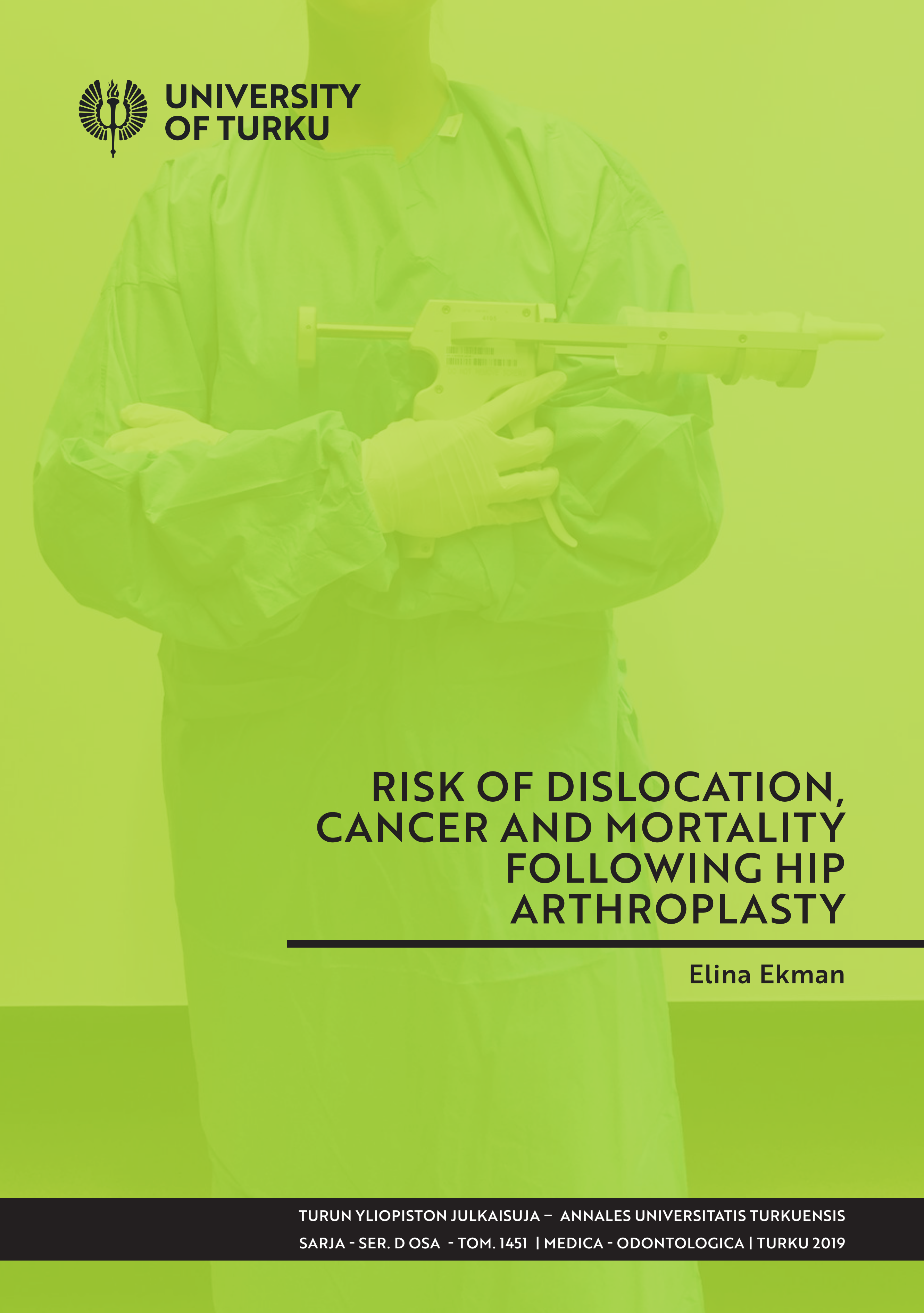

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To my family

“Kaikella on hintansa, mut mikään ei oo vielä mahdotonta”
- Don Huonot, Hyvää yötä ja huomenta,1997

UNIVERSITY OF TURKU
Faculty of Medicine
Department of Orthopaedics and Traumatology
ELINA EKMAN: Risk of dislocation, cancer and mortality following hip arthroplasty
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ABSTRACT

Since the introduction of the first modern hip implants in the 1960s, total hip arthroplasty (THA) and hemiarthroplasty (HA) have continued to evolve towards minimizing implant-related complications. Developments in surgical techniques and anaesthesiological methods have also made the procedure safer for patients.

Cementing is the gold standard for implant fixation, especially in elderly patients in both elective surgery for osteoarthritis (OA) and facture surgery due to femoral neck fracture. Lower revision rates for cemented implants in elderly patients has been found in all major registries compared to uncemented implants. In addition, national guidelines in several countries recommend cemented HA in femoral neck fracture. However, earlier in the development of THA it was thought that cemented hip arthroplasty is associated with higher peri- and post-operative mortality compared to uncemented hip arthroplasty due to bone cement implanting syndrome (BCIS), especially in fracture surgery.

In THA, dislocation is the second most common reason for revision surgery in Finland. Both patient-related and surgical factors may predispose to THA dislocation. Large-diameter head (LDH) metal-on-metal (MoM) THA and hip resurfacing arthroplasty (HRA) were developed to address this problem. However, these devices have their own unique problems, and increased risk of cancer has been suggested to be related to the metal particles resulting from corrosion and wear of MoM hip implants.

The main aims of this doctoral thesis were 1) to determine the mortality associated with the use of bone cement in THA and HA, especially during and immediately after surgery; 2) to investigate the risk of cancer in patients with MoM hip devices; and 3) to examine the predisposing factors for revision for dislocation after primary THA. This thesis is based on observational registry studies gathering information from the Finnish Arthroplasty Register (FAR), Finnish Cancer Register, the PERFECT database of the National Institute for Health and Welfare in Finland and the electronic patient record system at Turku University Hospital.

In this study, we found no statistically significant difference in early postoperative mortality when using bone cement in THA or HA. With MoM hip implants no increase in the overall risk of cancer was detected during midterm follow-up. However, the risk of basalioma was higher in the MoM cohort than in the general Finnish population and in patients with other bearing surfaces. Posterior approach, fracture diagnosis and American Society of Anesthesiologists (ASA) class III–IV were found to be associated with increased risk of revision due to dislocation after total hip arthroplasty.

KEYWORDS: Metal-on-metal, cancer, bone cement implantation syndrome, mortality, total hip arthroplasty, hemiarthroplasty, dislocation

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
Ortopedia ja traumatologia
ELINA EKMAN: Lonkan tekoniveliin liittyvä sijoiltaanmenon, syövän ja kuolleisuuden riski
Turun kliininen tohtoriohjelma
Marraskuu 2019

TIIVISTELMÄ

Ensimmäisen modernin lonkan kokotekonivelleikkauksen jälkeen 1960-luvulla, lonkan koko- ja osatekonivelet ovat olleet jatkuvan kehitystyön kohteina, jotta tekoniveliin liittyvien haittojen riskit saataisiin mahdollisimman vähäisiksi. Lisäksi leikkaustekniikkaan ja anestesiaan liittyvät muutokset ovat tehneet tekonivelleikkauksista potilaalle aiempaa turvallisempia.

Tekonivelen sementtikiinnitys on vakiintunut käytäntö erityisesti iäkkäillä potilailla sekä elektiivisissä nivelrikon vuoksi tehtävissä leikkauksissa että reisiluun kaulan murtuman vuoksi tehtävissä leikkauksissa. Verrattuna sementittömiin tekoniveliin sementtikiinnitteisiin tekoniveliin on havaittu liittyvän vähemmän uusintaleikkauksia iäkkäillä ihmisillä useissa tekonivelrekistereissä kansainvälisesti. Lisäksi kansalliset hoitosuositukset useissa maissa suosittelevat sementtikiinnitteisen osatekonivelen käyttöä reisiluun kaulan murtuma potilailla. Kuitenkin, tekonivelien kehityksen alkutaipaleella epäiltiin sementtikiinnitteisiin lonkan tekoniveliin liittyvän suurentunutta leikkauksen aikaista ja leikkauksen jälkeistä kuolleisuutta luusementti -oireyhtymästä johtuen, verrattuna sementittömiin tekoniveliin, erityisesti reisiluun kaulan murtumaleikkauksiin liittyen.

Tekonivelen sijoiltaanmeno on yleisimpiä uusintaleikkauksen syitä lonkan kokotekonivelleikkauksen jälkeen. Sijoiltaanmenolle altistavat sekä potilaaseen liittyvät että leikkaukseen liittyvät tekijät. Suurinuppiset metalli-metalli -liukupintaiset kokotekonivelet ja pinnoitetekonivelet kehitettiin ratkaisuksi muun muassa tähän ongelmaan. Kuitenkin myös näihin tekonivelmalleihin liittyy niille ominaisia ongelmia. Metalli-metalli –liukupinnasta kulumisen seurauksena irtoavan metallihierteen on epäilty lisäävän näiden potilaiden syöpäriskiä.

Tässä väitöskirjatutkimuksessa selvitettiin liittyykö luusementin käyttöön lonkan tekonivelleikkauksessa lisääntynyttä kuolleisuutta verrattuna sementittömiin tekoniveliin, erityisesti leikkauksen aikana ja ensimmäisinä päivinä leikkauksen jälkeen. Lisäksi selvitimme metalli-metalli -liukupintaisiin lonkan tekoniveliin ja pinnoitetekoniveliin mahdollisesti liittyvää syöpäriskiä keskipitkällä aikavälillä sekä riskitekijöitä lonkan kokotekonivelleikkauksen jälkeiselle uusintaleikkaukselle tekonivelen sijoiltaanmenosta johtuen. Tämä väitöskirja perustuu Suomen Endoproteesirekisterin, Suomen Syöpärekisterin, Terveyden ja hyvinvoinnin laitoksen PERFECT tietokannan sekä TYKS:in sähköisen potilastietokannan tietojen pohjalta tehtyihin rekisteritutkimuksiin.

Tutkimuksessa ei havaittu tilastollisesti merkitsevää eroa varhaisvaiheen kuolleisuudessa sementtikiinnitteisten ja sementittömien lonkkaproteesien välillä, olivatpa nämä osa- tai kokotekoniveliä. Metalli-metalli -liukupintaisiin lonkan tekoniveliin ei liittynyt lisääntynyttä syövän kokonaisriskiä keskipitkällä aikavälillä. Kuitenkin tyvisolusyövän riski oli metalli-metalli -ryhmässä suurempi kuin keskimääräisessä suomalaisessa väestössä tai potilailla, joille oli asetettu muista liukupareista koostuva tekonivel. Lonkan taka-avauksen, murtumadiagnoosin ja ASA luokkien III–IV havaittiin altistavan uusintaleikkaukselle tekonivelen sijoiltaanmenon vuoksi.

AVAINSANAT: metalli-metalli -liukupinta, syöpä, luusementti -oireyhtymä, kuolleisuus, lonkan tekonivelleikkaus, lonkan osatekonivelleikkaus, sijoiltaanmeno

Table of Contents

Abbreviations

ALTR	Adverse local tissue reaction
AOANJRR	Australian Orthopaedic Association National Joint Replacement Registry
ARMD	Adverse reaction to metal debris
ASA	American Society of Anesthesiologists
BCIS	Bone cement implantation syndrome
BMI	Body mass index
CI	Confidence interval
CoC	Ceramic on ceramic
CoCr	Cobalt-chromium
CoP	Ceramic on polyethylene
FAR	Finnish Arthroplasty Register
FHDR	Finnish Hospital Discharge Register
HA	Hemiarthroplasty
HR	Hazard ratio
HRA	Hip resurfacing arthroplasty
ICD	International Classification of Diseases
LDH MoM THA	Large-diameter metal-on-metal total hip arthroplasty
LIA	Local infiltrative anaesthesia
LMWH	Low molecular weight heparin
MoM	Metal on metal
MoP	Metal on polyethylene
NAR	Norwegian Arthroplasty Register
NJR	National Joint Registry for England, Wales, Northern Ireland and the Isle of Man
OA	Osteoarthritis
OR	Odds ratio
PERFECT	PERFormance, Efficiency, and Costs of Treatment Episodes
PMMA	Polymethyl methacrylate
RR	Risk ratio
SHAR	Swedish Hip Arthroplasty Register

SIR	Standardized incidence ratio
THA	Total hip arthroplasty
UHXLPE	Ultra-highly cross-linked polyethylene

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Ekman E, Laaksonen I, Eskelinen A, Pulkkinen P, Pukkala E, Mäkelä K. Midterm risk of cancer with metal-on-metal hip replacements: a concise report of the Finnish population Acta Orthop 2018;89(5):575-579.

II Ekman E, Palomäki A, Laaksonen I, Peltola M, Häkkinen U, Mäkelä K. Early postoperative mortality similar between cemented and uncemented hip arthroplasty: a register study based on Finnish national data. Acta Orthop 2019;90(1):6-10.

III Ekman E, Inari Laaksonen, Kari Isotalo, Antti Liukas, Tero Vahlberg, Keijo Mäkelä. Cementing does not increase the immediate post-operative risk of death after total hip arthroplasty or hemiarthroplasty. Acta Orthop 2019;90(3):270-274.

