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Advancements in Total Hip Arthroplasty

-polyethylene, articulation and factors associated with dislocation

PhD Clinical Thesis

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It's unbelievable how much you don't know about the game you've been playing all your life
-Mickey Mantle

1. Acknowledgments

There are many people I would like to thank and acknowledge in my journey towards this degree. My interest for the material sciences and orthopedics has been a gradual process and finally culminated in a passion towards joint prosthesis surgery.

First of all, I would like to thank the two most influential people during my undergraduate education at St. Olaf College (Northfield, MN). Professor Emeritus Wesley Pearson (Chemistry Department) who was my main adviser and proponent. I wish to posthumously sincerely thank him for all assistance and guidance he has given me. Then there is Professor Richard Allen (Mathematics Department) who guided me through 4 years of study. Without Richard I would not have made it through my first two semesters of Mathematics with distinction. He has helped me immensely and been a constant motivator.

My first research endeavor was during the summer of 2001. I worked as a research assistant at the Institute of Immunology at Rikshospitalet in Oslo maintaining cell cultures, running gel electrophoresis and PCR. Professor Emeritus Jacob Natvig was my supervisor and he made a great impression on me and was the person who first advocated a career in research, which galvanized me towards continued study and with a focus on the basic sciences.

By the time I entered medical school (University of Queensland, Brisbane), my interest in orthopedics and joint prosthesis surgery had become apparent. I used much of my spare time and elective periods shadowing and assisting Simon Journeaux, consultant in orthopedic surgery at the Mater Hospital, during hip and knee prosthesis surgery. I thank Simon for being my mentor and advocating an interest towards medical research during medical school.

After medical school, I wanted to begin my training towards becoming an orthopedic surgeon. Therefore, I was fortunate to acquire a residency position at Lillehammer Hospital. During residency I met Eirik Aunan, an immensely skilled orthopedic surgeon, who introduced me to prosthesis surgery as a junior surgeon in training. Eirik taught me in particular about different aspects within knee prosthesis surgery and we collaborated on my first research project within the field of orthopedics involving non-operative treatment of proximal humerus fractures. Later, I continued my orthopedic training at Drammen Hospital. From my time in Drammen, I would like to give special notice and thanks to Lukas Månsson and Bjørn Bragenes for helping me hone my skills in hip and knee prosthesis surgery respectively. Both Lukas and Bjørn have shared openhandedly their knowledge and experience for which I am very grateful.

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I would also like to thank my colleagues and especially Kari Indrekvam at the Coastal Hospital at Hagevik, and my current colleagues at Vestfold Hospital Trust in Tønsberg and Larvik, in particular Siri Vedeld Hammer who has been an important proponent towards this thesis completion.

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20th of June, 2021
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2. Abbreviations

AP	Anteroposterior
BMD	Bone mineral density
CI	Confidence interval
CIRRO	Center of Implant and Radiostereometric Research in Oslo
CoC	Ceramic-on-ceramic
CoP	Ceramic-on-polyethylene
CONSORT	Consolidated Standards of Reporting Trials
DAG	Directed acyclic graph
DEXA	Dual-Energy X-ray Absorptiometry
DM	Dual-mobility
DRG	Diagnosis related group
EQ-5D	EuroQol-5 Dimension
HHS	Harris Hip Score
HOOS	Hip Disability and Osteoarthritis Outcome Score
HXLPE	Highly cross-linked polyethylene
IRSA	International Radiostereometry Society
KM	Kaplan-Meier
MDR	Medical device regulation
ModXLPE	Moderately cross-linked polyethylene
MoM	Metal-on-metal
MoP	Metal-on-polyethylene
MW	Molecular weight
NAR	Norwegian Arthroplasty Register
NARA	Nordic Arthroplasty Register Association
NOF	Norwegian Orthopedic Society
NSAIDS	Non-steroidal anti-inflammatory drugs
NSHKS	Norwegian Society of Hip and Knee Surgery
OA	Osteoarthritis
OHS	Oxford Hip Score
PCR	Polymer chain reaction
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PROMs	Patient related outcome measures
QALY	Quality Adjusted Life Years
RCT	Randomized controlled trial
REC	Regional Committees of Medical and Health Research Ethics
RECORD	Reporting of studies conducted using observational routinely-collected health data
R-RCT	Register-based randomized controlled trials
ROI	Region of interest
RSA	Radiostereometric analysis
STROBE	Strengthening the reporting of observational studies in epidemiology
THA	Total hip arthroplasty
UCLA	University of California Los Angeles
UHMWPE	Ultra-high molecular weight polyethylene
VAS	Visual analogue scale
VEPE	Vitamin E highly cross-linked polyethylene
XLPE	Cross-linked polyethylene

3. Preview of thesis

Thesis at a glance (abstract)

Total hip arthroplasty (THA) is one of the most successful treatments offered within the field of orthopedic surgery. There is considerable patient satisfaction, pain reduction and increased activity level for patients with end stage primary osteoarthritis treated with THA resulting in improved quality of life. Nevertheless, as with all types of surgical interventions, patients with THA are at risk of complications. Complications may be prosthesis component loosening, polyethylene wear and hip prosthesis dislocations. These complications often result in revision surgery, which may be devastating for the individual patient and culminates in a significant socioeconomic burden.

Primarily, our research group set out to evaluate Vitamin E infused polyethylene in THA. The primary aim was to assess whether this type of polyethylene improved wear resistance and thereby contributing to overall improved prosthesis longevity. Advancements in polyethylene wear characteristics could also potentially allow for larger femoral head size diameters without increasing wear. Hip prosthesis stability is enhanced by using larger femoral head size, which again reduces the risk of hip prosthesis dislocation. Our secondary aim was to consider factors that were associated with hip prosthesis dislocation in the Norwegian population in recent time, and how the influence of these factors varies during different time-periods.

We have in two clinical trials demonstrated that Vitamin E infused polyethylene in THA exhibits low polyethylene wear at mid-term follow-up (5- and 6-years), and less wear compared to a more commonly used polyethylene employed throughout Norway today. Also, increasing femoral head size diameters from 32mm to 36mm did not result in higher polyethylene wear rates using ceramic femoral heads on Vitamin E infused polyethylene. Importantly, there was no demonstratable adverse effects at mid-term follow-up regarding both uncemented and cemented acetabular cup components with this type of Vitamin E infused polyethylene. Also, we demonstrated that cemented acetabular cup components with Vitamin E infused polyethylene were stable at mid-term follow-up. Lastly, we showed in a register study that there was an increased risk of revision surgery due to hip prosthesis dislocation in modern THA in Norway when using 28mm femoral head size, posterior approach, and uncemented fixation. In addition, there was an increased risk of revision due to dislocation for patients with duration of

surgery >90 minutes, male gender, and prior operations. There was also an increased risk for revision due to dislocation in patients operated in the last time-period (2015-2019) compared to 2010-2014.

The clinical impact of our work is that Vitamin E infused polyethylene used both in uncemented and cemented acetabular cups show promising polyethylene wear characteristics, cup stability, and no observable detrimental effects mid-term at 5-6 years follow-up. Also, orthopedic surgeons can with good conscience increase femoral head size diameters from 32mm to 36mm, when using this particular articulation, in situations where additional stability is warranted, and the acetabular cup can accommodate for a larger head size. Results from the register study can guide medical practitioners when evaluating patients for THA. Study findings support the use of larger head sizes to prevent dislocations. Also, the shift from lateral to posterior approach is a plausible explanation for the increased risk due to dislocation observed in the last time-period.

Norwegian translation (sammenfatning)

Hofteprotesekirurgi er en av de mest fordelaktige behandlingsmetodene innen ortopedi. Det er stor grad av pasientfornøydhet, smerte reduksjon, og økt aktivitetsnivå for pasienter behandlet med hofteprotesekirurgi på bakgrunn av langtkommen slitasjegikt. Dette resulterer i økt livskvalitet for disse pasientene. Allikevel oppstår det i enkelte tilfeller komplikasjoner. Som kjent kan komplikasjoner forekomme ved alle former for kirurgisk behandling. Ved hofteprotesekirurgi kan komplikasjoner være løsning av protesekomponenter, polyethyleneslitasje og hofteprotesedislokasjon (proteseleddet går ut av ledd eller posisjon). Disse komplikasjonene kan ofte resultere i hofteprotese revisjonskirurgi, noe som kan være ødeleggende for resultatet til pasienten og medfører også stor sosioøkonomisk byrde.

Forskningsgruppen vår hadde i dette prosjektet som hovedhensikt å evaluere E vitamin infundert polyethylene i sammenheng med hofteprotesekirurgi. Primærmålet var å vurdere hvorvidt denne typen polyethylene forbedret slitasje egenskapene til hofteproteser og dermed bidra inn mot å øke den totale overlevelsen (holdbarheten) til hofteproteser. Det å forbedre polyethylenet's slitasje egenskaper ville også gjøre det mulig å bruke større hodestørrelser på lårbenskomponenten uten å øke polyethylene slitasje i betydelig grad. Ved å bruke større hodestørrelser økes stabiliteten i hofteproteseleddet, og dette bidrar til å redusere risiko for dislokasjon. Sekundærmålet i prosjektet var å se på faktorer assosiert med hofteprotese dislokasjon i den norske befolkning de senere årene (2005-2019), og analysere hvordan disse faktorene påvirkes gjennom forskjellige tidsperioder.

Oppsummert har vi i dette prosjektet og i to kliniske studier demonstrert at bruken av E vitamin infundert polyethylene i hofteprotesekirurgi er assosiert med lave slitasje verdier ved 5- og 6-års oppfølging. I tillegg viste det seg at E vitamin infundert polyethylene har lavere slitasjehastighet enn annen konvensjonell polyethylene som brukes i Norge idag. Vi har også demonstrert at det å øke hodestørrelsene (keramiske hoder) i hofteproteser fra 32mm til 36mm ikke resulterte i økt polyethylene slitasje. Det er også viktig å bemerke at det ikke ble påvist noen uheldige bivirkninger ved 5- og 6-års oppfølging ved hverken den sementerte eller usementerte hofteprotesekoppen med den typen E vitamin polyethylene som vi testet i to kliniske studier. I tillegg ble det vist at sementerte kopper med E vitamin polyethylene er stabile ved 5-års oppfølging. Til slutt ble det i en registerstudie demonstrert økt risiko for hofteprotese revisjon på bakgrunn av hofteprotese dislokasjon i Norge ved å bruke 28mm hodestørrelse, bakre tilgang til hofteleddet, og ved bruk av usementert fiksering av hofteprotesen. I tillegg var

det økt risiko for revisjon grunnet dislokasjon for pasienter med operasjonstid >90 minutter, mannlig kjønn, og ved gjennomgått tidligere hofteoperasjoner. Det var også økt risiko for revisjon grunnet dislokasjon for pasienter operert i den siste tidsperioden (2015-2019) sammenlignede med 2010-2014.

De kliniske implikasjonene av dette arbeidet er at E vitamin infundert polyethylene brukt både i sammenheng med sementerte og usementerte hofteprotesekopper viser lovende polyethylene slitasje egenskaper, koppstabilitet over tid, og til nå ingen åpenbare negative bivirkninger ved henholdsvis 5- og 6-års oppfølging. Ortopediske kirurger kan med god samvittighet øke hodestørrelse fra 32mm til 36mm ved å bruke denne typen E vitamin infundert polyethylene sammen med keramikk hoder i situasjoner hvor man ønsker økt stabilitet, og hvor hofteprotesekoppen tillater større hodediameter. Resultater fra denne registerstudien kan bidra inn mot kliniske vurderinger vedrørende pasienter som er kandidater for hofteprotesekirurgi. Registerstudien understøtter det å bruke større hodestørrelser for å redusere risiko for hofteprotese dislokasjon. I tillegg viser det seg at endringen fra lateral til bakre tilgang til hofteleddet er en plausibel forklaring på at det er observert økt risiko for revisjon grunnet dislokasjon i siste tidsperiode i registerstudien.

4. Included papers in thesis (I-III)

I) Vitamin E polyethylene (VEPE) in 32mm vs. 36mm uncemented THA – RCT

Lindalen E, Thoen PS, Nordsletten L, Høvik Ø, Röhrl SM. **Low wear rate at 6-year follow-up of vitamin E-infused cross-linked polyethylene: a randomised trial using 32- and 36-mm heads.**
Hip Int. 2019 Jul;29(4):355-362. doi: 10.1177/1120700018798790. Epub 2018 Sep 19. PMID: 30227721 Clinical Trial. (1)

II) VEPE vs. Moderately cross-linked polyethylene in reverse hybrid THA – RCT

Thoen PS, Nordsletten L, Pripp AH, Röhrl SM. **Results of a randomized controlled trial with five-year radiostereometric analysis results of vitamin E-infused highly crosslinked versus moderately crosslinked polyethylene in reverse total hip arthroplasty.**
Bone Joint J. 2020 Dec;102-B(12):1646-1653. doi: 10.1302/0301-620X.102B12.BJJ-2020-0721.R1. PMID: 33249906 Clinical Trial. (2)

III) Factors associated with revision for dislocation after primary THA – Registry study

Thoen PS, Lygre SHL, Nordsletten L, Furnes O, Stigum H, Hallan G, Röhrl SM. **Factors associated with revision due to dislocation within 1 year after primary total hip arthroplasty – a study from the Norwegian Arthroplasty Register.**
Submission in progress (ACTA Orthopaedica). (3)

5. Introduction

Total hip arthroplasty (THA)

Total hip arthroplasty (THA) is the complete replacement of a hip joint with artificial materials through a surgical procedure. The hip joint consists of many joint structures including articular cartilage, labrum, capsule, ligaments and tendons to muscles (Figure 1). There are many indications for THA and the most common being primary osteoarthritis (OA). Secondary OA may arise from joint trauma or for example rheumatological joint disease such rheumatoid arthritis or psoriatic arthritis.

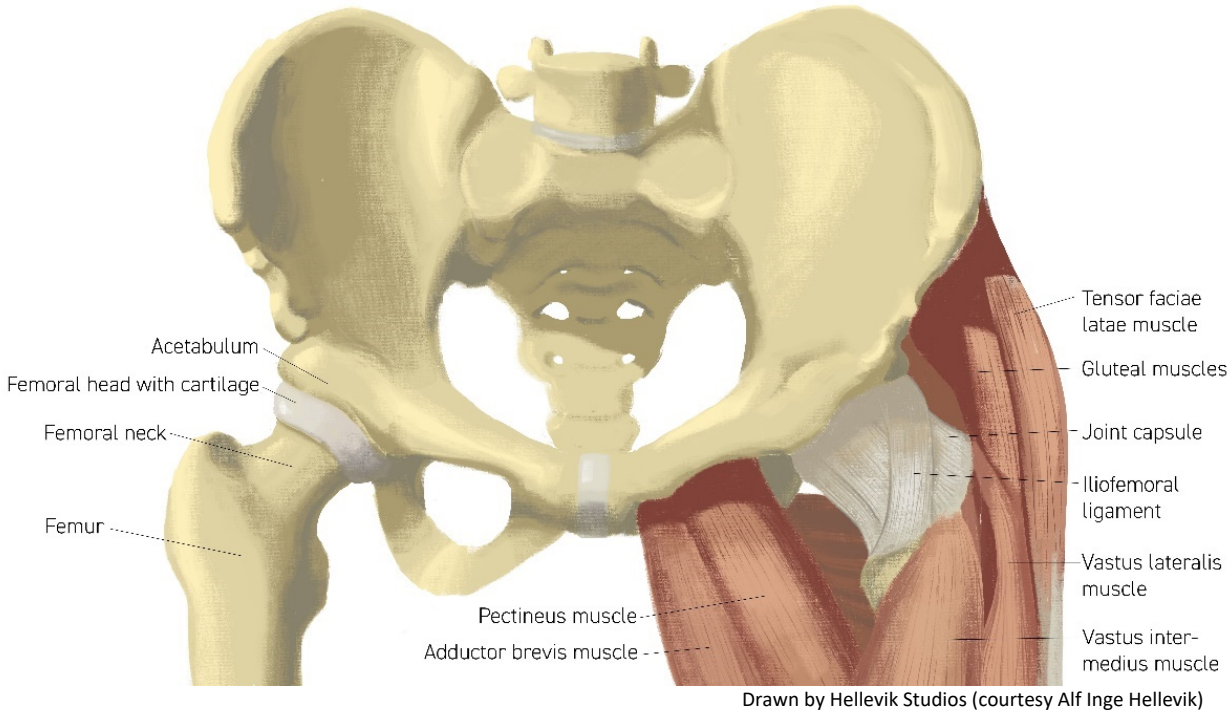
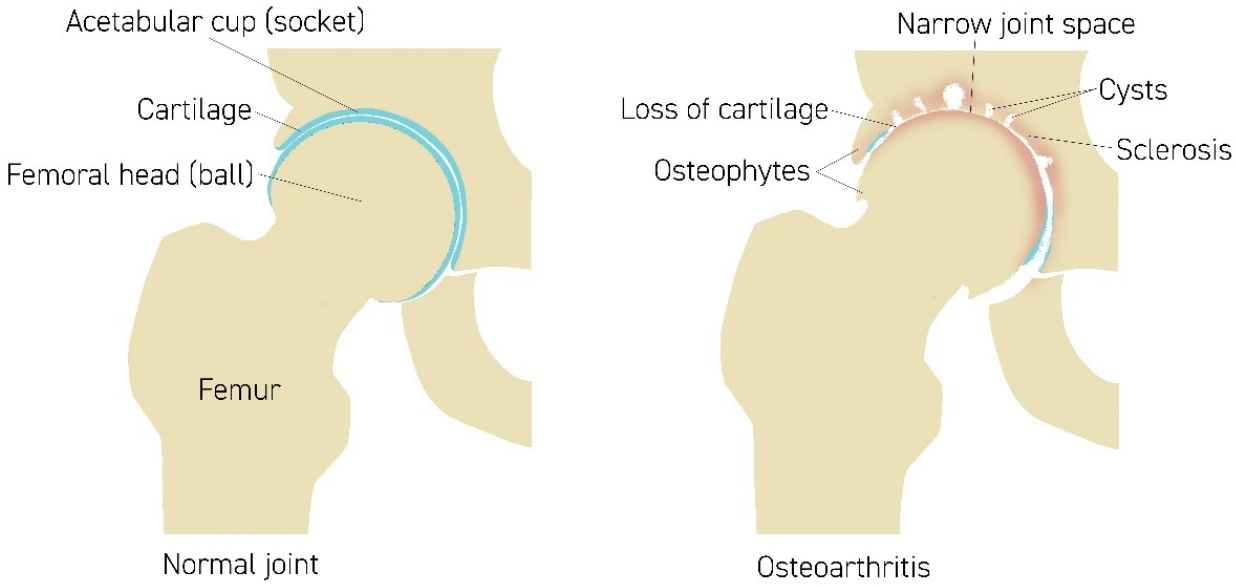


Figure 1 Anatomy. Representation of the hip joint with associated structures.

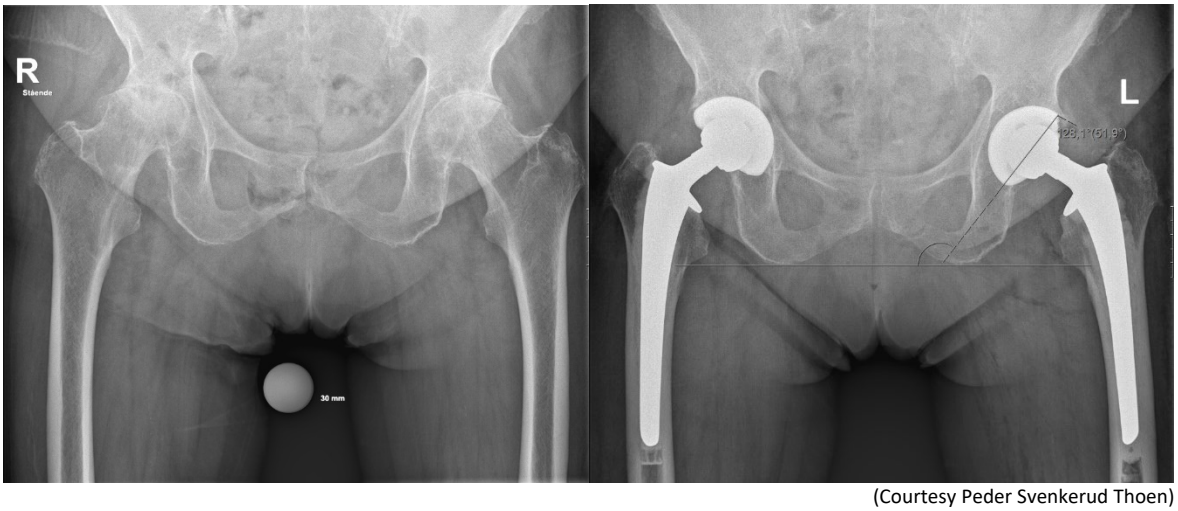
Primary OA is a degenerative process that may affect all synovial joints in the body. It involves the degeneration of all joint structures (Figure 2). In the hip, primary OA results in joint space narrowing (thinning of articular cartilage), osteophyte formation, subchondral cysts and labrum degeneration/tears. Primary OA has a multifactorial pathogenesis (4-6) and patients may suffer immensely with pain and reduced function with diminished quality of life culminating in less quality-adjusted-life-years (QALY) (7).



