Tampere University

MIKA NIEMELÄINEN

Outcome of Contemporary Knee Arthroplasty

In terms of survivorship and patient reported outcome measures with special reference to patients less than 65 years of age

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ACADEMIC DISSERTATION
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To Irene, Lotta, Lilja and Eelis

Abstract

In patients with symptomatic severe knee osteoarthritis (OA), total knee arthroplasty (TKA) has good long-term outcomes and results in greater pain relief and increased functional improvement compared with nonsurgical treatment. Because of good long-term implant survivorship, TKA also become a common treatment for severe knee OA among younger patients. However, the outcomes and implant survivorship of TKA have been reported to be inferior in younger patients. To date, cemented fixation has been regarded as the gold standard fixation method in TKA, but there has been controversy regarding the optimal fixation method among working-age patients.

In many countries, reported increases in the rate of TKAs and estimates of future demand predict a substantial increase in the incidence of TKAs. Both a broadening of indications for younger patients and an increase in the total incidence of TKA have raised concerns over a possible increase in revision burden in the long-term. Differences between geographic location and age groups have been observed in the incidences of TKA. The major increase in incidence has been found in patients from the "baby boomer" (born between 1946 and 1964) generation.

Working-age patients have high expectations for the outcome of TKA, and between 11 and 25% of these patients have been reported to be dissatisfied after the operation. These results, however, have been derived from studies without a true prospective observational set-up.

Adequate postoperative pain management plays a key role in enabling proper early recovery after TKA. However, the effect of postoperative pain management on the final outcome of this operation in terms of function and quality of life is not well known.

The aim of this study was to evaluate the incidence and outcomes of contemporary knee arthroplasty with special reference to working-age patients. Both the implant survivorship of different fixation methods of TKA and also patient-reported outcome measures (PROMs) were assessed. Secondly, we aimed to study the efficacy of local infiltration analgesia (LIA) and the effect of early pain management on the outcomes of TKA.

In the study I, based on Nordic Arthroplasty Register Association (NARA) data, a total of 385 310 primary knee arthroplasties in patients aged 30 years or older performed in 4 Nordic countries were analyzed from 1997 to 2012 in Denmark, Norway, and Sweden, and from 2000 to 2012 in Finland.

In the study II, 115 177 TKAs selected from NARA data in patients aged less than 65 years of age who had undergone an unconstrained primary TKA for primary OA from 2000 to 2016 were included to assess the survivorship of cemented, uncemented, hybrid, and inverse hybrid TKAs.

In the study III, based on Finnish Arthroplasty Register (FAR) data, 1 151 TKAs that were performed between 2003 and 2010 using an uncemented porous tantalum metal (TM) tibial component were analyzed.

In the study IV a total of 232 (254 knees) patients were enrolled between March 1st, 2012 and October 30th, 2014 for a prospective observational study to analyze the outcomes of knee arthroplasty using PROMs.

In the study V a total of 60 patients who underwent unilateral TKA between March 2011 and March 2012 were enrolled into a randomized, double-blinded, placebo-controlled study to analyze the effect of LIA on early pain management and also on PROMs over a 1-year follow-up.

There was an equal increase in total incidence, comprising both TKAs and unicondylar knee arthroplasties (UKA), in all countries. The increase in surgical procedures in Finland from 2004 to 2006 may be explained by the new social and health care law that forced hospitals to shorten patient waiting times for surgery. Despite having comparable socio-economic situations and health care systems, the differences in the incidence of knee arthroplasties between countries were notable. The total increase in the number of arthroplasties in all countries was mainly due to an increased incidence of TKAs. In Sweden, there was a significant decrease in the incidence of UKAs in patients 65 years or older. In Finland, Denmark, and Norway, variations in the incidences of UKAs were more heterogeneous.

Both cemented and hybrid TKAs evinced excellent 10-year survival rates in patients aged less than 65 years in the Nordic countries. Even though hybrid/inverse hybrid versions of the well-performing contemporary TKA designs provided younger patients with a good mid-term outcome in our study, they were still only used in a limited number of patients. In the inverse hybrid group, one single TKA design comprised the vast majority of the whole group.

An uncemented porous TM monoblock tibial component had excellent mid-term survivorship in a population-based setting in Finland. The most common reasons for revisions were instability and prosthetic joint infection (PJI). During the study period, only one revision was performed due to aseptic loosening of the tantalum monoblock tibial component. Neither age nor any of the other variables showed any effect on the risk of revision in the multivariate regression analyses.

The mean Oxford Knee Score (OKS) and all the Knee Injury and Osteoarthritis Outcome Score (KOOS) subscales increased significantly ($p<0.001$) from the preoperative situation to 2-year follow-up in working-age patients who underwent knee arthroplasty at our institution. A significant increase ($p<0.001$) in physical activity was detected in High-Activity Arthroplasty Score (HAAS) and in RAND-36 Physical Component Score (PCS). Pain was also significantly ($p<0.001$) relieved during the follow-up. However, the total disappearance of pain was rare at 2 years. Patients with milder Kellgren-Lawrence (KL) grade 2 osteoarthritis (OA) were less satisfied and reported poorer PROM outcomes than those with advanced OA (KL 3–4). There was no difference in the outcome (any PROM) between patients who underwent total knee arthroplasty (TKA) and those who received unicondylar knee arthroplasty (UKA).

A single intraoperative drug infiltration containing levobupivacaine, ketorolac, and adrenaline decreased the total consumption of oxycodone during the first 48 hours postoperatively. The effect of LIA was most pronounced during the first 6 hours postoperatively. LIA also improved the early knee ROM, but no long-term functional benefit was observed in PROMs.

The increase in the overall incidence of knee arthroplasties was the consequence of an increase in incidence of TKAs, whereas the incidence of UKAs varied between countries. The proportional growth in incidence of TKAs during the study period was highest in patients younger than 65 years. Despite this, the incidence of knee arthroplasty in the youngest age group was clearly lower than in patients aged 65 years or older. Based on this finding, the majority of knee arthroplasties will probably be performed on elderly patients also in future. Even though knee arthroplasties were still performed clearly more often on patients aged 65 or older in Nordic countries, working-age patients should be considered as an important subgroup because of their higher physical activity, demands for surgery, and the multi-factorial reasons behind the success of TKA.

Cemented TKA still merits the status of gold standard in TKA irrespective of the patients' age. Even though hybrid/inverse hybrid versions of the well performing contemporary TKA designs provided younger patients with a good mid-term outcomes in our study, these results do not support the systematic use of these more expensive components in younger patients.

Early loosening of uncemented TM tibial component was very rare and the risks for revision for other reasons were as rare as with contemporary cemented TKAs.

TKA provided patients aged 65 years or less with clinically significant pain relief as well as improvements in ADL and quality of life. The patients′ physical activity was low or moderate preoperatively but improved significantly during the 2-year follow-up. Some pain and functional deficiencies remained after knee arthroplasty, and this should be emphasized in the preoperative guidance given to patients who are considering or who are scheduled for such surgery. Mild radiographic OA preoperatively is a clear risk factor for patient dissatisfaction after knee arthroplasty.

A single perioperative infiltration of LIA reduced opiate consumption until 48 hours after TKA, and the routine use of perioperative infiltration analgesia as an adjunct to oral pain medication may be recommended in patients undergoing TKA. The use of LIA did not have any effect on the functional outcome of TKA over the first postoperative year.

Tiivistelmä

Pitkälle edenneen oireisen polvinivelrikon hoidossa tekonivelleikkauksen tulokset ovat erinomaiset: kipu lievittyy, ja sekä toimintakyky että myös elämänlaatu parantuvat merkittävästi. Tekonivelen hyvä pitkäaikaispysyvyys on lisännyt tämän hoitomenetelmän käyttöä pitkälle edenneen polven nivelrikon hoidossa myös nuoremmilla potilailla, vaikka toiminnalliset tulokset ja tekonivelen pysyvyys onkin raportoitu huonommaksi verrattuna vanhempiin potilaisiin.

Sementtikiinnitystä voidaan pitää kultaisena standardina polven kokotekonivelleikkauksessa. Nuoremmilla, työikäisillä potilailla paras komponenttien kiinnitysmenetelmä on kuitenkin edelleen kiistanalainen.

Polven tekonivelleikkausten ilmaantuvuus on lisääntynyt viimeisten vuosikymmenten aikana, ja ilmaantuvuuden kasvun on ennustettu edelleen jatkuvan lähitulevaisuudessa. Sekä leikkausaiheiden laajentuminen nuorempiin potilaisiin että toisaalta leikkausmäärien lisääntyminen nuoremmilla potilailla ovat lisänneet huolta siitä, että kasvaako myös uusintaleikkausten määrä merkittävästi lähivuosikymmeninä. Ilmaantuvuudessa on havaittu lisäksi eroja sekä maantieteellisesti että potilaiden ikäryhmien välillä. Suurin polven tekonivelleikkausten ilmaantuvuuden kasvu on havaittu nk. suurissa ikäluokissa.

Työikäisillä potilailla on korkeat odotukset polven tekonivelleikkauksen tuloksesta, ja noin 11–25 % potilaista on tähänastisissa tutkimuksissa ollut tyytymättömiä leikkauksen tulokseen. Prospektiivista seurantatutkimusta aiheesta on kuitenkin julkaistu vain vähän.

Leikkauksen yhteydessä annettava kipulääkitys sekä leikkauksen jälkeinen kivun hoito on yksi avaintekijä polven tekonivelleikkauksen onnistumissa. Hyvä kivun hoito mahdollistaa kunnollisen kuntoutusharjoittelun, vähentää leikkauksen jälkeisiä välittömiä komplikaatioita ja voi myös heijastua tuloksissa ja tyytyväisyydessä pitkällä aikavälillä.

Tässä tutkimuksessa arvioitiin nykyisten polven tekonivelleikkausten ilmaantuvuutta, eri kiinnitysmenetelmien kestävyyttä ja työikäisten potilaiden tuloksia potilaiden raportoimilla vaikutusmittareilla. Lisäksi arvioitiin paikallispuudutuksen vaikutusta kivun hoitoon ja leikkauksen pitkäaikaistuloksiin.

I:ssä ja II:ssa osatyössä käytettiin tutkimusaineistona Pohjoismaista tekonivelrekisteriä (NARA), joka koostuu Suomen, Ruotsin, Norjan ja Tanskan yhdistyneistä tekonivelrekistereistä. I osatyö sisälsi 358 310 potilasta ja II osatyö 115 177 potilasta. III osatyön materiaali koostui Suomen tekonivelrekisterin aineistosta sisältäen 1 151 potilasta. IV osatyö oli puolestaan etenevä seurantatutkimus, jossa Tekonivelsairaala Coxassa polven tekonivelleikkauksen läpikäyneiden 232 potilaan leikkaustulokset arvioitiin 2 vuoden seurannassa. V osatyössä 60 potilasta satunnaistettiin Tekonivelsairaala Coxassa polven tekonivelleikkauksessa saamaan joko LIA-puudute tai plaseboinjektio, ja heidän toipumistaan leikkauksesta seurattiin vuoden ajan tulokset rekisteröiden.

Tässä tutkimuksessa todettiin, että polven tekonivelleikkausten kokonaisilmaantuvuus lisääntyi kaikissa Pohjoismaissa. Suomessa ilmaantuvuus oli erityisen suurta vuosina 2004–2006, mikä selittyy tuolloin voimaan tulleella hoitotakuulailla, joka ohjasi sairaaloita lyhentämään leikkausjonoja. Vaikka Pohjoismaissa väestön elintaso ja terveydenhuoltojärjestelmä ovat verrattavissa toisiinsa, olivat erot ilmaantuvuuksissa huomattavia. Ilmaantuvuuden lisääntyminen johtui pääosin nimenomaan kokotekonivelleikkausten lisääntymisestä. Osatekonivelleikkausten ilmaantuvuudessa oli maiden välillä huomattavaa vaihtelua, ja yli 65-vuotiaiden osatekonivelleikkausten ilmaantuvuus väheni selvästi Ruotsissa,.

Sementtikiinnitteisillä ja nk. hybridi polvitekonivelillä oli erinomaiset pysyvyydet 10-vuoden seurannassa. Kaikilla kiinnitysmenetelmillä saavutettiin hyväksyttävät pysyvyydet, mutta muiden kuin sementtikiinnitteisten polven tekonivelten määrät tutkimuksessa olivat vähäisemmät, mikä vaikeuttaa ryhmien vertailua.

Sementittömällä tantaalimetallisella säärikomponentilla todettiin erinomainen pysyvyys eikä tekonivelen irtoamisen riski eronnut vastaavasta sementtikiinnitteisestä tekonivelmallista.

Kaikissa PROM-mittareissa todettiin merkittävä paraneminen 2 vuoden seurannassa ja sekä fyysinen että psyykkinen toimintakyky lisääntyivät merkittävästi. Oireettomuus oli harvinaista. Potilaat, joiden radiologinen nivelrikko oli ennen leikkausta lievempi (KL2), olivat tyytymättömämpiä leikkauksen tulokseen kuin ne potilaat, joiden nivelrikko luokiteltiin pitkälle edenneeksi (KL3–4). Kokotekonivelellä ja osatekonivelellä hoidettujen potilaiden tuloksissa ei ollut eroa.

Polven tekonivelleikkauksen yhteydessä annettu paikallispuudutus vähensi opiaattilääkityksen määrää merkittävimmin ensimmäisen 6 tunnin aikana. Se paransi myös polven liikelaajuutta heti leikkauksen jälkeen, mutta pitkäaikaisia vaikutuksia toiminnallisilla mittareilla ei havaittu 1 vuoden seurannassa.

Vaikka polven tekonivelleikkausten ilmaantuvuus lisääntyi suhteessa eniten alle 65-vuotiailla potilailla, oli kokonaisilmaantuvuus kuitenkin edelleen selvästi suurempaa yli 65-vuotiailla. Tämän johdosta suurin osa polven tekonivelleikkauksista tehdään tulevaisuudessakin vanhemmille ikäryhmille. Kuitenkin nuorempien potilaiden fyysinen aktiivisuus, vaatimustaso sekä moniulotteiset taustatekijät tyytyväisyyden taustalla muodostavat erityispiirteensä nuoremmilla potilailla.

Kaikilla kiinnitysmenetelmillä saavutettiin erinomainen pysyvyys 10 vuoden seurannassa. Sementtikiinnitteistä polven tekoniveltä voidaan edelleen pitää kultaisena standardina huolimatta hybridin ja käänteisen hybridin hyvistä tuloksista työikäisillä potilailla. Tantaalimetallisella sementittömällä säärikomponentilla irtoaman riski on sementtikiinnitteistä vastaava.

Polven tekonivelleikkauksella saavutetaan yleisesti ottaen merkittävä kivun lievitys ja toimintakyvyn parantuminen työikäisillä potilailla. Osalle potilaista voi kuitenkin jäädä sekä kipua että myös toimintakyvyn rajoitteita, ja erityisesti lieväasteinen nivelrikko ennen leikkausta on selkeä leikkaustulokseen tyytymättömyyttä lisäävä riskitekijä.

Leikkauksen aikana annettava paikallispuudutus on tehokas lisä polven tekonivelleikkauksen jälkeiseen kivun hoitoon. Puudutuksella ei kuitenkaan ole vaikutusta leikkauksen lopputulokseen kivun ja toimintakyvyn osalta.

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The dissertation is based on the following original publications referred to in the text by their Roman numerals I to V.

I Niemeläinen M, Mäkelä K, Robertsson O, W-Dahl A, Furnes O, Fenstad A, Pedersen A, Schrøder H, Huhtala H, Eskelinen A. Different incidences of knee arthroplasties in the Nordic countries. A population-based study from the Nordic Arthroplasty Register Association. Acta Orthop. 2017 Apr;88(2):173-178.

II Niemeläinen M, Mäkelä K, Robertsson O, W-Dahl A, Furnes O, Fenstad A, Pedersen A, Schrøder H, Reito A, Eskelinen A. The effect of fixation type on the survivorship of contemporary total knee replacements in patients younger than 65 years of age: a register-based study of 115 177 knees in the Nordic Arthroplasty Register Association (NARA) 2000-2016. Accepted to Acta Orthopaedica.

III Niemeläinen M, Skyttä E, Remes V, Mäkelä K, Eskelinen A. Total knee arthroplasty with an uncemented trabecular metal tibial component – a registry-based analysis. The Journal of Arthroplasty 2014 Jan;29(1):57-60.

IV Niemeläinen M, Moilanen T, Huhtala H, Eskelinen A. Outcome of knee arthroplasty in patients aged 65 years or less: A prospective study of 232 patients with 2-year follow-up. Scandinavian Journal of Surgery 2019, vol 108(4), 313-320.

V Niemeläinen M, Eskelinen A, Kalliovalkama J, Moilanen T. Single periarticular local infiltration analgesia reduces opiate consumption until 48 hours after total knee arthroplasty. A randomized placebo-controlled trial involving 56 patients. Acta Orthop. 2014 Dec;85(6):614-9.

Abbreviations

ADL	Activities of Daily Living
BMD	Bone Mineral Density
BMI	Body Mass Index
CCK	Constrained Condylar Knee
CPSP	Chronic Post-Surgical Pain
CR/PS	Cruciate Retaining/Posterior Substituting
EQ-5D	EuroQol five-dimensional
EULAR	European League Against Rheumatism
FAR	Finnish Arthroplasty Register
HAAS	High Activity and Arthroplasty Score
ICLH	Imperial College London Hospital
KM	Kaplan-Meier
KOOS	Knee Injury and Osteoarthritis Outcome Score
LIA	Local Infiltration Analgesia
MCID	Minimal Clinically Important Difference
MUA	Mobilization Under Anesthesia
NJR	National Joint Register
NZJR	New Zealand Joint Register
OA	Osteoarthritis
OECD	Organization for Economic Co-operation and Development
OKS	Oxford Knee Score
PMMA	polymethylmethacrylate

PJI	Periprosthetic Joint Infection
PROM	Patient-Reported Outcome Measures
RA	Rheumatoid Arthritis
RCT	Randomized controlled trial
ROM	Range of Motion
SKAR	Swedish Knee Arthroplasty Register
TKA	Total Knee Arthroplasty
TKFQ	Total Knee Function Questionnaire
TM	Tantalum Metal
TUG	Timed Up and Go
UKA	Unicompartmental Knee Arthroplasty
VAS	Visual Analog Scale

1 Introduction

In patients with severe symptomatic knee OA, TKA has good long-term outcomes and results in greater pain relief and increased functional improvement compared with nonsurgical treatment (Carr et al. 2012, Skou et al. 2015). Options for operative treatment of knee OA are high tibial osteotomy (HTO), UKA and TKA. The use of UKA has been focused on mainly medial, unicondylar disease in patients of all ages whereas HTO has mainly been offered to younger and more physically active patients. In the selected cases HTO and UKA have been reported to be less extensive and bone sparing compared to TKA (W-Dahl et al. 2010a). Because of good long-term implant survivorship, TKA has also become a common treatment for severe knee OA among younger patients. However, the outcomes and implant survivorship of TKA have been reported to be inferior in younger patients (Lonner et al. 2000a, Rand et al. 2003, Julin et al. 2010, Price et al. 2010a).

Reported increases in the rate of TKAs and estimates of future demand predict a substantial increase in the incidence of TKAs in many countries (Jain et al. 2005, Kurtz et al. 2007, Kim et al. 2008a, W-Dahl et al. 2010a, Culliford et al. 2010a, Nemes et al. 2015a, Singh et al. 2019). Both the broadening of indications for younger patients and an increase in the total incidence of TKA have raised concerns over a possible increase in revision burden in the long-term (Kurtz et al. 2007, Gioe et al. 2007a). Differences between geographic location and age groups have been observed in the incidences of TKA (Katz et al. 1996, Wells et al. 2002).

Previous studies have reported both the proportionally highest increase in incidence of TKAs and also the highest risk for revision in patients younger than 65 years of age (Julin et al. 2010, W-Dahl et al. 2010a, Carr et al. 2012, Leskinen et al. 2012, Meehan et al. 2014, Nemes et al. 2015a, Dyrhovden et al. 2017). This has led to an increased interest in finding a more durable fixation method for TKA. A previous systematic review did not report any differences in survival or functional outcome between cemented and uncemented TKAs in patients aged 60 years or less (Franceschetti et al. 2017). A meta-analysis without age limit showed better survival rates with cemented TKAs when all studies were combined.

In randomized studies, however, survival rates were equivocal (Gandhi et al. 2009). In a few studies, uncemented fixation in TKA has been reported to offer similar outcomes to cemented TKA, but the higher costs of uncemented components has meant that cemented TKA remains the gold standard fixation method (Dalury. 2016, Miller et al. 2018, Zhou et al. 2018).

A previous study using radiostereometric analysis (RSA) showed that the early migration seen with uncemented tibial components settled within two years, whereas cemented tibial components continued to migrate (Wilson et al. 2012a, Henricson and Nilsson. 2016a). The failures of uncemented TKAs have traditionally been mostly due to uncemented metal-back patellar resurfacing, but also to aseptic loosening of the tibial component (Lombardi et al. 1988, Stulberg et al. 1988). Aseptic loosening is characterized by poorly vascularized connective tissue dominated by fibroblasts and macrophages that forms the interface tissue between the bone and implant or cement (Gallo et al. 2002). As aseptic loosening occurs as a reactive process to wear debris from polyethylene inserts, ways of reducing volumetric wear have been sought (Odland et al. 2011). To date, the use of uncemented TKAs has been limited, but previous studies have reported an increased risk for aseptic loosening of the tibial component in patients treated with uncemented TKA (Collins et al. 1991, Bassett. 1998, Duffy et al. 1998a, Berger et al. 2001a, Barrack et al. 2004, Goldberg and Kraay. 2004, Carlsson et al. 2005). However, due to the evolvement of designs and materials, uncemented fixation has become an interesting choice, especially for younger patients with good bone quality (Hu et al. 2017). The trabecular metal (TM) tibial component has shown promising results in both prospective observational and RCT studies (Henricson et al. 2013a, Pulido et al. 2015). Although significant differences have been observed between different fixation concepts in terms of revision rates, functional outcomes have been equivalent irrespective of the fixation method (Gandhi et al. 2009, Gao et al. 2009, Demey et al. 2011, Arnold et al. 2013). The most optimal fixation method in TKA still remains controversial for younger patients, however.

An uncemented porous tantalum tibial component has a highly porous tantalum tray with a fixed polyethylene (PE) insert which eliminates backside wear and may thus reduce the long-term PE particle burden. The PE insert is molded into the trabecular metal cells to a depth of about 1.5 mm. The biological incorporation of trabecular metal implants has been well documented (O'Keefe et al. 2010, Wilson et al. 2010a, Unger and Duggan. 2011, Kamath et al. 2011a), and the elastic properties of this implant are comparable to those of normal bone structure (Patil et al. 2009). The lower stiffness of the tantalum implant may cause less stress shielding than in conventional metal-backed components. However, the increased surface area of the extremely porous tantalum metal and also a lack of antibiotics-loaded bone cement may, in theory, increase the risk of periprosthetic joint infections (PJIs).

Younger patients have high expectations for the outcome of total knee arthroplasty (TKA), and this may predispose them to dissatisfaction after the operation (Noble et al. 2006a, Parvizi et al. 2014, Scott et al. 2016). Arthroscopic surgery of the degenerative knee has been shown to be ineffective (Sihvonen et al. 2013), and the incidence of high tibial osteotomy has also steadily decreased (W-Dahl et al. 2010a, Niinimaki et al. 2012). Hence, increasing numbers of younger patients with mild knee OA are being offered knee arthroplasty. As both young age (Julin et al. 2010, Meehan et al. 2014) and mild knee OA (Niinimaki et al. 2011) are known to be risk factors for revision surgery, it is of critical importance to assess the outcome of knee arthroplasty within this demanding patient group.

A few recent studies have reported the outcome of TKA measured with patient-reported outcome measures (PROMs) in younger patients (Klit et al. 2014, Scott et al. 2016, Goh et al. 2016a). However, only one of these previous trials was a true prospective observational study (Klit et al. 2014). Further, patient physical activity was not assessed with a specific activity score in any of these studies. All of them reported the overall positive effect of TKA on symptoms, activities of daily living, and quality of life. However, a variable proportion of patients (11–25%) were dissatisfied with the outcome of their surgery. Scott et al. reported that dissatisfaction was also related to a low grade of radiographic OA, previous surgery, and obesity (Scott et al. 2016). Thus, there is an obvious need for valid observational (real-world) data on the actual performance of knee arthroplasty in routine settings, and especially among younger working-age patients (Malmivaara. 2013).

The goal of local infiltration analgesia (LIA) after TKA is to provide simple, effective and safe pain relief during the first postoperative days with reduced opiate consumption (Kerr and Kohan. 2008a). Adequate postoperative pain control is usually achieved using multimodal pain management. However, the control of pain continues to be a challenge in many TKA patients and disturbs postoperative rehabilitation. Therefore, in addition to providing better pain relief, multimodal analgesia aims to reduce the amount of opiate medication.

There is a scarcity of studies that have analyzed the long-term influence of infiltration analgesia on functional outcome. The only previous study evaluating this effect found no difference in functional outcome between placebo and drug infiltration groups at 3 months postoperatively measured with TUG test, OKS, or EQ5D (Essving et al. 2010a). Another review reported the poor documentation of the long-term effects of LIA on knee function and quality of life (Ganapathy et al. 2011).

2 Review of the Literature

2.1 Concept of knee arhtroplasty

2.1.1 The history of knee arthroplasty

The first modern type of total knee arthroplasty (TKA) involved replacing the knee joint with ivory components attached to the bone using a cement made from copper amalgam, plaster of Paris, and stone putty. This technique was introduced by the German surgeon Themistocles Gluck in 1890 (Figure 1). He was also the first to introduce the term arthroplasty in 1902. Unfortunately, his technique was unsuccessful in most cases, and septic infections were a major problem (Brand et al. 2011).

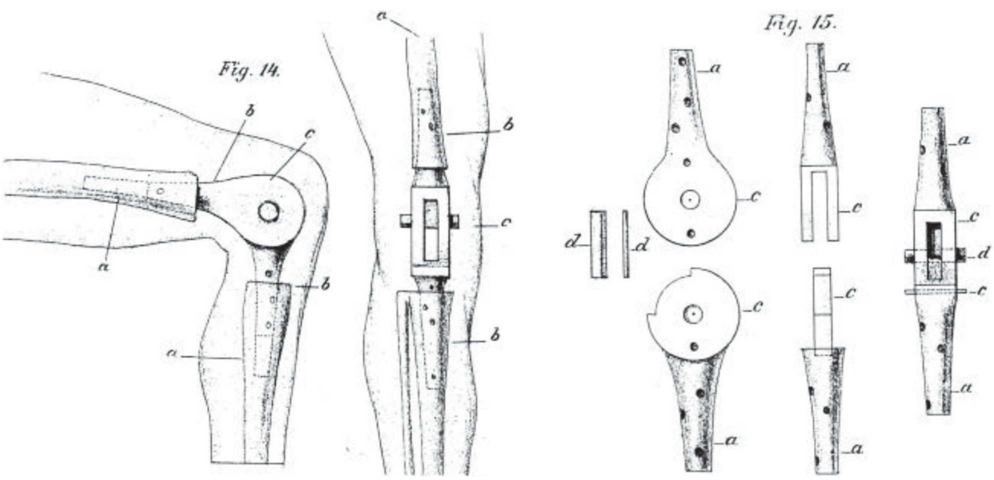


Figure 1. Gluck's knee prosthesis
(Reprinted from Gluck T. *Arch klin chir.* 1891; 41:187–239.)

In 1951, the Walldius hinge joint was introduced. Originally made from acrylic, in 1958, it began to be made from cobalt and chrome. Walldius published a comparison of hinge knee prostheses and resection arthroplasties in 1957. The results of his work led to a new era in knee replacements. Before his study, a limited range of motion was the only acceptable indication for an artificial joint. Moreover, this was the first study to introduce pain as an indication for joint replacement. The modern era of total knee replacement began with Gunston who followed the example of the work of Charnley. In 1968, he designed a surface replacing unicondylar prosthesis with a metal component articulating against a polyethylene component. Both components were attached to the bone using bone cement made from polymethyl-methacrylate (PMMA) (Figure 2) (Gunston. 1971). In his design, he concentrated on the kinematics of the knee, but the lack of an appropriate fixation method resulted in early failures. However, the design of the unicondylar prosthesis was suitable for either the medial or the lateral compartment of the knee or both.

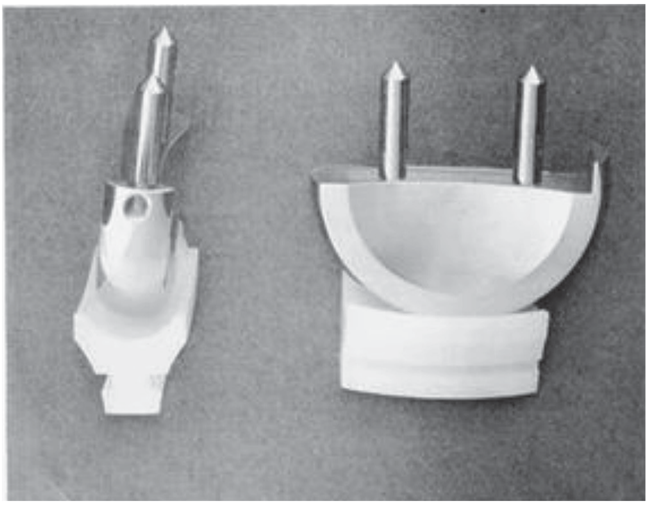


Figure 2. Gunston unicondylar prosthesis
(Gunston, Frank H.: Polycentric knee arthoplasty: Prosthetic simulation of normal knee movement J. Bone Jt. Surg., 53 B. London, Messers E. & Livingstone, 1971)

Freeman and Swanson (1972) designed a bi-condylar total knee prosthesis of the condylar type and inserted the first one in 1970. Modifications of this design are still in use today (Swanson and Freeman. 1974, Robertsson et al. 2000). They noticed that many of the knees with OA had a significant angular deformity. Therefore, they concluded that mechanical alignment could be achieved by sacrificing the cruciate ligaments, and thus the implants were placed in mechanical alignment. The first design lacked the anterior flange.

In 1973, Freeman and Swanson produced the next generation of their implant named ICLH (Imperial College London Hospital) and added an anterior flange to the femoral component and a patellar button to resurface the patella.

In 1971, John Insall, Chitranjan Ranawat, and Peter Walker developed the first design of a knee arthroplasty called the Duocondylar Knee. In contrast to the Freeman-Swanson implant, the Duocondylar knee was based on preserving the cruciate ligaments in order to mimic the native kinematics of the knee. The tibial component comprised two flat pads that were allowed free movements (Figure 3). This design relied on native soft tissue balance (Ranawat and Shine. 1973, Insall and Walker. 1976).

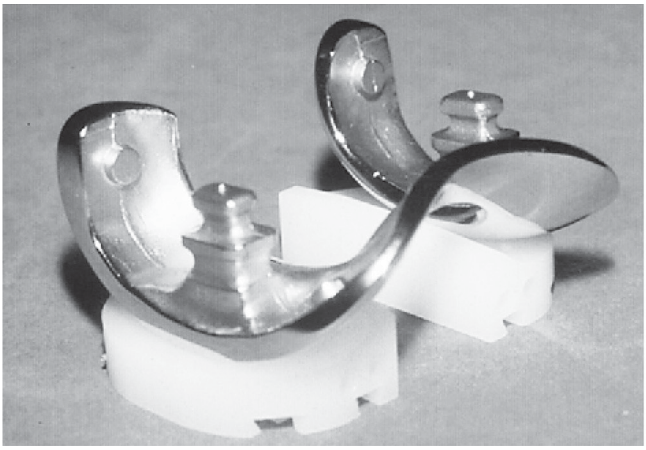


Figure 3. Duocondylar knee

In 1974, Insall et al. developed the Total Condylar prosthesis, which was the first true TKA with reliable and reproducible functional outcomes and long-term survivorship. This design was an improvement on the ICLH because it used both articular geometry and soft tissue tension to provide stability and kinematic guidance. All the components were cemented. Short-term good results were reported in 1979 (Insall et al. 1979). With the Total Condylar prosthesis, the cruciate ligaments were sacrificed (posterior-stabilized) and a monoblock type of tibial component was used. The name "Total Condylar" described the total replacement of all of the condylar bearing surfaces in the knee. This concept is still considered to be "the gold standard" of total knee arthroplasty (Figure 4).

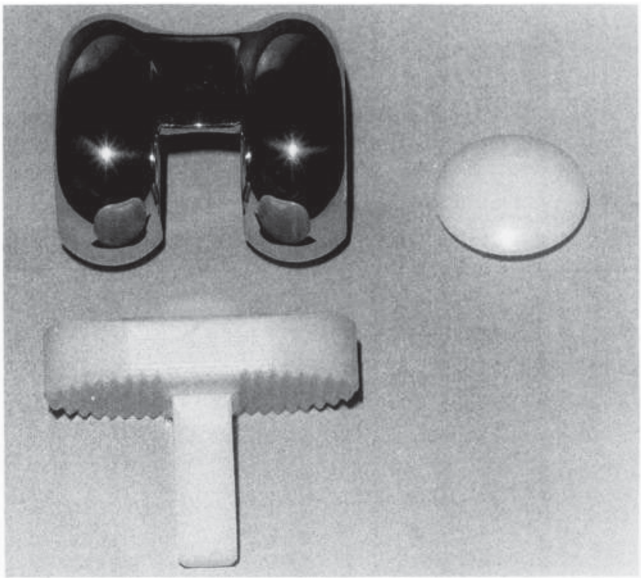


Figure 4. Total Condylar Prosthesis mark I (Vince et al. 1989)

2.1.1.1 Different concepts of TKA

Knee stability is one of the most important factors affecting the long-term durability of TKA. In most cases, ligament and soft tissue asymmetry may be corrected by soft tissue balancing techniques that allow symmetric tension in both flexion and extension, which enables the use of standard implants (cruciate retaining=CR or posterior stabilized=PS). Constrained implants (Constrained Condylar Knee=CCK) may be used if persistent laxity occurs despite the soft tissue balancing. Constrained implants improve stability and are useful in the treatment of severe malalignment and laxity. In the case of absent ligament support, a rotating-type hinge TKA may also be needed to restore stabilization of the knee (Sculco. 2006). Examples of the different constrained implant designs are shown in figure 5. The routinely used implants are made of titanium or cobalt-chromium based alloys where former is used in the tibial side and latter in the tibial or femoral side. There are also implants available which are made of ceramics or ceramic coated metals and these may be utilized in the patients with known hypersensitivity with metals, e.g. nickel (Heyse et al. 2012). The plastic parts are made of ultra high molecular weight polyethylene which are processed to reduce free radicals to lenghthen the durability of polyethylene. These prosecces include irradiation, melting, annealing and incorporating of vitamin E as anti-oxidant (Chakravarty et al. 2015, Lambert et al. 2019).

Figure 5. Examples of different constrained implants: CR (far left), PS (left middle), CCK (right middle), hinge (far right)

2.1.1.2 Unicondylar arthroplasty

The work of Charnley and Gunston with the unicondylar knee prosthesis preceded the idea of using unicondylar designs. The first versions, which were models for modern unicondylar arthroplasties, were the St Georg (1969) and the Marmor (1972) implants (Figure 6). These models had polycentric metal femoral condyles and the tibial articulation was made of polyethylene that was nearly flat to avoid constraint of the articulation (Marmor. 1985, Heinert and Engelbrecht. 1988). Because of the thinness of the polyethylene component, wear was a common problem, and thus metal backed tibial implants were introduced to solve this problem (Palmer et al. 1998).

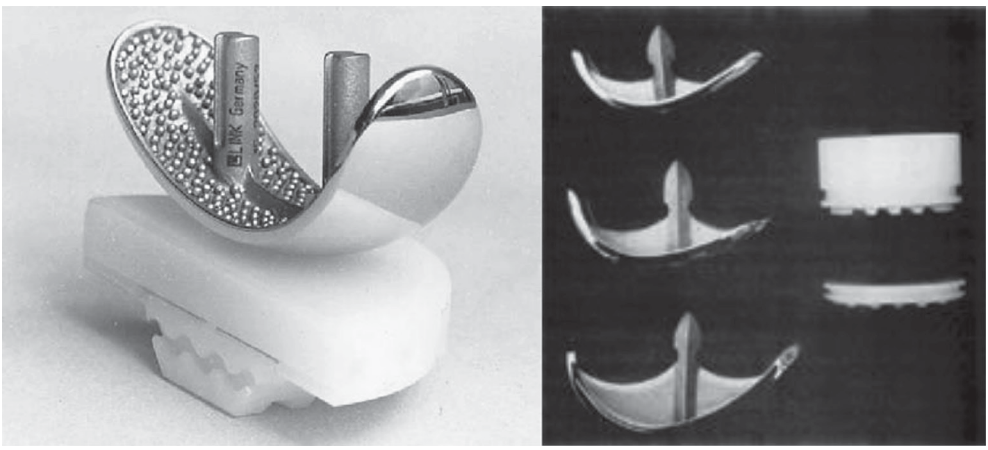


Figure 6. The St Georg (left) and Marmor (right) unicondylar prostheses

In 1974, the first Oxford unicondylar knee was introduced. It had a metal femoral component with a spherical articular surface, a metal flat tibial component, and a polyethylene mobile bearing insert. The design was fully congruent at both surfaces, and because of the mobile bearing it was fully unconstrained to allow unrestricted movement (Goodfellow et al. 1987).

In 1987, the Oxford phase 2 design was introduced that could be used both medially and laterally. This design was followed in 1998 by the Oxford phase 3 design, which introduced the minimally invasive approach (Price et al. 2001) (Figure 7).

Figure 7. The Oxford unicondylar knee prosthesis (phase 3)

2.2 Indications for knee arthroplasty

2.2.1 Osteoarthritis of the knee in general

Osteoarthritis (OA) is a whole joint disease which involves hyaline articular cartilage, subchondral bone, ligaments, capsular structures, synovium, and periarticular muscles. The disease is an active dynamic mixture of imbalanced repair and destruction of joint tissues, and not only a simple, passive wear-and-tear disease. OA is typically described as a heterogeneous disease with a wide range of underlying pathways that lead to similar joint destruction as the end-point (Hunter and Bierma-Zeinstra. 2019).

According to EULAR criteria, OA of the knee includes knee pain, no morning stiffness or stiffness <30 minutes, and functional limitation as symptoms and crepitus, restricted ROM, and bone enlargement as clinical signs.

Risk factors for OA include age, female sex, obesity, previous knee injury (Silverwood et al. 2015a), knee malalignment (Brouwer et al. 2007), and knee extensor muscle weakness (Oiestad et al. 2015). The heritable contribution to primary OA susceptibility has been established by twin and sibling studies to be about 50% (Zengini et al. 2016). Bone mineral density may also have effect on development of symptomatic knee OA (Multanen et al. 2015, Barbour et al. 2017).

2.2.2 Primary idiopathic osteoarthritis

Primary knee osteoarthritis is inflammatory process which results progressive loss of articular cartilage without any known reason, leading to wear and tear of the cartilage (Glyn-Jones et al. 2015). The main clinical indication for TKA is primary osteoarthritis, which accounts for between 94 and 97% of operations (Robertsson et al. 2010a) (NJR annual report 2018). The development of knee osteoarthritis involves a complex mixture of constitutional and mechanical factors. These factors include bone density, bone morphology, meniscal derangement, sex, sex hormones, and trauma. However, the largest risk factors for knee osteoarthritis are age, obesity and genetic components (Arden and Nevitt. 2006, Zengini et al. 2016). Both obesity and the size of the aging populations of the developed countries are increasing the burden of knee osteoarthritis (Cross et al. 2014a).

2.2.3 Secondary osteoarthritis

Secondary osteoarthritis is the result of articular cartilage degeneration due to a known reason which may also be, for example, the consequence of an abnormal concentration of force across the joint. The listed reasons for secondary OA are posttraumatic, postsurgical, congenital or malformation of the limb, malposition (varus/valgus), scoliosis, rickets, hemochromatosis, chondrocalcinosis, ochronosis, Wilson disease, acromegaly, avascular necrosis, hemophilia, Paget disease, sickle cell disease, gout, pseudogout, and infectious arthritis (Doherty et al. 1983, Altman et al. 1986, Manlapaz et al. 2019).

2.2.4 Inflammatory arthritis

Rheumatoid arthritis (RA) is the most common inflammatory arthritis. Spondyloarthropathies, which include psoriatic arthritis, reactive arthritis, and ankylosing spondylitis, are less common (Ledingham et al. 2017). Rheumatoid arthritis is a progressive inflammatory disease that multidimensionally affects the synovial joints, leading to erosion, destruction, and disability (Scott et al. 2010). The disease primarily involves the joints, but it is also a syndrome that involves extra-articular manifestations, such as rheumatoid nodules, pulmonary involvement, vasculitis, and systemic comorbidities (Smolen et al. 2016). New biological agents have been developed to decrease inflammatory processes and prevent joint destruction, i.e., the late-stage of the disease (Scott et al. 2010). RA patients with multiorgan disease involvement are often treated with multiple pharmacological drugs. They are likely to use several immune-modulatory medications, such as TNF-alpha inhibitors, glucocorticoids, and disease-modifying antirheumatic drugs (Smolen et al. 2016). RA affects the knee in about 27% of all joints (Tanaka et al. 2005).

TKA is a highly successful procedure for advanced RA destruction of the knee joint, and it both enhances functionality and increases the quality of life of patients (Lee and Choi. 2012, Goodman et al. 2016). The risk for complications after TKA, however, is increased in patients with RA because of the complex systemic nature of the disease (Jauregui et al. 2016).

2.3 Epidemiology of knee arthroplasty

2.3.1 Patient demographics

The epidemiology of knee arthroplasty can be evaluated based on incidence, prevalence, or lifetime risk of arthroplasty. The lifetime risk for TKA refers to the probability of having this surgical procedure over an individual's lifetime. Lifetime risk estimates provide a complementary approach to quantifying population-level disease burden and related use of health-care services (Ackerman et al. 2017). In 2010, the global prevalence of radiographically confirmed symptomatic knee OA was estimated to be 3.8% (95% CI 3.6% to 4.1%) (Cross et al. 2014b). At the patient level, discordance between OA symptoms and radiographic findings exists, meaning that some patients may not experience symptoms even if they are showing osteoarthritic changes in imaging tests (Glyn-Jones et al. 2015). OA of the knee contributes to most of the treatment burden resulting in the need for knee replacement surgery (Carr et al. 2012, Price et al. 2018). It is known that OA is more common in women than in men, and the prevalence of OA increases with age (Busija et al. 2010). With the aging of the population and an increase in obesity throughout the world, it is anticipated that the burden of OA will increase the number of knee arthroplasties globally (Cross et al. 2014b). Toivanen et al. analyzed possible risk factors for the prediction of the incidence of knee OA in the long-term based on the nationwide Mini-Finland Health Survey. They found that obesity, heavy work load, and prior knee injury were associated with the risk of developing knee OA (Toivanen et al. 2010).