IV Panula V, Ekman E, Venäläinen M, Laaksonen I, Klén R, Haapakoski J, Eskelinen A, Elo L. Mäkelä K. Posterior approach, fracture diagnosis and ASA class III-IV are associated with increased risk of revision for dislocation after total hip arthroplasty: An analysis of 33,661 operations from the Finnish Arthroplasty Register. Scandinavian Journal of Surgery 2019. In press.

1 Introduction

Total hip arthroplasty is the treatment of choice in cases of severe hip destruction, offering patients pain relief, improved hip function and good quality of life (Learmonth et al. 2007). In Finland, 9,631 elective primary THAs and 1,537 revision THAs were carried out in 2018 (FAR 2019). The first modern THA was introduced by Sir John Charnley in the early 1960s as a cemented THA with metal-on-polyethylene (MoP) bearing surfaces (Charnley 1960b). Bearing surfaces and fixation methods have been evolving ever since. New innovations led to the development of second generation metal-on-metal (MoM) THA and hip resurfacing arthroplasty (HRA) in the 1990s and 2000s (McMinn et al. 1996). For implant fixation, cemented, uncemented, hybrid (cemented femoral stem only) and reverse-hybrid (cemented acetabular cup only) methods are currently available. In Finland, uncemented components are used more frequently than cemented, hybrid or reverse-hybrid components, although the proportion of hybrid THA is increasing (FAR 2019).

THA is considered a relatively safe procedure (Illingworth et al. 2015). The early postoperative mortality is low and has continued to drop in recent years (Aynardi et al. 2009, McMinn et al. 2012, Lalmohamed et al. 2014). Other less severe complications include infection, dislocation, periprosthetic fracture and aseptic loosening. These complications often lead to revision surgery and can be devastating to the patient. Based on the combined Nordic database, around 10% of implanted hip prostheses will require revision surgery within 10 years (Mäkelä et al. 2014a).

The development of MoM THA and HRA has allowed for the use of large diameter heads (LDH), leading to low rates of dislocation (Jameson et al. 2011). However, in the early 2010s multiple studies showed high revision rates and pseudotumor formation due to metal debris emanating from corrosion and wear of MoM hip implants (Pandit et al. 2008, Smith et al. 2012a). Metal debris has also been associated with chromosomal aberrations and DNA damage (Bonassi et al. 2000, Sarhadi et al. 2015).

The aim of this thesis was to examine the possible correlation of MoM hip implants with risk of cancer based on the Finnish Arthroplasty Register (FAR) and Finnish Cancer Registry. Another objective was to investigate whether the use of bone cement is associated with higher immediate mortality in patients treated with THA or HA, based on information in the PERFECT database of the National Institute for Health and Welfare and the electronic patient record system of Turku University Hospital. The third objective was to determine risk factors for revision surgery due to dislocation after primary THA based on the revised data contents of FAR.

2 Review of the Literature

2.1 Hip joint arthroplasty

Total hip arthroplasty is the treatment of choice for severe hip destruction, whereby diseased articular surfaces are replaced with synthetic materials. The earliest known attempts at hip arthroplasty took place in Germany in 1891 with the use of ivory to replace the femoral heads of patients whose hip joints had been destroyed by tuberculosis (Gluck 1891). In the late 19th and early 20th centuries, interpositional arthroplasty and mould arthroplasty of glass were experimented with (Learmonth et al. 2007, Knight et al. 2011), but the era of total hip arthroplasties is considered to have been initiated by Smith-Petersen and Wiles in 1938 with the first THA (Smith-Petersen 1948, Wiles 1958). Smith-Petersen used a vitallium mould instead of glass (Smith-Petersen 1948).

The first modern cemented low-friction THA with MoP bearing surfaces was introduced by orthopaedic surgeon Sir John Charnley in the early 1960s (Charnley 1960b). Charnley also popularized the use of polymethyl methacrylate (PMMA) bone cement for THA fixation, although he was not the first surgeon to use bone cement in THA fixation (Charnley 1960a). Over the years the chemical composition of bone cement has essentially stayed the same, but the cementing technique has changed significantly. In the early days the cement was not pressurized and was introduced antegrade, resulting in poor bone penetration, inadequate cement mantles, and lamination of the cement. Further research gradually led from the first-generation cementing technique to the current-day technique, which includes cleaning of the endosteal bone with pulsed lavage, retrograde insertion, and sustained pressurization to optimize micro-interlock. This modern cementing technique creates a uniform cement mantle with intrusion into the bone, leading to enhanced shear strength at the bone-cement interface (Learmonth et al. 2007). Good implant survival rates with the use of modern cementing techniques in long-term follow-up have been reported in all major registries (SHAR 2018, NJR 2018, AOANJRR 2018, FAR 2018). Cemented THA with MoP bearing is considered the gold standard to which new designs and techniques are compared to.

With the first-generation cementing technique, early failure was common. This was due to a local inflammatory response initiated by cement particles and leading to osteolysis, but also due to poor implant design (Yamada et al. 2009). Charnley's cemented low-friction THA had good 25-year outcomes, but other stem designs had poor results due to loosening of the implant (Sutherland et al. 1982, Callaghan et al. 2000). At the time, the cement itself was considered to be the cause of implant loosening and the soft tissue reaction associated with it; hence the condition was named "cement disease". The problems with the first-generation cementing technique led to the development of cementless THA. Early cementless hip implants had smooth surfaces and therefore did not adhere to bone, leading to loosening and poor results. In the 1980s, porous cobalt-chromium and titanium implants were developed allowing bone ingrowth and stable, biological fixation of the implant with good survival rates (Yamada et al. 2009).

2.1.1 Total hip arthroplasty

Currently, THA is used for primary and secondary osteoarthritis (OA) of the hip joint, but also to treat patients with femoral neck fractures. There is still an ongoing debate over the indication to use THA on fracture patients. Primary OA is a disease that leads to cartilage breakdown. Factors like mechanical stress on the joint, genetics and aging contribute to the development of the disease (Hunter and Bierma-Zeinstra 2019). Several factors can cause secondary OA, including posttraumatic conditions, inflammatory arthritis developmental issues and osteonecrosis of the femoral head (FAR 2018). The diagnosis of OA is based on symptoms, radiological findings and hip function. The first line treatment is conservative, including exercise, weight loss and pharmacological management (Polvi- ja lonkkanivelrikko: Käypä hoito -suositus 2018). When these methods fail, THA can be recommended. However, weighing complication risks against the potential benefits of the surgery in patient selection is essential.

Currently, four different bearing surfaces are in use worldwide: metal-on-cross-linked polyethylene MoP, ceramic-on-cross-linked polyethylene (CoP), ceramic-on-ceramic (CoC) and metal-on-metal (MoM). The superiority of any bearing surface is yet to be proven. For THA fixation also four different methods are being used: fully cemented THA where both the stem and the cup are cemented (Figure 1), fully cementless THA for both components (Figure 2), hybrid THA where the stem is cemented and the cup is cementless (Figure 3), and reverse hybrid THA with cementless stem and cemented cup.

According to registry data, cementless THA has good results in younger patients with good bone quality, whereas in the older population cemented THA can offer better implant survival than uncemented THA (Mäkelä et al. 2014a, AOANJRR 2018). In general, over 90% of THAs are working well, pain-free, and without complication 10–15 years postoperatively (Beswick et al. 2012).

Figure 1. Cemented total hip arthroplasty

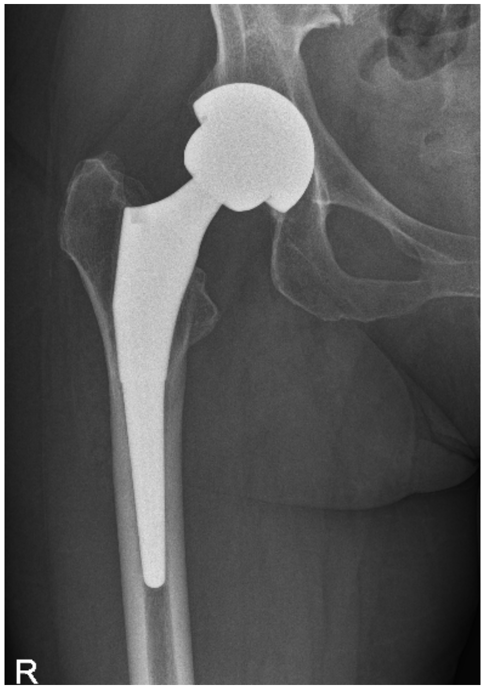

Figure 2. Cementless total hip arthroplasty

Figure 3. Hybrid total hip arthroplasty

2.1.1.1 Appraaches to the hip joint

In the beginning of the era of modern THA in 1960s sir Charnley used a transtrochanteric approach. This approach includes osteotomy of the greater trochanter with a saw to visualize the hip joint. Repair of the osteotomy was done by a variety of techniques including wire knots and the Dall-Miles cable grip system. The major disadvantages to this approach was trochanteric nonunion, which has been reported to range from 5% to 28%. Other complications include trochanteric migration, which if greater than 3 cm has been shown to correlate with poor abductor power (Charnley J 1979, Frankel et al. 1993, Emerson et al. 2001).

Currently the most commonly used surgical approaches to the hip joint are: anterolateral (modified Hardinge) approach, posterior approach and anterior (Smith-Peterson) approach (Meermans et al. 2017). Each approach has its own unique complication profile and the superiority of a certain approach is yet to be proven.

The posterior approach was popularized by Moore in the 1950s (Moore 1957). In this approach the patient is placed in the lateral decubitus position, the skin incision is made over the trochanter major and continued distally along the femoral shaft. The tensor fascia latae is exposed and incised along with the gluteus maximus proximally. The gemeli and obturator externus tendons are identified and their femoral insertion is released. The piriformis can be preserved or cut. An L-shaped capsulotomy is performed. After insertion of THA, the femoral attachment of the short external rotators and hip capsule should be repaired to reduce the risk of postoperative dislocation. Registry studies have found a higher risk of revision due to dislocation with the posterior approach (1.1%) than with the anterior and anterolateral approaches (0.6%) (Zijlstra et al. 2017b).

The anterolateral (modified Hardinge) approach was described by Hardinge in 1982 (Hardinge 1982). In this approach the patient is placed in the lateral decubitus position, the skin incition is made over the trochanter major and continued distally along the femoral shaft. The tensor fascia latae is exposed and incised along with the gluteus maximus proximally. The anterior one-third of the gluteus medius, the underlying gluteus minimus, and the anterior portion of the vastus lateralis are sharply separated from the greater trochanter. The dissection should not extend more than 5 cm proximal to the greater trochanter to avoid injury of the superior gluteal nerve. The capsule is exposed and a T-shaped capsulotomy is performed. After insertion of THA, the incised muscles are re-attached to the trochanter major. There is a risk of nerve damage and gait problems after the anterolateral approach, and patients report more postoperative pain than with other approaches to the hip joint. Incidence as high as 17% has been reported for nerve damage (Ramesh et al. 1996, Peters et al. 2018).

The anterior (Smith-Petersen) approach was first described by Smith-Petersen in the 1940s, and was later modified by Heuter in the 1950s (Light and Keggi 1980).

In this approach the patient is positioned supine, the skin incision begins 2–4 cm lateral to the anterior superior iliac spine of the pelvis. The incision is then curved distally and laterally to finish below the level of the lesser trochanter. The lateral femoral cutaneous nerve is identified and protected. A plane is developed between the tensor fascia latae and sartorius. The surgeon will then encounter the interval between the rectus femoris and gluteus medius. The rectus femoris is displaced medially and the gluteus medius laterally to expose the joint capsule. The capsule is incised transversely. After insertion of THA, implant positioning is verified with fluoroscopy. The anterior approach has a steep learning curve associated with a risk of nerve damage and calcar and greater trochanter fracture. The reported incidence for nerve damage varies greatly from 1% to 67% (Post et al. 2014). For trochanteric fractures incidence of 2.3% has been suggested (Jewett and Collis 2011).

2.1.1.2 Metal-on-metal hip arthroplasties

Identifying polyethylene wear and debris formation as the cause of implant loosening led to the development of other bearing surfaces. CoC, MoM and cross-linked ultrahigh-molecular-weight polyethylene bearings were introduced (Learmonth et al. 2007). The first generation MoM THAs were widely used in the 1960s but were abandoned during the 1980s due to high loosening rates but also due to high infection rates and concerns about carcinogenesis and metal sensitivity (Amstutz and Grigoris 1996).

Large diameter head (LDH) MoM HRA is a procedure in which the femoral head is only partially resected. This femoral bone-preserving nature of the procedure was favoured for young and active patients. LDH MoM HRA was developed and popularized in the 1990s by McMinn. He chose to use cobalt-chromium (CoCr) in his HRA procedures due to the reported good track record of this material in clinical use (McMinn et al. 1996). HRA was proposed to have increased stability due to the large diameter of the articulating surface, less wear of the bearing surfaces, and better function than conventional THAs. The short-term results were encouraging (Treacy et al. 2005). Also MoM THA was re-introduced with large diameter heads (Figure 4). Due to the above potential benefits of LDH hip arthroplasties and problems with polyethylene wear in long-term follow-up, LDH MoM TRA and HRA quickly became popular and were widely used at the beginning of the 21st century (NJR 2016, AOANJRR 2017, FAR 2018). In the United States of Amerika from 2005 to 2006 35% of THAs were MoM THAs (Bozic et al. 2009). In Finland, at its peak MoM bearings were as widely used (FAR 2018).