Drawn by Hellevik Studios (courtesy Alf Inge Hellevik)

Figure 2 Primary osteoarthritis (OA). Representation of a normal and affected osteoarthritic hip joint.

Patients with end stage primary OA of the hip may be offered THA in collaboration with their orthopedic surgeon and based on a complete evaluation involving a thorough history, examination, radiological imaging and full disclosure of risk factors associated with the surgical procedure (Figure 3). All patients should have been treated initially with non-operative measures (i.e. physiotherapy, non-steroidal anti-inflammatory drugs (NSAIDS), weight loss) before going forward with surgery (8, 9).



(Courtesy Peder Svenkerud Thoen)

Figure 3 X-ray. Representation of bilaterally affected primary osteoarthritis (OA) joints before surgery, and post-operatively after bilateral hybrid THA.

THA has been referred to as the operation of the century (10) and is an effective intervention for improving life quality (11). THA is also among the most cost-effective measures in medicine, ranking high among medical treatments in terms of low-cost per quality-adjusted-life-years (12). In the Johnston County Osteoarthritis Project symptomatic hip OA in African Americans and Caucasians was reported to affect 9.7% of the studied population (13). In 2019, there were in total 9879 primary THA performed in Norway (14).

Hip prosthesis history

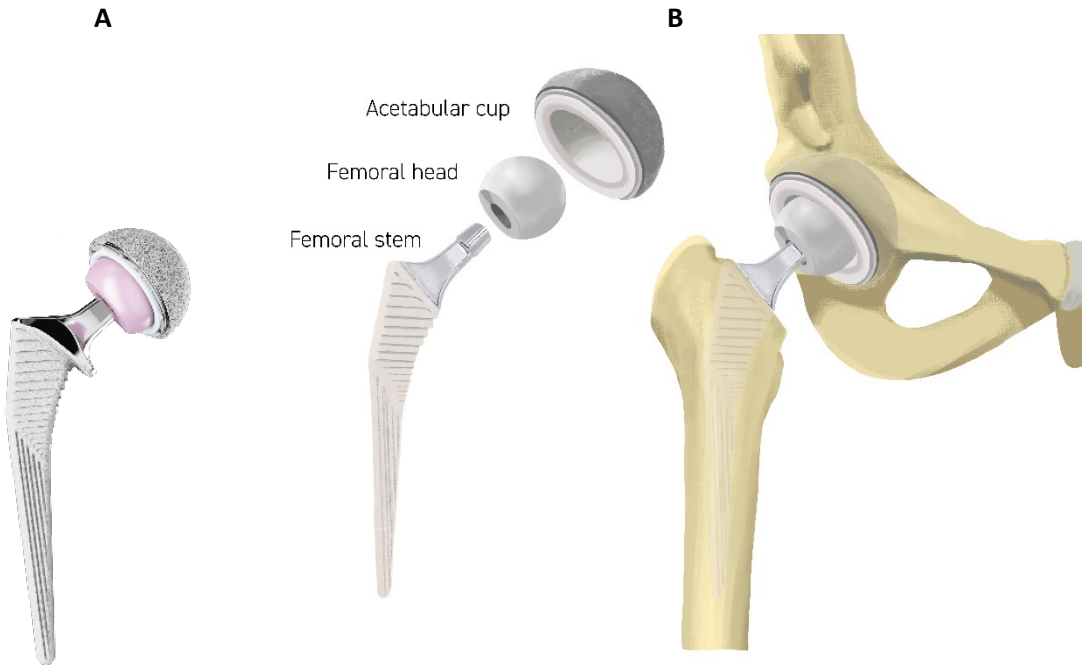
The earliest attempt of joint replacement surgery was in 1890 by a German named Themistocles Gluck who used ivory bone first to operate a total knee replacement and then later the same year other joints including the hip joint (15, 16). In 1940, the American surgeon Austin T. Moore performed the first metallic hip replacement. He was instrumental in the development of the Austin-Moore prosthesis which was introduced in 1952 (17).

The father of modern hip joint replacement surgery is considered to be Sir John Charnley (10). In 1962, Charnley introduced what we still today consider the gold standard bearing surface combination for THA – a femoral stem with a head articulating against polyethylene, which is a special type of plastic composite able to withstand pressure and friction (18).

These early hip prosthesis versions are also precursors to current hemiarthroplasty options, which involve implantation of only a femoral component. Today, these types of hip prosthesis are mainly used exclusively in hip fracture treatment and therefore will not be addressed further in this thesis.

Components

The hip joint is a ball and socket joint. Therefore, the artificial hip prosthesis is constructed to mimic a ball and socket and consists of a stem topped with a ball articulating with a socket. THA consists of primarily three components: 1) femoral stem, 2) femoral head and 3) acetabular cup (Figure 4). There are numerous variations within this theme, but all involve these three components in one way or another. In addition, there are different materials used for all components including the prosthesis joint articulations.



Courtesy Ortomedic

Drawn by Hellevik Studios (courtesy Alf Inge Hellevik)

Figure 4 Hip prosthesis. THA consists of three main components including femoral stem, femoral head and acetabular cup. Figure 4A is an actual uncemented hip prosthesis with uncemented acetabular cup with a polyethylene liner, ceramic femoral head (purple), and uncemented femoral stem. Figure 4B is a schematic representation of an implanted uncemented hip prosthesis.

1) Femoral stem: There are several femoral stem shapes and forms (i.e. long, short) which are constructed from different types of metal alloys. Also, fixation of these stems varies and may involve cemented or uncemented fixation (with or without hydroxyapatite coating) (Figure 5). In addition, there exists resurfacing options where only part of the femoral head is removed, and a small peg is introduced into the remaining bone.

Photo by Ine Eriksen, UiO

Figure 5 Femoral stem. An example of a uncemented femoral stem with hydroxyapatite coating (white) along the stem.

2) Femoral head: Femoral heads consist of different types of materials (metal, ceramic, zirconium) and head sizes (i.e. 22mm, 26mm, 28mm, 32mm, 36mm, 40mm) (Figure 6).

Photo by Ine Eriksen, UiO

36mm 32mm 28mm

Figure 6 Femoral heads. Three examples of different femoral heads. 36mm ceramic head (purple), 32mm and 28mm metal (cobalt-chrome) heads.

3) Acetabular cup: As with the femoral stems there exists many different kinds of acetabular cup constructs and they may be fixated with cement or without cement – uncemented. Cemented options may consist of polyethylene entirely or with a metal back (i.e. cemented dual-mobility cups). Uncemented options are made up of a metal alloy and are lodged into the acetabular socket with or without additional screws and can also be hydroxyapatite coated. Acetabular components consisting of metal have a polyethylene liner inside of them unless they are coupled with a ceramic liner or a metal-on-metal (MoM) resurfacing prosthesis. When ceramic liners are used, they are couplet with a ceramic femoral head.

Photo by Ine Eriksen, UiO

Figure 7 Acetabular cups. There are many different kinds of acetabular cups. Among these are uncemented cups (left), dual-mobility cups (middle), and cemented cups (right).

Prosthesis fixation

Prosthesis components can be fixated to bone using cement or without cement (uncemented). Both options are used for femoral stems and acetabular cups today. Components that are used with cement are constructed differently than those that are uncemented. Many factors influence the decision whether to use cemented or uncemented components, including patient and surgeon aspects, in addition to hospital or country traditions (19-21).

Cemented components

The cement used in THA today is acrylic based and in Norway contains antibiotics (14). It can be used for fixation of both femoral and acetabular components. It is vital to obtain a well-integrated prosthesis and the bone-cement interface is important for prosthesis longevity. Different cementing techniques exist and also varies depending on whether a femoral stem, acetabular cup or both are going to be implanted.

Uncemented components

There are both uncemented femoral stems and uncemented acetabular cups. The main concept is for these components to be lodged and fitted to the surrounding bone structures. In addition, these components can be coated with hydroxyapatite which is a substance that promotes bony ingrowth into and around the prosthesis (22). Also, there exists different methods to coat the surfaces with different 3D architecture that also promotes bone ingrowth. Uncemented acetabular cups can also be fixated with screws for additional primary stability.

Fixation combinations - uncemented vs. cemented vs. reverse hybrid vs. hybrid

Different fixation combinations of femoral stems and acetabular cups can be coupled together. These include both cemented and uncemented options. The four fixation combinations of THA are:

1) both components are uncemented **(uncemented THA)**
2) both components are cemented **(cemented THA)**
3) cemented stem with uncemented cup **(hybrid THA)**
4) uncemented stem with cemented cup **(reverse hybrid THA)**

There does not exist any optimal mode of prosthesis fixation. However, registry studies have shown that certain combinations are suited better for certain patient groups than others. A factor

that is often addressed is age. Age is correlated with bone stock and activity-level and is likely to influence outcome when evaluating prosthesis fixation. In a Norwegian registry study by Dale et al. from 2020, different modes of fixation were stratified based on age and sex. They concluded that women over the age of 55 years should likely not have uncemented femoral stems when considering overall survival of the prosthesis (21).

Modularity

Modularity allows for the exchange of prosthesis components and permits fitting different sizes without having to change the entire implant. This has led to a wide range of head sizes and a variety of different modularity options including different femoral prothesis neck alternatives. On the acetabular side modularity allows for interchange of cup liners including exchange between polyethylene, ceramic and dual-mobility articulations.

Dual-mobility (DM). Dual-mobility (DM) cups have an extra modularity component (Figure 8). They may be used in both primary cases and situations where greater prosthesis joint stability is warranted or during revision surgery. DM cups may be cemented or uncemented. During 2015-2019 there were only 1356 DM cups used in primary THA in Norway (3). In Denmark, the proportion of primary THAs that are operated with DM is much larger (23).

Photo by Ine Eriksen, UiO

Figure 8 Dual-mobility (DM) cup. Depiction of a dual-mobility construct with 3 components. Metal acetabular cup (in this case designed for cement fixation), polyethylene component, and metal femoral head (in case 28mm in size) lodged in the polyethylene component. There is mobility between femoral head and polyethylene component in addition to mobility between polyethylene and metal acetabular cup component (dual-mobility).

Fretting corrosion. Fretting corrosion is induced damage that occurs during load and repeated motion between two metal surfaces (22, 24, 25). It may arise when a separate femoral head is placed on a femoral cone. This is also an issue for femoral prosthesis were version and lengths can be changed with different neck options (26-28). Also, metal fretting between uncemented acetabular cups and additional screw fixation may develop over time.

Articulation

The articulation of THA consists of the bearing surface of the internal lining of the acetabular cup and the external spherical bearing surface of the femoral head (Figure 9). There exist many different bearing surface materials including polyethylene, ceramic and metal alloys. These can make up different bearing surface combinations including metal-on-polyethylene (MoP), ceramic-on-polyethylene (CoP), ceramic-on-ceramic (CoC) and metal-on-metal (MoM).

Photo by Ine Eriksen, UiO

Figure 9 Hip prosthesis articulation. This is a representation of an uncemented acetabular cup (grey) with a polyethylene liner (white) which is articulating with a metal femoral head (metallic). In this case (representing a uncemented THA articulation), the polyethylene liner is fixed in the acetabular cup. This is different than with dual-mobility articulations where the polyethylene articulates both within the acetabular cup and the femoral head.

Polyethylene. Polyethylene is a special type of plastic (synthetic organic polymer) consisting of hydrocarbon chains made up of ethylene monomers (Figure 10). Polyethylenes can be categorized based on their molecular weight (MW). Ultra-high molecular weight polyethylene (UHMWPE) is a particular polyethylene that has been used for industrial purposes (automotive, bottling, and shipping sectors) since the 1950's and as a bearing material for artificial joints since the 1960's (18). Before UHMWPE was introduced in orthopedics, there was in particular one material that John Charnley experimented with named polytetrafluoroethylene (PTFE), which is a different synthetic polymer containing fluorine atoms (22). UHMWPE is known for its high molecular weight which is responsible for unique characteristics such as its chemical inertness in addition to being abrasion and impact resistant (18).

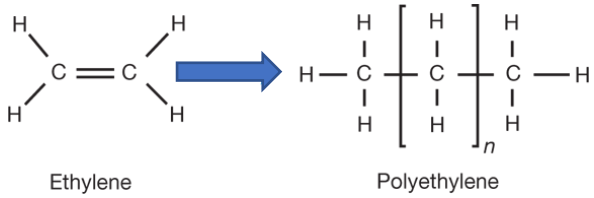


Figure 10 Hydrocarbon chain. Molecular representation of ethylene (monomer) and polyethylene (polymer).

There are three principal steps in manufacturing UHMWPE; 1) polymerization of ethylene gas into resin powder, 2) resin powder needs to be consolidated into a sheet or rod, 3) sheet or rod is machined to form acetabular component. Some components are consolidated directly without going through a separate machine phase, which is called direct compression molding (18).

Once the acetabular component has been formed there are several processes that influence the characteristics of the implant. These include degree of cross-linking by gamma irradiation, temperature cycles to reduce free radicals (i.e. annealing, both number of cycles and heating temperatures), mode of sterilization (i.e. gamma irradiation, ethylene oxide, plasma), and lastly packaging and shelf-life.

Cross-linking occurs when the polyethylene is gamma irradiated. Annealing is the process by which free radicals that are formed during the gamma irradiation are removed. Depending on the particular annealing process, including the specific heating temperatures and number of

cycles, free radicals are removed to varying extent. Not all free radicals are removed through the annealing process.

The beginning of the 21st century has seen the arrival of Vitamin E infused highly cross-linked polyethylene (VEPE), which has the potential to further improve the wear properties of other UHMWPE used in THA (Figure 11). During the high-energy gamma irradiation process cross-linking of the polyethylene occurs and free radicals are formed (29). One type of UHMWPE that has been cross-linked by this process is highly cross-linked polyethylene (HXLPE). The free radicals formed during the gamma irradiation process may react with oxygen in vivo which has caused concern regarding the mechanical properties of the polyethylene long-term (30). Re-melting and annealing the polyethylene after the cross-linking process aids in removing free radicals. However, after annealing there may still be free radicals capable of causing oxidative stress. Re-melting the polyethylene may change its mechanical properties. Vitamin E is an antioxidant and therefore a scavenger of free radicals. The infusion of Vitamin E into HXLPE following the gamma irradiation process, allows Vitamin E to exert its effects as an antioxidant. This may protect the polyethylene against oxidative degradation without compromising its mechanical properties over time (31, 32).

There are two ways of introducing Vitamin E into polyethylene during the manufacturing process – blending or infusion. Introducing Vitamin E by blending allows for Vitamin E to be incorporated before molding of the resin, while still in powder form prior to consolidation, and before gamma irradiation and cross-linking. Blending has the potential to reduce the extent of cross-linking since Vitamin E acts as a scavenger of the free radicals formed during the gamma irradiation process. On the other hand, introducing Vitamin E by infusion may not affect the cross-linking process to the same extent since the consolidated molded polyethylene (polyethylene cup or liner) is treated in a tempered solution containing Vitamin E after the gamma irradiation process. Vitamin E solutions are viscous at room temperature with a yellow color (slight amber tinge), which oxidizes and darkens further on exposure to air or light (Figure 11).

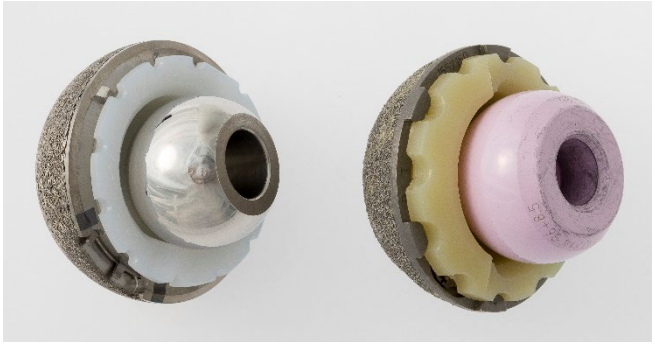


Photo by Ine Eriksen, UiO

Figure 11 Polyethylene liners. In this photo there are two different uncemented cups. One has a HXLPE liner (white) and the other has a VEPE (yellow) liner. The yellow tinge is characteristic for polyethylene which has been infused with Vitamin E. There is also an example of a ceramic (purple) and a metal femoral head.

Ceramic. Ceramic materials are made of sand. They are very dense and hard substances which if remain undamaged may exhibit very little friction. The first application of ceramic materials in hip prosthesis surgery was in 1971 (18, 33). Today ceramic liners that can be inserted into the acetabular cup are available and are used with ceramic femoral heads (Figure 11). Another option is to use a ceramic femoral head with a polyethylene cup (ceramic-on-polyethylene).

Metal. The cobalt-chrome metal alloy is often used as material for femoral heads (Figure 11). Ceramicized metals (metal alloy exposed to an oxidized process yielding a ceramic surface) as femoral heads are also available, such as oxidized zirconium (Oxinium) (18). For the acetabular cup titanium alloys are used. Metal-on-metal prosthesis consists of different types of metals.

Bearing surface combinations. Tribology is the study of how two materials interact and behave towards one another when in contact and motion. It is the science of friction and the consequent resulting wear. Therefore, tribology is central when considering bearing surface combinations. The goal of a bearing surface is that it has as little friction as possible to reduce wear and wear particle formation. There are four bearing surface combinations in THA:

1) Metal-on-polyethylene, MoP (polyethylene on acetabular side with metal femoral head)
2) Ceramic-on-polyethylene, CoP (polyethylene on acetabulum with ceramic femoral head)
3) Ceramic-on-ceramic, CoC (ceramic on acetabular side with ceramic femoral head)
4) Metal-on-metal, MoM (metal on acetabular side with a metal femoral head)

A registry study from New Zealand found that CoP was the superior bearing surface combination option (34). In contrary, a study by the Nordic Arthroplasty Register Association (NARA) from 2020 found no difference or lower risk of revision with MoP compared to CoP (not published, Bronze Abstract Award, EFORT Conference 2020).

Biomechanics (head size/stability/dislocations)

By increasing femoral head size diameter, one achieves additional hip prosthesis joint stability which may result in lower rates of hip prosthesis dislocations. Improved wear properties of Vitamin E infused HXLPE (VEPE) may allow for using larger head size diameters in THA, which are known to provide better range of motion and have lower incidence of dislocation (22). Head size can also influence wear of the polyethylene and mechanical stability of the prosthetic hip joint, and it has previously been shown that using low or non cross-linked polyethylene and increasing the head size leads to increased wear rates and higher revision rates (35). Given the stronger mechanical properties of HXLPE and potentially even better characteristics with VEPE, surgeons may be able to use larger heads in THA, and thereby reduce the dislocation rate, without increasing the revision rate due to wear, but evidence is lacking. Therefore, the optimal head size in regards to both polyethylene wear rate and mechanical stability of hip prosthesis joint still needs further elucidation.

Complications and revision surgery

As with any surgical procedure, THA is associated with complications (36-39). Even though complications occur seldomly (40), many are devastating for the patient. These complications may require additional surgical intervention (revision surgery), placing additional burden on the patient and increasing social cost. There are many different types of complications that are associated with THA. The most common are prosthesis loosening, infection, dislocation, polyethylene wear, fracture, and nerve injury (38). According to the Norwegian Arthroplasty Register (NAR) annual report 2020, the 5 most common causes for revision surgery were #1 loose acetabular component, #2 prosthesis joint infection, #3 dislocation, #4 loose femoral component and #5 periprosthetic fracture (14). Of these loosening of prosthesis components (#1 and #4) and dislocation (#3) are causally related to polyethylene wear and other factors associated with articulation, both of which we address in this thesis.

Polyethylene wear. Polyethylene wear is a contributor to hip prosthesis revision surgery (41-44) and may be correlated to loosening of prosthesis components through the development of wear particles and the biological process that is elicited through coping with these particles. Polyethylene wear may be influenced by many factors such as choice of material and activity-level. Low polyethylene wear rates in vivo are documented with HXLPE (45-48).