2.3.1.1 Gender

In a study on regional variations in the USA by Katz et al., TKAs were almost twice as likely to be performed on women than on men (odds-ratio (OR) = 1.95). Furthermore, differences between races were reported. On average, TKAs were over one and a half times more likely for African American women than for African American men (OR= 1.66), whereas the difference was only 24 percent for white women versus white men (OR = 1.24) (Katz et al. 1996). In a national register-based study by Kim et al., the rate of TKA increased over the 4 years (2002–2005) of the study and was much higher in women than in men. Compared with men, the age-standardized rate ratios for TKA in women were 8.0 (95% CI: 7.4–8.6) for 2002, 7.9 (95% CI: 7.4–8.4) for 2003, 7.5 (95% CI: 7.0–7.9) for 2004, and 7.4 (95% CI: 7.0–7.8) for 2005, respectively (Kim et al. 2008b). In a register- based analysis, females consistently demonstrated the greatest lifetime risk for TKA (Ackerman et al. 2017). The prevalence of knee OA was higher in females (mean 4.8%; 95% UI 4.4% to 5.2%) than in males (mean 2.8%; 95% UI 2.6% to 3.1%). Moreover, there was no evidence of a change in age-standardized prevalence between 1990 (mean 3.8%; 95% UI 3.6% to 4.0%) and 2010 (mean 3.8%; 95% UI 3.6% to 4.1%) for either males or females (Cross et al. 2014b). In a study based on the General Practice Research Database in the UK, the female-to-male ratio for the estimated incidence rates remained stable at between 1.18:1 and 1.42:1 for knees between 1995 and 2006 (Culliford et al. 2010b). In the same study, the estimated age-standardized primary TKA rates increased in the UK from 42.5 (95% CI 37.0 to 48.0) to 138.7 (95% CI 132.3 to 145.0) for women and from 28.7 (95% CI 23.9 to 33.6) to 99.4 (95% CI 93.9 to 104.8) for men between 1991 and 2006.

2.3.1.2 Age

The increasing incidence of OA with age is the result of cumulative exposure to various risk factors and biological age-related changes in the joint structures (Hunter and Bierma-Zeinstra. 2019). In an older nation-wide study by Katz et al., TKAs were reported to be consistently more likely to be performed on individuals aged between 70 and 84 years than younger patients between 1985 and 1990 (Katz et al. 1996). In a study from South Korea during the study period 2002 to 2005, the rate of TKA increased with age and reached a peak over the age of 65 to 70 years for women and 70 to 75 years for men, after which it levelled off (Kim et al. 2008b). In a study from British data the mean age at operation for TKA was 70.1 years (95% CI 69.6 to 70.5) for women and 69.2 years (95% CI 68.6 to 69.7) for men in 2006 (Culliford et al. 2010b). In a Swedish study based on SKAR data, the number of TKAs in patients younger than 55 year of age started to increase in 2000. This increase continued so that in 2007 the number had become 5 times that at the beginning of the study period in 1998 (W-Dahl et al. 2010a). In a study comparing epidemiology of 3 different Nordic countries, there was an increase in the proportion of younger patients (between 55 and 64 years of age) in all countries, particularly in Denmark (Robertsson et al. 2010a).

2.3.1.3 BMI

In a study from the UK that analyzed future projections of the numbers of TKAs, obesity was assumed to increase TKA count 9% by 2035 compared with patients with normal BMI. The same effect was not, however, shown with total hip arthroplasty (THA) (Culliford et al. 2015). Kremers et al. analyzed 6 475 primary TKAs with study end points as length of stay in hospital and direct medical costs. The mean age of patients was 68 years. The proportion of obese patients (BMI>30 kg/m^2) increased between 2000 and 2008 from 49% to 59% in primary TKAs. Length of stay and costs were lowest for normal BMI or slightly overweight patients and highest for patients at the extreme ends of the BMI spectrum. They calculated that beyond 30 kg/m^2, every 5-unit increase in BMI was associated with higher hospitalization costs of approximately $250 to $300 for patients undergoing primary TKA (Kremers et al. 2014). A case-control study from the USA reported a strong association between increasing BMI and amount of replacement surgery in both primary THAs and TKAs. In males, the highest risk was associated with a BMI of 37.50–39.99, whereas in females the highest risk was reported when BMI was >40. An association between obesity and risk for revision of TKA or THA was not found in this analysis (Wendelboe et al. 2003).

2.3.1.4 Indications

In a register-based study from Sweden, Norway, and Denmark, primary OA was the cause of surgery in 88% of all cases and RA in 5% of all cases between 1997 and 2007. The relative proportion of surgeries for RA decreased during the study period in all 3 countries (Robertsson et al. 2010a). In a Finnish study, the unadjusted occurrence of primary TKA increased from 17 to 187 / 100 000 persons in non-rheumatoid arthritis women and from 6 to 76 / 100 000 persons in men between 1986 and 2003. In 2003, the age-adjusted incidence rate ratios (95% CI) were 1.2 (0.6 to 2.3) for TKA in female patients and 0.7 (0.2 to 3.6) in male patients with RA. In patients with non-rheumatoid arthritis, the age-adjusted incidence rate ratios (95% CI) were 9.8 (6 to 15.8) for TKA in female and 9.8 (4.3 to 22.5) in male patients. Patients with rheumatoid arthritis were a few years younger than patients with other diagnoses, 67 vs 71 years (Sokka et al. 2007). In this study, the occurrence of TKA in patients with rheumatoid arthritis did not increase. This was possibly due to the improved treatment of rheumatoid arthritis, which is in line with other reports (Robertsson et al. 2010a, Price et al. 2018). The same effect was reported in a study of patients with rheumatoid arthritis in California, where the relative risk for total knee arthroplasty was 9% higher between 1993 and 1997 than between 1983 and 1987, but was significantly lower by 8% between 1998 and 2002 (Louie and Ward. 2010). Indications for knee arthroplasty according to the New Zealand Joint Registry (NZJR) and the National Joint Registry for England and Wales (NJR) are listed in Table 1.

Table 1. Indications for knee arthroplasty in the NZJR and the NJR annual reports 2017

Indication	NZJR	NJR
Osteoarthritis	94.7%	96.1%
Rheumatoid arthritis	2.3%	2.1%
Post fracture	1.0%	0.1%
Other inflammatory	0.8%	-
Post ligament disruption	0.8%	0.6%
Avascular necrosis	0.4%	0.4%
Tumor	0.1%	-

2.3.1.5 Prevalence

The prevalence of total knee replacement is the proportion of individuals who are alive on a certain date and who have undergone a total knee replacement, regardless of the timing of the initial procedure. Kremers et al. reported prevalence in the USA estimated from data between 1969 and 2010. They estimated that the prevalence of TKAs among the total US population was 1.52% in 2010. The prevalence of total knee replacement at 50 years of age was 0.68%, and increased to 2.92% at 60 years, 7.29% at 70 years, 10.38% at 80 years, and 8.48% at 90 years of age. Prevalence was higher among women than among men (Maradit Kremers et al. 2015).

2.3.1.6 Incidence

In an Australian study, the incidence of primary TKA in 1994 was $56.4/10^5$ and it increased to $76.8/10^5$ in 1998 (Wells et al. 2002). In a study of the US population, information on 443 008 patients who underwent TKA between 1990 and 2000 was analyzed based on the Nationwide Inpatient Sample databases. They found that even if the majority of TKAs were performed on patients over 70 years of age, the proportion of younger patients undergoing TKA also significantly increased during the study period. The rates of TKA increased from $40.4/10^4$ persons to $54.7/10^4$ persons between 1990 and 2000 for patients over 70 years of age. They also reported a difference in the rates of TKA between white and ethnic minority patients. White patients comprised the vast majority of those receiving TKAs throughout the 1990s, with black patients making up the next largest group, followed by Hispanics. White patients comprised 93% of TKA recipients in the early 1990s, but this proportion decreased to 87.5% by the end of study period (Jain et al. 2005). In a Swedish study, information on all knee arthroplasties performed in Sweden from 1975 to 2013 was analyzed based on SKAR data. In the study, the magnitude of the growth rate changed in 1988. Before 1988, the incidence increased by 2.8 (CI 1.1–4.7) per year, and thereafter the increase in incidence was higher and amounted to 9.1 (CI 8.4–9.7) per year (Nemes et al. 2015b). Also in Finland incidences have increased both in females and males. Based on FAR, incidences in Finland are shown in Figure 8.

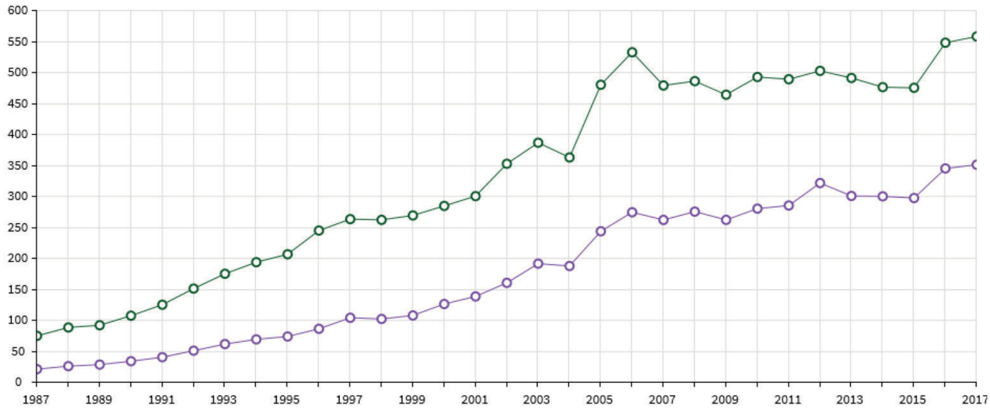


Figure 8. Annual incidences of knee arthroplasty in Finland from 1987 (FAR report). Incidences are shown as operations 10^5/ person year. Green line for females and purple line for males

2.3.1.6.1 Future trends

A study of predictions of future trends estimated the future incidence rate and volume of primary TKA in the United States from 2015 to 2050 using both a conservative projection model and a model assuming exponential growth. This study reported a 143% projected increase in TKA volume using the conservative model and an 855% projected increase using the Poisson model (Inacio et al. 2017). Another future projection study from the United States based on Nationwide Inpatient Sample and United States Census Bureau data from the period 1990 to 2003 estimated future trends until 2030. They concluded that if the number of TKAs performed continues at the same rate as during the data period, the demand for primary TKA is projected to grow by 673%, from 450 000 (CI 425 000–477 000) in 2005 to 3.48 million procedures (CI 2.95×10^6–4.14×10^6) by 2030 (Kurtz et al. 2007). Another study, based on the UK Clinical Practice Research Datalink (CPRD) between 1991 and 2010, projected future numbers of TKAs in 2035 using two models: static and exponential. In the static model the number of TKAs increased from 85 019 (2015) to 118 666 (2035). By comparison, an exponential extrapolation of historical rates using a log-linear model produced much higher estimates of TKA counts in 2035 at 1 219 362 (Culliford et al. 2015). However, a study by Singh et al. showed that the method of analysis may be reflected in the results. They used polynomial regression with a Poisson distribution in their analysis, and they reported 10 to 30% higher TKA estimates in 2030 than Kurtz et al. (Singh et al. 2019).

2.3.1.7 Regional variations

Katz el al. described variations in the numbers of TKAs in patients older than 65 years from 1985 to 1990. They analyzed data from hospitals in the United States that performed TKA on the Medicare system. The increase in TKA rates differed among different regions. For example, the regions of New York and Atlanta had the largest increases while the Seattle region had the smallest relative increase. They reported an 18.45% total annual rate of increase. Even after adjusting for demographic factors, significant regional variation remained and much of this variation remained unexplained (Katz et al. 1996). In a study from Australia, large regional variations between states were reported between 1994 and 1998, with an incidence of $4.8/10^5$ in the Northern Territory and $104.5/10^5$ in South Australia. This variation was explained by the Northern Territory having fewer orthopaedic surgeons and a younger population (Wells et al. 2002).

A study by Pabinger at al. analyzed economic and medical data on knee arthroplasty performed in OECD countries from 1990 to 2011. The analysis was based on the OECD Health Data 2013 database relating to knee arthroplasty for 28 countries. In addition, they divided the results into groups of patients aged 65 years or over and 64 years or younger. The mean compound annual growth rate for knee arthroplasty from 2005 to 2011 was 5.5% (range 1.2–26.7) for the total population. They observed a 10-fold variation in knee arthroplasty utilization between the different OECD countries. Patients aged 64 years or younger showed a considerably higher annual growth rate of 7.1% (range 4.4–27) than those patients aged 65 years or older who had a rate of 4.4% (range 0.3–26.2). This growth rate led to an absolute increase in total implants of 38% between 2005 and 2011. The highest growth rate, 63%, was found in patients aged 64 years or less compared with a growth rate of 29% in patients aged 65 years or older. These variations were explained by differences in economic power and medical conditions. Obesity in earlier years (1991–2006) correlated very strongly with the need for knee arthroplasty 5 to 20 years later. Moreover, obesity was underlined as a major cause for late knee OA (Pabinger et al. 2015).

2.4 Evaluation of outcomes of knee arthroplasty

2.4.1 Clinical evaluation

Pain and stiffness of the knee are the main clinical symptoms in patients with knee OA, and knee arthroplasty should effectively alleviate these symptoms. Range of motion (ROM) and stability of the joint are basic evaluation methods both pre- and postoperatively. Moreover, there are a vast variety of performance-based tests to assess knee function, and one of the most commonly used is the Timed Up and GO, (TUG), test (Podsiadlo and Richardson. 1991). In the TUG test, the patient stands up from a chair, walks 3 meters, turns around, walks back to the chair and sits down. The time taken is measured and the result is evaluated using reference times.

In a review, 26 performance-based methods used for the evaluation of knee and/or hip OA pre- and postoperatively were evaluated and multi-activity tests were found to be more valid than single-activity tests. However, the review could not make any conclusions as to which tests might be the most useful because no consensus on what activities and functional parameters should be included exists (Terwee et al. 2006). Kennedy et al. compared the reliability and sensitivity of the six-minute walk test (6MWT), timed up and go test (TUG), stair measure (ST), and a fast self-paced walk test (SPWT), and all measurements were found to be responsive to detecting improvements in the early postoperative period (Kennedy et al. 2005). Boonstra et al. aimed to study the most selective test between the TUG test and the sit-to-stand test, and both were reported to be selective and functionally valid (Boonstra et al. 2008).

It would be interesting if the outcome of a TKA could be predicted preoperatively with scoring system. Previous studies have shown that satisfaction after TKA may be associated with the expectations of the patient (Hepinstall et al. 2011, Styron et al. 2011, Yoo et al. 2011).

2.4.2 Surgeon-reported outcome measures

Traditional clinical rating systems report the functions of the joint, i.e., the range of motion or stability assessed by the clinician. One of these tools that is still widely used in evaluating the outcome of knee arthroplasty is the Knee Society Score (KSS) (Insall et al. 1989). Because clinical measurements are not robust, criticism of the reliability of this rating system has been reported (Ryd et al. 1997). In many studies, the sensitivity of the KSS has been shown to be inadequate, and it lacks the power to distinguish differences between outcomes (Bullens et al. 2001, Harrington et al. 2009, Rahman et al. 2010, Choi et al. 2010, Becker et al. 2011).

2.4.3 Patient-reported outcome measures

Patient-reported outcome measures (PROMs) are standardized questionnaires which are completed by the patients to analyze their perception of health, level of impairment, disability, and health-related quality of life. PROMs may also allow the measurement of the efficacy of medical, i.e., surgical, intervention. PROMs can be either generic or disease specific and both types are often used for evaluation.

2.4.3.1 OKS

The Oxford Knee Score (OKS) comprises 12 items regarding pain and activities of daily living (ADL). The assessment of the reliability and validity of the OKS has been thoroughly carried out (Dawson et al. 1998, Davies. 2002, Murray et al. 2007a, Jenny and Diesinger. 2012). The minimal clinically important difference (MCID) for the OKS score is 5 points when comparing 2 different patient cohorts, 7–8 points when comparing the change in 1 patient, and 9 points when comparing the change in the same patient cohort (Murray et al. 2007a, Beard et al. 2015).

2.4.3.2 KOOS

The Knee injury and Osteoarthritis Outcome Score (KOOS) comprises 5 subscales: pain, other symptoms, activities in daily living (ADL), function in sport and recreation (Sport/Rec), and knee-related Quality of life (QOL). The MCID is suggested to be 8 to 10 (Roos and Toksvig-Larsen. 2003).

2.4.3.3 RAND 36-Item Health Survey

The RAND 36-item health survey (RAND-36) comprises 36 items that assess eight general health concepts. The Physical Component Scale (PCS) and the Mental Component Scale (MCS) are also derived from the eight RAND-36 scales (Kantz et al. 1992, Ware and Sherbourne. 1992, Ware et al. 1995). The MCID for the subscales is suggested to be 3 to 5 points (Hays and Morales. 2001).

2.4.3.4 HAAS

The High-Activity Arthroplasty Score (HAAS) was specifically developed to assess the subtle variations in functional ability after lower limb arthroplasty with particular regard to highly active individuals. The score covers the 4 domains of walking, running, stair climbing, and general activities (Talbot et al. 2010, Jenny et al. 2014). Possible scores range from 0 to 18 points. The MCID has not been defined for HAAS.

2.4.3.5 TKFQ

First described by Weiss et al. (Weiss et al. 2002a), the Total Knee Function Questionnaire (TKFQ) was developed to assess a wide spectrum of activities involving the knee. The questionnaire comprises 55 multiple-choice questions, 42 of which query the personal importance of as well as the frequency and difficulty of performing 3 types of functional activities: baseline activities, advanced activities, and 12 recreational activities and exercises (Conditt et al. 2004). The MCID has not been defined for TKFQ.

2.4.3.6 15-D

The 15D is a generic, comprehensive, 15-dimensional, self-administered instrument for measuring health-related quality of life (Sintonen. 2001). The questionnaire comprises 15 dimensions with 5 ordinal levels on each dimension. From each dimension, the respondents choose the level that best describes their present health status. A set of population-based preference and utility weights is used to generate the 15D score on a 0 (being dead) to 1 (full health) scale. Moreover, the 15D scores are generalizable and valid for deriving quality-adjusted life years (QALYs). The generic MCID for the change of 15D scores is ± 0.15 (Alanne et al. 2015).

2.4.3.7 Visual Analog Scale

The 100 mm visual analog scale (VAS) is widely used to measure pain and satisfaction intensity pre- and post-surgery. Several studies have found that a pain scale PASS value of 40 can be used as an outcome criterion for knee osteoarthritis (Tubach et al. 2012, Perrot and Bertin. 2013). It is generally accepted that a pain VAS score of 30, 70, and 100 indicates the upper boundaries of mild, moderate, and severe pain intensity. The MCID is defined as 10 points for VAS (Myles et al. 2017). Satisfaction can be also scored on a VAS (Robinson et al. 1997, Dolan and Sutton. 1997). Moreover, the VAS can also be used to evaluate pain, satisfaction, and restrictions both before and after knee arthroplasty. The VAS satisfaction scale is divided into four sections: 0 to 25 dissatisfied, 26 to 50 unsure, 51 to 75 satisfied, and 76 to 100 very satisfied (Scott et al. 2016).

2.4.4 Radiographical evaluation

The severity of knee OA is assessed from preoperative standing fixed flexion view (FFV) radiographs using the Kellgren-Lawrence (KL) (KELLGREN and LAWRENCE. 1957) classification system. The Kellgren and Lawrence grading system is used to classify the severity of OA (grade 0: no OA; grade 1: doubtful OA; grade 2: minimal OA; grade 3: moderate OA, and grade 4: severe OA). KL grade 2 requires definite osteophyte(s) and joint space narrowing. The KL grades 3 and 4 require multiple moderate osteophytes, definite joint space narrowing with deformity, and sclerosis is also present for KL grade 4. A mild preoperative radiographic grade of OA has been shown to be the reason for residual symptoms after knee arthroplasty, and therefore should be taken into account when analyzing the postoperative outcome of knee arthroplasty (Niinimaki et al. 2011, Scott et al. 2016).

Postoperative plain radiographs are used to identify radiolucency in the bone-cement interface or the implant-cement interface, and also implant subsidence. In younger patients, aseptic loosening has been reported to be the most common reason for revision when infections are excluded (Odland et al. 2011).

2.4.5 Implant survivorship

2.4.5.1 Arthroplasty registers

National registers collect information on a combination of different knee arthroplasty implants. These registers were originally designed to collect data on surgeon and implant performance and the main outcome collected was implant failure. Recently, patient-reported outcome measures have been collected by some of the registers to measure patients' subjective outcomes related to knee arthroplasty. The most commonly cited national registers are listed in the table 2.

Table 2. Common national knee arthroplasty registers

Country	Type	Year started	Abbreviation
UK	National	2003	NJR
Australia	National	1999	AOANJRR
Sweden	National	1975	SKAR
Canada	National	2003	CJRR
Holland	National	2007	LROI
New Zealand	National	1999	NZJR
Denmark	National	1997	DKR
Norway	National	1994	NAR
Finland	National	1980	FAR
USA	National	2010	AJRR

2.4.5.1.1 Nordic Arthroplasty Register Association

The Nordic Arthroplasty Register Association (NARA) was established in 2007 and the database includes all primary hip and knee replacement procedures performed in Norway, Denmark, Sweden, and Finland since 1995 for hip procedures and since 1997 for knee procedures. The overall aim of NARA is to improve the quality of research and the understanding of the clinical course of patients undergoing joint replacement surgery, and thereby to enhance the possibilities for improving the quality of the treatment associated with joint replacement surgery. The NARA database includes only variables which all countries can deliver, and 20 variables are included in the knee datasets. Based on NARA, for national registries to be successful as collaborating registers, the following key points must be met: 1. an adequate number of inhabitants in the countries, 2. a uniform health care system, 3. long traditions of nationwide registries, 4. high data quality due to regular validation processes, 5. uniform unique personal ID-systems, 6. possibility to follow up all patients registered in the National Arthroplasty register, 7. 100% unambiguous linkage of the index operation to all types of complications and outcomes, 8. possibility to link the database to all other national quality registries (NARA report 2016).

The NARA includes the following national registers: The Danish Hip Arthroplasty Register, The Danish Knee Arthroplasty Register, The Finnish Arthroplasty Register, The Norwegian Arthroplasty Register, The Swedish Hip Arthroplasty Register, and The Swedish Knee Arthroplasty Register (NARA report 2016).

2.4.5.1.2 Level of evidence

Good quality register-based studies have been commonly qualified as level II studies in the level of evidence. Originally the levels of evidence were described in a report by the Canadian Task Force on the Periodic Health Examination in 1979 (Spitzer et al 1979). The levels of evidence were further described and expanded by Sackett in an article on levels of evidence for antithrombotic agents (Sackett. 1989). Since the introduction of levels of evidence, several other organizations and journals have adopted variation of the classification system (Burns et al. 2011). The hierarchies rank studies according to the probability of bias. RCTs are typically given the highest level because they are designed to be unbiased and have less risk of systematic errors but due to low quality of RCT study it may not always to be considered as class I study and the same principle comprise with other levels of evidence (Burns et al. 2011). Examples of different modifications of level of evidence gradings are shown in the tables 3 and 4.

Table 3. Type of evidence by Sackett (Sackett. 1989)

I Large RCTs with clear cut results
II Small RCTs with unclear results
III Cohort and case-control studies
IV Historical cohort or case-control studies
V Case series, studies with no controls

Table 4. Type of evidence by the Centre for Evidence-Based Medicine

1A	Systematic review (with homogeneity) of RCTs
1B	Individual RCT (with narrow confidence intervals)
1C	All or none study
2A	Systematic review (with homogeneity) of cohort studies
2B	Individual Cohort study (including low quality RCT, e.g. <80% follow-up)
2C	“Outcomes” research; Ecological studies
3A	Systematic review (with homogeneity) of case-control studies
3B	Individual Case-control study
4	Case series (and poor quality cohort and case-control study
5	Expert opinion without explicit critical appraisal or based on physiology bench research or “first principles”

2.5 Reasons for failures in knee arthroplasty

2.5.1 Failures in registers

The most common reason for failures in the NJR and NZJR annual reports are listed in table 5. Failures may be divided into early and late failures where non-wear-related early failures are most commonly infections.

Table 5. Reasons for revisions in NJR and NZJR annual reports 2017

Reason of revision	NJR (%)	NZJR (%)
Aseptic loosening	25	30
Other indication	12	-
Patellar resurfacing	-	20
Infection	11	22
Pain	11	25
Instability	10	-
Implant wear	9	-
Lysis	7	-
Malalignment	5	-
Stiffness	4	-
Subluxation / dislocation	3	-
Periprosthetic fracture	2	-
Implant fracture	1	3

2.5.2 Age-dependence

Charette et al. retrospectively reviewed 4 259 primary TKAs performed over a 4-year period in the USA. In their analysis, they divided patients into a less than 55 years of age group and a more than 55 years of age group. The reasons for revision were different between these groups with instability being a leading cause of revision in younger patients, while infection and loosening more commonly led to failure in older patients. Younger patients were more susceptible to the early risk for reoperation and non-wear-related complications (Charette et al. 2019). Aggarwal et al. retrospectively reviewed the reasons for and the results of revision TKA performed over a ten-year time period (1999–2009) in the USA. They divided 84 patients into a less than 50 years of age group and the 60 to 70 years of age group. The most common reasons for revision in the younger and older groups were the following: aseptic loosening 27% vs 27%, infection 23% vs 30%, arthrofibrosis (stiffness) 14% vs 6%, polyethylene wear 11% vs 14%, and instability of joint 10% vs 14%, respectively (Aggarwal et al. 2014).

2.5.3 Aseptic loosening and osteolysis

Aseptic loosening may occur as the result of inadequate initial fixation, mechanical loss of fixation over time, or the biologic loss of fixation caused by particle-induced osteolysis around the implant. Biologic and mechanical factors have been associated with the early and late stages of the development of osteolysis following joint replacement (Abu-Amer et al. 2007). The initial response is a localized inflammatory response that is characterized by the formation of fibrous tissue that encapsulates the implant. Aseptic loosening is characterized by poorly vascularized connective tissue dominated by fibroblasts and macrophages which form the interface tissue between the bone and implant or cement (Gallo et al. 2002). After TKA there have been reported changes in the periprosthetic BMD which may have effect in fixation of knee arthroplasty but this relation is controversial (Levitz et al. 1995, Li and Nilsson. 2000, Saari et al. 2007).

During the 1980s, biomechanical studies indicated that a metal reinforcement of the polyethylene tibial component would result in lower implant-derived stresses to the underlying bone, and thus better fixation (Bartel et al. 1982, Reilly et al. 1982, Lewis et al. 1982). At that time, the major cause of failure was the loosening of tibial components (Moreland. 1988) and the designs of TKAs were changed to metal-backed tibial components with less conformed implants to decrease shear forces between the interfaces.

Despite the introduction of these new designs, revisions due to aseptic loosening were still reported (Knutson et al. 1994). The cement itself was assumed to cause problems due to heat injury or chemical toxicity inducing aseptic loosening (Mjoberg. 1986, Sturup et al. 1994). Uncemented designs were developed to achieve bone ingrowth (Blaha et al. 1982, Hungerford et al. 1989, Rosenberg et al. 1990). Although good survival rates were reported with uncemented implants, they were still not better than those of cemented designs (McCaskie et al. 1998, Hofmann et al. 2001). In radiostereometric analysis (RSA), no differences in migration between cemented and uncemented implants were reported (Nilsson et al. 1991, Toksvig-Larsen et al. 1998), but uncemented components showed increased tilting (Nilsson and Karrholm. 1993). Moreover, higher revision rates were reported with uncemented prostheses (Robertsson et al. 1997, Duffy et al. 1998b, Berger et al. 2001b).

Kutzner et al. reported an increased number of aseptic loosening cases with cemented LCS implants in a Norwegian study population. They assumed that one of the reasons for aseptic loosening was a too thin cement mantle between the implant and the bone (Kutzner et al. 2018). Other reasons for aseptic loosening in TKA that been reported are as follows: wear particle exposure (Le et al. 2014, Lombardi et al. 2014); implant alignment (Ritter et al. 2011, Kim et al. 2014a); cement mantle thickness (Walker et al. 1984, Vanlommel et al. 2011); resurfacing the patella (Lygre et al. 2011); and implant design (Namba et al. 2012, Gothesen et al. 2013, Namba et al. 2014).

In the SKAR annual report 2018, aseptic loosening was one of the main reasons for revision during a 10-year period. Previously, aseptic loosening has been reported as being the main reason for revision. However, in the latest annual report, it is equal with infections (SKAR annual report). In the New Zealand arthroplasty register annual report 2017, aseptic loosening was the main reason for revision in TKAs when both femoral and tibia loosening were calculated. Loosening of the tibia component was more common than loosening of the femoral component. In the NJR, aseptic loosening was the most common reason for revision, accounting for approximately 38% of all single-stage revision operations (NJR annual report 2018).

A study by Vessely et al. reported survivorship of 1 000 patients treated consecutively with the same prosthesis, component combination, and fixation at a mean 15.7 years of follow-up. The survivorship of this cemented cruciate-retaining implant was excellent, with a survivorship free of revision for any reason of 95.9% at 15 years, and a survivorship free of revision for aseptic loosening of 98.8% at 15 years (Vessely et al. 2006).

In a multicenter prospective observational cohort study with 318 patients, Mulhall et al. reported that aseptic loosening was one of the three main reasons for revision with instability and wear (Mulhall et al. 2006). In this study, the mean time from primary to revision TKA was 7.9 years.

In another study, septic loosening and polyethylene wear were the most important indications after 8 years, whereas infections occurred in the earlier phase (Koh et al. 2017).

A study concerning younger patients reported the risk for aseptic mechanical failure to be 4.7 times higher in patients less than 50 years of age compared with patients more than 65 years of age (Meehan et al. 2014).

The mobile bearing concept, which was firstly introduced in unicompartmental knee arthroplasty, could theoretically decrease the forces on the implant-bone interface and improve fixation (Buechel and Pappas. 1986, Goodfellow and O'Connor. 1986). These designs have reported reasonable survival rates (Buechel. 2004, Callaghan et al. 2005, Tarkin et al. 2005), but an increased risk for aseptic loosening compared with fixed bearing TKAs have also been reported (Gothesen et al. 2017, Kutzner et al. 2018).

The coating of implants may also decrease the risk for aseptic loosening. Hydroxyapatite-coated components have shown less migration and better or equal fixation with the bone compared with cemented implants (Onsten et al. 1998, Nelissen et al. 1998, Regner et al. 2000, Toksvig-Larsen et al. 2000). In a prospective study of 1 000 TKAs, Cross at al. reported a 10-year cumulative survival rate of 99.14% (CI 92.5–99.8) (Cross and Parish. 2005).

In another prospective study of 118 hydroxyapatite-coated and uncemented TKAs in patients less than 55 years of age, there were two revisions of the tibial components because of aseptic loosening. At 12 years, the overall rate of implant survival was 97.5% (Tai and Cross. 2006a).

Voigt et al. concluded that in patients less than 65 years of age, an HA-coated tibial implant may provide better durability than other forms of tibial fixation (Voigt and Mosier. 2011a).

2.5.4 Infections

The incidence of periprosthetic joint infection (PJI) is between 1% and 4% (Peersman et al. 2001, Phillips et al. 2006). The risk factors for developing PJI following total joint arthroplasty include male gender, higher age, higher BMI, and the presence of comorbidities, especially cardiac conditions (Zmistowski et al. 2013).

A study by Vessely et al. reported that more than 1/3 of implant failures are related to deep infections. In this series, the total rate of deep infection was 1.8% (Vessely et al. 2006).

Another study reported that the annual incidence of PJI was highest during the first 4 years after primary TKA. In this study, the cumulative incidence of PJI was 0.8% at 1 year, 1% at 2 years, 1.5% at 5 years, and 2% at 15 years after the index operation (Koh et al. 2017).

O'Toole et al. predicted that because diabetes and obesity will affect approximately 50% of the increasing total population of TKA patients, this will potentially have great financial implications given the increased rate of PJI within this patient population (O'Toole et al. 2016).

Younger age is also associated with higher infection rate in the early stages after primary TKA. In a risk-adjusted model reported by Meehan et al, the risk for PJI was 1.8 times higher in patients younger than 50 years of age compared with patients 65 years of age or older (Meehan et al. 2014).

In the NZJR annual report 2017, infections were the reason for revision in about 25% of cases, and this level has remained stable during the last 10 years of surveillance (NZJR annual report 2017).

In the SKAR annual report 2018, infections were the reason for revision in about 30% of all revisions in TKAs and less than 5% in UKAs, if the indication for knee arthroplasty was OA (SKAR annual report 2018).

In the NJR, infections accounted for 6% of one-stage revisions and 84% of two-stage revisions (NJR annual report 2018).

In the AOANJRR, infection is the most common reason for revision with TKAs during the first 5 years following surgery. After that, loosening becomes more common (AOANJRR annual report 2018).

2.5.5 Pain

Chronic post-surgical pain (CPSP) is defined as moderate to severe pain that continues for at least three months post-operatively (Treede et al. 2019). Many studies have reported that 15% to 20% of patients are not satisfied after knee arthroplasty, and pain is the main cause of this dissatisfaction (Parvizi et al. 2014, Lavand'homme and Thienpont. 2015, Scott et al. 2016, Goh et al. 2016a).

Intrinsic causes of pain include pathology within the knee joint: infection, implant failure, implant loosening, instability, subluxation/dislocation, arthrofibrosis, impingement, or disorders of the extensor mechanism. Extrinsic causes of pain after knee arthroplasty include pathology derived outside of the knee: hip disease, spine pathology, vascular insufficiency, tendinitis, or bursitis (Dennis. 2004a, Flierl et al. 2019).

Other reasons for CPSP can be absence of end-stage arthritis preoperatively, compression damage caused by a tourniquet during surgery, synovitis, recurring hemarthrosis, and fibromyalgia (Worland et al. 1997, Saksena et al. 2010, D'Apuzzo et al. 2012). Heterotopic ossification may cause pain and loss of motion after TKA (Roth et al. 2014). Moreover, preoperative financial worker's compensation or psychiatric diagnoses may decrease satisfaction after TKA (Saleh et al. 2004a). In the NZJR annual report, pain is reported to be the reason for revision in 25 to 30% of cases during a 10-year period (NZJR annual report 2017). In the NJR, pain accounted for almost 17% of revision cases (NJR annual report 2018). In a study from New Zealand, the cumulative incidence for secondary patella resurfacing performed due to anterior knee pain was highest during the first 5 years after primary TKA (0.5%) (Koh et al. 2017). Patients with CPSP often continue the use of pain drugs even if the amounts of these are reduced compared to the period before TKA. Worryingly there have been papers reporting also continuous use of opiates even after 2 years postoperatively (Goesling et al. 2016, Rajamaki et al. 2019).

2.5.5.1 Mental health aspects

Depression is known to be a predictor of inferior outcomes in TKA in older patients (Faller et al. 2003, Brander et al. 2007, Lingard and Riddle. 2007). Klit et al. reported that patients with preoperative depression achieved less improvement and had statistically significant lower OKS, SF-36 PCS, and SF-36 MCS scores at 12-month follow-up compared with non-depressed patients (Klit et al. 2014).

Patients with preoperative neuropathic pain, long-term systematic opiate consumption and / or central sensitization might benefit from specific pre- or peri-operative management with antihyperalgesic drugs (Lavand'homme and Thienpont. 2015).

Catastrophizing is a negative cognitive and affective response to pain. It is multidimensional, comprising elements of rumination, magnification, and helplessness (Burns et al. 2015). Typically, catastrophizing remains constant after the operation and is not affected by changes in the severity of pain. Depression may be one reflection of catastrophizing. A systematic review could not conclude which risk factors among those psychological processes, such as catastrophizing, anxiety, and depression, contribute to chronic pain after TKA (Burns et al. 2015). Catastrophizing can be a significant predictor of pain felt at night after TKA, because catastrophizing is associated with insomnia, which, in turn, may contribute to a generalized state of hyperalgesia (Edwards et al. 2009).

2.5.6 Instability

In the NJR, instability accounted for almost 18% of revisions (NJR annual report 2018). In the SKAR, instability as a reason for revision accounted for 15% of revisions with TKAs but for less than 10% with UKAs.

Instability is often associated with malalignment of either the femoral or tibial component or a combination of these (Berger et al. 1998, Nicoll and Rowley. 2010). Preoperative evaluation of the rotation of components using computed tomography (CT) has improved the accuracy of indication for revision, but a real connection between component rotations and clinical outcome may still be controversial (Babazadeh et al. 2019).

Song et al. divided the reasons for TKA instability into six groups: flexion/extension gap mismatch, implant malposition, isolated ligament insufficiency, extensor mechanism insufficiency, implant loosening, and global instability (Song et al. 2014).

Sometimes, patients present a painful TKA even if radiographs, CT scans, and other diagnostic methods appear normal. In these patients, the possibility of soft tissue imbalance has to be identified with clinical methods, but periodic repeated evaluations are recommended until the etiology of pain is determined (Dennis. 2004b).

2.5.7 Other reasons

Today, the causes of pain after TKA can be better determined using evolved diagnostic methods than before, and it is assumed that fewer revisions are being performed due to unexplained or unspecified reasons. Pietrzak et al. reported the reason for revision to be an unknown reason in 0.4% of their French study population of 255 patients (Pietrzak et al. 2019).

Among arthroplasty registers, the SKAR and NJR report the unspecified reason as a reason for revision, and the difficulty in defining the exact reason for revision in real life may be the variation between registers. In the SKAR, for example, unspecified reason included about 5% of all revisions (SKAR annual report 2018), whereas unspecified reasons accounted for 21% in the NJR (NJR annual report 2018).

2.5.8 Unicondylar Knee Arthroplasty

With unicondylar knee arthroplasty (UKA), the progression of the OA disease is the specific reason for revision, and it accounted for 32% of revisions with UKAs in the AOANJRR annual report 2018 and for approximately 40% in the SKAR annual report 2018.

UKA may be performed on patients with isolated cartilage damage on the medial side of the knee, and who have no damage in the lateral and patellofemoral joints, which includes the risk for operating early arthritis of the knee. Knee arthroplasty, both UKA or TKA, has been reported to be an unreliable treatment method in early knee OA. Furthermore, patients tend to have poorer results than in end-stage arthritis and an increased risk for conversion to TKA (Murray et al. 2015).

A retrospective review reported the reasons for the revision of 559 Oxford medial UKAs performed between 2007 and 2013. The study included 19 revisions. Disease progression was the most common reason for revision (52.63%). Other reasons for revision included tibial component loosening (21.05%), oversized tibial component (10.52%), unexplained pain (10.52%), and femoral component loosening (5.26%) (Borrego Paredes et al. 2017).

A study from a USA population compared the MarketScan Commercial and Medicare Supplemental Databases to evaluate the risk for complications, hospital re-admission for any reason, and mortality within 90 days of surgery between UKA and TKA patients operated on from 2002 to 2012. They also divided the study populations as younger (<65 years) and older (>65 years) patients to analyze the effect of age on the results. At 7 years, the risk for subsequent revision was significantly higher (34%) for UKA than for TKA in the younger population. This study concluded that patients who undergo UKA have fewer post-operative complications but have a higher rate of re-operation and revision at up to 10 years of follow-up compared with patients who undergo TKA. In addition, patient age as well as surgeon and hospital volume were found to be significant factors effecting UKA survivorship (Hansen et al. 2019).

A study from the Finnish population compared short-term results with cemented and uncemented Oxford UKAs. In this study, the most common reason for revision was the unspecified reason registered in the FAR, which may reflect the difficulty in diagnostics in pre-revision evaluation. The reasons identified were insert dislocation, aseptic loosening of the tibia component, malposition, or pain only (Knifsund et al. 2019).

2.6 Survivorship of different fixation concepts in knee arthroplasty in patients less than 65 years of age

2.6.1 Differences in survivorship of knee arthroplasty in different ages

In the registers, there is a strong association between age and survival of knee arthroplasty, an association that is reflected by the increasing risk for revision in younger primary OA patients. The risk for revision within different age-groups reported in the NZJR and AOANJRR annual reports are presented in figure 9.

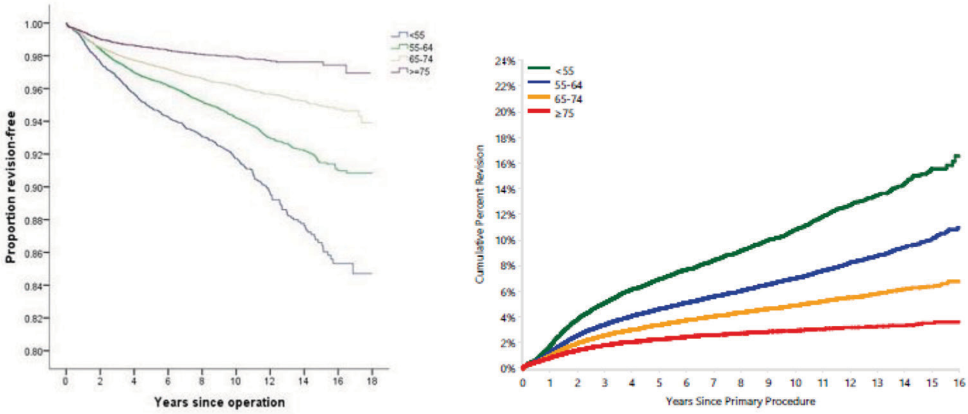


Figure 9. Age-dependent risk for revision in knee arthroplasty the NZJR (left) and the AOANJRR (right) annual reports 2017, OA primary diagnosis)

2.6.2 Cemented TKA

In a study cohort of 84 patients (108 knees) between 1977 and 1992, experiences with TKAs performed on patients who were less than 55 years of age (22–55) were reviewed. All but one of the TKAs were posterior stabilized designs. In total, 20 patients were operated with bilateral TKA. In this study, the average annual rate of failure was 0.3% and the over-all rate of survival of the prostheses was 94% at 18 years when revision of the femoral or tibial component alone was considered as a failure. The rate of survival was 90% at 18 years when 3 isolated patellar revisions were included as failures. The rate of survival at 18 years was 87% when any operative intervention that altered the knee component was included. Late infection developed in 2 patients, 1 patient was revised because of wear, and 3 patients had posterior dislocation of the tibial component. The average Hospitalized for Special Surgery (HSS) knee score for the 103 unrevised knees was 55 points (22–80) preoperatively and 92 points (75-100 points) postoperatively. Of the 103 knees, 9% had tibial radiolucent lines of no more than two millimeters in width that were present immediately postoperatively but did not progress during the study period (Diduch et al. 1997a).