In the late 2000s and early 2010s, evidence of problems with LDH MoM hip devices began to accumulate via national joint registries (AOANJR 2007, NJR 2009). Generation of metal particles from corrosion and wear of MoM hip implants was observed (Clarke et al. 2003). Reactions around the periarticular area were reported, including gluteal muscle necrosis, soft tissue masses and fluid collections (Ollivere et al. 2009). These findings are called adverse local tissue reaction (ALTR) or adverse reaction to metal debris (ARMD). Metal particles and ions can also disseminate throughout the body, and these particles have been found in patients' blood and several organs including lymphatic tissue, bone marrow, liver and spleen (Case et al. 1994, Shea et al. 1997, Urban et al. 2000, Shimmin and Back 2005). Metal debris from hip implants have been associated with chromosomal aberrations and DNA damage (Case et al. 1996, Bonassi et al. 2000, Daley et al. 2004, Polyzois et al. 2012, Sarhadi et al. 2015). MoM implant patients can also be at increased risk of malignant tumours and haematopoietic cancer (Wagner et al. 2012, Mäkelä et al. 2014c). Even systemic toxicity due to high levels of cobalt in the circulation has been reported (Bradberry et al. 2014). Factors affecting the amount of wear debris include component size and positioning, diameter clearance, which allows fluid to lubricate between bearing surfaces, and the roughness of the surfaces (Mont et al. 2007).

Local effects of metal debris, such as pseudotumours and muscle necrosis around the hip implant, can cause failure of the implant (Langton et al. 2010). According to the National Joint Registry for England, Wales and Northern Ireland, the 10-year revision rate for MoM HRA is 12.6% and for LDH MoM THA 19.8% (Hunt et al. 2018). In Finland the use of LDH MoM hip implants was discontinued in 2012 (SAY 2012).

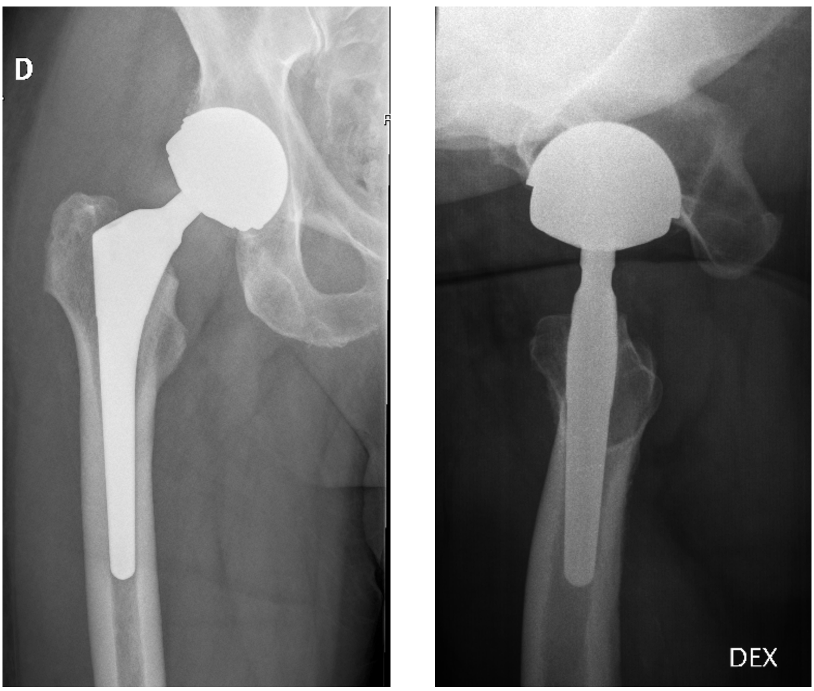

Figure 4. Metal-on-metal total hip arthroplasty

2.1.2 Hemiarthroplasty

In hemiarthroplasty (HA), only the proximal femur is replaced with a prosthesis and the acetabulum is left intact (Figure 5). The very first hip arthroplasty by Glûck in 1891 was a monoblock hemiarthroplasty made of ivory (Gluck 1891). A surgeon from Myanmar adopted the use of ivory HA and continued using it in Myanmar until 1995 (Szostakowski et al. 2017). As the name suggests, a monoblock prosthesis is manufactured as one piece. The size of the patient's native femoral head determines the size of the monoblock HA, thus there is minimal control over leg length or offset. The design gradually developed from monoblock to the modern modular HA design to better account for every patient's unique anatomy. A modular prosthesis is manufactured using a separate stem and head. This allows the surgeon to combine stems with different neck offsets and angles for different head sizes. Modularity allows conversion to THA without stem removal. The modular stem design is also hypothesized to reduce the risk of prosthetic dislocation (Sims et al. 2017). These properties offer potential benefits compared to monoblock HA. With superior results of modern modular HA over monoblock designs also reported elsewhere (Rogmark et al. 2012, Dawe et al. 2014), the use of monoblock HA has decreased rapidly in recent decades (AOANJRR 2018).

The head of a HA can be unipolar or bipolar. The bipolar design was introduced in the 1960s and was meant to reduce the acetabular wear experienced with unipolar HA (Verberne 1983, Phillips 1987). The bipolar head consists of a metal ball head articulating with a head piece of polyethylene covered by a polished metal shell. However, the bipolar design has its own unique problems including polyethylene wear, osteolysis and aseptic loosening of the femoral stem (Coleman et al. 2011). So far, randomized controlled trials have shown equal results with unipolar and bipolar HAs (Davison et al. 2001, Raia et al. 2003, Kanto et al. 2014).

Both cemented and uncemented HAs are available; currently in Finland, the former is used more often. There is evidence that cementing the stem in place reduces postoperative pain and leads to better mobility (Parker et al. 2010), and there is some evidence that cementing lowers the risk for re-operations compared to uncemented hemiarthroplasty in hip fracture patients (Gjertsen et al. 2012, Yli-Kyyny et al. 2014).

Figure 5. Cemented hemiarthroplasty

2.1.3 Arthroplasty registries

National arthroplasty registries were established to assess hip and knee arthroplasty devices, and detect outlier products as early as possible. The most important arthroplasty registries are: the Swedish Hip Arthroplasty Register, the Finnish Arthroplasty Register, the Norwegian Arthroplasty Register, the National Joint Registry for England, Wales, Northern Ireland and the Isle of Man, and the Australian Orthopaedic Association National Joint Replacement Registry.

The Swedish Hip Arthroplasty Register (SHAR) was established in 1979 being the oldest nationwide hip arthroplasty register in the world. Since 1999 SHAR has reported implant survival and hospital level data openly in the annual reports (SHAR). FAR was founded in 1980 by the Finnish Society of Orthopaedic Surgeons and it is the second oldest arthroplasty register in the world. In November 2009 FAR became a part of National Institute for Health and Welfare. All-electrical national Finnish Arthroplasty Register started on May 19th 2014 and a major revision of the data contents of FAR was also carried out in 2014 to include parameters such as surgical approach, BMI, ASA class, intra-operative bleeding and duration of the operation. In Finland open access yearly reports and implantwise survival estimates are available in the internet (FAR). The Norwegian Arthroplasty Register (NAR) was established in 1987. NAR publishes annual reports with demographic data about operating volumes, use of different types of prostheses and cements, and other characteristics of the procedure. Implant survival data is published mainly by peer-reviewed papers (NAR). Australian Orthopaedic Association Nation Joint Replacement Registry (AOANJRR) was established in 1998. Currently more than 85,000 hip and knee arthroplasties are undertaken each year in Australia and the strength of AOANJRR is the large number of registered patients. It gives detailed information on implant usage and performance nationwide (AOANJRR). The National Joint Registry (NJR) for England, Wales, Northern Ireland and the Isle of Man was established in 2002 and it was set up by the Department of Health and Welsh Government. Northern Ireland joined in 2013, and the Isle of Man in July 2015. NJR is the largest arthroplasty register in the world with more than 2 million procedures. Over 200,000 procedures are added yearly. NJR reports implant, hospital and surgeon performance yearly (NJR).

All arthroplasty registries mentioned above report high data completeness in primary THA: SHAR 98%, FAR 95%, NAR 97%, AOANJRR 99% and NJR 95%. For revision THA data completeness is somewhat lower: SHAR 93%, FAR 81%, NAR 93%, and NJR 90% (FAR 2018, NAR 2018, NJR 2018, SHAR 2018). The advantage of registries is the possibility of detecting outlier products and guiding clinical practice. For example, according to SHAR, cemented THA has yielded high implant survival rates and therefore the use of cemented fixation in the elderly patients is very common in Sweden (Hailer et al. 2010). Also, problems associated with metal-on-metal issue became evident based on the AOANJRR and NJR Annual Reports and led to a worldwide recall of LDH MoM hip devices (AOANJRR 2007, NJR 2009). Collaboration between national arthroplasty registries, such as the Nordic Arthroplasty Register Association established in 2007 allows the use of registry data form Denmark, Finland, Norway and Sweden. This allows access to a larger number of patients with relatively rare conditions such as patients who have been revised due to infection or periprosthetic fracture. In the future patient-reported outcome measures may also guide clinical practice as registries such as SHAR and NAR have added this information into their data contents.

The disadvantage of registries is that registries are only as accurate as is their data content. Revision surgeries are not as well documented as primary surgeries. For example, some concerns about the reliability of NJR data has risen, suggesting that NJR reports may underestimate rates of revision (Sabah et al. 2015).

2.2 Hip arthroplasty and peri- and postoperative mortality

Historically, cemented THA has been associated with somewhat high postoperative mortality. The 30-day mortality has been reported to be 1.5 – 2% (Ivins et al. 1967, Johnston and Larson 1969). In the 1960s and 70s, the procedure lasted longer and resulted in higher intraoperative blood loss than today; general anaesthesia was used, patients were bedridden for several days post-operatively, and anticoagulation therapy was started days after the operation with sodium warfarin (Coventry et al. 1974). Improvements in surgical and anaesthesiological techniques, improvements in surgical implants, the introduction of low molecular weight heparins (LMWHs) in the 1980s, and operative room sterility have significantly reduced mortality risks (Nurmohamed et al. 1992, Harris 2009). The decrease in post-operative mortality after elective THA seems to continue in the 21st century; in the United Kingdom, from 2003 to 2011 the 90-day mortality dropped from 0.6% to 0.3% (Hunt et al. 2013). In-hospital mortality decreased from 0.5% to 0.2% between 1991 and 2008 (Cram et al. 2011). On the other hand, the surgery is now being performed on older patients who often have multiple comorbidities. It has been shown that adverse outcomes increase with a higher number of comorbid conditions (Mahomed et al. 2003, Bozic et al. 2012). However, a reduction in the 30-day post-operative mortality has been reported between 1991 and 2008, despite a mean increase of one year in age and a mean increase from one to two in the number of comorbid medical conditions (Cram et al. 2011).

Three recent publications have indicated that the overall 90-day mortality after primary THA performed for any indication is 0.7% (Cram et al. 2011, Singh et al. 2011, Garland et al. 2015). The 30-day mortality after HA has been reported to be 7 – 9% (Costain et al. 2011, Olsen et al. 2014). The higher mortality in the HA patients when compared to the THA patients can be explained by HA patients being older and having more comorbidities than THA patients (Olsen et al. 2014).

2.2.1 Bone cement implantation syndrome

The use of PMMA in orthopaedics was adopted from dentistry. Its use as a grout to improve hip implant fixation was pioneered in 1953 by Haboush (Haboush 1953). In the first-generation cementing technique, the bone cement was introduced into the femoral canal by hand and thereafter the femoral implant was placed in the femur with no additional procedures (Learmonth et al. 2007). The second-generation cementing technique involved adding an intramedullary plug in the femoral canal to keep the cement in place, cleaning the endosteal bone with pulsed lavage, and retrograde insertion of the cement (Mulroy et al. 1995). In the third-generation technique, the cement was mixed in a vacuum and pressurized when inserting into the femoral canal (Rasquinha et al. 2003). The current fourth-generation technique involves adding proximal and distal centralizing devices in the femoral stem to ensure that the prosthesis is implanted in a neutral position and that a cement mantle of optimal thickness is achieved both proximally and distally (Fottner et al. 2010).

The disadvantage of using bone cement is the possibility of bone cement implantation syndrome (BCIS), characterized by perioperative hypotension and hypoxia, and at worst resuscitation or even death of the patient. The supposed mechanism of BCIS is that cementation and prosthesis insertion cause high intramedullary pressures, leading to embolization of fat, bone marrow and cement debris in the circulation (Orsini et al. 1987). It has been demonstrated using transoesophageal echocardiography that embolization happens both with cemented and uncemented THA, but the embolic load is bigger with cemented THA (Ereth et al. 1992). Post-mortem examinations have demonstrated embolization in the lungs after cemented THA (Parvizi et al. 1999). However, it seems that although embolic events are relatively common, they are not always associated with haemodynamic changes and the amount of embolization correlates poorly with the degree of hypotension and hypoxaemia (Lafont et al. 1997).