Prosthesis loosening. There are many reasons why hip prosthesis may loosen after implantation (49). Cemented implants may have suboptimal cement mantel and bone-cement interface. Uncemented implants may not have integrated properly or not be fixated properly initially. Issues related to polyethylene wear are related to the particular type of material used, which can be addressed by optimizing existing working materials.

Dislocations. Many factors are associated with hip prosthesis dislocation and causality is multi-faceted involving aspects related to the patient (age, gender, past medical history), surgical technique (surgical approach, prosthesis component positioning) and prosthesis design (head size, fixation, articulation) (50-55). Also, the biomechanics in relation to hip prosthesis joint stability and dislocation are intricate. It involves jump distance (amount translation of femoral head out of cup required for dislocation) (22), and how large the articulating femoral head is in comparison to other prosthesis components and the soft tissue balance around the implants which is governed by the individual patient. Surgeon related factors such as placement of prosthesis components influence the risk of dislocation as does patient related factors such as comorbidities (i.e. epilepsy, Parkinson disease), activity-level, life-style and trauma. In clinical practice one dislocation may not require revision surgery depending on the cause that triggered the dislocation. However, if there are one or more dislocations patients often discuss with their surgeon whether to undergo hip prosthesis revision surgery.

Knowledge gap

Vitamin E infused HXLPE (VEPE) liners in uncemented acetabular cups or in cemented cups are available for clinical use, however there is sparse mid-term documentation on these types of implants (56-60). Therefore, it is important to further evaluate VEPE and to identify any unwanted side-effects. It is also necessary to determine whether VEPE and its wear particles may cause a different biological response around implants compared to other polyethylenes, and what sort of impact that this may have. Moreover, Vitamin E may influence the long-term mechanical properties and elasticity of HXLPE, and it is important to determine whether VEPE retains the same or better wear resistance as seen in other conventional UHMWPE and HXLPE over time. In addition, it is important to assess the maintenance of adequate bone stock around implants when using VEPE to show that mechanical properties of both stem and cup are retained and that the biological processes are not altered when Vitamin E is added.

Infusing Vitamin E into highly cross-linked polyethylene (HXLPE) is a manufacturing technique that has been developed fairly recently, with the first laboratory related scientific papers on this topic appearing between 1999 and 2002 (18). If this new material is shown to improve wear resistance, larger heads may be a feasible next step towards increasing hip joint stability and reducing revision rates related to wear and instability after THA. Even though short term results are promising, it is vital to document that VEPE has good clinical and radiological long-term outcomes, without showing signs of unwanted side-effects such as osteolysis (61). Also, Vitamin E may reduce the development of osteolysis by inhibiting the bioactivity of polyethylene debris, and potentially surface adhesion of bacteria and thereby hindering biofilm formation (62). However, new implants should be thoroughly investigated and documented before widespread use. This could save many patients from possible disastrous failures as the past has taught us (e.g., Boneloc, Carbon compressed Poly) (63-66). The new Medical Device Regulation (MDR) requires manufacturers to document benefit for patients as well as security and performance for newly introduced implants on the market. Systematic strategies are required to record and analyze data from clinical practice. Existing registries play an important part in evaluating clinical practice and are accessible instruments efficacious in meeting the new standards (67-69).

Today, we have an aging population, many of whom suffer from degenerative disease. In 2019, there were 9879 primary THAs performed in Norway (14). Complications after THA can have

devastating consequences for an individual. Some patients are at a greater risk than others, and especially for these patients it is important to make treatment adjustments to reduce complication rates. Often complications can lead to hip revision surgery, which in itself comes at a great cost both in regard to patient morbidity and also on a socioeconomic level.

According to the Norwegian Arthroplasty Register (NAR) (14) there were 1384 hip prosthesis revision surgeries in 2019. Of these revisions, 730 were due to factors related to wear (such as loosening of components, osteolysis and polyethylene wear), and 279 were due to hip prosthesis dislocations. In the US, 17-23% of revisions were caused by dislocation (70). One study has reported a re-dislocation rate of 39% after a 1st dislocation (71). For patients having their 1st dislocation close to the time of primary THA surgery there has been found a lower risk of re-dislocation and revision surgery (72). Patients who sustain 1 or more dislocations end up with revision surgery in about 50% of the cases (73). Considering current diagnosis-related group (DRG) rates, this amounts to an annual cost of approximately 310 million Norwegian kroner (74). This only takes into account diagnosis related group (DRG) subsidy, and factors such as patient sick leave, employers' loss of workforce, in addition to rehabilitation costs, are also important to consider when estimating the total socioeconomic burden.

Therefore, it is a desirable goal to evaluate prosthesis characteristics that may contribute to complications, and to implement new methods or treatment options in order to minimize them. This thesis is designed to conduct a medium-term evaluation of a recently developed hip prosthesis polyethylene in terms of its wear resistance and mechanical properties, both characteristics known to impact implant survival. In addition, factors that are associated with the risk of revision surgery due to hip prosthesis dislocation will be addressed for THAs operated in Norway the past 15 years. Greater knowledge regarding these associated factors may aid in reducing the number of revision surgeries due to dislocation, and thereby limiting both the individual patient suffering and the societal burden associated with revision surgery.

6. Aims of thesis

The **overarching aim** of this thesis was to further advance THA treatment and knowledge by addressing certain aspects, which still today account for shortcomings and illicit potential for further improvement. These aspects include polyethylene composition, articulation (modularity), and understanding and reducing the influence of factors associated with hip prosthesis dislocation.

The **primary aim** of this thesis was to document results and outcomes of recently implemented Vitamin E infused highly cross-linked polyethylene (VEPE) hip prosthesis components. Evaluating specifically VEPE wear with respect to different head sizes (32mm vs. 36mm), wear in comparison to a conventional polyethylene without Vitamin E (moderately highly cross-linked polyethylene, ModXLPE), and acetabular cup stability. The **secondary aim** was to evaluate factors associated with hip prosthesis dislocation in the Norwegian population in recent time.

We defined the following **three research questions**:

1. What are mid-term polyethylene wear outcomes of uncemented VEPE cups and do they differ with 32mm versus 36mm head sizes?

2. Are there differences mid-term regarding polyethylene wear and cup stability between a cemented VEPE cup versus a cemented ModXLPE cup (without Vitamin E)?

3. Which factors are associated with revision surgery due to hip prosthesis dislocation in Norwegian patients operated with primary THA the past 15 years?

7. Material and methods

The research team involved in this thesis was multidisciplinary including nurses, research coordinators, orthopedic surgeons, physiotherapists, radiographers, radiologists, and statisticians. In order to answer the three research questions, three individual projects were developed culminating in three articles:

Article 1 (6-year RCT uncemented VEPE 32mm vs. 36mm):
Low wear rate at 6-year follow-up of vitamin E-infused cross-linked polyethylene: a randomised trial using 32- and 36-mm heads.(1)
(published July 2019, Hip International)

Article 2 (5-year RCT cemented VEPE vs. ModXLPE cups):
Results of a randomized controlled trial with five-year radiostereometric analysis results of vitamin E-infused highly crosslinked versus moderately crosslinked polyethylene in reverse total hip arthroplasty.(2)
(published December 2020, Bone and Joint Journal, BJJ)

Article 3 (Register study – risk factors associated with revision due to dislocation):
Factors associated with revision due to dislocation within 1 year after primary total hip arthroplasty – a study from the Norwegian Arthroplasty Register.(3)
(submission in progress)

The study design and material & methods used are presented in Table I.

Table I Material and Methods. Description of material and methods included in the three articles.

Table I	Article 1	Article 2	Article 3
Study design	RCT	RCT	Register study
Inclusion period	2009-2010	2011-2013	2005-2019
Follow-up time	6 years	5 years	0-1 year after primary THA
Number of participants (n)	n=64 (66 hips)	n=68	n=111 711
Primary outcome	Polyethylene wear	Polyethylene wear and cup stability	Revision due to dislocation
Prosthesis components	-Uncemented E poly cups -Corail stems -Biolox Delta 32mm or 36mm heads	-Cemented E1 cup or Marathon cup -Corail stems -Articul/EZE 32mm heads	-All THAs with 28, 32, 36mm heads or DM cups
Statistics	T-test Mann-Whitney U test Wilcoxon signed rank test	T-test Mann-Whitney U test	Cox regression analysis (hazard ratios) Kaplan-Meier estimate of survival curves
Eligibility criteria	50-65 years, primary OA, THA	<80 years, primary OA, THA	All primary THA in Norway 2005-2019 with 28, 32, 36mm and DM cups
Exclusion criteria	Systemic inflammatory disease, former surgery, rheumatoid arthritis, dysplasia	Immunosuppressant medication, significant systemic disease, major anatomical abnormalities	22mm (not including those with DM cups), 26mm, 30mm and >36mm heads, MoM

These three articles utilized seven main research designs and methods:

- **Randomized controlled trial, RCT** (Article 1 and 2)
- **Radiostereometric analysis, RSA** (Article 1 and 2)
- **Dual-energy x-ray absorptiometry, DEXA** (Article 1)
- **Conventional radiographs** (Article 1 and 2)
- **Registry studies** (Article 3)
- **Directed acyclic graphs DAGs** (Article 3)
- **Cox regression and Kaplan-Meier estimate of survival** (Article 3)

Randomized controlled trial (RCT)

A randomized controlled trial (RCT) is an experiment where participants are randomly allocated to two or more study groups to test the effect of a treatment (typically a drug or intervention). The aim of the random distribution of participants to the groups is to ensure that the groups are similar regarding patient characteristics. This limits selection bias and allows statistical comparison of treatment effects. Participants in one group are given the intervention (intervention group), participants in the other group or groups are given an alternative treatment or no treatment at all (control group). Because the study groups are similar by design, but receive different treatments, the difference in treatment effect can be attributed to the given treatments. Therefore, the randomized controlled trial design is considered the gold standard for evaluating treatment effect (75) and is traditionally regarded as high-level evidence (76, 77). However, both the design and methodology need to be appropriate to ensure high-level evidence and a trustworthy effect estimate.

The Consolidated Standards of Reporting Trials (CONSORT) Guidelines provide a framework for the design and methodology of RCTs (78, 79). Patient inclusion in a RCT is based on informed consent. RCTs test the effect of interventions and depending on what is tested, sufficient power is required to be able to answer the research question. If the difference in treatment effect is small, a limited number of study participant may not provide evidence for rejecting the null hypothesis, however a larger sample of patients may detect this difference and provide evidence for rejecting the null hypothesis. Power calculation must be performed a priori and provides a sample size estimate. This estimate describes the minimal number of patients necessary to be included in the study in order to be able to detect an effect (based on the desired significance level of the effect and the power of the outcome measure). Adjustments based on clinical knowledge must be made to allow for possible dropouts, cross-over or other factors that are likely to interfere with group sizes.

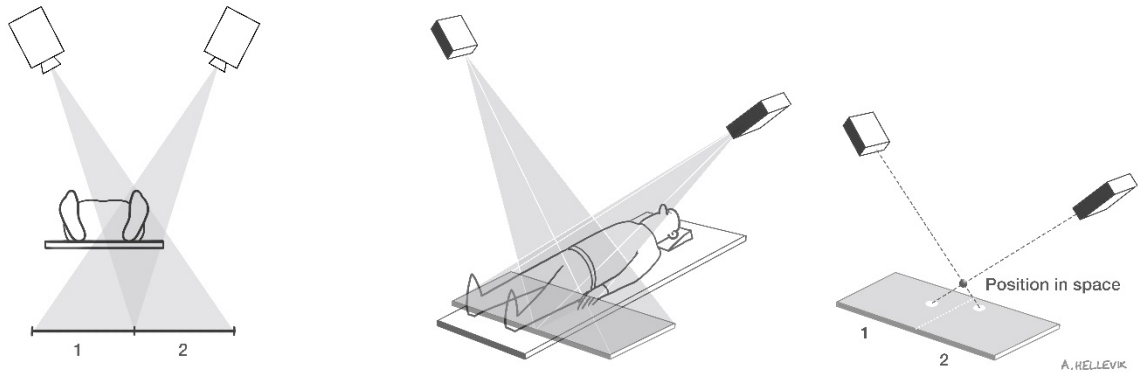
Randomization aims to ensure equal groups which eliminates selection bias and allocation bias. The choice of treatment is randomized rather than being the result of the clinical situation and the patient, which is the case in observation studies. Block randomization provides equal number of patients in each group. Ideally, RCTs should be blinded to reduce experimental bias such as different placebo effect between the groups (80). Blinding is a strategy that prevents those involved in the study from knowing what intervention was given to the participant. Double blinding means that both the patient and the clinician treating/evaluating the patient is

unaware of the allocated treatment. In theory, all groups involved in the study can be blinded: patients, surgeons, radiologists, physiotherapists etc. Blinding may be challenging in studies evaluating surgical treatment because the surgeon must know what treatment is randomized in order to perform the surgery, and in certain instances blinding is not possible for the patient (i.e. hip replacement surgery versus non-operative treatment) (81). Also, in studies using conventional radiographs post-operative images may reveal the treatment the patient received.

Radiostereometric analysis (RSA)

The main method in the first two studies in this thesis is radiostereometric analysis (RSA). RSA is a highly accurate technique used to detect movement and wear of prosthesis components on a micrometer scale using radiography. RSA is a methodology that has been implemented in joint replacement research to foresee how certain implants will behave with regard to migration and wear on a micrometer scale over time. Implant migration measured with RSA has been shown to be predictive of long-term prosthesis survival (82-85). Following patients over short- to mid-term (2-5 years) may be a substitutional outcome measure which requires relatively small number of patients in each treatment arm in RCTs because of the inherent accuracy of RSA as a method (86-88). The method has been extensively used and validated in research environments.

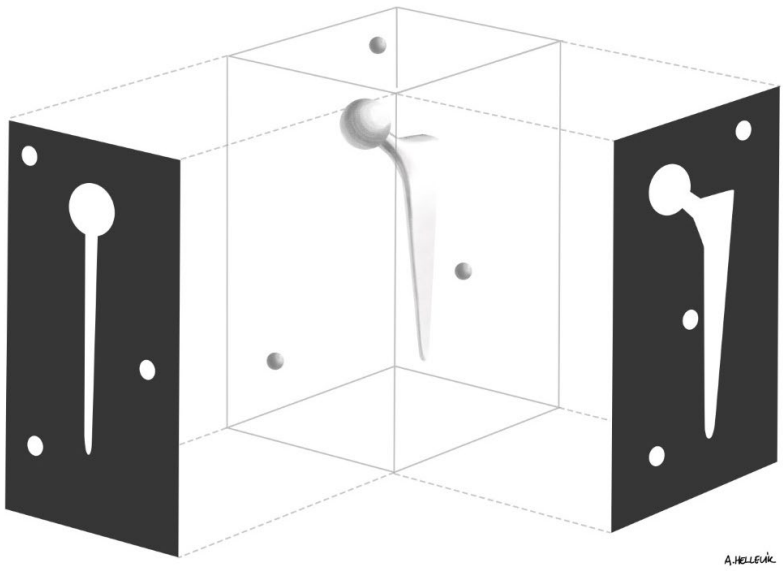
RSA was first introduced in 1974 by Göran Selvik (89-91). The main concept is to measure movement in three dimensions (x, y, and z) of one object in the body in relation to another object. The original principles of RSA are based on defining a certain area or region within the body and evaluating how this defined area moves relative to a given standard. The defined area is based on at least three markers (e.g. tantalum beads), which may be implanted into bone, polyethylene or attached as markers on prosthesis components. A given standard is a cage with tantalum markers attached. The cage has tantalum markers at the bottom (fiducial markers – which define a coordinate system as a standard) and at the top (control markers – used to calculate x-ray exposure geometry such as to standardize x-ray foci and x-ray source distance). The cage needs to be placed directly beneath the patient, while x-rays are emitted from two different sources at exactly the same time in order to obtain a simultaneous biplanar representation of all markers on the two radiograph plates (Figure 12).



Drawn by Hellevik Studios (courtesy Alf Inge Hellevik)

Figure 12 RSA imaging technique. Rendition of how two simultaneous x-rays of the prosthesis are acquired. This is the foundation for the pinpoint accuracy of RSA and it is the framework for the calculations required to estimate movement between segments in question. X-rays travel from the source through the patients before passing through the cage and hitting the two radiograph plates.

By acquiring two simultaneous x-ray images, from two different sources, the three-dimensional (3D) position of a defined area (such as an implant or bony region) can be calculated using computer software and accurately determined (Figure 13). The movement or migration of the defined area can be represented by translation or rotation in the three orthogonal directions (x, y, and z) (92).



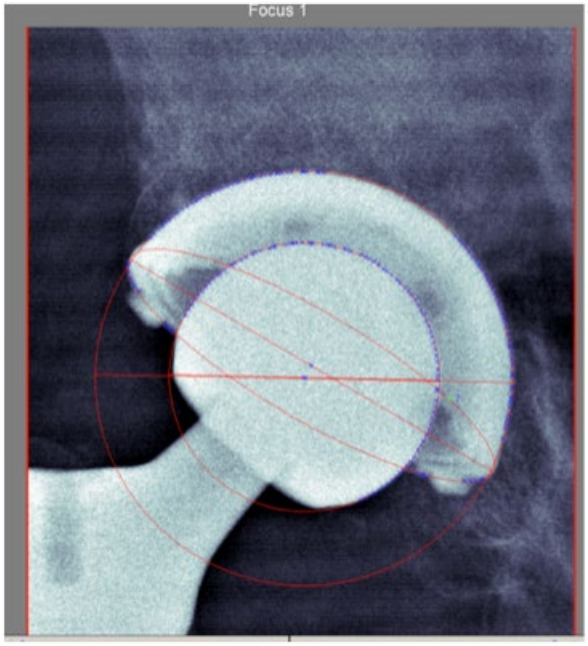
Drawn by Hellevik Studios (courtesy Alf Inge Hellevik)

Figure 13 Three-dimensional (3D) representation. Illustration depicting the 3D position of a prosthesis in relation to two plain radiographs (black squares). The 3D position is calculated based on the information gathered from the two radiographs.

Migration of components measured by RSA has been extensively studied. Acetabular cup migration in the proximal direction (y-axis) has been evaluated in relation to revision rates and it has been established that proximal migration correlates with higher revision rates (82, 84, 85). Proximal cup migration has been solidified as being predictive of acetabular cup loosening.

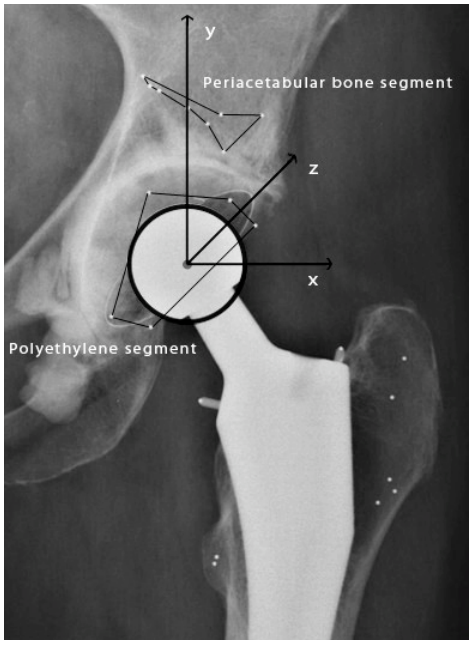
Although significant advancements have been made since the initial introduction of RSA, challenges still remain, as well as opportunities for further advancement. The current state-of-the art RSA techniques can be divided into two main research areas:

1. The first area as mentioned above involves using RSA in detecting early implant migration or loosening and polyethylene wear. This is particularly important in the validation process of new implant designs. The most significant recent advancement has been the development of a model-based RSA technique (markerless RSA) for tracking implants (93, 94). By fitting the contours of the implant to the projected contours of a surface model of the implant, the position and orientation of the implant can be determined (computer-aided drafting, CAD). Alternatively, one can reconstruct the implant using multiple elementary geometrical shapes (EGS). These techniques no longer require the expensive and difficult task of attaching markers to the implant. Model-based RSA shows comparative accuracy and precision to marker-based RSA, apart from rotational precision which is somewhat less and may depend on the shape of the implant (95-98). However, markers in the bone continue to be used to determine the position of the bone and thereby allowing cup stability evaluation in addition to polyethylene wear (99). Both markerless RSA (Article 1) and marker-based RSA (Article 2) was implemented in this thesis.