A study by Duffy et al. included 52 cemented TKAs which were performed using the Press-Fit Condylar knee system that included both components cemented, patella resurfaced, and modular tibia implant. Patients were aged 55 years or younger and they were operated from1988 to 1994. The patients were followed for a minimum of 10 years with an average follow-up of 12 years (10–15). There were 8 total revisions (15%). These included 1 early revision due to sepsis at 1 year and 1 revision for instability at 8 years. Six revisions occurred between 10 and 15 years, and they were all associated with polyethylene wear combined with osteolysis. Implant survival rate was estimated to be 96% at 10 years and 85% at 15 years follow-up. The knee score improved from an average of 36 points preoperatively to 92 points, and the function score improved from 40 to 86 points. At an average of 8 years of radiographic follow-up (range, 2–15 years), there were 2 knees with radiographic evidence of loosening (Duffy et al. 2007a).

A study with non-modular tibial components was done by Ranawat et al. They reported results on 430 Press Fit Condylar (PFC) TKAs with an all-polyethylene, posterior-stabilized cemented tibial component between 1992 and 2000. Average age was 57 years, and 13 TKAs were bilateral. With the exception of 1 posttraumatic failure, they did not find any radiographic evidence of component loosening, progressive radiolucent lines, osteolysis, or severe malalignment. In this study cohort, the overall failure rate was 1.8% with average follow-up of 5 years. KS clinical scores improved from an average of 43 to 95 (72–100) and KS functional scores from 53 to 98 (90–100) (Ranawat et al. 2005a).

In a study by Lonner et al., the reported results of 32 TKAs performed for osteoarthritis on 32 patients who were 40 years of age or younger were reviewed. At a mean follow-up of 7.9 years, KSS increased from an average of 47 to 88 points and the function scores increased from 45 to 70 points. Three revisions were performed for aseptic failures causing an aseptic failure rate of 12.5% at 8 years (Lonner et al. 2000b).

2.6.3 Uncemented TKA

In their register-based study, Gioe et al. prospectively followed 1 047 patients 55 years old or younger who underwent knee arthroplasty over a 14-year period. The mean age of the patients in this study was 49.8 years (range, 28–55 years) and the majority of the patients were female (62.8%). The preoperative diagnosis was OA in 93.3% of cases. The main designs of the implants (85%) were: DePuySynthes/Johnson&Johnson 47%, Stryker/Osteonics 23.4%, and Wright Medical 14.1%. Compared with patients with cemented implants, patients with uncemented implants were 2.7 times more likely to be revised. The 14-year cumulative survival rate for uncemented implants was 65.9% (47.9–83.9%) compared to a survival rate for cemented implants of 84.5% (75.3–93.7%) (Gioe et al. 2007b).

Kim et al. compared the results of cemented vs uncemented TKAs in the same patient. They performed 170 bilateral, sequential, simultaneous TKAs in 85 patients aged 55 years or less between 1995 and 1996. In total, 80 patients (160 knees) were available for clinical and radiographic evaluation at a mean of 16.6 (16–17) years follow-up. Patients were randomized into cemented or uncemented groups, and all patients were operated with Nexgen CR implants. No patient in either group had undergone previous knee surgery. Complication rates were low and similar in both groups. Pre- and postoperative KSS, ROM, WOMAC, and UCLA activity scores did not differ significantly between groups. Kaplan–Meier survivorship analysis revealed a femoral component survival rate of 100% (95%CI 0.93–1.0) in both groups at 17 years, with loosening or revision considered as the end point for failure. The tibial component survival rate was 100% (95% CI 0.93–1.0) in the cemented group and 98.7% (95% CI 0.92–1.0) in the uncemented group at 17 years, with loosening or revision considered as the end point for failure. (Kim et al. 2014b.)

A total of 93 patients with OA aged 55 or younger were randomized to compare outcomes between cemented tibial fixation (48 patients) and uncemented fixation with screw augmentation (45 patients). The femoral component was uncemented in both groups. The Multigen (Lima, San Daniele, Italy) knee system was used in both groups. Clinical and radiological evaluations were made pre- and post-operatively at 3 and 6 months, 1 year, and then annually until 5 years, and biannually thereafter. There was no difference in revision rate, and the cumulative survival rate at 9 years for aseptic reasons was 93.7% (95% CI, 82–100%) in the uncemented group and 90.0% (95% CI, 80–100%) in the cemented group. At the end of the follow-up, the uncemented group had significantly better ROM (p=0.042) and WOMAC scores (p = 0.036) (Lizaur-Utrilla et al. 2014).

2.6.4 Hybrid TKA

In a Norwegian register-based study, 7 174 primary TKAs operated on between 1994 and 2000 were analyzed, and 10% of these had hybrid fixation. The mean age of all patients was 70 years but a separate analysis of the less than 60 years age group was also conducted. A Cox multiple regression model was used to evaluate the differences in survival among the prosthesis brands, their types of fixation, and whether or not the patella was resurfaced. In patients less than 60 years of age, no statistically significant differences between the cemented, hybrid, and uncemented prostheses in bi-and tricompartmental prostheses were found. The 5-year KM estimated survival was 98.5 (96.8–100) in the tricompartmental hybrid TKA and 94.0 (90.7–97.3) in the bicompartmental hybrid TKA (Furnes et al. 2002a).

Another register-based study from Norway compared 4 585 hybrid TKAs with 20 095 cemented TKAs. The analysis included 3 brands of prostheses: the LCS classic, the LCS complete, and the Profix. Overall, the hybrid group had lower risk for revision than the cemented group. There was design dependence with the results: the Profix hybrid TKa had lower risk for revision than the cemented TKA, but the LCS classic and the LCS complete did not. In the analysis, they adjusted the patients in the three age groups (<60 years, 60–70 years, and >70 years) and there was no statistically significant difference between the groups. At 11 years, the KM survivorship was 94.3% (CI: 93.9–94.7) in the cemented TKR group and 96.3% (CI: 95.3–97.3) in the hybrid TKR group (Petursson et al. 2015).

Conversely, a prospective study of 1 046 patients by Gioe et al. reported that patients with hybrid implants were 1.8 times more likely to be revised compared with cemented implants. Other factors, such as age, gender, cruciate ligament status, or index surgery year, did not influence the risk for revision. Moreover, the cumulative 14-year survival rate for the hybrid implant was 66.5% (51.2–81.8%) (Gioe et al. 2007b).

2.6.5 Inverse hybrid TKA

In a series of 2 studies, Wilson et al. reported the results of uncemented TM compared with cemented tibias. In total, 70 subjects with severe osteoarthritis were randomized to receive either the Nexgen LPS monoblock trabecular metal tibial component (37 patients), or the cemented NexGen LPS tibial component (33 patients). Femoral components were cemented in both groups. Radiostereophotogrammetric (RSA) analysis was used to calculate the changes in placement and fixation of the components. In the first 2-year report, they expressed uncertainty concerning the long-term stability of the trabecular metal tibial implant due to the high early migration in some cases (Wilson et al. 2010b).

In the second analysis, they found that the TM implants had stabilized at 5 years and migration had ended. At 5 years, there were 27 patients in the TM group and 18 in the cemented group left for analysis. The mean ages (SD) of the patients were 61(9) years in the cemented group and 60(8) years in the trabecular metal group. Based on the RSA measurements at 5 years, they concluded that TM implants appeared to achieve solid fixation despite high initial migration (Wilson et al. 2012b).

2.6.5.1 Tantalum metal

Tantalum metal (TM) is a transition metal with an open cell tantalum structure composed of repeating dodecahedrons with an appearance similar to cancellous bone. Porous tantalum implants are fabricated through a multistage process involving the pyrolysis of polyurethane foam to create a vitreous carbon scaffold followed by the chemical deposition of tantalum metal. The tantalum coating is typically composed of 99% tantalum and 1% vitreous carbon with a volume porosity of between 75 and 80% (Bobyn et al. 1999). Conventional porous coatings usually have a porosity of between 30 and 40%. The elasticity of tantalum (3 GPa) compares favorably with subchondral (2 Gpa) or cancellous bone (1.2 GPa) (Patil et al. 2009). Tantalum (Ta) has been in clinical use since before 1940. It has been used in diagnostic and implant applications, e.g., as a radiographic marker (Ta powder) (Black. 1994). When tantalum metal implants have been tested in bone or soft tissue surfaces, integration has occurred (Bobyn et al. 1999, Hacking et al. 2000, Matsuno et al. 2001).

Due to its interesting potential for osteointegration, trabecular metal has been used in tibial implants for uncemented use. In these implants, the polyethylene is attached to the metal using a direct compression molding process that infuses the polyethylene into the trabecular metal with a penetration depth of approximately 1.5 mm. It is expected that this component will produce less stress shielding of the proximal tibia compared with conventional tibial components owing to its lower stiffness. However, documentation on this mechanism is lacking in the literature (Patil et al. 2009). In theory, fixation with TM implants would be ideal for the stiff bone of younger patients, where cement penetration may be suboptimal (Figure 10).

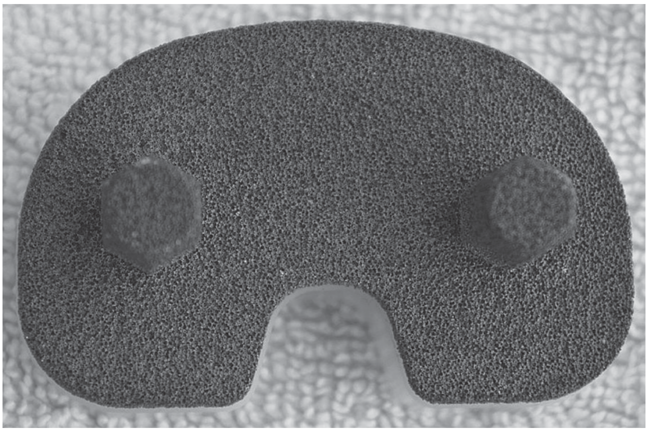


Figure 10. TM monoblock implant

2.6.5.2 Fixation of the tibial component with tantalum metal

Behery at al. compared uncemented tibias (NexGen Trabecular Metal tibial trays vs Vanguard Regenerex tibial trays) with comparable cemented tibias (Vanguard Ascent/ Maxim tibial trays vs NexGen Precoat Stemmed tibia trays) in 2 different TKA designs. Clinical outcomes measured with UCLA, EQ-5D, SF-12, KSS, and ROM were comparable between the uncemented and cemented implants. Over the 5-year follow-up period, patients with uncemented tibial implants experienced a significantly higher rate of radiographic aseptic tibial loosening than those with cemented implants (10% uncemented, 0% cemented (Behery et al. 2017)

De Martino et al. retrospectively evaluated the clinical and radiographical results of 3 primary TKAs using uncemented porous tantalum monoblock tibial components. The average age of patients was 67 years (41–82 years). All patients were followed for a minimum of 10 years (10–13), and no patients were lost to follow-up. The 10-year survivorship was 96.9% with revision for any reason as the end point and 100% with tibial component revision for aseptic loosening or osteolysis as the end point. The mean KSS scores improved from 56 points (28–71) preoperatively to 93 points (75–100) postoperatively. The mean KSS function scores improved from 54 points (10–65) preoperatively to 90 points (75–100) postoperatively (De Martino et al. 2016).

In a study from the USA, Kamath et al. compared 100 uncemented posterior stabilized tantalum metal tibias with 312 cemented posterior stabilized TKAs using the same design (NexGen). Patients were younger than 55 years with a diagnosis of osteoarthritis. All femoral components were uncemented cobalt-chromium components with a cemented all-polyethylene patellar component. The average follow-up was more than 5 years for both cohorts (60–83 months). In the uncemented group, there was no radiographic loosening greater than 1 mm in any zone or that progressed over the study period. However, 2 patients in the cemented group demonstrated evidence of radiographic aseptic loosening and clinical symptoms during follow-up. There were 3 revisions in the uncemented group and 5 revisions in the cemented group, but none of these were due to aseptic loosening (Kamath et al. 2011b).

Henricson et al. compared the subsidence of uncemented trabecular metal tibial components with that of cemented tibial components in patients younger than 60 years using RSA analysis for a 2-year period. A total of 22 patients (mean age 53 years) received an uncemented NexGen trabecular metal cruciate-retaining monobloc tibial component and 19 patients (mean age 53 years) a cemented NexGen cruciate-retaining modular tibial component. The clinical results were measured with Knee Society knee and pain scores. The improvements in the median knee score was 51 points in the trabecular metal group and 46 points in the cemented group. All the trabecular metal components migrated during the initial three months and then stabilized. The exception was external rotation, which did not stabilize until 12 months. Subsidence was stable with no lift-off from the resected tibia which had been reported in other uncemented designs (Henricson et al. 2008)

The same authors (Henricson et al.) published the following results on the same patient population at 5 years (Henricson et al. 2013b) and at 10 years (Henricson and Nilsson. 2016b). In the study with 10 years follow-up, 16 patients (19 knees) with TM tibial components and 17 patients (18 knees) with cemented tibial components remained for analysis. Excluding the initial migration over the first 3 months, the annual migration was very low in both implant groups. At 2 years, thin radiolucent lines (<1 mm) were found in 1 TM TKA and in 10 cemented TKAs on postoperative radiographs. At 10 years, no radiolucent lines could be detected in the TM TKAs and in 3 cemented TKAs. Moreover, there were no statistically significant differences in Knee Society knee score, pain score, or function score between the groups at 10 years. (Henricson and Nilsson. 2016b).

Comparable results on the early postoperative subsidence of the tibia component with the later stabilization of TM tibias has also been reported earlier in an RCT study (Dunbar et al. 2009).

Most of the studies reporting the results of TM tibial components have reported comparable and acceptable results compared with cemented components. However, a series of 106 uncemented TKAs in 93 patients reported contrary results. In this study, TKAs were performed without cement, with a PCL-substituting design, and tibial components composed of monoblock TM tibias. The mean age of the patients was 65 years (32–87). In total, 9 failures were reported at a mean 18 months (3–41 months) follow-up. All failures except one occurred in male patients with medial tibial collapse. The tibial components demonstrated a consistent radiographic failure mode characterized by medial subsidence of the tibial baseplate. They concluded that the failures were due to the tall height and weight of the male patients. Conversely, all TKAs were performed by a single surgeon, which may have affected the results (Meneghini and de Beaubien. 2013).

2.6.6 Effect of age on revision rates in young patients

In patients younger than 65 years, the risk for revision differs between fixation methods and genders. The NJR annual report 2018 reported a higher risk for revision in males in both the less than 55 years and the 55 to 64 years age groups with cemented TKA and in patients less than 55 years of age with uncemented TKAs compared with females. Males with hybrid TKAs had a lower risk for revision in both age groups (Table 6).

Table 6. Comparison of different fixation methods in knee arthroplasty in the National Joint Registry. KM estimates of cumulative revision risk (CI95%) at 10 years. Fixation method and age groups less than 55 years and 55 to 64 years in the National Joint Registry annual report 2018. Results of total knee arthroplasty include unconstrained/fixed bearings and unicondylar arthroplasty results include mobile bearings.

Fixation method	Age < 55 years	Age 55–64 years
All cemented males	8.10 (7.40–8.87)	4.53 (4.29–4.77)
All cemented females	6.67 (6.13–7.26)	3.91 (3.71–4.12)
All uncemented males	9.38 (7.10–12.34)	3.62 (2.87–4.56)
All uncemented females	7.48 (5.43–10.27)	5.28 (4.28–6.49)
All hybrid males	6.86 (4.03–11.51)	3.83 (2.51–5.81)
All hybrid females	7.54 (4.72–11.93)	4.71 (3.36–6.60)

In the NZJR 19th annual report, revision rates increased with uncemented TKA in patients less than 55 years of age and in UKA patients (Table 7). The report did not include separate revision rates for cemented and uncemented UKAs.

Table 7. Comparison of different fixation methods in knee arthroplasty in the New Zealand Joint Registry. Revision rate / 100 component-years (CI 95%) in the New Zealand Joint Registry annual report 2018.

Fixation method	Age < 55 years	Age 55–64 years
Cemented	0.90 (0.82–0.98)	0.61 (0.58–0.65)
Uncemented	1.32 (1.03–1.65)	0.78 (0.61–0.96)
Hybrid	0.97 (0.71–1.29)	0.62 (0.49–0.77)
Unicondylar	1.83 (1.57–2.12)	1.52 (1.38–1.67)

2.7 Outcome of knee arthroplasty in patients less than 65 years of age

2.7.1 Concept of working-age patients

An EU Health Program report defined the working-age population as a group of people aged between16 years and 64 years (Oortwijn W et al.)

The International Classification of Functioning (ICF) model proposed by the World Health Organization (WHO) divides working-ability into six mutually related components: 1) disease and disorder, 2) functions and structures, 3) activities pertaining to the execution of a task or action by an individual, 4) participation pertaining to the involvement in a life situation, 5) environmental factors, and 6) personal factors. These components all contain different aspects that influence participation in work.

The increasing need for knee arthroplasty in younger patients (Laskin. 2002, Kurtz et al. 2007, Leskinen et al. 2012) and the tendency for higher revision rates in these patients (Furnes et al. 2002b, Harrysson et al. 2004, Julin et al. 2010) constitutes a major challenge for the future to decide the best available concepts of knee replacement that will last the burden of time, considering the long life expectancy of patients.

2.7.2 Return to work

In a study by Jorn et al., shorter postoperative sick-leave was associated with a light workload and preoperative sick-leave shorter than 180 days. Preoperative sick-leave longer than 180 days increased the risk for partial or complete disability pension. Moreover, the operation also fulfilled the expectations of the patients to a larger degree among those patients who went back to work (Jorn et al. 1999).

In a systematic review of 5 studies, the time of return to work after TKA ranged from 8 to 12 weeks in the UK and the USA after TKA (Tilbury et al. 2014). This finding was comparable with another clinical series from the same authors, where the mean time to return to work was 12.9 weeks after TKA (Tilbury et al. 2015). The employment rate at 1 year postoperatively was 83% after TKA. An interesting finding with respect to productivity was that 19% of TKA patients worked fewer hours postoperatively than preoperatively.

In a study population from the United Kingdom, 40% of patients aged 65 years or less who were working before TKA returned to work at a mean of 13.5 weeks postoperatively. As was reported in the study by Jorn et al (Jorn et al. 1999), the better functional outcomes of TKA, assessed by PROMs, reported in this study were significantly associated with a better return to work. However, TKA did not facilitate a return to work for those patient who were not working before the operation. The greatest predictor for a better return to work was younger age (Scott et al. 2017).

2.7.2.1 Effects of socio-economical features

A prospective cohort study of 120 patients from the USA reported those factors associated with return to work. The factors associated with a faster return to work included a sense of urgency about returning, working in a handicap accessible workplace, being female, being self-employed, a higher functional comorbidity index score, a higher WOMAC physical function score, and a higher mental composite summary score on the SF-12. These results indicated that patients who had a sense of urgency about returning to work do so in half the time taken by those without a sense of urgency. Factors associated with a slower return to work included receiving workers' compensation, having a more physically demanding job, and having less pain preoperatively (and higher WOMAC pain score). The physical demands of the patient's job played a marginal role in the patients' return to work after TKA. Indeed, the study showed that properly managed and highly motivated patients are capable of returning to work in physically demanding jobs (Styron et al. 2011).

In another study by Saleh et al., receiving workers' compensation also resulted in lower functional scores compared with a control group, and only 24% of patients from the compensation group returned to their previous job (Saleh et al. 2004b).

The same effect was noticed in a study from a Canadian patient cohort. Patients who received workers' compensation had significantly higher pain scores, poorer self-perceived functional outcomes, and a lower range of knee flexion than the control group postoperatively. These patients also required more readmission visits and were more reluctant to answer questions about functional outcomes (de Beer et al. 2005).

2.7.3 Special aspects regarding knee arthroplasty in patients less than 65 years

A cross-sectional study from the Dutch population concluded that a majority of patients who were treated with TKA were overweight, had multiple comorbidities, performed a high amount of light-intensity physical activity, and a few patients were depressed. In a comparison of retired patients and the general population of the Netherlands, working-age patients scored better on preoperative characteristics than retired patients with quality of life and symptoms scores, except for physical activity level which scored worse than the general population (Hylkema et al. 2017).

Noble et al. conducted a prospective study of 253 patients with at least 1-year follow-up where they reported patients' satisfaction after unilateral TKA. According to this study, satisfaction was age dependent. For example, 96% of patients 60 years of age or younger, 81% of patients aged 60 to 75 years, and 86% of patients older than 75 years reported satisfaction after TKA (Noble et al. 2006b).

2.7.4 Previous studies of working-age patients

Several previous studies have reported the outcomes of TKA in younger patients. However, a comparison with the existing literature is difficult because of the variations in the cohorts of patients with differences in time periods and demographic features (Goh et al. 2016a). Although patient-related scores had been used in earlier studies, Morgan et al. were the first to include the OKS in the population of younger patients, and thereafter PROMs have become routinely reported in studies (Morgan et al. 2007). Those previous studies that have included a cohort of working-age patients and the outcome measurements applied in these studies are presented in Table 8.

Table 8. Previous studies reporting outcomes of working-age patients

Author	Year[a]	Study design	Age[b]	Follow-up	KSS	PROM -/+
(Stern et al. 1990)	1990	-	50	6.2	92	-
(Diduch et al. 1997b)	1997	Prospective	51 (22–55)	-	94	-
(Gill et al. 1997)	1997	Prospective	50.7 (30–55)	9.9 (5.7–18.0)	97	-
(Duffy et al. 1998c)	1998	prospective	43	13 (10–17)	84	-
(Hofmann et al. 2002a)	2002	retrospective	42 (31–50)	9.2	-	-
(Mont et al. 2002)	2002	retrospective	43 (31–50)	7.2 (5–8.9)	89	-
(Ranawat et al. 2005b)	2005	prospective	57 (47–60)	5 (2–11)	95	-
(Tai and Cross. 2006b)	2006	prospective	50.7 (32–55)	7.9 (5–12.5)	-	-
(Ritter et al. 2007a)	2007	retrospective	50 (18–55)	9.1 (4.9–20.5)	91	-
(Duffy et al. 2007a)	2007	retrospective	53 (29–55)	12 (10–15)	92	-
(Morgan et al. 2007)	2007	retrospective	50.7 (31–59)	7.3 (3–12)	98	+
(Price et al. 2010b)	2010	prospective	55.4 (32–60)	15.5 (12–19)	74.8	+
(Kim et al. 2012)	2012	prospective	45 (29–50)	16.8 (15–18)	94	-
(Klit et al. 2014)	2014	prospective	54 (49,57)	1.0		+
(Parvizi et al. 2014)	2014	prospective	54 (19–60)	2.6 (1–4.7)		-
(Goh et al. 2016a)	2016	retrospective	47 (30–50)	6.7 (3–16)	83.1	+

a The year the study was published

b Mean age (range) or median (Q1, Q3)

2.7.4.1 Special features with outcome measures

Over time, evaluation methods have shifted from surgeon-reported scores to PROMs. Traditionally, the results of knee arthroplasty have been measured with surgeon-reported measures, implant survival rates, complications, ROM, and radiographic results. The focus of outcome measurement has shifted towards the use of PROMs and alternative end points, such as influence on socioeconomic status and sex life after TKA (Klit et al. 2014).

Measuring outcomes pre- and postoperatively should meet the expectations that patients consider important (Bourne et al. 2010). Pain relief is the main target of knee arthroplasty, but functional and physical activities are emphasized in younger patients. Even in younger patients, physical activity is not necessarily shown in real-world functions but more in desirable expectations (Keeney et al. 2014). This may also present unrealistic expectations of the effects of knee arthroplasty, which is then reflected in dissatisfaction with outcomes.

2.7.4.2 Expectations

Klit et al. evaluated outcomes of patients less than 60 years of age with 12 months follow-up. PROMs increased from preoperative to 12 months postoperative (Q1, Q3): SF-36 PCS from 31.3 (26.7–36.6) to 46.8 (37.8–53.2), SF-36 MCS from 50.6 (39.0–61.5) to 58.5 (52.9–61.6), and OKS from 21 (16–26) to 40 (30–45). At the 12-month follow-up, 68% of the patients reported that "all expectations" or "most expectations" were fulfilled, and 71% reported they were "very satisfied" or "satisfied" with the outcome (Klit et al. 2014).

Goh et al. conducted a retrospective study with 136 primary TKAs in 114 patients aged 50 years or younger to evaluate functional outcomes with PROMs. At 2 years, the range of motion, KSS, OKS, and SF-36 physical and mental scores had increased significantly. At the same time, 88.8% of patients were satisfied with their surgeries, whereas 86.8% had their expectations fulfilled (Goh et al. 2016b).

Parvizi et al. retrospectively interviewed 661 patients aged less than 60 years at an average time of 2.6 years follow-up. They found that 90% of patients were satisfied with the overall functioning of their knees, 89% were satisfied with their ability to perform normal activities of daily living, and 91% were satisfied with the degree of pain relief (Parvizi et al. 2014).

In a study from the Korean population, the top three expectations of 454 patients were evaluated. These three expectations were pain relief, restoration of walking ability, and psychological well-being. When the expectations were divided into 5 categories, pain relief was ranked the highest. The second highest was psychological well-being, the third restoration of baseline activity, the fourth the ability to perform high flexion activities, and the fifth the ability to participate in social activities. Moreover, age of less than 65 years, being employed, a high WOMAC osteoarthritis index function score, and a low SF-36 social score were found to be significantly associated with higher overall expectations (Yoo et al. 2011).

2.7.4.3 Physical activity

In a prospective study of patients aged 65 years or less, activity levels improved significantly following TKA from mild to moderate activity measured with UCLA (Scott et al. 2017).

The same improvement level with UCLA score has been reported in older, retired patients in two other studies with 36 months follow-up (Bauman et al. 2007) and 5.7 years follow-up (Dahm et al. 2008).

Keeney et al. compared the preoperative and postoperative physical activity levels of patients 55 years or less with patients 65 years or older with 33 months follow-up. Only 13% of patients 55 years or younger reported being moderately or highly active before their TKA compared with 23% of older patients. In total, 29% of younger and 23% of older patients did not increase their activity levels, and 14% of patients in both groups experienced a decline in activity (Keeney et al. 2014).

In a retrospective study, Parvizi et al. reported that after recovery 47% of patients had complete absence of a limp and 50% had participated in their most preferred sport or recreational activity in the past 30 days (Parvizi et al. 2014).

2.7.4.4 Unicondylar knee arthroplasty

Goh et al. compared the register-based results of 160 UKA patients and 360 TKA patients using patient-reported outcomes, health-related quality of life scores, patient satisfaction, and fulfilment of expectations in patients younger than 55 years. They did not find any significant difference in KSS, OKS, or Short-Form 36 at 2 years. In total, 89.4% of the TKA group and 88.8% of the UKA group were satisfied with the results. In addition, 86.9% of the TKA patients and 86.3% of the UKA patients had their expectations fulfilled, even though the UKA group had significantly greater flexion at 6 months and at 2 years (Goh et al. 2018).

An analysis from the Norwegian Arthroplasty Register compared the outcomes of 972 TKAs and 372 UKAs. They reported that patients younger than 65 years performed worse than older patients with the exception of the outcomes related to activities of daily living and improvement in health-related quality of life (Lygre et al. 2010a).

In a study by Schai et al., 28 patients less than 60 years of age were treated using the PFC UKA system with a mean follow-up time of 40 months. Pain relief was satisfactory in 25 of the 28 knees (90%). Average knee flexion was 124° and no patient had an extension lag reported. The KSS improved postoperatively from 52 points to 93 points (Schai et al. 1998).

A retrospective study of 101 patients (118 knees) aged 60 years or younger treated with the Oxford UKA reported a return-to-activity rate of 93% with a minimum follow-up of 2 years. This study reported that patients mostly took part in low- or mid-impact activities, whereas high-impact activities had mostly been given up. The reason for the decline in their activity level was mainly based on the patients' decision to preserve the prosthesis rather than by the limited functional performance of the joint arthroplasty (Walker et al. 2015b).

A retrospective study compared HTO (2 wedge plates (Aescula; Medyssey, Dongducheon, Korea)) and medial unicompartmental arthroplasty (cemented Miller-Galante fixed-bearing prosthesis (Zimmer, Warsaw, Indiana)) in patients less than 65 years of age with a minimum follow-up of 2 years. This study could not identify any significant differences between HTO and UKA in terms of return to recreational activity and short-term clinical outcomes. (Yim et al. 2013.)

A systematic review was done to find answers to the following questions: was there an improvement in physical activity based on validated activity scores following UKA? What are the sport disciplines and the sport patterns of UKA patients? What are the pre- and post-operative sport participation rates and the return to activity rates of UKA patients? Analysis showed a significant increase in low-impact activities and a decrease in high-impact activities after UKA. The total number of different sport activities decreased, whereas the session length und frequency remained unchanged overall. Moreover, 2 studies in this review included patients 65 years or less (Waldstein et al. 2017) (Table 9).

Table 9. Summary of pre- and post-operative sport participation rates and the return to activity rate according to a systematic review. Studies including patients 65 years or less are highlighted in bold font (Waldstein et al. 2017).

Study	Mean age	Pre-operative sport	Post-operative sport	Return to activity rate
(Fisher et al. 2006)	64 (49–81)	64%	59%	93%
(Walton et al. 2006)	71.5 SD 9.85	79%	86%	-
(Naal et al. 2009)	66.0 (46–84)	93%	88%	95%
(Hopper and Leach. 2008)	62.1 (35–75)	88%	85%	97%
(**Yim et al. 2013**)	58.3 (43–65)	84%	60%	-
(Pietschmann et al. 2013)	65.3 (44–90)	60%	53%	80%
(Jahnke et al. 2015)	63.5 (36–86)	90%	93%	-
(Walker et al. 2015a)	60.1 (36–81)	93%	91%	98%
(**Walker et al. 2015b**)	55 (36–60)	93%	91%	93%
Ho et al.(Ho et al. 2016)	-	83%	72%	87%

2.8 Local infiltration analgesia in knee arthroplasty

2.8.1 Different infiltration techniques

Local infiltration analgesia (LIA) is a multimodal wound infiltration method for treating postoperative pain after knee arthroplasty. This pain management method is based on the systematic infiltration of a mixture of drugs around all the structures subject to surgical trauma during knee arthroplasty. Before multimodal drug infiltration methods came into clinical use, a single local anesthetic was reported to be effective in pain control after knee arthroplasty (Bianconi et al. 2003).

Kerr and Kohan developed a local infiltration analgesia technique which served as the basis for the wide-spread use of such techniques to improve pain relief in knee arthroplasty surgery. A long-acting local anesthetic (ropivacaine), a nonsteroidal anti-inflammatory drug (ketorolac), and epinephrine were infiltrated periarticularly during the operation and for 15 to 20 hours postoperatively by hand through the wound catheter (Kerr and Kohan. 2008b).

Different infiltration techniques, such as periarticular infiltration, intra-articular infiltration, peri- or intra-articular infiltration combined with secondary postoperative infiltration, and postoperative infiltration though wound catheter, have been introduced. However, there is no consensus on which local anesthetic agent or infiltration technique is the most effective and tolerated. A wide RCT review reported better pain control in the periarticular group than the intra-articular group, and the use of LIA provided better pain relief and improved range of motion after TKA (Seangleulur et al. 2016).

The demographic factors of patients may also affect the pain level after knee arthroplasty. In a LIA study, postoperative pain was found to be higher in females and younger patients, whereas BMI, race, or ethnicity did not affect postoperative pain (Barrington et al. 2016).

Pre- and postoperative complications which may be related to LIA are infections and systemic toxicity of drugs used but in a systematic review and meta-analysis increased incidence of these were not reported in the studies included (Seangleulur et al. 2016).

2.8.2 Effect of local infiltration analgesia on pain

A review by Seangleulur et al. divided LIA into 4 different techniques and reported the efficacy of each technique (Seangleulur et al. 2016). Opiate consumption referred to the amount of intravenous morphine or morphine equivalents that were converted using an opioid analgesic conversion table.

2.8.2.1 Periarticular infiltration

Studies that reported the periarticular infiltration technique to be effective or ineffective compared with placebo or no injection measured with VAS rest pain at 24 hours (results reported as weighted mean difference (CI95)) are listed in the table 10.

Table 10. Effect with periarticular infiltration

LIA ineffective		LIA effective	
0.53 (-0.59, 1,65)	(Busch et al. 2006)	-0.50 (-0.84, -0,16)	(Fu et al. 2009)
-0.21 (-0.54, 0.12)	(Zhang et al. 2011)	-0.63 (-0.92, -0.34)	(Fu et al. 2010)
		-1.13 (-1.70, -0.56)	(Chen et al. 2012)
		-3.50 (-4.12, -2.88)	(Lamplot et al. 2014)
		-0.37 (-0.78, -0.04)	(Nakai et al. 2013)
		-0.34 (-0.67, -0.01)	(Milani et al. 2015)

2.8.2.2. Intra-articular infiltration

Studies that reported the intra-articular infiltration technique to be ineffective or effective compared with placebo or no injection measured with VAS rest pain at 24 hours (results reported as weighted mean difference (CI95)) are listed in the table 11.

Table 11. Effect with intra-articular infiltration

LIA ineffective		LIA effective	
1.03 (0.54, -1.52)	(Nakai et al. 2013)	-1.48 (-1.98, -0.98)	(Tanaka et al. 2001)
0.40 (-0.90, -1.70)	(Rosen et al. 2010)	-1.60 (-2.12, -1.08)	(Fajardo et al. 2011)
1.47 (-0.09, 3.03)	(Klasen et al. 1999)	-0.10 (-1.55, -1.35)	(Guara Sobrinho et al. 2012)
-0.80 (-1.69, 0.09)	(Browne et al. 2004)	-3.10 (-4.40, -1.80)	(Shen et al. 2015)
-0.66 (-1.79, 0,47)	(Mauerhan et al. 1997)		

2.8.2.3 Periarticular infiltration combined with postoperative infiltration

Studies that reported periarticular infiltration with postoperative additional bolus to be ineffective or effective compared with placebo or no injection measured with VAS rest pain at 24 hours (results reported as weighted mean difference (CI95)) are listed in the table 12:

Table 12. Effect with periarticular infiltration combined with postoperative bolus

LIA ineffective		LIA effective	
-0.80 (-2.34, 0.74)	(Vendittoli et al. 2006)	-2.04 (-2.55, -1.53)	(Essving et al. 2010b)
-0.64 (-1.96, 0.68)	(Andersen et al. 2008)	-1.119 (-2.34, -0.78)	(Kazak Bengisun et al. 2010)
		-1.70 (-2.00, -1.40)	(Zhang et al. 2011)

2.8.2.4 Postoperative infiltration

Studies that reported the postoperative infiltration technique to be effective compared with placebo or no injection measured with VAS rest pain at 24 hours (results reported as weighted mean difference (CI95)) are listed in the table 13.

Table 13. Effect with postoperative infiltration

LIA ineffective	LIA effective	
-	-1.90 (-2.39, -1.41)	(Gomez-Cardero and Rodriguez-Merchan. 2010)
	-2.02 (-3.14, -0.90)	(Ong et al. 2010)
	-1.31 (-2.37, -0.25)	(Ikeuchi et al. 2013)

This review concluded that pain control in the periarticular group was found to be better than in the intra-articular group. Periarticular injection reduced 24-h VAS for pain, whereas intra-articular injection did not. Both peri- and intra-articular injection reduced opioid consumptions in the first 24 h compared with no injection or placebo, even if a greater reduction was shown after periarticular injection. In addition, an improvement in 24-h ROM was shown after periarticular injection but not after intra-articular injection. The analgesic effects can be extended up to 48 h with postoperative injection through a catheter, but the risk for catheter-related infection was uncertain.

Signicant pain relief in rest at 48 hours was reported in 1 study with periarticular infiltration (Lamplot et al. 2014), in 2 studies with periarticular infiltration with postoperative bolus (Kazak Bengisun et al. 2010, Zhang et al. 2011) and in 3 studies with postoperative bolus (Gomez-Cardero and Rodriguez-Merchan. 2010, Ong et al. 2010, Ikeuchi et al. 2013). Intra-articular infiltration was not reported effective at 48 hours measured with pain at rest (Seangleulur et al. 2016).

2.8.3 Effect of local infiltration analgesia on patient-related outcome measures

Most of the studies concerning the outcomes of the LIA report results 24 hours or 48 hours postoperatively. The long-term effectiveness of LIA has not, however, been reported using PROMs.

Tanikawa et al. conducted a randomized study which compared the effectiveness of sciatic nerve block (SNB) to LIA with 21-days follow-up. All patients underwent general anesthesia combined with femoral nerve block. The LIA solution contained ropivacaine, dexamethasone, and adrenaline, whereas SNB was done with ropivacaine. They reported that SNB was more effective than LIA in reducing pain immediately after surgery but that SNB was less effective than LIA at 24 h after the surgery. For between 3 and 21 postoperative days, there was no difference in VAS score between the SNB and the LIA groups (Tanikawa et al. 2017).

In another randomized study, Carli et al. compared knee functions after total arthroplasty combined with periarticular LIA or with continuous femoral nerve block with 6-weeks follow-up. In this study, outcomes were significantly better in the FNB group measured with KSS and WOMAC at 6 weeks and the results also favored the use of continuous FNB in other measures (Carli et al. 2010).

3 Aims of the Present Study

The main purpose of this study was to evaluate the outcomes of contemporary knee arthroplasty in terms of survivorship and patient-reported outcome measures with special reference to patients less than 65 years of age.

The specific aims of the studies were to investigate the following:

Study I: The trends and differences of incidences of TKA and UKA based on NARA data from four Nordic countries.

Study II: The survivorship of different fixation methods in total knee arthroplasty based on the NARA register in patients less than 65 years of age.

Study III: The survivorship of TM tibia based on FAR data.

Study IV: The effectiveness of TKA and UKA in terms of PROMs and satisfaction.

Study V: The effectiveness of LIA with pain and PROMs.

4 Patients and Methods

4.1 Patients

A summary of the study designs, type of data, patients, and follow-up are presented in table 14.

Table 14. Summary of studies, type of data, patient characteristics, follow-up, and study period

Study	I	II	III	IV	V
Study design	Register-based	Register-based	Register-based	Prospective observational	RCT
Patients	344 695	115 177	1143	250	60
Females[a]	64%/57%	56%/58%/ 59%/60%	57%	61%/ 52%	56%/ 48%
Age[b]	70 (9.0)/ 65(9.4)	57.3 (5.6)/ 57.0 (5.4)/ 58.1 (5.2)/ 58.7 (4.9)	63.6 (30–91)	58 (5.1)/56 (5.4)	65 (4.9)/64 (6.7)
Follow-up %[c]	-	-	-	93%	93%
Follow-up time[d]	-	6.4 (4.3)/ 4.7 (3.4)/ 6.0 (4.3)/ 6.1 (3.2)	2.7 (0–7.9)	2 years	1 year
Study period[e]	1997–2012	2000–2016	2003–2010	2012–2014	2011–2012

[a] Study I and IV: TKA/UKA, study V: LIA/Placebo, Study II: cemented/uncemented/hybrid/inverse hybrid.

[b] Mean age (SD or range). Study I and IV: TKA/UKA, study V: LIA/Placebo.

[c] Number of patients at the end of follow-up.

[d] Mean follow-up time (SD or range). Study II: cemented/uncemented/hybrid/inverse hybrid.

[e] Study IV and V: Enrollment time of patients.

For study I, we included patients aged 30 years or older who had undergone a TKA or UKA surgical procedure due to primary osteoarthritis of the knees according to NARA data. This data comprised information on the TKAs and UKAs performed in Denmark, Norway and Sweden from 1997 to 2012 and in Finland from 2000 to 2012. Patients who were less than 30 years old were excluded because of the small number of these patients.

In total, 385 310 primary knee arthroplasties were registered in the 4 countries during the study period. During the study period, we observed an increase in OA from 84% to 90% and simultaneously a decline in rheumatoid arthritis (RA) from 10% to 4% as indication for knee arthroplasty. Among these operations, 317 008 TKAs and 27 687 UKAs were performed for knee OA in patients aged 30 years or older. Female patients represented 202 940 (64%) of the TKA cases and 15 778 (57%) of the UKA cases. The mean age of the patients was 70 years (9.0) in the TKA group and 65 years (9.4) in the UKA group. The characteristics of the patients in the different countries are presented in table 15.

Table 15. Patient characteristics for Study I

	Denmark	Norway	Sweden	Finland	Total
Mean age (SD)	69.0 (9.5)	69.7 (9.2)	69.8 (9.0)	69.0 (9.0)	
Females	63.2%	65.8%	60.0%	67.5%	

For study II, we included patients from the NARA data aged less than 65 years who had undergone an unconstrained primary TKA for primary OA between 2000 and 2016 to assess the survivorship of cemented, uncemented, hybrid, and inverse hybrid TKAs in these patients. This sample comprised 115 177 TKAs, and the demographics of the patients are listed in table 16.

Table 16. Patient demographics for Study II

Fixation concept	Uncemented	Inverse hybrid	Hybrid	Cemented
No of TKAs (%)	6 132 (5.3)	546 (0.5)	6 329 (5.5)	102 170 (88.7)
Mean age, years (SD)	57.3 (5.6)	57.0 (5.4)	58.1 (5.2)	58.7 (4.9)
Men, %	44	42	41	40

For study III, we included 1 151 TKAs which were performed using an uncemented porous tantalum tibial component. Of these operations, 1 143 (99%) were primary TKAs and 8 (1%) revision TKAs. Only the primary TKAs were included in the study. Of the 1 143 primary TKRs using the TM Monoblock Tibia, 647 (57%) were performed on women and 597 (52%) on the right knee. At the time of the surgery, the mean age of the patients was 63.6 years (range: 30-91). The majority of these procedures were performed due to primary osteoarthritis (n=1,086; 95%). Other indications included posttraumatic osteoarthritis (n=32; 2.8%), rheumatoid or other chronic inflammatory arthritis (n=20; 1.7%), and other unclassified indications (n=5; 0.4%).