The risk of BCIS has been associated with cementing the femoral stem component based on observations of thromboembolic events and increased early mortality in patients treated with a classical hybrid compared to patients treated with a reverse hybrid THA (Garland et al. 2017). BCIS risk factors include patient-related factors such as increasing age, male sex, use of diuretic medication, pre-existing pulmonary hypertension, significant cardiac disease, osteoporosis, poor ASA class, and surgical factors such as pathologic fracture, intertrochanteric fracture, and long-stem prosthesis (Parvizi et al. 1999, Donaldson et al. 2009, Griffiths et al. 2015).

The most obvious manifestation of BCIS is intraoperative death of the patient. The true incidence of cardiac arrest due to BCIS is unknown, and mortality data are not systematically collected or published (Donaldson et al. 2009). Only three large case reviews of intraoperative mortality during cemented THA exist, and the data from these studies suggest an incidence of 0.11%. However, the studies were published the 1970s and 1990s (Coventry et al. 1974, Ereth et al. 1992, Parvizi et al. 1999). Improvements in surgical and anaesthesiological techniques and implants, the use of low molecular weight heparins (LMWHs) in the 1980s, and operating room sterility have significantly reduced overall mortality risks associated with hip arthroplasty (Parvizi et al. 1999). By the end of the 1990s a greater than three-fold reduction in intraoperative mortality rate had been reported and the mortality has fallen even more during the 21st century (Parvizi et al. 1999, Hunt et al. 2013). A retrospective study of patients undergoing HA for femoral neck fracture found a 28% incidence of BCIS (Olsen et al. 2014). All-cause perioperative mortality (death within 48 hours after surgery) of 1.3 – 2.5% has previously been reported (Costain et al. 2011, Hossain and Andrew 2012). The effects of BCIS can be somewhat long-lasting, as an earlier study found that severe BCIS symptoms during HA operation led to a 16-fold increase in 30-day postoperative mortality (Olsen et al. 2014).

Similarly, a systematic review found that the majority of excess mortality risk following THA occurs in the first 30 days (Berstock et al. 2014).

2.3 Hip arthroplasty and complications

Besides mortality there are several other, more common complications related to THA and HA. Based on registry data, the most common complications are aseptic loosening, dislocation, infection and periprosthetic fracture (AOANJRR 2017, NJR 2018). The incidence of each complication varies as a function of time, some being more common early after the index surgery and some late (Table 1). According to registry data, the complication profile changes around 5 years after the index procedure (AOANJRR 2017).

Table 1. The incidence of the most common early (5 years after the index surgery) and late (10 to 15 years after the index surgery) complications following total hip arthroplasty.

	Incidence	References
Early complications		
Dislocation	5%	(Fender et al. 1999)
Infection	1.4%	(Fender et al. 1999)
Periprosthetic fracture	0.8%	(Cook et al. 2008)
Aseptic loosening	0.4%	(Fevang et al. 2010)
Late complications		
Aseptic loosening	8.5%	(Gundtoft et al. 2016)
Periprosthetic fracture	3.5%	(Cook et al. 2008)
Dislocation	2.5%	(Kostensalo et al. 2013)
Infection	1.5%	(Gundtoft et al. 2016)

The two most common early complications are dislocation and periprosthetic joint infection. As discussed above, posterior approach especially in fracture patients increases the risk of dislocation (Hailer et al. 2012). Also patient-related factors predispose to complications in THA surgery. For example, high ASA class and neurological and cognitive disorders are associated with the risk of dislocation (Meek et al. 2008, Werner and Brown 2012). Periprosthetic joint infection can be devastating to the patient and expensive to treat for the healthcare system. The incidence of infection following primary THA has been estimated to be from 1 to 2% (Voigt et al. 2015). Tobacco abuse, obesity, rheumatoid arthritis, a neoplasm, immunosuppression and diabetes mellitus are known to increase the risk of periprosthetic infection (Del Pozo and Patel 2009). Regardless of extensive study efforts to reduce the infection rate, no improvement has been seen in arthroplasty registries (Springer et al. 2017). On the contrary, the infection burden is likely to increase due to the number of primary and revision procedures which is expected to rise dramatically over the next 20 years (Kurtz et al. 2008).

Aseptic loosening and periprosthetic fracture are more common late than early after the index surgery. Aseptic loosening is caused by osteolysis due to polyethylene or metal wear debris released from MoP, CoP and MoM bearings. CoC bearing has a low wear rate but a risk of implant (ceramic) fracture (Hu et al. 2015). For cementless THA, elderly age and poor bone quality influence primary fixation of the implant and can therefore predispose to aseptic loosening (Piarulli et al. 2013). Both cemented and uncemented femoral stems can lead to periprosthetic fracture, but as bone cement is thought to strengthen bone from inside, periprosthetic fractures are more common with uncemented stems (AOANJRR 2017).

The first evidence of inferiority of MoM hip implants due to ALTR came in 2007 when AOANJRR identified HRAs as having a higher than anticipated rate of revision (AOANJRR 2007). In the history of orthopaedic surgery there are several failed products that have usually had insufficient preclinical data, lack of long-term studies and limited multicentre cohort studies before the general release of these devices, leading to recall of the products after several years of clinical use. Post-marketing surveillance using national arthroplasty registries has proven to be an effective method for detecting outlier implants (Malchau et al. 2015). Registries in general offer a valuable tool for identifying and studying the reasons for implant failure and revision surgery. However, one must keep in mind that only complications leading to revision surgery are recorded in the national joint registries.

2.3.1 Risk of cancer

The first MoM THA was performed in 1938 by Wiles (Wiles 1958). Several types of MoM THAs were developed in the 1960s, but MoP bearings completely replaced MoM bearings in the 1970s and 80s. Also, concerns about the carcinogenic and toxic effects of released metal particles and ions were raised early in the development of MoM bearings. Wear particles obtained from CoCr alloy prostheses injected into laboratory rats were reported to cause tumours (Amstutz and Grigoris 1996).

Metal wear nanoparticles are released both from MoM and MoP bearings (Brewster et al. 2013) and can disseminate throughout the body (Case et al. 1994, Ollivere et al. 2009). When compared to MoP bearings, MoM bearings have less volumetric wear, but because of nano-sized metal wear particles, the absolute number of wear particles is greatly increased (Doom et al. 1998, Rieker and Köttig 2002). Around one trillion nanoparticles are released per year from a MoM bearing, which is 14,000 times the number of particles released from a typical MoP bearing (Daniel et al. 2012). Metal debris from hip implants has been associated with chromosomal aberrations and DNA damage (Case et al. 1996, Bonassi et al. 2000, Daley et al. 2004, Polyzois et al. 2012, Sarhadi et al. 2015). The most relevant systems and organs that might be affected in the medium term (the first 10–20 years) are the haematopoietic system, the urogenital system and the skin. In the long term (20–40 years), the solid organs might be affected (Little 2009). Some studies have found increased risk of prostate cancer, multiple myeloma and other immunoproliferative neoplasms with conventional THAs with any bearing surface (Gillespie et al. 1988, Brewster et al. 2013). Also, there is conflicting evidence regarding the association of conventional non-MoM THAs with melanoma incidence (Nyrén et al. 1995, Olsen et al. 1999, Visuri et al. 2003, 2006, 2010, Levasic et al. 2018). However, the overall risk of cancer is not increased after conventional MoP THAs or first-generation MoM THAs (Visuri et al. 1996, 2010). Further, a Working Group established by the International Agency for Research on Cancer concluded that there is inadequate evidence in humans for the carcinogenicity of metallic implants, metallic foreign bodies, and orthopaedic implants of complex composition (IARC 1999). However, the evidence reviewed pre-dated the emergence of the second generation of MoM hip implants.

Several studies with short-term follow-up report no increase in the overall risk of cancer after second-generation MoM hip arthroplasty when compared to other bearing types (non-MoM) (Mäkelä et al. 2012, Smith et al. 2012b, Brewster et al. 2013, Lalmohamed et al. 2013). However, one study from Slovenia found a slightly higher risk of overall cancer in patients treated with MoM bearings than in the general population or non-MoM patients (Levasic et al. 2018). Reports of higher risk of sarcomas, skin cancers (excluding melanoma) and prostate cancer also exist (Brewster et al. 2013, Mäkelä et al. 2014c, Levasic et al. 2018).

2.3.2 Risk of revision for dislocation

In THA, the most common reason for revision varies with time. In the first 5 years, dislocation is the most frequent reason for revision. After 7 years, loosening is the predominant reason (AOANJRR 2017). In Finland, dislocation is the second most common reason for revision surgery (FAR 2019). The majority of dislocations (roughly 70%) occur during the first postoperative year, and the incidence of primary THA dislocation during this time is reported to be between 2% and 4% (Phillips et al. 2003, Meek et al. 2008). It has been suggested that dislocation rates increase in the late postoperative period in association with increasing wear and declining muscle function (Parvizi et al. 2006). However, a registry study from Scotland with up to 15 years of follow-up reported no sudden increased rate of late dislocations from 5 to 12 years. Dislocation is a costly complication that diminishes the cost-effectiveness of THA (Sanchez-Sotelo et al. 2006).

When planning THA it is important to understand the reasons for dislocation. Both patient-related and surgical factors may predispose to THA dislocation. Patient-related risk factors for dislocation are high ASA class, increasing age, high BMI, fracture diagnosis, rheumatoid arthritis and neurological and cognitive disorders (Jolles et al. 2002, Meek et al. 2008, Hailer et al. 2012, Rowan et al. 2018). The connection between female sex and dislocation risk is contradictory, but a recent meta-analysis found no increase in the risk of dislocation in females compared to males (Rowan et al. 2018).

Surgical factors increasing the risk of dislocation are poor component positioning, small femoral head size, posterior approach, and insufficient surgeon experience (Hailer et al. 2012, García-Rey and García-Cimbrelo 2016, Rowan et al. 2018). The idea of a "safe zone" for acetabular cup positioning to prevent dislocation was first introduced by Lewinnek et al. in 1978, who determined the safe zone to be 40° ± 10° of inclination and 15° ± 10° of anteversion (Lewinnek et al. 1978). However, this cup orientation has lately been questioned because it does not take into account individual patient morphology, such as variation in pelvic tilt, biological or surgical spinal fusion, and the surgical approach used that may alter component-positioning goals (Malik et al. 2010, Seagrave et al. 2017, Stefl et al. 2017). Regarding head size, large heads dislocate less frequently than small ones due to the increase in jumping distance as the head diameter increases. Jumping distance is the degree of lateral translation of the femoral head centre required before dislocation occurs (Sariali et al. 2009). A recent meta-analysis concluded that 22-mm and 28-mm heads have higher dislocation rates compared with 32-mm and 36-mm heads (Rowan et al. 2018). The somewhat high dislocation rate after the posterior approach has been shown to diminish when repairing posterior soft tissues (Suh et al. 2004). Still, the posterior approach is associated with a higher risk of revision due to dislocation compared to other approaches to the hip joint (Hailer et al. 2012, Zijlstra et al. 2017a). However, the risk of dislocation with high risk patients has been shown to decrease when using dual mobility cup (Tarasevicius et al. 2010, Gonzalez et al. 2017). Surgeon experience is also related to the risk of dislocation according to a recent meta-analysis (Rowan et al. 2018).

Dislocation may be single or recurrent. Fist-time dislocations in general respond well to conservative treatment and remain stable after closed reduction (Sanchez-Sotelo et al. 2006). When assessing dislocation rates, it must be noted that the FAR and other arthroplasty registries only document revision surgeries due to dislocation. However, revision surgery is often needed only in cases of recurrent dislocations.

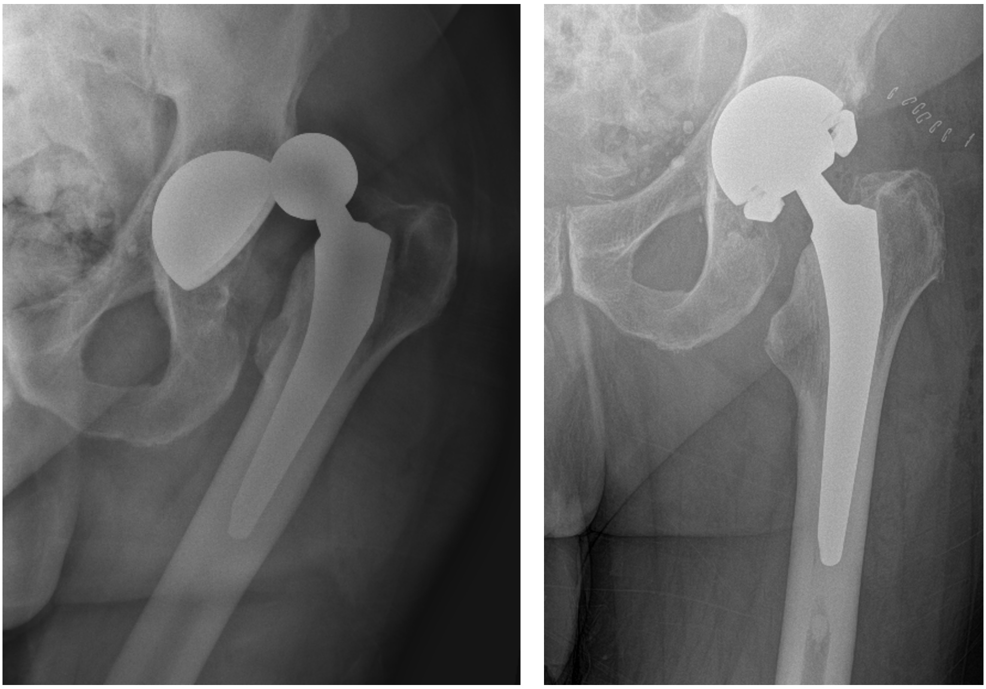

Figure 6. Dislocation of total hip arthroplasty and postoperative radiographs after revision to a constrained acetabular device.

