73, 78, 86]. If there are preexisting multiple longitudinal incisions, the most lateral of these incisions should be used [78].

The type of surgical approaches chosen by the surgeon should facilitate the joint reconstruction rather than complicate it. A revision knee joint is usually entered through a medial parapatellar incision through the extensor mechanism, and followed by extensile release as needed. If extensile exposure is necessary, the surgeon should be prepared to perform a tibial tubercle osteotomy [73, 78, 86]. If the surgeon has a difficulty of everting the patella after a standard medial parapatellar arthrotomy, then a tight knee protocol should be used and the decision has to be made whether to perform a rectus snip, a V-Y plasty, quadriceps turndown, or to perform tibial tubercle osteotomy [73, 78].

Implant components removal

Removal of an implant may be complex, time-consuming, and result in excessive bone loss and bone fracture which may affect the type and quality of subsequent reconstruction [87]. Revision operations are also increasingly being performed due to other reasons than loosening; and removal of well-fixed implant components can be a difficult task and require many special instruments which can facilitate the removal. Osteotomes, power oscillating saws, Gigli saws, disimpaction punches, burrs and metal cutting instruments, and component-specific extraction devices are among many instruments that may potentially be needed for component removal during revision knee arthroplasty [73, 78, 86, 87].

The surgeon should keep in mind that the underlying bone of a failed knee arthroplasty is often weak and prone to fracture or collapse. Thus, safe implant removal requires adequate exposure. To allow better exposure, the implant should be removed in the following order: (1) tibial polyethylene, (2) femoral component (Fig. 6A), (3) tibial component (Fig. 6B), and patellar component [87]. Of component removals in revision knee arthroplasty, removal of the patella component can often be the most challenging part of the revision operation because removal of the patella component may lead to fracture of the patella bone and thus lead to a poor functional outcome [73, 78, 86].

With the components out, the bone surfaces are thoroughly cleaned of cement, debris, and granulation tissue. However, in the absence of infection, leaving any remaining well-fixed cements in the bone canal is accepted since removal can lead to excessive bone loss or perforation of the bone canal when trying to remove it [73, 86].
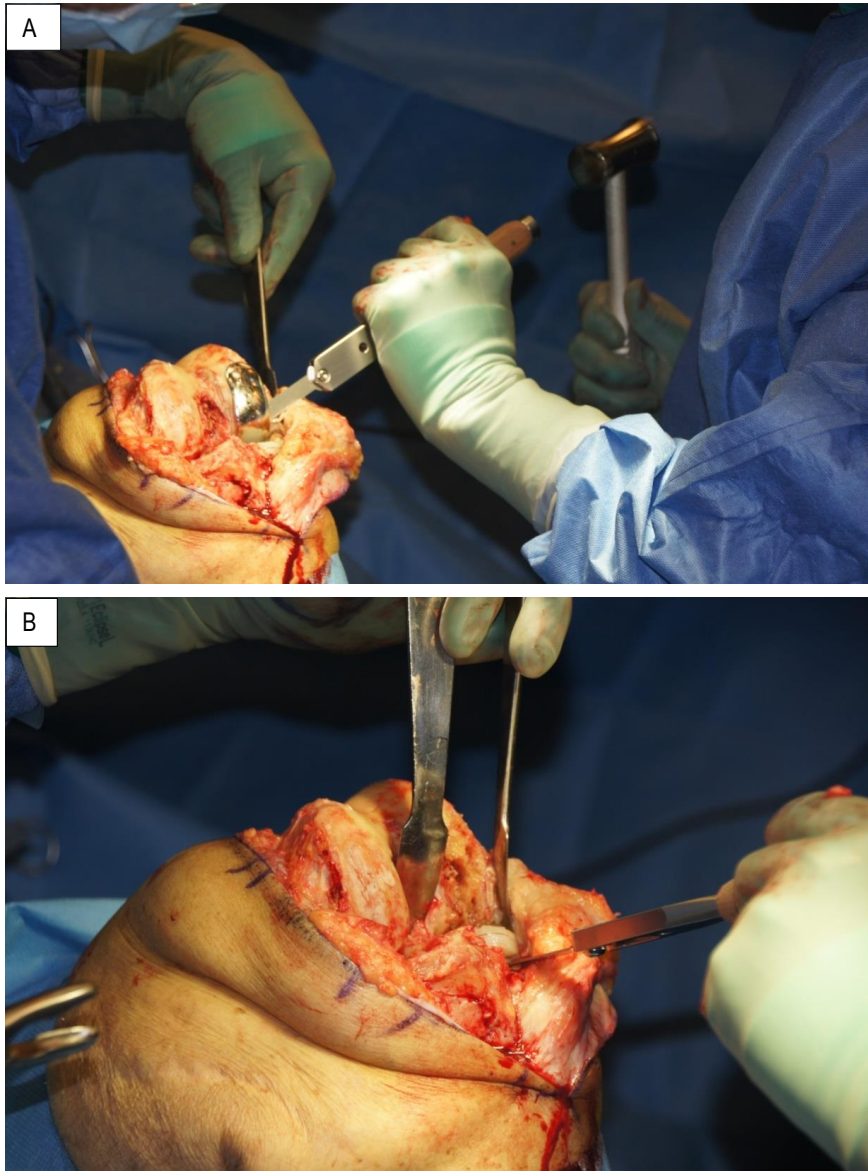
Fig. 6. *Removal of well-fixed (A) femoral component and (B) tibial component of failed primary unicompart-mental knee arthroplasty. The revision surgery was performed due to the progression of arthrosis on the lateral compartment. Photo: by Tesfaye H. Leta, at Haukeland University Hospital, April 2015. Patient's permission was obtained.*

Bone defects management

Bone defects are commonly encountered in revision knee arthroplasty [50, 73, 78, 86].

With adequate exposure and removal of the components, the remaining bone stock can

be assessed and facilitated for reconstruction of the bone defects. Preoperatively classi-

fying bone damage helps the surgeon to select an appropriate implant for revision. Many classification systems have been proposed in classifying bone defects based on size, depth, location, and ability to contain appropriate graft or cement [88] but the most widely used classification system is the Anderson Orthopaedic Research Institute classification [78]. This system allows separate classification of femoral and tibial bone defect and its management (Table 1 and Fig. 7).

Table 1. Anderson Orthopaedic Research Institute Classification of bone defect and surgical options as presented by Thongtrangan et al. [78].

Classification	Bone defects	Surgical options
Type 1:	Intact metaphyseal bone, minor bone defects, revision component expected to be stable	Small defects can be filled with cement or morselized bone graft
Femur (F1)	Normal joint line, condyles intact	
Tibial (T1)	Component above fibular head and metaphysis intact	
Type 2 (2A-one condyle; 2B- both condyles):	Damaged metaphysis bone, cancellous bone loss	Most defects are able to be reconstructed with an augmented component; stems required.
Femur (F2)	Joint line elevated and condyles damaged	
Tibial (T2)	Component at or below the tip of the fibular head and tibial width reduced	
Type 3:	Deficient metaphyseal segment, major bone defect, collateral or patellar ligaments possibly detached.	Reconstruction with structural bone graft or large augments; maximally constrained or hinged components may be required
Femur (F3)	Implant migration or osteolysis to the level of the epicondyles	
Tibial (T3)	Component migration or osteolysis causing loss of the tibial flare.	

Bone cement and screws, block augments, metaphyseal sleeves and cones, impaction or bulk allografts, are some of the reconstructive methods of defected bone in revision knee arthroplasty. Selection of such reconstructive methods is determined by the location and quantity of osseous defects in the femur and tibia [89].

Impaction bone grafting is one of the different techniques used to treat major defects of bone loss. Theoretically, the impacted cancellous bone graft has been shown to incorporate into host bone and remodel over time, achieving the goal of reconstituting lost bone stock [90, 91].
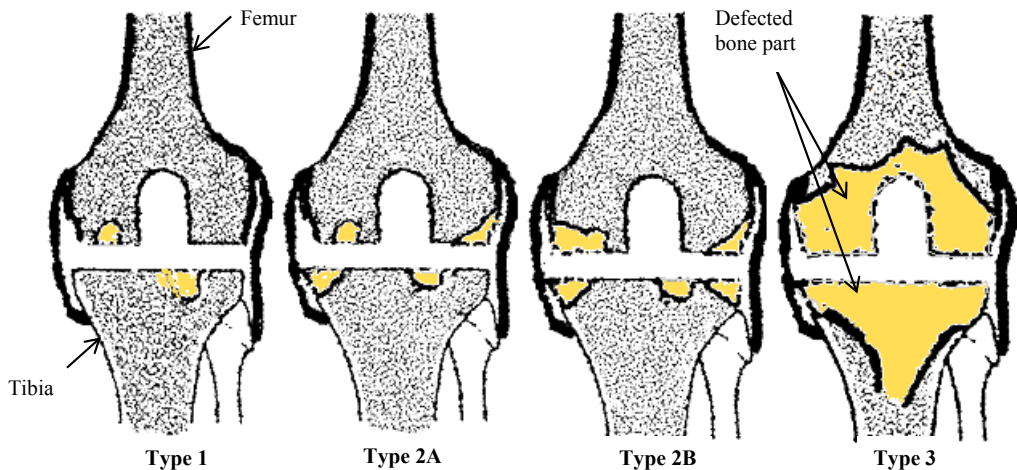
Fig. 7. Anderson Orthopaedic Research Institute classification of bone defects as presented by Qiu et. al. [92]. The images are modified and reprinted with permission.

Reconstruction

i. *Joint line restoration, stability, flexion-extension gap balancing, and component rotation*

Optimal stability and kinematics of the knee joint can be achieved by reestablishing the joint line at the original anatomic level [73, 78, 86]. This involves the residual bone and soft tissue management. Creating equal flexion and extension gap is also the key to revision knee arthroplasty surgery, however, when such equal gaps are not readily achieved, adjustments need to be made. Any adjustment on the tibial side will affect the knee both in flexion and extension, whereas adjustment on the femoral side can affect the knee in either flexion or extension [86]. As recommended by Brassard et al. [86], when performing a revision surgery, a three step method is preferable: 1st recreating the flat tibial surface, 2nd recreating the femur and rebuilding the flexion space, and 3rd rebuilding the extension space.

It is vital to the stability of the knee joint that the knee is balanced in flexion and extension; that the joint line is restored as close as possible to its original level; that the appropriate implant size and design is chosen; and that the collateral ligaments are kept intact [73]. The majority of revision knee arthroplasty can be performed using posterior cruciate stabilizing (PCS), deep dish or posterior cruciate-retaining (CR) implants (Fig. 8A-C). Otherwise, a more constrained device such as a non-liked constrained (Constrained Condylar Knee (CCK)) or rotating hinge designs are preferred if

stability cannot be achieved with less constrained implants such as a CR, deep dished or PCS implant [87]. For patients with moderate bone loss and intermediate ligamentous insufficiency, CCK systems are required whereas in the presence of severe bone loss and / or complete disruption of the ligaments, rotating hinge systems are required [87, 93]. The practical options for flexion-extension gap imbalance management as reported by Thongtrangan et al. [78] are presented in Table 2.
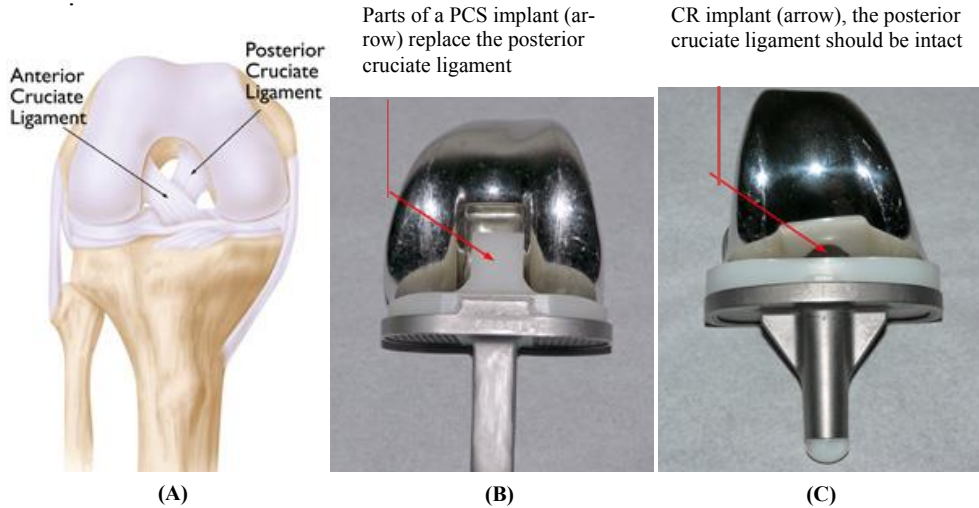
Fig. 8. *(A) Healthy knee: In a healthy knee, ligaments support the joint. (i.e. keep the joint stable). (B) Posterior-Stabilized Designs: One of the most commonly (but not in Norway) used types of implant in knee replacement (e.g. TKA) is a posterior-stabilized component which substitutes patients own ligaments. In this design, the cruciate ligaments are removed and parts of the implant substitute for the posterior cruciate ligament. (C) Cruciate-Retaining Designs: In this design, the anterior cruciate ligament is removed but the posterior cruciate ligament is kept . Cruciate-retaining implants do lack the center post and cam design. This implant may be appropriate for a patient whose posterior cruciate ligament is healthy enough to continue stabilizing the knee joint. The images were reprinted with permission [51].*

Table 2. Flexion-Extension gap imbalance management [78, 94].

	Extension loose	Extension adequate	Extension tight
Flexion loose	Select thicker tibial component	Select larger femoral component with posterior augmentation	Select larger femoral component with posterior augmentation, and resect distal femur.
Flexion adequate	Augment distal, femur. Bone graft distal femur	Make no changes	Resect distal femur. Perform posterior release. Resect posterior osteophytes
Flexion tight	Select smaller femoral component with distal augmentation. Consider PCS.	Select smaller femoral component. Perform posteriorly angled tibial resection. Consider PCS.	Select thinner tibial component. Resect tibia.