Courtesy Stephan M. Röhrl (UmRSA Biomedical Program)

Figure 14 Markerless RSA. Surface edge of prosthesis components act as reference points and one can determine change in position between femoral head and acetabular cup as a representation of polyethylene wear.



Courtesy Stephan M. Röhrl (UmRSA Biomedical Program)

Figure 15 Marker-based RSA. Tantalum beads are implanted in acetabulum, polyethylene cemented cup and in femoral bone. In this example markers are also attached to the femoral prosthesis. This allows for determining movement between three segments: acetabulum and cemented cup, cemented cup and femoral head and femoral stem and femur.

2. The second main field where RSA is applicable is within kinematic research. In kinematic studies, the aim is to determine how bones move with respect to each other during dynamic loading conditions using a hybrid RSA and fluoroscopic technique. The dynamic sequence can be used to analyze the motion of the implant and determine instability of the implant components (100, 101).

Even though RSA is the gold standard, computer tomography (CT) based analysis methods have been developed. The CT-based spatial analysis (CTSA) method reconstructs the 3D shape of the prosthesis without markers. An in vitro study by Scheerlinck et al. has shown comparable accuracy and precision with CTSA compared to marker-based RSA (102), resulting in well-founded continued attention towards this method. There has also been some interest towards validating certain conventional radiograph-based software and methods to evaluate head

penetration and polyethylene wear (103, 104). In this thesis we have concentrated on RSA as method to evaluate polyethylene wear and cup stability as this is the gold standard.

Dual-energy x-ray absorptiometry (DEXA)

Hip prosthesis components affect the adjacent bone architecture and bone mineral density (BMD). Dual-energy x-ray absorptiometry (DEXA) is a non-invasive method to investigate bone mineral density and the gold standard for the diagnosis of osteoporosis (22). Using DEXA as a method to measure periprosthetic BMD is an accurate and reproducible procedure (105-107). Changes in BMD that may occur could be as a result of developing osteolysis or stress shielding and loss of mineralization around the prosthesis components (acetabular cups and femoral stems) – adaptive remodeling. The reporting of DEXA results is often using the three regions of interest (ROI) defined by DeLee and Charnley for the acetabular cup (108), and the seven Gruen zones for the femoral component (109).

Conventional radiographs

Conventional radiographs are used in THA to evaluate certain radiographic changes that may occur adjacent to prosthesis components (both acetabular and femoral) over time such as radiolucency, implant migration, and osteolysis. When evaluating femoral components one can in addition evaluate whether calcar atrophy and pedestal formation are present. All these changes are associated with loosening of implants and may give an early prediction of whether the implants become loose and require revision surgery (110-113). Serial radiographs can display radiolucency such as radiolucent lines (RLL), osteolytic lesions, as well as more diffuse changes in bone structure (bone density remodeling).

Prosthesis component placement is also evaluated using conventional radiographs. Femoral stem placement (e.g. stem version, height, offset) and acetabular cup positioning (e.g. anteversion, inclination) are both assessed post-operatively.

Registry studies

Registry studies are observational in nature and utilize large data sets through registries. These are often ongoing national registries, which produce an enormous amount of data over time and may be referred to as big data (114). Many national prosthesis joint registries have been established and data gathered is valuable in monitoring for adverse effects (115, 116). The data are typically gathered prospectively in a population-based setting and thus represent the clinical practice norm at the time. Research questions are often defined retrospectively. The study design is therefore typically retrospective observational based on prospectively collected data. The observational design is not appropriate for evaluating treatment effect of interventions. Selection and allocation bias are likely to influence the effect of treatment. As a result, these studies are not able to determine causality, but rather associations between factors. But they have proven valuable to identify inferior methods and designs (117). Registry studies may be regarded as a reflection of clinical practice with very high external validity to the target population. The external validity however is a result of the completeness and coverage of data collection. Continuous validation is necessary to ensure that completeness and coverage is satisfactory (117). The different qualities of RCTs and register studies may be combined in pragmatic randomized studies within existing registries. These studies are referred to as register-based RCTs (R-RCTs). Two examples of such studies are currently ongoing in Norway; (1) a trial of anterior cruciate ligament injury treatment randomized to either early reconstruction or rehabilitation through the national ACL registry (IMPROVE study), and (2) an inferiority trial between antibiotic loaded bone cement versus plain bone cement in primary total knee arthroplasty (ALBA study) (118).

Directed acyclic graphs (DAGs)

Causal graphs also known as directed acyclic graphs (DAGs) are useful when considering factors or variables associated with a certain outcome (119-122). In epidemiology and specifically register studies there often exists information regarding numerous variables. To mitigate possible confounding effect DAGs may be implemented. These variables may be associated with a given outcome by one of several different paths. In order to get a grasp and overview of how these influence one another it is important to define them in a formalized DAG (123). There are many scientific areas of application for DAG. In the applied sciences, including

medicine, DAGs are used most commonly within epidemiology and specifically observational studies (124, 125).

DAGs are visualized representations of pathways linking causes and effects. They are acyclic which makes them non-cyclical. During the initial planning stages of a register study, it is important to consider causal inference. An important aspect of causal inference is to determine which variables to evaluate and adjust for when implementing regression analysis. First of all, an exposure and outcome are defined and then the different variables influencing these are categorized as for example a confounder, mediator or collider. Confounders should be adjusted for, while mediators (i.e. total effect consideration) and colliders should not be adjusted for. It is important to only adjust for factors that are confounders because these influence both the exposure and outcome. Adjusting for other factors may introduce confounding where it may not have existed prior to adjusting for it.

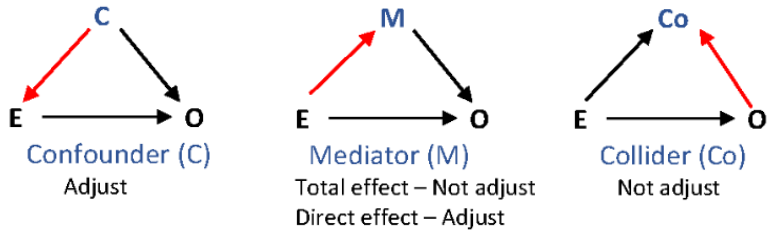
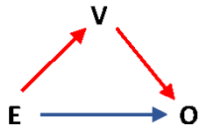


Figure 16 Three DAG examples. The DAGs consist of an exposure (E), outcome (O) and measured/unmeasured variable, which can be a confounder (C), mediator (M), or collider (Co). Depending on how the variable influences the exposure and outcome, one should either adjust for the variable or not adjust for it.

When estimating the extent of influence different variables may exert on a given exposure, diagrams may quickly become undiscernible and difficult to evaluate. Using a program such as DAGitty may be particularly valuable in these instances (126, 127). DAGitty allows for defining an exposure and later changing this exposure without having to draw up an entirely new DAG. Also, it is possible to choose between options where you adjust for the total effect or the direct effect an exposure has on a given outcome.



Total effect = Indirect effect + Direct effect

Figure 17 DAG total effect. Adding the indirect and direct effect results in total effect. The indirect effect is the effect that the exposure (E) has on the outcome (O) through a variable (V).

For each exposure, DAGitty provides a list of variables that should be adjusted for. In the example below, where exposure is defined as head size and revision (due to dislocation) is the outcome, we can see that all variables except duration of surgery should be adjusted for in a regression model. However, if age is set as the exposure only time-periods should be adjusted for, which makes sense because no other variable influences age. On the other hand, if fixation is set as the exposure, all variables should be adjusted for except head size and duration of surgery. This is because in this DAG model, fixation exerts an influence on head size and not the other way around. One could maybe argue that head size influenced fixation, but it is not possible for an arrow to go back and forth since this does not comply with the acyclic nature of a DAG. In the example below (Figure 18), smoking, BMI, and hospital routines are unmeasured factors.

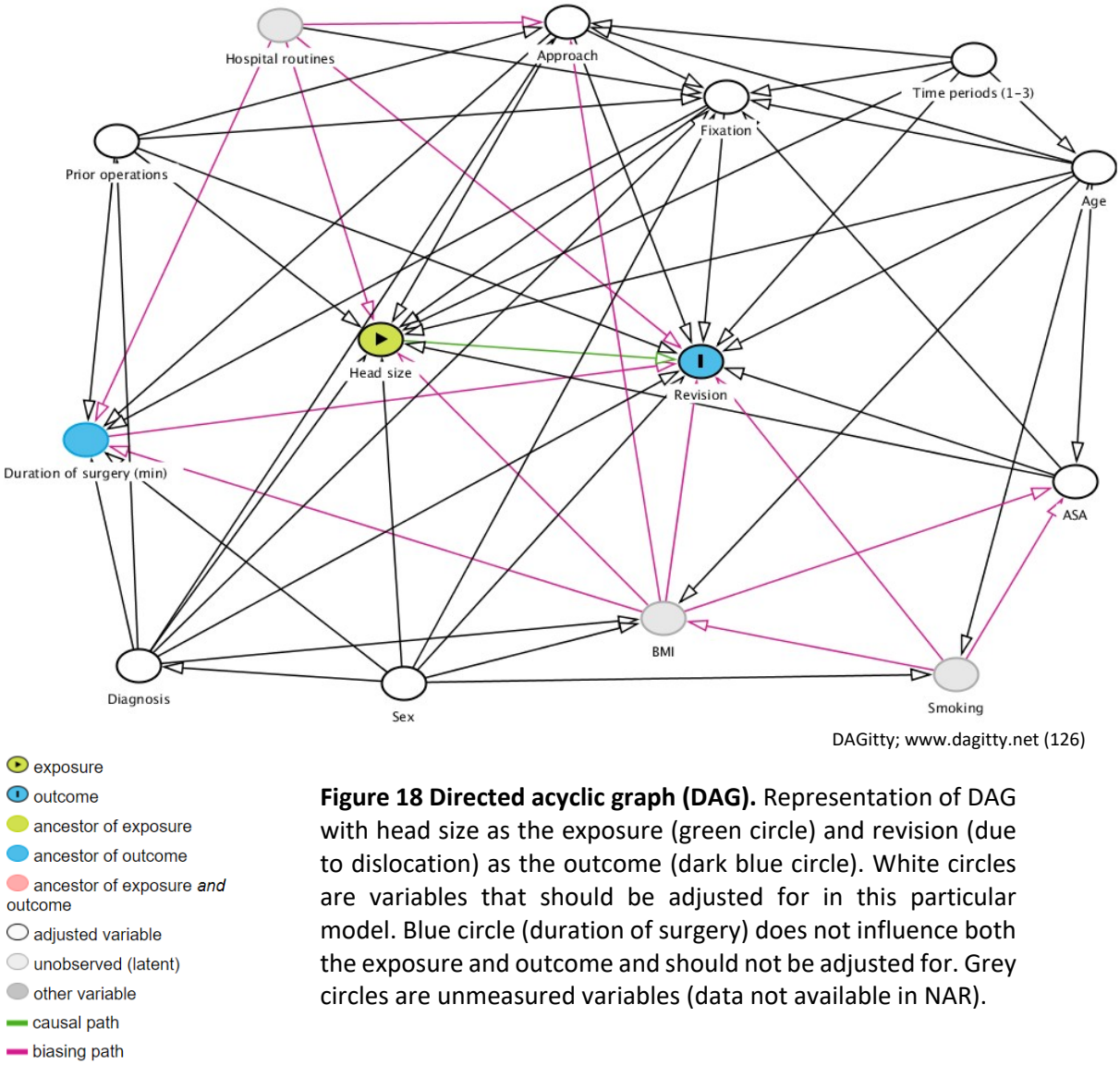


Figure 18 Directed acyclic graph (DAG). Representation of DAG with head size as the exposure (green circle) and revision (due to dislocation) as the outcome (dark blue circle). White circles are variables that should be adjusted for in this particular model. Blue circle (duration of surgery) does not influence both the exposure and outcome and should not be adjusted for. Grey circles are unmeasured variables (data not available in NAR).

Cox regression and Kaplan-Meier estimate of survival

Regression analysis is widely used in registry studies in order to evaluate large data sets. Regression analysis is a statistical method to evaluate associations between dependent and independent factors. Mathematical models are developed, and these may be adjusted according to anticipated confounding effects. One type of regression analysis is Cox regression, which models the association between one or more variables against the hazard rate (128). Cox regression is a survival model that looks at the relationship between the time quantity required for a certain event to occur and different variables that may be associated with that a particular time quantity (128, 129). The Kaplan-Meier estimate of survival is a method to analyze time to event data. In epidemiology and medicine, this method is based on following a patient until a

particular event occurs such as when a particular illness presents itself or until a censoring event (i.e. end of follow-up time or death). The data can be presented in Kaplan-Meier curves, which may be stratified based on different sets of variables and confounding factors may be controlled for as found appropriate (128, 130)

Article 1 (6-year RCT uncemented VEPE 32mm vs. 36mm)

The aim of Article 1 was to measure polyethylene wear in uncemented THA with VEPE and comparing two different head sizes (32mm vs. 36mm) by utilizing RSA as the primary outcome measure at 6 years follow-up. Article 1 was a continuation of a RCT that was initiated in 2009 and 2-year results were published in 2015 (131). Our research team continued to follow these patients and as part of this thesis we published 6-year results in 2019 (1).

Methodology used in Article 1:

Study design: RCT (block randomization)

Primary outcome: Polyethylene wear measured by RSA.

Patient characteristics and setting: 66 hips (64 patients) with primary osteoarthritis without structural abnormality were randomized to receive a uncemented THA containing VEPE with either a 32mm or 36mm ceramic femoral head (Figure 19 and Figure 20). Inclusion period January 2009 - February 2010. Patients were between 50-65 years old. 40 hips (39 patients) were available for RSA at 6-year follow-up (20 hips with 32mm, 20 hips with 36mm).

RSA: Markerless RSA (model-based RSA) was conducted post-operatively, 3 months, 1 year, 2 years and 6 years. For all follow-up times we completed double examinations (precision was defined as 1.96 x standard deviation) (1, 91, 92, 132, 133).

DEXA: Scan was taken post-operatively, 1, 2 and 6 years (134, 135).

Radiological imaging: Anteroposterior (AP) pelvic radiographs and lateral views of the femur were performed at 3 months, 2 years, and 6 years to measure signs of radiolucency around implants.

PROMs: Harris Hip Score (HHS) and Oxford Hip Score (OHS) was registered pre-operatively, at 2 years and 6 years (136, 137). University of California at Los Angeles (UCLA) activity score was used to estimate patient activity level pre-operatively, at 2 years and 6 years (138).

Data analysis: Effect size was calculated using an independent sample t-test. The non-parametric Mann-Whitney U test was used to test for differences between the two groups. To test for changes between different time periods the Wilcoxon signed rank test for related samples was used.

Figure 19 Femoral heads. Patients were randomized to either 32mm or 36mm ceramic femoral heads in Article 1.

Photo by Ine Eriksen, UiO

Figure 20 Vitamin E polyethylene liner. The Vitamin E polyethylene liner is inserted into the uncemented Exceed acetabular cup. A Biolox delta ceramic femoral head is connected to the Corail uncemented femoral stem. This particular set of prosthesis components were used in Article 1.

Article 2 (5-year RCT cemented VEPE vs. ModXLPE cups)

The purpose of Article 2 was to evaluate polyethylene wear and cup stability in reversed hybrid THA in both VEPE and ModXLPE cemented cups using RSA as primary outcome. It was initiated in 2011 and 5-year results were published as part of this thesis in 2020 (2).

Methodology used in Article 2:

Study design: RCT (sequential randomization)

Primary outcome: Polyethylene wear and cup stability measured by RSA.

Patient characteristics and setting: 68 patients (< 80 years old) with primary- or secondary osteoarthritis were randomized to reverse hybrid THA with a cemented VEPE cup or a cemented ModXLPE cup (Figure 21 and Figure 22). Power calculation was based on detecting difference with regard to polyethylene wear (139, 140). Exclusion criteria were immunosuppressant medication, significant systemic disease, or major anatomical abnormalities. Patients were operated from June 2011 to February 2014. In total, 53 patients (29 VEPE, 24 ModXLPE) were available for 5-year RSA analysis.

RSA: Marker-based RSA (Figure 23) was conducted post-operatively, 3 months, 1 year, 2 years and 5 years. For all follow-up times we completed double examinations (precision was defined as 1.96 x standard deviation) (2, 91, 92, 132, 133).

Radiological imaging: AP and lateral projections of the hip were taken post-operatively, 2 years and 5 years to evaluate cup position (141, 142), offset and signs of radiolucency around the cup (108, 143).

PROMs: Hip Disability and Osteoarthritis Outcome Score (HOOS) (144), EQ-5D (145), Visual Analogue Scale for pain (VAS pain) (146), University of California Los Angeles (UCLA) activity score (147) and Harris Hip Score (HHS) (148) were used in order to evaluate clinical performance pre-operatively, at 2 years and 5 years.

Data analysis: RSA results were analyzed with Mann-Whitney U tests (non-parametric) to detect differences. Independent sample T-tests were performed to analyze differences in radiological observations and PROMs.

VEPE

Courtesy Zimmer Biomet
E1™ (ArCom®)

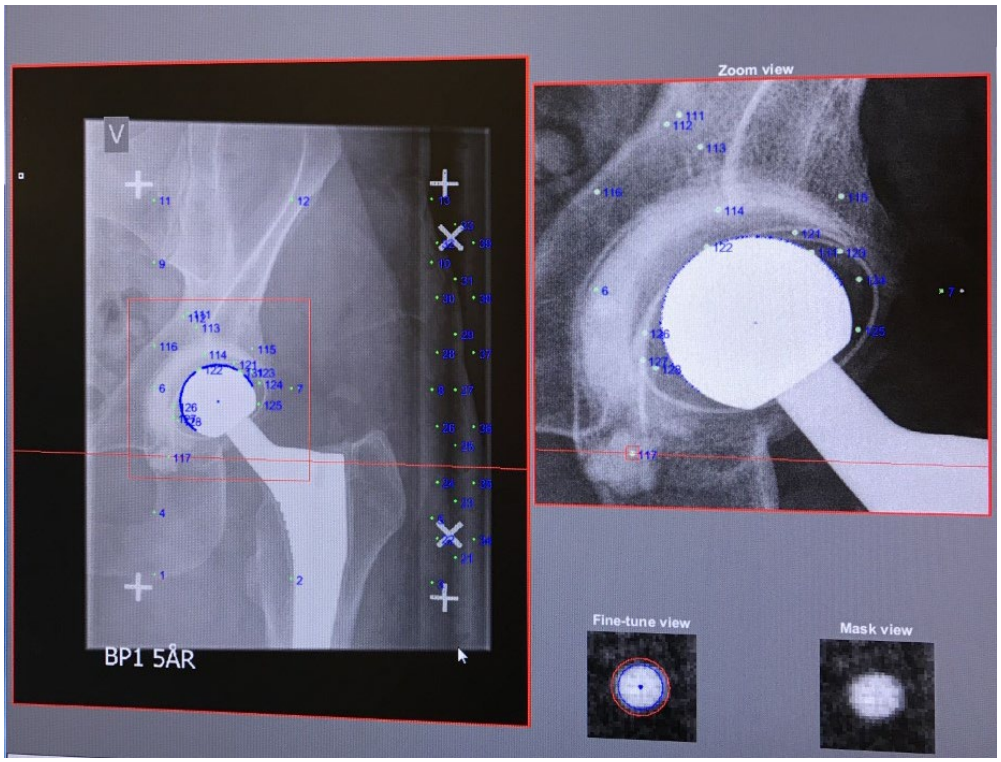
ModXLPE

Courtesy Ortomedic
Marathon™ (Marathon®Polyethylene)

Figure 21 VEPE and MODXLPE cups. Representation of the cemented VEPE cup (E1) and ModXLPE (Marathon) cups which patients were randomized to receive in Article 2. The slight yellow tinge is characteristic of polyethylene infused with Vitamin E (left).

Photo by Ine Eriksen, UiO

Figure 22. Reverse hybrid THA. This is an example of a reverse hybrid THA with a cemented ModXLPE cup, 32mm cobalt-chrome femoral head and a uncemented femoral stem. These particular prosthesis components were used for patients in the ModXLPE group in Article 2.



UmRSA Biomedical Program

Figure 23 Tantalum bead demarcation. Point correction with cage markers and tantalum beads in acetabulum and cemented polyethylene cup. In addition, the femoral head serves as an independent reference allowing for determining the change in the polyethylene cup – femoral head segment, which represents polyethylene wear.

Article 3 (Registry study – risk factors associated with dislocation)

The intention of Article 3 was to evaluate factors associated with the risk of revision due to hip prosthesis dislocation in recent time in Norway. Previously, data up to year 2000 had been published by the Norwegian Arthroplasty Register (NAR) (149). Article 3 is currently in submission process (3).