3 Aims of the Present Study

1. To evaluate the risk of cancer in MoM hip implant patients when compared to hip implant patients with other bearing surfaces and the general population (I),
2. To evaluate the early post-operative mortality in cemented THA when compared to uncemented and hybrid THA (II and III),
3. To evaluate the early post-operative mortality in cemented HA when compared to uncemented HA (III), and
4. To investigate the risk factors for revision surgery due to dislocation after primary THA (IV).

4 Materials and Methods

4.1 Patients

4.1.1 Studies I and IV

Studies I and IV are based on data from the Finnish Arthroplasty Register (FAR), which has been collecting information on THAs since 1980. Healthcare authorities, institutions and orthopaedic units are obliged to provide the National Institute for Health and Welfare with information essential for maintenance of the registry. Currently, around 92% of primary total hip implants are recorded in the FAR (www.thl.fi/far/). The data contents of the FAR were revised in 2014 to include parameters such as surgical approach, BMI, ASA score, intra-operative bleeding and duration of surgery. Study IV is based on these revised contents.

In study I, LDH MoM THAs and hip HRAs performed in Finland between 2001 and 2010 were extracted from the FAR and formed the MoM cohort. Patients who underwent MoP, CoP or CoC THA during the study period formed the non-MoM reference cohort. All of these study subjects were followed-up until 31st December 2014 for emigration and vital status via the Population Registry, and for cancer incidence via the Finnish Cancer Registry through a personal identity code. There were 10,728 patients in the MoM cohort and 18,235 in the non-MoM THA cohort included in the study, 46% of whom were men. The number of person years at follow-up was 79,521 for the MoM cohort and 152,358 for the non-MoM cohort. Of all our patients, 497 (4.6%) had bilateral MoM implants. The mean duration of follow-up was 7.4 years (0–14) in the MoM cohort and 8.4 years (0–14) in the non-MoM cohort.

In study IV, data from 33,661 uni- and bilateral THAs performed in Finland between 2014 and 2018 were extracted from the FAR and included in the study. Revisions were linked to the primary operation through a patient-specific personal identification number. The survival endpoint was defined as revision where any component, including isolated liner exchange, was removed or exchanged due to dislocation. The minimum follow-up time ranged from 0 to 3.5 years.

4.1.2 Study II

Study II is based on the PERFECT (PERFormance, Efficiency, and Costs of Treatment Episodes) hip arthroplasty database, which uses data from numerous registries such as the Hospital Discharge Register (FHDR, maintained by the Finnish National Institute of Health and Welfare), cause-of-death statistics maintained by Statistics Finland, the Social Insurance Institution's drug prescription register and drug reimbursement register, and the Finnish Arthroplasty Register. All public and private hospitals in Finland are obliged to report all surgical procedures to the Finnish National Institute of Health and Welfare. The validity of the individual registries mentioned above has been studied. The FHDR data have been compared to external audit data in 32 studies (Sund 2012). The coverage and positive predictive values have been over 90% in those studies. The prescription database data have been found to be in high concordance with self-reported medication (Haukka et al. 2007).

The study population was identified from FHDR using the 10th revision of the International Classification of Diseases (ICD-10) diagnosis codes M16.0 to M16.9, and the Finnish version of NOMESCO Classification Procedural Codes NFB30 (uncemented THA), NFB40 (hybrid THA when only the femoral stem has been cemented), or NFB50 (cemented THA). During the study period from January 1st, 1998 to December 31st, 2013, 73,915 patients were treated with THA for a primary or secondary OA in Finland. Definitive data on fixation method and comorbidities were available for 62,221 THAs that formed the final study population.

To assess BCIS and cardiovascular reasons separately as a cause of death, mortality reported with the associated diagnostic codes (codes I21 acute myocardial infarction, I25 ischaemic heart disease, I26 pulmonary embolism, I50 heart failure and I63 stroke in the ICD-10 classification) within 90 days since the index procedure were extracted from the national Causes of Death Statistics. The validity of the Finnish mortality statistics is reliable (Lahti and Penttilä 2003, Pajunen et al. 2005). The primary outcome used in this study was total mortality and secondary-outcome cardiovascular mortality and mortality associated with pulmonary embolism. The patients were followed up for 1 year post-operatively.

4.1.3 Study III

In study III, patients were selected from the ImplantDB database (BCB Medical). Patients operated for OA, rheumatoid arthritis, psoriatic arthritis, juvenile arthritis, unspecified arthritis or femoral neck fracture (ICD-10 codes M16.0–M16.9, M05.8, M05.9, M06.0, M07.3, M08.0, M08.3, M13.9, S72.0) with uncemented, cemented, or hybrid THA (ICD-10 codes NFB30, NFB40 and NFB50) or with cemented or uncemented HA (ICD-10 code NFB10, NFB20) were included in the study. During the study period from January 1st, 2004 to May 8th, 2015, 7,569 primary THAs and 3,108 HAs were performed at Turku University Hospital. For each patient the preoperative diagnosis and sex, age, and ASA class at the time of surgery was recorded. Time of death was obtained from the National Causes of Death Statistics maintained by Statistics Finland.

Of the 7,569 primary THAs, 74% were uncemented,18% cemented and 8.5% hybrid. Sixty percent of the THA operations were performed on women and the most common preoperative diagnosis was OA (75%). Of the HAs, 38% were uncemented and 62% were cemented. In the HA group, 71% of the operations were performed on women and all of these were for femoral neck fracture. In all study groups, ASA I, IV and V were highly uncommon, and we therefore grouped ASA I-II and IV-V together. Simultaneous bilateral THAs were not included.

4.2 Methods and statistical analyses

4.2.1 Study I

For MoM and non-MoM cohorts the person-years at risk were calculated within stratification of sex, calendar period (2001–05 and 2006–10), 5-year age groups, and follow-up time (<2, 2-5, and ≥5 years since the operation). The expected number of each type of cancer within each stratum was calculated by multiplying the person-years in the stratum by the stratum's age, sex and calendar period specific cancer incidence rate for the Finnish population. The total expected numbers of cancers were summed over the strata. The cancer risk relative to the Finnish population, *i.e.* standardized incidence ratio (SIR), was expressed as the ratio of observed to expected number of cases. For the 95% confidence intervals (CI), we assumed that the number of observed cases followed a Poisson distribution.

Poisson regression analysis was used to estimate the relative cancer risk between the MoM and non-MoM cohorts for soft tissue sarcomas, melanoma and basalioma. Soft-tissue sarcoma and basalioma were chosen for Poisson regression due to earlier results by Mäkelä et al. (2012, 2014c) and skin melanoma due to earlier results with conventional THA (Visuri et al. 2003, Onega et al. 2006). The risk estimate (incidence rate ratio) was adjusted for age (0–49,50–59, 60–69, 70–79, 80+) and follow-up time (<2, 2–5, and ≥5 years since the operation). The Poisson regression analysis was checked for over-dispersion.

4.2.2 Study II

Overall mortality and cause of death for the follow-up periods 0 – 2 days, 3 – 10 days, 11 – 20 days, 21 – 30 days, 30 days, 90 days and 1 year was assessed. Mortality between the cemented, uncemented and hybrid groups was examined using logistic regression analysis. The analysis was repeated for 365 outcomes that each described the status of the patient (alive/dead) on a certain day after the operation. In order to reduce confounding effects in this observational study, differences in distributions of observed covariates between the groups were adjusted: fixation method, sex, age group (<50, 50-59, 60-69, 70-79, ≥80), comorbidities and year of operation. In the model, treatment assignment (cemented/uncemented/hybrid) was the dependent variable and all observed background variables were independent variables, as the aim was to balance all observed covariates between the groups. 95% CI were calculated for adjusted mortality.

4.2.3 Study III

Overall mortality at 2 days, 10 days, 30 days, 90 days, 180 days and 1 year was assessed. Binary logistic regression was used to compare the mortality in the cemented HA group with that in the uncemented HA group, and the mortality in the hybrid THA and cemented THA groups with that in the uncemented THA group. The random intercept logistic model was used to account for the dependency between operations performed for the same patient. Analyses were adjusted for the potential confounding factors age, sex, ASA class and year of surgery. In addition, subgroup analysis for patients of ASA IV was applied to compare the mortality between the cemented and uncemented HA groups. This analysis was also adjusted for age, sex and year of surgery. Statistical analyses were done with SAS System for Windows, version 9.4 (SAS Institute Inc., Cary, NC). P-values of less than 0.05 were considered statistically significant.

4.2.4 Study IV

Kaplan–Meier analysis was used to estimate the unadjusted cumulative revision probabilities for dislocation, with 95% CI. Univariate and multivariable Cox proportional hazards regression models were used to estimate HR with 95% CI for first dislocation revision. Proportional hazards assumption of the Cox model was assessed by visual inspection of Kaplan-Meier curves and with a test based on the scaled Schoenfeld residuals. Since sex did not fulfil the assumption of proportional hazards, it was used as a stratification variable. After stratification, only comparison ASA I vs. ASA II in the multivariable model showed minor violation of the proportional hazards according to the Schoenfeld residuals test (P=0.04). The corresponding Kaplan-Meier plot is available as an online appendix. However, to make our results easier to comprehend, we decided to present the data as such without dividing follow-up into different time periods.

We also performed a sensitivity analysis for the findings obtained for different surgical approaches using univariate Cox proportional hazards regression analysis in a subpopulation of only so-called healthy standard patients (primary OA, ASA I–II, cementless or hybrid THA, metal-on-ultra-highly cross-linked polyethylene (UHXLPE) or ceramic-on-UHXLPE bearing surface and head size 36 mm). Additionally, we assessed how the used surgical approach affected the occurrence of revision due to dislocation among patients with a diagnosis of femoral neck fracture. The following risk factors were considered as covariates: age group (≤ 55, 56–65, 66–75, ≥ 76 years), sex, diagnosis (primary osteoarthritis, fracture, other), hospital volume (low, medium, high), surgical approach (posterior, anterolateral, anterior), head size (28, 32, 36, >36 mm), BMI (< 25, 25–30, > 30 kg/m^2), ASA class (I, II, III–IV), fixation method (cementless, cemented, hybrid, reverse hybrid), previous operation to the same joint like osteotomy or osteosynthesis (yes, no), level of education of the surgeon (specialist, resident), level of education of the first assistant (specialist, resident, other), bleeding (<500ml, ≥500ml), duration of the operation (minutes), anaesthesia form (spinal, epidural, general), local infiltrative anaesthesia (LIA) (yes, no), perioperative complication during surgery (no complication, calcar fracture, trochanteric fracture, femoral shaft fracture, acetabular fracture), bearing surface used (CoC, ceramic-on-UHXLPE, metal-on-UHXLPE, ceramized metal-on-UHXLPE, other) and use of oblique liner (yes, no). Only patients without any missing data for variables of interest (N=21,706) were included in the final multivariable models. All statistical analyses were carried out using R version 3.4.2 (R Development Core Team, http://www.r-project.org). Implant survival was analysed using R package survival (Therneau 2015). The level of significance was set at $p < 0.05$.

5 Results

5.1 Midterm risk of cancer with metal-on-metal hip replacements (Study I)

The overall risk of cancer in patients treated with MoM hip implants was slightly lower than in the general Finnish population (SIR 0.9, 95% CI 0.9–1.0) (Table 2). There were eight soft-tissue sarcomas in the MoM cohort during the follow-up period (SIR 1.4, CI 0.6–2.8) (Table 2). The risk of soft-tissue sarcoma in the MoM cohort was the same as in the non-MoM cohort (RR 0.9, CI 0.4–2.0, p=0.8). The incidence of basalioma in the MoM cohort was higher than in the general Finnish population (SIR 1.2, CI 1.1–1.4; p < 0.001) (Table 2) and also higher than in the non-MoM cohort (RR 1.2, CI 1.0–1.4, p=0.02). The SIR of skin melanoma in the MoM cohort was 1.1 (CI 0.8–1.5) and that in the non-MoM cohort 1.2 (CI 1.0–1.5). Risk of melanoma in the MoM cohort was not higher than in the non-MoM cohort (RR 0.9, CI 0.6–1.4, p=0.7) (Table 2).

Table 2. Observed numbers of cancer cases, expected numbers of cancer cases approximated from the Finnish population, and standardized incidence ratios with 95% confidence intervals – according to site – for the MoM cohort and non-MoM cohort. The latter cohort consisted of implants with MoP, CoP and CoC bearing surfaces.