For study IV, 250 patients were enrolled between March 1st, 2012 and October 30th, 2014. PROM data and patient background questionnaires were collected via surface mail preoperatively at 2 to 3 months and at 1 and 2 years postoperatively. In total, 250 patients (272 knees) were recruited to the study, and all patients gave written informed consent to participate. As 5 (2%) patients cancelled surgery, 6 (2.4%) were revised, 5 (2%) were lost to follow-up, and 2 (0.8%) died during the follow-up, 232 patients (93%; 254 knees) were available for the 2-year follow-up visits, and the analysis of the final results was based on these patients. While simultaneous bilateral TKAs were performed for 22 patients, none of the patients received bilateral UKAs. The final patient population comprised 227 TKAs and 27 UKAs.

Of the 232 patients (254 knees), 227 knees (89%) underwent cemented TKA using either PFC (182 knees; DePuy Synthes, Warsaw, IN) or Nexgen (45 knees; Zimmer Biomet, Warsaw, IN), which were selected based on the personal preference of the surgeon. In 12 (5.3%) of the TKAs, the patella was resurfaced. Of the 227 TKAs, 218 (96%) were cruciate retaining (CR) and the remaining 9 were posterior stabilized (PS). UKA was performed for 27 patients using the uncemented Oxford phase 3 (Zimmer Biomet, Warsaw, IN) prosthesis. The patients' preoperative ASA classifications, KL grade, and working status are presented in table 17.

Table 17. Patient preoperative KL grade, ASA classification, and working status for Study III

	TKA (n=227)		UKA (n=27)	
	n	%	n	%
Kellgren-Lawrence (knees)				
KL 2	33	15	5	18
KL 3	105	46	12	46
KL 4	89	39	10	36
ASA				
1	73	32	11	41
2	116	51	15	56
3	38	17	1	3
At work preoperatively	110	53	18	65

For study V, we enrolled 60 patients undergoing unilateral TKA in this randomized, double-blinded, placebo-controlled study. For the final analysis at 2 years follow-up, 56 patients completed the study, including 27 patients in the LIA group and 29 patients in the Placebo group. All patients included in this study were operated at Coxa Hospital between March 2011 and March 2012. The characteristics of the patients are presented in table 14.

4.2 Methods

4.2.1 Register-based studies (Study I, II, and III)

4.2.1.1 NARA

NARA compiles data on 4 Nordic countries that have similar health care organizations and comparable patient characteristics. The NARA data comprises information on the TKAs and UKAs performed in Denmark, Norway, and Sweden from 1997 onwards and in Finland from 2000 onwards.

The knee arthroplasty registers of Sweden (SKAR) and Denmark (DKR) and the arthroplasty registries of Norway (NAR) and Finland (FAR) participated in studies I and II. All 4 registers have used individual-based registration of operations and patients. A NARA minimal dataset was created to contain data that all 4 registers could deliver. However, for administrative reasons, the Finnish Arthroplasty Register has only been able to provide Finnish data according to the NARA data definitions from the beginning of 2000. A pilot study from NARA data did not include FAR data and it did not have an age cut-off (Robertsson et al. 2010b). The NARA database includes data on patients that enables TKA and UKA incidence analyses, i.e., patient-level data on both demographics and implant types.

The selection and transformation of the respective datasets and the de-identification of the patients, which included the deletion of the unique personal identification numbers, were performed within each national register. The anonymous data were then merged into a common database.

Data were treated with full confidentiality, according to the rules of the respective countries. The quality of data in the Nordic registries is high, and the registries have both national coverage and a high degree of completeness (annual reports: Danish knee arthroplasty register, Norwegian Arthroplasty Register, Swedish Knee Arthroplasty Register, Finnish Arthroplasty Register) (Espehaug et al. 2006).

4.2.1.2 FAR (Study III)

Study III was based on information recorded in the FAR that was related to patients that underwent TKA with an uncemented porous tantalum tibial component (Trabecular Metal Monoblock Tibia; Zimmer, Warsaw) between January 1, 2003 and December 31, 2010. At the time of the study period, coverage of the FAR was over 95%. Revisions are linked to the primary surgery using the unique personal identification number assigned to each resident of Finland. Three hospitals in Finland were involved in this study cohort.

To assess the impact of age on implant survival, we analyzed age as a linear variable using age groups 1) age under 55 years (n=167; 15%), 2) age from 55 to 65 years (n=458; 40%), and 3) age over 65 years (n=518; 45%). The impact of gender on survival was also assessed. For the end points, we used all revisions and revisions for aseptic loosening of the TM Monoblock Tibia.

4.2.2 Prospective and RCT studies (study IV and V)

In study IV, the inclusion criteria were as follows: 1) age 65 or less and 2) scheduled for either TKA or UKA. UKA was considered if the patient was evaluated to be suitable for UKA both on a radiological and patient-derived basis. The exclusion criteria were as follows: 1) rheumatoid arthritis or other inflammatory diseases, 2) unwilling to provide informed consent, 3) physical, mental, or neurological conditions that could compromise the patient's ability and compliance with postoperative rehabilitation and follow-up (e.g., drug or alcohol abuse, serious mental illness, general neurological conditions, such as Parkinson's disease, multiple sclerosis, etc.), and 4) known sensitivity to materials in the devices.

All operations were performed by senior orthopaedic surgeons, and all patients were treated with the same routine postoperative rehabilitation and pain management protocol. Four different PROMs were used to measure the effectiveness of knee arthroplasty in these patients: OKS, KOOS, HAAS, and the RAND 36 general quality of life (QoL) questionnaire. Primary outcome was defined as the effect of knee arthroplasty on pain and function as measured with OKS and KOOS. Secondary outcomes were the effect of knee arthroplasty on QoL (RAND 36), physical activity (HAAS), and satisfaction. A background questionnaire included information on working status, physical activities, and medical comorbidities. The Visual Analogue Scale (VAS) was measured using a scale from 0 to 100 to evaluate pain and satisfaction caused by knee arthroplasty both before and after surgery. The VAS satisfaction scale was divided into four sections: 0 to 25 dissatisfied, 26 to 50 unsure, 51 to 75 satisfied, and 76 to 100 very satisfied, as proposed previously by Scott et al. (Scott et al. 2016).

The severity of knee OA was assessed from preoperative standing fixed flexion view (FFV) radiographs using the Kellgren-Lawrence (KL) (KELLGREN and LAWRENCE. 1957) classification.

In study V, inclusion criteria consisted of (1) patients requiring primary TKA for primary osteoarthritis and (2) aged 18 to 75 years. Exclusion criteria were (1) rheumatoid arthritis or other inflammatory diseases, (2) BMI >35, (3) American Society of Anesthesiologists' physical score >3, (4) renal dysfunction, (5) allergy to any of the study drugs, (6) previous high tibial osteotomy or previous osteosynthesis, (7) >15 degrees varus or valgus malalignment, and (8) physical, emotional, or neurological conditions which could compromise the patient's compliance with postoperative rehabilitation and follow-up.

4.2.2.1 Randomization and blinding

On the morning of the surgery, an independent research nurse not involved in patient care performed the randomization sequence by drawing 1 opaque-sealed envelope from a mixture of 60 alternatives (allocation ratio: 1:1). The nurse prepared the study solution and delivered it to the operating room just before surgery. In the local infiltration analgesia (LIA) group, the study solution contained levobupivacaine (150 mg) mixed with ketorolac (30 mg) and adrenaline (0.5 mg). In the control (Placebo) group, the solution contained isotonic saline. Total volume of the solution was 100 mL in both groups. The allocation list was stored at the office of the research nurse until all patients had been included and all 1-year follow-up materials had been completed. Only the research nurse who opened the envelope and prepared the study solution was aware of the infiltration's quality and all other personnel involved in the patient's care remained blinded throughout the study.

4.2.2.2. Preparation and pain management

Oral paracetamol 1 g was given approximately 1 h before operation as premedication. Single shot spinal anesthesia was induced at the L4-5 or L3-4 level by using a 27 G spinal needle with a dose of 3 mL bupivacaine 5 mg/mL. A single 3.0 g bolus of cefuroxime was used as antibiotic prophylaxis and tranexamic acid 1g was given at the end of surgery. In the postanesthesia care unit, an ice pack was used for all patients. All patients were treated with oral paracetamol 1 g every 6 h and oral meloxicam 15 mg every 24 h, initiated 2 h after surgery. Patient-controlled analgesia (PCA) with oxycodone (dose 2 mg, lock-out time 8 min) was used in all patients to ensure adequate pain relief. No other analgesic drugs were used. If the pain management was insufficient, a lumbar epidural catheter was inserted and levobupivacaine infusion was initiated as rescue analgesic causing the patient to drop out of the study. Nausea was treated with intravenous ondansetron 4 mg when needed. For thromboprophylaxis, subcutaneous enoxaparin 40 mg every 24 h was started 6 to 10 h after the end of operation.

4.2.2.3 Surgery and infiltration technique

All patients were operated using standard knee replacement techniques by 4 experienced orthopaedic surgeons. Both groups received a periarticular infiltration intra-operatively. All infiltrations were done using 50 mL syringes and 7 cm long 20 G needles. The solution was infiltrated in 2 stages: the first after the bone surfaces were prepared, but before the components were inserted, and the second after the components were inserted, but before both tourniquet´s release and wound closure. The first 50 mL infiltration was aimed at both sides through the posterior capsule and in the areas of the resected menisci. The second was aimed periosteally next to the resected bone surfaces and parapatellar approach, but not in subcutaneous tissue. The tourniquet was released before closure and hemostasis was ensured. Drainage and compression bandage were applied in all patients.

4.2.2.4 Recovery

In the recovery room, all patients were mobilized by a physiotherapist soon after recovery of motoric function. Patients were advised to use a PCA pump for oxycodone delivery and the consumption of oxycodone was calculated at 6, 12, 24, and 48 hours postoperatively. The Visual Analog Scale (VAS) was used to quantify the pain intensity, with a target level under 3. The VAS reading was recorded at 3, 9, 18, and 48 hours postoperatively by a nurse or physiotherapist. The range of motion (ROM) was measured at 6, 12, and 24 hours postoperatively by a physiotherapist.

4.2.2.5 Outcomes

The primary outcome was the oxycodone consumption during the first 48 hours postoperatively. A secondary outcome was functional outcome 1 year after surgery. All patients were evaluated by a physiotherapist blinded to the study solution at a routine follow-up visit 3 months postoperatively. Total Knee Function Questionnaire (TKFQ), Oxford Knee Score (OKS), High-Activity Arthroplasty Score (HAAS), and 15D quality of life instrument were collected preoperatively at 3 months and at 1 year postoperatively for prospective outcome analysis.

4.3 Statistical methods

4.3.1 Study I

In study I, we described patient characteristics, categorized into sex and age groups, using descriptive statistics presented as mean and standard deviation (SD). Incidences are presented as the number of operations performed per 104. Age was categorized into 3 groups: <65 years, 65 to 74 years and 75+ years. We analyzed trends in the general incidence of TKAs and UKAs in Denmark, Norway, and Sweden from 1997 to 2012 and in Finland from 2000 to 2012. The incidence was calculated as incidence density, which is defined as the number of new cases in a population during a given time period relative to the sum of the person-time of the at-risk population. Negative binomial regression was used to estimate the incident rate ratios (IRR) and the 95% confidence intervals (CI) of UKAs and TKAs for each country due to evidence of overdispersion of the data. IRR reports the estimated average annual increase of incidence. Analyses were stratified by sex and age group. The statistical analyses were conducted using SPSS software (IBM SPSS Statistics for Windows, Version 22 Armonk, NY: IBM Corp.) and Stata 8.2 software (StataCorp 4905 Lakeway Drive, College Station, Texas 77845 USA).

4.3.2 Study II

In study II, we assessed the descriptive statistics of the included patients. The inclusion time period was 2000 to 2016. We used Kaplan-Meier survival analysis to assess implant survival probability (with respective 95% confidence interval (CI)) of the TKA fixation at 7, 10, and 15 years. The results in tables and figures were not shown when fewer than 40 were at risk. Outcome was defined as the removal, addition, or exchange of at least one of the components. This included polyethylene insert exchanges of the modular tibial components for any reason. Differences between groups were considered to be statistically significant if the p-values were less than 0.05 in a two-tailed test.

Cox regression analysis was used to estimate the hazard ratios associated with implant survival. The covariates included in the analysis were fixation type, sex, country, and age. Age was included as a continuous variable, whereas the others were categorical. The correlation of scaled Schoenfeld residuals with time was examined to investigate violation of the proportional hazard (PH) assumption. Log-log survival curves were also inspected visually to see whether the PH assumption was met. Multiple violations of the PH assumption were detected. In order to deal with the PH violation, we used time-dependent coefficients using step function. Based on the log-log curves, cut-offs were set as 1, 3, and 6 years. We did stratified analyses based on age and implant brand group and a similar time axis division was made according to the log-log curves and residual testing. For the time-dependent coefficients, the data were broken down into time-dependent parts according to the time intervals used in the time axis division. For each final analysis, the PH test investigating Schoenfeld residuals was performed.

Statistical analyses were performed using SPSS Statistics version 23 (IBM Corporation, Armonk, NY, USA).

4.3.3. Study III

In study III, the endpoint for survival was defined as revision with either one component or the whole implant being removed or exchanged. All survival analyses were performed using all revisions and revisions for aseptic loosening of the tibial component as the end points. Kaplan-Meier survival data were used to construct the survival probabilities of implants at 1, 5, and 7 years. The Cox multiple-regression model was used to study the differences in revision risk (RR) between revision indications and to adjust for potential confounding factors. The variables included in the Cox model were as follows: primary osteoarthritis (reference indication) vs other indications, cemented vs uncemented femur (reference implant), unresurfaced vs resurfaced patella (reference technique), gender, and age both as a continuous and as a categorized variable. The following age groups were analyzed: 1) age under 55 years and 2) age from 55 to 65 years with 3) age over 65 years as a reference age group. During the study period, the reasons for failures and revisions among the patients were ascertained from the patients′ medical records and radiographs taken at the hospitals where the revisions had been performed. The Cox regression analyses provided estimates of survival probabilities and adjusted risk ratios (ARR) for the various factors. Estimates from the Cox analyses were used to construct adjusted survival curves at the mean values of the risk factors. The Wald test was used to calculate p-values for the data obtained from the Cox multiple regression analysis. Differences between groups were considered statistically significant if the p-values were less than 0.05 in a two-tailed test. We used SPSS version 20 statistical software (IBM, Armonk, New York, U.S.A.) for statistical analyses.

4.3.4 Study IV

In study IV, data were presented as median with quartiles (Q1 to Q3) or as mean (SD) or (CI95%). The Wilcoxon signed rank test and paired t-test for paired data were used to compare preoperative and postoperative values. The differences in distributions in the 3 measured time points were calculated with Friedman test. A P-value less than 0.05 was considered statistically significant. Data were analyzed using the SPSS version 23 statistical package (IBM, Armonk, NY, USA.)

To prevent potential bias with TKA and UKA, the results were analyzed for both TKA and UKA together, and also separately for TKA and UKA.

4.3.5 Study V

In study V, the calculation of sample size was based on an expectation of a 40% difference in opiate consumption between the groups. The study was designed to have a power of 80% to detect a 40% difference between the 2 groups (type-I error probability 0.05). Based on the power calculation, 17 patients per group would be needed. Demographics and results are shown as percentages, mean values (SD), or as median (range). Differences between the groups were analyzed using the Mann-Whitney U-test. The Bonferroni method was used to correct for multiple measures. IBM SPSS Statistics version 20 statistical software (IBM, Armonk, New York, U.S.A.) was used for the statistical analysis.

4.4 Ethical considerations

In the NARA-based studies I and II and FAR-based study III, the ethical approvals for the studies were attained through the ethical approval process of each national registry: the Ethics Board of Lund University (LU20-02) (Sweden), the National Institute of Health and Welfare (Dnro THL/1743/5.05.00/2014) (Finland), the Norwegian Data Inspectorate (ref 24.1.2017: 16/01622-3/CDG) (Norway) and the Danish Data protection agency (1-16-02-54-17) (Denmark).

In study IV, the study protocol (R11178) was approved by the Ethics Committee of the hospital district. The study was registered with ClinicalTrials.gov (NCT03233620). All patients gave written informed consent to participate in the study.

With study V, the study protocol was approved by the local Ethics Committee (R10108). The Finnish Medicines Agency (Fimea) approved the study protocol for the drugs to be used (EudraCT 2010-024315-14). The study was registered with ClinicalTrials.gov (NCT01305733). All patients gave their informed consent before inclusion in the study.

5 Results

5.1 Incidences of knee arthroplasty (Study I)

At the beginning of the study, incidences were 3.4 in Denmark, 3.6 in Norway, 9.0 in Sweden, and 13.1 in Finland (/10^4 inhabitants). At the end of study, incidences were 20.5 in Denmark, 14.1 in Norway, 20.9 in Sweden, and 27.5 in Finland (/10^4 inhabitants). During the study period, the total incidence of knee arthroplasties increased in all four national registers. The change in incidence was analyzed from the beginning to the end of the study period. The total increase was 6.0-fold in Denmark, 3.9-fold in Norway, 2.3-fold in Sweden, and 2.1-fold in Finland. In 2012, the total incidence of TKAs was highest in Finland and lowest in Norway. The total incidence in Finland was 2.0-fold higher compared with Norway, 1.3-fold higher compared with Sweden, and 1.3-fold higher compared with Denmark. The increase in incidence was steady over time except for Finland where it was especially high between 2004 and 2006 for both TKA and UKA (Figure 11). The incidence of UKAs varied between countries, whereas that of TKAs increased constantly in every

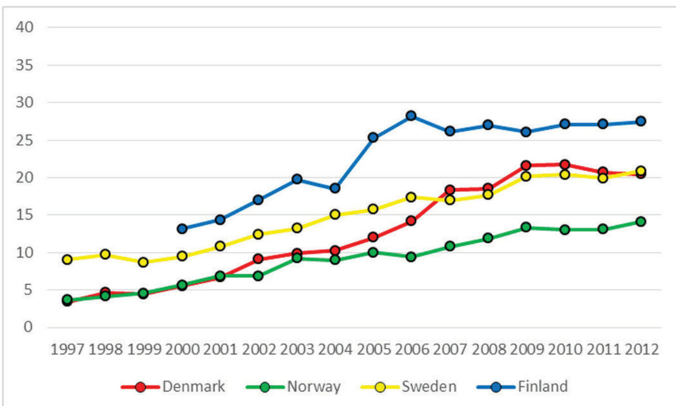


Figure 11. Total incidence of TKA and UKA by year of operation in patients 30 years or older. Incidences are shown per 10^4 inhabitants

register. In Sweden, the incidence of UKA decreased significantly during the study period. A similar trend was also seen in Finland after 2006.

The increase in the incidence of UKA was 10.0-fold in Denmark, 1.5-fold in Finland, and 7.1-fold in Norway. However, the incidence of UKA decreased 0.5-fold in Sweden.

During the study period, the estimated average annual increase in the general incidence of TKAs between age and gender groups was statistically significant in all countries ($p<0.001$), with the exception of Finnish females aged 65 to 74 years (1.017 (Cl 1.00–1.04), $p=0.129$) (Table 18).

Table 18. Negative binomial regression analysis. Incident rate ratios (IRR) with 95% confidence intervals

	Age (y)	Male		Female	
		IRR	95% CI	IRR	95% CI
Denmark	30–64	1.18	1.15–1.20	1.16	1.14–1.18
	65–74	1.09	1.04–1.14	1.12	1.10–1.14
	75–	1.12	1.10–1.14	1.10	1.08–1.12
Norway	30–64	1.16	1.13–1.19	1.13	1.11–1.16
	65–74	1.12	1.10–1.13	1.08	1.06–1.09
	75–	1.09	1.08–1.11	1.06	1.04–1.07
Sweden	30–64	1.12	1.11–1.14	1.11	1.09–1.12
	65–74	1.06	1.05–1.07	1.04	1.03–1.05
	75–	1.06	1.05–1.06	1.04	1.03–1.04
Finland	30–64	1.13	1.10–1.16	1.11	1.08–1.13
	65–74	1.04	1.02–1.05	1.02	1.00–1.04
	75–	1.04	1.02–1.06	1.03	1.01–1.05

5.2 Incidence by gender

5.2.1 TKA

The incidences of TKAs were higher in women than in men in all countries. The trend of increase was similar between countries. The increase in the incidence of TKA was 4.2-fold in males and 5.2-fold in females in Denmark. Corresponding increases were 5.9-fold vs 3.1-fold in Norway, 2.8-fold vs 2.4-fold in Sweden, and 2.7-fold vs 1.9-fold in Finland, respectively (Figure 12 and 13).

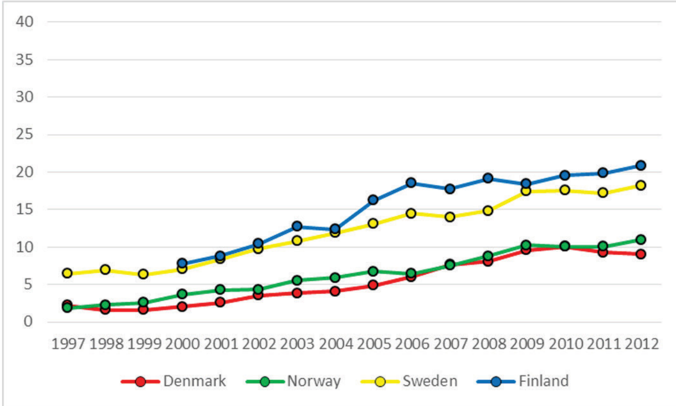


Figure 12. Incidence of TKA in males 30 years or older. Incidences are shown per 10^4 inhabitants

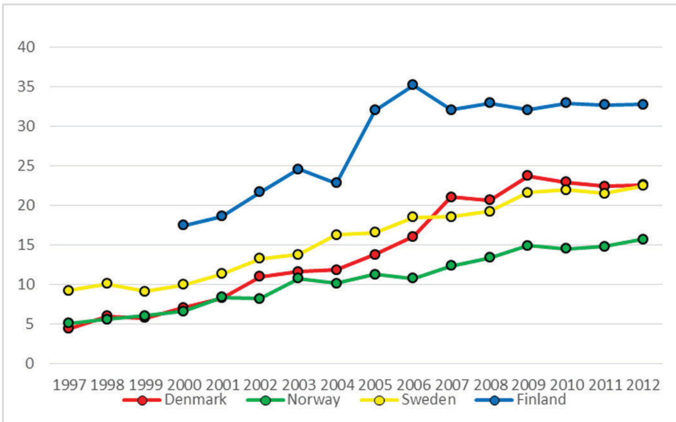


Figure 13. Incidence of TKA in females 30 years or older. Incidences are shown per 10^4 inhabitants

5.2.2 UKA

The increase in UKA incidence was 6.6-fold in males and 9.2-fold in females in Denmark. Corresponding changes in UKA incidences were 10.6-fold vs 5.1-fold in Norway, 0.5-fold vs 0.4-fold in Sweden, and 2.0-fold vs 1.3-fold in Finland, respectively (Figures 14 and 15).

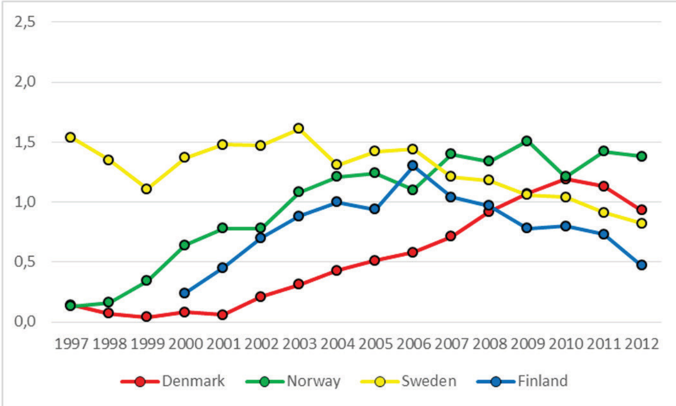


Figure 14. Incidence of UKA in males 30 years or older. Incidences are shown per 10^4 inhabitants

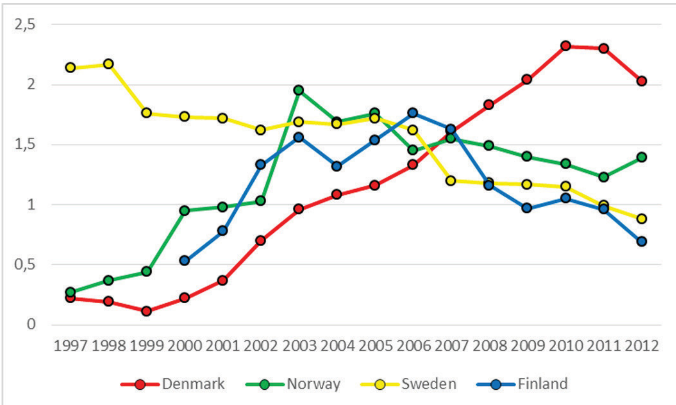


Figure 15. Incidence of UKA in females 30 years or older. Incidences are shown per 10^4 inhabitants

5.3 Incidence by age group

5.3.1 TKA

The incidence of TKAs was highest in Finland in patients aged 65 years and older. The total incidence was lowest in the youngest age group in all countries. However, an increase in the incidence of TKA was detected in all age groups. Between the less than 65 years age group, the 65 to 74 years age group, and the 75+ years age group, the increase in incidence of TKAs was 7.4-fold vs 5.0-fold vs 4.3-fold in Denmark, 7.6-fold vs 3.7-fold vs 2.6-fold in Norway, 5.8-fold vs 2.2-fold vs 1.9-fold in Sweden, and 3.9-fold vs 1.3-fold vs 1.5-fold in Finland, respectively (Figure 16).

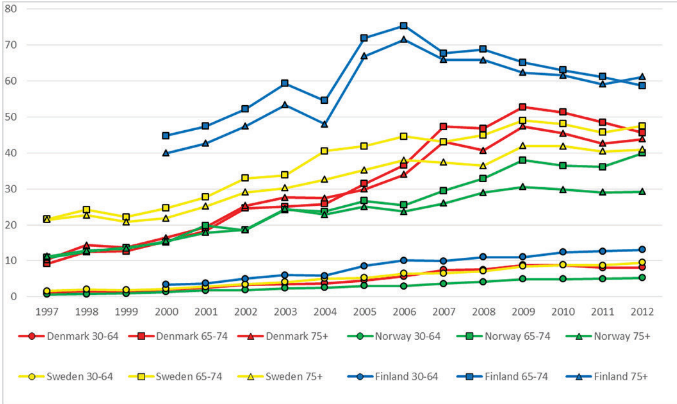


Figure 16. Incidence of TKA by age group. Incidences are shown per 10^4 inhabitants

5.3.2 UKA

Corresponding differences between the age-groups in the incidence of UKA were 13.4-fold vs 9.3-fold vs 4.6-fold in Denmark, 14.0-fold vs 6.8-fold vs 2.3-fold in Norway, 1.3-fold vs 0.2-fold vs 0.2-fold in Sweden, and 2.0-fold vs 0.9-fold vs 1.0-fold in Finland. The incidence of UKAs decreased significantly in Sweden in patients aged 65 years or older, and a similar but minor trend was also detected in patients aged 65 years or older in Finland. During the study period, the incidence of UKA increased in Denmark and Norway in all age groups and in patients younger than 65 years of age in Finland (Figure 17).

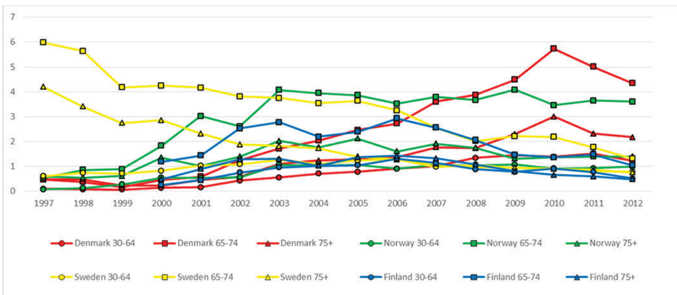


Figure 17. Incidence of UKA by age group. Incidences are shown per 10^4 inhabitants

5.4 Fixation methods and survivorship (Study II and III)

In the KM analysis, the inverse hybrid group had the lowest risk for revision at 10 years (Figure 18). The proportion of cemented TKAs of all TKAs was 88.7%, and that of uncemented was 5.3%, hybrid 5.5%, and inverse hybrid 0.5%, respectively.

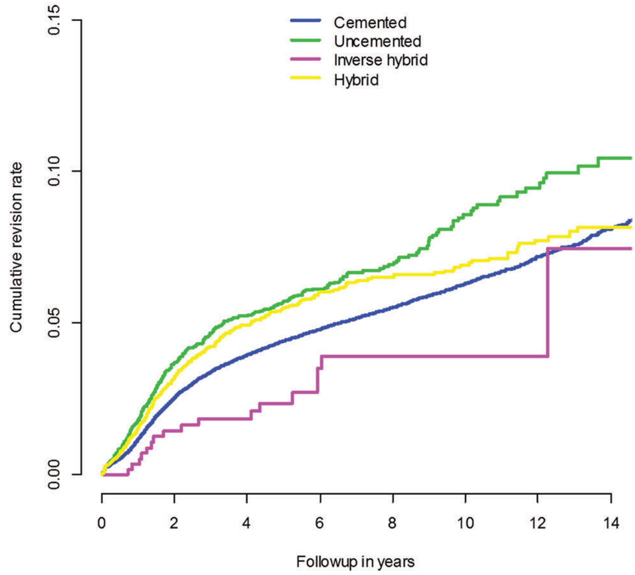


Figure 18. Unadjusted Kaplan-Meier cumulative risk for revision by fixation type

At 10 years, KM-based survival rates were in descending order: inverse hybrid 96.0% (CI 94.1–98.1), cemented 93.6% (Cl 93.4–93.8), hybrid 93.0% (CI 92.2–93.8), and uncemented 91.2% (CI 90.1–92.2) (Table 19). At 15 years, the uncemented group evinced a slightly worse survival rate than the hybrid and cemented fixation groups; in the inverse hybrid group there were not enough patients at risk to calculate the survival rate at 15 years.

Table 19. Unadjusted Kaplan-Meier (KM) 10- and 15-year survival rates with 95% confidence intervals (CI) for uncemented, inverse hybrid, hybrid, and cemented TKA

Type of fixation	N of knees	N of revisions	At risk at 10 years	KM-survivorship (%) at 10 years	At risk at 15 years	KM-survivorship (%) at 15 years
Uncemented	6 132	363	915	91.2 (90.1–92.2)	214	88.7 (87.0–90.4)
Inverse Hybrid	546	16	66	96.0 (94.1–98.1)	-	-
Hybrid	6 329	330	1 349	93.0 (92.2–93.8)	239	91.4 (90.2–92.6)
Cemented	102 170	5 040	24 954	93.6 (93.4–93.8)	4 259	91.3 (91.0–91.7)

In Cox regression analysis in patients aged less than 65 years, uncemented fixation evinced an increased risk of revision compared with the cemented group both during the first postoperative year and after 6 years of follow-up. Hybrid fixation, on the other hand, was associated with a significantly decreased risk for revision compared with cemented fixation after 6 years of follow-up. The inverse hybrid group had a comparable risk for revision compared with cemented TKAs (Table 20). Because the survival of TKAs is age-dependent, an additional Cox regression analysis was conducted for two different age groups: 55 to 64 years of age and less than 55 years of age (Tables 21 and 22).

Table 20. Cox regression with time-dependent coefficients (all patients aged <65 years included, cemented TKA as reference)

Type of fixation	Follow-up	HR	95% CI
Uncemented	<1 years	1.38	1.13–1.70
	1–3 years	1.14	0.97–1.35
	3–6 years	0.95	0.72–1.25
	>6 years	1.32	1.00–1.73
Inv hybrid	<1 years	0.29	0.07–1.16
	1–3 years	0.67	0.34–1.35
	3–6 years	0.91	0.38–2.19
	>6 years	0.54	0.13–2.15
Hybrid	<1 years	1.11	0.88–1.39
	1–3 years	0.94	0.78–1.12
	3–6 years	1.07	0.82–1.40
	>6 years	0.54	0.38–0.78
Cemented (ref.)		1.0	-

In patients aged 55 to 64 years, the risk for revision with uncemented TKAs increased in comparison with the cemented reference group during the first 3 years of follow-up. After 6 years of follow-up, Hybrid TKAs still showed a significantly decreased risk for revision; a finding that was seen in the whole study cohort (Table 21).

Table 21. Cox regression with time-dependent coefficients in patients aged 55 to 64 years

Type of fixation	Follow-up	HR	95% CI
Uncemented	<1.5 years	1.37	1.13–1.67
	1.5–3 years	1.31	1.01–1.69
	3–6 years	0.86	0.59–1.24
	>6 years	1.32	0.96–1.83
Inv hybrid	<1.5 years	0.44	0.14–1.37
	1.5–3 years	0.65	0.21–2.02
	3–6 years	0.88	0.28–2.75
	>6 years	0.49	0.07–3.48
Hybrid	<1.5 years	1.15	0.94–1.41
	1.5–3 years	0.90	0.68–1.20
	3–6 years	1.14	0.85–1.53
	>6 years	0.55	0.37–0.83
Cemented		1.0	

In patients aged less than 55 years, there were no differences in survival between fixations (Table 22).

Table 22. Cox regression with time-dependent coefficients in patients aged <55 years

Type of fixation	HR	95% CI
Uncemented	1.10	0.91–1.32
Inv hybrid	0.62	0.29–1.29
Hybrid	0.83	0.67–1.04
Cemented	1.0	-

Because of the lower total number of TKAs in the inverse hybrid group compared with other groups, we conducted an additional sensitivity analysis to diminish bias between the groups. For this analysis, we only included patients with Nexgen TKAs.

In this sensitivity analysis, KM survival rates of different fixations at 7 years were in descending order: the inverse hybrid 96.6% (CI94.7–98.5), cemented 95.8% (CI 95.5–96.1), uncemented 93.2% (CI 91.9–94.6), and hybrid 92.0% (CI 90.4–93.7).

In the Cox analysis of the Nexgen subgroup, an increased risk for revision was seen in uncemented and hybrid TKAs compared with cemented TKA. With inverse hybrid TKAs, the risk for revision was comparable to cemented TKAs (Table 23).

Table 23. Cox regression with time-dependent coefficients in patients aged <65 years in the Nexgen subgroup

Type of fixation	HR	95% CI
Uncemented	1.37	1.12–1.67
Inv hybrid	0.59	0.34–1.03
Hybrid	1.47	1.16–1.87
Cemented	1	-

5.4.1 Survivorship of the TM tibial component

Survivorship of the whole study cohort was 100% (95% CI 99–100) at 1, 5, and 7 years postoperatively using revision for aseptic loosening of the tibial component as the end-point. When revision for any reason was used as the end-point, 1-, 5-, and 7-year survivorship was 99% (95% CI 98–100), 97% (95% CI 96–98), and 97% (95% CI 96–98), respectively. Kaplan-Meier survival curves with the end-point as revision of the tibia component for any reason are shown in figure 19.

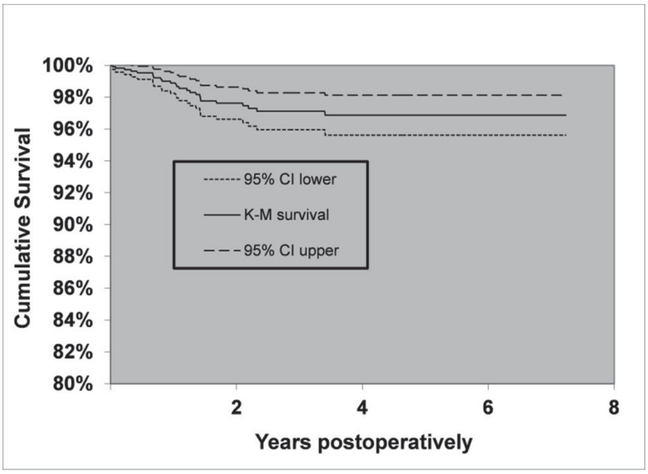


Figure 19. Kaplan-Meier survival curves for 1 143 primary total knee arthroplasties using the Trabecular Metal Monoblock Tibia (mean follow-up 2.7 years). The end-point was defined as revision of the tibia component for any reason

In the analysis of different age groups, the survivorship of TM tibias were comparable at 5 years (Table 24).

Table 24. Kaplan-Meier survivorship with end-point as revision of the tibia component for any reason in different age groups

Cohort	Na	MF (range)	AR 1 yr	1-year survival % (95% CI)	AR 5 yr	5-year survival % (95% CI)
All	20/1143	2.7 (0–7.9)	866	99 (99–100)	175	97 (96–99)
Age <55 years	3/167	2.5 (0–7.9)	126	99 (97–100)	25	98 (95–100)
Age 55–65 years	10/457	2.6 (0–7.9)	353	100 (99–100)	53	97 (95–99)
Age >65 years	7/519	2.8 (0–7.9)	387	99 (99–100)	97	98 (96–100)

[a] Number of revisions / number of total operations. MF = mean follow-up (years). AR = at risk.

In the Cox multiple regression model, there was no difference in risk for revision between any of the variables studied (Table 25).

Table 25. Risk for revision between demographic variables

Cohort	Na	MF (range)	Adjusted RR for revision (95% CI)	p
All	20/1143	2.7 (0–7.9)	-	-
Women	14/647	2.7 (0–7.9)	1.8 (0.7–4.7)	0.22
Men	6/496	2.6 (0–6.9)	1.0	-
Primary osteoarthritis	19/1087	2.7 (0–6.9)	1.0	-
Other indications	1/56	2.7 (0–6.9)	1.1 (0.1–8.6)	0.94
Cemented femur	13/548	3.6 (0–7.8)	1.0	-
Uncemented femur	7/595	1.8 (0–7.9)	1.1 (0.4–3.1)	0.82
Patella not resurfaced	15/974	2.5 (0–7.9)	0.6 (0.2–1.9)	0.40
Patella resurfaced	5/168	3.5 (0–6.9)	1.0	-
Age <55 years	3/167	2.5 (0–7.9)	2.7 (0.6–13.5)	0.21
Age 55–65 years	10/457	2.6 (0–7.9)	3.3 (0.2–47.5)	0.37
Age >65 years	7/519	2.8 (0–7.9)	1.0	-

a Number of revisions / number of total operations. MF = mean follow-up (years). RR = risk ratio from the Cox regression analysis (adjustment was made for age and sex).

5.4.2 Revision operations

In total, 20 knee revisions including removal or replacement of the uncemented porous tantalum tibial component with or without revision of the femoral component were reported during the period 2003 to 2010. The indications for revisions were ascertained from the patients' medical records from the hospital concerned.

The most common reason for revision was tibiofemoral joint instability with or without malposition of the TKR components (n=12, 60%). This was followed by PJI (n=7, 35%). Aseptic loosening was the reason for revision in one patient (5%).

5.5 Patient-reported outcomes (Study IV)

5.5.1 OKS

Mean OKS increased both statistically (18 points (CI 17–19), p<0.001) (TKA and UKA together) and clinically (exceeding MCID) significantly from the preoperative situation to 2-year follow-up (Figure 20). The mean increase did not differ between TKAs and UKAs (Table 26).

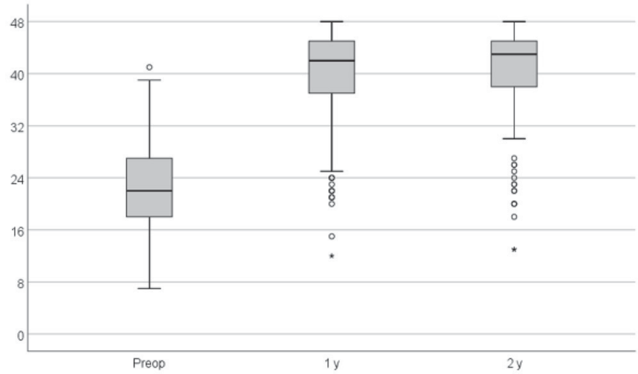


Figure 20. OKS with 2-year follow-up (TKA and UKA together)

Table 26. OKS scores preoperatively and at 2-years analyzed separately for TKA (n=227) and UKA (n=27). The scores are shown as mean and 95% CI

	TKA					UKA				
	Preoperative		2 years		p	Preoperative		2 years		p
OKS	22	(21–23)	41	(40–42)	<0.001	24	(21–28)	42	(40–43)	<0.001

5.5.2 KOOS

In study IV, a significant increase (p<0.001) was observed in all KOOS subscales, all of which also exceeded MCID. The mean increase of score between preoperative and 2-year follow-up were (TKA and UKA together): KOOS pain 41 (CI 39–43), KOOS symptoms 35 (CI 32–37), KOOS ADL 37 (CI 35–40), KOOS sport/rec 40 (CI 37–44), and KOOS QoL 48 (CI 45–51) (Figure 21, Table 27).

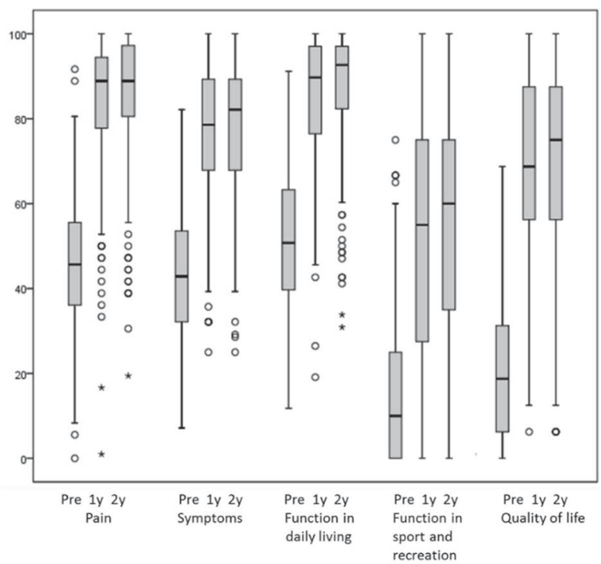


Figure 21. Outcome measured with KOOS subscales. Values presented as median (Q_1 to Q_3)

Table 27. KOOS scores preoperatively and at 2-years analyzed separately for TKA (n=227) and UKA (n=27). The scores are shown as mean and 95% CI.