Methodology used in Article 3:

Study design: Observational registry study

Primary outcome: Revision surgery due to hip prosthesis dislocation

Patient characteristics and setting: All THAs in Norway with 28mm, 32mm, 36mm or dual-mobility cups operated from 2005 through 2019 (Figure 24). Form filled out by surgeon. Patient identification is based on a unique 11-digit number which each inhabitant receives at immigration or birth. Prospectively collected data and retrospective question. Patients were followed from 0-1 year.

Variables investigated: age, gender, diagnosis, femoral head size, fixation, surgical approach, ASA-classification, duration of surgery, prior operations, and time-period of operation.

Data analysis: Cox regression analysis and hazard ratios. Kaplan-Meier estimate of survival curves.

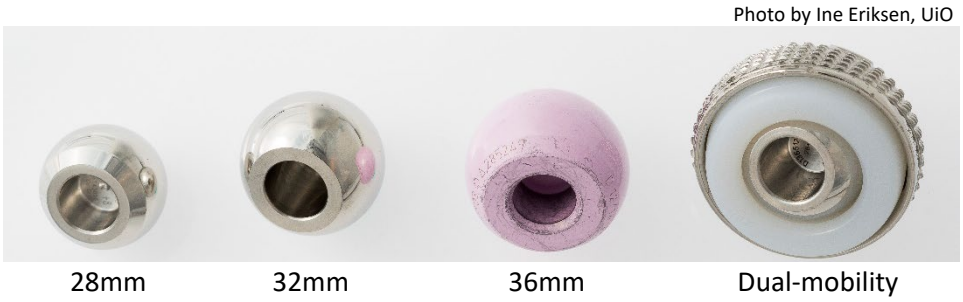


Figure 24 Included head sizes. Representation of the femoral head sizes that were included in Article 3 (28mm, 32mm, 36mm and dual-mobility articulation).

8. Summary of results

Article 1 (6-year RCT uncemented VEPE 32mm vs. 36mm)

Article 1 examined polyethylene wear in uncemented VEPE cups with either 32mm or 36mm ceramic femoral heads (1).

Key findings. There was low polyethylene wear in both the 32mm and 36mm groups at 6-years follow-up (Table I), and no significant difference between the groups when removing the "bedding in" period – first three months (Table II). There was less "bedding in" for the 36mm group (131, 150). Wear in the proximal direction was 0.099 mm in the 32mm group compared to 0.050 mm in the 36mm group in the time-period from 3 months to 6 years follow-up (excluding the "bedding in" period – first 3 months) and there was no significant difference between the groups over time.

DEXA scans showed no significant difference in BMD around the uncemented acetabular cups between the two groups (32mm vs. 36mm) and there was no apparent BMD change when comparing baseline scans to those taken at 6 years follow-up.

There was no difference in acetabular cup inclination between the two groups. Radiographs displayed all implants (both cups and stems) being well-fixed and osseointegrated at 6 years and there were no signs of significant progression of radiolucent lines through the study period.

There was no significant difference in PROMs or Harris Hip Score between the two groups at 6 years. Oxford Hip Score and the UCLA activity score were both comparable.

Table II Wear from baseline to 6 years. Proximal wear in the y-direction is depicted for both the 32mm- and 36mm femoral head groups. There is a significant difference between the two groups when considering the period from baseline to 6 years - the first 3 months are included ("bedding in" period included).

	32mm head	36mm head	Mean difference	P
Proximal wear (y-axis)	0.147 mm (SD 0.134)	0.057 mm (SD 0.126)	0.090 mm (95% CI 0.007-0.173)	0.015

Table III Wear from 3 months to 6 years. Proximal wear is shown for the period from 3 months to 6 years – excluding "bedding in" period. There is no significant difference between the 32mm- and 36mm femoral head groups.

	32mm head	36mm head	Mean difference	P
Proximal wear (y-axis)	0.099 mm (SD 0.105)	0.050 mm (SD 0.122)	0.049 mm (95% CI -0.025-0.123)	0.27

Impact. For the particular ceramic femoral head, uncemented cup and VEPE liner used in this study the mid-term results are promising and there are no signs of detrimental effects at 6 years follow-up. There were for both the 32mm and 36mm ceramic femoral head groups very little polyethylene wear and no signs of increased wear with the larger 36mm femoral head diameter. There were no signs of detrimental loss of BMD around the uncemented acetabular cup circumference and no signs of radiolucency which both indicate a well-fixed and osseointegrated uncemented acetabular cup component at 6 years follow-up.

Article 2 (5-year RCT cemented VEPE vs. ModXLPE cups)

In **Article 2** we investigated polyethylene wear and cups stability in VEPE and ModXLPE cemented cups (2).

Key findings. Both these particular VEPE and ModXLPE cemented cups showed low polyethylene wear in combination with a 28mm cobalt-chrome femoral head at 5-years follow-up (Table IV). There was 0.17 mm wear and 0.20 mm wear in the proximal direction for the VEPE and ModXLPE groups, respectively. There was significantly less polyethylene wear in the VEPE group. Also, both cups were stable at 5-years and there was no difference between the two cups (Table V).

Conventional radiographs showed no difference between the groups with regard to cup positioning (inclination or anteversion). There were in total 7 out of 53 hips that displayed noteworthy radiolucent lines >1 mm around the cemented cup at 5 years follow up (VEPE n=5, ModXLPE n=2).

Considering PROMs and Harris Hip Score there was no significant difference between the two groups at any time point (2- and 5-years). HOOS, VAS pain, EQ-5D, and UCLA activity score were all comparable in both groups.

Table IV Wear from baseline to 5 years. Proximal polyethylene wear in the y-direction for both the VEPE and ModXLPE groups. Significantly less polyethylene wear in the VEPE group at 5 years.

	VEPE	ModXLPE	Mean difference (95% CI)	P
Proximal wear (y-axis)	0.17 mm (SD 0.15)	0.20 mm (SD 0.09)	-0.06 mm (-0.14-0.02)	0.005

Table V Cup stability from baseline to 5 years. Cup stability (total 3D translation) at 5 years is shown for both the VEPE and ModXLPE groups. Both cups are stable at 5 years and no significant difference between the two groups.

	VEPE	ModXLPE	Mean difference (95% CI)	P
Total 3D translation	0.72 mm (SD 0.70)	0.50 mm (SD 0.44)	0.21 mm (-0.16-0.58)	0.404

Impact. At 5-years there was miniscule polyethylene wear with both the VEPE and ModXLPE cemented cups and both cups were stable (less wear in VEPE group). Based on 5-year results surgeons may be confident when using both this particular VEPE and ModXLPE cemented cup in combination with a 32mm metal (cobalt-chrome) femoral head.

Article 3 (Registry study – risk factors associated with revision)

Article 3 evaluated risk factors associated with revision due to hip prosthesis dislocation in the Norwegian population during the past 15 years using data from the Norwegian Arthroplasty Register (NAR) (3).

Key findings. Results showed that there was an increased risk of revision due to dislocation for patients with 28mm heads compared to 32mm and 36mm heads and dual-mobility articulations. Also, there was an increased risk for the posterior approach, uncemented fixation, male gender,

patients with duration of surgery >90 minutes, ASA class ≥3, diagnosis other than primary osteoarthritis, and having undergone prior operations. Patients in the 70-80 years age group had a lower risk of revision due to dislocation compared to >80 years age group, but a higher risk than those <70 years old. We also found that patients operated in the time-period 2010-2014 had significantly lower risk of revision due to dislocation than those operated in the latest time-period (2015-2019) (Table VI). Cumulative survival represented in the Kaplan-Meier survival curves stratified by time-period showed highest survival (free of revision due to dislocation) for the Time-period 2 (2010-2014) even when adjusting for head size and/or approach. Kaplan-Meier curves stratified by approach shows lowest survival for the two anterior approaches in Time-period 1 (Figure 25) and the highest survival rate for the anterolateral approach in Time-period 2 and 3 (Figure 26 and 27). The posterior approach has the lowest survival rate in Time-period 3 (Figure 27).

Our results from the current NAR data (2015-2019) shows that most patients in Norway who are operated with primary THA receive an uncemented prosthesis (38%) and 32mm femoral head (79%) with a posterior approach (64%). Most patients are women (64%) with a mean age 68 years old, and the diagnosis of primary osteoarthritis (80%) and with duration of surgery between 60-90 minutes (44%).

We found that of all revisions that were undertaken due to dislocation (n=1188) during the study period (2005-2019), 53% (n=627) were conducted within 1 year of the primary THA. In total, there were 5996 revisions due to all causes registered in NAR during the study period.

Impact. Clinicians may use the results in Article 3 to aid in their clinical decision making regarding THA. Study results reinforce the concept of using larger head sizes or dual-mobility articulations to prevent dislocations.

Table VI Hazard Ratio (HR). Results of the Cox regression model showing hazard ratios for associated factors related to risk for revision due dislocation. Adjusted results are depicted based on the a priori DAG evaluation.

Table VI Hazard ratio (HR)	Adjusted Cox regression		
	HR	CI	p
[1]Head size (reference 32mm)	1		
28mm	2.64	2.05 - 3.39	<0.001
36mm	0.78	0.56 - 1.10	0.2
Dual-mobility	0.73	0.41 - 1.30	0.3
[2]Duration of surgery (ref. 60-90 min)	1		
0-60 minutes	0.84	0.63 - 1.11	0.2
90-120 minutes	1.32	1.08 - 1.63	0.008
>120 minutes	1.70	1.34 - 2.15	<0.001
[3]Prior operations (ref. No)	1		
Yes	1.57	1.21 - 2.03	<0.001
*[4]Time periods (1-3) (ref. 2015-2019)	1		
2005-2009	0.95	0.78 – 1.15	0.7
2010-2014	0.64	0.53 – 0.78	<0.001
[5]ASA classification (ref. ASA 1-2)	1		
≥3	1.73	1.44 - 2.07	<0.001
[6]Age, years (ref. 70-80 years)	1		
<60	0.79	0.62 - 1.00	0.046
60-70	0.79	0.64 - 0.97	0.03
>80	1.28	1.02 - 1.61	0.03
[7]Approach (ref. Posterior)	1		
Direct anterior (S-P)	0.75	0.50 - 1.11	0.1
Anterolateral (W-J)	0.46	0.33 - 0.66	<0.001
Direct lateral	0.58	0.48 - 0.72	<0.001
[8]Diagnosis (ref. Primary osteoarthritis)	1		
Other	1.97	1.66 - 2.33	<0.001
[9]Fixation (ref. Uncemented)	1		
Cemented	0.59	0.48 - 0.74	<0.001
Hybrid	0.74	0.51 - 1.07	0.1
Reverse hybrid	0.58	0.46 - 0.75	<0.001
**[10]Sex (ref. Female)	1		
Male	1.53	1.30 – 1.79	<0.001

[1]Adjustments for ASA classification, Age, Approach, Diagnosis, Fixation, Prior operations, Sex, Time periods
[2] Adjustments for Approach, Diagnosis, Fixation, Prior operations, Sex
[3] Adjustment for Diagnosis
*[4] No adjustment
[5] Adjustment for Age
[6] Adjustment for Time periods
[7] Adjustments for Age, Diagnosis, Prior operations, Time periods
[8] Adjustment for Sex
[9] Adjustments for Age, Approach, Diagnosis, Prior operations, Sex, Time periods
**[10] No adjustment

Figure 25. Kaplan-Meier curve 2005-2009

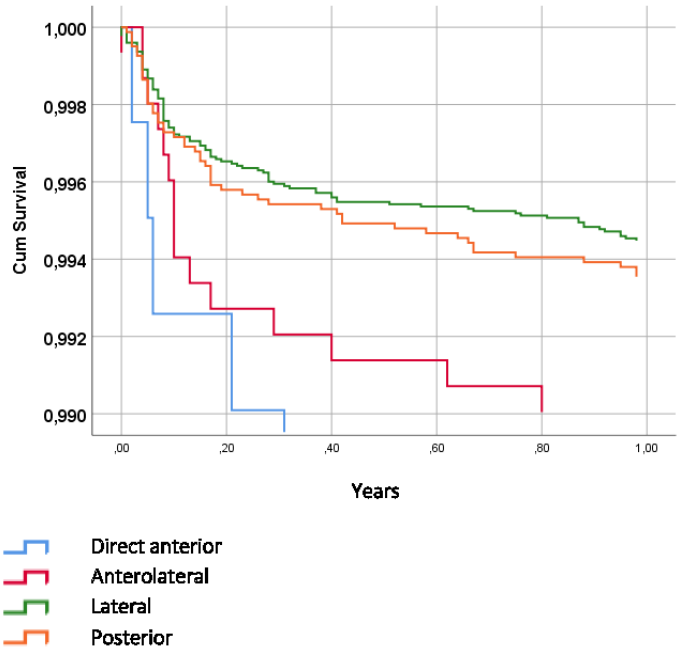


Figure 25 Kaplan-Meier curve 2005-2009. Survival curves stratified by approach representing rates (free of revision due to dislocation) for Time-period 1 (2005-2009). Lateral and posterior approaches have the highest survival rates, while the two anterior approaches have the lowest.

Figure 26. Kaplan-Meier curve 2010-2014

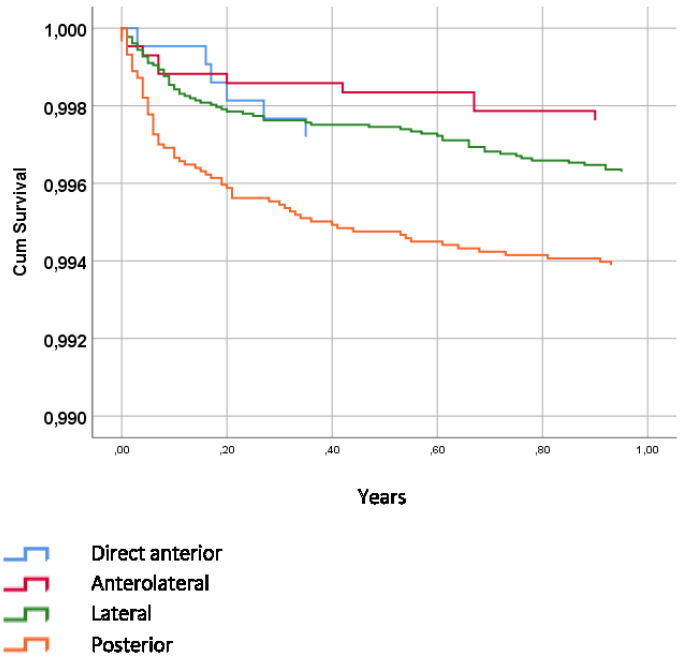


Figure 26 Kaplan-Meier curve 2010-2014. Survival curves stratified by approach representing rates (free of revision due to dislocation) for Time-period 2 (2010-2014). The anterolateral approach has the highest rate of survival and the posterior approach the lowest.

Figure 27. Kaplan-Meier curve 2015-2019

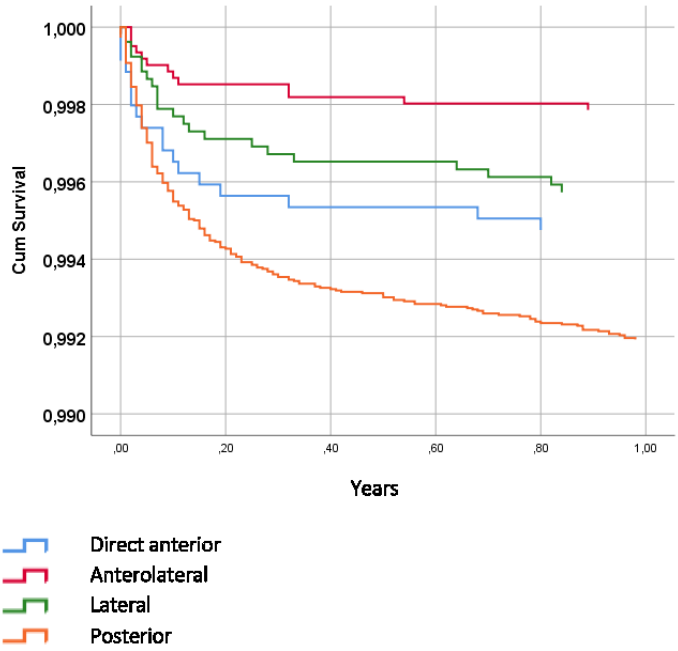


Figure 27 Kaplan-Meier curve 2015-2019. Survival curves stratified by approach representing rates (free of revision due to dislocation) for Time-period 3 (2015-2019). The posterior approach has a lower survival rate than in Time-period 2 (Figure 26), while the anterolateral approach has the highest rate of survival.

How study results address the research questions (1-3):

1. What are mid-term polyethylene wear outcomes of uncemented VEPE cups and do they differ with 32mm versus 36mm head sizes?

Taking into account this particular articulation combination (ceramic-on-VEPE), there was very little polyethylene wear at 6 years follow-up for both the 32mm- and 36mm femoral head groups. Also, there was no indication that there was increased polyethylene wear and debris particle formation when increasing femoral head size from a 32mm- to 36mm diameter.

2. Are there differences mid-term regarding polyethylene wear and cup stability between a cemented VEPE cup compared to a cemented ModXLPE cup (without Vitamin E)?

There was significantly less polyethylene wear at mid-term (5-years) follow-up with the VEPE cup compared to the ModXLPE. However, there was very low levels of polyethylene wear with both these particular cemented cups in combination with 32mm metal (cobalt-chrome) femoral heads. Regarding cup stability there was no significant difference between the groups and both cups were stable at 5 years follow-up.

3. Which factors influence the risk of revision due to hip prosthesis dislocation in Norwegian patients operated with a primary THA the past 15 years?

By evaluating NAR data, we found that the following factors were associated with risk of revision due to dislocation; age, gender, diagnosis, femoral head size, fixation, surgical approach, ASA-classification, duration of surgery, prior operations, and time-period of operation.

9. Discussion of main findings

Findings from the first RCT (Article 1) showed that there was very limited polyethylene wear at 6 years when using a VEPE liner (uncemented cup) with both 32mm- and 36mm ceramic femoral heads. There was no difference in polyethylene wear when increasing head size diameter from 32mm to 36mm heads. Results from the second RCT (Article 2) displayed that both VEPE and ModXLPE cemented cups retained low polyethylene wear rates up to 5 years when used in combination with a 32mm metal (cobalt-chrome) femoral head. However, there was less polyethylene wear with the VEPE cemented cup. Both cemented cups were stable at 5-years. The registry study (Article 3) demonstrated an increased risk of revision surgery due to hip prosthesis dislocation when using 28mm femoral head size, posterior approach, and uncemented fixation. Findings supported the use of larger head sizes or dual-mobility articulations to lower the risk of revision due to dislocation.

Radiostereometric analysis (RSA)

Wear. Both RCTs (Article 1 and Article 2) evaluating VEPE cup components showed very little polyethylene wear at 6- and 5-years respectively. Also, the ModXLPE cemented cup without Vitamin-E used in Article 2 showed low polyethylene wear rates up to 5 years, but not as low as the VEPE cemented cup. Our study results demonstrated that both ceramic and metal (cobalt-chrome) femoral head options articulating against VEPE are good alternatives when considering polyethylene wear mid-term. In this thesis, both uncemented (Article 1) and cemented (Article 2) VEPE cup options were evaluated. Several studies have documented lower polyethylene wear rates using RSA with uncemented cups and VEPE liners (151-154). One study with 7-year follow-up showed no difference (99). To our knowledge only one study has documented polyethylene wear results using RSA with cemented VEPE cups (56).

In a RCT study by Rochcongar et al., reporting 5-year model-based RSA results using an uncemented cup with either VEPE or UHMWPE liners they found an annual wear rate of 0.02 mm/year (VEPE) and 0.06 mm/year (UHMWPE) (152). In comparison, our results at 6-years in Article 1 (uncemented cup with VEPE liner) showed annual wear rate of 0.02 mm/year (32mm) and 0.01 (36mm).