Primary site	**Metal-on-metal cohort**					**Non-metal-on-metal cohort**				
	Obs	**Exp**	**SIR**	**95% CI**	**% of cancer**	**Obs**	**Exp**	**SIR**	**95% CI**	**% of cancer**
All sites	915	973	0.9	0.9-1.0	9	2851	2852	1.0	1.0-1.0	16
Stomach	23	21	1.11	0.7-1.7	0.2	75	74	1.0	0.8-1.3	0.4
Colon	48	55	0.87	0.6-1.2	0.4	187	199	0.9	0.8-1.1	1
Lung	61	95	0.64	0.5-0.8[a]	0.6	203	260	0.78	0.7-0.9[a]	1
Corpus uteri	24	22	1.1	0.7-1.6	0.2	78	82	1.0	0.8-1.2	0.4
Prostate	239	216	1.1	1.0-1.2	2	478	461	1.0	1.0-1.1	3
Kidney	31	29	1.1	0.7-1.5	0.3	83	82	1.0	0.8-1.2	0.5
Bladder	32	41	0.8	0.5-1.1	0.3	131	128	1.0	0.9-1.2	0.7
Soft-tissue sarcoma	8	6	1.4	0.6-2.8	0.07	20	17	1.2	0.7-1.8	0.1
Non-Hodgkin lymphoma	37	38	1.0	0.7-1.4	0.3	118	108	1.1	0.9-1.3	0.7
Hodgkin lymphoma	2	2	0.9	0.1-3.1	0.02	3	4	0.7	0.1-2.0	0.02
Multiple myeloma	13	12	1.1	0.6-1.8	0.1	36	41	0.9	0.6-1.2	0.2
Leukaemia	17	18	1.0	0.6-1.5	0.2	60	58	1.0	0.8-1.3	0.3
Melanoma	38	36	1.1	0.8-1.5	0.4	105	87	1.2	1.0-1.5	0.6
Basalioma	306	246	1.2	1.1-1.4[a]	3	913	878	1.0	1.0-1.1	5

Obs = observed number of cancer cases; Exp = expected number of cancer cases based on cancer incidence in the comparable Finnish population; SIR = standardized incidence ratio; CI = confidence interval; % of cancer = percentage of patients diagnosed with a certain cancer during follow-up.
[a] $p < 0.001$

5.2 Early post-operative mortality in cemented THA and HA compared to uncemented and hybrid THA or cemented HA (Studies II and III)

The use of cemented THA decreased in Finland during the study period, whereas that of uncemented THA increased (Figure 7). Based on the PERFECT hip arthroplasty database, the adjusted overall mortality or mortality associated with cardiovascular causes or pulmonary embolism were similar between cemented THA and uncemented or hybrid THA at any of the studied time points (Figure 8). There were nine deaths during days 1 and 2 in the cemented THA group, four in the uncemented THA group, and none in the hybrid group (Table 3). The 1 and 2-day adjusted mortality in the cemented THA group was the same as in the uncemented THA group (OR 1.2; CI 0.2–6.5) (Table 4).

There were 45 deaths during days 3 to 10 in the cemented THA group, 23 in the uncemented THA group, and six in the hybrid group (Table 3). The 3 to 10-day adjusted mortality in the cemented THA group was similar to that in the uncemented THA group (OR 0.5; CI 0.3–1.1), and in the hybrid THA group (OR 0.6, CI 0.3–1.6) (Table 4). There were no deaths due to pulmonary embolism during days 1 and 2 in any of the groups. There were five deaths during days 1 and 2 in the cemented THA group due to cardiovascular causes, four in the uncemented THA group, and none in the hybrid group (Table 5).

Based on the Turku University Hospital database there were no statistically significant differences in mortality at any time point between patients with hybrid THA and those with uncemented THA (Table 6). There were no deaths during the first 2 days postoperatively in the uncemented THA group, one (0.2%) in the hybrid group and three (0.2%) in the cemented group (Table 7). There were more deaths in the cemented THA group than in the uncemented THA group after adjusting the groups for age, sex, ASA class and year of surgery at 180 days (OR 2.0; CI 1.0–3.7; p=0.04) postoperatively (Table 6). No statistically significant difference was found at other time points.

Looking at HA, in the unadjusted data there were more deaths in the cemented (50 deaths, 2.6%) than in the uncemented HA group (22 deaths, 1.9%) during the first 2 days postoperatively (Table 7). Of these patients, 30 in the cemented HA group and 10 in the uncemented group were classified as ASA IV. Age, sex, ASA class and year of surgery adjusted mortality did not differ between the groups during the first 2 post-operative days (OR 1.4; CI 0.8–2.3; p=0.3) (Table 8), nor was there was any statistically significant difference in the mortality rate between cemented and uncemented HA groups at any other time point.

In the subgroup analyses of ASA IV patients, there was a difference in mortality that did not quite reach the set criteria of statistical significance during the first 2 post-operative days between the cemented HA and uncemented HA group (OR 2.1; CI 0.9–4.7; p=0.07). Nor was a statistically significant difference in mortality found thereafter, at 10 days (OR 1.3; CI 0.8–2.2; p=0.3), 30 days (OR 1.3; CI 0.9–2.0; p=0.2), 90 days (OR 1.3; CI 0.9–1.8; p=0.1), 180 days (OR 1.1; CI 0.8–1.5; p=0.6) or 365 days (OR 1.1; CI 0.8–1.6; p=0.4).

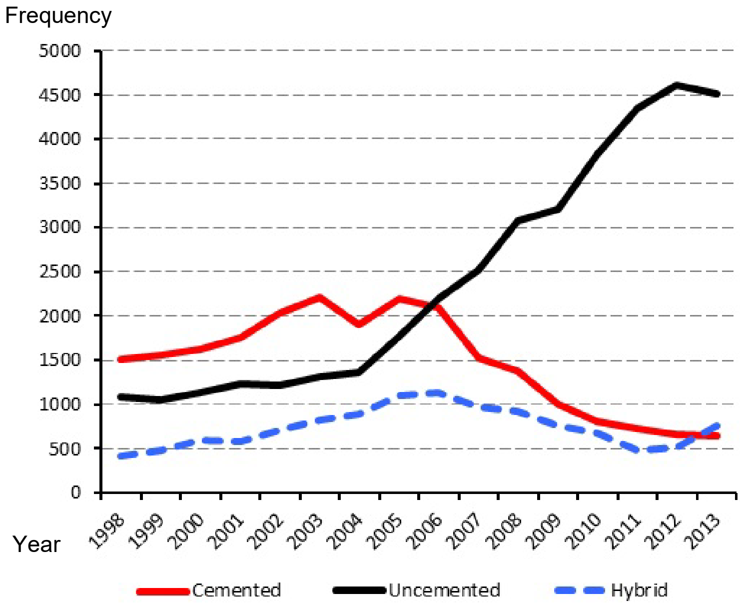

Figure 7. Annual numbers of cemented, uncemented and hybrid THA in Finland during the study period.

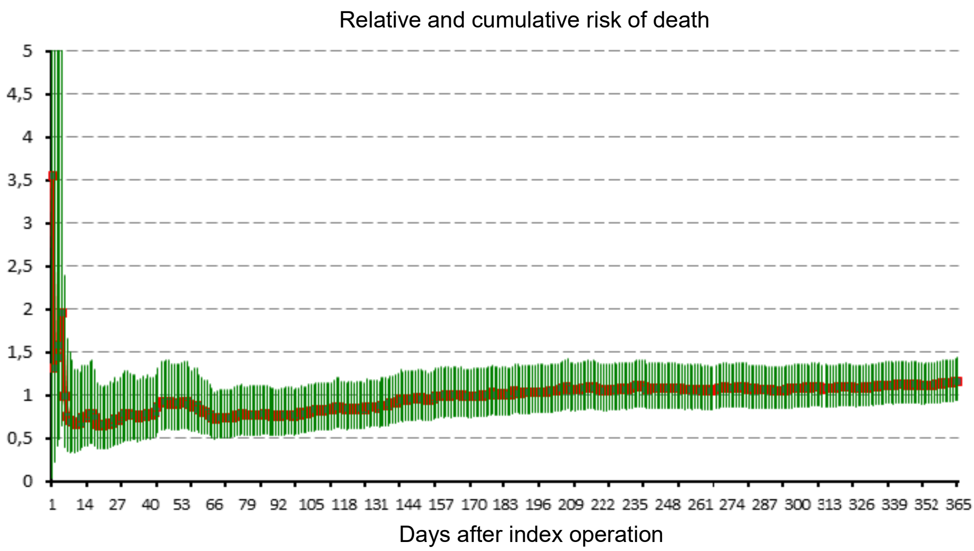

Figure 8. Relative and cumulative risk of death in patients receiving a cemented THA compared to patients receiving an uncemented THA. No statistically significant difference in mortality was found.

Table 3. Mortality of the patients, raw data.

	Cemented THA		Uncemented THA		Hybrid THA	
	n	%	n	%	n	%
Number of patients	23 636		38 477		11 802	
Mortality						
30-day mortality	111	0.5	45	0.1	15	0.1
90-day mortality	228	1.0	93	0.2	29	0.2
180-day mortality	389	1.6	155	0.4	52	0.4
365-day mortality	712	3.0	254	0.7	115	1.0
1 and 2-day mortality	9	0.0	4	0.0	0	0.0
3 to 10-day mortality	45	0.2	23	0.1	6	0.1
11 to 20-day mortality	35	0.1	14	0.0	6	0.1
21 to 30-day mortality	22	0.1	4	0.0	3	0.0

THA = total hip arthroplasty, n = number.

Table 4. Postoperative mortality risk for cemented total hip arthroplasty (THA) compared to uncemented and hybrid THA, OR (95% CI)

	2 days	3 to 10 days	11 to 20 days	21 to 30 days	30 days	90 days	365 days
Cemented	1.2 (0.2-6.5)	0.5 (0.3-1.1)	0.7 (0.3-1.8)	2.8 (0.8-10.0)	0.8 (0.5-1.3)	0.8 (0.6-1.1)	1.2 (1.0-1.4)
Hybrid	0 (0.0-999.9)	0.6 (0.3-1.6)	0.9 (0.3-2.5)	1.9 (0.4-8.8)	0.8 (0.4-1.4)	0.7 (0.5-1.1)	1.2 (0.9-1.5)

Table 5. Causes of death. All cardiovascular: acute myocardial infarction, ischaemic heart disease, pulmonary embolism, heart failure, stroke. Follow-up of causes of death is to the end of 2013.

	Cemented THA		Uncemented THA		Hybrid THA	
	n	%	n	%	n	%
Number of patients	23 636		38 477		11 802	
Cause of death, 1-2 days						
Pulmonary embolism	0	0.00	0		0	
Other cardiovascular	5	0.02	4	0.01	0	
Cause of death, 3-10 days						
Pulmonary embolism	1	0.00	2	0.01	0	
All cardiovascular	11	0.05	19	0.05	4	0.03
Cause of death, 11-20 days						
Pulmonary embolism	5	0.02	1	0.00	1	0.01
All cardiovascular	15	0.06	9	0.02	5	0.04
Cause of death, 21-30 days						
Pulmonary embolism	3	0.01	1	0.00	0	0.00
All cardiovascular	8	0.03	3	0.01	2	0.02
Cause of death, 90 days						
Pulmonary embolism	15	0.06	14	0.04	4	0.03
All cardiovascular	76	0.32	60	0.16	22	0.19
Cause of death, 365 days						
Pulmonary embolism	30	0.13	20	0.05	7	0.06
All cardiovascular	208	0.88	127	0.33	62	0.53

THA = total hip arthroplasty, n = number.

Table 6. Postoperative mortality risk for uncemented total hip arthroplasty compared to hybrid and cemented THA, OR, 95% CI and p-value (p) (adjusted for age, sex, ASA class and year of surgery)

	0-2 days	0-10 days	p-value	0-30 days	p-value	0-90 days	p-value	0-180 days	p-value	0-365 days	p-value
Uncemented THA	1	1		1		1		1		1	
Hybrid THA	**NA**	3.2 (0.5-20.2)	0.2	1.7 (0.6-4.9)	0.4	1.7 (0.6-4.9)	0.4	1.7 (0.7-3.9)	0.2	1.5 (0.8-2.9)	0.2
Cemented THA	**NA**	1.7 (0.3-8.7)	0.5	1.6 (0.7-3.6)	0.3	1.6 (0.7-3.6)	0.3	2.0 (1.0-3.7)	0.04	1.6 (0.9-2.7)	0.08

NA = not available due to zero deaths during the first two days post-operatively in the uncemented THA group

Table 7. Number of deaths.

	Uncemented HA	Cemented HA	Uncemented THA	Hybrid THA	Cemented THA
Number of operations	1 173	1 935	5 563	640	1 366
Number of deaths					
0–2 days, n (%)	22 (1.9)	50 (2.6)	0	1 (0.2)	3 (0.2)
0–10 days, n (%)	61 (5.2)	99 (5.1)	4 (0.1)	2 (0.3)	5 (0.4)
0-30 days, n (%)	105 (9.0)	171 (8.9)	6 (0.1)	2 (0.3)	9 (0.7)
0-90 days, n (%)	173 (14.8)	303 (15.7)	17 (0.3)	5 (0.8)	19 (1.4)
0-180 days, n (%)	227 (19.4)	388 (20.1)	29 (0.5)	8 (0.3)	29 (2.1)
0-365 days, n (%)	279 (23.8)	503 (26.0)	50 (0.9)	14 (2.2)	41 (3.0)

THA = total hip arthroplasty. HA = hemiarthroplasty, n = number.