	TKA					**UKA**				
	Preoperative		2 years			Preoperative		2 years		
KOOS pain	45	(43–47)	86	(84–88)	<0.001	46	(39–53)	86	(81–91)	<0.001
KOOS symptoms	43	(41–46)	79	(76–81)	<0.001	48	(40–55)	77	(70–84)	<0.001
KOOS ADL	50	(48–52)	88	(86–90)	<0.001	56	(50–62)	89	(84–94)	<0.001
KOOS sport/rec	14	(12–17)	55	(51–59)	<0.001	16	(10–23)	55	(44–67)	<0.001
KOOS QoL	21	(19–23)	70	(67–73)	<0.001	25	(18–31)	68	(58–77)	<0.001

ADL=Activity of Daily Living, sport/rec= Function in sports and recreation, QoL=Quality of Life.

5.5.3 HAAS

In study IV, the preoperative baseline (mean) in physical activity according to HAAS was moderate: 6/18 in patients in the TKA group and 7/18 in the UKA group, respectively. The increase in mean HAAS (TKA and UKA together) was 5 points (CI 4.6–5.5) over the 2-year follow-up period and the improvement was significant (p<0.001) (Figure 22). Outcomes were comparable between UKA and TKA (Table 28).

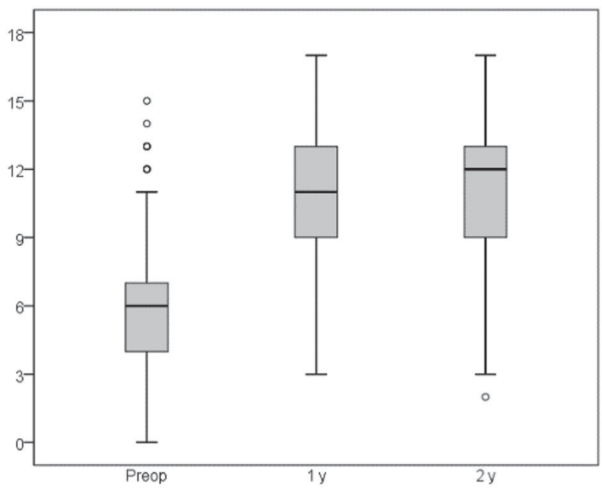


Figure 22. Outcome measured with HAAS. Values presented as median (Q_1 to Q_3)

Table 28. Outcome measured with HAAS. TKA and UKA separately. The scores are shown as mean and 95% CI

	TKA					UKA				
	Preoperative		2 years		p	Preoperative		2 years		p
HAAS	6	(5–6)	11	(10–11)	<0.001	7	(6-9)	12	(11-13)	<0.001

5.5.4 RAND-36

RAND-36 score was analyzed with mental (MCS) and physical (PCS) subscales. Over the 2-year follow-up period, the mean MCS increased (TKA and UKA together) 18 points (CI 15–20) and the mean PCS 31 points (CI 28–34). The change seen in both subscales was both significant ($p<0.001$) and also exceeded MCID (Figure 23 and Table 29).

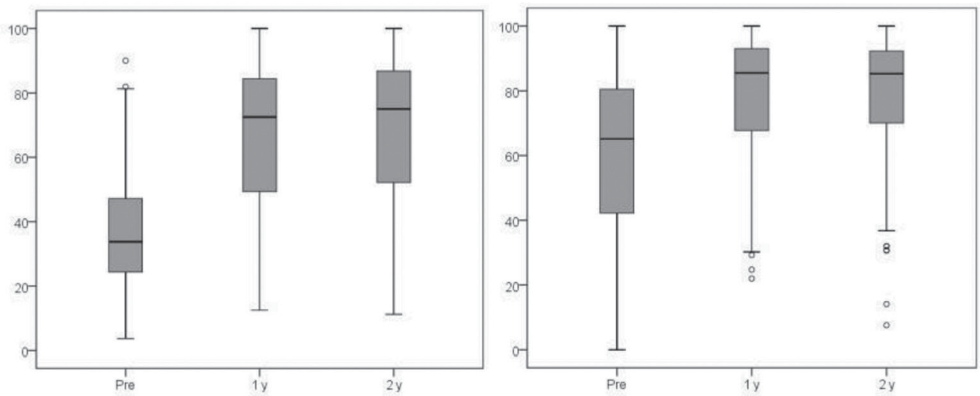


Figure 23. Outcome measured with RAND-36. PCS (left) and MCS (right) separately. Values presented as median (Q_1 to Q_3)

Table 29. Outcome measured with RAND-36. TKA and UKA separately. The scores are shown as mean and 95% CI

	TKA					UKA				
	Preoperative		2 years		p	Preoperative		2 years		p
RAND-36 MCS	61	(58–64)	79	(77–81)	<0.001	65	(56–73)	78	(69–87)	0.007
RAND-36 PCS	37	(34–39)	68	(65–71)	<0.001	39	(34–45)	70	(61–79)	<0.001

MCS= mental component score, PCS= physical component score.

5.5.5 VAS pain

Pain relief was measured with the VAS (exercise and rest). A significant positive change of median value (in exercise: 80 (72.90) vs 13 (4.32), p<0.001 and in rest: 49 (26.71) vs 3 (0.7), p<0.001) from the preoperative situation to the 2-year follow-up was detected (Figure 24). In 16 (7%) patients, all of whom had undergone TKA, severe knee pain (VAS>30) was still reported 2 years after knee arthroplasty.

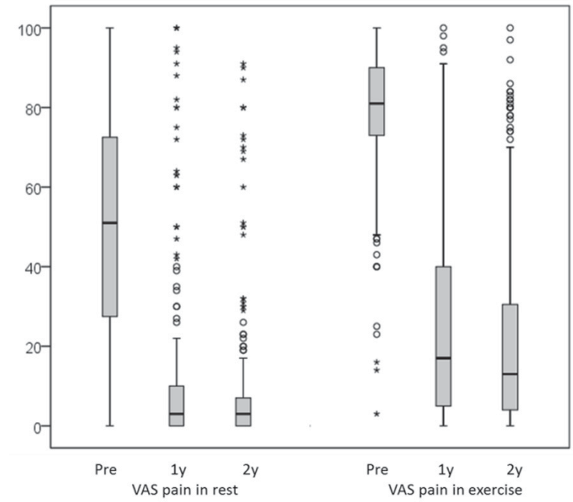
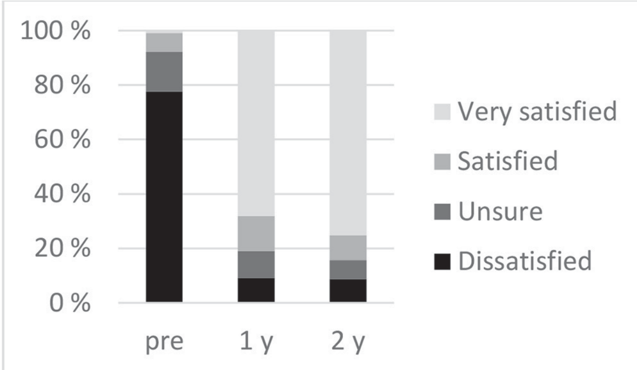


Figure 24. VAS pain in rest and exercise. Values presented as median (Q_1 to Q_3)

5.5.6 VAS satisfaction

At the time of the 2-year follow-up visit, 85% of patients were either satisfied (9%) or very satisfied (76%) with the outcome of their knee arthroplasty. Between 1- and 2-year follow-up evaluations, 16 patients (6.7%) who had been either unsure or satisfied with the outcome at the 1-year visit had become more satisfied by the 2-year follow-up evaluation. The number of patients who were dissatisfied with the outcome did not change between the 1- and 2-year follow-up evaluations (Figure 25). At the 2-year follow-up visit, 98% of all patients reported that they would choose to undergo knee arthroplasty again, and 96% reported that they would recommend this operation to their best friend. Regarding satisfaction, there was no difference between patients in the UKA and TKA groups.

Figure 25. VAS satisfaction



5.5.6.1 Effect of preoperative KL grade

Preoperative KL grade significantly affected both satisfaction and PROM outcomes measured at 2 years. The median VAS satisfaction was significantly poorer in patients with preoperative KL grade 2 OA compared with both patients with KL 3 (85 (51,97) vs 94 (80,100) points, p=0.006) as well as those with KL 4 OA (85 (51,97) vs 91 (81,99) points, p=0.015) at the time of the 2-year follow-up visit (Figure 26). Furthermore, there was also a significant difference in median OKS between the groups at the time of the 2-year follow-up visit: median OKS was worse in the KL 2 group than in both the KL 3 group (41 (36,44) vs 44 (38,46) points, p=0.015) and the KL 4 group (41 (36,44) vs 43 (40,45) points, p=0.037). However, this difference fulfilled the MCID criteria only when the KL 2 and KL 3 groups were compared. Similarly, patients with preoperative KL 2 OA, ended up with significantly poorer median subscale scores than those patients with more advanced radiographic OA (KL 4) at the time of the 2-year follow-up visit: KOOS symptoms (75 (61,89) vs 86 (78,93), p=0.001), KOOS ADL (88 (76,96) vs 93 (85,97), p=0.041), and KOOS sport/rec (40 (25,75) vs 60 (38,75), p=0.028). The significant improvements between preoperative and 2-year follow-up were observed in all PROMs and also in KL 2 patients (p<0.001).

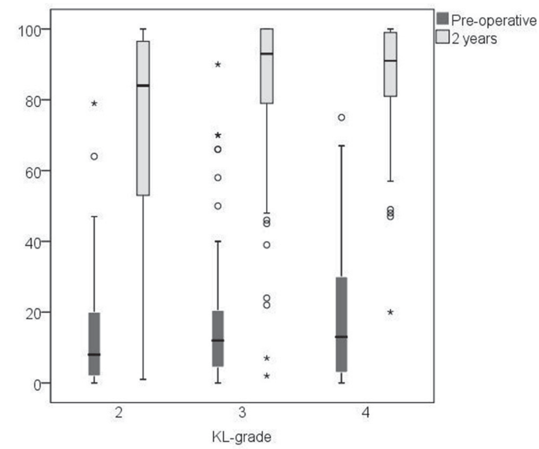


Figure 26. VAS satisfaction in different KL groups. Scores presented as median (Q_1 to Q_3)

Dissatisfaction in patients with unilateral TKA was analyzed to diminish bias with UKA and bilateral knee concerning satisfaction with knee arthroplasty. Crosstabulation and the chi square test were used to analyse the effect of the severity of preoperative OA with dissatisfaction. The difference was even more significant compared to the analysis shown in Figure 25. In the KL 2 group, the dissatisfaction rate was significantly higher compared with the KL 3 and KL 4 groups (Table 30).

Table 30. Proportion of dissatisfied patients and MCID (Δ10 points) in different KL groups measured with satisfaction VAS (0–100). Unilateral TKAs are included and KL2 is compared to KL3 and KL4 in dissatisfaction analysis.

	KL 2	**KL3**	**KL4**	p
Dissatisfied (%)	27.3	5.2	6.7	0.007
MCID (%)	94	99	97	0.64

5.5.7 Revisions (study IV)

Of the 254 knee replacements originally operated, 6 (2.4%; 4 TKAs and 2 UKAs) had to be revised during the 2-year follow-up period. Two patients in the TKA group underwent secondary patellar resurfacing because of persistent anterior knee pain, one TKA was revised for prosthetic joint infection, and one TKA for stiffness due to arthrofibrosis. Of the 2 UKAs that underwent revision surgery, one was revised for dislocation of the polyethylene insert and the other for impingement. Revised patients were excluded from the final outcome assessment.

5.6 Effect of LIA on immediate pain management and PROMs (study V)

5.6.1 Effect of LIA on oxycodone consumption and pain management

The cumulative consumption of oxycodone was smaller in the LIA group than in the Placebo group at all measured time-points until 48 hours (Figure 27). A trend for decreased consumption of oxycodone in the LIA group persisted up to 24 hours postoperatively. The differences of means in the cumulative consumption of oxycodone were 17 mg (95%CI 11–22) at 6 hours, 20 mg (Cl 11–30) at 12 hours, 28 mg (Cl 11–45) at 24 hours, and 35 mg (Cl 5–64) at 48 hours.

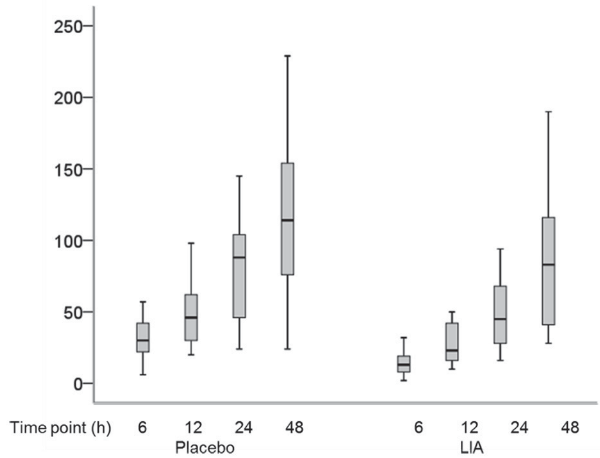


Figure 27. Median cumulative consumption of oxycodone during 48-hour interval postoperatively

In comparison of the different time intervals, the LIA group used statistically less oxycodone than the Placebo group during the first 6-hour interval: 14 (2–34) mg vs 30 (6–57) mg, $p<0.001$ (Figure 28). The differences of means in the time intervals were 17 mg (Cl 11–22) in the 0–6 hours interval, 4 mg (Cl -1–10) in the 6–12 hours interval, 7 mg (CI -2–16) in the 12–24 hours interval, and 5 mg (CI -11–21) in the 24–48 hours interval.

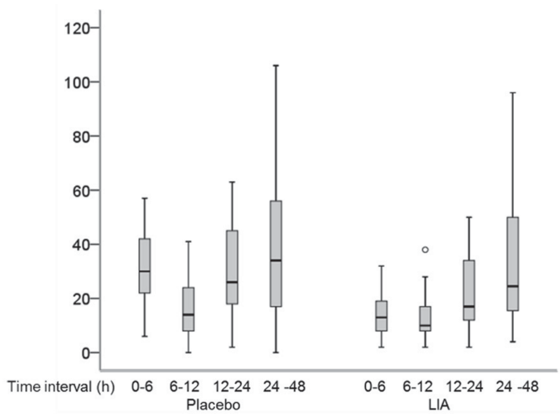


Figure 28. Consumption of oxycodone during the time intervals. Consumption is presented as median (Q_1, Q_3)

A median level of under 3 in VAS score was considered to be an adequate pain management level and was achieved in both groups until 48 hours postoperatively (Figure 29). The differences of means in VAS were 0.5 (CI -0.3–1.4) at 3 hours, 1.0 (CI -0.2–2.1) at 9 hours, 0.5 (CI -0.6–1.5) at 18 hours, and 0.4 (CI -0.7–1.4) at 48 hours showing that the groups had no significant differences in pain management.

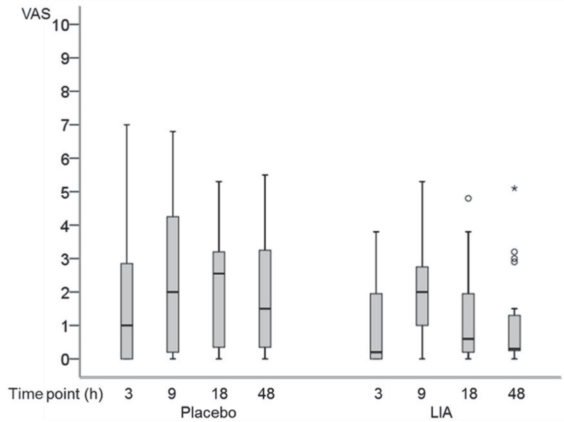


Figure 29. Postoperative pain at rest. VAS scores are presented as median (Q_1, Q_3). 3 h p=0.4, 9 h p=0.2, 18 h p=0.4, 48 h p=0.5

Postoperatively, 3 patients in the Placebo group discontinued participation in the study because of intense pain and were treated with epidural analgesia. In the LIA group, however, none of the patients discontinued the study because of pain.

5.6.2 Effect of LIA measured with OKS

The functional outcomes between the groups differed in mean values, but the difference was not statistically significant as measured with OKS (Table 31). There was, however, a trend for higher mean values in OKS for patients in the LIA group at 12 months postoperatively.

Table 31. Outcomes measured with OKS in LIA and Placebo groups

	LIA n=27	Placebo n=29	Mean difference	(95%CI)
OKS				
pre op	23 (7.74)	22 (6.04)	-1.365	(-5.099–2.369)
3 months	37 (6.87)	36 (5.38)	-0.654	(-4.093–2.785)
1 year	44 (4.43)	41 (5.50)	-2.706	(-5.480–0.069)

5.6.3 Effect of LIA measured with HAAS

The functional outcomes between the groups did not have a significant difference as measured with HAAS (Table 32).

Table 32. Effect of LIA measured with HAAS at 1-year follow-up

	LIA	Placebo	Mean difference	(95%CI)
HAAS				
pre op	8 (3.11)	7 (2.67)	-0.447	(-2.010–1.116)
3 months	11 (2.36)	11 (2.78)	-0.047	(-1.489–1.394)
1 year	12 (2.44)	11 (3.45)	-1.111	(-2.744–0.521)

5.6.4 Effect of LIA measured with 15-D

The functional outcomes between the groups did not have a significant difference as measured with 15-D (Table 33).

Table 33. Effect of LIA measured with 15-D at 1-year follow-up

	LIA	Placebo	Mean difference	(95%CI)
15D				
preop	0.88 (0.08)	0.87 (0.07)	-0.017	(-0.056–0.023)
3 months	0.92 (0.05)	0.92 (0.05)	0.001	(-0.028–0.030)
1 year	0.93 (0.07)	0.91 (0.07)	-0.018	(-0.056–0.020)

5.6.5 Effect of LIA measured with TKFQ

There was a statistically significant difference between the groups in 1 subscale of the TKFQ questionnaire. At 12 months postoperatively, it was easier for patients in the LIA group to sit for a long period of time (Table 34).

Table 34. Effect of LIA measured with TKFQ (Sitting for a long period of time) at 1-year follow-up

	LIA	Placebo	Mean difference	(95%CI)
TKFQ				
Sitting for a long period of time				
pre op	2 (0.72)	2 (0.57)	-0.255	(-0.607–0.096)
3 months	2 (0.58)	2 (0.50)	0.077	(-0.227–0.380)
1 year	1 (0.49)	1 (0.47)	-0.299	(-0.558– -0.040)

5.6.6 Effect of LIA in ROM

The difference of means in ROM at 6 hours between LIA and the placebo group was -26 (CI -39– -12). At 24 hours -10 (CI -21–1) and 48 hours -1.5 (CI -13–10), the differences were not significant between the groups (Figure 30).

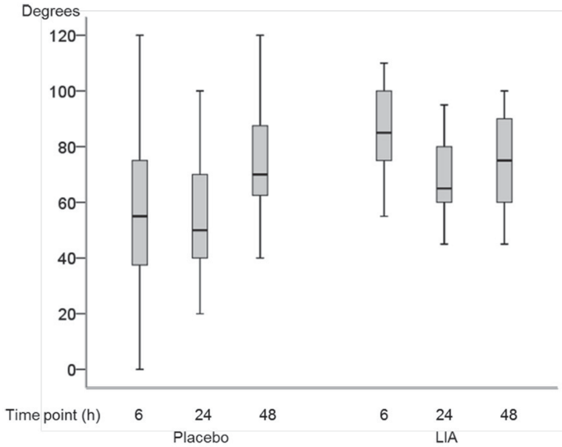


Figure 30. ROM at measured time point. ROMs are presented as median (Q_1, Q_3). 6 h p=0.001, 24 h p=0.08, 48 h p=0.6. Bonferroni adjusted p-value for 6 h time point, p=0.004

6 Discussion

6.1 Incidences

Traditionally, knee arthroplasty surgery has been reserved for elderly patients, for those with severe disease (Robertsson et al. 2014), and for younger patients with rheumatoid arthritis. In recent years, it seems that the indications have widened to include younger patients. This has resulted in a proportionally higher increase in incidence in patients younger than 65 years, when compared with patients 65 years or more (Robertsson et al. 2010b, Leskinen et al. 2012). In a study from the Finnish Arthroplasty Registry, the annual cumulative incidence of UKAs and TKAs increased rapidly between 1980 and 2006, especially in patients aged 50 to 59 years, the so-called baby-boomer generation (Leskinen et al. 2012).

6.1.1 TKA

The total increase in the number of arthroplasties in all countries was mainly caused by an increased incidence of TKAs. The reasons for the increasing incidence of younger TKA patients may be multifactorial. However, increasing obesity among young patients (Kautiainen. 2005, Lohmander et al. 2009), participation in contact sports (Driban et al. 2015), and the introduction of fast track surgery which better suits working-age patients are probable reasons. Of the 3 age groups, patients younger than 65 years of age represented the lowest incidence of TKAs. The relative incidence increase was, however, higher in that age group than in the other age groups. In our study, the incidence of TKAs steadily increased in all the participating countries, which is in line with finding from other studies (Kurtz et al. 2007, W-Dahl et al. 2010a, Leskinen et al. 2012). The incidence of TKA in females was found to be greater than in males in our study, but the results of previous studies have also shown that the proportion of female patients compared with males has decreased over time (Nemes et al. 2015a). Moreover, sex distribution may also vary between nations (Paxton et al. 2011, Nemes et al. 2015b).

6.1.2 UKA

Concerning UKA, there was a significant decrease in the incidence of UKAs in patients 65 years or older in Sweden. In 3 other countries, the variations of incidences in UKAs between groups were more heterogeneous. The reasons for the changes between UKA incidences are also multifactorial. Previous studies from national registers have affected UKA incidences as most registries show a higher overall revision rate for UKAs compared with TKAs (Furnes et al. 2007, Koskinen et al. 2008, W-Dahl et al. 2010b). However, there are also studies that claim UKAs have a better clinical outcome and are more cost effectiveness (Slover et al. 2006, Lygre et al. 2010b). Different UKA implant models with a longer learning curve compared with TKA, indications for primary UKA surgery, and a higher revision risk compared with TKA may explain the differences in the incidence. The increase in the incidence of UKA in patients younger than 65 years may be explained by the increase in minimally invasive surgery (MIS) that enables a shorter postoperative stay in hospital.

6.1.3 Working-age patients

Concerns have been raised about the long-term outcome of TKAs and the possibility of an increasing revision burden because younger age has been associated with a higher risk for early periprosthetic joint infection and aseptic mechanical failure after TKA (Meehan et al. 2014). In another study, young age impaired the prognosis of TKA and was associated with increased revision rates for non-infectious reasons (Julin et al. 2010). A comparison study undertaken by the Norwegian Knee Arthroplasty Register and a United States Arthroplasty Registry showed an increased risk for revision in patients younger than 65 years compared with patients 65 years or older (Paxton et al. 2011).

In our study, the proportional growth of TKAs during the study period was highest in patients younger than 65 years. Despite this, the incidence of knee arthroplasty in the youngest age group was lower than in patients aged 65 years or older. Based on this finding, the majority of knee arthroplasties will probably be performed on elderly patients also in future. Even though patients less than 65 years old represented a lower incidence level than patients 65 or older in our study, these working-age patients should be considered as an important subgroup because of their higher physical activity, their demands for surgery, and the multi-factorial reasons behind the success of TKA (Keeney et al. 2014, Klit et al. 2014, Parvizi et al. 2014).

6.1.4 Future projections

Even if incidences showed an increasing trend during the study period, some plateauing in the trends was seen during the last few years in our study. One study delivered projections for primary and revision hip and knee arthroplasty in the United States from 2005 to 2030 (Kurtz et al. 2007). In that study, the authors predicted that if the number of total knee arthroplasties performed continues at the current rate, the demand for primary total knee arthroplasty is projected to grow 7-fold by 2030. Another projection of the same but newer data from the USA reported that significant increases in the use of total hip arthroplasty (THA) and TKA are expected in the United States in both females and males in future (Singh et al. 2019).

Obesity is also a growing burden in many countries and, as this has been shown to be a certain risk factor for knee osteoarthritis, especially in young patients, it may also contribute to the increasing demand for TKAs in future (Apold et al. 2014a, Apold et al. 2014b, Silverwood et al. 2015b).

6.1.5 Strengths and limitations of the study (study I)

The major strength is the unique collaboration of 4 national registers in the creation of a multinational database comprising a large number of patients that enables international comparison to reveal possible differences and may help to estimate future demands. Further, completeness and data validity were high in the Nordic countries at the end of study period: NAR 95%, SKAR 97%, DKR 97%, FAR 96% (annual reports 2015: Danish knee arthroplasty register, Norwegian Arthroplasty Register, Swedish Knee Arthroplasty Register, Finnish Arthroplasty Register). Previously, the completeness in the DKR was reported to be 89% in 2007 (Robertsson et al. 2010b). This may have caused a 10 to 15% underestimation of incidence in Denmark over the period 1997 to 2007. Indeed, the total relative change of incidence was highest in Denmark and that may have been due to the influence of the lower completeness of the DKR in the early years of study period. A lack of data on BMI and other subgroups could also be considered a limitation of our study.

6.2 Survivals of different fixations (studies II and III)

We found that both cemented and hybrid TKAs evinced excellent 15-year survival rates in patients aged <65 years. Even though hybrid/inverse hybrid versions of the well performing contemporary TKA designs provided younger patients with a good mid-term outcome in our study, they were still used in a limited number of patients. Especially in the inverse hybrid group, one single TKA design, with a very good track record comprised the vast majority of the whole group. Bone density tends to be higher in younger patients than in older patients, and this may cause suboptimal integration of bone cement even when using a good cementing technique. In theory, younger patients might benefit from biologic fixation, i.e., bone ingrowth into uncemented implants. A meta-analysis (Gandhi et al. 2009) based on five RCTs and 10 observational studies with different mean ages of patients and with a minimum follow-up of two years, found improved survival for cemented compared with uncemented implants when revision for aseptic loosening was used as an endpoint. Another systematic review and meta-analysis (Voigt and Mosier. 2011b) compared hydroxyapatite-coated, porous coated, and cemented tibial components. Evidence of more stable fixation after two years with hydroxyapatite-coated components compared with porous-coated and cemented implants was found, but there was no difference between revision rates at 10-year follow-up. In an RCT, no difference was shown in revision rates and survival between cemented and uncemented TKAs with a mean follow-up of 15 years (Baker et al. 2007a). Arnold et al. conducted a systematic review of 11 RCTs to identify whether there was an association between fixation method and clinical outcome. They found that short- and long-term outcomes were not influenced by fixation type but, especially with uncemented TKAs, outcomes are implant- dependent (Arnold et al. 2013).

6.2.1 Trends between fixations

In our study, the majority of TKAs performed for younger patients in the four participating Nordic countries were still cemented. The same trend in general has also been reported from other national registers. For example, the annual report 2017 of the National Joint Registry for England, Wales and Northern Ireland (NJR) reported that the proportion of all cemented TKA implants increased from 81.5% in 2003 to 87.3% in 2016. During the same time period, uncemented implants decreased from 6.7% to 2.0% and hybrid implants from 2.8% to 0.4%. The same increasing trend of using cemented implants was seen in the Australian Joint Registry (AOANJRR annual report 2017) which reported a change from 44.8% in 2003 to 66.4% in 2016. The use of uncemented implants decreased from a peak of 23.4% in 2003 to 11.8% in 2016. In our study, the proportional number per year of cemented TKAs decreased from 95.8% in 2000 to 90.8% in 2016 and an increase in uncemented TKAs was observed from 2.5% to 6.5%, respectively.

6.2.2 Risk for revision

In our study, hybrid TKAs, showed a decreased risk for revision after 6 years of follow-up, which may predict good long-term survival. Inverse hybrid TKAs showed a comparable risk with cemented TKAs, whereas uncemented TKAs had the most probable risk for revision. These findings are in line with some previous reports, even if the risk for revision with inverse hybrid TKAs has not been reported before. In a Finnish register-based study, uncemented TKAs had a 1.4 times elevated adjusted risk for revision compared to that of cemented TKAs (Julin et al. 2010). In the AOANJRR annual report in 2017, the cumulative 10-year revision percent of minimally stabilized TKA was 4.5 (4.3, 4.6) with cemented TKA, 6.1 (5.9, 6.3) with uncemented TKA and 4.6 (4.4, 4.7) with hybrid TKA. In the New Zealand Joint Register annual report in 2017, the revision rate for patient 55 to 64 years of age was the highest with uncemented implant: 0.84 (CI 0.67–1.05)/100 component-years) compared with 0.62 (CI 0.58–0.66)/100 component-years) with cemented implants and 0.61 (CI 0.47–0.77)/100 component-years) with hybrid implants.

Based on our results, it seems that fixation methods other than cemented TKA may also result in good mid-term survivorship in working-age patients. Only uncemented fixation showed an increased risk for revision in comparison with the cemented reference group. In previous studies, early failures of uncemented TKAs were mainly caused by aseptic loosening of the patellar button and the tibial component (Collins et al. 1991, Bassett. 1998, Duffy et al. 1998a, Berger et al. 2001c, Barrack et al. 2004, Goldberg and Kraay. 2004, Carlsson et al. 2005). Uncemented fixation has been associated with a high failure rate due to inadequate bone ingrowth in TKAs (Lombardi et al. 2007). The same finding of inferior early results were also found in this study, especially in patients 55 to 65 years of age. Survivorship of certain uncemented TKA designs has subsequently been reported to be comparable to that of cemented designs, but these reports have originated from single centers and may, at least in part, be explained by patient selection and also the fact that these are the results of high-volume surgeons (Whiteside. 1994, Hofmann et al. 2002b, Beaupre et al. 2007, Baker et al. 2007b).

6.2.3 Tantalum metal tibias

The first TM monoblock tibial components were cemented ones. In 2010, O'Keefe, Winter et al. published a series of 125 TKRs in which a cemented TM monoblock tibial component was combined with cemented femoral and patellar components (O'Keefe et al. 2010). In that study, only two tibial components were revised during follow-up (a minimum of 5 years). Another prospective study that compared 100 uncemented TM monoblock tibias to 312 cemented controls reported excellent survivorship of the TM monoblock tibial components at a minimum follow-up of 5 years. In that study, none of the uncemented tibial components loosened, neither were there any signs of osteolysis among these patients (Kamath et al. 2011a).

A TM tibia has a highly porous tantalum tray with a fixed polyethylene insert and the reduced stiffness of the tantalum implant may cause less stress shielding than in conventional metal-backed components (Patil et al. 2009). Further, inducible displacement of uncemented TM tibia have reported less stiffness than cemented ones (Wilson et al. 2010a). The uncemented TM tibial component has been shown to yield good results both in randomized clinical trials (RCT) series (Pulido et al. 2015, Henricson and Nilsson.

2016a) as well as in our study. Moreover, functional results have been comparable with cemented TKA (Fernandez-Fairen et al. 2013). The higher costs of TM tibial components may, however, have restricted its more general use in the Nordic countries.

In study II, TM tibial components were used both in a group of uncemented TKAs as well as in inverse hybrid TKAs. In our study, the Nexgen TKA comprised the majority of the TKAs in the inverse hybrid group. Moreover, 87% of the Nexgen TKAs used TM tibial components. At 10 years, inverse hybrid TKAs showed a comparable survival rate with cemented TKA and also exceeded that of cemented TKAs in KM analysis. In an additional subgroup analysis of Nexgen TKAs, it appeared that there was no difference in mid-term survival rates between inverse hybrid and cemented Nexgen TKAs. Thus, it seems to be a safe option for selected younger patients undergoing TKA, but its superiority to cemented fixation remains unproven.

In study III, the majority of revisions were performed due to either instability alone or a combination of instability and component malalignment. One disadvantage of using a monoblock tibial component is the risk for instability or excessive tightness due to the lack of modularity after the tibial and femoral components are in place. With a monoblock type of implant, there is no potential for isolated polyethylene insert exchange if instability is observed after the primary operation, necessitating revision surgery. In this cohort, there were two patients with instability without malalignment of components and who could have been candidates for polyethylene insert exchange alone.

In theory, the lack of antibiotics-loaded bone cement and the huge surface area of the trabecular tibial component might predispose to PJI. However, the incidence of revisions due to PJI was only 0.7% in study III. In another paper based on Finnish Arthroplasty Registry data, the incidence of revisions due to PJI was 0.6% among 32 019 TKRs (Julin et al. 2010). Thus, this evidence from the population-based setting does not support this theory.

In study III, only one revision was performed due to aseptic loosening of this tibial component. Neither age nor any of the other variables showed any effect on the risk for revision in multivariate regression analyses.

6.2.4 Strengths and limitations of the study (study II and III)

In study II, the major strength was the unique collaboration of four national registers in the creation of a multinational database comprising a high number of patients. This NARA database enables international comparisons to reveal possible differences in trends and outcomes of TKA. Further, completeness and data validity were high in the Nordic countries at the end of study period: SKAR 97%, DKR 97%, NAR 95%, and FAR 96% (annual reports: Danish knee arthroplasty register, Norwegian Arthroplasty Register, Swedish Knee Arthroplasty Register, Finnish Arthroplasty Register). To the best of our knowledge, this is the first multi-national, register-based study analyzing the effect of all four fixation method together on TKA survivorship. There are also a few limitations in study II. First, there were clearly fewer patients in the alternative fixation groups compared with the cemented reference group. This may have caused some selection bias as most of these operations were performed in only a few hospitals. Second, we did not have exact information on whether some of the uncemented implants were hydroxy-apatite coated or not.

In study III, one of the limitations was the lack of clinical data, including patient-reported outcome measurements. Further, the register-based study setting with a large number of patients did not allow us to conduct radiographic analyses apart from those in revision surgery. Thus, radiographic signs of component loosening or osteolysis could not be analyzed in the total study cohort. Selection bias in the study cohort is a possibility because most of the patients (55%) were younger than 65 years. The mean age of the study cohort was only 64 years, whereas the mean age of all patients undergoing TKR in Finland during the study period was 69 years.

6.3 Outcomes of knee arthroplasty

6.3.1 PROMs

The functional outcomes of knee arthroplasty have traditionally been measured using surgeon-driven clinical scores, such as the Knee Society Score (Ranawat et al. 2005c, Duffy et al. 2007b, Ritter et al. 2007b). Nevertheless, there has been an increasing demand for the subjective, patient-originated evaluation of the outcomes (Goh et al. 2016a). There have been earlier studies on functional gain following TKA in young patients, but these have lacked a true prospective follow-up. These studies have used the upper age limit of 50 (Goh et al. 2016b) or 55 (Scott et al. 2016). In everyday clinical practice, however, these subgroups are marginal. Instead, the rising incidence of TKA has occurred in patients aged 50 to 59 years (Leskinen et al. 2012), which is among the target group of our study. In practice, however, only a few such studies have been published so far that report PROM outcomes in working-age patients (Klit et al. 2014, Parvizi et al. 2014, Goh et al. 2016b). The increasing incidence of TKA also raises the question as to whether the financial resources invested in this treatment provide sufficient beneficial results in the face of the intensifying need for cost containment (NiemelaInen et al. 2017).

In studies IV and V, we utilized a wide set of PROMs to assess the real-world effectiveness of knee arthroplasty in a prospective non-selected cohort and in a randomized clinical trial of patients undergoing TKA or UKA. In study IV, we found that patients aged 65 years or less benefited significantly from knee arthroplasty in terms of pain relief as well as in terms of improved physical activity and quality of life measured with PROMs. However, the total disappearance of symptoms was rare.

6.3.2 Satisfaction

Scott el al. divided the satisfaction scale into four categories: very satisfied, satisfied, dissatisfied, and as the fourth group they included those patients who were unsure about their satisfaction (Scott et al. 2016). In study IV, we found that a small proportion of patients who were "unsure" at the time of the 1-year follow-up reported being satisfied at the time of the 2-year follow-up (7 patients, 2.9%). Thus, in some patients, complete recovery after knee arthroplasty may take up to 2 years. Dissatisfied patients, on the other hand, still held the same view at the time of the 2-year follow-up. Satisfaction is clearly a multidimensional experience because 98% of patients reported being willing to undergo knee arthroplasty again despite the fact that 15% of patients were dissatisfied with or unsure about the outcome of their surgery. The patient's own perspective of the preoperative symptoms and functional disability may partly explain this difference; i.e., they may still have considered the outcome of knee arthroplasty to be better than the preoperative situation despite their residual knee symptoms.

In study IV, 85% of patients were satisfied or very satisfied with the outcome at 2 years postoperatively. Furthermore, an even higher proportion of patients (98%) reported a willingness to undergo knee arthroplasty again. In other recent studies, the subgroups who are dissatisfied with their surgery have been reported to range from 10% to 20% (Parvizi et al. 2014, Scott et al. 2016, Goh et al. 2016b). In this respect, knee arthroplasty is clearly inferior to total hip arthroplasty, and the problem of dissatisfied knee arthroplasty patients clearly needs further research.

Scott et al. reported a high (59%) dissatisfaction rate with TKA in patients with KL1–2 grade OA preoperatively (Scott et al. 2016). In our study, satisfaction at 2 years was also significantly lower in the KL 2 group, both when compared with the KL 3 group and to the KL 4 group. The same effect of preoperative KL grade was highlighted even more in the analysis of unilateral TKAs (Figure 23 and Table 24). A significant improvement, however, was achieved in all KL subgroups when compared with the preoperative situation. As there was no difference in the KOOS pain subscale between the KL subgroups at 2 years, it seems that despite their higher dissatisfaction rate, patients with milder OA (KL 2) also achieved good pain relief. In patients with mild radiographic knee OA, there may be other factors than pain, such as depression or catastrophizing behavior, that could explain higher dissatisfaction rates despite the good pain relief achieved with surgery (Lavand'homme and Thienpont. 2015).

6.3.3 Pain

In study IV, knee arthroplasty resulted in significant pain relief, and most of this effect was seen already during the first postoperative year. Moreover, between 1 and 2 years postoperative, the number of patients with persistent knee pain continued to decrease.

Thus, some patients experienced a clearly delayed recovery, but the small subgroup (7%) of patients who reported severe knee pain still had persistent pain at the time of the 2-year follow-up. Previous studies have shown that persistent pain after knee arthroplasty is strongly associated with psychological aspects and young age (Singh and Lewallen. 2013, Lewis et al. 2015).

6.3.3.1 Effect of LIA on immediate pain

In study V, we found that single periarticular infiltration decreased total consumption of oxycodone for 48 hours, although most of this effect was achieved during the first 6 hours. Sufficient pain relief immediately after surgery also aids in controlling pain at a later stage. In a recent review, the benefits of delayed administration have been questioned, and the authors suggested the use of a single intraoperative administration of an anesthetic cocktail (Gibbs et al. 2012). On the other hand, the use of intra-articular catheter for additional drug administration may reduce the total consumption of opiates up to 48 hours postoperatively compared with the situation where additional bolus is not given. This is supported by a recent randomized study with 48 hours follow-up and intra-articular catheter (Essving et al. 2010), that reported the total median consumption of opiate in the drug infiltration group to be 54 (4–114) mg compared with 86 (28–190) mg in our study. Whether the additional postoperative intra-articular bolus is given or not, supplementary oral medications, such as NSAIDs, are still needed as an adjunct to infiltration analgesia.

In our study, a compression bandage was used in all patients in both groups until the second postoperative day. The use of a compression bandage has been shown to improve pain control at rest at 8 hours and at 90 degrees knee flexion at 5, 6, and 8 hours postoperatively after TKA in a previous randomized study (Andersen et al. 2008a).

6.3.4 Physical activity

The clinically significant improvement in physical activity in younger knee arthroplasty patients is an important finding. Young patients may be self-evidently considered physically active. This may therefore restrict their access to knee arthroplasty because of the fear of compromised implant survival. A recent study by Keeney et al. showed that preoperatively there was no difference in physical activity levels between younger (55 years or less) and older patients (65 to 75 years), and that physical activity increased in both groups after knee arthroplasty (Keeney et al. 2014). In study IV, only 42 (17%) patients reported a preoperative activity level of over 50% according to the HAAS scale. Respectively, the preoperative physical activity level points were less than 50% when also measured with the KOOS (93% of patients) and SF-36 (76% of patients) subscales. However, significant improvement was seen in physical activity postoperatively in the HAAS as well as in the KOOS and SF-36 physical activity subscales. Thus, in younger patients, the ability to exercise can also be improved with knee arthroplasty.

Weiss et al. reported that patients undergoing TKA consider climbing stairs, the ability to walk, and kneeling to be especially important activities in their daily living (Scott et al. 2012). Because the preoperative physical activity of patients undergoing TKA has been shown to be low, more demanding activities, such as cycling or carrying heavy objects, have not been so important for them (Weiss et al. 2002b).

In the working-age population, functions related to daily living are associated with working capability. In our study, 104 (45%) patients had retired or were about to retire preoperatively. Of the 128 (55%) patients who were working preoperatively, a high proportion (89%) returned to work during the 2-year follow-up period, and significant improvements in scores related to daily living supported this finding.

6.3.5 Quality of life

Changes in quality of life are based on both physical and mental improvements and are also related to pain relief. Even if physical scores improved more distinctly, it is notable that mental scores also improved significantly after knee arthroplasty. The Mental Component Score (MCS) of RAND 36 showed comparable improvement with the Physical Component Score (PCS) of RAND 36, emphasizing a comprehensive improvement in outcomes. Previously, Goh et al. also reported significant, albeit slightly smaller, improvements in these scores than the scores we found in the present study (PCS 16.9 vs 31.5 and MCS 4.4 vs 17.5) (Goh et al. 2016b).

6.3.6 UKA

In study IV, UKA and TKA yielded similar results. Thus, the theoretical advantages of UKA over TKA (Mohammad et al. 2017) did not result in better clinical outcome in any of the PROMs used or higher satisfaction. This finding warrants further research, and future work should compare the outcome and effectiveness of UKAs and TKAs in randomized controlled trials.

6.3.7 Strengths and limitations of the study (study IV)

The obvious strength of the current study was the evaluation of the outcomes using multiple PROM data that have not been included in previous studies and a non-selected real-world cohort of patients. In addition, only a very small proportion (7%) of patients was lost to follow-up during the 2-year study period. Our study is also the first to evaluate the real-world effectiveness of TKA and UKA in younger patients utilizing a wide set of PROMs.