A prospective clinical outcome study evaluating 47 patients with an uncemented cup and VEPE liner (Nebergall et al.) reported a mean proximal head penetration 0.06 mm at 5 years (153). This is also well below the polyethylene wear limit of 0.1 mm/year where concern about osteolysis arises (155, 156). The femoral head penetration seen in this study and also the one we reported in Article 1, was less than that observed in 1st generation HXLPE (157, 158)

Galea et al. published in 2018 a prospective clinical outcome study with 221 THA operated at 4 centers with head penetration in polyethylene liners (different types of uncemented cups – all from the same manufacturer). Both VEPE and ModXLPE liners were used in these patients and 5-year model-based RSA results were reported. This study showed that the mean total femoral head penetration at 5 years was 0.06 mm for VEPE liners and 0.13 mm for ModXLPE liners (154), which corresponds to the aforementioned studies. In 2019, Galea et al. published a RCT evaluating RSA results including polyethylene wear (markerless RSA) and acetabular shell migration (marker-based RSA). All patients received a porous titanium-coated (PTC) shell and either a VEPE or ModXLPE liner. At 7 years, there was no difference between the two groups with total polyethylene wear of 0.03 mm (VEPE) and 0.04 mm (ModXLPE) (99).

As for results regarding polyethylene wear in cemented VEPE cups there is only one other study reporting data in addition to Article 2 in this thesis. Sköldenberg et al. published an RCT evaluating polyethylene wear and cup stability of patients with either a VEPE cemented cup or a ModXLPE cup without Vitamin E. This study found mean total femoral head penetration at 2 years of 0.23 mm (56). We reported in Article 2 with an identical VEPE cemented cup a mean proximal (y-direction) polyethylene wear of 0.10 mm at 2 years and 0.17 mm at 5 years.

Bedding-in reflects femoral head penetration that is not related to polyethylene wear (e.g. creep). Initially, bedding-in occurs the first few months, but may continue as long as up to 2 years after prosthesis implantation. Therefore, penetration measurements should begin after the bedding-in period (minimum 3 months post-operative) because it is the polyethylene wear which is of interest (159). In Article 1, we found less “bedding in” in the 36mm group than 32mm group at 3 months (1, 131). An in vitro study by Takahashi et al. compared the effect of bedding inn for VEPE and UHMWPE. Results showed that VEPE liners have a greater resistance to creep than UHMWPE. Also, creep was affected by the thickness and the internal

diameter of the liner for both VEPE and UHMWPE. Increasing the internal diameter (allowing for larger femoral heads) decreased the rate of creep strain (150).

Cup stability. Many RSA studies evaluating polyethylene wear also include cup stability as an outcome. The stability of acetabular cups over time is important for good long-term outcomes (143), and may be influenced by several factors. These factors may weigh differently depending on whether the cup is uncemented or cemented. The different interfaces between the cup perimeter (titanium alloy in uncemented cups and cement in cemented cups) and the bone structures allow for different physical and biological integration of the various uncemented and cemented cup options that are available.

In the first RCT (Article 1) we used markerless RSA when evaluating uncemented cups with a VEPE liner. This allowed us to measure femoral head penetration in relation to the perimeter of the uncemented cup in an "edge detection" fashion without using tantalum beads (160). However, without tantalum beads or other reference markers in the acetabular bony regions surrounding the uncemented cup it was not possible to evaluate cup stability and this was not the primary outcome of Article 1. Other studies using tantalum beads have evaluated cup stability with VEPE liners in uncemented cups and shown little change over time (99). The study by Galea et al. from 2019 evaluated cup stability in addition to polyethylene wear as mentioned above. This study used tantalum beads in the surround acetabular bone and by using marker-based RSA evaluated cups stability. During the 7 years follow-up there was no difference in cup stability between the VEPE and ModXLPE groups and no components appeared radiologically loose (99).

For the second RCT (Article 2) we used marker-based RSA and we evaluated cemented cups with both VEPE and ModXLPE. In this instance, we were able to measure the movement between the implanted polyethylene tantalum beads in the cemented polyethylene cup and the markers in the bony structures of the acetabulum surrounding the cemented polyethylene cups. We found that at 5-years both the VEPE and ModXLPE cups were stable. Some issues were present the first 2-years but after this they levelled off and were stable. However, a study with 2-year follow-up raised questions regarding cup stability in the same VEPE cemented cup that we used (56). 13 out of 18 patients with the VEPE cemented cup showed a proximal migration larger than the proposed "safe" threshold of 0.2 mm (82, 84). Therefore, it will be interesting

to see the anticipated 5-year results (IRSA conference in Oslo, May 2021) from this study and whether migration patterns will level off in a similar fashion as we saw in our 5-year results in Article 2.

In a case series study by Flatøy et al. the same ModXLPE cemented cup as we used in Article 2 was evaluated with regard to both cup stability and polyethylene wear using marker-based RSA at 2 years follow-up. Measured 2-year proximal migration was 0.01 mm (161), which was deemed as being stable based on the stipulated acceptable limits of 0.2-1 mm proximal migration at 2 years (82).

Issues related to cup stability that occur late (after having had primary fixation) can be related to aseptic loosening as a result of osteolysis. Osteolysis can occur as a result of biological reaction and macrophage aggregation in response to debris particle formation around the prosthesis joint (22). In our studies at 6- and 5-years follow-up we did not see any alarming effects based on RSA results (Article 1 and 2), DEXA scan (Article 1) or conventional radiography (Article 1 and 2).

Dual-Energy X-ray Absorptiometry (DEXA)

In Article 1, we evaluated periacetabular bone remodeling by analyzing BMD using DEXA around the uncemented acetabular cups in 3 regions of interest (ROIs) as modified DeLee and Charnley zones (162, 163). Results were measured at baseline, 1, 2 and 6 years. There was no difference in mean BMD from baseline to 6 years in any of the 3 ROIs, and there was no difference between the 32mm and 36mm groups at 6 years (1). Our results are comparable to existing literature (164, 165). However, there has been issues with osteolysis around the circumference of other uncemented acetabular cups with certain types of polyethylenes including low or non-highly cross-linked UHMWPE. The development of osteolysis may be a precursor to aseptic loosening of the cup (166).

Conventional radiographs

In the two clinical studies (Article 1 and Article 2) conventional radiographs were included mainly to 1) document prosthesis component placement and 2) survey over time any changes in the bone architecture around prosthesis components such as radiolucency, cup migration and osteolysis.

1) Documenting prosthesis placement: There has been some conflicting evidence regarding to what extent polyethylene wear may be influenced by acetabular cup placement. Previous studies evaluating conventional polyethylene have found higher wear rates with increasing cup inclination angle. However, this same relationship has not been documented with HXLPE (167, 168). In Article 1, there was no difference in cup inclination (uncemented cups) between the two groups, 41 degrees (32mm) and 42 degrees (36mm) respectively. The placement of the cemented cups in Article 2 did not show any difference either, 45 degrees (VEPE) and 47 degrees (ModXLPE). This leads to the conclusion that there is no confounding that could potentially account for differences in polyethylene wear in any of the two articles between the test groups.

2) Surveying for radiolucency: In Article 1 there were no signs of progression of any radiolucent lines (RLL) around either the acetabular cups or femoral stems. All implants seemed well-fixed and osseointegrated at 6 years follow-up and there were no differences between the 32mm and 36mm groups. No radiological signs of component loosening were present. In Article 2, we evaluated radiolucency around the cemented acetabular component and recorded RLL >1 mm width at 5-year follow-up and graded according to the three DeLee-Charnley zones (108, 132). There were 7 patients (n=5 VEPE, n=2 ModXLPE) that displayed radiolucent lines around the cemented cup at 5 years. None of these were considered to be loose components or presented with symptoms that would imply anything else than well-integrated components.

Patient related outcome measures (PROMs)

In this thesis patient related outcome measures (PROMs) were not the primary outcome in any of the three articles. Therefore, the clinical studies (Article 1 and 2) were not with sufficient power to evaluate PROMs. However, PROMs were included in these two studies in order to determine if there were any significant differences in the groups both with regard to

randomization and also post-operatively with regard to activity-level. Our PROM data was comparable to THA studies with PROMs as the primary outcome. Activity-level as a confounding factor when looking at polyethylene wear could basically be ruled out based on our data being comparable to other THA studies with PROMs as a primary outcome.

In Article 1, the UCLA activity score was 7.0 and 6.7 for the 32mm and 36mm groups, respectively. As for the Harris Hip Score (HHS) at 6 years results showed 97 (32mm) and 98 (36mm), pre-operatively HHS was 56 for both groups. As a comparison results in Article 2 showed HHS pre-operatively of 49 (VEPE) and 51 (ModXLPE). At 5 years HHS was 90 (VEPE) and 88 (ModXLPE) for the two groups. UCLA activity score was at 5 years 7 for the VEPE group and 8 for ModXLPE group. These results are consistent with PROMs and HHS reported in other studies where the primary focus has been evaluating these parameters (169, 170). From this one can deduct that the patients in our two clinical studies reflect common and satisfactory activity-levels after THA, and thereby it is less likely that activity-level is a confounding factor when considering polyethylene wear and cup stability.

PROMs data are currently collected as part of NAR, but it is still in the beginning phase and not all hospitals include PROMs (14). Therefore, it was premature for Article 3 in this thesis to discuss aspects related to PROMs. Had PROMs been instituted in NAR one could have evaluated this factor as an independent associated risk for revision due to dislocation.

Epidemiological THA data from Norway

From the inception of NAR in 1987 and including 2019, there have been 209 792 primary THAs reported in NAR (14). As previously mentioned in this thesis, hip prosthesis dislocation is the third most common cause for THA revision surgery (14). In a NAR study from 2003, Byström et al. focused on femoral head size as a risk factor for dislocation during the time-period from 1987 to 2000 (149). However, much has changed since the turn of the millennium and other factors in addition to femoral head size are highly relevant when considering risk of revision due to dislocation.

During the early 2000's head sizes of 22mm became completely obsolete, and 28mm heads dominated up until around year 2010. Then 32mm heads began to take over while at the same

time larger heads such as 36mm heads became relevant. Dual-mobility cups were implemented in Norway during the mid-2000's (14). Hip resurfacing options (metal-on-metal) which are available on the international marked today are no longer considered a viable treatment option in Norway due to inferior results (171, 172). New trends regarding the approach to the hip joint have also evolved and in 2015 the posterior approach surpassed the lateral approach as the most used approach in Norway. In 2019, the posterior approach accounted for 71% and the lateral for 4% of all primary THA. Also, during the 2000's the direct anterior and anterolateral approaches have been used in Norway and these currently account in combination for 21% of all primary THA (14). When considering the method of hip prosthesis fixation during the last 20 years, there is a trend towards uncemented fixation, and importantly most of the prosthesis designs used prior to year 2000 are no longer in use today (14). Especially, the trends towards using increasingly larger femoral head sizes are universal in both the American, Australian, Danish, Norwegian, Swedish and New Zealand registers (14, 173-177). Uncemented fixation is steadily increasing in Norway and Sweden, however in the Australia and U.S. uncemented fixation is on a small decline the last couple of years, which has much to do with such a large proportion being uncemented fixation since the 2000's (14, 173, 174, 176).

When finalizing the study protocol for Article 3 and looking at revision due to dislocation as an endpoint, we decided to define the patient setting from January 1st 2005 – December 31st 2019. Since ASA was included as a measured variable in NAR from 2005 this was a logical beginning for the patient setting. Final inclusion would be at the end of 2019 because we required 1 year follow-up for all patients (patients operated in 2019 would have 2020 for follow-up). Data analysis for Article 3 could be finalized in early 2021 once all NAR follow-up data for 2020 was available. It is important to be aware that the numbers registered in NAR are cases of primary THA and revisions, not patients. As one patient has two hips the patient may have been reported twice in NAR. Also, THAs may be revised several times. Therefore, the rates we report is cases, not patients. However, the number of cases is probably similar to the number of patients, but the number of patients is likely to be lower than the number of cases both for THAs and for revisions due to dislocations as patients have two hips and may be revised several times.

The findings from this thesis (Article 3) reflects common practice in Norway because NAR has a high coverage ratio (97.3% of primary THAs, 93.3% of revisions) (14, 178). This strengthens the external validity of the findings. In total, there were 111 711 primary THAs included during

the study period (2005-2019) and this large number of patients adds to the power and significance of results.

Time of revision due to dislocation

The total number of THA revisions for any cause registered in NAR during 2005-2019 was 5996. About 20% (n=1188) were revisions due to dislocation. In total, 53% (n=627) of all THA revisions due dislocation in this material were revised within 1 year after primary THA. In a New Zealand joint register study, it was reported that 470 out of 867 (54%) revisions due to dislocation within a 10-year period were performed after the first year, which conversely is 46% revised within 1 year after primary THA (179).

Late dislocations do therefore occur to a great extent and as time passes causes for dislocation change and could potentially include polyethylene wear and osteolysis with cup loosening as the resulting cause for the dislocation.

Revisions due to dislocation is an underestimation of the frequency of dislocation. Many patients that suffer a hip prosthesis dislocation are considered for revision surgery after a trial of 1-2 closed reductions. This is because of the risks associated with the revision surgery such as for instance infection. An individualized treatment approach is necessary, where the surgeon and patient together take into consideration factors such as the number of times the hip prosthesis has dislocated, the magnitude of trauma leading to dislocation, and patient factors such as age, activity-level, quality of life, comorbidities etc.

The frequency (cumulative incidence) of hip prosthesis dislocations varies between 1.7-3.9 (180-182). However, in these reported studies the follow-up time after primary THA surgery differs between 6 months and 2 years. The cumulative incidence is dependent on the length of follow-up time. In a study by Berry et al. from 2004, the cumulative incidence for a 1st time dislocation was 1% at 1 month, then 1.9% at 1 year and with a steady increase of 1% for every 5 years up to 7% at 25 years (183). In the NAR material we used revision due to dislocation as the endpoint because currently closed reductions of dislocated hip prosthesis are not registered in NAR. With the conversion to electronic NAR registration there will be the possibility to register closed reductions.

When evaluating the frequency of revision due to dislocation in Article 3 one could consider calculating the number of revisions due to dislocation (n=1188) divided by number of included primary THAs (n=111 711) times 100%. This would yield 1.06% of primary THAs included in the study would be revised due to dislocation during the study period, 2005-2019 (follow-up 0-15 years). This is likely a somewhat of an overestimation as potentially some THAs could be revised due to dislocation more than one time and therefore n=1188 could be less and yielding a smaller percent.

Hazard ratios (HR)

In the register-study (Article 3) we implemented Cox regression analysis and calculated HR in order to evaluate differences within each measured variable included in NAR. Adjustments in the Cox regression model were based on the DAG (Figure 18) and listed at the bottom of Table VI. Reference categories were based on the most frequent, most recent, or most common category. All THAs included in the Cox regression model had between 0-1 years follow-up.

Femoral head size (reference 32mm)

Head size is a measured variable in NAR that influences the risk of revision due to dislocation. Using 28mm femoral head size compared to 32mm head size increases the risk almost 3-fold (HR 2.64). Several studies have shown that increasing head size from 28mm to 32mm reduces the risk of dislocation (51, 184). Our data also showed a trend towards an even lower risk when increasing head size further to 36mm (HR 0.78) or with dual-mobility cup (HR 0.73). However, a study from the Nordic Arthroplasty Register Association (NARA) did not demonstrate any added benefit (reduced risk of revision due to dislocation) when going from 32mm to 36mm head size (185). It is important to mention that the authors of this study report that less females and more uncemented THAs through a posterior approach in the 36mm group, all of which may influence results since they are associated with an increased risk of revision due to dislocation. Orthopedic surgeons in Norway implement 36mm heads often due to one of the following three reasons: 1) patient in question is thought to have increased risk of hip prosthesis dislocation or being active with high functional demand, 2) acetabular cup size allows for 36mm head, or 3) additional head length is required for prosthesis stability and biomechanics and the surgeon does not want to compensate with a different stem or a sleeved head. Therefore, this gives

greater credence when there is no added risk of revision for 36mm heads (and to a certain extent dual-mobility cups regarding stability) compared to 32mm heads. A study by NARA from 2019 concluded that using dual-mobility articulation in primary THA following hip fracture reduced the overall risk of revision and specifically the risk of revision due to dislocation (186). However, no such reduction was found when using 36mm heads in primary THA following hip fracture compared to 32mm heads (187).

Surgical approach (reference Posterior)

Posterior approach is associated with the highest risk of revision due to dislocation when compared to anterolateral (HR 0.46) and lateral (HR 0.58) approaches. There is also a trend towards lower risk for the direct anterior approach (HR 0.75). The finding that the posterior approach is associated with a higher risk of dislocation and revision due to dislocation is consistent with other studies (51, 52, 54, 188). In Table VI it is evident that the adjusted HR (not adjusted for head size) is nearly cut in half when going from a posterior approach to a lateral approach (HR 0.58). Correspondingly, there is more than double the risk when going from the unadjusted HR for 28mm head size (HR 1.28) to the adjusted HR (HR 2.64) where we adjusted for approach and time-period (3). It may seem that going from 28mm head size to 32mm head size does not fully compensate for the change in approach from lateral to posterior. However, when considering approach it is important to keep in mind the overall complication rate which has been shown to be lower with the posterior approach compared to the anterior approach (189), and also the infrequent occurrence of Trendelenburg gait (abductor deficient gait) with the posterior approach more commonly reported with a lateral approach (190).

Fixation (reference Uncemented)

Uncemented fixation (uncemented stem and cup) is associated with the greatest risk of revision due to hip prosthesis dislocation. Both cemented (HR 0.59, p-value=<0.001) and reversed hybrid (HR 0.58, p-value=<0.001) were associated with lower risk of revision due to dislocation compared to uncemented. Hybrid fixation did not show a significantly lower risk (HR 0.74, p-value=0.1). One explanation may be that the placement of uncemented acetabular cups in “safe zones”, is more technically challenging than placing a cemented cup correctly. The concept of “safe zones” in THA is a highly opinionated topic and defining such zones is dependent on a multitude of factors (191-195). In a review, Clement et al. found that there was a higher rate of

dislocation in patients with uncemented cups (196). Considering the somewhat lower risk for hybrid fixation (HR 0.74), even though not significantly lower than uncemented, one could speculate that hospital volume and surgeon factors may affect the results. In Norway, hybrid fixation (uncemented cup) is performed at high-volume centers where surgeons are more experienced with uncemented acetabular components. This may negate the technical aspect of placing an uncemented cup in a so-called "safe zone". Also, during the study period (2005-2019), only 5036 hybrid fixations were performed in comparison to 41140 cemented, 32716 uncemented, and 31748 reverse hybrid fixations. Perhaps the HR for hybrid fixation would be different (more narrow confidence interval – more precise effect estimate) if there were a larger number of hybrid fixations in the study material.

Sex (reference Female)

Men were associated with an increased risk for revision (HR 1.53) compared to women. From an orthopedic surgeon standpoint there can in certain instances during hip prosthesis surgery be somewhat technically challenging to uphold pre-operative global offset for some men of large stature. Whether this problem arises due to a reduction in acetabular offset when a cup is placed more medial (surgeon needs to compensate with increasing femoral offset using a femoral component with a lower CCD angle often with high-offset stem and larger head size), or a reduction in femoral offset due to the patient's native anatomy being larger than what the different femoral component sizes can adjust for (surgeon may place cup more laterally or use uncemented acetabular component with a lateralized liner), or a combination of both. Reducing global femoral offset post-operatively may influence muscle tension and lever arm resulting in suboptimal muscle strength and function, which may ultimately lead to instability and hip prosthesis dislocation. It is also important to acknowledge that 32mm heads for men with large femoral and acetabular components may not be biomechanically comparable to a 32mm head for a person of smaller stature with femoral and acetabular components on the lower end of the standardized prosthesis portfolio. Also, larger heads for patients with larger sized prosthesis components is biomechanically a sound concept and a way to equalize jump distance issues that may arise (197). Head size should be comparative to individual patient stature.

Time-period (reference 2015-2019)

There was a lower risk of revision in the 2010-2014 time-period (HR 0.64) compared to 2015-2019. None of the measured variables influenced time-period and therefore we did not adjust for any factors. With the shift from the lateral to posterior approach during the same time frame this risk difference can be explained. It is also noteworthy that the increase in head size from 28mm to 32mm has not been able to compensate for increased risk associated with the posterior approach (198). Also, one influencing factor is that there might have been a change in revision due to dislocation practice among orthopedic surgeons in Norway in the last time-period (2005-2019). Patients may today be revised after 1st or 2nd dislocation, and during the earlier time period (2010-2014), common practice may have been towards a more conservative philosophy and wait until patients sustained a 3rd or maybe a 4th hip prosthesis dislocation. Threshold for going through with revision surgery may have become lower in recent years.