Table 8. Postoperative mortality risk for cemented hemiarthroplasty (HA) compared to uncemented HA, OR, 95% CI and p-value (p) (adjusted for age, sex, ASA-class and year of surgery)

	0-2 days	p-value	0-10 days	p-value	0-30 days	p-value	0-90 days	p-value	0-180 days	p-value	0-365 days	p-value
Uncemented HA	1		1		1		1		1		1	
Cemented HA	1.4 (0.8-2.3)	0.3	1.0 (0.7-1.4)	1.0	1.0 (0.8-1.3)	1.0	1.1 (0.9-1.3)	0.5	1.0 (0.8-1.2)	0.9	1.1 (0.9-1.3)	0.4

5.3 Risk factors for revision surgery due to dislocation after primary THA (Study IV)

Altogether 33,337 THAs performed in Finland between 2014 and 2018 were analysed (see original publication IV). The largest age group with primary THA were patients aged 66 to 75 years (37%). Most of the study population were women (19,002; 57%). Most of the patients were ASA II (49%) or combined III and IV (39%) and received a THA with cementless fixation (62%) and a metal-on-UHXLPE (50%) or ceramic-on-UHXLPE (28%) bearing surface. The main reason for primary THA was primary osteoarthritis (87%) and the most common surgical approach posterior (80%) (see original publication IV). The overall Kaplan-Meier survival revision for dislocation as the endpoint at 3.5 years was 98.9% (CI: 98.8-99.1).

The posterior surgical approach was significantly associated with increased risk of revision for dislocation compared to the anterolateral approach in both univariate analysis [HR 2.6 (CI 1.7-4.1, p<0.001)] (see original publication IV) and multivariable analysis [HR of 3.1 (CI 1.7–5.5, p<0.001)] (see original publication IV). The anterior approach was not associated with dislocation revision in univariate analysis [HR 2.9 (CI 0.9–9.6), p=0.09] (see original publication IV) but did have an increased risk of revision in multivariable analysis [HR 3.6 (CI 1.0–13.1), p=0.05] (Table 10). In the sensitivity analysis, HR with the posterior compared to the anterolateral approach for dislocation revision was 2.1 (CI 0.7–5.8, p=0.2). Also, THAs performed for femoral neck fracture had an increased risk of revision for dislocation compared to THAs performed for primary OA in both univariate [HR 3.6 (CI 2.5–5.2, p<0.001)] (see original publication IV) and multivariable analysis [HR 3.0 (CI 1.9–4.7, p<0.001)] (Table 10). Patients who received THA for other reasons were not associated with dislocation revision univariate [HR 1.5 (CI 1.0–2.1), p=0.05] (see original publication IV) or multivariable analysis [HR 1.4 (CI 0.9–2.2), p=0.2] (Table 10).

Patients with higher ASA class had significantly increased risk of revision for dislocation in univariate analysis [ASA II vs. ASA I HR 1.8 (CI 1.0–3.0, p=0.03) and ASA III–IV vs. ASA I HR 2.7 (CI 1.6–4.5, p<0.001)] and in multivariable analysis [ASA III–IV vs. ASA I HR 2.0 (CI 1.0–3.9, p=0.04)] (see original publication IV and Table 10). In the multivariable analysis, ASA II compared to ASA I was not significant [HR 1.7 (CI 0.9–3.3, p=0.09)] (Table 10).

The use of 36 mm femoral head size decreased the risk of revision for dislocation compared to a 32 mm head in univariate [HR 0.6 (CI 0.5–0.8, p<0.001)] (see original publication IV) and multivariable analysis [HR 0.5 (CI 0.4–0.7, p<0.001)] (Table 10). We found no association between the risk for dislocation revision and the use of other head sizes (28 mm and >36 mm) in either univariate [28 mm vs. 32 mm HR 0.8 (CI 0.2–2.4, p=0.7) and >36 mm vs. 32 mm HR 1.1 (CI 0.4–3.1, p=0.8)] or multivariable analysis [28 mm vs. 32 mm HR 0.5 (CI 0.1–3.4, p=0.4) and >36 mm vs. 32 mm HR 0.4 (CI 0.0–2.6, p=0.3)] (see original publication IV and Table 10).

We found a significantly increased risk of revision for dislocation in univariate but not in multivariable analysis for the following parameters: high vs. low hospital volume, intraoperative bleeding ≥ 500 ml vs < 500ml, epidural anaesthesia, and cemented or hybrid fixation vs. cementless fixation (see original publication IV). There was a significantly decreased risk of revision for dislocation in the univariate but not in the multivariable analysis for 1) the use of LIA and 2) ceramic-on-ceramic, ceramic-on-UHXLPE, or ceramized metal-on-UHXLPE vs. metal-on-UHXLPE (see original publication IV).

The demographics of the used surgical approaches and occurrence of revision due to dislocation among patients with femoral neck fracture diagnosis are described in Table 11. There were dislocation revisions only among patients who had been operated using the posterior approach (Table 11). Therefore, we were not able to perform further statistical analyses on this issue. The data on all tested variables is given in Appendices 1 – 3 (see original publication IV).

Table 10. Statistically significant predictors for revision for dislocation in the multivariable analysis. Only patients without any missing data for variables of interest (n=21,706) were included in the final multivariable models.

	Hazard ratio	95% CI	p-value
ASA class			**0.09**
I	Reference		
II	1.7	0.9 – 3.3	0.09
III–IV	2.0	1.0 – 3.9	0.04
Surgical approach			**<0.001**
Anterolateral (modified Hardinge)	Reference		
Posterior	3.1	1.7 – 5.5	<0.001
Anterior (Smith-Peterson)	3.6	1.0 – 13.1	0.05
Femoral head size (mm)			**0.004**
28	0.5	0.1 – 3.4	0.4
32	Reference		
36	0.5	0.4 – 0.7	<0.001
>36	0.4	0.0 – 2.6	0.3
Preoperative diagnosis			**<0.001**
OA	Reference		
Fracture	3.0	1.9 – 4.7	<0.001
Other	1.4	0.9 – 2.2	0.2
Bearing			**0.1**
Metal-on-UHXLPE	Reference		
Ceramic-on-ceramic	0.6	0.3 – 1.3	0.2
Ceramic-on-UHXLPE	0.9	0.6 – 1.3	0.5
Ceramized metal-on-UHXLPE	0.3	0.1 – 1.0	0.06
Other	0.6	0.2 – 1.3	0.2

ASA class = American Society of Anesthesiology classification, OA = primary osteoarthritis, UHXLPE = ultra-highly crosslinked polyethylene

Table 11. Used surgical approaches and occurrence of revision due to dislocation among patients with femoral neck fracture diagnosis (n=1,366).

Characteristic	**Total number of patients with pre-operative femoral neck fracture**			**Number of revisions due to dislocation**			**Number of patients without subsequent dislocation**		
	n available	**n**	**%**	**n available**	**n**	**%**	**n available**	**n**	**%**
Number of hips	1366			33			1333		
Surgical approach	1341			33			1308		
Anterolateral (modified Hardinge)		247	(18)		0	(0)		247	(19)
Posterior		1083	(81)		33	(100)		1050	(80)
Anterior (Smith–Peterson)		11	(1)		0	(0)		11	(1)

n = number

6 Discussion

In the unadjusted data there were more perioperative deaths in patients treated with cemented arthroplasty than in patients treated with uncemented or hybrid arthroplasty. After adjustin for comorbidities this difference disappeared, implicating that the most important factor in perioperative mortality is the patients' general health not the use of bone cement. It is possible that surgical technique plays a minor role in mortality, but it is very difficult to investigate this with statistical methods. However, no difference in mortality when using bone cement could be shown even in our large patient group. Hence, the main finding of this thesis was that the use of bone cement is safe.

Another important finding of this thesis was that patients treated with MoM hip implants had a comparable cancer risk with patients treated with non-MoM hip implants and the general Finnish population. They did not have increased risk for soft-tissue sarcoma or skin melanoma. Only the incidence for basalioma was increased in the MoM cohort compared to the non-MoM cohort and compared to the general population.

There was no statistically significant difference in adjusted perioperative and short-term postoperative mortality between patients treated with cemented HA or THA and patients treated with uncemented HA or THA or hybrid THA in our material. For THA, cardiovascular and pulmonary embolism mortality was studied separately, and the mortality was similar after cemented THA compared to uncemented or hybrid THA. Based on our results and earlier literature, cemented THA and HA are a safe option and should be the gold standard in the elderly patient population. Excess mortality of cemented THA and HA in the longer term is comorbidity related, not due to BCIS. In conclusion, the use of bone cement should not be feared even in the older and more comorbid fracture patients and the safety of cementing needs no further studies.

The risk of revision for dislocation increased with use of the posterior approach compared to the anterolateral approach, with fracture diagnosis compared to primary OA, and with ASA III–IV compared to ASA I. Head size 36mm was associated with decreased revision risk compared to 32mm heads. These factors should be considered especially when treating patients with increased dislocation risk.

6.1 Risk of cancer

We found that the overall midterm risk of cancer was not increased in patients treated with MoM hip implants compared to the general Finnish population in midterm follow-up. This is in line with previous short-term follow-up studies on second-generation MoM hip implants (Mäkelä et al. 2012, Smith et al. 2012b, Brewster et al. 2013, Lalmohamed et al. 2013, Mäkelä et al. 2014c). The slightly lower overall risk of cancer in the MoM group could be influenced by MoM patients tending to be young and possibly healthier than the average population, which might cause some selection bias. A recent study from Slovenia including only THAs found a slightly higher risk of overall cancer in patients treated with MoM bearings than in the general population or non-MoM patients (Levasic et al. 2018). In that study, the specific cancer types with higher prevalence in the MoM cohort than in the general population were skin cancers excluding melanoma. Comparably, we found a higher risk for basalioma in our MoM cohort. This confirmation of our results from another country is an interesting finding and needs further research. The study cohort size in the study by Levasic et al. was smaller than ours (338 MoM THAs).

In our previous short-term follow-up study of this same study population, the risk of soft-tissue sarcomas was elevated in the MoM group compared to the non-MoM group (Mäkelä et al. 2014c). Furthermore, in that study all sarcomas were diagnosed during the last 4 years of the follow-up, raising the concern that during longer follow-up soft-tissue sarcomas might be overrepresented in the MoM cohort and that there might be a causative relationship between metal wear debris and soft-tissue sarcomas. However, in the current study only one additional soft tissue sarcoma was observed during the additional follow-up years 2012–2014, and the incidence was similar in the MoM patient population compared to the general Finnish population and similar to the risk in the non-MoM group. A recent study also reported a similar incidence of sarcomas between MoM and non-MoM patients during a mean follow-up of 9.0 years (Levasic et al. 2018). To our knowledge, there are no other studies reporting increased incidence of soft-tissue sarcomas in patients treated with MoM hip implants.

The incidence of basalioma was higher in the MoM than in the non-MoM cohort and also increased when compared to the Finnish population. A similar finding has previously been reported only with conventional THAs (Brewster et al. 2013). The majority of previous studies on MoM hip implants either exclude non-melanoma skin cancer or include basaliomas in the category of other skin cancers, and the data on basalioma incidence in patients treated with MoM implants is limited (Visuri et al. 2006, Smith et al. 2012b, Lalmohamed et al. 2013). Due to its benign nature, basalioma is traditionally not included in the official national cancer statistics. In Finland only the first basalioma for each person is recorded in the Finnish Cancer Registry (Pukkala et al. 2017). This may bias our results, since patients treated with

HRA are generally younger than those treated with conventional THA and may be more likely to be diagnosed with basalioma for the first time during our follow-up.

We found that the incidence of skin melanoma was not elevated in the MoM cohort compared to the general Finnish population. Earlier studies have found conflicting evidence on the association of conventional non-MoM THAs with melanoma incidence. Some have reported a higher melanoma incidence in patients treated with non-MoM implants than in the general population (Nyrén et al. 1995, Olsen et al. 1999, Visuri et al. 2003, 2006) while others have found no difference (Visuri et al. 2010, Levasic et al. 2018). No increase in the risk of melanoma was found for patients treated with a MoM resurfacing device (Brewster et al. 2013).

The study by Brewster et al. (2013) found an increased risk of multiple myeloma and other immunoproliferative neoplasms in THA patients during the first 4 years after arthroplasty. However, their study did not differentiate MoM bearings from other types of bearings, and the study also included patients with rheumatic conditions, which are known to increase the risk of immunoproliferative neoplasms (Isomäki et al. 1978). Our study found no excess risk of myeloma in MoM hip implant patients.

6.2 Post-operative mortality

Based on Finnish Registry data, the adjusted early postoperative mortality after cemented THA compared to uncemented or hybrid THA was similar as regards death for any reason, death for pulmonary embolism or death for cardiovascular reasons. However, using unadjusted data the proportion of perioperative deaths was higher in patients with cemented THA than in patients with uncemented or hybrid THA. Similarly, in the study based on the Turku University Hospital database, we found no statistically significant difference in the adjusted early postoperative mortality after cemented THA compared to uncemented or hybrid THA. Further, we found no statistically significant differences in the adjusted mortality between cemented and uncemented HA at any time point. Even in the subgroup analyses of ASA-IV HA patients during the first 2 days post-operatively there was no statistically significant difference in the cemented HA group compared to the uncemented HA group. Based on our results, cementing is a safe option in both elective and fracture hip surgery.