Restoring the mechanical axis and balancing the joint capsule and ligaments are important factors in obtaining proper rotational alignment of the femoral and tibial components of knee arthroplasty [95, 96]. There are several possible landmarks to be used as a reference line (axis) to achieve the correct alignment of the femoral and tibial components [96-98]. Using a combination of the transepicondylar axis, the antero-posterior axis (Whitesides line) and posterior condyles line as references to ensure proper rotational alignment of the femur is widely accepted [97, 98] (Fig. 9); whereas the medial third of the tibial tubercle is the most popular surgical method used to secure the rotational alignment of the tibial component [96]. These landmarks, however, vary greatly among patients [96].
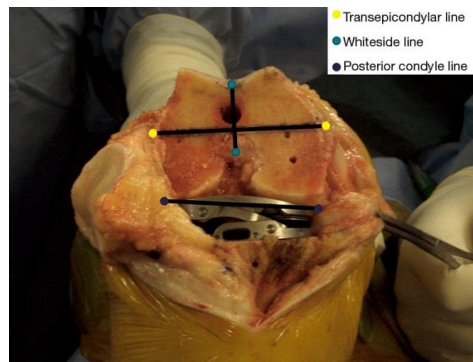
Fig. 9. *Intraoperative image with reference axis. The transepicondylar line should be perpendicular to Whiteside line and parallel to tibial cutting line.[97].*

ii. *Implant selection and fixation*

When removing the revised implants, it is important to measure its width and an-teroposterior diameter in order to give an indication of the size for the revision compo-nent. To avoid replication of the same problems in the revision surgery it is also im-portant to ascertain if the previous implant was too large, causing anterior or lateral knee pain, or too small giving instability [73] Since the long–term durability of the pros-thetic component and fixation is inversely proportional to prosthetic constraint, the least constrained prosthetic component that provides satisfactory stability should be selected [73, 78].

In revision knee arthroplasty the quality of femoral and tibial bone is usually compromised to a variable degree, thus, using stem extensions (Fig. 10A-ii, -iii and -

vi) is preferable to enhance fixation, particularly if a constrained implant is used [86]. The purpose of stems during revision knee arthroplasties is to bypass bone defects and reduce interface stresses of damaged bone in the distal femur as well as the proximal tibia. Furthermore, it has been reported that use of stem extensions has been shown to be beneficial in improving the survival (by reducing aseptic loosening) and clinical outcomes of revision knee arthroplasty [99, 100].

Nowadays, cemented, cementless, and hybrid fixations are common types of fixation used to connect knee implants to the bone. However, debates exist as to whether the femoral and tibial stem extension should be cemented. Bourne and Crawford [73] recommend to cement the femoral and tibial components, the proximal part of tibial stems, and around the housing mechanism of femoral stems but to press-fit (sometimes called a cementless) the intramedullary stem; whereas the Mayo Clinic advocate all cemented stems [101].

In cemented fixation, implants are held in place with fast-curing bone cement (polymethylmethacrylate). A cemented prosthesis has a bone cement layer between the patient's natural bone and the implant's components. In cementless fixation, the fixation relies on new bone growing into the surface of the implant, thus, cementless prosthesis are made of a material (most often titan) that attracts new bone growth. Most cementless prosthesis has a rough surface or porous coating so that the new bone actually grows into the surface of the implant. In the hybrid fixation, the femoral component is inserted without cement, and the tibial and/or patellar components are inserted with cement or vice versa [51]. Despite cementless reconstruction in revision knee arthroplasty has its advocates; most revision knee arthroplasties are cemented to the host bone because cement use ensures that the new implants will fit perfectly on the bone surfaces, which are inherently irregular. The objective of cement use in addition to fixation is to level the bone ends and provide even loading beneath the implant. The cement should contain an antibiotic powder to prevent infections [86, 102].

Rehabilitation and avoiding complication

As important as preoperative assessment, rehabilitation of the revision knee arthroplasty is crucial to the final outcome. Early postoperative mobilization as soon as possible is helpful to maximize the range of motion as well as to minimize risk of

postoperative complications associated with inactivity including thromboembolic disease, urinary retention, gastrointestinal ileus, and pneumonia [73, 78, 86]. Educating patients on the importance of the exercises to restore full flexion and extension is vital. Initially, crutches are required; however, full weight bearing should be encouraged soon as possible postoperatively unless contraindicated. Weight bearing is, for example, individualized based on the quality of fixation and the strength of the remaining condylar and metaphyseal bone [73, 78, 86].

1.2.6.2. When to revise a UKA to TKA

The surgical options of revision UKA ranges from polyethylene insert exchange to conversion to TKA depending upon the cause(s) of failure [103]. UKA to UKA revision may be indicated with polyethylene wear or loosening of one or both implant components if there is no progression of disease in the opposite compartment and patellofemoral joint, and if suitable bone stock available for revision [103]. However, since the supporting bone is often weak and is accompanied by degenerative changes in other part of the knee joint, a revision procedure to TKA is often recommended [39, 43]. If any doubt exists regarding the indication for UKA to UKA revision, conversion to TKA should be used [103]. Thus, with thorough understanding of the causes of failure of a UKA, and the principle of revision knee arthroplasty, the orthopaedic surgeon can successfully convert a failed UKA to a TKA.

1.2.6.3. Secondary patella resurfacing (SPR)

Treatment of patients with knee osteoarthritis using TKA is reported as highly successful and cost-effective and usually leads to a significant improvement in quality of life and function. However, patient dissatisfaction following TKA procedure remains as high as10 -50 % [16, 66, 104-106] and residual knee pain (anterior knee pain) has been reported as a major factor that contributes to patient dissatisfaction [16, 66, 106, 107].

The evaluation of the causes of anterior knee pain following TKAs and its treatment is a great challenge. The advocates of routine patella resurfacing TKA associate residual knee pain with a patella unresurfaced TKA [106] arguing that the rate of anterior knee pain after patella unresurfaced TKA is higher (25.1 %) than that of the patella resurfaced TKA (5.3 %) [27] and up to 10 % them require SPR [31, 108, 109]. Oth-

ers have not found any difference in survival or pain between resurfaced or non-resurfaced TKAs [110-113]. However, it has not been conclusively proven whether SPR would lead to a resolution of anterior knee pain and varied outcomes of SPR were reported [15, 17, 31-36, 66]. When anterior knee pain is diagnosed in a patient with a patella unresurfaced TKA, consideration to do SPR must only be done after other etiologies have been excluded [114]. A step-by-step diagnostic algorithm including extended history, type of pain analysis, psychological exploration, clinical examination, test infiltration, laboratory tests, joint aspiration, radiographic analysis, special imaging and trial of conservative therapy is the prerequisite for a successful revision surgery in patients with painful TKA [104-106, 115].

1.2.6.4. Challenges of revision knee arthroplasty
<u>Surgical related challenges</u>

During the revision process, the surgeon is faced with problems which are not seen or less frequently seen during primary knee arthroplasty. Bone reconstruction, balancing of the soft tissues and restoration of the alignment (both axial and rotational alignment) is highly important to achieve a good outcome from the revision surgery [50, 116].

Due to the increased operative time, poor vascularization of the tissues (soft as well as bone) resulting from multiple surgeries, previous wound-healing problems or scars and the increased age of the patients; the risk of infection is three to four times greater in revision knee arthroplasty than that with primary knee arthroplasty. Since an increased risk of wound-healing complications as well as skin sloughs due to the friable nature of their skin often observed with immune-compromised patients, the risk of infection is even greater in immune-compromised patients. Thus, skin closure may consequently be difficult and often soft tissue coverage procedures are necessary [87].

<u>Outcomes assessment related challenges</u>

Revision is usually used as an endpoint to assess a success or failure rate of joint arthroplasties. However, the definitions of revision vary among studies and/or national joint arthroplasty registries and make a direct comparison of study findings difficult [82, 117]. Liebs et al. [117] compared the definition of revision used in 13 national joint arthroplasty registries and concluded that revision is not universally defined even among

the arthroplasty registries where revision is used as the most common main endpoint. Surgeries that are considered as a revision in one registry are not regarded as a revision in another registry [117]. Comparisons of implant success or failure using data from different arthroplasty registries have to be made with caution and harmonization of the definitions of revision across the world's arthroplasty registries is needed [82, 117].

    Moreover, different national joint arthroplasty registries categorize the reasons for knee arthroplasty revisions differently, and there is a wide range of percentages presented. The differences in percentages of reasons for revision may not be fully explained by the different outcome results in the different countries [82]. Such heterogeneity of the national joint arthroplasty registries may guide the recording of the reasons for revisions. Thus, there is a definite need to standardize the structure of the national joint arthroplasty registries, and to validate the data therein as well as a greater collaboration between the registries is essential [82]. Joint arthroplasty registers in the Nordic countries have, for example, started such collaboration in 2007 to facilitate research on joint arthroplasty surgeries by establishing a common Nordic database with harmonized definitions of variables [118, 119].

    The central issues of all studies included in this thesis were based on the outcomes of three revision knee arthroplasty procedures: (i) failed primary TKA revised to TKA, (ii) revision of painful non-resurfaced primary TKA with isolated SPR, and (iii) revision of failed primary UKA into TKA. We defined 'revision' as the removal, addition, or exchange of part of an implant or the whole implant for the first time whereas 're-revision' is defined as revision of a previously revised knee arthroplasty (second time revision) (Paper I-III).

1.2.7. Radiological examples

    In this section, some radiological examples of pre- and post-revision or re-revision knee arthroplasties are presented (Fig. 10A-C). Radiological pictures are published with permission from the individual patients who had undergone knee arthroplasty surgery at Haukeland University Hospital, Kysthospitalet in Hagavik, and Haraldplass Deaconess Hospital. Individual patient's permissions as well as the pictures were obtained by Professor Ove Furnes.

(i)

(ii)

(iii)

(iv)

(v)

(vi)

Fig. 10A. *A fourty-six year-old man received a cemented primary TKA without patella component in the right knee. (i) A radiographic picture taken six years after the primary arthroplasty revealed loosening of the tibial component. The knee was revised with the exchange of all components using a stemmed tibia component with a deep dished polyethylene; ((ii) front view and (iii) side view)).One month after the revision; a re-revision due to deep infection was done with removal of the implants and implantation of cement spacers and treatment with antibiotics ((iv) front view and (v) side view), and (vi) three months later a TKA without patella component was inserted with cement, stems, and deep dish stabilization.*
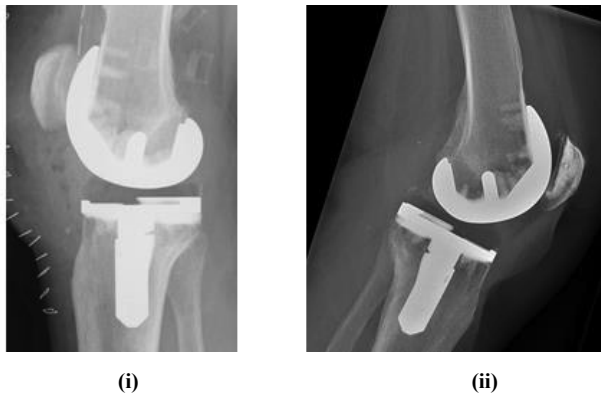
Fig. 10B. *A seventy-three year-old women received a primary non-resurfaced TKA due to RA of the left knee. (i) A radiographic picture that has been taken four years after the primary prosthesis showed no mechanical failure but (ii) the patient was complaining of anterior knee pain and thus, the prosthesis was revised with isolated SPR.*
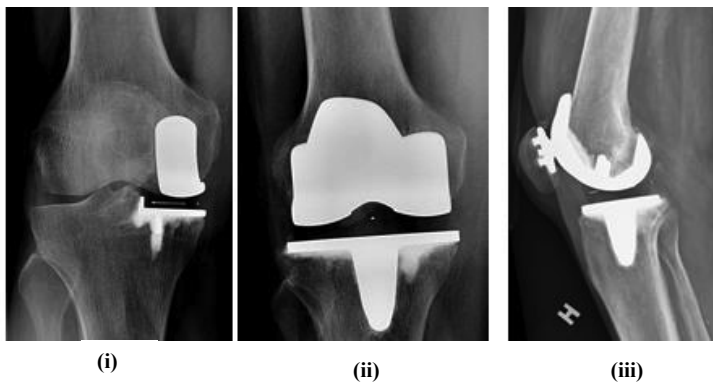
Fig. 10C. *(i) A fifty-six year-old woman received primary UKA due to OA in the medial compartment of the right knee. (ii) Six months after the primary operation the prosthesis was revised with a cemented non-resurfaced TKA due to loose tibial component. (iii) Six years after the revision procedures, the prosthesis was re-revised with isolated SPR due to antrior knee pain alone.*

1.3. PATIENT REPORTED OUTCOME (PRO)

1.3.1. Definition

According to the US Food and Drug Administration [120] *"A PRO is any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else. The outcome can be measured in absolute terms (e.g., severity of a symptom, sign, or state of a disease) or as a change from a previous measure"*

(*http://www.fda.gov/downloads/Drugs/.../Guidances/UCM193282.pdf*).

1.3.2. Why patient reported outcome (PRO)?

Traditionally, health status including the outcome of arthroplasty surgery has been assessed using mortality and morbidity (i.e. revision) as an endpoint [121]. The disease-centered model of conventional medicine has been widely criticized since the 1960s and the importance of a bio-psycho-social approach has been suggested. The latter approach has led to a new model called patient-centered approach and this model was conceptualized for the first time in the 1980s and is the basis for the development of today's PROs [122].

Patients are experts on their own illness and health. Thus, facts that are known by the health care professionals should be supplemented by the values known by the individual patients [123]. Besides, the perception of patients and their surgeons regarding the success of the joint arthroplasty procedure is often different, in which the view of surgeons is often more optimistic [124-126]. The immediate expectation of patients undergoing arthroplasty surgery is pain relief and being able to perform activities of daily living (ADL) with few limitation [127, 128], while the surgeons' evaluation of arthroplasty surgery depends on the definition of a 'success or failure' of the treatment [125]. Such differences between patients and their surgeon in evaluating the outcomes of arthroplasty surgery have led to the search for an ideal PRO measure to evaluate these procedures [125].