ASA classification (reference ASA 1-2)

American Society of Anesthesiologists (ASA) classification is a grading system used to evaluate the physical health of patients prior to surgery. In Article 3, we found that an ASA ≥3 classification was associated with an increased risk of revision due to dislocation (HR 1.73). A higher ASA classification reflects a greater degree of comorbidity and complexity of associated systemic disease. For instance, a higher ASA classification could reflect lower muscle tension/mass or greater fall tendency both of which could lead to a higher rate of dislocation (199). Several other studies support this finding including a study by Zijlstra et al. from 2017, where the HR was 1.40 for ASA ≥3 compared to ASA 1 (54). Another study (Hermansen et al.) showed HR 1.64 for ASA ≥3 compared to ASA 2 (23).

Duration of surgery (reference 60-90 minutes)

We found that surgeries lasting >90 minutes were associated with an increased risk of revision due to dislocation (90-120 minutes HR 1.32, >120 minutes HR 1.70). Duration of surgery is a proxy for the complexity of a procedure (altered or abnormal anatomy, challenging patient characteristics) and surgeon experience. Low-volume surgeons are at greater risk of operating patients that sustain a dislocation and should refer complex patients (199). For every ten THAs annually performed by a surgeon the risk of dislocation is reduced by 50% (200).

Age (reference 70-80 years)

Older patients (>80 years) were associated with a higher risk of revision (HR 1.28) compared to those in the 70-80 years group. Also, there was a lower risk for patients <70 years old. These findings are consistent with those from the Danish Hip Arthroplasty Register in 2021 where those patients >75 years old had a higher risk of hip prosthesis dislocation (OR 1.32) compared to the 65-75 years age group, and those <65 had a lower risk (OR 0.70) (23).

Diagnosis (reference Primary osteoarthritis)

There is about a two-fold increase in risk of revision due to dislocation for diagnosis other than primary osteoarthritis (HR 1.97). "Other diagnosis" includes rheumatoid arthritis, ankylosing spondylitis, acute femoral neck fracture, dysplasia, Perthes disease and epiphysiolysis. A Swedish Hip Arthroplasty Register study from 2012 found similar results, specifically there was an increased risk of revision for those with a diagnosis of femoral neck fracture and idiopathic femoral head necrosis (52).

Prior operations (reference No)

Prior operations adds to the complexity of a procedure and may alter anatomy which increasingly becomes challenging for the surgeon. Our data shows that there was an increased risk for revision due to dislocation when there were registered prior operations (HR 1.57). As discussed in Article 3, patients with prior operations is a very heterogenous group and would include patients such as those having undertaken periacetabular osteotomy and hip arthroscopy which are very different from a pathological standpoint (3).

By implementing Cox regression analyses and calculating hazard ratios, we found that there was an increased risk of revision due to dislocation for patients with uncemented fixation, 28mm head size or posterior approach. The lowest risk of revision due to dislocation was observed in Time-period 2 (2010-2014).

Revision surgery due to dislocation is a definitive and undisputed endpoint. For most of the variables evaluated in Article 3 such as head size, approach, fixation, time-period, gender, duration of surgery and diagnosis there is little reason to believe that there are differences in

the decision to revise for dislocation. For age and ASA-classification the decision to revise may be influenced.

In the NAR article published by Byström et al. from 2003, including THAs from 1987-2000, factors such as old age, diagnosis, surgical approach and head size influenced the risk of revision due to dislocation (149). Both the material published by Byström et al. and our material in Article 3 (2005-2019) showed that posterior approach, 28mm head size and patients >80 years old all had an increased risk of revision due to dislocation. Factors such as gender and duration of surgery did not exert an influence in the article by Byström et al., even though we found in our material (Article 3) that male gender and duration of surgery >90 minutes increased the risk of revision due to dislocation. Importantly, different implants were used in 1987-2000 (i.e. monobloc 22mm stems, Charnley) (149).

Kaplan-Meier survival curves

The Kaplan-Meier survival curve stratified by time-period demonstrated that Time-period 2 (2010-2014) had the highest survival rate (free of revision due to dislocation) regardless of adjustments (including adjusting for approach, head size, fixation, approach + head size). This implies that increasing head size from 28mm to 32mm has not been sufficient to compensate for the change from lateral to posterior approach.

Using Kaplan-Meier survival curves stratified by surgical approach we found a discrepancy between the survival rate of the anterior approaches for different times. In Time-period 1, the direct anterior and anterolateral approaches had the lowest survival rates, while in Time-period 3 the anterolateral had the highest survival and the direct anterior the third highest. Thus, the effect of approach on risk of revision due to dislocation differ between the three time-periods. This difference in survival rates between the time-periods is most likely due to a learning curve effect (201).

A study from 2017 by Mjaaland et al., comparing implant survival following different surgical approaches in THAs registered in NAR, omitted the anterolateral and direct anterior approaches prior to 2008 due to few patients and a proposed learning curve effect (202). Mjaaland et al. did not find any differences in survival between the two anterior approaches and the posterior or lateral approaches.

The posterior approach had a lower survival rate in Time-period 3 than in Time-period 1. Also, there was a lower survival rate for the posterior approach compared to the lateral in Time-period 3, but no difference between the two in Time-period 1. An explanation for this could be that there is an observed learning curve effect since many orthopedic surgeons have converted to a posterior approach from the lateral in recent time. In Time-period 1, the hospitals in Norway using a posterior approach were high-volume centers having used this approach over a long time-period.

10. Methodological considerations

Our research group strived to establish an appropriate framework for each of the three included articles in this thesis. This involved adhering to published guidelines for different research methodology (CONSORT for Article 1 and 2, STROBE/RECORD for Article 3).

RCTs versus Registry studies

Randomized controlled trials (RCTs) and registry studies present different types of information and contrasting level of evidence – but complement each other.

RCTs are the gold standard for evaluating treatment effect and rank high on the hierarchy of evidence (76), typically regarded as Level 1 evidence (77). Because treatment is allocated randomly to similar groups the risk of bias is lower and this allows evaluation of effect for different interventions. However, this treatment effect may be based on a limited sample of patients and a particular setting (high intrinsic validity). These factors will influence the external validity (low) of a RCT study. At the same time detecting harmful, but rather rare complications may not be possible in the research population.

Register studies on the other hand, if coverage/compliance and completeness is high, reflect clinical practice and provide results with high external validity. However, register studies rank low on the hierarchy of evidence and are not able to determine true causality between an intervention and outcome in the population. However, they can describe associations and trends over time. This is helpful in detecting inferior designs or methods that may not easily be detected in more controlled studies. Malchau et al. have advocated a change in framework to utilize register studies to ensure a stepwise introduction of new hip prosthesis designs (37). This has proven useful to detect harmful prothesis designs earlier than by other methods (Boneloc, metal-on-metal) (63, 171).

In order to combine the different qualities of these research designs register-based randomized controlled trials (R-RCT) have recently been developed. The Norwegian Arthroplasty Registry (ALBA study) (118), and the Norwegian Knee Ligament Registry (IMPROVE study) are currently working on two such register-based RCTs. Big data versus precision data (patient

specific data) is important to be aware of in orthopedic surgery due to the large surge in the number of publications in recent years (114).

Limiting bias in research

Research biases are systematic errors or factors that influence study results and may even skew results completely. Therefore, in all aspects of research it is important to be aware of possible research bias and strive to reduce bias in research to an absolute minimum. In the process of planning a research project the choice of designs and methods should be dictated by the aim to limit bias. The research guidelines (CONSORT, STROBE/RECORD, PRISMA) all advocate transparency and limiting bias in research. There are many different types of research bias including selection bias, recall bias, attrition bias, publication bias. The main bias relevant in our articles is selection bias. An example would be that patients with dual-mobility cups are more prone to dislocation.

We used block randomization in Article 1 and sequential randomization (not block randomization) in Article 2. In both studies patients were blinded to the intervention, but surgeons were not (single-blinded study). As part of the data analyses, we checked patient characteristic data to ensure that the groups did not deviate after randomization. This was important when interpreting results (check for successful randomization). Successful randomization ensures equal groups and removes confounding.

The types of measuring properties and characteristics of the outcome measure determines effect size (power calculation). In both Article 1 and 2, the primary outcome was measured with RSA, which is a method with high accuracy and therefore power calculation yielded a relatively small sample size (17 patients in each group for both studies). To allow for potential drop-outs sample size was increased to 64 patients (66 hips) and 68 patients respectively for the two studies. If primary outcome for the two studies was PROMs, sample sizes would be required to be much larger based on the extent of accuracy and precision in PROMs .

Article 3 is an observational study. Exposures/interventions (i.e. head size, approach, fixation etc.) are not randomized, but rather influenced by the clinical situation; patient and surgeon factors. Therefore, confounding factors may alter the results. Confounding factors are factors

that affect both the intervention and the outcome. For example, if exposure/intervention is head size and outcome is revision due to dislocation, approach is a confounder because it may increasingly influence the surgeon to choose a larger head size diameter when using a posterior approach and at the same time posterior approach increases the likelihood of revision due to dislocation. In this case, if we do not adjust for posterior approach in the analysis, this confounder is likely to underestimate the risk of using a smaller head size diameter. This tendency is very clear in our data and shows a much higher risk of using small head diameters if approach is adjusted for in the Cox regression model. In order to plan what factors to adjust for in the analysis we constructed a DAG. Current evidence, clinical experience and common sense are all utilized to map which factors that affect clinical results for each exposure/intervention and outcome. This map (DAG) governs which factors to adjust for in the regression analysis. By actively evaluating which factors to adjust for we avoid the Table II Fallacy, which is to adjust for all measured factors without accounting for potential confounding for each individual exposure (203).

Radiostereometric (RSA) application and measurement error

RSA is highly accurate in evaluating the 3D migration of prosthesis components in relation to the surrounding bony structures in which they have been implanted. As any other method, RSA relies on accuracy and precision in order to limit measurement error. Accuracy being the closeness of agreement of one measurement compared to the actual value. Precision being how close one measurement is to another measurement given unchanged conditions and parameters. In order to have a set standard and a way to compare RSA methods across research groups the International Organization for Standardization (ISO) developed in 2013 the ISO 16087 (92).

Mean error (ME)

In RSA, the mean error (ME) is a representation of the mean change of markers over time – degree of change in position of markers in the same individual between the different follow-up times compared to the baseline. The ME should typically be ≤0.35. For Article 1 the ME was set at 0.30 and in Article 2 it was set at 0.35 which is acceptable and indicating that markers were localized within appropriate limits between the different time points for the examinations (204).

Condition number (CN)

The condition number (CN) is a number used to represent the distribution between markers. A high CN reflects poor distribution of the markers – markers more closely aggregated. CN number lower than a set threshold indicates appropriate distribution. For prosthesis studies involving larger joints such as the hip, knee and shoulder the recommendation is that CN should be <120. However, for smaller joints (cervical spine, hand/fingers) it is preferred that the CN is <150. For studies that accept higher CN numbers it is very important to validate the precision of the measurement.

The CN in Article 1 was set at <100 which is well within acceptable limits (1). However, despite the threshold setting for CN <100 the precision we reported was somewhat poorer than that reported by Börlin et al. in a comparable study (160). We have speculated that the precision may have been influenced by the particular uncemented acetabular shell that was used. The Exceed ABT shell has a rim flare and pegs to prevent rotation of the liner. The pegs made it in certain instances challenging to detect the actual opening of the cup. Also, we used ceramic heads in this study which could influence the marking of the femoral head. There could also potentially be differences in the difficulty of RSA marking 32mm heads compared to 36mm femoral heads (131).

In Article 2, we used a threshold setting for CN <150. This is a higher threshold than recommended for evaluating prosthesis components around the hip joint. However, there was a somewhat narrow field since only evaluation of polyethylene wear and cup stability was of interest and no RSA evaluation of the femoral stem was part of the study outcome. Since the threshold setting was higher than the recommended (<120) the precision of the measurements were particularly important. The differences between the double examinations were normally distributed and precision was given as 1.96 x standard deviation (SD). The absolute mean precision values for all the parameters (wear, translation and rotation) were lower than the standard deviations (2), which indicate adequate precision (92).

Strengths and limitations

Article 1 (6-year RCT uncemented VEPE 32mm vs. 36mm)

Methodological considerations to keep in mind regarding interpretation of this study, is that the study evaluated polyethylene wear properties at 6 years following a specific component combination with either 32mm or 36mm femoral head diameter. Inclusion criteria were specific, and all patients were operated at the same center. The randomized controlled design and the details mentioned above does not allow a broad translation of these research findings to the entire THA population. The external validity is narrowed down to the research setting described. Also, only VEPE uncemented cups were used and there was no control against a conventional polyethylene in this study, but a mitigating factor is that this was not an objective for this study.

The main limitation in this study was that the particular uncemented acetabular cup may have introduced bias as there were some edge detection problems. The anti-rotational pegs of the cup protrude and this may have made the markings on the periphery more challenging to detect. This may reduce the accuracy of the measurements thereby introducing bias. There were two outliers in the material which may be explained by the edge detection problems. Furthermore, our study sample fulfilled the preclinical power calculation, but the precision at 2-years was lower than expected based on previous studies.

The UCLA activity score was used to measure activity-level in the study population and to ensure similar groups. As this score is developed for an English-speaking population, this may have introduced bias due to less precise estimates of activity-level in the two groups consisting of a Norwegian speaking population. However, activity-level was not the main outcome of this study.

The strength of this study was that it was one of very few to measure polyethylene wear following patients with VEPE uncemented cups at mid-term follow-up (6 years). Also, the population was quite young, and follow-up was acceptable and allowed for few dropouts.

Article 2 (5-year RCT cemented VEPE vs. ModXLPE cups)

Methodological consideration regarding this RCT was that block randomization was not used. Block randomization ensures an equal number of patients in each study group and thus is more robust towards achieving sufficient power and equal number of patients in each group. The main limitation in this study was that the cemented acetabular cups used in the groups were not identical. Ideally, the only difference between the cups should have been that one contained infused Vitamin E and the other not. Therefore, outcome may be affected by other differences in the design of the cups than just the infused Vitamin E. This may introduce bias and affect the estimate. However, the issue of mixing components from different manufacturers has been shown in a study from the National Joint Registry of England and Wales not to increase revision rates as long as different femoral stems and modular heads are not used together (205). In our study, femoral stems and modular heads were from the same manufacturer and were the same in all patients.

Also, this study used a Vitamin E infused polyethylene which is for many a preferred method of introducing Vitamin E since it does not influence the cross-linking process that occurs during gamma irradiation. Adding Vitamin E to the resin powder (blending), which is the other option of introducing Vitamin E could potentially lead to less cross-linking since the free radicals that are produced during gamma irradiation are scavenged by Vitamin E as it acts as an antioxidant. This could potentially lead to less cross-linking of the hydrocarbon chains and thereby influencing the inert properties of the polyethylene.

Reorganization of Oslo University Hospital during the study inclusion period (2011-2013) reduced surgical capacity and increased waiting lists for elective patients with the consequence that these patients, although consented and included, underwent surgery at neighboring hospitals. As a result, data were missing for 15 patients (only demographic data were recorded for these 15 patients). However, the study sample was within the power calculation for RSA as polyethylene wear was the primary outcome. It was also within power calculation for measuring cup stability as other studies with cup stability as primary outcome had similar number of patients (56).

In this study, there were 12 different designated primary surgeons. However, five of these surgeons were experienced hip prosthesis surgeons, with prior experience with tantalum bead placement, and at least one of these five surgeons were present in all cases. One could argue

that 12 different primary surgeons add to the external validity of surgical technique (cup placement and cementing technique).

Article 3 (Registry study – risk factors associated with revision due to dislocation)

There are some important considerations to point out when interpreting results from this register study. Firstly, we are evaluating the risk of revision due to dislocation, not the risk for dislocation. Revision is a definitive endpoint which is reported in NAR, but closed reduction of dislocation is not. As a result, we used revision due to dislocation as a proxy for dislocation, because we were not able to calculate the risk for dislocation in the registry material. Therefore, because non-operated cases with dislocation are not reported, we must bear in mind that the number of dislocations most likely is much larger than the number of revisions due to dislocation. However, because revision is a definitive endpoint and coverage is high, the estimate of revision due to dislocation is likely to be precise.

The NAR register form is suboptimal with regards to evaluating polyethylene wear which may be related to prosthesis loosening and both late dislocations and late revisions due to dislocation. Since we included 1-year follow-up we concluded that articulation combinations (only material considerations and not head size evaluation) would play an insignificant role with regard to revision due to dislocation. Ceramic-on-ceramic articulation would potentially add an additional consideration since component placement (surgeon dependent) may be even more critical (206), and this articulation combination may have shown increased risk compared to other combinations. Regardless, this did not warrant undertaking an entire articulation evaluation based on 1-year follow-up. Also, there is quite a short time for follow-up of HXLPE in NAR, and even if there was longer follow-up time one would have had a shortcoming such as one would not only test polyethylene as a variable but rather also different types of prosthesis (late versus recent prosthesis types). Unknown variables would then play a role in addition to just the polyethylene. There could be additional surgeon factors or other types of methods that are not measured in the register which could confound results. There will for instance be a different time-period for UHMWPE and HXPLE and therefore difficult to evaluated results – UHMWPE and HXPLE are not likely to have been used during the same time-periods.

We could have simplified the articulation evaluation by dividing into three main categories including 1) metal-on-polyethylene (regardless of type of metal or polyethylene, both UHMWPE and HXLPE), 2) ceramic-on-polyethylene (indifferent regarding both type of ceramic and polyethylene), and 3) ceramic-on-ceramic (indifferent regarding type of ceramic). By doing this one could evaluate in a similar fashion as was done in a study by Cafri et al., where dislocation was evaluated within the first year based on metal vs ceramic on HXPLE and different head sizes. They found higher risk of dislocation with ceramic heads compared to metal femoral heads <32mm, but not with >32mm head sizes (184).

Revision surgery is also a challenging outcome measure because it is based on the clinical situation and shared decision-making (55). Thus, the decision to undergo revision surgery depends both on the patient and the surgeon – and there is no clinical consensus or guideline to depend on. The true estimate of risk for revision due to dislocation is likely to be precise in this study, but the risk of dislocation is likely to be substantially higher, but not lower.

This study reflects clinical THA practice in Norway. Both the coverage and completeness are high (14, 178). In fact, all centers and surgeons in Norway involved in THA report data. All patients who undergo primary THA or revision surgery are included unless they do not sign the informed consent form, or the form is not reported to NAR which is rare. The completeness of reporting was 97.5% and 93.1% for primary THA and revision surgery respectively for 2017-2018 (14, 178). Also, the study setting is multi-center and multi-surgeon.

This is a register study with an observational design. All included patients in this study have undergone THA, but the intervention (i.e. head size, approach, fixation etc.) was not randomized, but guided by a complex clinical situation (i.e. comorbidities, routines at operating center, surgeon and patient preferences). Factors that affect both the exposure (i.e. approach) and the outcome (i.e. revision due to dislocation) are called confounders and should be adjusted for. Factors that affect the outcome, but not the exposure are mediators and should not be adjusted for. In order, to develop a plan for adjusting our analysis we constructed a direct acyclic graph (DAG). This is a causal graph which helps to determine what factors to adjust for in the Cox regression analysis. We developed an assessment for all the factors or exposures we had access to in the data set. In addition, we identified some additional factors that may be relevant, but were unmeasured. The reason for conducting a causal graph was to limit bias and avoid Table II Fallacy (203).

The major limitation in the study is the unknown effect of unmeasured possible confounding factors such as activity-level, surgical experience, BMI, smoking and hospital routines. Interestingly, a recent Danish registry study from 2020 showed results indicating that a BMI >35 protected against hip prosthesis dislocation (180).

When interpreting register research, it is important to be aware of the inherent limitations in such observational, uncontrolled designs (207). We are not able to determine causality, but rather only associations (208).

The strengths of this study are the high external validity for THAs in Norway and the high precision (narrow point estimate) due to the large number of patients. Also, the measures taken to limit bias and the study setting, which allows for detecting trends over time, are strengths of this particular study.

11. Ethical perspectives

Declaration of Helsinki

Our research is in compliance with the Declaration of Helsinki (Statement #1–37) (209). In clinical research, we deal with individual patients. Respect and self-determination are both fundamental (Statement #8). In research and clinical practice, the patient has a right to make informed decisions (Statement #20, #21 and #22). Researchers and clinicians are therefore obliged to provide the necessary information to make these decisions. The patients decide whether they want to be included in research and they can at any time decide to withdraw from the study. In our two RCT studies, the patients eligible for inclusion were informed by orthopedic surgeons with oral and written information and signed informed consent forms prior to inclusion in the study. If the patient did not want to participate, they received the standard treatment of care. The main focus for investigators is the welfare for the patient/participants (Statement #2, #3, #5 and #10) rather than the research or society. Personal information was de-identified, and participants were labelled with a number which was documented in a key table for referral and was securely locked up at the study center. Only the principal investigator and study coordinator had access to this key table. All personal information and data were handled in accordance with appropriate guidelines and was stored anonymously. Each patient received a study ID. The randomization key and identity were stored separately. Informed consent was obtained from all included study participants.