This approach showed that satisfaction is clearly a multidimensional issue that may not be adequately assessed with a single question about satisfaction.

A limitation is that study IV did not include a specific control group of patients above the age of 65 that would have enabled the comparison of our results with those of the older patient population. The UKA group was also markedly smaller than the TKA group.

6.3.8 Effect of LIA on PROMs

There have not been any studies that analyze the influence of infiltration analgesia on the functional outcome in at least 1-year follow-up. One previous study with 3- months follow-up found no difference in functional outcomes between placebo and drug infiltration groups measured with TUG test, OKS, or EQ5D (Essving et al. 2010). We found minor differences in functional outcomes as measured with the 15D, HAAS, and OKS instruments, but the clinical relevance of these findings is questionable, and the only significant finding was in 1 TKFQ subscale. The TKFQ scoring system has many subscales indicating different functional capabilities. The only statistically significant difference was observed at 12 months (sitting for a long period of time) but this was not evident earlier. Any statistical difference between groups in this TKFQ subscale probably occurred by chance, without any relation to LIA. Murray et al. concluded that the minimal clinically important difference (MCID) in OKS is expected to be between 3 and 5 points (Murray et al. 2007b). In our data, the difference in mean values in OKS at 1-year between the groups was 3 points, but this difference was not statistically significant.

6.3.9 Strengths and limitations of the study (study V)

The strength of study V was the 1-year follow-up and randomized set-up with study cohort.

The limitation was that the length of hospital stay between groups was not measured. Effective postoperative pain relief might have allowed a shorter length of hospital stay. Moreover, the plasma concentrations of the infiltration drugs were also not measured. However, none of the patients suffered any identified side effects during the 1-year follow-up period.

6.4 Future considerations

Even if mechanisms in the etiology of OA have studied more thoroughly and new treatments are tested, the knee arthroplasty will be significant option for end stage symptomatic knee OA in the future. As knee OA and also knee pain in general are multidimensional issues, the treatment of these should be based on the healthy lifestyle and moderate physical activities, which may help to control the associated problems e.g. increasing obesity. The lower grade knee OA is associated with lower outcomes and dissatisfaction after knee arthroplasty. This may be associated with both multifactorial reasons causing knee pain and insufficient effect of operative treatment to manage the whole spectrum of symptoms which may derive e.g. from the phase of the inflammatory cascade of knee arthritis or from degenerative meniscal tear which is commonly related to low grade OA. The correct timing of knee arthroplasty seems to be critical for desirable outcome and information on realistic effect and increase of outcomes may help for correct timing of knee arthroplasty. As the survivorship of TKAs has shown to be acceptable, this has led to broaden the indication towards younger patients. The age do not seems to be a limitation for acceptable outcome of TKA when OA is at end-stage. The risk of revision is associated with younger age in registers and this will probably be shown as increasing number of re-operations in the future both for increasing number of primary TKAs, longer time of living and desire to continue physical activities in younger TKA patients. Early reasons for revision are commonly related to comorbidities and treatment of diseases like diabetes and related obesity may decrease early revisions. Wear-related late reasons for revision are commonly shown as aseptic loosening and for this reason the surface between bone and implant should resist both the shearing forces from the movement of joint and depris burden from the polyethylene insert. All fixation methods have shown comparable and acceptable survivals and the use of uncemented TKAs may increase in some extend in younger patients with good bone quality in the future, especially if costs of uncemented implants will decrease near the cemented implants. Concerning UKAs, survivorships between cemented and uncemented have reported to be equal, which may guide the use towards uncemented implants because of lower time of operation and more convenient operative technic. Still obvious advantage of UKA compared to TKA remains controversial because of increased risk of revision of UKA compared to TKA and comparable functional outcomes with both systems.

7 Conclusions

Study I

The incidence of knee arthroplasties continuously increased in the 4 Nordic countries over the study period. This increase was caused by an increase in the incidence of TKAs, whereas the incidence of UKAs varied between countries. The proportional increase in incidence was highest in patients aged younger than 65 years. Patients aged 65 years or older still comprise the majority of patients undergoing knee arthroplasty and are therefore the main contributor to the increase in the total number of TKA operations. Because of the trend of increasing incidences in younger age groups, the impact of this trend may be reflected in the revision burden in the future.

Study II

All four TKA fixation methods used in working-age patients showed reliable mid-term outcomes in terms of good implant survivorship. Cemented TKA still deserves the status of gold standard in TKA irrespective of the patients' age: it works very reliably in the hands of many. Hybrid and inverse hybrid fixations are promising alternatives, but more research with larger patient numbers and longer follow-up are needed to see whether they really endure the test of time as well as cemented fixation.

Study III

Uncemented porous tantalum monoblock tibial components achieved excellent mid-term survivorship in this Finnish Arthroplasty Register-based study. Early loosening of the uncemented tibial component was rare, and PJIs were as rare as with contemporary cemented TKAs.

Study IV

We found that knee arthroplasty provided patients aged 65 years or less with clinically significant pain relief as well improvements in ADL and quality of life. TKA and UKA had comparable outcomes. The patients´ physical activity was low or moderate preoperatively but improved significantly during the 2-year follow-up. Some pain and functional deficiencies remained after knee arthroplasty, and this should be emphasized in the preoperative guidance given to patients who are considering or who are scheduled for such surgery. Mild radiographic OA preoperatively is a clear risk factor for patient dissatisfaction with the outcome of knee arthroplasty.

Study V

This study showed that a single perioperative infiltration of levobupivacaine, ketorolac, and adrenaline reduced opiate consumption until 48 hours after TKA. The effect was the most emphasized during the first 6 hours but persisted to some extend up to 24 hours. LIA also improved the early knee ROM, but no long-term functional benefits were observed in PROMs during 1-year follow-up.

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Original Publications

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Different incidences of knee arthroplasty in the Nordic countries

A population-based study from the Nordic Arthroplasty Register Association

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Background and purpose — The annual number of total knee arthroplasties (TKAs) has increased worldwide in recent years. To make projections regarding future needs for primaries and revisions, additional knowledge is important. We analyzed and compared the incidences among 4 Nordic countries

Patients and methods — Using Nordic Arthroplasty Register Association (NARA) data from 4 countries, we analyzed differences between age and sex groups. We included patients over 30 years of age who were operated with TKA or unicompartmental knee arthroplasty (UKA) during the period 1997–2012. The negative binomial regression model was used to analyze changes in general trends and in sex and age groups.

Results — The average annual increase in the incidence of TKA was statistically significant in all countries. The incidence of TKA was higher in women than in men in all 4 countries. It was highest in Finland in patients aged 65 years or more. At the end of the study period in 2012, Finland's total incidence was double that of Norway, 1.3 times that of Sweden and 1.4 times that of Denmark. The incidence was lowest in the youngest age groups (< 65 years) in all 4 countries. The proportional increase in incidence was highest in patients who were younger than 65 years.

Interpretation — The incidence of knee arthroplasty steadily increased in the 4 countries over the study period. The differences between the countries were considerable, with the highest incidence in Finland. Patients aged 65 years or more contributed to most of the total incidence of knee arthroplasty.

Total knee arthroplasty (TKA) for severe osteoarthritis (OA) has good long-term outcomes, and gives greater pain relief and better functional improvement than non-surgical treatment (Carr et al. 2012, Skou et al. 2015). Good long-term implant survivorship has resulted in TKA also becoming a treatment for severe knee OA in younger patients, although outcomes and implant survivorship have been reported to be worse than in elderly patients (Lonner et al. 2000, Rand et al. 2003, Price et al. 2010, Julin et al. 2010).

Reported increases in the rate of TKA and estimates of future demand predict a substantial increase in the incidence of TKA in many countries (Jain et al. 2005, Kurtz et al. 2007, Kim et al. 2008, Culliford et al. 2010, W-Dahl et al. 2010a, Nemes et al. 2015). Both the broadening of indications for younger patients and the increase in total incidence of TKA have raised concerns of a possible increase in revision burden in the long term (Kurtz et al. 2007, Gioe et al. 2007). Differences between geographic locations and age groups have been noted in the incidences of TKA (Katz et al. 1996, Wells et al. 2002). The major increase in the incidence of TKA has been found in people born in the period 1946–1964 (the baby-boomer generation) (Leskinen et al. 2012).

The aim of this study was to analyze trends in the incidence of TKA and unicompartmental knee arthroplasty (UKA) using Nordic Arthroplasty Register Association (NARA) data from between 1997 and 2012, to identify any changes or differences in (or between) age groups, the sexes, and countries.

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Table 1. Patient characteristics. Mean age applies to both TKA and UKA. The number of operations has been divided into age groups. Study period 1997–2012, except for Finland (2000–2012)

	Denmark	Norway	Sweden	Finland	Total
Mean age (SD)	69.0 (9.5)	69.7 (9.2)	69.8 (9.0)	69.0 (9.0)	
Females, %	63	66	60	68	
UKA (n)	5,395	5,054	12,956	4,282	
Age groups, n (%)					
30–64	21,624 (33)	12,872 (31)	42,084 (30)	30,264 (31)	106,844
65–74	24,577 (38)	15,751 (37)	53,492 (39)	38,305 (39)	132,125
75+	18,587 (29)	13,412 (32)	43,403 (31)	30,324 (31)	105,726
Total	64,788	42,035	138,979	98,893	344,695

Patients and methods

The NARA compiles data on 4 Nordic countries that have similar organization of healthcare and comparable patient characteristics (Table 1). The NARA has information on the TKAs and UKAs performed in Denmark, Norway, and Sweden from 1997 through 2012 and in Finland from 2000 through 2012.

The knee arthroplasty registries of Sweden (SKAR) and Denmark (DKR) and the arthroplasty registries of Norway (NAR) and Finland (FAR) participated in the present study. All 4 registries have used individual-based registration of operations and patients. A minimal NARA dataset was created to contain data that all 4 registries could deliver, but for administrative reasons the Finnish Arthroplasty Register has been able to provide Finnish data according to the NARA data definitions from the beginning of 2000. A pilot study carried out from NARA data did not include FAR data and it did not have an age cutoff (Robertsson et al. 2010). The NARA database includes data on the patients that enable TKA and UKA incidence analyses, i.e. patient-level data on both demographics and implant types.

Selection and transformation of the respective datasets and de-identification of the patients, which included deletion of the national civil registration numbers, were performed within each national register. The anonymous data were then merged into a common database. Because of the small number of patients aged 30 years or less who were operated, in the present study we only included patients aged 30 years or more who had undergone a TKA or UKA surgical procedure due to primary osteoarthritis of the knee.

The data were treated with full confidentiality, according to the regulations of the respective countries. This included restricted access to the common database, which was limited to the authors of the present paper. The quality of data in the Nordic registries is high, and the registries have both national coverage and a high degree of completeness (annual reports 2015: Danish Knee Arthroplasty Register, Norwegian Arthroplasty Register, Swedish Knee Arthroplasty Register, Finnish Arthroplasty Register) (Arthursson et al. 2005, Espehaug et al. 2006).

Ethics

Ethical approval for the study was obtained through the ethical approval process of each national registry.

Statistics

We described patient characteristics, categorized into sex and age groups, using descriptive statistics presented as mean and standard deviation (SD). Incidences are presented as the number of operations performed per 104 of population. Age was categorized into 3 groups: < 65 years, 65–74 years and ≥ 75 years. We analyzed trends in the general incidence of TKAs and UKAs in Denmark, Norway, and Sweden from 1997 to 2012 and in Finland from 2000 to 2012. The incidence was calculated as incidence density, which is defined as the number of new cases in a population during a given time period relative to the sum of the person-time values of the at-risk population. Negative binomial regression was used to estimate the incidence rate ratios (IRRs) and the 95% confidence intervals (CIs) of UKAs and TKAs for each country because of evidence of overdispersion of data. IRR reports the estimated average annual increase of incidence. Analyses were stratified by sex and age group. The statistical analyses were conducted with SPSS 22.0 and Stata 8.2 software.

Results

Patient characteristics

385,310 primary knee arthroplasties were registered in the 4 countries during the study period. During this period, we observed an increase in OA from 84% to 90% and simultaneously a decline in rheumatoid arthritis from 10% to 4% as indication for knee arthroplasty. Of these operations, 317,008 TKAs and 27,687 UKAs were performed for knee OA in patients aged 30 years or more. Female patients represented 202,940 (64%) of the TKA cases and 15,778 (57%) of the UKA cases. The mean age of the patients was 70 years (SD 9.0) in the TKA group and 65 years (SD 9.4) in the UKA group (Table 1).

Incidence of knee arthroplasty (TKA and UKA)

In all 4 countries, the incidences of knee arthroplasty increased during the study period (Figure 1). At the beginning of the study, the incidences were 3.4 in Denmark, 3.6 in Norway, 9.0 in Sweden, and 13 in Finland per 10,000 population. At the end of the study, the incidences were 21 in Denmark, 14 in Norway, 21 in Sweden, and 28 in Finland per 10,000 population. The relative change in incidence of knee arthroplasty was 6.0-fold in Denmark, 3.9-fold in Norway, 2.3-fold in Sweden, and 2.1-fold in Finland from the start of the study to the end.

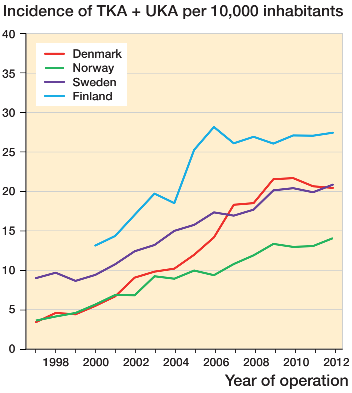

Figure 1. Total incidence of TKA and UKA by year of operation in patients aged 30 years or more. Incidences are shown per 10,000 inhabitants. The incidence in Denmark is estimated to include 10–15% underestimation between 1997 and 2007 due to lower completeness.

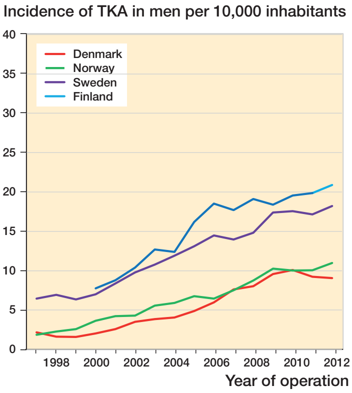

Figure 2. Incidence of TKA in males aged 30 years or more. Incidences are shown per 10,000 inhabitants.

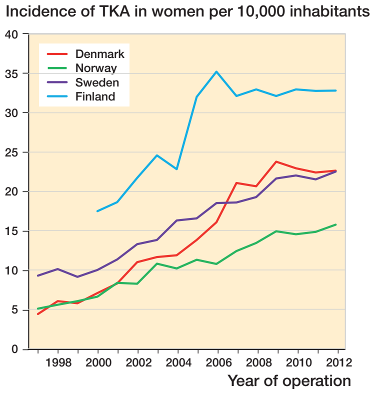

Figure 3. Incidence of TKA in females aged 30 years or more. Incidences are shown per 10,000 inhabitants.

Table 2. Negative binomial regression analysis. Incidence rate ratios (IRRs) with 95% confidence intervals

Arthroplasty	Male		Female	
Age, years	IRR	95% CI	IRR	95% CI
Denmark				
TKA 30–64	1.17	1.14–1.19	1.15	1.13–1.17
UKA 30–64	1.26	1.20–1.32	1.24	1.17–1.30
TKA 65–74	1.08	1.04–1.13	1.12	1.10–1.13
UKA 65–74	1.25	1.18–1.31	1.20	1.16–1.24
TKA 75+	1.12	1.10–1.13	1.10	1.08–1.12
UKA 75+	1.20	1.14–1.26	1.14	1.11–1.17
Norway				
TKA 30–64	1.16	1.14–1.18	1.13	1.12–1.15
UKA 30–64	1.13	1.07–1.19	1.11	1.05–1.18
TKA 65–74	1.11	1.10–1.13	1.08	1.07–1.09
UKA 65–74	1.12	1.08–1.16	1.07	1.01–1.13
TKA 75+	1.09	1.08–1.10	1.06	1.04–1.07
UKA 75+	1.09	1.05–1.14	1.02	0.96–1.06
Sweden				
TKA 30–64	1.15	1.13–1.16	1.13	1.11–1.14
UKA 30–64	1.02	0.99–1.05	1.00	0.98–1.02
TKA 65–74	1.07	1.06–1.09	1.05	1.04–1.07
UKA 65–74	0.93	0.92–0.94	0.91	0.90–0.92
TKA 75+	1.07	1.06–1.08	1.05	1.04–1.05
UKA 75+	0.90	0.89–0.91	0.88	0.87–0.89
Finland				
TKA 30–64	1.13	1.11–1.16	1.11	1.09–1.14
UKA 30–64	10.5	0.99–1.11	1.02	0.95–1.09
TKA 65–74	1.04	1.02–1.06	1.02	1.00–1.04
UKA 65–74	0.99	0.91–1.06	0.96	0.92–1.00
TKA 75+	1.04	1.03–1.06	1.03	1.01–1.05
UKA 75+	0.99	0.92–1.06	0.95	0.90–1.00

The relative change in incidence of UKA was 10-fold in Denmark, 1.5-fold in Finland, 7.1-fold in Norway, and 0.5-fold in Sweden from the start of the study to the end.

During the study period, the estimated average annual increase in the incidence of TKA by age groups and sex was statistically significant in all countries, with the exception of Finnish females aged 65–74 years (IRR = 1.02, 95% CI: 1.00–1.03) (Table 2). IRR was highest in the youngest age group in both sexes and a decreasing trend was detected as age increased. Females had lower IRRs, except in Denmark in patients aged 65–74 years. A statistically significant decrease in UKAs was detected in Sweden in patients who were 65 years or more, whereas in Denmark and in Norway there was a significantly higher annual incidence of UKA in all age groups—except for UKAs in women aged 75 years or more in Norway. There was no significant change in the annual incidence of UKA over the study period in Finland, in men or women of any age group (Table 2).

Incidence by sex

The incidences of TKA according to sex are shown in Figures 2 and 3. The incidence was higher in women than in men in all 4 countries. At the end of the study period, the incidences of TKA were 9.1 in Denmark, 11.0 in Norway, 18.2 in Sweden, and 20.9 in Finland per 10,000 men—giving a relative change of 4.2-fold in Denmark, 5.9-fold in Norway, 2.8-fold in Sweden, and 2.7-fold in Finland from the start of the study to the end. In women, the incidences of TKA were 22.6 in Denmark, 15.7 in Norway, 22.5 in Sweden, and 32.8 in Finland per 10,000 women at the end of the study, and the relative change was 5.2-fold in Denmark, 3.1-fold in Norway, 2.4-fold in Sweden, and 1.9-fold in Finland from the start of the study to the end.

The incidence of UKA was higher in Sweden in both men and women at the start of the study than at the end of the study, whereas in the other 3 countries the incidence of UKA was higher at the end of the study than at the start of the study (Figures 4 and 5).

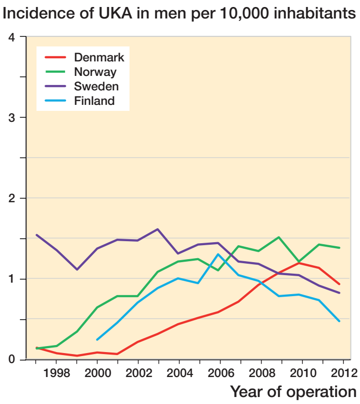

Figure 4. Incidence of UKA in males aged 30 years or more. Incidences are shown per 10,000 inhabitants.

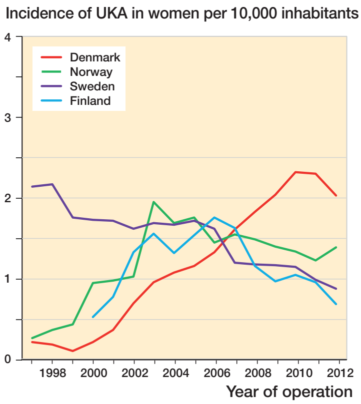

Figure 5. Incidence of UKA in females aged 30 years or more. Incidences are shown per 10,000 inhabitants.

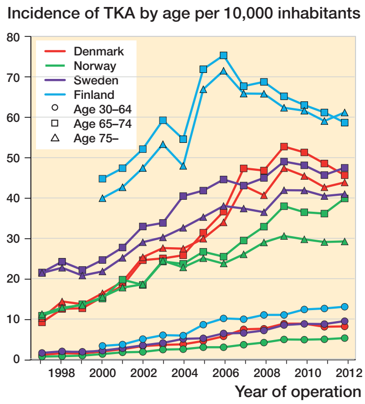

Figure 6. Incidence of TKA according to age group. Incidences are shown per 10,000 inhabitants.

Incidence by age group

The incidence of TKA was highest in Finland in patients aged 65 years or more. The total incidence was lowest in the youngest age group in all countries. The incidence was higher at the start of the study than at the end in all age groups (Figure 6).

Discussion

We found that the total incidence, comprising both TKAs and UKAs, increased in all countries and the trends of increase were comparable between countries. The increase in surgical procedures in Finland from 2004 to 2006 may be explained by the coming into force of a new social and healthcare regulation that instructed hospitals to shorten patient waiting times for surgery. Despite having comparable socioeconomic situations and healthcare systems, differences in the incidence of knee arthroplasty between countries were notable. A pilot study from the NARA data tested a common dataset and reported results from the period 1997–2007 (Robertsson et al. 2010). The present study continued to analyze changes in the incidence of arthroplasty until 2012, based on experience gained from the pilot study.

The total increase in the number of arthroplasties in all countries was mainly caused by an increased incidence of TKA. In Sweden, there was a significant decrease in the incidence of UKA in patients aged 65 years or more. In 3 other countries, variations in incidences of UKA between groups were more heterogeneous (Table 2, Figures 4 and 5). The reasons for the changes in incidence of UKA are multifactorial. Previous studies from national registries have affected UKA incidences, as most registries show higher overall revision rates of UKAs than of TKAs (Furnes et al. 2007, Koskinen et al. 2008, W-Dahl et al. 2010b). However, there have also been studies claiming better clinical outcome from UKA and also more cost-effectiveness (Slover et al. 2006, Lygre et al. 2010). Different UKA implant models with a longer learning curve compared to TKA, indications for primary UKA surgery, and a higher revision risk than with TKA may explain the differences in the incidence compared to TKA. The increase in the incidence of UKA in patients less than 65 years of age may be explained by the increase in minimally invasive surgery (MIS), which enables a shorter postoperative stay in hospital.

The 4 countries had comparable populations with regard to age and sex, and therefore instead of age-standardized data we analyzed incidence between age groups. Of the 3 age groups, patients less than 65 years of age had the lowest incidence of TKA. However, the relative increase in incidence was higher in that age group than in the other age groups. In recent years, it appears that the indications have widened to include younger patients, which has resulted in a proportionally higher increase in incidence in patients less than 65 years of age, compared to patients aged 65 years or less (Robertsson et al. 2010, Leskinen et al. 2012). Before this, knee arthroplasty surgery was initially reserved for elderly patients and those with severe disease (Robertsson et al. 2014), and younger patients with rheumatoid arthritis. The reasons for increasing incidence in younger TKA patients may be multifactorial. Increasing obesity in young people (Kautiainen 2005, Lohmander et al. 2009), participation in contact sports (Driban et al. 2015), and the introduction of fast-track surgery (which suits younger patients well) are probable reasons.

The present study had some strengths and limitations. The major strength was the unique collaboration of 4 national registries in the creation of a multinational database covering a large number of patients, which enabled international comparisons to reveal possible differences and which might help to estimate future demands. Furthermore, the completeness and validity of data were high in the Nordic countries at the end of the study period (completeness, NAR: 95%; SKAR: 97%; DKR: 97%; FAR: 96%) (annual reports 2015: Danish Knee Arthroplasty Register, Norwegian Arthroplasty Register, Swedish Knee Arthroplasty Register, Finnish Arthroplasty Register). Completeness in the DKR was reported to be 89% in 2007 (Robertsson et al. 2010), which may have caused 10–15% underestimation of incidence in Denmark over the period 1997–2007. Total relative change in incidence was highest in Denmark, and that may have been due to the influence of a lower completeness for the DKR in the early years of the study period (Table 3). The lack of data on BMI and other subgroups could also be considered a limitation of the present study.

The incidence of TKA steadily increased in all participating countries in this study, which is in line with findings from other studies (Kurtz et al. 2007, W-Dahl et al. 2010a, Leskinen et al. 2012). The incidence of knee arthroplasty in females was found to be greater than that in males in our study, but the results of previous studies have also shown that the proportion of female patients has decreased with time (Nemes et al. 2015). Moreover, the sex distribution may also vary between nations (Paxton et al. 2011, Nemes et al. 2015). One study delivered projections for primary and revision hip and knee arthroplasty in the United States from 2005 to 2030 (Kurtz et al. 2007). In that study, the authors predicted that if the number of total knee arthroplasties performed continues at the current rate, the demand for primary TKA would be projected to grow by a factor of 7 by 2030. In another previous study from the Finnish Arthroplasty Registry, the annual cumulative incidence of UKA and TKA increased rapidly between 1980 and 2006, especially in patients aged 50–59 years, the so-called baby-boomer generation (Leskinen et al. 2012). In our study, the increase in incidence was mainly due to the increase in incidence of TKAs. This finding is consistent with a study by W-Dahl et al. (2010a) from the Swedish Knee Arthroplasty Register, which showed that although the incidence of TKA has increased in patients under 55 years of age, the incidence of UKA and high tibial osteotomy (HTO) has decreased. Obesity is also a growing burden in many countries and, as this has been shown to be a certain risk factor for knee osteoarthritis, especially in young patients, it may contribute to the increasing demand for TKAs in future (Apold et al. 2014a, b, Silverwood et al. 2015).

A previous study has raised concerns about the long-term outcome of TKAs and the possibility of an increasing revision burden, because younger age has been associated with a higher risk of early periprosthetic joint infection and aseptic mechanical failure after TKA (Meehan et al. 2014). In another study, young age was found to impair the prognosis of TKA and was associated with increased revision rates for non-infectious reasons (Julin et al. 2010). A comparison study undertaken by the Norwegian Knee Arthroplasty Register and a United States arthroplasty registry showed an increased risk of revision in patients less than 65 years of age compared to patients aged 65 years or older (Paxton et al. 2011). In our study, the proportional growth of TKAs during the study period was highest in patients who were younger than 65 years. Despite this, the incidence of knee arthroplasty in the youngest age group was lower than in patients aged 65 years or more. Based on this finding, the majority of knee arthroplasties will probably be performed on elderly patients in the future also. Even though patients less than 65 years old represented a lower incidence level than patients who were 65 or older in our study, these working-age patients should be considered to be an important subgroup because of their higher physical activity and higher demands for surgery, and the multifactorial reasons behind the success of TKA (Keeney et al. 2014, Klit et al. 2014, Parvizi et al. 2014). An effect on the revision burden can therefore be anticipated in future.

In summary, the incidence of knee arthroplasty has steadily increased in the 4 Nordic countries. This increase was caused by an increase in the incidence of TKA, whereas the incidence of UKA varied between countries. The proportional increase in incidence was highest in patients aged less than 65 years. However, patients who are 65 years or more still comprise the majority of those who undergo knee arthroplasty, and they are the main contributory factor to the increase in the total number of TKA operations.

Study design: MN and AE. Analysis of data and statistics: HH and MN. Review and interpretation of the results: MN, HH, and AE. Revision and approval of the final manuscript: MN, KM, OR, AW-D, OF, AF, AP, HS, and AE.

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The effect of fixation type on the survivorship of contemporary total knee arthroplasty in patients younger than 65 years of age: a register-based study of 115 177 knees in the Nordic Arthroplasty Register Association (NARA) 2000-2016

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Abstract

Background Cemented fixation is regarded as gold standard in total knee arthroplasty (TKA). Among working age patients, there has been controversy regarding the optimal fixation method in TKA. To address this issue, we conducted a register-based study to assess the survivorship of cemented, uncemented, hybrid and inverse hybrid TKAs in patients aged < 65 years.

Methods We used the Nordic Arthroplasty Register Association data of 115 177 unconstrained TKAs performed for patients aged < 65 years with primary knee osteoarthritis over 2000-2016. Kaplan-Meier (KM) survival analysis with 95% confidence intervals (CI) and Cox multiple-regression model with adjustment for age, sex, and nation were used to compare fixation methods in relation to revision for any reason.

Results The 10-year KM survivorship of cemented TKAs was 93.6% (CI 93.4-93.8), uncemented 91.2% (CI 90.1-92.2), hybrid 93.0% (Cl 92.2-93.8) and inverse hybrid 96.0% (CI 94.1-98.1). In the Cox model, hybrid TKA showed decreased risk of revision after 6 years' follow-up compared to the reference group (cemented) (hazard ratio (HR) 0.5 (CI 0.4-0.8)), while uncemented TKAs showed increased risk of revision both <1 year (HR 1.4 (1.1-1.7)) and > 6 years' (HR 1.3 (1.0-1.7)) follow-up compared to the reference.

Interpretation Both cemented and hybrid TKAs had 10-year survival rates exceeding 92% in patients aged < 65 years. Cemented TKA, however, was used in vast majority (89%) of the operations in the current study. As it performs reliably in the hands of many, it still deserves the status of gold standard in TKA in working age patients.

Introduction

Previous studies reported both highest increase in incidence of TKAs and also highest risk for revision in patients younger than 65 years of age (Julin et al. 2010, Carr et al. 2012, Leskinen et al. 2012, Meehan et al. 2014, Nemes et al. 2015, Niemelainen et al. 2017). This has increased the interest to find a more durable fixation method for TKA. A previous systematic review did not report any differences in survival or functional outcome between cemented and uncemented TKAs in patients aged 60 years or less (Franceschetti et al. 2017). A meta-analysis without age limit showed better survival rates with cemented TKAs when all studies were combined, but in randomized studies survivals were equivocal (Gandhi et al. 2009). Uncemented fixation in TKA has offered comparable outcomes with cemented TKA in a few studies, but higher costs of uncemented components have favored cemented TKA still as gold standard (Dalury. 2016, Miller et al. 2018, Zhou et al. 2018).

A previous study applying radiostereometric analysis (RSA) showed that early migration seen with uncemented tibial components settled until 2 years whereas cemented ones continued to migrate (Wilson et al. 2012, Henricson and Nilsson 2016). So far, the use of uncemented TKAs has been limited. Previous studies have reported an increased risk for aseptic loosening of the tibial component in patients treated with uncemented TKA (Bassett. 1998, Duffy et al. 1998, Berger, Lyon et al. 2001, Goldberg and Kraay. 2004, Carlsson et al. 2005), but due to evolvement of designs and materials uncemented fixation has become an interesting choice especially for younger patients with good bone quality (Hu et al. 2017). Trabecular metal (TM) has showed promising results in both register and clinical studies (Niemelainen et al. 2013, Henricson et al. 2013, Pulido et al. 2015). Although differences have been observed between different fixation concepts in terms of revision rates, functional outcomes have been equivalent irrespective of the fixation method (Gandhi et al. 2009, Gao et al. 2009, Demey et al. 2011, Arnold et al. 2013). The most optimal fixation method in TKA still remains controversial for these younger patients.

We assessed survivorships of 4 different fixation methods (cemented, uncemented, hybrid, and inverse hybrid) in patients younger than 65 years of age based on the Nordic Arthroplasty Register Association (NARA) database.

Materials and methods

We included all uni- or bilateral unconstrained primary TKAs that had been implanted in patients aged less than 65 years for primary OA over 2000-2016 (Figure 1). Previous reports have shown that the effect of including bilateral cases in studies of hip and knee joint prosthesis survival is negligible (Robertsson and Ranstam. 2003, Lie et al. 2004). The Swedish Knee Arthroplasty Register (SKAR), The Danish Knee Arthroplasty Register (DKR), The Norwegian Arthroplasty Register (NAR) and The Finnish Arthroplasty Register (FAR) participated in the study. The Nordic Arthroplasty Register Association (NARA) compiles data on 4 Nordic countries that have similar health care organizations and comparable patient characteristics (Robertsson et al. 2010). A NARA minimal dataset was created to contain data that all 4 registers could deliver (NARA report 2016). The NARA dataset includes 20 different main variables and in total 90 variables. All registers use individual-based registration of operations. Selection and transformation of the respective data sets and de-identification of the patients, which included the deletion of the personal identity numbers, were performed within each national register. The anonymous data were then merged into a common database. Data were treated with full confidentiality, according to the rules of the respective countries. The quality of data in the Nordic registers is high, including both 100% coverage and following completeness: SKAR 97%, DKR 97%, NAR 97%, FAR 96% (NARA report 2016) (Espehaug et al. 2006). The fixation of TKAs was divided into 4 groups: 1) cemented, 2) uncemented, 3) hybrid (uncemented femur with cemented tibia), and 4) inverse hybrid (cemented femur with uncemented tibia).

Statistics

We assessed the descriptive statistics of the patients included. The inclusion time period was 2000-2016. We used Kaplan-Meier (KM) survival analysis to assess implant survival probability (with respective 95% confidence interval (CI)) of the TKA fixation at 10 and 15 years. The results in Tables and Figures were not shown when less than 40 knees were at risk. Outcome was defined as removal, addition or exchange of at least one of the components, including polyethylene insert exchanges of modular tibial components, for any reason.

We used Cox regression analysis to estimate hazard ratios associated to implant survival. Covariates included in the analysis were fixation type, sex, country and age. Age was included as a continuous variable whereas the others were categorical. Correlation of scaled Schoenfeld residuals with time was examined to investigate violation of proportional hazard (PH) assumption. Log-log survival curves were also inspected visually to see if assumption was met. We detected multiple violations of PH assumption. In order to deal with PH violation, we used time dependent coefficients (fixation, age, sex and nation) using step function. Based on the log-log curves cut-offs were set as follows: 1, 3 and 6 years. We did stratified analyses based on age and implant brand group and similar time axis division was made according to log-log curves and residual testing. For the time dependent coefficients the data was broken into time dependent parts according to the time intervals used in the time axis division. For each final analysis the PH test investigating Schoenfeld residuals was performed.

Statistical analyses were performed using R 3.5.2, survival package (R Foundation, Vienna).

Ethics

Ethical approval for the study was attained through the ethical approval process of each national registry: the Ethics Board of Lund University (LU20-02) (Sweden), the National Institute of Health and Welfare (Dnro THL/1743/5.05.00/2014) (Finland), the Norwegian Data Inspectorate (ref 24.1.2017: 16/01622-3/CDG) (Norway) and the Danish Data protection agency (1-16-02-54-17) (Denmark).

Results

The mean follow-up time standard deviation (SD) was 6.4 (4.3) years for cemented TKA, 4.7 (3.4) years for uncemented TKA, 6.0 (4.3) years for hybrid TKA and 6.1 (3.2) years for inverse hybrid TKA. There were slight differences in the proportion of men between the fixation groups, ranging from 40% in cemented to 44% in uncemented group (Table 1). TKA models varied between countries without a common trend and the most commonly used TKA models in the participating countries are showed in the Appendix 1. Nexgen®, PFC® and Triathlon® were the most commonly used models within the fixation concepts (Appendix 2). The number of TKAs performed annually grew substantially over 2000-2009, and remained rather stable after that; cemented fixation was used in vast majority of TKAs over the whole study period (Figure 2). Altogether, cemented fixation was used in 89 % of all TKAs, and uncemented in 5.3%, hybrid in 5.5% and inverse hybrid in 0.5%, respectively. Patella was resurfaced in 24 487 TKAs (21%) and uncemented patellar buttons were used in only 151 (0.1%) TKAs. In the subgroup of Nexgen® TKAs, patella was resurfaced in 5821 (22%) TKAs, and an uncemented patellar button was only used in 2 knees (both of them in cemented Nexgen group).

At 15 years, KM-based survival rates were: cemented 91.3% (Cl 91.0-91.7), hybrid 91.4% (CI 90.2-92.6), uncemented 88.7% (CI 87.0-90.4). For inverse hybrid only 10-year survival was available (96.0% (CI 94.1-98.1)) (Table 2, Figure 3).

In the Cox regression analysis, uncemented fixation showed an increased risk of revision compared to the reference group (cemented TKA) both during the first postoperative year and also after 6 years of follow-up. Hybrid fixation was associated with a decreased risk of revision compared to the cemented fixation after 6 years of follow-up. The risk of revision was similar between the inverse hybrid and the reference group (Table 4). Because of the age dependence of TKA survivorship, the additional Cox regression analyses were conducted for 2 different age groups: 55-64 years of age (Table 5) and less than 55 years of age (Table 6). In patients aged 55-64 years, risk of revision with uncemented TKAs was increased in comparison with the cemented reference group during the first 3 years of follow-up and after that similar compared to reference. Hybrid TKAs still showed a decreased risk of revision after 6 years of follow-up; a finding that was already seen in the whole study cohort (Table 5). In patients aged less than 55 years, revision risks were similar between fixation methods (Table 6). Differences between age, sex, and country were the other covariates in the Cox regression analysis and their results are listed in Appendix 4.

The inverse hybrid group mainly comprised Nexgen TKAs (95% of the knees) (Appendix 2), and approximately more than 80% of the inverse hybrid Nexgen TKAs used TM monoblock tibial components (an estimate from national registers' data). Because of the obvious risk for selection bias, we conducted an additional sensitivity analysis to diminish bias between groups. For this analysis, we only included patients operated on with Nexgen TKAs (Appendix 3). In this sensitivity analysis, survival rates of different fixations were in descending order: the inverse hybrid 96.6% (CI94.7-98.5), cemented 95.8% (CI 95.5-96.1), uncemented 93.2% (CI 91.9-94.6) and hybrid 92.0% (CI 90.4-93.7) at 7 years (Table 3). In the Cox analysis of the Nexgen subgroup, increased risk of revision was found for uncemented and hybrid TKAs compared to cemented TKAs, and for inverse hybrid TKAs the risk of revision was comparable to cemented TKAs (Table 7).

Discussion

We found that both cemented and hybrid TKAs showed 10-year survival rates exceeding 92% in patients aged < 65 years. Even though hybrid / inverse hybrid versions of the well performing contemporary TKA designs provided younger patients with a good mid-term outcome in our study, they were still used in a limited number of patients. And especially in the inverse hybrid group, one single TKA design, with a very good track record comprised the vast majority of the whole group. It is thus safe to conclude, that cemented TKA still fulfils the most important task of a TKA: it works very reliably in the hands of many. Also, cemented TKA should still be considered as the gold standard in TKA of all OA patients irrespective of their age.

We acknowledge certain strengths and limitations in our study. The major strength of our study is the unique collaboration of 4 national registers in the creation of a multinational database comprising a high number of patients. This NARA database enables international comparisons to reveal possible differences in trends and outcomes of TKA. To our knowledge, this is the first multi-national, register-based study comparing the outcomes of all 4 fixation methods in TKA. There are also a few obvious limitations in our study. First, there were clearly less patients in the alternative fixation groups as compared to the cemented reference group (Figure 2). There are potential sources of selection bias in our data. Other concepts than cemented TKAs may have been done in higher volume units, and there may have been less preoperative bone loss or less severe deformity. On the other hand, uncemented components may have been used in patients with higher demands and also there may have been concerns about cemented fixation during operation. If the choice of fixation had been constant at hospital level in our study population, this might lower this risk of bias. Further, especially inverse hybrid fixation, but also hybrid fixation into some extent, had another obvious advantage over cemented fixation in our study setting. That is the monoblock uncemented tibial component, since wash-out procedures for infection in such knees (without exchange of any component) have not been regarded as revisions in the NARA data. Thus, due to a small number of patients and also possibility of some missing infection revisions, the results of inverse hybrids should be interpreted with caution. Further, Nexgen TKAs comprised 91% of the inverse hybrid group. This implant has been reported to have 97-99% 10-year survival rate in previous studies (Kim et al. 2012, Niemelainen et al. 2013, Robertsson et al. 2019). Further, in Finland Nexgen inverse hybrid TKAs (with TM tibial component) have been performed only in 3 hospitals, 1 of which is a high-volume specialized center (Niemelainen et al. 2013). In the hybrid group, 3 TKA designs with a very good track record (PFC, Nexgen, Profix) comprised 76% of all TKAs. Second limitation is that due to the nature of the NARA dataset, we had limited number of covariates for analysis and also, we didn't have exact information on whether some of the uncemented implants were hydroxide apatite coated or not. On the hip side, HA-coating does not seem to provide any added value in terms of improved survival rates (Hailer et al. 2015, Lazarinis et al. 2017), thus it most probably does not cause any bias to these TKA results.

In our study, vast majority of TKAs performed for younger patients in the attending 4 Nordic countries were still cemented, and very small changes, if any, were observed in the fixation methods used over the study period (Figure 2). The same trend in general has also been reported from other national registers: Annual report 2017 of the National Joint Registry for England, Wales and Northern Ireland (NJR) reported that the proportion of all cemented TKA implants increased from 82 % in 2003 to 87 % in 2016. During the same time period uncemented implants decreased from 6.7% to 2.0% and hybrid implants from 2.8% to 0.4%. The same increasing trend of using cemented implants was seen in the Australian Joint Registry (AOANJRR annual report 2017). In our study, the proportion of cemented TKAs only slightly decreased from 96 % in 2000 to 91 % in 2016, and a simultaneous small increase in usage of uncemented TKAs was seen (from 2.5% to 6.5 %), respectively.

In our study, both cemented and hybrid TKAs had up to 15-year survival rates exceeding 91% in patients aged < 65 years. Hybrid TKAs showed decreased risk of revision in comparison to cemented TKA after 6 years of follow-up. Inverse hybrid TKAs showed 96% survivorship at 10 years. Uncemented TKAs had the worst 10-year survival rate (91%). These findings are in line with previous literature. In a Finnish register-based study, uncemented TKAs had 1.4 times elevated adjusted hazard ratios (HR) for revision for any reason compared to cemented TKAs (Julin et al. 2010). In the AOANJRR annual report in 2017, the cumulative 10-year revision probability of minimally stabilized TKA was 4.5 (4.3, 4.6) with cemented TKA, 6.1 (5.9, 6.3) with uncemented TKA and 4.6 (4.4, 4.7) with hybrid TKAs. In The New Zealand Joint Register annual report in 2017, the revision rate with patient 55-64-years old was the highest with uncemented implant: 0.84 (CI 0.67-1.05) / 100 component-years compared to 0.62 (CI 0.58-0.66) / 100 component-years with cemented implants and 0.61 (CI 0.47-0.77) / 100 component-years with hybrid implants. To our knowledge, this study is the first to compare the survivorships of all 4 different fixation concepts in TKA.