In Norway, in 2014, the Ministry of Health gave a mission to the medical quality registries with respect to collecting patient self-reported feedback on given treatments. As stated by the Minister, it is a joint effort to improve the patient's health care service. Quality records should, therefore, include how patients experience the health services *(http://www.kvalitetsregistre.no/nytt/pasientens-tilbakemelding-paa-behandling-prom-article1885-157.html)*.

1.3.3. Health related quality of life (HRQOL)

The importance of measuring PROs in health service and research focusing on health outcome measurements is nowadays widely accepted [129], and HRQOL is among the most important of these outcomes [130]. Consequently, assessing HRQOL using PROs in joint arthroplasty is important because (1) the outcome of joint arthroplasty affect not only the joint but has an overall impact on health and (2) HRQOL

measurements enable the comparison of effectiveness of joint arthroplasty to other treatment modalities that are also measured with HRQOL [131].

The term HRQOL is a combination of two terms: 'health' and 'Quality of Life' (QoL). Numerous definitions of the term health and QoL have been given over years and the definitions provided have differed significantly in their content. In 1948, the World Health Organization (WHO) declared health as *"a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity*" [132]. The term QoL is used in a multitude of settings, and different meanings were attached to the term by different professional groups. To a town planner, for example, QoL may mean access to green space and other facilities whereas in the context of clinical practice QoL is rarely used in such a broad sense but is concerned only with the evaluation of QoL affected by disease or treatment of disease [132].

As mentioned above, the term HRQOL is a combination of two terms; but we may now raise a question of how and why we moved from the two terms health and QoL to the compound term HRQOL? According to Guyatt et al. [133] the term HRQOL was introduced to solve the problem that QoL denotes a variety of medical and non-medical conditions with an intention to narrow the focus of health, illness and treatment effects on QoL. Similarly as stated by Fayers and Machin [132] "*to distinguish between QoL in its more general sense and the requirement of clinical medicine the term HRQOL is frequently used in order to remove ambiguity*". However, the definition of HRQOL has been disputed and no single concept has been universally accepted because the available definitions of HRQOL differ significantly in their content [130].

However, according to Patrick and Ericsson [134], HRQOL is defined as "*the value assigned to duration of life as modified by the impairment, functional states, perception, and social opportunities that are influenced by disease, injury, treatment or policy*" and the concept of HRQOL in this thesis is based on this definition.

1.3.4. Conceptual model

Several useful conceptual models of health outcome measures have been published so far. Due to the multidimensional aspects of HRQOL, and its varied use across many different health and disease conditions, a variety of HRQOL models have been used by researchers [135]. In 1995, the causal model of HRQOL was developed by

Wilson and Cleary [136]. This model became a well-established bio-psycho-social model for health outcomes. In 2005, Ferrans et al. [137] further revised the Wilson and Cleary model. Both Ferrans et al. and the Wilson and Cleary model were claiming to be a model of HRQOL; however, the term HRQOL is not visible in neither of the models, but the term QoL is used instead. In 2008, Valderas and Alonso [130] presented an integrated model based on Wilson and Cleary's model and on the WHO international classification system of health states (International classification of disease and causes of death and international classification of functioning, disability, and health) (Fig. 11).
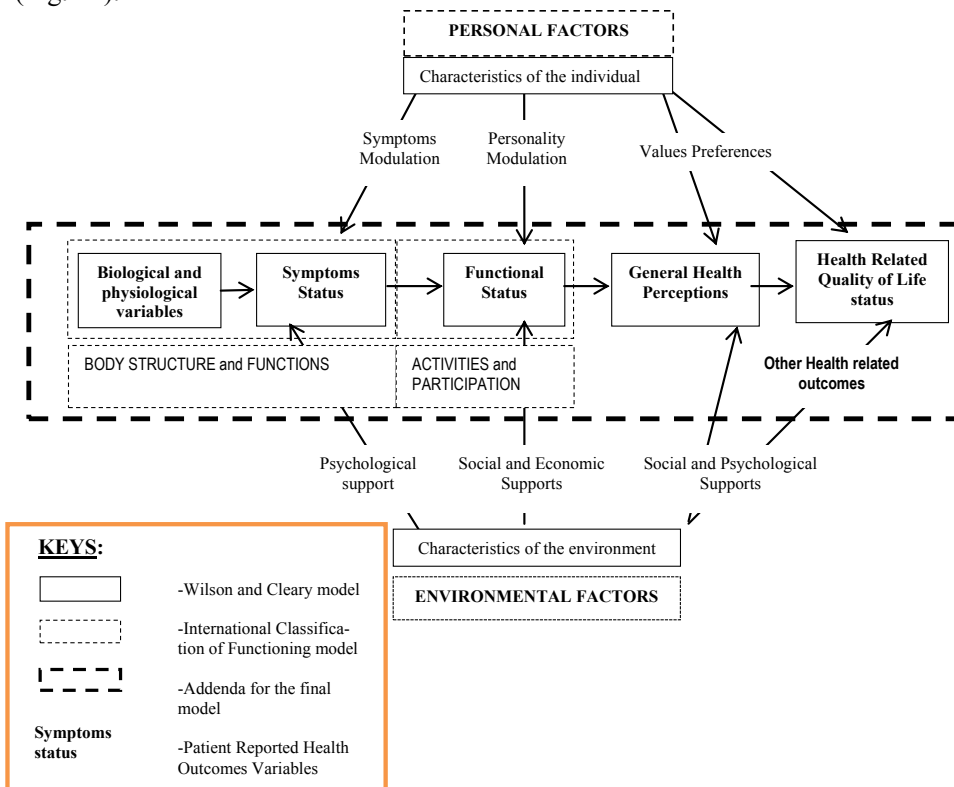
Fig. 11. *An integrated conceptual model for health outcomes according to Valderas and Alonso [130].*

In their model, Valderas and Alonso have changed the 'overall QoL' in the final right box of Wilson and Cleary's model to 'HRQOL'. In addition, they expanded the model to contain other health related outcomes such as satisfaction with health care (i.e. the patient's experience with health care compared to his/her expectation) and resilience (i.e. coping ability, handling stress and illness) that were not specified nei-

ther in Wilson and Clearys' model nor in the International Classification of Functioning model. The intention behind Valderas and Alonso's model was to develop a model that should constitute a conceptual basis to support the choice of PROMs along a continuum of increasing complexity from biological and physiological parameters through symptoms status, functional status, general health perception, and HRQOL [130] .

According to this model, patients may initially seek medical attention because they want to alleviate their symptoms, they are limited in certain functional activities or they are worried that something is seriously wrong. A patient with knee OA, for example, most likely will have relentless pain or difficulty in performing their ADL. In this thesis the symptoms status (e.g. pain) was assessed by KOOS, EQ-5D, and VAS; the functional status (e.g. ADL) was assessed by KOOS, and EQ-5D; the general health perceptions and HRQOL were assessed by EQ-5D whereas VAS was used to assess other health related outcomes such as patients' satisfaction with the result of revision knee arthroplasty surgery.

1.3.5. Patient reported outcome measures (PROMs)

Standardized instruments (questionnaires) designed to measure PROs are called PROM [120]. PROMs are not limited to the assessment of outcomes after an intervention, but also measure the patient's individual perception of functional ability, pain, and QoL with respect to his/her health at any point in time [138].

PROMs can be broadly categorized into two: generic health status questionnaires and disease-specific questionnaires. Both generic and disease-specific PROMs share valuable information about a patient's health status. However, each instrument provides a different view about a patient's condition. Generic PROMs broadly assess health status across different sub-populations, medical conditions, or treatment groups. Generic PROMs are designed to focus on a more global look at health and allow comparisons between populations or treatment groups, thus, they provide excellent external validity [132, 138, 139].

On the other hand, disease-specific PROMs are designed to target defined diagnostic groups, particular body parts or organ systems. Disease-specific PROMs are typically utilized to observe changes or responsiveness of an individual patient's specific health status following a given treatment or therapy [132, 139]. Disease-specific

PROMs provide a high level of specificity, however, they have low generalizability outside the target population [139].

Policy analysts involved in health service evaluation, health-economic assessment, or resource allocation are more interested in differences between patient groups rather than within patient-group changes of a particular treatment type, and thus, they use generic instruments [132, 139]. Investigators implementing disease-specific PROMs, design the survey (questionnaire) to the treatment of interest to understand specific patient concerns and detect small clinically significant changes after treatment [132, 139]. To mitigate drawbacks of generic versus disease-specific PROMs, utilizing both instruments are advisable [138, 139].

1.3.6. Challenges in PRO data collection and interpretation

To make proper use of PRO data, an organized system for distribution, collection, and retention of PRO surveys is crucial. To enhance patient's compliance rate, the questionnaire needs to be both brief and provide enough valuable information to justify the PRO data collection effort [138, 140]. When collecting PRO data, it is also crucial to choose PROMs which have been validated and tested for reliability to ensure that the PROM items are universally understood and measuring the same concept (outcomes regardless of geography and settings) across all intended patients [138, 140].

Follow-up time and intervals: The optimal time points and intervals to assess PROs also need to be established [138, 141]. Questionnaires need to be administered relatively frequently based on what information the clinician is interested in collecting. Surveying patients at consistent intervals may help in understanding how well a particular treatment is working as well as provide a picture of how the treatment influences change on health status over time [138]. Symptoms or health status reports may be biased due to factors related to poor questions, the recall process, or the research design used to assess the effectiveness of the treatment [142]. Researchers or health care providers interested in understanding how well the treatment (e.g. knee arthroplasty surgery) has worked, will need to administer their questionnaire both pre and postoperatively (i.e. prospectively) [138]. However, in a cross-sectional survey with data collection only at one-point in time, only a retrospective evaluation of change is possible.

Such approach is prone to recall bias but it prevents scale recalibration bias which is specific to prospective evaluation [143].

   Number of PRO instruments: In the literature, there are many different PRO instruments used in assessing treatment outcomes and each may contain several domain-specific scales [138, 144]. Thus, generalizability and direct comparisons of findings between patient groups, centers, regions, or nations can be limited. This could be attributed to the use of various PROMs with different scoring ranges and algorithms, and differences in presentations and interpretations of scores [131]. This limitation may arise even if the same PRO instrument is used because there can be differences among individuals in the way they use these response scales. Therefore, questions are often aggregated into multi-item scales and scores are presented as a mean score [138, 144]. EQ-5D is, for example, a preference-weighted measure and gives index value whereas SF-36 give health profile, but both are generic PROM and used in assessing HRQOL.

   End-aversion bias or *ceiling/floor effects*: The sensitivity, validity, responsiveness, and reliability of PRO instrument can be influenced by patient response trends including *end-aversion bias* or *ceiling/floor effects*. *End-aversion bias* occurs when patients are reluctant to select answers in the lower and upper extremes of the scale [138, 143, 145] whereas *ceiling/floor effects* occur when patients answer predominantly in the upper /lower extreme of the scale, respectively [138, 141]. Distortion of PRO data due to end-aversion or ceiling/floor effects may suggest that the PRO instrument is not reliable or sensitive to measure the area of interest in the target population [138].

   *Selective reporting and response shift bias*es are also another interpretability issue in reporting PRO data. Some patients may tend to ignore or discount any problems (i.e. items in a questionnaire) which they believe to be not related to their illness whereas other patients who believe they have illness-related problems may give accurate response. Such *selective reporting* can consequently distort the analysis and interpretation of PRO data [132]. In clinical practice and research patients are repeatedly asked to report their health status; over time patients may adapt to a change in their health status and their perception of health status (e.g. HRQOL) may change during this time. Such subjective changes in a patients' perception over time is called *response shift* [132, 141].

Minimal Important Difference (MID): The MID which is sometimes also known as Minimal Clinically Important Difference (MCID) is *" the smallest difference in score in the domain of interest that patients perceive as beneficial and which would cause clinicians to consider a change in patients management"* [145]. Whether the change measured corresponds to clinically relevant improvement or degradation is also a common question when interpreting PRO data [138, 144]. Policy makers and clinicians are interested in the MID of a given treatment as a means to assess the efficacy or differences between treatment groups. There exist several methodologies to calculate MIDs, however, these calculations differ greatly and the significance of a MID is dependent upon the population that was used to calculate the value [144, 146-148] and the patient's opinion is not always incorporated [144]. Thus, it would not be usual for a single MID to be appropriate for all applications and across all patient populations. However, its potential usefulness is to serve as a benchmark (threshold) value for improvement of individual patients [131, 149].

1.3.7. PROMs in assessing outcomes of knee arthroplasty

1.3.7.1. Generic PROMs

The Quality of Well-Being Index and the Sickness Impact Profile from the 1970s, the Nottingham Health Profile and the Quality of Life Index from the 1980s, and the Medical Outcome Study Short Form-36 (SF-36) and the EuroQOL EQ-5D from the 1990s are some of the widely used generic HRQOL instruments [150]. The SF-36 and EQ-5D are the two most frequently used generic HRQOL instruments in joint arthroplasty registers [151].

1.3.7.2. Disease/condition-specific PROMs

The Oxford Knee Score (OKS), The Knee Injury and Osteoarthritis Outcome Score (KOOS) and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) are the three most frequently used disease-specific PROMs commonly used in assessing the outcomes of knee arthroplasty surgery [125]. They all broadly assess pain and function. Of these three PROMS, the KOOS uniquely accounted for ADLs related to sports and recreation and it is the only PROM that provides items dealing with the patients' perception on quality of life items [125]. The drawback of the

KOOS and WOMAC is that they are more comprehensive than the OKS which may affect the response rate [48, 125].

Visual Analogue Scale (VAS) for pain and satisfaction has also been used as a condition/disease-specific PROM in assessing joint arthroplasty outcomes in some arthroplasty registries, i.e. the Swedish hip arthroplasty register [152, 153].

1.3.8. PROs in arthroplasty registries

Some arthroplasty registries incorporate PROs that focus on patient perception of pain relief and physical function [121]. The incorporation of PRO program into arthroplasty registries may introduce both opportunities and challenges.