Cementing is the gold standard for implant fixation, especially in elderly patients and patients treated for femoral neck fractures. Based on combined Nordic data, the risk for revision has been both statistically and clinically significantly lower with cemented implants than with uncemented implants in patients aged 65 years or more (Mäkelä et al. 2014, Varnum et al. 2015). Bone cement has been thought to strengthen bone from inside and therefore to decrease the risk of periprosthetic fracture, osteolysis and loosening. All major registries show lower revision rates for cemented implants in elderly patients with OA (SHAR 2018, AOANJRR 2018, NJR 2018, FAR 2018). Additionally, there is evidence that in HA patients, cementing the stem reduces postoperative pain and leads to better mobility (Parker et al. 2010). Cementing may also decrease the risk of re-operation when compared to uncemented HA in hip fracture patients (Gjertsen et al. 2012, Yli-Kyyny et al. 2014).

Due to these data, the proportion of cemented stems has been increasing recently and 62% of the HA patients in our study were cemented. Earlier studies reported that cementing of the hip device was associated with a risk of BCIS increasing peri-operative morbidity and mortality (Coventry et al. 1974, Ereth et al. 1992, Parvizi et al. 1999). It has been suggested that the risk of BCIS might be increased in hip fracture patients who are, in general, old and fragile and have several comorbidities (Keating et al. 2006, Moja et al. 2012). However, despite the superior implant survival of cemented THA in elderly patients, fear of BCIS has led many surgeons to use uncemented implant fixation (Dale et al. 2009, Fevang et al. 2010, Mäkelä et al. 2014b). BCIS is characterized by perioperative hypotension and hypoxia, and at worst cardiac arrest and death of the patient. The true incidence of cardiac arrest secondary to BCIS is unknown (Donaldson et al. 2009). In our study, the 1- and 2-day adjusted mortality was similar in the cemented and uncemented THA groups. Thus, BCIS is seldom a cause of death in elective THA patients in Finland.

A Swedish register study reported an increased adjusted risk of death during the first 14 days after surgery in patients who underwent cemented THA compared with matched controls (HR 1.3, 95% CI 1.11–1.44). This means five additional deaths per 10,000 observations. Such an increased risk of death was not found in patients with a cementless or hybrid THA. However, this risk in the cemented THA group disappeared during a follow-up of 90 days (Garland et al. 2017). In our study, the adjusted OR for mortality in the cemented THA group was not elevated during the first 20 postoperative days compared to the uncemented THA group. Also McMinn et al. (2012) reported a higher mortality rate in patients undergoing cemented THA compared with uncemented THA. However, this increase in mortality occurred gradually during 8 years after surgery and not early, as would be expected if the increased mortality was caused by BCIS. We found similar adjusted mortality regarding the use of bone cement at any time point up to 365 days postoperatively. This is in line with a study by Parvizi et al. (2001), who found no increased risk of death with cemented THA 30 days post operatively.

In a recent systematic review, the overall 30-day mortality was 0.30% and 90-day mortality 0.65% following THA. The leading cause of death was ischaemic heart disease (41% of deaths) followed by cerebrovascular accidents (23%) and pulmonary embolism (12%) (Berstock et al. 2014). In our material, the unadjusted mortality at 30 and 90 days for the cemented THA group was 0.5% and 1.0%, and 0.1% and 0.2% for the hybrid and uncemented groups, respectively. These differences are mainly explained by patient selection, and after adjusting for the elderly and sicker population in the cemented group, the mortality was similar between the cemented and uncemented groups. The leading cause of death was cardiovascular. Parvizi et al. (1999) studied intraoperative mortality during cemented THA and found an incidence of 0.03%, the leading cause of death being pulmonary embolism. In previous studies, increasing age, male sex, worse ASA class (>3) and higher number of comorbidities have been found to increase the risk of death after THA surgery (Bozic et al. 2012, Mahomed 2003, Parvizi et al. 2001, Hunt 2013). In our study we attempted to account for this by adjusting the treatment groups for sex, age and comorbidities, and found that the early overall mortality between the groups was similar at any time point.

There are earlier studies reporting increased early postoperative mortality in patients treated with cemented HA (Parvizi et al. 1999, Yli-Kyyny et al. 2014). We found a higher proportion of perioperative deaths (0–2 days postoperatively) in the cemented HA group than in the uncemented HA group. It is possible that these numbers include deaths due to BCIS; nonetheless, this could not be confirmed as we did not have access to the cause of death. However, this difference vanished after adjusting the data for age, sex and ASA class, suggesting that the difference was not due to cementing. This is in line with registry studies from Australia and the UK, which have not shown any increase in early postoperative mortality between cemented and uncemented implants (Costa et al. 2011, Costain et al. 2011). Also, in studies reporting increased early postoperative mortality when using bone cement, the risk disappeared after the first post-operative week or even reversed to a lower mortality for those treated with a cemented prosthesis (Costain et al. 2011, Yli-Kyyny et al. 2014).

We found in the adjusted data an increased risk of death in patients treated with cemented THA compared with those treated with uncemented THA at 180 days postoperatively. This late mortality, however, is not explained by BCIS. It is probably due to baseline differences in the treatment groups: patients treated with cemented THA were older than those treated with uncemented THA. Our finding is in line with an earlier study that found no increase in mortality with cemented THA compared to uncemented THA during the first 30 post-operative days (Parvizi et al. 2001).

6.3 Risk of revision for dislocation

Dislocation is still one of the main reasons for revision operation after primary THA (AOANJRR 2017, FAR 2018, NJR 2018). We used FAR data from 2014 to 2018 to assess risk factors for dislocation revisions after primary THA. We found that the posterior approach was associated with increased risk of dislocation revision compared to the anterolateral approach. Similar results have also been found in previous studies (Hailer et al. 2012, Higgins et al. 2015, Mjaaland et al. 2017). In the Dutch Arthroplasty Register, revision for dislocation risk has been 0.5 to 0.6 for the straight lateral, anterolateral, and anterior approaches compared to the posterior approach (Zijlstra et al. 2017b). A Norwegian register study found a 2.1-fold risk of dislocation revision for the posterior approach compared to the anterolateral approach (Mjaaland et al. 2017). It has previously been suggested that patients belonging to risk groups should be operated on using lateral approaches (Hailer et al. 2012). Our results support this proposal. The anterior approach had an increased risk of revision due to dislocation compared to the anterolateral approach in the current study, but the total amount of THAs performed using the anterior approach was very small. In sensitivity analysis, the difference in the dislocation revision rate between the posterior and anterolateral approaches was no longer statistically significant. The sensitivity analysis covered roughly 21% of all operations included, so lower power may be the reason for the non-significant result. However, a resent Swedish registry study shows similar results: they found that the risk of revision due to dislocation was not increased in OA patients when using the posterior approach compared to the anterolateral approach (Skoogh et al. 2019). The anterior and posterior approaches have been associated with better patient-reported outcome measures compared to the anterolateral and direct lateral approaches. Patients operated on using the posterior approach had less postoperative pain on Numeric Rating Scale pain scores during activity and at rest compared to patients operated on with the anterolateral approach (Peters et al. 2018). In the present study, there were dislocation revisions only among patients with pre-operative femoral neck fracture diagnosis who were operated on using the posterior approach. This finding is consistent with those of prior studies (Enocson et al. 2009, Sköldenberg et al. 2010, Cebatorius et al. 2015).

The Australian registry has reported a 2-fold and the Swedish registry a 4-fold dislocation revision risk for patients whose THA was for a femoral neck fracture compared to patients operated on because of OA (Conroy et al. 2008, Hailer et al. 2012). Our results are in line with these registry findings, with a 3-fold dislocation revision risk for THA for femoral neck fractures compared to patients operated on for primary OA. Special attention should be paid to implant choice and approach when treating fracture patients.

Another factor associated with increased dislocation revision risk in our multivariable model was ASA III–IV compared to ASA I. A previous study stated that patients with ASA II or above had an increased risk of dislocation in the Dutch Register (Zijlstra et al. 2017b). In our data, ASA II was a risk factor only in univariate analysis, but otherwise our results support the findings from the Dutch Register. Patients with increased ASA class have more comorbidities and are more fragile, which might predispose them to dislocations. The threshold for operating these patients may already be higher and the primary situation more demanding, which could increase the dislocation risk.

Large femoral head size has previously been associated with a smaller risk of revision for dislocation. Based on FAR data on 42,379 THAs and HRAs, the use of 28 mm femoral heads has been reported to have a 10-fold dislocation revision risk compared to >36 mm femoral heads (Kostensalo et al. 2013). However, this previous study included several thousand large head MoM THAs and HRAs and is therefore not directly comparable to the current study, which did not include any MoM bearings. In previous studies, the dislocation revision risk has been reported to be equal for 32 and 36 mm heads (Hailer et al. 2012, Kostensalo et al. 2013). A large registry study conducted by the Nordic Arthroplasty Registry Association from 2003 to 2014 found no difference between 36 mm and 32 mm heads in relation to dislocation revision risk (Tsikandylakis et al. 2018), contrary to our current finding of lower risk with 36 mm heads. Our finding is in line with the idea of jumping distance. A recent report from the Dutch Arthroplasty Register stated that 36 mm heads reduced the risk of revision for dislocation compared to 32 mm heads, although this finding considered only THAs performed using the posterior approach (Zijlstra et al. 2017b). Based on these most recent data, 36 mm femoral heads should be considered instead of 32 mm heads for patients with high dislocation risk.

6.4 Strengths, limitations and future aspects

The studies presented in this thesis have limitations. As with all registry-based studies there is a risk of selection bias. Registry-based studies have the advantage of reporting results from a large patient group and so-called “real world data”, but the disadvantage of possible confounding by indication (Freemantle et al. 2013). That is, the patients selected for THA or HRA may, for example, be healthier than the average population. Ideally this could be avoided by randomized controlled studies. Also, we did not have any blood metal ion measurements or imaging findings for the MoM patients. It is theoretically possible that a higher cancer risk might be associated with higher ion levels, but our study was not able to detect this subgroup. However, the findings of a meta-analysis by Christian et al. (2014) suggest that the concentrations and doses of Co/Cr required to induce a genotoxic or tumorigenic outcome are much higher than the systemic Co/Cr concentrations typically present in MoM hip implant patients.

As for the studies regarding the use of bone cement, we have no information about perioperative resuscitations because of cardiac arrest due to BCIS. It is possible that there is more morbidity due to cementing, which might affect the patient's quality of life. Also, data on revision surgeries of the study patients was not included. Thus, we do not know whether mortality is associated, for example, with multiple operations. The number of deaths from cardiovascular accidents or pulmonary embolism in our study was fairly small. It is possible that in a larger population some smaller differences in the mortality could be detected. Nonetheless, our material consisted of over 60,000 THAs; we therefore believe that there is no difference of clinical importance. Further the PERFECT database does not include information about patients' socioeconomic status, which is known to affect mortality after THA (Whitehouse et al. 2014, Garland et al. 2017). Therefore, some amount of residual confounding cannot be ruled out. Regarding the study based on the Turku University Hospital database, we did not have causes of death and do not therefore know the absolute number of deaths due to BCIS. However, we focused on overall mortality. Also, besides ASA class we did not have information on patients' comorbidities known to affect the risk of death (such as dementia or congestive heart failure); therefore our study groups could not be adjusted for these. Further, some surgeons may have hesitated to use bone cement due to the possibility of BCIS. This may cause some selection bias to our results, although we believe it to be of minor importance.

In study IV, comorbidity data for the patients was not available, although ASA class presents a crude estimate of medical condition. In addition, we were unable to assess radiographs or implant positioning. Further, we did not have data on closed repositions of dislocated THA. It is possible that some patients suffered one or two dislocations and that their hip had subsequently stabilized without the need for revision surgery.

The strength of this thesis is that included studies have clinical importance. I believe that we were able to testify that the use of bone cement is safe and it does not cause excess mortality in THA or HA patients in elective or trauma circumstances. The use of bone cement should not be feared even in the oldest and more comorbid patients. Also, MoM hip implants were frequently used in Finland and therefore it is important to study the possible adverse outcomes related to it. Because reactions around the MoM implants, such as ALTR, there is a clear need to know whether MoM hip implant patients are in an increased risk of cancer. Hip arthroplasty is a large topic and the limitation of this thesis is the heterogeneity of the studies included.

Far too often, we humans have short memories and we tend to repeat our errors. Hopefully this is not the case in healthcare and lessons have been learned. New implants and techniques should be carefully and systematically studied before their adaptations in clinical practise. Also, in the future, long-term results concerning the possible cancer risk in MoM hip implant patients should be studied as cancer takes years to develop. Our follow-up time reached the midterm point, however genetic alterations could still occur or manifest later, thus our current results need validation in longer follow-up.

7 Conclusions

Our study leads to the following conclusions:

1) We found that the risk of cancer was not increased in patients treated with MoM hip implants compared to patients treated with non-MoM hip implants and the general population.
2) There was no statistically significant difference in adjusted perioperative and short-term postoperative mortality between patients treated with cemented THA and patients treated with uncemented or hybrid THA.
3) There was no statistically significant difference in adjusted perioperative and short-term postoperative mortality between patients treated with cemented HA and patients treated with uncemented HA.
4) We found that the risk of revision for dislocation increased with use of the posterior approach compared to the anterolateral approach, with fracture diagnosis compared to primary OA, and with ASA III–IV compared to ASA I. A head size of 36mm was associated with a decreased revision risk compared to 32mm.

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