In theory, younger patients might benefit from biologic fixation, i.e. bone ingrowth into uncemented implants. A meta-analysis (Gandhi et al. 2009) based on 5 RCTs and 10 observational studies with different mean ages of patients and with a minimum follow-up of 2 years, found improved survival for cemented compared to uncemented implants when revision for aseptic loosening was used as an endpoint. Another systematic review and meta-analysis (Voigt and Mosier 2011) compared hydroxyapatite-coated, porous coated and cemented tibial components. Evidence of more stable fixation after 2 years with hydroxyapatite-coated components compared to porous-coated and cemented implants was found, but revision rates at 10 year follow-up were similar. In a RCT no revision rates and survival were similar between the cemented and uncemented TKAs with mean follow-up of 15 years (Baker et al. 2007). In a systematic review of 11 RCTs to identify if there was an association between fixation method and clinical outcome, and they found that short- and long-term outcomes were not influenced by fixation type (Arnold et al. 2013). In previous studies, early failures of uncemented TKAs were mainly caused by aseptic loosening of the patellar button and the tibial component (Collins et al. 1991, Bassett et al. 1998, Duffy et al. 1998, Berger et al. 2001, Barrack et al. 2004, Goldberg and Kraay. 2004, Carlsson et al. 2005). Uncemented fixation has been associated with a high failure rate due to inadequate bone ingrowth in TKAs (Lombardi et al. 2007).

As stated earlier, Nexgen comprised 95% of the TKAs in the inverse hybrid group, and 87% of these Nexgen TKAs had been used with TM tibial components, which are known to have good results (Niemelainen et al. 2013). We tried to tackle the obvious possibility of selection bias by conducting a sensitivity analysis including only patients with Nexgen TKAs (Tables 3 and 7). In that analysis, it appeared that there was no statistically significant difference in mid-term survival rates or Cox-adjusted revision risks between inverse hybrid and cemented Nexgen TKAs. Further, hybrid and uncemented fixation showed an increased risk for revision in this Nexgen subgroup. Thus, the more expensive uncemented / hybrid / inverse hybrid versions did not provide these younger patients with any advantage over cemented fixation in the 10-year follow-up of Nexgen TKAs.

To conclude, cemented TKA still deserves the status of gold standard in TKA irrespective of the patients' age. In addition to age, the optimal fixation method in younger patients may be also influenced by patient´s other characteristics such as level of activity, anatomy or bone quality. Even though hybrid / inverse hybrid versions of the well performing contemporary TKA designs provided younger patients with a good mid-term outcome in our study, these results do not support systematic use of these more expensive components in TKA of younger patients.

Author contributions: Study design: MN, AE. Analysis of data and statistics: AR, AE, MN. Review and interpretation of the results: MN, KM, OR, AW-D, OF, AF, AP, HS, AR, AE. Revision and approval of the final manuscript: MN, KM, OR, AW-D, OF, AF, AP, HS, AR, AE.

Supplementary data. Appendices 1-4 are available in the online version of this article.

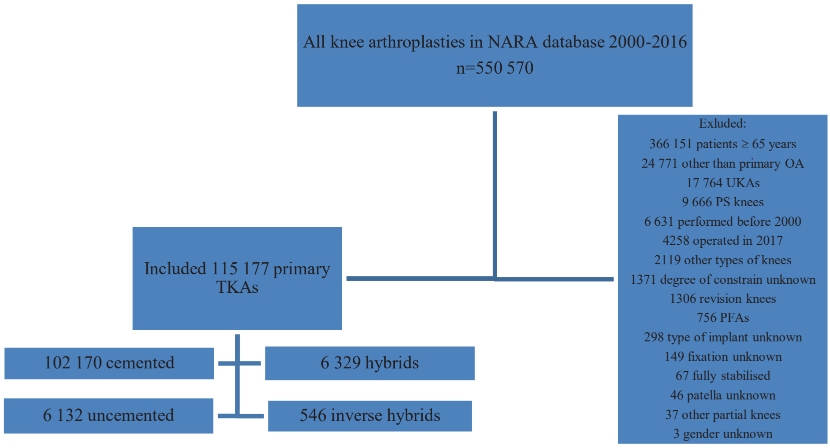

Figure 1. Flow chart.

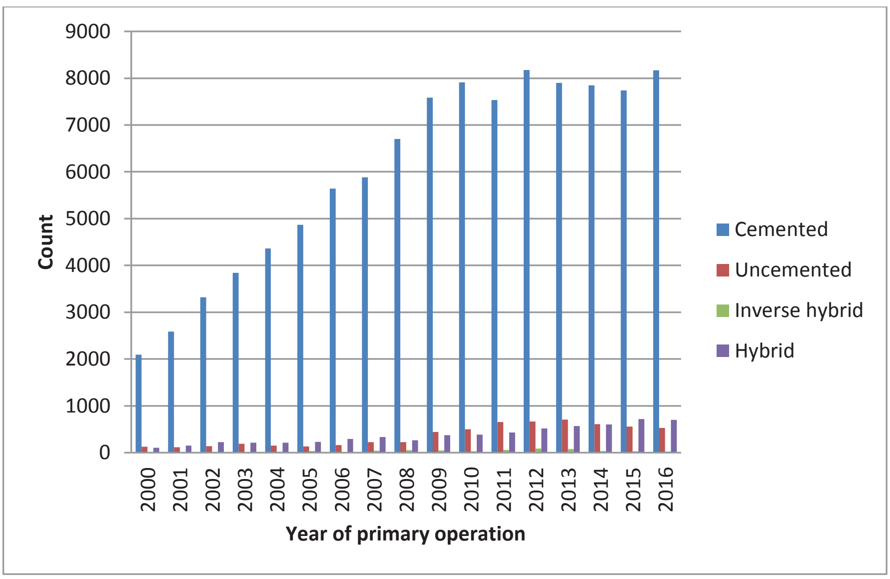

Figure 2. Number of operations.

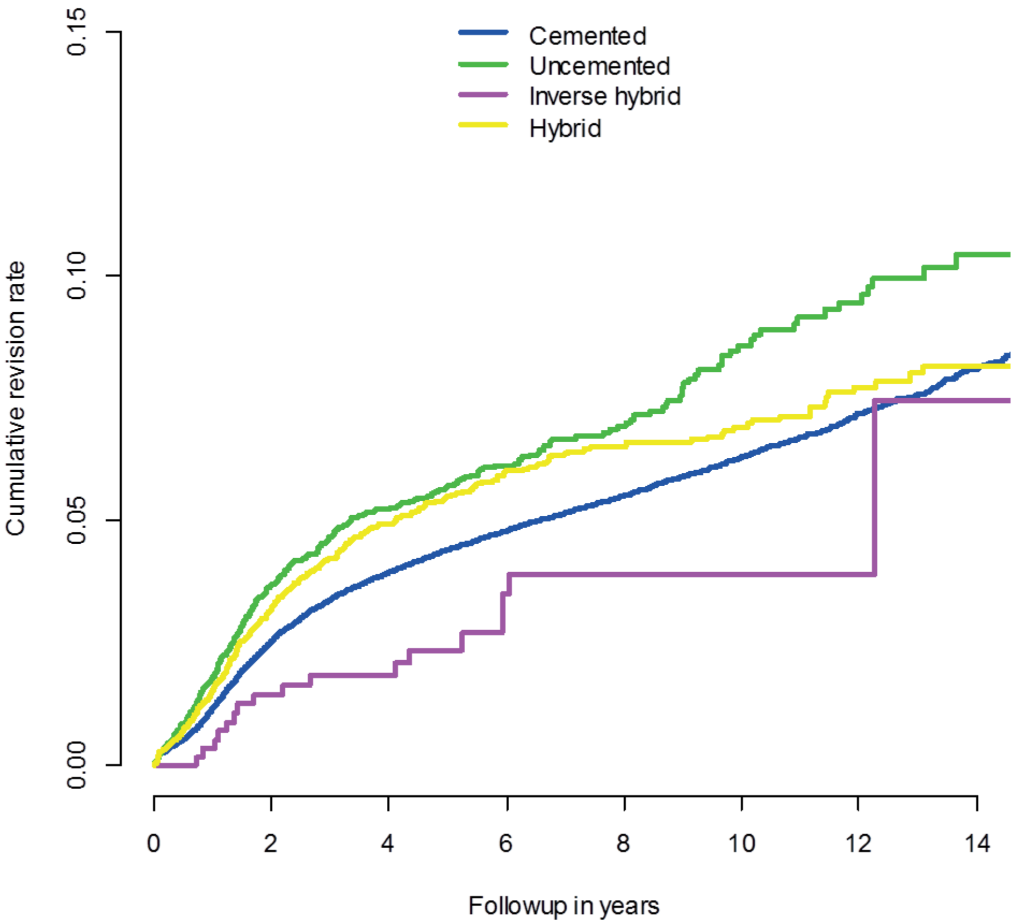

Figure 3. Unadjusted Kaplan-Meier cumulative risk of revision by fixation type in patients <65 years of age.

Table 1. Demographic data.

	Fixation concept			
	Uncemented	**Inverse hybrid**	**Hybrid**	**Cemented**
No of TKAs (%)	6 132 (5.3)	546 (0.5)	6 329 (5.5)	102 170 (88.7)
Mean age, years (SD)	57 (5.6)	57 (5.4)	58 (5.2)	59 (4.9)
Men, %	44	42	41	40
Country, n of TKAs (%)				
Finland	900 (2.5)	350 (1.0)	146 (0.4)	34 406 (96)
Norway	1 191 (8.7)	10 (0.1)	1 981 (14)	10 565 (77)
Sweden	2 284 (5.0)	128 (0.3)	74 (0.2)	43 268 (95)
Denmark	1 757 (8.8)	58 (0.3)	4 128 (21)	13 931 (70)

Table 2. Unadjusted Kaplan-Meier (KM) 10- and 15-year survival rates with 95% confidence intervals (CI) are presented for uncemented, inverse hybrid, hybrid, and cemented TKA.

Type of fixation	**N of knees**	**N of revisions**	**At risk at 10 years**	**KM-survivorship (%) at 10 years**	**At risk at 15 years**	**KM-survivorship (%) at 15 years**
Uncemented	6 132	363	915	91.2 (90.1 – 92.2)	214	88.7 (87.0 – 90.4)
Inverse Hybrid	546	16	66	96.0 (94.1 – 98.1)	-	-
Hybrid	6 329	330	1 349	93.0 (92.2 – 93.8)	239	91.4 (90.2 – 92.6)
Cemented	102 170	5 040	24 954	93.6 (93.4 – 93.8)	4 259	91.3 (91.0 – 91.7)

Table 3. Unadjusted Kaplan-Meier 7- and 10-year survival rates with 95% confidence intervals are presented for uncemented, inverse hybrid, hybrid, and cemented TKA in the Nexgen subgroup.

Type of fixation	N of knees	N of revisions	At risk at 7 years	KM-survivorship (%) at 7 years	At risk at 10 years	KM-survivorship (%) at 10 years
Uncemented	2 311	114	238	93.2 (91.9 – 94.6)	-	-
Inverse Hybrid	497	13	185	96.6 (94.7 – 98.5)	55	96.6 (94.7 – 98.5)
Hybrid	1 629	91	155	92.0 (90.4 – 93.7)	-	-
Cemented	27 934	901	8 477	95.8 (95.5 – 96.1)	3 691	94.9 (94.6 – 95.3)

Table 4. Cox regression with time-dependent coefficients (all patients aged <65 years included, cemented TKA as reference).

		Follow-up (yr)	Hazard ration (HR)	95% CI
Type of fixation	Uncemented	< 1	1.38	1.13-1.70
		1-3	1.14	0.97-1.35
		3-6	0.95	0.72-1.25
		> 6	1.32	1.00-1.73
	Inv hybrid	< 1	0.29	0.07-1.16
		1-3	0.67	0.34-1.35
		3-6	0.91	0.38-2.19
		> 6	0.54	0.13-2.15
	Hybrid	< 1	1.11	0.88-1.39
		1-3	0.94	0.78-1.12
		3-6	1.07	0.82-1.40
		> 6	0.54	0.38-0.78
	Cemented		1.0	Reference

Table 5. Cox regression with time-dependent coefficients in patients aged 55- 65 years.

		Follow-up (yr)	HR	95% CI
Type of fixation	Uncemented	< 1.5	1.37	1.13-1.67
		1.5-3	1.31	1.01-1.69
		3-6	0.86	0.59-1.24
		> 6	1.32	0.96-1.83
	Inv hybrid	< 1.5	0.44	0.14-1.37
		1.5-3	0.65	0.21-2.02
		3-6	0.88	0.28-2.75
		> 6	0.49	0.07-3.48
	Hybrid	< 1.5	1.15	0.94-1.41
		1.5-3	0.90	0.68-1.20
		3-6	1.14	0.85-1.53
		> 6	0.55	0.37-0.83
	Cemented		1.0	Reference

Table 6. Cox regression with time-dependent coefficients in patients aged < 55 years.

		HR	95% CI
Type of fixation	Uncemented	1.10	0.91-1.32
	Inv hybrid	0.62	0.29-1.29
	Hybrid	0.83	0.67-1.04
	Cemented	1.0	Reference

Table 7. Cox regression with time-dependent coefficients in patients aged < 65 years in the Nexgen subgroup.

		HR	95% CI
Type of fixation	Uncemented	1.37	1.12-1.67
	Inv hybrid	0.59	0.34-1.03
	Hybrid	1.47	1.16-1.87
	Cemented	1	Reference

Appendix 1.

The 5 most commonly used TKA designs in each country 2000-2016.

Norway		Sweden		Finland		Denmark	
LCS Complete	3 436	NexGen	16 734	Triathlon	12 834	PFC	6 967
Profix	3 319	PFC	12 984	Nexgen	7 515	Nexgen	4 407
Nexgen	3 034	AGC	3 635	PFC	5 168	AGC	3 426
LCS	816	Triathlon	3 393	Duracon	3 995	Vanguard	2 354
Triathlon	757	Vanguard	3 074	Vanguard	2 878	Advance	751

Appendix 2

The 5 most commonly used TKA designs in the fixation concepts over 2000-2016.

Cemented		Uncemented		Hybrid		Inverse hybrid	
Nexgen	27 948	Nexgen	2 204	PFC	2 248	Nexgen	497
PFC	22 360	Triathlon	1 375	Nexgen	1 629	PFC	10
Triathlon	15 664	PFC	1 221	Profix	906	Triathlon	7
AGC	8 575	Duracon	310	Legion	363	Duracon	5
Vanguard	8 297	Profix	235	AGC	194	Profix	5

Appendix 3.

Proportions of different fixation methods in the Nexgen subgroup during 2000-2016.

	Norway	Sweden	Finland	Denmark	Total	%
Cemented	2 669	15 839	6 471	2969	25 279	85
Uncemented	187	751	698	676	2312	8
Hybrid	177	34	5	1413	1629	5
Inverse hybrid	1	123	341	32	497	2

Appendix 4. Additional Cox regression covariates with time-dependent coefficients (in different age groups and the Nexgen subgroup).

		Follow-up (yr)	HR	95% CI
All patients aged <65 years				
Gender	Women	< 1	0.73	0.66-0.82
		1-3	1.15	1.06-1.26
		3-6	1.35	1.19-1.52
		> 6	0.98	0.86-1.11
Age	Per year	< 1	0.96	0.95-0.97
		1-3	0.95	0.94-0.96
		3-6	0.95	0.94-0.96
		> 6	0.95	0.94-0.96
Nation				
	Norway	< 1	1.51	1.27-1.79
		1-3	1.64	1.44-1.87
		3-6	1.67	1.39-2.00
		> 6	0.98	0.76-1.25
	Denmark	< 1	1.36	1.16-1.59
		1-3	1.53	1.36-1.73
		3-6	1.08	0.90-1.29
		> 6	1.52	1.27-1.81
	Finland	< 1	1.32	1.16-1.51
		1-3	1.18	1.06-1.31

		3-6	1.05	0.91-1.22
		> 6	1.35	1.17-1.56
	Sweden		1.0	-
Patients aged 55- 65 years				
Gender	Women	< 1.5	0.81	0.74-0.90
		1.5-3	1.24	1.09-1.41
		3-6	1.33	1.14-1.54
		> 6	0.99	0.85-1.15
Age			0.96	0.95-0.97
Nation	Denmark		1.40	1.28-1.53
	Finland		1.23	1.14-1.33
	Norway		1.50	1.36-1.66
	Sweden (ref.)		1.0	-
Patients aged < 55 years				
Gender	Women		1.07	0.96-1.18
Age			0.96	0.95-0.97
Nation	Denmark	< 1	1.37	1.01-1.85
		1-3	1.86	1.51-2.28
		3-6	0.83	0.60-1.16
		> 6	1.22	0.90-1.66
	Finland	< 1	1.55	1.19-2.01
		1-3	1.30	1.06-1.58
		3-6	1.01	0.77-1.32
		> 6	0.98	0.75-1.28
	Norway	< 1	1.52	1.08-2.13
		1-3	1.91	1.51-2.4
		3-6	1.59	1.15-2.2
		> 6	0.81	0.52-1.3
	Sweden	< 1	1.0	-
	(ref.)	1-3	1.0	-
		3-6	1.0	-
		> 6	1.0	-
Patients aged < 65 years in the Nexgen subgroup				
Gender	Women	< 1	0.61	0.49-0.76
		1-3	1.43	1.18-1.72
		3-6	1.34	1.01-1.79
		> 6	1.73	1.15-2.61
Age			0.95	0.94-0.96
Nation	Denmark		1.84	1.57-2.16
	Finland		1.39	1.20-1.62
	Norway		1.62	1.29-2.02
	Sweden		1	-

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Total Knee Arthroplasty with an Uncemented Trabecular Metal Tibial Component A Registry-Based Analysis

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ABSTRACT

Previous poor results have kept the appeal of uncemented total knee arthroplasties (TKAs) minimal. We analyzed the mid-term survivorship and reasons for failures of a contemporary uncemented porous tantalum monoblock tibial component nation-wide. During the study period (2003–2010), such tibial components were used in 1143 primary TKAs recorded in the Finnish Arthroplasty Registry. Seven-year survivorship of these TKAs was 100% (95% CI 99–100) with revision for aseptic loosening of the tibial component, and 97% (95% CI 96–98) with revision for any reason as the respective end points. The most common reasons for revisions were instability and prosthetic joint infections. In conclusion, TKAs using an uncemented porous tantalum monoblock tibial component showed excellent mid-term survivorship in a population-based setting.

Cemented total knee arthroplasty (TKA) is a reliable and cost-effective procedure for treating symptomatic end-stage osteoarthritis (OA) of the knee [1,2]. Cemented TKA is also regarded as the gold standard for patients undergoing TKA for knee OA [3]. The appeal of uncemented TKAs has been minimal due to poor results so far [4–10]. These failures were mostly due to uncemented metal-back patellar resurfacing, but also to aseptic loosening of the tibia component [11,12]. However, as the incidence of TKAs has increased dramatically among younger and more active patients in the last decade [13], increasing concern has arisen about the durability of contemporary cemented TKA designs for these patients. As aseptic loosening occurs as a reactive process to wear debris from the polyethylene insert, ways of reducing the volumetric wear have been sought [14]. Possible interventions include making the PE insert more resistant to wear, eliminating backside wear of the tibial tray and improving implant to bone integration.

An uncemented porous tantalum tibial component has a highly porous tantalum tray with a fixed polyethylene insert which eliminates backside wear and may thus reduce the long-term PE particle burden. The PE insert is moulded into the trabecular metal cells to a depth about 1.5 mm. The components are gamma irradiated to 3.5 Mrad. The biological incorporation of trabecular metal implants is well documented [15–18], and the elastic properties of this implant are comparable to those of normal bone structure [19]. The lower stiffness of the tantalum implant may cause less stress shielding than in conventional metal-backed components. On the other hand, an increased surface area of the extremely porous tantalum metal and also a lack of antibiotic-loaded bone cement may in theory increase the risk of periprosthetic joint infections (PJIs).

The aim of the present study was to analyze epidemiological trends, survivorship and the reasons for failures of this implant nation-wide based on data recorded on the Finnish Arthroplasty Registry.

Materials and Methods

Our study was based on information recorded on the Finnish Arthroplasty Registry relating to patients undergoing TKA with an uncemented porous tantalum tibial component (Trabecular Metal Monoblock Tibia; Zimmer, Warsaw) between January 1, 2003, and December 31, 2010. The coverage of the Finnish Arthroplasty Registry was analyzed in 1994–1995 by comparing its data with those of the discharge registers of the participating hospitals; it was found to cover 90% of implantations and implant removals. Since 1995, the data of the Registry have been compared with those of the hospital discharge registers every few years. Currently, over 95% of implantations are

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recorded. Revisions are linked to the primary surgery using the unique personal identification number assigned to each resident of Finland.

Patient Characteristics

Over the study period, 1151 TKAs were performed using an uncemented porous tantalum tibial component. Of these operations 1143 (99%) were primary TKAs and 8 (1%) revision TKAs. Only the primary TKAs were included. Of the 1143 primary TKAs using the TM Monoblock Tibia, 647 (57%) were performed on women and 597 (52%) on the right knee. At the time of the surgery, the mean age of the patients was 63.6 years (range: 30–91). The majority of these procedures were performed due to primary osteoarthritis (n = 1,086; 95%). Other indications included posttraumatic osteoarthritis (n = 32; 2.8%), rheumatoid or other chronic inflammatory arthritis (n = 20; 1.7%), and other unclassified indications (n = 5; 0.4%). Three hospitals in Finland were involved in this study cohort. The annual use of the TM Monoblock Tibia is shown in Fig. 1.

Implant-Dependent Trends

The femoral components among the 1,143 primary TKAs using an uncemented porous tantalum tibial component were cemented in 48% (n = 549), and uncemented in 52% (n = 594) of the cases. Furthermore, the patella was left unresurfaced in 85% (n = 974) and resurfaced with a cemented button in the remaining 15% (n = 169) of cases.

Other Confounders

To assess the impact of age on implant survival, we analyzed age as a linear variable, and also using age groups 1) age under 55 years (n = 167; 15%), 2) age from 55 to 65 years (n = 458; 40%), and 3) age over 65 years (n = 518; 45%). The impact of gender on survival was also assessed. As the end points we used all revisions and revisions for aseptic loosening of the TM Monoblock Tibia.

Statistics

The endpoint for survival was defined as revision with either one component or the whole implant removed or exchanged. All survival analyses were performed using all revisions and revisions for aseptic loosening of the tibial component as the end points. Kaplan–Meier survival data were used to construct the survival probabilities of implants at 1, 5, and 7 years. The Cox multiple-regression model was used to study differences in revision risk (RR) between revision indications and to adjust for potential confounding factors. The variables included in the Cox model were as follows: primary osteoarthritis (reference indication) vs. other indications, cemented vs. uncemented femur (reference implant), unresurfaced vs. resurfaced patella (reference technique), gender, and age both as a continuous and as a categorized variable. Age groups analyzed were: 1) age under 55 years and 2) age from 55 to 65 years with 3) age over 65 years (reference age group). The reasons for failures and revisions among these patients during the study period were ascertained from patients' medical records and radiographs from those hospitals where the revisions had been performed. The Cox regression analyses provided estimates of survival probabilities and adjusted risk ratios (ARR) for the various factors. Estimates from the Cox analyses were used to construct adjusted survival curves at mean values of the risk factors. The Wald test was used to calculate *P*-values for data obtained from the Cox multiple regression analysis. Differences between groups were considered statistically significant if the *P*-values were less than 0.05 in a two-tailed test. We used SPSS 20.0 statistical software (IBM, Armonk, New York, USA) for statistical analyses.

Results

Survivorship of the TM Tibia Component

Survivorship of the whole study cohort was 100% (95% CI 99–100) at 1, 5, and 7 years postoperatively using revision for aseptic loosening of the tibial component as the end-point. When revision for any reason was used as the end-point, 1-, 5-, and 7-year survivorships were 99% (95% CI 98–100), 97% (95% CI 96–98) and 97% (95% CI 96–98) respectively (Fig. 2, Table 1).

Multivariate Analysis

In the Cox multiple regression model, there was no difference in risk of revision between any of the variables studied (Table 1).

Revision Operations

Twenty knee revisions including removal or replacement of the uncemented porous tantalum tibial component with or without revision of the femoral component were reported during the period 2003–2010. The indications for revisions were ascertained from the patients' medical records from the hospital concerned. The most common reason for revision was tibiofemoral (TF) joint instability with or without malposition of the TKA components (n = 12, 60%). This was followed by PJI (n = 7, 35%) and aseptic loosening (n = 1, 5%). Five of the seven PJIs were treated with two-stage revisions, one

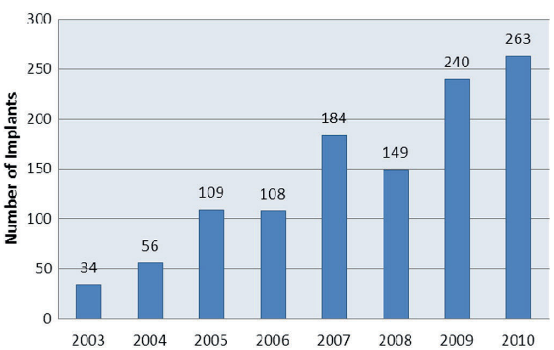

Fig 1. Number of trabecular metal monoblock tibias implanted in primary total knee arthroplasties in Finland per year, 2003–2010.

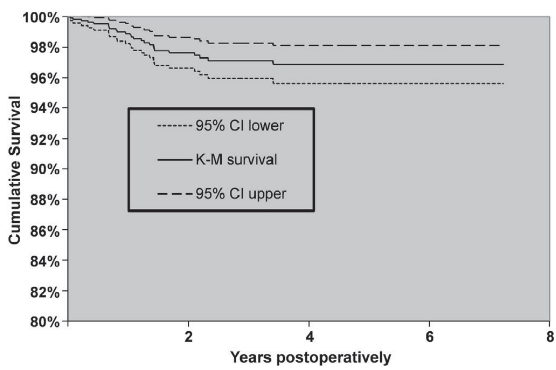

Fig 2. Kaplan-Meier survival curves for 1143 primary total knee arthroplasties using the Trabecular Metal Monoblock Tibia (mean follow-up 2.7 years). The end-point was defined as revision of the tibia component for any reason.

Table 1
Overall and Confounder-Based Survival and Cox-Adjusted Risk Ratio for Revision of TM Monoblock Tibia over 2003–2010 in Finland.

Cohort	N[a]	MF yr (Range)	AR 1 yr	% 1-Year Survival (95% CI)	AR 5 yr	% 5-Year Survival (95 % CI)	AR 7 yr	% 7-Year Survival (95% CI)	Adjusted RR for Revision (95% CI)	p
All	20/1143	2.7 (0–7.9)	866	99 (99–100)	175	97 (96–99)	29	97 (96–99)	-	-
Women	14/647	2.7 (0–7.9)	499	100 (99–100)	103	97 (95–98)	17	-	1.8 (0.7–4.7)	0.22
Men	6/496	2.6 (0–6.9)	367	99 (98–100)	72	98 (97–100)	12	-	1.0	-
Primary osteoarthritis	19/1087	2.7 (0–6.9)	825	99 (99–100)	164	97 (96–99)	28	97 (96–99)	1.0	-
Other indications	1/56	2.7 (0–6.9)	41	98 (95–100)	11	-	1	-	1.1 (0.1–8.6)	0.94
Cemented femur	13/548	3.6 (0–7.8)	486	99 (98–100)	164	97 (96–99)	20	97 (96–99)	1.0	-
Uncemented femur	7/595	1.8 (0–7.9)	380	100 (99–100)	11	-	8	-	1.1 (0.4–3.1)	0.82
Patella not resurfaced	15/974	2.5 (0–7.9)	733	99 (99–100)	126	98 (96–99)	29	98 (96–99)	0.6 (0.2–1.9)	0.40
Patella resurfaced	5/168	3.5 (0–6.9)	133	99 (98–100)	49	96 (93–99)	0	-	1.0	-
Age < 55 years	3/167	2.5 (0–7.9)	126	99 (97–100)	25	98 (95–100)	3	-	2.7 (0.6–13.5)	0.21
Age 55–65 years	10/457	2.6 (0–7.9)	353	100 (99–100)	53	97 (95–99)	9	-	3.3 (0.2–47.5)	0.37
Age > 65 years	7/519	2.8 (0–7.9)	387	99 (99–100)	97	98 (96–100)	17	-	1.0	-

The end-point was defined as revision for any reason of the tibia component.
[a] Number of revisions/number of total operations. MF = mean follow-up (years). AR = at risk. RR = risk ratio from the Cox regression analysis (adjustment was made for age and sex).

with one-stage revision, and one patient was treated by conservative means (antibiotic treatment) due to her severe medical co-morbidities. Six (0.5%) knees were revised due to instability alone, and another six (0.5%) due to instability combined with malalignment of the tibia component. All these unstable knees were reconstructed with a constrained TKA (LCCK, Zimmer, Warsaw, In). One knee (84-year-old male) was revised because of aseptic loosening of the tibia component five months after the primary surgery. In addition to these 20 revisions included in the survival analyses, four patients (four knees) underwent secondary patellar resurfacing because of anterior knee pain.

Discussion

We found that an uncemented porous tantalum monoblock tibial component had excellent mid-term survivorship in a population-based setting. The most common reasons for revisions were instability and PJIs. During the study period only one revision was performed due to aseptic loosening of this tibial component. Neither age nor any of the other variables showed any effect on the risk of revision in the multivariate regression analyses.

We concede that this register-based study has certain limitations. One of these is the lack of clinical data, including patient-reported outcome measurements. Further, the register-based study setting with a large number of patients did not allow us to conduct radiographic analyses apart from those in revision surgery. Thus radiographic signs of component loosening or osteolysis could not be analyzed. Selection bias in the study cohort is a possibility, as most of the patients (55%) were younger than 65 years. The mean age of the study cohort was only 64 years, whereas the mean age of all patients undergoing TKA in Finland during the study period was 69 years (Table 2). As young age increases the risk of revision after TKA [20], one might have expected increased failure rates in this study cohort compared to earlier reports with uncemented TKA components. However, despite this possible selection bias towards younger (and more active) patients, overall mid-term survivorship of the porous tantalum monoblock tibial component was excellent.

Table 2
Patient Demographics From the Finnish Arthroplasty Registry Between 2003 and 2010.

	TKAs With a TM Tibial Component	All TKAs
Women	647 (57%)	83414 (70%)
Men	496 (43%)	35024 (30%)
Mean age (range)	63.6 (30–91)	69.1 (9–106)
Indication: Primary OA	95%	93%

In the present study, the proportion of female patients was lower than in the general TKA population, as 70% of patients undergoing TKA in Finland during the study period were women (Table 2). The higher than anticipated proportion of males may suggest that uncemented tibial components have been more commonly used in physically active men with good bone quality.

Early failures of uncemented knee arthroplasties were mainly caused by aseptic loosening of the patellar resurfacing and the tibial component [4–10]. Cementless fixation has been associated with high failure rate due to inadequate bone ingrowth [21]. The reason for this has been the excessively stiff construction of the tibial implant leading to stress shielding and micro-motion at the prosthesis-bone interface. Survivorship of certain uncemented TKA designs has subsequently been reported comparable to that of cemented designs but these papers have originated from single centers and may, at least in part, be explained by good patient selection and high-volume surgeons [22–25]. In the Finnish register-based study uncemented TKA had a 1.4 times elevated adjusted hazard ratio compared to that of cemented TKA when revision was evaluated for any reason [20]. In the Australian National Joint Replacement Registry's annual report for 2012 the cumulative 10-year revision rate was 5.4 with cemented TKA and 6.1 with uncemented TKA.

The majority of revisions were performed due to either instability alone, or a combination of instability and component malalignment. One disadvantage of using a monoblock tibial component is the risk of instability or excessive tightness due to the lack of modularity after the tibial and femoral components are in place. With a monoblock type of implant there is no potential for isolated polyethylene insert exchange if instability is observed after the primary operation necessitating revision surgery. In this study cohort there were two patients with instability without malalignment of components and who thus could have been candidates for polyethylene insert exchange alone. Uncemented, porous metal tibial trays with modular polyethylene inserts are available in the market, but due to the greater stiffness of metal-backed components the stress-shielding effect on the bone-implant surface may be emphasized. In the present study the incidence of revisions due to instability (1.0%) was similar to that of the general TKA population in Finland (1.3%) [20]. The Finnish Arthroplasty Registry data, however, do not include information on the type of knee revisions. Thus, the incidence of isolated polyethylene insert exchange procedures cannot be analyzed from that data.

The early TM monoblock tibial components were cemented ones. In 2010, O'Keefe, Winter et al published a series of 125 TKAs in which a cemented TM monoblock tibial component was combined with cemented femoral and patellar components [16]. In that study, only two tibial components were revised during follow-up (minimum of 5 years). Another prospective study comparing 100 uncemented TM monoblock tibias to 312 cemented controls reported excellent survivorship of the TM Monoblock tibial components at a minimum follow-up of 5 years. In that study, none of the uncemented tibial components loosened, neither were there any signs of osteolysis among these patients [18]. Wilson, Astephen and co-workers reported early migration of TM tibial components which were analyzed by RSA [15]. However, when the authors analyzed the same patient cohort (45 patients out of an original 70 patients) at five years postoperatively, all uncemented tibial components had achieved solid fixation [26]. In another series, Unger, Duggan and colleagues reported an excellent outcome for 108 TKAs using TM monoblock tibial components at a mean follow-up of 4.5 years [17]. In that study, none of the tibial components were revised, although one migration was reported without need for revision. Our results, with only one out of 1143 TKAs revised due to tibial component loosening, are in accordance with these earlier reports.

In theory, lack of antibiotic-loaded bone cement and the huge surface area of the trabecular tibial component might predispose to PJI. However, the incidence of revisions due to PJI was only 0.7% in the present study. In another paper based on Finnish Arthroplasty Registry data, the incidence of revisions due to PJI was 0.6% among 32,019 TKAs [20]. Thus this evidence from the population-based setting does not support this theory.

In conclusion, an uncemented porous tantalum monoblock tibial component achieved excellent mid-term survivorship in a population-based study setting. Early loosening of this uncemented tibial component is very rare, even nation-wide, and PJIs are as rare as with contemporary cemented TKAs. Longer follow-up is required to see whether these results, especially in a cohort of fairly young TKA patients, stand the test of time.

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Original Research Article

OUTCOME OF KNEE ARTHROPLASTY IN PATIENTS AGED 65 YEARS OR LESS: A PROSPECTIVE STUDY OF 232 PATIENTS WITH 2-YEAR FOLLOW-UP

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ABSTRACT

Background and Aims: **Previous studies have reported lower implant survival rates, residual pain, and higher patient dissatisfaction rates following knee arthroplasty in younger knee arthroplasty patients. We aimed to assess the real-world effectiveness of knee arthroplasty in a prospective non-selected cohort of patients aged 65 years or less with 2-year follow-up.**

Material and Methods: **In total, 250 patients (272 knees) aged 65 years or less were enrolled into this prospective cohort study. Patient-reported outcome measures were used to assess the outcome.**

Results: **The mean Oxford Knee Score and all Knee Injury and Osteoarthritis Outcome Score subscales increased significantly ($p < 0.001$) from preoperative situation to the 2-year follow-up. Significant increase ($p < 0.001$) in physical activity was detected in High-Activity Arthroplasty Score and RAND-36 Physical Component Score (PCS). Pain was also significantly ($p < 0.001$) relieved during the follow-up. Total disappearance of pain was rare at 2 years. Patients with milder (Kellgren–Lawrence grade 2) osteoarthritis were less satisfied and reported poorer patient-reported outcome measure than those with advanced osteoarthritis (Kellgren–Lawrence grade 3–4). There was no difference in the outcome (any patient-reported outcome measure) between patients who underwent total knee arthroplasty and those who received unicondylar knee arthroplasty.**

Conclusion: **We found that measured with a wide set of patient-reported outcome measures, both total knee arthroplasty and unicondylar knee arthroplasty resulted in significant pain relief, as well as improvement in physical performance and quality of life in patients aged 65 years or less. Real-world effectiveness of these procedures seems to be excellent. 15% of patients still had residual symptoms and were dissatisfied with the outcome at 2 years after the operation.**

Key words: Knee arthroplasty; patient-related outcome measures; outcome; 65 years or less; young patients; satisfaction; pain

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INTRODUCTION

Younger patients have high expectations for the outcome of total knee arthroplasty (TKA), and this may predispose them to dissatisfaction after the operation (1–3). Furthermore, younger age is associated with higher rates of complications and an increased risk for revision surgery (4, 5). Arthroscopic surgery of the degenerative knee has been shown to be ineffective (6), and the incidence of high tibial osteotomy has also steadily decreased (7, 8). Hence, increasing number of younger patients with mild knee osteoarthritis (OA) are being offered knee arthroplasty. In the Nordic countries, the incidence of TKA has grown especially rapidly among patients younger than 65 years of age (9). As both young age (4, 5) and mild knee OA (10) are known to be risk factors for revision surgery, it is of critical importance to assess the outcome of knee arthroplasty within this demanding patient group.

Only a few recent studies have reported the outcome of TKA measured with patient-reported outcome measures (PROMs) in younger patients (1, 11, 12). Only one (12) of these previous trials was a true prospective observational study. Furthermore, patient activity was not assessed with a specific activity score in any of these studies. All of them reported an overall positive effect of TKA on symptoms, activities of daily living (ADL), and quality of life (QoL). However, a variable proportion of patients (11%–25%) were dissatisfied with the outcome of their surgery. Scott et al. (1) reported that dissatisfaction was also related to a low grade of radiographic OA, previous surgery, and obesity.

Randomized controlled trials (RCTs) provide the least biased information of the efficacy of surgical interventions (13). However, RCTs mostly assess effectiveness of interventions in ideal settings. Their ability to assess effectiveness of the whole clinical pathways is limited. Thus, there is an obvious need for valid observational (real-world) data on actual performance in routine settings (14).

The aim of our study was to assess the real-world effectiveness contemporary knee arthroplasty in patients aged 65 years or less. To achieve this goal, we conducted a prospective observational study with 2-year follow up. This study report outcomes measured comprehensively using various PROMs to provide information on the effect of knee arthroplasty on physical activity, ADL, QoL, pain, and satisfaction.

MATERIALS AND METHODS

For this 2-year prospective cohort study, 250 patients were enrolled between 1 March 2012 and 30 October 2014 at our high-volume academic tertiary referral center. PROM data and other study questionnaires were collected preoperatively, at 2 to 3 months and at 1 year (10 to 14 months) and at 2 years (22 to 26 months) postoperatively.

All patients were treated in their local health centers by general practitioners before they referred the patients for consultation to our institution. The inclusion criteria were as follows: (1) age 65 years or less and (2) scheduled for either TKA or unicondylar knee arthroplasty (UKA). The exclusion criteria were as follows: (1) rheumatoid arthritis or other inflammatory diseases; (2) unwilling to provide informed consent; (3) physical, mental, or neurological conditions that could compromise the patient’s ability and compliance with postoperative rehabilitation and follow-up (e.g. drug or alcohol abuse, serious mental illness, and general neurological conditions such as Parkinson’s disease and multiple sclerosis); and (4) known sensitivity to materials in the devices.

TABLE 1

Patient demographics.

	TKA		UKA	
	n = 227		n = 27	
Age, year, mean (SD)	58	(5.1)	56	(5.4)
BMI, mean (SD)	31	(5.3)	29	(4.0)
	n	%	n	%
Females	125	61	14	52
OA (knees)				
Primary	204	90	26	96
Secondary	23	10	1	4
KL (knees)				
KL 2	33	15	5	18
KL 3	105	46	12	46
KL 4	89	39	10	36
ASA				
1	73	32	11	41
2	116	51	15	56
3	38	17	1	3
At work preoperatively	110	53	18	65

TKA: total knee arthroplasty; UKA: unicondylar knee arthroplasty; SD: standard deviation; BMI: body mass index; OA: osteoarthritis; KL: Kellgren–Lawrence score; ASA: American Society of Anesthesiologists score.

A total of 373 recruitment letters were sent consecutively to patients of 65 years or less who were sent for consultation for knee arthroplasty, and the first 250 patients (272 knees) who returned written informed consent to participate were recruited on the study. As 5 (2%) patients canceled surgery, 6 (2.4%) were revised, 5 (2%) were lost to follow-up, and 2 (0.8%) died during the follow-up; 232 patients (93%; 254 knees) were available for the 2-year follow-up visits, and the analysis of the final results was based on these patients. If the patient had isolated antero-medial OA in the plain radiographs, then demiarthroplasty was considered. While simultaneous bilateral TKAs were performed for 22 patients, none of the patients received bilateral UKAs. The final patient population comprised 227 TKAs and 27 UKAs. Patient demographics are shown in Table 1.

All operations were performed by senior orthopedic surgeons, and all patients were treated with the same routine postoperative rehabilitation and pain management protocol.

Of the 232 patients (254 knees), 227 knees (89%) underwent cemented TKA using either press-fit condylar

TABLE 2

Patient-reported outcome measure (PROM) scores preoperatively and at 2 years analyzed separately for TKA (n = 227) and UKA (n = 27).

	TKA					UKA				
	Preoperative		2 years			Preoperative		2 years		
OKS	22	(21–23)	41	(40–42)	<0.001	24	(21–28)	42	(40–43)	<0.001
KOOS pain	45	(43–47)	86	(84–88)	<0.001	46	(39–53)	86	(81–91)	<0.001
KOOS symptoms	43	(41–46)	79	(76–81)	<0.001	48	(40–55)	77	(70–84)	<0.001
KOOS ADL	50	(48–52)	88	(86–90)	<0.001	56	(50–62)	89	(84–94)	<0.001
KOOS sport/rec	14	(12–17)	55	(51–59)	<0.001	16	(10–23)	55	(44–67)	<0.001
KOOS QoL	21	(19–23)	70	(67–73)	<0.001	25	(18–31)	68	(58–77)	<0.001
RAND-36 MCS	61	(58–64)	79	(77–81)	<0.001	65	(56–73)	78	(69–87)	0.007
RAND-36 PCS	37	(34–39)	68	(65–71)	<0.001	39	(34–45)	70	(61–79)	<0.001
HAAS	6	(5–6)	11	(10–11)	<0.001	7	(6–9)	12	(11–13)	<0.001

TKA: total knee arthroplasty; UKA: unicondylar knee arthroplasty; OKS: Oxford Knee Score; KOOS: Knee Injury and Osteoarthritis Outcome Score; ADL: activities of daily living; sport/rec: function in sports and recreation; QoL: quality of life; MCS: Mental Component Scale; PCS: Physical Component Scale; HAAS: High-Activity Arthroplasty Score.
Significant increase was observed in all scores. The scores are shown as mean and 95% CI. Differences were evaluated using paired t-test.