1.3.8.1. Opportunities

Traditionally, joint arthroplasty registers were designed to collect data to monitor implant survival and mortality. Revision-oriented registries, however, cannot determine whether unrevised implants are functioning well or poorly, or whether the patient achieved satisfactory pain relief and functional gain following joint arthroplasty surgery [121]. Thus, PROMs that measure pain relief or persistent pain, function and satisfaction with the surgery could be an important addition to revision data [121].

Arthroplasty registers typically attempt to enroll 100 % of patients from all hospitals to assure complete capture of data both at the time of primary and revision surgeries. Revision surgery (e.g. TKA) is a relatively rare event; 5 % of patients or less revised within 10 years from the index surgery. To identify relatively low annual implants failure rates, registers should incorporate a large number of joint arthroplasty surgeries [121]. In contrast to implant revision rates that concern a relatively few number of patients, pain relief and improvement in functional outcomes are relevant to all patients who had joint arthroplasty surgery [121]. Rolfson et al. [48] concluded that "*omitting patient-reported outcomes precludes us [surgeons] from having a full understanding of the factors that contribute to pain relief, restoration of function, and patient satisfaction*".

1.3.8.2. Challenges

The incorporation of PROs into arthroplasty registries may introduce some challenges; these challenges are primarily related to registry design, logistic of PROs col-

lection, cost, and sustainability which may necessitate modification of the traditional hospital- and implant-centric design of many arthroplasty registries [121].

The difficulty in selecting suitable PROMs is also a challenge because there is no universal consensus among arthroplasty registries on the ideal PROs tool or the ideal time points for data collection [121, 151].

1.3.9. PROMs versus performance-based measures

A performance-based measure is a measure in which an individual patient is asked to perform one or more specific tasks and the performance is evaluated in a standardized manner using predefined criteria. Examples of such measures are range of motion, the timed up and go test, stair climbing test, and the six minute walk test. PROM is a measure in which an individual patient is asked to report his/her perceived level of function during daily activities without observer's influence [154] (e.g. KOOS).

PROM and performance-based measures are both used for outcome assessment after joint arthroplasty [154-156]. Each of these methods has both advantages and limitations. PROMs are easier to administer, less time-consuming, and less of burden to the patients. PROMs cannot be influenced by observer bias; they have high internal consistency and cost-effectiveness and do not require a visit at the clinic that can relatively reduce the number of patients lost to follow-up [154-156]. However, PROMs are influenced by the patient's perception, and his/her actual functional ability may be over- or under- estimated. Factors that can influence patient perceptions after arthroplasty surgery include preoperative functional difficulties, level of pain and the level of expectations. Thus, PROM often corresponds strongly with improvements in patient's report of pain as well as their level of exertion during function tasks [154-157]. Therefore, a patient may be more likely to overestimate actual functional ability after, for example, TKA when pain levels are substantially reduced and the expectations are met [155].

On the other hand, performance-based measures are claimed to be less influenced by psychologic factors like patient's expectations and beliefs, cognitive impairments, culture, language, and education level. Performance-based measures quantify performance rather than a perception of performance; consequently, they provide a more objective measure of actual functional ability. However, performance-based measures have been considered less valid because they measure physical functioning in an artifi-

cial situation i.e. performance is not assessed in a natural environment. Furthermore, they are influenced by the individual patient's motivation to participate, they do not take into account patient perceptions of recovery, they are task specific rather than broadly based, and they may provide little information about how an individual patient copes with his/her own environment [154-156].

Generally, PROMs and performance–based measures provide different and complementary information regarding outcomes after arthroplasty surgery [155, 157, 158] Therefore, to fully characterize the outcomes after arthroplasty surgery, PROMs also need to be supplemented by performance-based measures [155, 157].

1.4. HEALTH REGISTERS

Health registers give a unique opportunity to study diseases and treatment modalities in large unselected populations and over a long time period [159]. Register studies minimize most biases [138] common in epidemiological studies. However, because health includes many aspects, not all variables related to health may be collected within each respective register. The NAR does, for example, not register data on degree of osteoarthritis, degree of bone loss (except for hip arthroplasty), degree of malposition of implant components, degree of ligament instability; and patient's body mass index, socio-economic status, and physical activity level which might affect the outcome of arthroplasty. The use of unique identification numbers given to the inhabitants of Norway, however, enables linkage studies between different national, regional or local registers and surveys. Thus, findings from register studies provide excellent external validity [159].

In Norway, there are about 200 medical health registers, and as of December 2015, 47 of them have national health registry status [160]. Seventeen of the national health registries are mandatory, and the Norwegian Institute of Public Health is responsible for 10 of them *(http://www.fhi.no, 2015)*. The NAR is one of the national medical quality health registries. The NAR is professionally owned by the Norwegian orthopaedic surgeons through the Norwegian Orthopaedic Association but financed and legally owned by the government through Helse-Bergen [4]. The surgeons' enthusiasm to improve the quality of the treatment of joint diseases inspired them to start the registry in 1987 [161].

2. AIM OF THE STUDY

The overall aim of this thesis was to evaluate the outcomes of aseptic revision knee arthroplasties in Norway in terms of implant survival rate, causes and risk of re-revision, pain relief, functional outcome, patient satisfaction, and HRQOL.

The specific aims were:

Paper I

- To analyze the survival rate of rev-TKAs.
- To study the causes of failure of rev-TKAs.
- To determine whether the survival of rev-TKAs is influenced by fixation techniques, brand of prosthesis, and resurfacing of the patella.

Paper II

- To assess prostheses survival and clinical outcomes of the SPR procedure done to painful non-resurfaced TKAs.
- To assess factors that predicts the outcome of the SPR procedure.

Paper III

- To compare prostheses survival, functional outcome, level of pain, patient satisfaction, and HRQOL of rev-UKAs and rev-TKAs.
- To compare the mode of failure and technical difficulty of the surgical procedure of rev-UKAs and rev-TKAs.

3. MATERIALS AND METHODS

3.1. PATIENTS AND SOURCE OF DATA

Patients with revision knee arthroplasty from the NAR were the focus of all the three papers included in this thesis. A total of 46838 primary TKA and UKA procedures were reported to the NAR between January 1994 and December 2011. Of these primary procedures 2431 knees failed and required a 1st time revision operation during this time period. 436 (18 %) of these 1st time revisions were done for periprosthetic infection. Revision of periprosthetic infection include treatment with antibiotic of infective organism(s), surgical debridement, and different revision strategies (i.e. single or multi-staged procedures) [162]. To make the material more homogenous, thus, only aseptic revision knee arthroplasties reported to the NAR in the period between 1994 and 2011 were eligible for the studies.

In addition to the NAR data, PRO data collected in 2006 through a postal survey were used to assess the clinical outcome of revision knee arthroplasty for the time period between 1994 and 2005 (Paper II and III). The clinical outcome was assessed in terms of pain relief, functional outcome, patient satisfaction, and HRQOL. Summary of study population numbers for each paper is presented in Table 3.

Table 3. Study population for each paper.

Paper	Number of knees, data source, and time period	
	NAR (1994-2011)	PRO (1994-2005)
	n	n
I	1016	-
II	308	114
III	1346	277
	(768 rev-TKA vs 578 rev-UKA)	(150 rev-TKA vs 127 rev-UKA)

3.1.1. The Norwegian Arthroplasty Register (NAR)

The NAR is one of the first national arthroplasty registers in the world together with the Swedish and Finish knee and hip arthroplasty registers. The NAR was initiated as a hip arthroplasty register in September 1987 and extended to include registration of arthroplasty of all other joints including the knee in 1994 [161].

The primary aim of the NAR is to detect inferior implants as early as possible after they are introduced to the market. Data is collected through a one-page form (Ap-

pendix I), which is completed by the operating surgeon just after the surgery. Reporting to the NAR is voluntarily for the patients and the surgeons, but recently the authorities encourage that the orthopaedic surgeons should report all their cases to the NAR. The unique identification number given to the inhabitants of Norway allows future revisions of the same joint in the same patient to be linked to the corresponding primary procedure [4, 60, 163]. Thus, the quality of the procedures can be measured in terms of implant survival rate (percentage).

By following patients with arthroplasty over time at a national level, the NAR is able to attain statistical power that is hard to attain in a single hospital or a clinical trial. The large sample from the NAR allows rare complications associated with implants and surgical techniques to be identified at an early stage. The NAR annually reports hospital-specific results back to all hospitals involved in arthroplasty surgery allowing direct comparison of local and mean national results, as well as facilitating local improvement in treatment [4, 164]. Thus, the NAR functions as a quality control both at national as well as local level.

3.1.2. Patient reported outcomes (PROs) data

The NAR does not record any prospective PROs related to any knee arthroplasty surgeries to date. In two of the studies included in this thesis, therefore, we used cross-sectional PROs data collected in 2006 as a part of (but not included in) an earlier PhD study project from the NAR [163]. The data was collected using a self-administered postal questionnaire sent to all patients with revision knee arthroplasties reported to the NAR between 1st January 1994 and 5th September 2005. It has been reported that it takes up to one year to achieve maximum pain relief and functional outcome after rev-TKA [165], thus, only patients who had a minimum of 1-year follow-up after the revision procedure were included in the survey. The PROMs used were the EQ-5D, KOOS, and VAS for pain and satisfaction. Besides, two musculoskeletal and comorbidity related questions (Charnley category) were included in the survey (Appendix II).

3.2. OUTCOMES AND OUTCOMES MEASURE

In this thesis, the quality of revision knee arthroplasty was assessed in terms of implants survival rates and clinical outcomes. Implant survival rates were assessed using re-revision as an endpoint. The clinical outcomes were assessed in terms of change in HRQOL (using EQ-5D), functional outcome, pain, and knee-related quality of life (using KOOS) and level of postoperative pain and satisfaction (using VAS) following revision knee arthroplasty. In Paper III, the technical difficulty of the surgical procedure was reflected as a proxy of the length of operative time, and need for bone impaction grafting, stem extensions, and/ or PCS or CCK.

The PROMs included in this thesis are well established and have satisfactory psychometric properties. To assess the extent to which items in each of these questionnaires are inter-correlated with one another (i.e. measure the same concept) in our study population setting, the internal consistency reliability of these questionnaires was measured using Cronbach's α (Table 4). Cronbach's α values ranges from 0 to 1 and as a rule of thumb Cronbach's α >0.7 is considered as acceptable internal consistency reliability [166].

3.2.1. Re-revision

Traditionally, arthroplasty registers are used to monitor the success or failure of the implants with survival defined by revision as an endpoint. The orthopedic surgeon reports the reason for revision or re-revision. Multiple reasons for revision or re-revision could be reported. In this thesis, all revisions that were caused by deep infection were excluded, also if other revision causes were given. Further, pain was only considered as a reason for revision when not combined with other reasons for revisions.

3.2.2. EuroQol (EQ-5D)

To account for possible differences in preoperative and postoperative health status of patients with revision knee arthroplasty, the EQ-5D instrument was used. EQ-5D is a standardized generic instrument consisting of a descriptive questionnaire and a VAS for describing and evaluating HRQOL [167]. The EQ-5D has five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and each

dimension has three possible response levels: no problem (score 1), some problems (score 2), and major problems (score 3) [167, 168].

Patients' preoperative health status was assessed retrospectively together with their postoperative health status. The preference-based EQ-5D index scores generated from a large European population were used [169]. The EQ-5D index scores range from "0" indicating a health status similar to death to "1" indicating best possible health status. A change in the EQ-5D index scores (ΔEQ-5D) i.e. the difference between the postoperative and preoperative EQ-5D index scores was used to assess change in HRQOL. To perform a mean score calculation for each of the five EQ-5D domains, however, we replaced the range of score 1 to 3 by 0 to 2 in which '0'indicating no problem and '2' indicating major problems (Paper II). Only completely answered questionnaires were included in the EQ-5D index scores calculation. The internal consistency (reliability) measured by Cronbach's α was 0.67 preoperatively and 0.78 postoperatively (Table 4).We used a validated Norwegian language version of the EQ-5D (*http://www.eurogol.org*).

There are several reasons why EQ-5D was used in this thesis. The EQ-5D is designed for self-completion, and respondents can also rate their overall health on a hash-marked, vertical VAS (EQ-VAS) ranging from 0 "worst" to 100 "best" imaginable health states in addition to ED-5D health index. The EQ-5D has been widely tested and used in both patient samples and general population, and it is available in many different languages [170]. In addition to the index value, EQ-5D can also be used to study the five dimensions separately [171], which gives the opportunity to see in which dimensions the problems lie, as opposed to just using mean values of the EQ-5D index. From the respondents' perspective, earlier studies have indicated that elderly people find the self-administrated EQ-5D easier to use compared to other HRQOL instrument such as SF-36 [172-174].

Although the EQ-5D has been shown to be a valid and reliable instrument [150], it is less responsive and prone to ceiling or floor effects, particularly when used in general population surveys and in some patient population settings [170]. Thus, its (EQ-5D-3L) ability to measure small changes in health, especially in patients with milder conditions may be questionable. For example, since one can only choose between no,

moderate, or severe problems, one may well have improved, but not enough to change from moderate to no problem. To some extent, these problems have been handled by the development of the 5 level versions (EQ-5D-5L). A validated version of the latter version [170] was however not available when the survey was completed in 2006.

3.2.3. Knee Injury and Osteoarthritis Outcome Score (KOOS)

KOOS is a valid and reliable self-administrated instrument which consists of 42 individual questions assessing five subscales: Pain (9 items), other symptoms (Symptoms, 7 items), function in daily living (ADL, 17 items), function in sport and recreation (Sport/rec., 5 items), and knee related quality of life (4 items) [175-177]. KOOS was used to evaluate patients' perception on the functional outcome, pain, and knee related quality of life of their revised knee arthroplasty. The levels of pain and general knee related problems during the last month were reported, however, only the last week should be considered when answering 40 of the 42 individual questions. Each item has 5 standard scores (answers) ranging from 0 (no symptoms) to 4 (extreme symptoms), and subscales scores are calibrated to 0-100 scales where 100 is the best score (no symptoms). Calculations of the KOOS subscales scores and treatment of missing answers were done in accordance with the KOOS scoring 2012 guidelines [178]. The internal consistency measured by Cronbach's α ranged from 0.63-0.87 (Table 4). We used the validated Norwegian language version of KOOS *(http://www.koos.nu)*.

The KOOS was chosen because (1) it had been demonstrated to be one of the most suitable instruments for assessment of knee-related health and outcomes from the patients' perspective [179]; (2) it is an extension of the WOMAC [175], thus, WOMAC scores could be calculated if needed; and (3) compared to the WOMAC, the KOOS have been found to be more sensitive for younger and active patients, particularly due to the extra subscales Sport/rec. and knee related quality of life [175, 177] which could be applicable when trying to reveal differences among younger patients who had a UKA [163].

3.2.4. Visual Analogue Scale (VAS)

VAS on pain from the revised knee (pain-VAS) and VAS on satisfaction with the revision operation (satisfaction-VAS) were also included in the questionnaire and used as outcome measures. The pain-VAS was a continuous scale from a complete absence

of pain (score 0) to intolerable pain (score 100) on a horizontal line. Patients were asked to mark the line at the point that matches the average degree of pain which they experienced in the last 4 weeks prior to the survey (Fig. 12A). For the satisfaction-VAS the scale consisted of a horizontal line ranging from complete satisfaction (score 0) to complete dissatisfaction (score 100) (Fig. 12B). Patients were asked to mark the line at a point that matched their level of satisfaction with the revision operation.

In this thesis, VAS was chosen because characteristics such as pain and satisfaction range across a continuum of values, and it may be difficult to measure them directly. VAS is, however, a measurement that tries to measure such attributes on a continuous scale [163]. These VAS scales have been validated and used as a disease/condition-specific PROM by some arthroplasty registers including the Swedish hip arthroplasty register [152].

In order to better portray the results together with the KOOS subscales in the analyses, these VAS-scores were reversed in which "100" indicated the best possible state and "0" indicated the worst possible state.

No pain   **Maximum pain**

| Mild | Moderate | Medium | Severe | Intolerable/ Extreme |

Fig. 12A. *Pain-VAS*

Satisfied   **Dissatisfied**

| Very satisfied | Satisfied | Medium satisfied | Dissatisfied | Very dissatisfied |
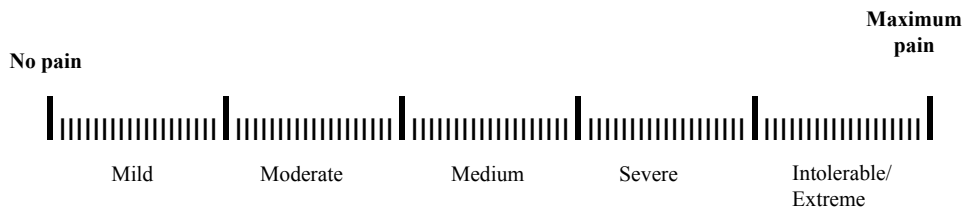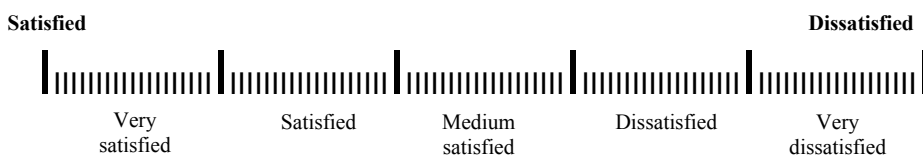
Fig. 12B. *Satisfaction-VAS*

3.2.5. Charnley category

The Charnley categories A, B, and C categorizes patients into three rough catego-ries [180]. Patients were asked postoperatively to report whether they have a problem with their contralateral knee and/or comorbidities related to other joints or systematic problems that may limit their general functional ability. Based on their answers, pa-tients were categorized as 'A' (involvement of the actual knee only), 'B' (also in-volvement of the other knee), and 'C' (also involvement of other joints or systematic problems limiting activity) [180, 181]. We used the Charnley category because it has been reported that (1) different musculoskeletal related co-morbidity burdens associated with walking capacity may influence the findings of arthroplasty studies and (2) Charnley functional categorization is one of the strongest predictors of PROs and is highly recommended in the assessment of results of arthroplasty [180]

Table 4. Description and internal consistency reliability (estimated by Cronbach's α) of PROMs used in this thesis in assessing the clinical outcome of revision knee arthroplasties performed in Norway (1994-2005).

Outcome	Questionnaire	Subscale/domain	Items	Response categories	Scoring	Total score	Cronbach's α *	Time point measured
Functional outcome, pain, and knee related quality of life	KOOS	Pain	9	Likert scale ranging from 0 to 4: 0= Never 1= Seldom 2= Sometimes 3= Often 4= Always	0-4	0-100	0.78	Postoperative
		Symptoms	7				0.63	
		ADL	17				0.87	
		Sport/Recreation	5				0.78	
		Knee related quality of life	4				0.65	
Pain	VAS		1	VAS range from 0 "extreme pain" to 100 "no pain"	0-100	0-100	One item	Postoperative
Satisfaction	VAS		1	VAS range from 0 "complete dissatisfaction" to 100 "complete satisfaction"	0-100	0-100	One item	Postoperative
HRQOL	EQ-5D	Self-care	1	Likert scale ranging from 1 to 3: 1= No problem 2= Some problem 3= Major problem	1-3	0-1	0.67 (preoperative)	Preoperative (asked retrospectively) and postoperative
		Mobility	1					
		Usual activities	1					
		Pain/discomfort	1				0.78 (postoperative)	
		Anxiety/depression	1					

* Cronbach's α internal consistency reliability coefficient normally ranges from 0 to 1. The rules of thumb for Cronbach's α as provided by George and Mallery were: " _ > 0.9 – Excellent, _ > 0.8 – Good, _ > 0.7 – Acceptable, _ > 0.6 – Questionable, _ > 0.5 – Poor, and _ < 0.5 – Unacceptable" [166] .

3.3. STATISTICAL POWER AND ANALYSES

3.3.1. Power

A comparative study was performed in Paper III and statistical power calculation was done both for the survival analysis and for the PROM. The power analysis for the survival analysis indicates that to detect a relative risk of 2 as statistically significant (2-sided test, α=0.05, 1-β=0.80) with a difference in cumulative survival at 15 years of 9 % (90 % and 81 % respectively), a total of 938 prostheses (469 in each group) is required. For the PROM, the power analyses were based on the Minimal Perceptible Clinical Difference (MPCD) or MCID. According to other publications, MPCD is 8–10 units in the mean scores for the KOOS subscales [176], 9–12 units on a VAS [182]. The MCID is 0.06-0.08 for EQ-5D index score [183, 184]. To have an 80 % chance of detecting a significant (at the 2-sided 5 % level) difference of 10 units in the mean outcome score between the treatment groups, with an assumed standard deviation (SD) of 20, 64 individuals were required in each group. Totally, 314 patients who had undergone aseptic revision knee arthroplasty between January 1994 and September 2005 were asked for participation in the survey. Of these, 277 patients (150 rev-UKAs vs 127 rev-TKAs) responded to the questionnaires, yielding a response rate of 85.5 %. This suggests that our study was sufficiently powered to detect the above mentioned differences if they existed.

3.3.2. Analyses

Summaries of statistical analyses utilized for each paper included in this thesis are presented in Table 5. The Pearson's Chi-square test was used for comparison of categorical variables in Paper I-III. In all the three papers, the Kaplan-Meier [185] and Cox-regression [186] analyses with any reason of re-revision as the endpoint were used to calculate implants survival rates and risk of re-revision, respectively. Statistically significant differences between groups in the Kaplan-Meier analyses were assessed using the log-rank test [187]. The median follow-up was calculated using the reverse Kaplan-Meier method [188, 189]. As mentioned in section 3.1.1, the NAR uses the unique identification number assigned to the inhabitants of Norway to link sequences of surgeries [4]. In addition, the NAR obtain information regarding patient status including

dates of emigration or death from the Statistics Norway [60]. Thus, the survival times of implants in all cases in all the three papers included in this thesis were censored at the date of emigration or death. Otherwise, the survival times were censored at the end of the study at December 31st, 2011.

In observational studies, such as arthroplasty register studies, there may be systematic differences between groups of patients with different types of prostheses, and such differences may affect the validity of the findings [190]. Such differences can be minimized or avoided by adjusting for covariates representing known or suspected confounders. The Cox regression model is a statistical tool to explore the effect of one or more of such factors on survival rate and to adjust for potential confounding factors [190, 191]. Thus, in all papers included in this thesis, we adjusted for potential confounding factors that are available in the NAR database in the multiple Cox regression model. Adjustment variables were selected based upon our own hypotheses and previous literature findings. The proportional hazard assumption of the Cox regression model was assessed by graphical examination (log minus log) (Paper I-III) and by goodness-of-fit test (which is based on Schoenfeld residuals) [192] (Paper I). If the conditions for the assumption were not fulfilled during the total time period, additional time-dependent survival analyses were performed by dividing the follow-up into appropriate time-periods (Paper I-III).

The KOOS subscales scores, pain-VAS, satisfaction-VAS, and EQ-5D index scores were reported as mean scores. A paired-sample t-test was conducted to evaluate the impact of revision TKA with isolated SPR on each domain in the EQ-5D (Paper II). Independent Student t-test was used to assess unadjusted differences in mean scores in PROMs between rev-UKAs and rev-TKAs (Paper III). Multiple linear regression [193] was performed to assess factors that might determine (predict) the clinical outcomes (Paper II) and to assess differences in mean scores in PROMs between the treatment groups (Paper III).

Overall and stratified survival analyses according to the use of patella resurfacing, prosthesis brands, use of bone impaction grafting, use of stems, use of stabilizing, year of revision operations, type of revision operations, age at revision, and type of fixation were calculated and reported. In the Cox-regression analyses, we adjusted for

gender, age at revision, primary diagnosis, type of fixation, use of patella resurfacing, type of revision operation, time between primary and revision operation, time since revision operation, and/or prosthesis brands used at primary operation (Paper I-III). In the multiple linear regression analyses, adjustments were made for gender, age at revision, primary diagnosis, Charnley category, time since revision operation, prosthesis brand used at primary operation, and type of fixation (Paper II and III).

In all analyses (Paper I-III), crude and adjusted results were presented with 95 % Confidence Intervals (CI), and p-values' < 0.05 was considered statistically significant. The statistical software IBM SPSS version 21 (Paper I) and 22 (Paper II and III) was used to perform the statistical analyses. The survival curves were done using R software version 3.1.1 (Paper I-III).

Table 5. Statistical analyses utilized for each paper.

Paper	Statistical Tests					
	Kaplan-Meier	Cox-Regression	Multiple Linear Regression	Independent Student t-test	Paired samples t-test	Chi-Squared test
I	x	x				x
II	x	x	x		x	x
III	x	x	x	X		x

3.4. ETHICAL APPROVAL

The NAR is registered as a national medical quality register and has a license from the Norwegian Data Inspectorate (reference number: 03/00058-20/CGN and date for latest license renewal: 18 September 2014) (Appendix III). All data files and results for all studies on which this thesis is based are presented according to the guidelines in the license given to the NAR (Paper I-III). Ethical approval for the postal questionnaire survey (Paper II and III) was obtained from The Regional Committee for Research Ethics in Western Norway (date of issue: 02/23/2006, registration number: 046:06); with extended permission (date of issue: 07/11/2012, registration number: 2012/1692/REK vest) (Appendix III).

4. SUMMARY OF PAPERS I-III

Paper I

<u>**Failure of aseptic revision total knee arthroplasties: 145 revision failures from the Norwegian Arthroplasty Register, 1994–2011.**</u>

Tesfaye H Leta, Stein Håkon L Lygre, Arne Skredderstuen, Geir Hallan, and Ove Furnes.

Background and purpose: In Norway, the proportion of revision knee arthroplasties has increased from 6.9 % in 1994 to 8.5 % in 2011. However, information on the epidemiology and causes of subsequent failure of revision knee arthroplasties is limited. Therefore, we analyzed survival rate and assessed the mode of failure of aseptic rev-TKAs.

Methods: This study was based on 1016 rev-TKAs reported to the NAR in the period between 1994 and 2011. Revisions done for infections and/or with isolated SPR were not included. Kaplan-Meier and Cox regression analyses were used to assess the survival rate and the relative risk for re-revision with all causes of re-revision as an endpoint.

Results: Overall, 145 knees failed after rev-TKAs at a median follow-up of 4.5 years (range 0-17 years). Deep infection was the most frequent cause of re-revision (28%) followed by instability (26 %), loose tibia component (17 %) and pain (10 %). The cumulative survival rate of rev-TKAs was 85 % at 5 years, 78 % at 10 years, and 71 % at 15 years. Rev-TKAs with an exchange of the femoral or tibial component exclusively had a higher risk of re-revision (Relative Risk (RR) =1.7; p=0.02) compared to those with an exchange of the whole prosthesis. The risk of re-revision was higher for men (RR=2.0, p<0.001) and for patients younger than 60 years (RR=1.6; p=0.03). No statistically significant differences in survival rate or risk of re-revision of TKAs, were identified among the prosthesis brands, nor did use of bone cement, long stems, and /or stabilization and resurfacing of the patella affect the results.

Conclusion: Revision of the whole implant performed better than revision of one component only in terms of implant survival. Younger age and male gender were risk factors for re-revision. Deep infection and instability were the most frequent cause of failure of revision of aseptic TKAs.

Paper II

Secondary patella resurfacing in painful non-resurfaced total knee arthroplasties. A study of survival and clinical outcome from the Norwegian Arthroplasty Register (1994-2011).

Tesfaye H Leta, Stein Håkon L Lygre, Arne Skredderstuen, Geir Hallan, Jan-Erik Gjertsen, Berit Rokne, and Ove Furnes.

International Orthopaedics 2015; 40(4):715-22.