(PFC; 182 knees; DePuy Synthes, Warsaw, IN, USA) or Nexgen (45 knees; Zimmer Biomet, Warsaw, IN, USA). In 12 (5.3%) of the TKAs, patella was resurfaced. Of the 227 TKAs, 218 (96%) were cruciate retaining (CR) and the rest 9 were posterior stabilized (PS). UKA was performed for 27 patients using the uncemented Oxford phase 3 (Zimmer Biomet) prosthesis.

OUTCOME MEASURES

Four different PROMs were used to measure the effectiveness of knee arthroplasty in these patients: Oxford Knee Score (OKS), Knee Injury and Osteoarthritis Outcome Score (KOOS), High-Activity Arthroplasty Score (HAAS), and the RAND-36 general QoL questionnaire. Primary outcome was defined as the effect of knee arthroplasty on pain and function as measured with OKS and KOOS. Secondary outcomes were as follows: the effect of knee arthroplasty on QoL (RAND-36), physical activity (HAAS), and satisfaction. A background questionnaire included information on working status and physical activities. The Visual Analog Scale (VAS) was measured with scale from 0 to 100 and it was used to evaluate pain and satisfaction caused by knee arthroplasty both before and after surgery. The VAS satisfaction scale was divided into four sections: 0 to 25, dissatisfied; 26 to 50, unsure; 51 to 75, satisfied; and 76 to 100, very satisfied as proposed previously by Scott et al. (1).

The severity of knee OA was assessed from preoperative standing fixed flexion view (FFV) radiographs using the Kellgren–Lawrence (KL) classification.

QUESTIONNAIRES

The OKS score comprises 12 items regarding pain and ADL. Scores vary from 0 to 48, with 48 being the best possible score. The minimal clinically important difference (MCID) for the OKS score is 3 to 5 points.

KOOS comprises five subscales: pain, other symptoms, ADL, function in sport and recreation (sport/rec), and knee-related QoL. A normalized score (100 indicating no symptoms and 0 indicating maximal symptoms) is calculated for each subscale. The MCID is suggested to be 8 to 10.

The HAAS was specifically developed to assess the subtle variations in functional ability after lower limb arthroplasty with particular regard to highly active individuals. The score covers the four domains: walking, running, stair climbing, and general activities. Possible score ranges from 0 to 18 points. The MCID has not been defined for HAAS.

The RAND-36 comprises 36 items that assess eight health concepts. The Physical Component Scale (PCS) and the Mental Component Scale (MCS) are also derived from the eight RAND-36 scales. Scores range from 0 (lowest) to 100 (best). The MCID for the subscales is suggested to be 3 to 5 points.

ETHICS

The study protocol (R11178) was approved by the Ethics Committee of our hospital district. The study was registered with ClinicalTrials.gov (NCT03233620). All patients gave written informed consent to participate in the study.

STATISTICAL ANALYSIS

Data were presented as median with quartiles (Q_1 to Q_3) or as mean (SD) or (95% confidence interval (CI)). The Wilcoxon signed rank test and paired t-test for paired data were used to compare preoperative and postoperative values. The differences in distributions in the three measured time points were calculated with Friedman test. A p-value less than 0.05 was considered statistically significant. Data were analyzed using the SPSS (version 23) statistical package (IBM, Armonk, NY, USA.)

To prevent potential bias with TKA and UKA, the results were analyzed for both TKA and UKA together and also separately for TKA and UKA only (Table 2).

RESULTS

Mean OKS increased both statistically (18 points, CI = 17–19, p < 0.001; TKA and UKA together) and clinically (exceeding MCID) significantly from the preoperative situation to the 2-year follow-up. The mean increase did not differ between TKAs and UKAs (Table 2).

Significant increase (p < 0.001) was also observed in all KOOS subscales, all of which also exceeded MCID. The mean increase in scores between preoperative and 2-year follow-up (TKA and UKA together) was as follows: KOOS pain 41 (CI = 39–43), KOOS symptoms 35 (CI = 32–37), KOOS ADL 37 (CI = 35–40), KOOS sport/rec 40 (CI = 37–44), and KOOS QoL 48 (CI = 45–51) (Table 2; Fig. 1).

The preoperative baseline (mean) in physical activity according to HAAS was moderate: 6/18 in patients in the TKA group and 7/18 in the UKA group, respectively. The increase in mean HAAS (TKA and UKA together) was 5 points (CI = 4.6–5.5) over the 2-year follow up, and the improvement was significant (p < 0.001) (Table 2).

RAND-36 score was analyzed with mental (MCS) and physical (PCS) subscales. Over the 2-year follow up, the mean MCS (TKA and UKA together) increased 18 points (CI = 15–20) and the mean PCS 31 points (CI = 28–34). The change seen in both subscales was significant (p < 0.001) and also exceeded MCID (Table 2).

Pain relief was measured with the VAS (exercise and rest). A significant positive change of median value (in exercise: 80 (72,90) versus 13 (4,32), p < 0.001; in rest: 49 (26,71) versus 3 (0,7), p < 0.001) from the preoperative situation to the 2-year follow-up was detected (Fig. 2). In 16 (7%) patients, all of whom had undergone TKA, severe knee pain (VAS > 30) was still reported 2 years after knee arthroplasty.

At the time of the 2-year follow-up visit, 85% of patients were either satisfied (9%) or very satisfied (76%) with the outcome of their knee arthroplasty. Between 1- and 2-year follow-up evaluations, 16 patients (6.7%), who had been either unsure or satisfied with the outcome at the 1-year visit, had become more satisfied by the 2-year follow-up evaluation. The number of patients who were dissatisfied with the outcome did not change between the 1- and 2-year follow-up evaluations (Table 3). At the 2-year follow-up visit, 98% of all patients reported that they would choose to undergo knee arthroplasty again, and 96% reported that they would recommend this operation to their best friend. Regarding satisfaction, there was no difference between patients in the UKA and TKA groups.

Preoperative KL-grade significantly affected both satisfaction and PROM outcomes measured at 2 years. The median VAS satisfaction was significantly poorer in patients with preoperative KL grade 2 OA compared to both patients with KL 3 (85 (51,97) versus 94 (80,100) points, p = 0.006) as well as those with KL 4 OA (85 (51,97) versus 91 (81,99) points, p = 0.015) at the time of the 2-year follow-up visit (Fig. 3). Furthermore, there was a significant difference in median OKS between the groups at the time of the 2-year follow-up visit: median OKS was worse in the KL 2 group than both in the KL 3 group (41 (36,44) versus 44 (38,46) points, p = 0.015) and in the KL 4 group (41 (36,44) versus 43 (40,45) points, p = 0.037). However, this difference fulfilled the MCID criteria only when the KL 2 and KL 3 groups were compared. Similarly, patients with KL 2 OA preoperative, ended up with significantly poorer median subscale scores than those patients with more advanced radiographic OA (KL 4)

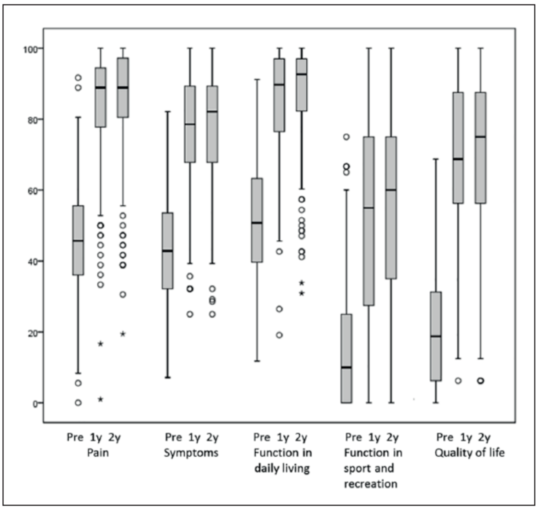

Fig. 1. Outcome measured with KOOS subscales (n = 254). Scores presented as median (Q_1 to Q_3). All differences between the preoperative and 2-year results were significant (p < 0.001 for all comparisons). Differences were evaluated using Friedman test.

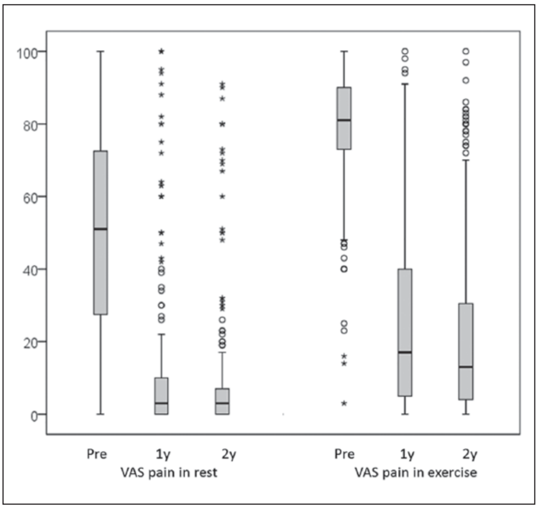

Fig. 2. Pain in rest and exercise assessed with VAS scores (n = 254). Values presented as median (Q_1 to Q_3). All differences between the preoperative and 2-year results were significant (p < 0.001 for all comparisons). Differences were evaluated using Friedman test.

TABLE 3

Satisfaction Visual Analog Scale (VAS) preoperatively, 1- and 2-year follow-ups.

	Pre	1 year	2 years
Very satisfied	1	68	75
Satisfied	7	13	9
Unsure	14	10	7
Dissatisfied	78	9	9

Scores are presented as percentage of satisfaction (0%–100%).

at the time of the 2-year follow-up visit: KOOS symptoms (75 (61,89) versus 86 (78,93), $p=0.001$), KOOS ADL (88 (76,96) versus 93 (85,97), $p=0.041$), and KOOS sport/rec (40 (25,75) versus 60 (38,75), $p=0.028$). However, the significant improvements between preoperative and 2-year follow-up were observed in all PROMs and also in the KL 2 patients ($p<0.001$).

REVISIONS

Of the 254 knee replacements originally operated, 6 (2.4%; 4 TKAs and 2 UKAs) had to be revised during the 2-year follow-up period. Two patients in the TKA group underwent secondary patellar resurfacing because of persistent anterior knee pain, one TKA was revised for prosthetic joint infection, and one TKA for stiffness due to arthrofibrosis. Of the two UKAs that underwent revision surgery, one was revised for dislocation of the polyethylene insert and the other for impingement. Revised patients were excluded from the final outcome assessment.

DISCUSSION

Earlier research on the success of knee arthroplasty has tended to focus on the survival of the implant. The functional outcome of knee arthroplasty has traditionally been measured using surgeon-driven clinical scores, such as the Knee Society Score (15–17). Recently, however, there has been an increasing demand for the subjective, patient-originated evaluation of the outcome (11). In practice, however, only a few such studies have been published so far (2, 11, 12). In this study, we utilized a wide set of PROMs to assess the real-world effectiveness of knee arthroplasty in a prospective non-selected cohort of patients undergoing TKA or UKA at our institution.

The increasing incidence of TKA also raises the question as to whether the financial resources invested in this treatment provide sufficient beneficial results in the face of the intensifying need for cost containment (9). Although we know that young age slightly increases the risk of revision, implant survival has been shown to be acceptable also in younger patients. Therefore, TKA is also a viable option for the treatment of end-stage OA in this patient population (18). Younger patients form a specific group with longer life time expectancy and also often with high demands for the outcome of surgery (19). In this study, we found that patients aged 65 years or less benefited significantly from knee arthroplasty in terms of pain relief, as well as in terms of improved physical activity and QoL. However, the total disappearance of knee symptoms was rare.

There have been earlier studies on functional gain following TKA in young patients but these have lacked true prospective follow up. These studies have used the upper age limits of 50 (11) or 55 (1) years of age. In everyday clinical practice, however, these subgroups are marginal. Instead, the rising incidence of TKA has occurred especially in patients aged 50 to 59 years (20), which is among the target group of our study. In our study, 85% of patients were satisfied or very satisfied with the outcome at 2 years postoperatively, and an even higher proportion of patients (98%) reported a willingness to undergo knee arthroplasty again. In other recent studies, the subgroups who are dissatisfied with their surgery have been reported to range from 10% to 20% (1, 2, 11). In this respect, knee arthroplasty is clearly inferior to total hip arthroplasty, and the topic of dissatisfied knee arthroplasty patients clearly needs further research. Previous studies have shown that persistent pain after knee arthroplasty is strongly associated with psychological aspects and young age (21, 22). In our study, knee arthroplasty resulted in significant pain relief, and most of this effect was seen already during the first postoperative year. Moreover, between 1 and 2 years postoperative, the number of patients with persistent knee pain continued to decrease (Fig. 2). Thus, some patients experienced a clearly delayed recovery, but the small subgroup (7%) of patients who reported severe knee pain persisted at the time of the 2-year follow-up.

Scott el al. (1) divided the satisfaction scale into four categories: very satisfied, satisfied, dissatisfied, and as the fourth group they included those patients who were unsure about their satisfaction. We found that a small proportion of patients who were "unsure" at the time of the 1-year follow-up reported being satisfied at the time of the 2-year follow-up (7 patients, 2.9%). Thus, in some patients, complete recovery after knee arthroplasty may take up to 2 years. Dissatisfied patients, however, still held the same view at the time of the 2-year follow-up. Satisfaction is clearly a multidimensional experience, as 98% of patients reported being willing to undergo knee arthroplasty again despite the fact that 15% of patients were dissatisfied or unsure with the outcome of their surgery. The patient's own perspective of the preoperative symptoms and functional disability may partly explain this difference, that is, they may still have considered the outcome of knee arthroplasty to be better than the preoperative situation despite their residual knee symptoms. The proportion of patients in our study who were satisfied with the outcome was in accordance with other recent studies on the subject (23–25).

Scott et al. (1) reported high (59%) dissatisfaction rate of TKA in patients with KL 1–2 grade OA preoperatively. Also, in our study, satisfaction at 2 years was significantly lower in the KL 2 group, both when compared to the KL 3 and the KL 4 groups. Significant improvement, however, was achieved in all KL subgroups as compared to the preoperative situation

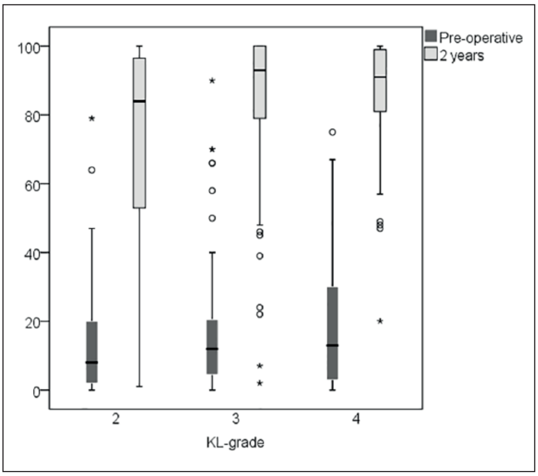

Fig. 3. VAS satisfaction in different Kellgren–Lawrence groups (n = 254). Scores presented in median (Q_1 to Q_3). All differences between the preoperative and 2-year results were significant ($p < 0.001$ for all comparisons). Differences were evaluated using Wilcoxon signed rank test.

(Fig. 3). As there was no difference in KOOS pain subscale between the KL subgroups at 2 years, it seems that despite their higher dissatisfaction rate, also patients with milder OA (KL 2) achieved good pain relief. In patients with mild radiographic knee OA, there may be other factors than pain, such as depression or catastrophizing behavior, that would explain higher dissatisfaction rates despite good pain relief achieved with surgery.

The clinically significant improvement in physical activity in these younger knee arthroplasty patients is an important finding. Young patients may be self-evidently considered physically active. This may restrict their access to knee arthroplasty because of the fear of compromised implant survival. A recent study by Keeney et al. (26) showed that preoperatively there was no difference in physical activity levels between younger (55 years or less) and older patients (65 to 75 years), and that physical activity increased in both groups after knee arthroplasty. In our study, only 42 (17%) patients reported a preoperative activity level of over 50% according to the HAAS scale. Respectively, the preoperative physical activity level points were less than 50% when also measured with the KOOS (93% of patients) and 36-Item Short Form Health Survey (SF-36; 76% of patients) subscales (Table 2). However, significant improvement was seen postoperatively in physical activity in the HAAS as well as in the KOOS and SF-36 physical activity subscales. Thus, the ability to exercise can also be improved with knee arthroplasty in younger patients. To the best of our knowledge, our study is the first to assess the effect of knee arthroplasty on patient activity levels using a specific activity score in a prospective observational (real-world) study.

Scott et al. (27) reported that patients undergoing TKA consider climbing stairs, ability to walk, and kneeling to be especially important activities in their daily living. Because the preoperative physical activity of patients undergoing TKA has been shown to be low, more demanding activities, such as cycling or carrying heavy objects, have not been so important for them (28). In the working-age population, functions related to daily living are associated with working capability. In our study, 104 (45%) patients were retired or about to retire preoperatively. Of the128 (55%) patients who were working preoperatively, a high proportion (89%) returned to work during the 2-year follow-up, and significant improvements in scores related to daily living supported this finding (Table 2).

Changes in QoL are based on both physical and mental improvements and are also related to pain relief. Even if physical scores improved more distinctly, it is notable that mental scores also improved significantly after knee arthroplasty. The Mental Component Score (MCS) of RAND-36 showed comparable improvement with the Physical Component Score (PCS) of RAND-36, emphasizing comprehensive improvement in outcomes (Table 2). Recently, Goh et al. (11) also reported significant albeit slightly smaller improvements in these scores than the scores we found in this study (PCS 16.9 versus 31.5 and MCS 4.4 versus 17.5).

We recruited younger patients with knee OA who were scheduled for knee arthroplasty at our institution. Our study was an observational intervention study with the focus on effectiveness, and the study setup mirrored everyday clinical practice. This setup has previously been applied only by Klit et al. (12), who conducted a prospective cohort study among patients aged less than 60 years. The difference between the study by Klit et al. and our study was that we included both patients who were listed for TKA and those who were scheduled for UKA. Furthermore, we applied a specific activity score (HAAS) to assess the effect of knee arthroplasty on patient activity levels. In our setup, UKA and TKA yielded similar results. Thus, the theoretical advantages of UKA over TKA (29) did not result in either better clinical outcome in any of the PROMs used or higher satisfaction. This finding warrants further research, and future work should compare the outcome and effectiveness of UKAs and TKAs in RCTs.

Our study is not without limitations. We did not have a specific control group of patients above the age of 65 years which would have enabled the comparison of our results with the older patient population. The UKA group was also markedly smaller than the TKA group. The obvious strength of this study was the evaluation of the outcome using multiple PROM data that have not been included in previous studies, a non-selected real-world cohort of patients, and also the fact that only a very small proportion (7%) of patients was lost to follow-up during the 2-year study period. Our study is also the first to evaluate the real-world effectiveness of TKA and UKA in younger patients utilizing a wide set of PROMs. To the best of our knowledge, our study is the first to assess both actual patient satisfaction and also their willingness to undergo the same surgery again. This approach showed that satisfaction is clearly a multidimensional issue that may not be adequately assessed with a single question about satisfaction.

CONCLUSION

We found that knee arthroplasty provided patients aged 65 years or less with clinically significant pain relief as well as improvement in ADL and QoL. The patients' physical activity was low or moderate preoperatively, but improved significantly during the 2-year follow-up. Some pain and functional deficiencies remained after knee arthroplasty, and this should be emphasized in the preoperative guidance given to patients who are considering or scheduled for such surgery. Mild radiographic OA preoperatively is a clear risk factor for patient dissatisfaction with the outcome of knee arthroplasty. Future research is warranted to clarify the preoperative risk factors for severe residual symptoms and dissatisfaction after knee arthroplasty.

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Peter Heath contributed to language revision; M.N. and A.E. designed the study; H.H. and M.N. analyzed the data and calculated statistics; M.N. prepared the manuscript; and T.M. and A.E. reviewed the results. All authors revised and approved the final manuscript.

DECLARATION OF CONFLICTING INTERESTS

M.N., T.M., and H.H. have no conflicting interests. A.E. has received research grant (Zimmer Biomet) and lecture fee (DePuy).

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ETHICAL APPROVAL

The study protocol (R11178) was approved by the Ethics Committee of Pirkanmaa Hospital District.

TRAIL REGISTRATION

The study was registered with ClinicalTrials.gov (NCT03233620).

INFORMAED CONSENT

All patients gave written informed consent to participate in the study.

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Single periarticular local infiltration analgesia reduces opiate consumption until 48 hours after total knee arthroplasty

A randomized placebo-controlled trial involving 56 patients

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Background — Randomized trials evaluating efficacy of local infiltration analgesia (LIA) have been published but many of these lack standardized analgesics. There is a paucity of reports on the effects of LIA on functional capability and quality of life.

Methods — 56 patients undergoing unilateral total knee arthroplasty (TKA) were randomized into 2 groups in this placebo-controlled study with 12-month follow-up. In the LIA group, a mixture of levobupivacaine (150 mg), ketorolac (30 mg), and adrenaline (0.5 mg) was infiltrated periarticularly. In the placebo group, infiltration contained saline. 4 different patient-reported outcome measures (PROMs) were used for evaluation of functional outcome and quality of life.

Results — During the first 48 hours postoperatively, patients in the LIA group used less oxycodone than patients in the placebo group in both cumulative and time-interval follow-up. The effect was most significant during the first 6 postoperative hours. The PROMs were similar between the groups during the 1-year follow-up.

Interpretation — Single periarticular infiltration reduced the amount of oxycodone used and enabled adequate pain management in conjunction with standardized peroral medication without adverse effects. No clinically marked effects on the functional outcome after TKA were detected.

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The goal of local infiltration analgesia (LIA) after TKA is to provide simple, effective, and safe pain relief during the first postoperative days, with reduced opiate consumption (Kerr and Kohan 2008). Adequate postoperative pain control is usually achieved using multimodal pain management, but it continues to be a challenge in many TKA patients. The recommended intraoperative anesthetic technique during TKA is either general anesthesia combined with femoral nerve block or spinal anesthesia combined with morphine (Fischer et al. 2008). Femoral nerve block is effective in reducing pain, but may cause falls after TKA (Ilfeld et al. 2010). Opiates, although effective in reducing pain, have severe side effects (nausea, itching, reduced gut mobility, and urinary retention), which may markedly retard the postoperative recovery. Thus, in addition to providing better pain relief, multimodal analgesia is aimed at reducing the amount of opiates used.

Several techniques of infiltration analgesia have been published, with enhanced pain relief for up to 48 hours (Kehlet and Andersen 2011). With longer follow-up time, the perioperatively administered LIA loses its efficacy (Essving et al. 2010). Furthermore, intra-articular LIA and extra-articular LIA have been reported to be equally effective in reducing postoperative pain (Andersen et al. 2008b). The benefit of using an intra-articular catheter has been questioned by some authors—concerning both the effectiveness of pain treatment and the theoretical increased risk of infection (Busch et al. 2006, Mullaji et al. 2010).

A recently published review divided LIA techniques into 2 groups—single administration and multiple administration—and it also compared different local infiltration techniques (Gibbs et al. 2012). Many studies included in that review were poorly controlled, with no standardization of oral analgesics. In the group of multiple administration methods, the reduction of opiate consumption was comparable to the results for the single administration group. Based on these findings, the authors of the review recommended the use of a single, intraoperative and systematic infiltration cocktail of high-dose ropivacaine, adrenaline, and ketorolac to all exposed tissues. Another review highlighted poor documentation of the long-term effect of LIA on knee function and quality of life (Ganapathy et al. 2011).

We studied the effects of a single, intraoperative periarticular infiltration on postoperative pain management after TKA.

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Patients and methods

We enrolled 60 patients undergoing unilateral TKA in this randomized, double-blind, placebo-controlled study. The inclusion criteria were: (1) need for primary TKA for primary osteoarthritis, and (2) age 18–75 years. Exclusion criteria were (1) rheumatoid arthritis or other inflammatory diseases, (2) BMI > 35, (3) American Society of Anesthesiologists physical score > 3, (4) renal dysfunction, (5) allergy to any of the study drugs, (6) previous high tibial osteotomy or previous osteosynthesis, (7) > 15 degrees varus or valgus malalignment, and (8) physical, emotional, or neurological conditions that could compromise the patient's compliance to postoperative rehabilitation and follow-up. All patients who were included in the study were operated at our institution between March 2011 and March 2012 (Figure 1).

Randomization and blinding

In the morning of surgery, an independent research nurse not involved in patient care performed the randomization sequence by drawing 1 opaque, sealed envelope from a collection of 60 alternatives (allocation ratio: 1:1). The nurse prepared the study solution and delivered it to the operation room just before surgery. In the LIA group, the study solution contained levobupivacaine (150 mg) mixed with ketorolac (30 mg) and adrenaline (0.5 mg). In the control (placebo) group, the study solution contained isotonic saline. The total volume of study solution was 100 mL in both groups. The allocation list was stored in the office of the research nurse until all patients had been included and all 1-year follow-up procedures had been completed. Only the research nurse who opened the envelope and prepared the study solution was aware of the type of infiltration, and all other personnel involved in the patient's care remained blind throughout the study.

Ethics

The study protocol was approved by the local ethics committee (R10108). The Finnish Medicines Agency (Fimea) approved the study protocol regarding the drugs to be used (EudraCT 2010-024315-14). The study was registered with ClinicalTrials.gov (NCT01305733). All patients gave their informed consent before inclusion in the study.

Preparation and pain management

Oral paracetamol (1 g) was given approximately 1 h before operation as premedication. Single-shot spinal anesthesia was induced at the L4-5 or L3-4 level using a 27-G spinal needle with a dose of 15 mg bupivacaine in 3 mL. A single 3.0-g bolus dose of cefuroxime was used as antibiotic prophylaxis, and tranexamic acid (1 g) was given at the end of surgery. In the post-anesthesia care unit, ice pack was used for all patients. All of them were treated with oral paracetamol (1 g) every 6 h and oral meloxicam (15 mg) every 24 h, starting 2 h after surgery. Patient-controlled analgesia (PCA) with

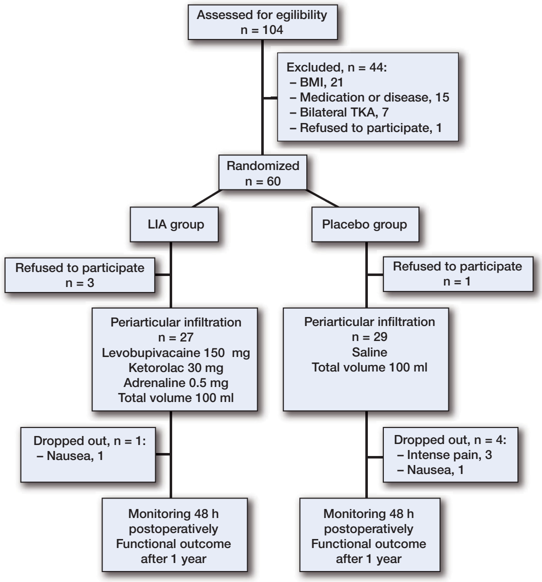

Figure 1. The study protocol.

oxycodone (dose: 2 mg; lock-out time: 8 min) was used in all patients to ensure adequate pain relief. No other analgesic drugs were used. If the pain management was insufficient, a lumbar epidural catheter was inserted and levobupivacaine infusion was initiated as rescue analgesic, causing the patient to drop out from the study. Nausea was treated with intravenous ondansetron (4 mg) when needed. As thromboprofylaxis, subcutaneous enoxaparin (40 mg) every 24 h was started 6–10 h after the end of surgery.

Surgery and infiltration technique

All patients were operated with standard knee replacement technique by 4 experienced orthopedic surgeons. Both groups received a periarticular infiltration intraoperatively. All infiltrations were done using 50-mL syringes and 7-cm long 20-G needles. The solution was infiltrated in 2 stages: the first after the bone surfaces were prepared but before the components were inserted, and the second after the components were inserted but before release of both tourniquets and wound closure. The first 50-mL infiltration was aimed from both sides through the posterior capsule and in the areas of resected menisci, and the second was aimed periosteally next to the resected bone surfaces and with parapatellar approach, but not in subcutaneous tissue. The tourniquet was released before closure and before hemostasis was ensured. Drainage and compression bandage were used in all patients.

Recovery

In the recovery room, all patients were mobilized by a phys-

Table 1. Patient demographic data. Data are mean (SD), number, or median (range)

	LIA n = 27	Placebo n = 29
Age, years	65 (4.9)	64 (6.7)
Sex, male/female	12/15	15/14
Body mass index	29 (3.9)	30 (3.7)
Preoperative KSS	43 (16–69)	49 (26–89)
Preoperative KSS function subscale	40 (15–90)	35 (15–90)

KSS: Knee Society score.

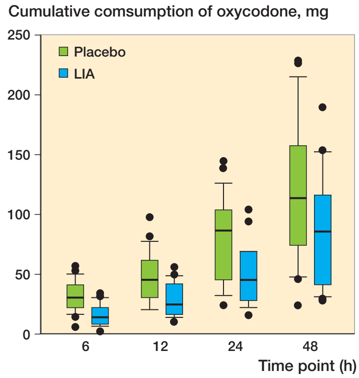

Figure 2. Median cumulative consumption of oxycodone over 48 h postoperatively. 6 h: p = < 0.001; 12 h: p = < 0.001; 24 h: p = 0.03; 48 h: p = 0.03. The Bonferroni-adjusted p-value for the 48-h time point was 0.1. The line in the middle of the box represents the median. The lower and the upper edges of the box are the 1st and 3rd quartile, respectively. If an observation is beyond 1.5 times interquartile range it is considered as an outlier and marked by a dot. Whiskers are the lowest and highest values that are not outliers.

iotherapist soon after recovery of motoric function. Patients were advised to use a PCA pump for oxycodone delivery and the consumption of oxycodone was calculated at 6, 12, 24, and 48 hours postoperatively. The visual analog scale (VAS) was used to quantify the pain intensity, with a target level under 3. VAS reading was recorded by a nurse or physiotherapist 3, 9, 18, and 48 h postoperatively. The range of motion (ROM) was measured by a physiotherapist 6, 12, and 24 h postoperatively.

Outcomes

The primary outcome was oxycodone consumption over 48 h postoperatively. The secondary endpoint was functional outcome 1 year after surgery. All patients were evaluated by a physiotherapist (who was blind regarding the study solution) at a routine follow-up visit 3 months postoperatively. Total knee function questionnaire (TKFQ), Oxford knee score (OKS), high-activity arthroplasty score (HAAS), and the 15D quality-of-life instrument were used preoperatively, at 3 months, and at 1 year after surgery for prospective outcome analysis.

Statistics

Calculation of sample size was based on an expectation of 40% difference in opiate consumption between the groups. The study was designed to have a power of 80% to detect a 40% difference between the 2 groups (type-I error probability: 0.05). Based on power calculation, 17 patients in each group would be needed. Demographics and results are shown as percentage, as mean value (SD), or as median (range). Differences between the groups were analyzed using the Mann-Whitney U-test. Bonferroni method was used to correct for multiple measures. IBM SPSS Statistics version 20.0 was used for statistical analysis.

Results

56 patients completed the study—27 patients in the LIA group and 29 patients in the placebo group. Baseline demographics showed similar values in both groups (Table 1). The cumulative consumption of oxycodone was smaller in the LIA group to that in the placebo group, at all measured time-points until 48 h (Figure 2). A trend of reduced consumption of oxycodone in the LIA group persisted up to 24 h postoperatively. The differences in means of cumulative consumption of oxycodone were 17 mg (95% CI: 11–22) at 6 h, 20 mg (CI: 11–30) at 12 h, 28 mg (CI: 11–45) at 24 h, and 35 mg (CI: 5–64) at 48 h.

In comparison of the different time intervals, the LIA group used statistically significantly less oxycodone than the placebo group during the first 6 h: mean 14 (2–34) mg as opposed to 30 (6–57) mg ($p < 0.001$) (Figure 3). The differences in means according to time intervals were 17 mg (CI: 11–22) at the 0–6 h interval, 4 mg (CI: –1 to 10) at the 6–12 h interval, 7 mg (CI: –2 to 16) at 12–24 h interval, and 5 mg (CI: –11 to 21) at the 24–48 h interval.

A median level of < 3 in VAS score was considered to be an adequate level of pain management, and this was achieved in both groups until 48 h postoperatively (Figure 4). The differences in means in VAS were 0.5 (CI: –0.3 to 1.4) at 3 h, 1.0 (CI: –0.2 to 2.1) at 9 h, 0.5 (CI: –0.6 to 1.5) at 18 h, and 0.4 (CI: –0.7 to 1.4) at 48 h.

The difference in mean ROM at 6 hours between the LIA group and the placebo group was –26 (CI: –39 to –12). At 24 h (mean difference –10, CI: –21 to 1) and at 48 h (mean difference –1.5, CI: –13 to 10), the mean differences were not statistically significantly different from that at 0 h.

Postoperatively, 3 patients in the placebo group discontinued the study because of intense pain and they were treated with epidural analgesia. On the other hand, in the LIA group none of the patients discontinued the study because of pain. 1 patient in each group discontinued because of nausea. There was no significant difference in overall blood loss between the LIA group and the placebo group (441 mL vs. 540 mL; p =

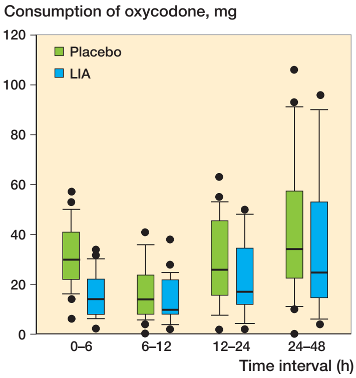

Figure 3. Consumption of oxycodone in different time intervals. Consumption is presented as median with 25th and 75th percentiles. 0–6 h: p < 0.001; 6–12 h: p = 0.09; 12–24 h: p = 0.1; 24–48 h: p = 0.4. For the 0–6 h interval, the Bonferroni adjusted p-value was < 0.001.

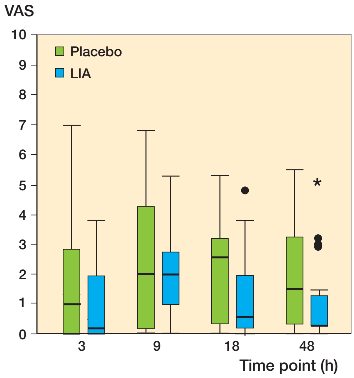

Figure 4. Postoperative pain at rest. VAS scores are presented as median with 25th and 75th percentiles. 3 h: p = 0.4; 9 h: p = 0.2; 18 h: p = 0.4; 48 h: p = 0.5.

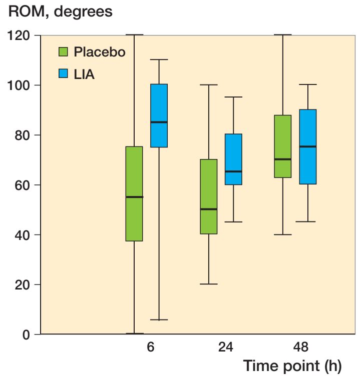

Figure 5. ROM at measured time point. ROMs are presented as median with 25th and 75th percentiles. 6 h: p = 0.001; 24 h: p = 0.08; 48 h: p = 0.6. The Bonferroni-adjusted p-value for the 6-h time point was 0.004.

Table 2. Functional and quality-of-life results with 1-year follow-up. Results are mean (SD) and mean difference with 95% CI

	LIA n = 27	Placebo n = 29	Mean difference	95% CI
15D				
preop.	0.88 (0.08)	0.87 (0.07)	–0.017	–0.056 to 0.023
3 months	0.92 (0.05)	0.92 (0.05)	0.001	–0.028 to 0.030
1 year	0.93 (0.07)	0.91 (0.07)	–0.018	–0.056 to 0.020
HAAS				
preop.	8 (3.1)	7 (2.7)	–0.45	–2.01 to 1.12
3 months	11 (2.4)	11 (2.8)	–0.05	–1.49 to 1.39
1 year	12 (2.4)	11 (3.5)	–1.11	–2.74 to 0.52
OKS				
preop.	23 (7.7)	22 (6.0)	–1.36	–5.10 to 2.37
3 months	37 (6.9)	36 (5.4)	–0.65	–4.09 to 2.79
1 year	44 (4.4)	41 (5.5)	–2.70	–5.48 to 0.07
Sitting for a long period of time				
preop.	2 (0.72)	2 (0.57)	–0.26	–0.61 to 0.10
3 months	2 (0.58)	2 (0.50)	–0.08	–0.23 to 0.38
1 year	1 (0.49)	1 (0.47)	–0.30	–0.56 to –0.04

0.3). No prosthetic joint infections were detected during the first postoperative year.

The functional outcomes between the groups differed in mean values, but the difference was not statistically significant as measured with HAAS and OKS or as measured with the 15D instrument for quality of life (Table 2). However, there was a statistically significant difference between the groups in 1 subscale of the TKFQ questionnaire: at 12 months postoperatively, it was easier for patients in the LIA group to sit for a long period of time (Table 2). There was also a trend of higher mean values in OKS for patients in the LIA group 12 months postoperatively (Table 2).

Discussion

A single intraoperative drug infiltration containing levobupivacaine, ketorolac, and adrenaline reduced the total consumption of oxycodone during the first 48 h postoperatively. The effect of LIA was most pronounced during the first 6 h after surgery. The efficacy of infiltration analgesia was highlighted by the fact that 3 patients in the placebo group discontinued the study because of intensive pain, while none of the patients in LIA group had to do the same. LIA also improved the early knee ROM, but no long-term functional benefit was seen.

In previous studies, the most used local anesthetic drugs have been ropivacaine and racemic bupivacaine. Levobupivacaine is the S-enantiomer of bupivacaine. Compared to ropivacaine, levobupivacaine has a longer duration of action (Burlacu and Buggy 2008). Compared to bupivacaine, levobupivacaine appears to have a wider margin of safety in terms of cardiovascular and central nervous system adverse effects when used in large doses (Morrison et al. 2000, Burlacu and Buggy. 2008). A previous study compared intra-articularly administered bupivacaine and levobupivacaine to placebo and both were found to be more effective than placebo (Bengisun et al. 2010). Levobupivacaine has a longer effect time than ropivacaine—which might in theory prolong postoperative analgesia. To maximize the theoretical analgesic effect, we chose the combination of levobupivacaine, ketorolac, and adrenaline. A comparison of 4 different mixtures of LIA (Kelley et al. 2013) showed that adding ketorolac to the solution results in better analgesia, and it called into question the significance of other drugs in extending the effect. In the present study, both levobupicaine and ketorolac were administered at maximum dose to ensure maximum effect. The concern with ketorolac—as with all non-steroidal anti-inflammatory drugs (NSAIDs)—has been the increased risk of bleeding problems postoperatively. However, in our study the total amount of blood loss was the same in both study groups.

We found that a single periarticular infiltration reduced total consumption of oxycodone for 48 h, although most of this effect was achieved during the first 6 h. Sufficient pain relief immediately after surgery aids in controlling the pain at a later stage also. In a recent review, the benefits of delayed administration were questioned and the authors suggested the use of single intraoperative administration of anesthetic cocktail (Gibbs et al. 2012). On the other hand, the use of an intra-articular catheter for additional drug administration may reduce total consumption of opiates up to 48 h postoperatively, compared to the situation where an additional bolus is not given. This is supported by a recent randomized study with 48 h of follow-up and an intra-articular catheter (Essving et al. 2010). The total median consumption of opiate in the drug infiltration group was 54 (4–114) mg, as compared to 86 (28–190) mg in our study. Whether or not the additional postoperative, intra-articular bolus is given, supplementary oral medications, e.g. NSAIDs, are needed as an adjunct to infiltration analgesia.

In a randomized study, use of a compression bandage was shown to improve pain control at rest at 8 h, and at 5, 6, and 8 h postoperatively with 90 degrees of knee flexion after TKA (Andersen et al. 2008a). We used a compression bandage in all patients (both groups) until the second postoperative day.

There have been few studies analyzing the long-term influence of infiltration analgesia on the functional outcome. The only previous study to evaluate this effect found no difference in functional outcome in the placebo and drug infiltration groups at 3 months postoperatively, as measured with TUG test, OKS, and EQ5D (Essving et al. 2010). We found minor differences in functional outcomes as measured with the 15D, HAAS, and OKS instruments, but the clinical relevance of these findings is questionable. The TKFQ scoring system has many subscales for different functional capabilities. The only statistically significant difference was observed at 12 months (sitting for a long period of time), but this was not evident earlier. The statistically significant difference in this TKFQ subscale between groups probably occurred by chance, without any relation to LIA. Murray et al. (2007) concluded that the minimal clinically important difference (MCID) in OKS can be expected to be between 3 and 5 points. In our data, the difference in mean values in OKS between groups at 1 year was 3 points, but the difference was not statistically significant.

We acknowledge that the study had some limitations. Patients were treated according to a routine postoperative rehabilitation protocol, and the length of hospital stay between groups was not measured. Effective postoperative pain relief might have allowed a shorter length of hospital stay. Plasma concentrations of infiltration drugs were not measured, but none of the patients had any side effects identified during the 1-year follow-up period.

In summary, this randomized double-blind study showed that a single perioperative infiltration of levobupivacaine, ketorolac, and adrenaline reduced opiate consumption until 48 h after TKA. The effect was most apparent during the first 6 h, but persisted to some extent up to 24 h. We recommend routine use of perioperative infiltration analgesia as an adjunct to oral pain medication in patients undergoing TKA. However, use of LIA infiltration did not have any effect on the functional outcome of TKA during the first postoperative year.

Design of the protocol: MN, JK, and AE. Enrollment of the patients and surgery: MN, TM, and AE. Anesthetic procedures: JK and AA. Data collection: MN. Data analysis: MN, AE, JK, and AA. All the authors contributed to writing of the manuscript.

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No competing interests declared.

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