Background and purpose: In Norway, 19 % of revisions of non-resurfaced TKAs were isolated SPR done for knee pain in the time period between 1994 and 2011. It is, however, unclear whether isolated SPR actually resolves the pain. The aim of our study was to investigate prostheses survival rates and clinical outcomes following isolated SPR.

Methods: Prostheses survival was assessed based on data from a cohort of 308 knees (301 patients) with isolated SPR reported to the NAR in the period between 1994 and 2011. The clinical outcomes (pain, function, HRQOL, and satisfaction) were assessed based on a sub-cohort (n=114 out of 301 patients) had PROs data. EQ-5D, KOOS, Charnley Category, and VAS were used to collect PRO data. Kaplan-Meier and Cox regression analyses were used to assess prostheses survival; and multiple linear regression analyses were used to assess the clinical outcomes.

Results: The 5 and 10 years Kaplan-Meier survival percentage was 91% and 87 %, respectively. Overall, 35 knees were re-revised at a median follow-up of 8 years (range 0-17 years). Pain alone (10 knees) was the main cause of re-revision followed by loose femoral component (5 knees), loose tibia component (4 knees), deep infection

(4 knees), and instability (4 knees). Younger patients (<60 years) had nearly 9 times higher risk of re-revision compared to older patients (>70years) (RR=8.6; p<0.001). Mean EQ-5D index score improved from 0.41 (SD 0.21) preoperative to 0.56 (SD 0.25) postoperative following isolated SPR. Sixty-nine percent of patients who had preoperative severe pain/discomfort in EQ-5D domain reported an improvement post-operatively. Sixty-three percent of patients that had reported PRO were satisfied with the outcomes of isolated SPR. Male patients had a better improvement in mean EQ-5D index score following SPR, whereas patients in Charnley category 'A' had a significantly better mean scores in KOOS subscales as compared to the other categories.

Conclusion: The long-term prostheses survival following isolated SPR was satisfactory, although not as good as for primary knee replacement. Patients' HRQOL improved significantly following SPR. Patients who had preoperative severe pain in the EQ-5D domain and patients with unilateral knee problem (Charnley category 'A') had the best effect of the intervention. However, more than one-third of patients that had reported PROs were dissatisfied with the outcomes of the SPR procedure.

Paper III

Outcomes of unicompartmental knee arthroplasty after aseptic revision to total knee arthroplasty. A comparative study of 768 TKAs and 578 UKAs revised to TKAs from the Norwegian Arthroplasty Register (1994-2011).

Tesfaye H Leta, Stein Håkon L Lygre, Arne Skredderstuen, Geir Hallan, Jan-Erik Gjertsen, Berit Rokne, and Ove Furnes.

Journal of Bone & Joint Surgery (Am) 2016; 98 (6):431-40.

Background and purpose: The general recommendation for a failed primary UKA is revision to a TKA. The purpose of the present study was to compare the outcomes, surgical procedures, and mode of failure of rev-UKAs and rev-TKAs.

Methods: The study was based on 768 rev-TKAs and 578 rev-UKAs reported to the NAR between 1994 and 2011. PROMs including the EQ-5D, KOOS, Charnley Category, and VAS were used to assess the clinical outcome. We performed Kaplan-

Meier and Cox-regression analyses adjusting for propensity score to assess the survival rate and the risk of re-revision, respectively. Multiple linear regression analyses were used to estimate the differences in mean scores in PROMs between rev-UKAs and rev-TKAs.

Results: Overall, 12% of rev-UKAs and 13% of rev-TKAs were re-revised at a median follow-up of 4.6 and 4.1 (range 0-17) years, respectively. The 10 years survival percentage of rev-UKAs vs rev-TKAs was 82 vs 81%, respectively (p=0.1). There was no statistically significant difference in the overall risk of re-revision for rev-UKAs vs rev-TKAs (RR= 1.2; p=0.2), nor in the PROM scores. However, in age stratified analysis, the risk of re-revision was 2 times higher for rev-TKA patients aged >70 years (RR= 2.1; p=0.05). Loose tibia (28 vs 17%), pain alone (22 vs 12%), instability (19 vs 19%), and deep infection (16 vs 31%) were main causes of re-revision for rev-UKAs vs rev-TKAs, respectively. The observed differences in reason for re-revision were not statistically significant except that rev-TKA was more frequently re-revised for deep infection compared to rev-TKA (RR=2.2; p=0.03). The surgical procedure for rev-TKAs took longer time (mean =150 vs 114 minutes), and more of the operations needed stems (58 vs 19%), or stabilization (27 vs 9%) compared to rev-UKAs.

Conclusion: The overall outcomes of rev-UKAs and rev-TKAs in terms of survival, functional outcome, level of pain, patient satisfaction, and change in HRQOL were similar. However, rev-TKAs seeming a technically more difficult surgical procedure, being re-revised more frequently due to deep infection, and had double risk of re-revision for patient groups aged >70 years compared to that of rev-UKAs.

5. DISCUSSION

5.1. METHODOLOGICAL CONSIDERATIONS

5.1.1. Study design

This thesis is based on three papers with observational study designs: prospective register study design (Paper I-III) and cross-sectional study design (Paper II and III). Observational studies are not designed to draw conclusions about causation, but they may discover an association between exposure factors and the predominant outcomes [159]. A Randomized Control Trial (RCT) is the best study method for the comparison of treatment modalities, but RCTs may be difficult to conduct for surgical interventions.

Knee arthroplasty surgery is overall a successful treatment, and adverse events (e.g. revision surgery) are relatively rare. To examine such rare adverse events with RCTs is impractical [194]; the study would require long follow-up time (10-15 years) and large number of patients since the differences in outcome in the study groups would be quite small. Consider, for example, an approximate cumulative re-revision rate of 5 % at 10 years after revision knee arthroplasty. To detect a significant difference for an implant with a 30 % higher re-revision rate (6.5 % vs 5 %) with 80 % power, almost 4000 patients with revision knee arthroplasty would have to be randomized and followed for ten years. It is clearly difficult (laborious and costly) to arrange an RCT with these numbers of patients. Thus, register study design is appropriate for treatment outcome studies with relatively rare adverse events and small differences. Even national registers struggle to reach these numbers especially in revision surgery.

Observational (register) studies have the potential for bias due to confounding. However, confounding factors can be controlled for to some extent, and observational studies may have some advantages that make them valuable. Some studies claim that the results from observational studies are often the same as from RCTs on the same subject [195-197]. RCTs do not always represent the average outcomes in an average patient because both the patient and the health care supplier are handpicked for the study. Since national register studies are performed on the whole population of patients and health care suppliers, their external validity is often better than that of RCTs [159, 195-198].

In our studies, we used national register data with high completeness of reporting and long follow-up time, and cross-sectional survey data with high response rate.

Traditionally, implant survival is an important measure in register studies using revision as the endpoint. However, patients' HRQOL is probably the most important outcome. The aims of joint arthroplasty surgery are to relieve pain and to improve function and consequently improving HRQOL. Since traditional survival analysis of implants cannot determine whether unrevised implants are functioning well or not, the addition of HRQOL measurements is important [48, 107]. Thus, a cross-sectional survey was conducted to assess the patients' perception of pain, function in daily living, satisfaction, and HRQOL to better assess the outcome of revision knee arthroplasty performed in Norway and reported to the NAR in the time period between 1994 and 2005 (Paper II and III). We believe that the combination of HRQOL- and implant revision data gives a fuller picture of the outcome of revision knee arthroplasty.

5.1.2. PRO instruments

To evaluate the efficacy of a treatment, choosing the most appropriate outcome measurement is essential. The selection of PROMs used in this thesis was based on earlier studies and the aims of the present studies. Widely used PROM allows you to compare your own findings with findings from other studies. All the PROMs used in this thesis have been validated and used in earlier studies in different countries, and on different patient groups. In this thesis we used one generic and one disease specific PROM, as well as two single-item PROMs (1 for joint pain and 1 for satisfaction with the results of revision surgery) which could consequently complement/supplement each other in strengthening both the internal as well as the external validity of the studies included in this thesis.

Further, the PROMs used in the present studies have shown satisfactory reliability (Cronbach's α > 0.7) both in earlier studies and in this thesis, except for the two KOOS subscales: symptoms (Cronbach's α=0.63) and knee related quality of life (Cronbach's α=0.65) and for preoperative EQ-5D (Cronbach's α=0.67) (Table 4). The reason for the lower Cronbach's α value of the subscale 'other symptoms' might be attributed to that patients present with a differing pattern of symptoms. Consequently, this subscale may vary more than other subscales in KOOS. The

Cronbach's α value is sensitive to the number of items in the scale. The KOOS sub-scale: 'knee related quality of life' has only 4 items and this is a possible explanation for its lower Cronbach's α value. The lower Cronbach's α value in the preoperative EQ-5D could be attributed to recall bias and /or to a response shift caused by the individual's perception of their HRQOL which may change over time as their circumstance and perspective changes.

Using a conceptual model like Wilson and Cleary's is essential to facilitate the selection of PROM(s) to be used in research and clinical practice [130, 140]. In the present studies, we did not use a conceptual model to select the PROMs. However, the PROMs used were able to measure almost all the central concepts of Wilson and Cleary's HRQOL conceptual model (Fig. 11). Using this latter model could be helpful in the selection of PROMs for the evaluation of clinical outcome of joint arthroplasty, also in a register setting.

5.1.3. Quality of data

5.1.3.1. Completeness and coverage

A high rate of reporting completeness is essential for the validity of the data. The NAR is one of the 12 full member registers of the International Society of Arthroplasty Registers (ISAR). ISAR demands over 80 % coverage of the hospitals and 90 % of procedures in order to be a full member [199].

Validation of the data reported to the NAR has been done by comparing databases with other nation-wide databases like the Norwegian Patient Register (NPR) [164, 200]. Furthermore, the NAR data have been compared with local data from reporting hospitals [164], and 100 % coverage of hospitals performing hip and/ or knee joint replacement surgery in Norway was reported in 2008-2012 [201]. Compared to the NPR data, completeness of the NAR data on primary and revision knee-arthroplasties has been found to be >95 % and 88-89 %, respectively [201].

As mentioned in section 3.1.2., the NAR does not collect prospective PRO data. However, the PRO data used in Paper II and III were collected in 2006 through a self-administered postal questionnaire survey as part of an earlier PhD study project from the NAR. The employees at the NAR performed the data entry (registration of returned questionnaires). Interpretation of erroneous marking of Likert boxes in the question-

naire was performed as stated in the guidelines for each instrument (EQ-5D, KOOS, Charnley Category, and VAS) [163]. The response rate of the survey participants was high (85.5 % to 94.2 %).

5.1.3.2. Validity

Validity is the extent to which a study can answer the questions it is intended to answer. Validity is categorized into internal and external validity [202].

Internal validity indicates whether the study was performed correctly and the conclusion is valid for the population in the study. Internal validity is a pre-condition for external validity, and it can be violated by systematic error: selection bias, information/observation bias, and confounding [202].

Selection bias is a distortion in a study due to the method used to select the study subjects. It occurs, for example, if the study sample is not representative for the study population from which it is selected. Possible causes of selection bias are individuals refusing to participate at the start of the study or dropouts during follow-up. Registration (participation) into the NAR is based on written consent from all patients, and therefore it is possible to refuse to participate from the start. All studies included in this thesis were based on data from the NAR. The NAR has demonstrated very high completeness of patients (> 95% of primary cases and ≥88 % in revision cases) and complete coverage of hospitals (100 %) [4, 164, 200], although revision procedures particularly due to infection as endpoint were vulnerable to be underreported [164]. Thus, the data used in this thesis can be considered population-based, and selection bias due to the reasons mentioned above is less likely to be present.

Selection bias can also arise when the exposure and outcome association differs between the responders and non-responders [203]. Non-response can lead to both under- and over-estimation of study findings. To assess the presence of selection bias due to individuals that are not willing to participate in the study, performing a comparison of the characteristics of responders and non-responders is often essential [163]. In Paper III, responders were relatively older (mean = 67.2 vs 64.5 years), had longer follow-up since revision operation (mean = 8.8 vs 8.1 years), were more likely to be male (30 % vs 19 %), and had more OA as a primary diagnosis (80 % vs 49 %) compared to non-responders. The difference in characteristics between responders and non-responders

is, however, less important if a high response rate was achieved [163] or if there is no difference in response rate between the compared study groups. In Paper II and III, 94.2 % and 85.5 % of the invited participants, responded to the questionnaire. These response rates were relatively high. Thus, we claim that the effect of selection bias on PRO data used in this thesis due to the discrepancy between responders and non-responders is probably of less significance.

Information bias is a measurement error that distorts the true association between the exposure and the outcome variables. Information bias mainly occurs during data collection and data entry (registration). Like the selection bias, information bias can introduce bias either by over- or under-estimating the findings [203]. Since the information reported to the NAR is completed by the operating orthopaedic surgeon at the operating theater just after each surgery, we believe that the accuracy for revision knee arthroplasty is high. However, there might be an under- or over reporting of reasons for a revision procedure. Arthursson et al. [164], reported that 1.2% of overall revisions and 10.5% of revisions due to infection for revision hip arthroplasty surgeries performed in the period between 1987 and 2003 were not reported to the NAR. In this thesis, however, we have excluded primary knee arthroplasties revised due to infection; thus, we believe that the effect of bias due to such underreporting is minimal.

The PROs data used in Paper II and III may be prone to some biases; e.g. recall bias (i.e. a wrong assessment of preoperative HRQOL status) and measurement errors. Except for the ΔEQ-5D index score, all outcome measures included in the survey (Paper II and III) were based on patient's perception of pain and function experienced in the last week prior to the survey. The preoperative EQ-5D (to assess preoperative HRQOL status) was assessed retrospectively minimum one (ranges 1-12) year after the revision surgery. Thus, it may be difficult for patients to recall the exact level of preoperative symptoms. This might affect the change in HRQOL status. It would seem logical that a prospective assessment of HRQOL is more accurate than a retrospective one. However, a prospective evaluation may be biased by recalibration of scale i.e. a change in understanding of the response scale [143]. Blome and Augustin [143] stated that *«In studies aiming to determine treatment benefit as perceived by the patient (instead of «true effect»), retrospective QOL assessment should even be more appropriate».*

Other studies have also reported moderate to good correlation between prospective data and recall data on preoperative status [204, 205]. We believe that the distortion effect of recall bias on the changes in HRQOL status (Paper II and III) is small; yet, the findings should be interpreted with caution.

When reporting their cases to the NAR, the operating surgeons attach the stickers with the catalogue numbers of each prosthesis component supplied by the manufacturer to the form [206]. The use of stickers with exact prosthesis information for registration [4, 60, 163] hopefully leads to a low number of registration errors, which will lead to a low risk of information bias.

Two studies from the NAR [207, 208] and one study from the Danish Arthroplasty Register [209] have validated the accuracy of the reported reason (diagnosis) for primary hip arthroplasty. They concluded that the information was valid, reliable, and provides an excellent basis for clinically relevant information regarding hip arthroplasty. There is no reason to believe that the rate of this kind of information bias is higher for knee arthroplasties.

Confounders and confounding: As defined by Rothman et al.[202], confounders are "*the extraneous factors that are responsible for the difference in the disease frequency between the exposed and unexposed*". For a variable to be a confounder it must: (i) be an extraneous risk factor for the disease, (ii) be associated with the exposure under the study in the source population, and (iii) not be affected by the exposure or the disease (i.e. it cannot be an intermediate step in the causal path between the exposure and the disease) [202]. Confounding is a distortion of the actual association between the exposure and the outcome due to an effect of a third variable (extraneous risk factors) [202]. Thus, controlling for potential confounders is an important part of a study. Unlike selection and information biases, confounding can be controlled for at the data analysis stage even if it was not prevented at the design stage [203].

A well designed RCT with a high number of subjects will secure an even distribution of both unknown and known factors and consequently, will limit (prevent) the potential effect of confounding factors [202]. In observational studies like register studies, however, such an even distribution (adjustment) of confounding factors can only be achieved for the factors that are collected. To increase the validity of the results

from observational studies, adjustment for known or suspected confounders is essential [202]. In the studies included in this thesis, the potential confounders that are available in the registry database have been controlled for. However, there are other variables, such as the surgeons' operations volume and skill, the level of patient physical activity, the co-morbidity, the degree of bone loss, and the radiological result that have not been taken into account and may bias our findings.

Bias may also be introduced if there is a systematic difference in certain patient characteristics in the study groups. In a register setting we can check for a set of characteristics including age, sex, diagnosis, American Society of Anesthesiologists (ASA) class and some others. Still, there are factors that we do not know and that could be skewed in one or another direction and influence the results systematically. Besides, each revision knee arthroplasty is a bespoke operation because each one is different and the surgeon must tailor their surgical approach depending on the problems each individual case presents. Consequently, confounding by indication may influence the findings.

Bilateral observations: We did not take into account a potential effect of bilateral knee arthroplasties in these studies. The statistical methods that are most often used to analyze arthroplasty register data assume that observations are independent. This assumption may not be fulfilled when bilateral observations are included in the analysis. Two observations (bilateral revision knee arthroplasty) in the same patient can be assumed to be correlated, and this may theoretically have consequences for the precision and validity of our study findings. However, earlier studies have shown that ignoring the effect of bilateral prostheses will not bias the result [210, 211]. Besides, the number of bilateral knee arthroplasties in the studies included in this thesis were relatively low (Paper I, n=16; Paper II, n=7; and Paper III, n=27).

External validity refers to the generalizability of the observed findings in the study population to the general population [202]. External validity is dependent on the internal validity [212]. Observational studies such as national arthroplasty register studies are by some considered to have greater generalizability than RCTs due to a broader range of patients, hospitals, implants, operation procedures, and surgeon's skill and operation volumes [159, 163]. This thesis is based on national register data with high

completeness and complete coverage, and on PRO survey data with high response rate. Thus, it is possible to generalize results and conclusions from this national study to other countries.

5.2. DISCUSSION REGARDING RESULTS

5.2.1. Revision total knee arthroplasties (Rev-TKAs)

Implant survival

In Paper I, we found that the 5, 10, and 15 years cumulative Kaplan-Meier survival percentage of rev-TKAs with all causes of re-revision as the endpoint was 85 %, 78 %, and 71 %, respectively. Similar implants survival percentages were also reported by a study from the Finnish Arthroplasty Register [9]. Sierra et al. [213] also found a re-revision rate of 16 %, 26 %, and 34 % at 5, 10, and 15 years, respectively after rev-TKAs, which also is in accordance with our findings.

In Paper I, we did not find any statistically significant difference in the risk of re-revision between patella resurfaced and non-resurfaced rev-TKAs. Kim et al. [214] also reported that patella resurfacing or non-resurfacing did not affect re-revision rate of rev-TKAs. They also reported that the clinical outcome of non-resurfaced patella were similar to that of patella resurfaced TKAs [214]. However, in their study, all the knees were revised with CCK prostheses. Thus, direct comparison of their findings with our findings in Paper I is difficult.

The findings in Paper I also showed that revisions done with the exchange of either the femoral or tibial component had nearly 2 times higher risk of re-revision compared to a complete TKA revision. The exchange of a tibial liner also had a non-significant tendency towards higher risk of re-revision compared to complete revision (RR= 1.5; 95 % CI: 0.9-2.3). Similar results have been published by others. [215-219]. Mackay and Siddique in their comparative study, for example, reported that patients treated with tibial tray revision and retention of the femoral component had a higher rate of re-revision (28 %) than those treated with revision of both components (7 %) [216]. The failure of revision knee arthroplasty could be multifactorial and related to the surgeon's decision to perform either a complete or a partial revision. This decision again might be influenced by patient-, implant- and /or surgeon-related factors.

Mode of failure

In Paper I, 14.3 % of rev-TKAs were re-revised at a median follow-up of 4.5 (range 0-17) years. Deep infection (28 %), instability (26 %), loose tibia (17 %), and pain alone (10 %) were the most frequent causes of re-revision of rev-TKAs. Similar re-revision rates (ranges 8.0-18.3 %) have been reported by others [219-221]. These earlier studies found even higher rates of re-revision due to deep infection (ranges 35-46 %) compared to our numbers. In our study none of the first revisions were done due to infection whereas in the other mentioned studies infection as a cause for the index revision was included. Patients revised for infection in the first place are more likely to have their revision implant revised for infection as well. This is probably the main cause for the differences in infection rates between ours and the other studies.

Even if our infection rates were lower than what were reported in some other series, infection is the dominant cause of a re-revision. Repeat surgery, scarring, long duration of surgery, bulky implants and older patients with comorbidity are factors that increase infection incidence and are common with revisions. Another possible explanation for the relatively high frequency of re-revision for infection could be the presence of occult low-grade infection(s) that were not detected preoperatively by the available detection modalities.

Risk factors for re-revision

In Paper I, we found 4 potential risk factors associated with failure of rev-TKA: younger age, male gender, partial revision operation, and revision without bone impaction. The relative risk of failure of rev-TKAs in patients aged < 60 years was 1.6 times higher than patients aged >70 years A study from the Finnish Arthroplasty Register also reported that patients aged >70 years had a lower risk of re-revision compared to patients aged ≤55 years [9]. The greater activity level and higher expectations in younger patients, and /or surgeon's reluctance to re-revise older patients due to medical comorbidities could be an explanation. In our study, male patients had a double risk for re-revision compared to female patients. In the Finnish study there was a non-significant tendency towards a lower risk of re-revision of rev-TKA in females than in males [9]. The gender associated difference in risk of re-revision might be attributed to

a lower body weight and a lower intensity of use of the prosthetic joint in women [9] and a higher risk of revision arthroplasty due to infection in males [222-224].

Furthermore, in Paper I, we found that TKAs revised without bone impaction grafting had 3 times higher risk of re-revision compared to those with bone impaction. Lotke et al. [91] reported no mechanical failures of TKAs revised with impaction grafting at an average follow-up of 3.6 years and the authors' conclusion was that impaction grafting had excellent durability and versatility in bone loss in rev-TKAs. However, it seems illogical that knees with substantial bone loss treated with impaction grafting had better effect than those which did not require impaction grafting. Besides, because we lack information on the exact grade of bone loss, the surgical technique used, and whether the impaction involved the meta- or diaphysis for the individual cases, the result must be interpreted with caution.

Restoring the original joint line of the knee, regaining function, providing optimal stability, creating equal flexion-extension gaps and restoring compromised damaged bone are some of the principles of revision knee arthroplasty [72-77]. In Paper I, we assessed if the risk of re-revision of rev-TKAs was affected by the type of fixation (cement, cementless or hybrid), long stem extensions, and /or stabilization (PCS or CCK) and prosthesis brands. However, we did not find a statistically significant effect of these surgical techniques and prosthesis brands on the outcome of rev-TKA. The number of cases in each subgroup probably was too low to reveal statistically significant differences if such differences existed. Besides, the femoral and tibial stems were not entered into the database at the catalog number level, and in a sample test comparing the 1-page form filled by the orthopedic surgeons and the database showed that nearly one-third of stems used were underreported in the NAR database.

5.2.2. Isolated secondary patella resurfacing (SPR)

Implants survival

In Paper II, we found that 11.3 % of 308 TKAs revised with isolated SPR were re-revised at a median follow-up of 8 (range 0-17) years. The survival rate was 91 % at 5 years, and 87 % at 10 years. In contrast to our findings, earlier studies have reported poorer results: 11 -18 % re-revisions at 3 -5 years of follow-up (n=22-566 knees) [14, 17, 34, 225]. The difference in patient profiles, number of cases, length of follow-up, sur-

geons and hospitals volumes, threshold for revision as well as number of prostheses brands, could explain this difference.

In Paper II pain alone (10 knees) and loosening (9 knees) were the main cause of failure which could indicate that SPR did not resolve the problem. Probably the cause of pain following the primary TKA was not only related to the patellofemoral joint. Although not obvious in the preoperative examination, loosening, malrotation, mal-tracking of the patella, low-grade infection, subtle instability or even hip- or spine problems may have caused the pain. A secondary insertion of a patellar button cannot solve these problems alone.

Clinical outcomes

From the cohort of 114 patients with PROMs in Paper II, we found that the mean EQ-5D index scores significantly improved following SPR by 0.15 points. The improvement following such revision procedure was observed mostly among patients with severe preoperative pain (69 % of 71 patients) in the EQ-5D pain/discomfort dimension. To our knowledge, no previous study has reported HRQOL following isolated SPR. However, it has been reported that the greatest potential for improvement following joint arthroplasty surgery is associated with patients with the most severe preoperative symptoms [226, 227].

It has been reported that to specify the degree of change in health status and to define a successful outcome after a treatment (e.g. surgical intervention), the MCID can be used. For the EQ-5D index score, the MCID has been determined to be 0.06-0.08 by some investigators [183, 184]. Thus, our finding regarding the mean change in HRQOL status following isolated SPR was both clinically as well as statistically significant.

The functional outcomes, postoperative pain, knee related quality of life, and satisfaction following isolated SPR were also assessed in Paper II and reported as mean KOOS subscales and VAS scores. The mean scores in KOOS subscales were 55 for pain, 64 for symptoms, 52 for ADL, 17 for sport/rec., and 38 for knee related QOL. The mean pain- and satisfaction-VAS score were 55 and 51, respectively. Scheurer et al. [36] also found a similar trend but with higher mean scores in KOOS subscales (ranges 42 to 68 points). Scheurer et al.'s [36] study was based on relatively few cases

(n=58), used one single prosthetic design, and was a single-center clinical study. This could account for this difference.

Berliner et al. [228] reported that for a patient to experience a clinically meaningful improvement after knee arthroplasty surgery, the maximum baseline (preoperative) KOOS score was 58. The authors suggested that patients with preoperative KOOS score above 58 are less likely to experience a clinically meaningful improvement. In the present thesis, we lack information on preoperative KOOS and pain-VAS. Therefore we could not assess whether the patients experienced a clinically meaningful improvement in pain and function following SPR or not.

In Paper II, more than one-third of the survey participants were dissatisfied with the result of SPR. It has been reported that satisfaction can be affected by pain relief, functional improvement, and patient's expectation and satisfaction with the health management in general (e.g. waiting time) [229]. However, since we lack information about patient expectation and experience, X-ray information as well as preoperative KOOS and Pain-VAS score, it is difficult to assess the reasons for the degree of satisfaction in our population.

Many would think that the outcome of rev-TKAs with isolated SPR would be better than that of complete revision TKAs, and similar to that of a patella resurfaced primary TKA. However, this was not the case according to our findings in Paper II (Fig. 13) [31, 41, 111, 230, 231]. As we mentioned above, pain following primary non-resurfaced TKA is probably multifactorial and could be caused by the implants design, the surgical technique [29, 232] and to patient-related factors like anxiety and / or depression [233] or pain from other regions like the spine and hip. Therefore, deciding to add a patellar component to a non-resurfaced TKA due to unexplained pain needs great caution.
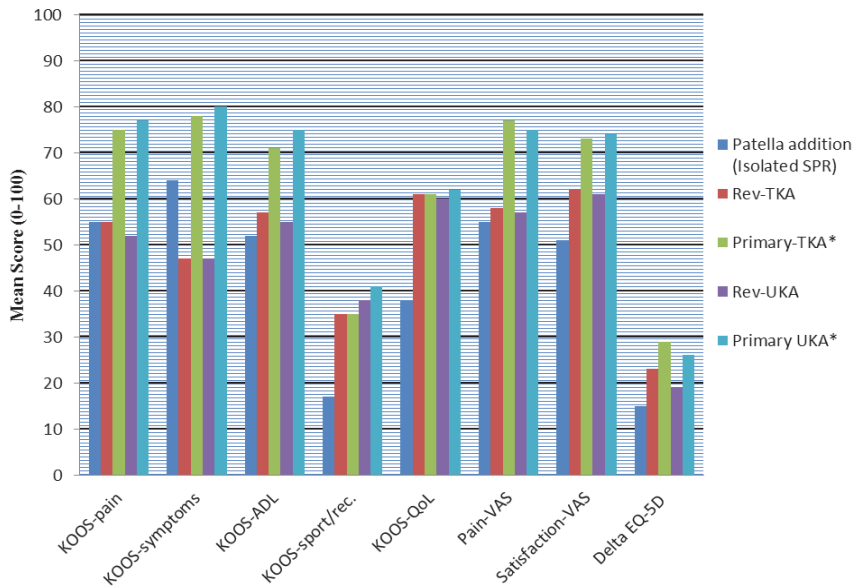
Fig. 13. *Mean scores in KOOS subscales, pain- and satisfaction-VAS and ΔEQ-5D index score after primary TKA and primary UKA [41], rev-TKA and rev-UKA [230], and revision TKA with isolated SPR [231]. Delta (Δ) EQ-5D= postoperative- minus preoperative- EQ-5D index score. The KOOS subscales and VAS- scores, the EQ-5D index scores were multiplied by 100 (ranges 0-100). * The mean scores are from an earlier PhD study from the NAR.*

Predicting factors

In Paper II, we also attempted to determine which factors, if any, which affect the clinical outcomes of SPR. We observed that male patients had a significantly higher mean ΔEQ-5D index score compared to female patients. The variation seen with gender may be because musculoskeletal pain is less common in men than women in the general population [234] and women have been reported to have higher pain perception than men [235]. Patients with a unilateral knee problem (Charnley category 'A') had better scores than patients with a bilateral knee joint problem or multilateral joint problem/general health problems (Charnley category 'B' and 'C') on mean KOOS subscales (except for KOOS-Sport/rec) scores. A similar effect of Charnley category on KOOS subscale scores were also reported in earlier studies on primary TKAs [111, 180]. A better mean score in KOOS-symptoms was observed in the older patients (> 70 years) than the younger patients (<60 years). A positive effect of older age on such outcomes was also found in a study on primary TKA from the NAR [111]. The greater expectations of a younger patient regarding the clinical outcome of knee arthroplasty

and their higher daily activity level compared to older patients could be a possible explanation for this difference [111].

5.2.3. Revision of unicompartmental knee arthroplasties (Rev-UKAs)

Implant survival

In Paper III, we compared implant survival after rev-UKA with survival after rev-TKA. There were no differences after 5, 10, and 15 years. The overall risk of re-revision for rev-UKAs vs rev-TKAs was also similar but with a slight tendency towards better results with rev-UKA (RR=1.2, 95 % CI: 0.9-1.7). This tendency has also been described by others [25, 39, 44, 45, 236]. In Paper III, we performed an age-stratified analysis. For patients older than 70 years the risk of re-revision was double after rev-TKA compared to rev-UKA. Although many orthopaedic surgeons prefer to use UKA for younger patients only, our findings strengthen the indication to use UKA in older patients [237, 238]. Such disagreement might be attributed to surgeon's volume and experience with initial patient selection, surgical technique, and indication for revision [239].

Mode of failure

In Paper III, 12 % of rev-UKAs and 13 % of rev-TKAs were re-revised at a median follow-up of 4.6 and 4.1 (range 0-17) years, respectively. Loose tibia component (28 vs 17 %), pain alone (22 vs 12 %), instability (19 vs 19 %), and deep infection (16 vs 31.3 %) were the major causes of re-revision of rev-UKAs and rev-TKAs, respectively. This shows that rev-UKAs were more often re-revised due to loose tibia and pain whereas rev-TKAs were most often re-revised due to deep infection. However, the observed differences in the proportion of reason for re-revision of rev-UKA vs rev-TKA were not statistically significant except that rev-TKA were 2 times more frequently re-revised for deep infection than rev-UKA. The lower rate of revision due to infection following UKA surgery compared to that of TKA confirms the earlier findings on the primary procedure [42].

Surgical procedure's technical challenge

In paper III, we found that the surgical procedure for rev-TKAs took a longer operative time and that a relatively higher proportion of the revision operations needed long stems, bone impaction, and stabilization compared to rev-UKAs. Some earlier studies

also reported such less technical difficulties of surgical procedure for rev-UKA compared to that of rev-TKA [45, 236]. In contrast, some other earlier studies reported that the surgical procedure for rev-UKA is technically more demanding than for rev-TKA, reporting significant bone loss requiring grafting, the need for stems or custom implants in 50-76 % of knees/patients [18, 23, 240]. The possible explanation for such conflicting reports could be attributed to differences in hospital's and surgeon's operations volume (experience) in doing the primary UKA surgery. Surgeon's technical experience in doing conservative bone cuts during primary UKA operations are probably important and can make the revision surgery more straightforward [25].

Clinical outcomes

In Paper III, we compared the clinical outcomes in terms of functional outcome, level of postoperative pain, satisfaction, and change in HRQOL status following rev-UKA versus rev-TKA and the outcomes were statistically not significantly different. Similar findings were also reported by some earlier studies [21, 45]. Cross et al.[236], however, reported better improvement in Knee Society Score (mean= 34 vs 29) and Knee Society Function scores (mean=31 vs 21) for rev-UKA compared to rev-TKA patients.

In Paper III, 25 % of 127 rev-UKA and 22 % of 150 rev-TKA patients were dissatisfied (satisfaction-VAS <40 points) with the revision surgery. In agreement with our findings, Robertsson et al. [16] also reported no statistically significant difference between the overall proportion of satisfied rev-UKA and rev-TKA patients.

Compared to an earlier study on primary knee arthroplasty from the NAR [41], the finding in Paper III indicates that the clinical outcomes of rev-UKA were inferior to that of primary TKA and primary UKA (Fig. 13). Lunebourg et al. [45] also reported that the clinical outcomes of primary UKA revised to TKA were more similar to revision TKA than to that of a primary TKA.

In Paper III, alike in Paper II, the preoperative EQ-5D score was assessed retrospectively and was therefore possibly subject to recall bias. Besides, we lack baseline information on KOOS and Pain VAS scores. Therefore we could not calculate the pre- and post-intervention difference in these PROMs in the individual cases. We also lack data on patients' physical activity level which could influence on the patients-reported outcomes.

6. STRENGTHS AND LIMITATIONS

The general strength of studies included in this thesis is that the work was mainly based on data on a large number of patients from a prospective database collected from a complete nationwide dataset over a long time period. Consequently, the probability of bias, which can occur due to patient's recruitment from selected surgeons and hospitals, is minimal. The larger number of participants and long follow-up can enable us to detect small differences among subgroups although the studies have a limitation in explaining the reasons for the detected differences. The NAR has high registration completeness as well as complete coverage of hospitals. Thus, the data are reliable and the external validity solid. We used validated PRO instruments which have been used in several earlier studies including arthroplasty register studies. The response rate in the PRO survey study was high (94.2 % in Paper II and 85.5 % in Paper III). Thus, the study population is likely to be representative for the Norwegian revision knee arthroplasty population.

Traditionally, the outcomes of arthroplasty in registers are assessed in terms of implant survival as the main endpoint. This endpoint does not give the full picture. In order to present a more complete and accurate picture of arthroplasty outcome both implant survival and PROs is recommended [46], as we did in the last two papers (Paper II and III). PROM is a subjective instrument, and the patient's actual functional ability may be under- or over- estimated. To fully characterize the outcome of arthroplasty, PROM could also be supplemented by an objective instrument (i.e. a performance-based measure) which is not done in this thesis.

As mentioned in section 5.1.3.2., any change on individual patient's HRQOL status due to treatment effects varies depending on whether the baseline information in HRQOL status was measured prospectively or retrospectively. This could lead to different sorts of bias and to an under- or over- estimation of change in HRQOL status [143]. In Paper II and III, patients were asked to report their preoperative HRQOL status minimum one year after the index revision surgery. Howell et al. [204] in their study on total hip arthroplasty found no statistically significant differences between postoperative recollection and preoperative collection of mean QoL scores (Oxford-12, WOMAC, and SF-12) 3 days, 6 weeks, and 3 months after the surgery. Murphy et al. [241]

also found no statistically significant differences between the actual and recalled pre-operative mean Oxford Knee Score one year after knee arthroplasty. Besides, Blome and Augustin [143] reported that a retrospective assessment of HRQOL status is more appropriate in studies aiming to determine treatment benefit (efficacy) from patients perception. Thus, we believe that the distortion of our findings (in Paper II and III) due to recall bias is small and the estimation of change in HRQOL status is valid.

Earlier studies reported that preoperative pain and functional status, as measured by PROMs, have been shown to predict level of pain and functional ability after knee arthroplasty surgery [228, 242, 243]. More specifically, patients with higher levels of pre-operative pain and functional disability demonstrated the greatest improvements in PROM scores, although they did not achieve absolute postoperative scores quit as high as patients with less preoperative pain and better baseline function [244, 245].

In paper II and III we lack baseline information (on preoperative KOOS and pain-VAS scores). Therefore, we could not evaluate the effect size of revision knee arthroplasty surgery on patients' level of pain, knee related quality of life, and func-tional status, nor whether the effects are improvement or not based on the KOOS score.

Furthermore, we did not have access to radiographic data (Paper I-III) before and after the revision procedure. Thus, we could not evaluate the degree of OA at primary operation, the degree of bone loss or any malpositioning of the implants. All these fac-tors and several others, including patient and surgery related ones could affect the out-come for the individual patient.

7. CONCLUSIONS

The overall conclusion of this PhD study is that the long-term implant survival following aseptic revision knee arthroplasty in Norway in the period between 1994 and 2011 was satisfactory (range 78-87 % at 10 years), and a number of points were noted. Specifically:

i)   Complete TKA revisions had better implant survival rate than partial revisions. Thus, partial revisions should only be done after careful consideration in specific instances. Male gender and younger age (<60 years) were risk factors for re-revision. Patellar resurfacing, prosthesis brands, constrained implants, the use of stem extensions, and/or fixation method had no effect on the survival of rev-TKAs, whereas cases with bone impaction grafting had better results in terms of survival. Deep infection and instability were the most frequent causes of failure of rev-TKAs (Paper I).

ii)   For isolated SPR procedures pain and loosening were the main causes for re-revision. Young age (<60 years) was a risk factor for re-revision after these procedures. The mean HRQOL significantly improved following SPR. Isolated SPR procedure can provide a solution to patients with severe preoperative pain. Still, more than one-third of patients were dissatisfied with the outcomes of the SPR procedure. Male patients had a better post-revision improvement in mean EQ-5D index score, and patients with a unilateral joint problem (Charnley category 'A') had significantly better mean score in KOOS subscales than the other categories following revision TKA with isolated SPR (Paper II).

iii)   The overall outcomes of rev-UKAs and rev-TKAs in terms of implant survival rates, functional outcome, level of postoperative pain, patient satisfaction, and change on HRQOL status were similar. However, rev-TKAs seemed to be a technically more difficult surgical procedure, were re-revised more frequently due to deep infection, and had a double risk of re-revision for patient older than 70 years compared to that of rev-UKAs (Paper III).

8. IMPLICATIONS AND FURTHER RESEARCH

Our findings provide an overview of the quality of revision knee arthroplasty surgery in Norway, and highlight the modes of failure and surgical related risk factors that may lead to a poor outcome after revision knee arthroplasty surgery. Hopefully this knowledge can improve the surgery.

Patients undergo arthroplasty surgery with the prospect of pain relief, and improvement of their function in daily life. However, if either of these areas (i.e. pain and/or function) should not improve, it is very likely that the patient will be dissatisfied with the treatment, and their HRQOL might even be worsened [127, 128]. It is important that orthopaedic surgeons inform patients about the risks as well as setting realistic expectations for outcomes from revision knee arthroplasties. A revision knee arthroplasty operation is more expensive, technically more difficult and complicated, and consumes more time and supplies compared to a primary knee arthroplasty. Identification of patients who will benefit most from revision knee arthroplasty and informing those at risk of poorer outcomes may eventually improve patient satisfaction and consequently, reduce the number of subsequent revisions as well as leading to significant cost saving for society.

Hopefully, the findings in the studies included in this thesis will contribute to better preoperative patient information, and to aid surgeons in the decision process when facing unhappy knee arthroplasty patients.

Further research and improvement of the register

- In this thesis, we used PRO data collected retrospectively. Further clinical outcomes studies with prospective preoperative and postoperative (e.g. 1 and 10 years postoperative) PRO data are warranted. The NAR should implement prospective PRO reports. Because PROM is a subjective instrument, further outcome studies which involve objective assessment methods such as performance based measures and X-ray and CT evaluation are also warranted.

- Over one-third of patients that had reported PROs were dissatisfied with revision TKA with isolated SPR, and the clinical outcomes of SPR were inferior compared to that of primary patellar resurfacing. It seems that the problem of knee pain fol-

lowing non-resurfaced TKAs can be due to a multifactorial etiology. Further studies on the clinical outcomes of SPR in relation to patient expectation, selection (X-ray finding), surgical technique, and implants component designs are also needed.

- In this thesis, the outcome of revision knee arthroplasties done due to infection of the primary implant was not studied. Thus, the overall success and failure rates in the treatment of first-time revision knee arthroplasties due to deep infection need further studies.

- Compared to the primary knee arthroplasty, revision is more costly, technically more difficult and complicated, but still effective in improving function, pain level, and quality of life. Despite being clinical and cost-effective, complications associated with such revision surgery occur and may lead to prolonged inpatient care, unplanned hospital readmission, or even further surgery. Thus, studies on the rate and causes of unplanned readmissions, postoperative complications (surgical and medical complications not leading to revision surgery such as thromboembolic and cardiovascular events), mortality, volume of surgery, and the cost burden following revision knee arthroplasties in a Norwegian population setting are also warranted.

- In this thesis, we have assessed the effect of various fixation technique as well as prosthesis brands on implant survival rate. However, we did not assess whether or not the modes of failure of revision knee arthroplasty varies according to the level of implant constraint.

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NB: Searchs for relevant litreatures included in this thesis were stopped on November 20, 2016