The research builds on current scientific knowledge and explores current knowledge gaps (Statement #11). Potential risks, harms, and side-effects as well as benefits need to be thoroughly evaluated to be sure that the research is safe and beneficiary (Statement #16 and #17). In the two RCTs the potential risks were worse outcome following “new” implants. Prior clinical experience and documented research including both in vitro and in vivo studies showed no apparent detrimental effects. Nevertheless, history has shown that it is important to keep in mind Henry Malchau’s stepwise pyramid for including new technologies in order to avoid pitfalls (210, 211).

In Norway, the local hospital ethics boards, the Regional Committees of Medical and Health Research Ethics (REC) and the Norwegian Data Registry review and oversee research. For the interventional studies (Article 1 and 2) research protocols and informed consent forms were

reviewed and ethical approval obtained from the Regional Committees for Medical and Health Research Ethics (REC South-East). The REC numbers were #2008/10436 and #2014/1875 (Article 1), and #2010/2621a (Article 2). The registry study (Article 3) was observational, clinical data was registered but not altered by research. A priori developed research protocol (including ethical perspectives) was presented to the Norwegian Arthroplasty Register (NAR) board. NAR has precedent concession from Norwegian Data Registry (Statement #23). Trained investigators were involved in designing, conducting, and preparing the study for publication (Statement #15).

There were no conflicts of interests identified in the research group and this was declared in all three publications (Statement #27). Comparator groups were included in both RCTs. The patients were able to contact the research coordinator and were able to contact the research group if it was required or if any problems arose (Statement #30). We have an obligation to patients, who are willing to participate in research, to ensure that their contribution matters. When data is available, the data should in general be published to inform the public. Also, efforts should be undertaken to inform the contributing patient group.

Guidelines and registration

We adhered to established research guidelines to ensure transparency and limit bias in our research. Article 1 and 2 was based on CONSORT guidelines. Both RCTs were registered in clinical.trials.gov. Article 3 was based on RECORD which is an extension of STROBE developed for observational register studies.

Dissemination of results

Dissemination of research results is a very important aspect of research activity and a societal ethical obligation. The results culminating from the three articles have been published in (Article 1 and 2) or prepared for submission (Article 3) to internationally recognized peer-reviewed journals. The two clinical interventional studies have been published in Hip International and the Bone and Joint Journal, and the register study is currently in submission process (ACTA Orthopaedica). In addition, results have been presented (Article 1, 2 and 3) at leading national and international conferences (EFORT 2020 and 2021, International RSA Meeting 2021) as well as at the annual research day at Oslo University Hospital. The main

supervisor (Stephan M. Röhrl) is the former Head of the Norwegian Society of Hip and Knee Surgery (NSHKS) and member of Norwegian Arthroplasty Registrar (NAR) Reference Group. These are both organizations connected to the Norwegian Orthopedic Society (NOF). Through these associations, dissemination will be possible on a multitude of levels, reaching out to joint replacement surgeons in Norway through seminars at the annual conference and by annual national reports. Also, it will be important to reach out to the European Hip Society, which will enable us to promote final research results to European orthopedic arthroplasty surgeons through newsletters and presentations at the biannual conference. Dissemination to patients will be achieved through user involvement and through patient organizations (newsletters and web sites). However, it is important to keep in mind that all research findings need to be interpreted carefully and discussed in light of potential limitations in the methods used to obtain the data and who the data is representative for (publication bias).

12. Conclusion and clinical implications

Highly cross-linked polyethylene (HXLPE) infused with Vitamin E may show greater resistance to oxidative stress than the polyethylene used commonly today. If that proves to be the case, with its good wear rate resistance properties, there may be a shift in standard practice towards using Vitamin E infused HXLPE acetabular cups and liners. Implementing even larger head diameters could be an option if it is verified that these do not lead to excessive wear, thereby reducing dislocation rates. This may contribute to improved longevity of hip implants, and reducing the rate of revision surgery (both revision due to polyethylene wear/osteolysis/implant loosening and dislocation), which is an undesired concomitant to hip prosthesis surgery. Most of all, this would benefit the individual patient resulting in less comorbidities, and secondly it would have a significant impact on a socioeconomic level.

Many aspects within hip prosthesis surgery in Norway have since the turn of the century changed. Also, the information one may acquire from this thesis will be clinically relevant for health care personnel in that it may be a guide when deciding on local departmental routines while supporting clinicians in treatment decision making.

13. Future research

In the future I would like to continue working on incorporating new technologies to evaluate prosthesis longevity. Two areas that have been promising and of interest are within the field of computer tomography based modalities for evaluating prosthesis integration during real-time (Computer Tomography Implant Movement Analysis, CT-IMA), and wear and stability patterns over time (Computer Tomography Implant Micromotion Analysis, CT-MA) (212).

There are several possible continuations regarding register studies and hip prosthesis dislocation. One potential study would be to evaluate different types of polyethylene as a factor associated with the risk of revision due to dislocation. Potentially this would be valuable to consider in the Norwegian data set when there has been longer follow-up for the HXLPE alternatives. There are issues with regard to late dislocation once polyethylene wear and bone osteolysis develops. These issues will be interesting to evaluate in a few years once 10-15 years of HXLPE register follow-up data is available. Also, a register study addressing revision incidence for different types of polyethylene (1st generation HXLPE, ModXLPE, 2nd generation HXLPE) while looking at the association with different femoral head sizes (28mm vs 32mm vs 36mm) may be of interest. An interesting trend we found, which has also been discussed thoroughly in literature is whether 36mm heads reduce the risk of hip prosthesis dislocation compared to 32mm heads, and whether 40mm heads will result in still further benefit.

Another issue is that NAR is about to change to electronic registration and as part of this change the forms will allow for registration of closed reduction of hip prosthesis dislocations which would be a more direct measure of instability compared to revision due to dislocation.

NAR is also conducting register-based RCTs within knee prosthesis surgery and developing these types of studies for hip prosthesis surgery is a natural progression of this work (118).

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15. Papers I-III (appendix)

I

Original research article

HIP International

Low wear rate at 6-year follow-up of vitamin E-infused cross-linked polyethylene: a randomised trial using 32- and 36-mm heads

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Abstract

Background: Free radicals formed in the cross-linking process may over time alter the mechanical properties of highly cross-linked polyethylene. Vitamin E-infused highly cross-linked polyethylene was therefore developed to achieve low wear-rate and good mechanical properties in the long term.

Aim: To present 6-year results from the initial randomised controlled trial.

Patients and methods: We measured wear and periacetabular bone remodelling in cementless total hip arthroplasty; 32- or 36-mm Biolox Delta heads and vitamin E-infused highly cross-linked polyethylene (E-Poly) were used. Markerless radiosterometric analysis measured the *in vivo* wear and dual energy x-ray absorptiometry was used to analyse bone remodelling in 40 hips at 6-year follow-up.

Results: In the proximal direction the wear for 32- and 36-mm heads was 0.15 mm (95% confidence interval [CI], 0.08–0.21) and 0.06 mm (95% CI, -0.002–0.12), respectively ($p = 0.015$). However, between 3 months and 6 years (excluding the period of "bedding in"), the proximal wear for 32- and 36-mm heads was 0.10 mm (95% CI, 0.05–0.15) and 0.05 mm (95% CI, -0.01–0.11), respectively ($p = 0.12$). The annual proximal wear rate for 32- and 36-mm heads from 3 months to 6 years was 0.02 mm and 0.01 mm, respectively. There was no difference in bone remodelling around the cup from baseline to 6 years for the total material and no differences between study groups.

Conclusion: Wear of this vitamin E-infused highly cross-linked polyethylene is still low at 6-year follow-up, with no significant difference in wear from 3 months to 6 years between 32- and 36-mm heads.

Keywords
Cross-linked, hip, radiosterometric, RSA, THA, vitamin E

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Introduction

Polyethylene wear is a major factor contributing to revision of total hip arthroplasty (THA),[1–4] although loosening of these implants may be multifactorial.[5] Highly cross-linked polyethylene has documented low wear rates *in vivo*,[6–9] and seems to be superior to low or non-cross-linked ultra-high-molecular-weight polyethylene (UHMWPE) at mid-term follow-up in achieving low wear rates and less osteolysis.[10] Cross-linking of UHMWPE during the gamma irradiation generates free radicals and there has been some concern about whether these radicals may react with oxygen *in vivo*, leading to poorer mechanical properties of the polyethylene in the long term.[11] Infusion of vitamin E, after cross-linking the polyethylene, may be effective to protect against these free radicals.[12] When embedded in the polyethylene,

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vitamin E, with its anti-oxidative properties, then acts as a scavenger against free radicals.[12] We have previously reported early clinical results and low wear rate using this polyethylene in a randomised clinical trial (RCT).[13] There have been a few clinical trials presenting 2- and 3-year results,[14–16] and 2 studies have presented 5-year results.[17,18] To our knowledge, no long-term clinical follow-up studies have been published, and thus, the aim of this study was to present 6-year results from the initial RCT.

Material and methods

This study is an extension of a RCT comparing the wear of E-Poly (Biomet) highly cross-linked polyethylene high-wall liner using either 32- or 36-mm Biolox Delta ceramic heads (Manufactured by Ceramtec for DePuy).[13] A cementless Exceed ABT (Biomet) shell and a Corail (DePuy) cementless femoral stem were used in all patients. In the E-Poly (Biomet) liner vitamin E is infused after the polyethylene is irradiated.

Initially, 50 hips (49 patients aged 50–65 years, 35 women) were randomised; however, 6 patients were not available for 6-year follow-up (Figure 1). The details of randomisation, inclusion criteria, operation method, postoperative regime and clinical scoring have been previously published.[13]

To detect a wear difference of 0.1 mm (standard deviation [SD] 0.1), we calculated that 17 patients had to be included in each group to achieve a power of 80% with alpha 0.05. To allow for possible dropouts, we planned to include 50 patients.

All patients were operated on at a single institution in the period from January 2009 to February 2010. The study was conducted in accordance with the Helsinki Declaration and approved by the Regional Ethics Committee (REK) Sør-Øst, in Norway. The study was registered with Clinicaltrials.gov (Identifier: NCT00804388). All patients gave informed consent to participate in the study.

Patients

39 patients with 40 hips were available at 6-year follow-up for radiostereometric analysis (RSA) (Flow chart, Figure 1). To quantify wear rate from 3 months until 6-year follow-up (excluding the period of "bedding in") 19 hips in the 32-mm group and 20 hips in the 36-mm group were available for RSA. Regarding patient demographics and early complications we refer to results published after 2 years.[13] We used the Harris and Oxford Hip Scores preoperatively and at 2- and 6-year follow-up.[19,20] The University of California at Los Angeles (UCLA) score was used at 2- and 6-year follow-up to estimate the activity level of the patients.[21]

RSA (radiostereometric analysis)

Markerless RSA was performed postoperatively (mean 4 days, range 1–7 days), at 3 months and at 1, 2 and 6 years. We used a uniplanar calibration cage number 43 (RSA Biomedical, Umeå, Sweden), and a combination of one fixed and one mobile x-ray tube. Plain radiographs were taken in the supine position. Data analysis was conducted using UmRSA digital measure 6.0 (RSA Biomedical Umeå, Sweden). Mean error (ME) should be 0.30 or lower and condition number should not be higher than 100. Precision was estimated by 96 double examinations postoperatively and at 2-year follow-up.[13] It was expressed as an absolute mean plus 2 times the standard deviation (SD).[22] The precision of the 3-dimensional (3D) vector was based on the uncertainty of the three cardinal axis, given by the 2 SD of these axes.[13]

DEXA (dual energy x-ray absorptiometry)

Bone mineral density around the cementless implants was measured with DEXA on a Prodigy scanner (Lunar, Madison, WT). The scan taken postoperatively served as the baseline. Bone remodelling was measured as a change in bone mineral density from postoperative to 1, 2 and 6 years. During scanning, the patient was placed in a supine position and a foot brace was used to standardise the position. Our aim was to include the distal sacroiliac joint and the tip of the femoral stem in the scan. The paint facility option was used to exclude non-bony structures. Around the cup we analysed three regions of interest (ROIs) as modified DeLee and Charnley zones. These zones have been described by Field et al.[23] and we have used these zones in a previous study using cemented cups.[24] We positioned all ROIs in each patient and they were copied and placed as accurately as possible in the same manner in all subsequent scans for each individual. We performed double examinations. In between these examinations the patients were asked to stand up and they were then repositioned to estimate the coefficient of variation (CV). To calculate the CV, we used the formula: $CV\% = 100\ [(\delta/\sqrt{2})/\mu)]$, where δ is the standard deviation of the difference of bone mineral density (BMD) between the double examinations in each individual, and μ is the mean of all the BMD measurements for each ROI.[25,26]

Radiology

Anteroposterior (AP) pelvic radiographs and lateral views of the femur were taken at 3 months and at 2 and 6 years. We used Mdesk version 3.0 (UmRSA Biomedical,Umeå, Sweden) to measure implant position and to identify any signs of radiolucency at 2-year follow-up.[13] This tool was

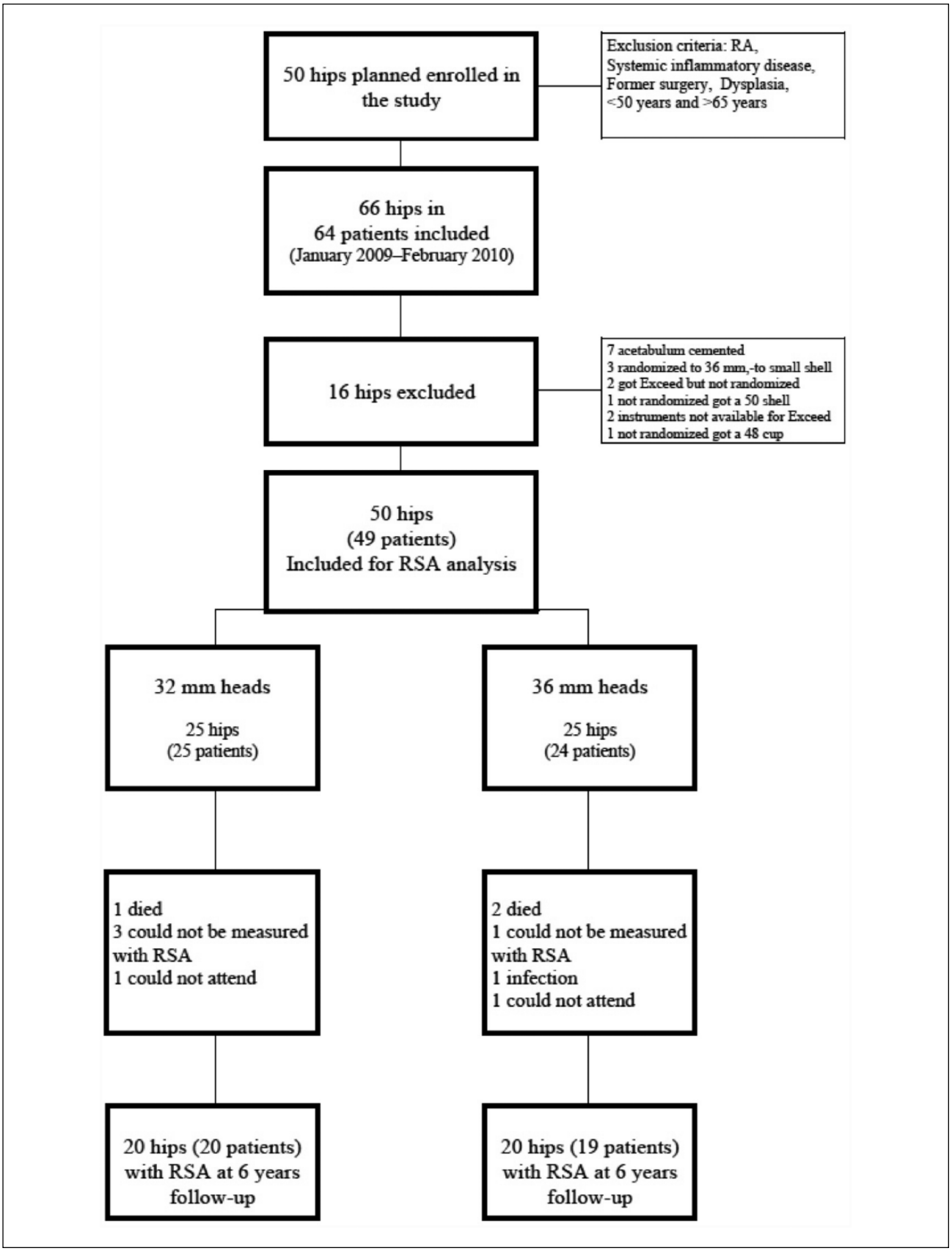

Figure 1. Flow-chart showing the inclusion and exclusion of patients and reasons for not attending 6 years follow-up of RSA.

Table 1. Wear from baseline (including "bedding in" to 6 years [mm]) using 32- and 36-mm heads.

Wear direction	32-mm heads		36-mm heads		Mean difference (95% CI)	*p**
	Mean	SD	Mean	SD		
x	0.087	0.119	0.020	0.090	0.068 (0.000–0.135)	0.091
y	0.147	0.134	0.057	0.126	0.090 (0.007–0.173)	0.015
z	0.121	0.199	0.054	0.110	0.066 (-0.037–0.170)	0.327
Total 3D	0.290	0.170	0.184	0.086	0.107 (0.192–0.194)	0.015

SD, standard deviation; CI, confidence interval.
*Non-parametric Mann-Whitney U-test.

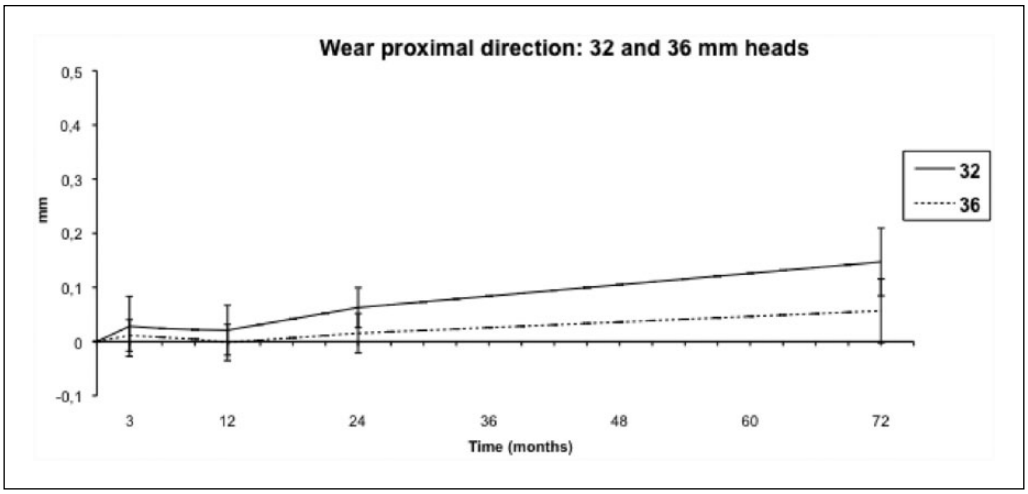

Figure 2. Wear for 32- and 36-mm heads in the proximal direction.

also used at the 6-year follow-up to measure radiolucency around the implants. The bone had no tantalum markers so we could not measure the migration of the stem with RSA. Subsidence of the stem on conventional radiographs was not measured.

Statistical methods

We used the SPSS statistical software, version 22 (IBM corp., Armonk, NY) for all statistical analyses. The non-parametric independent samples Mann-Whitney U-test was used to test for differences between the 2 groups (32- and 36-mm heads). Wilcoxon signed rank test for related samples was used to test for changes between different time periods. To calculate the effect size we used an independent sample t-test. *P* values less than 0.05 were regarded as statistically significant.

Results

Clinical

At 6-year follow-up, the mean Harris Hip Score (HHS) was 97 (95% confidence interval [CI], 94.5–99.4) and the mean Oxford Hip Score (OHS) was 14 (95% CI, 12.7–15.9) for the 32-mm group compared to 98 (95% CI, 96.7–99.4) and 13 (95% CI, 12.2–14.2) for the 36-mm group. Neither the HHS nor the OHS differed significantly between the 2 study groups. The UCLA score was 7.0 (95% CI, 6.3–7.6) and 6.7 (95% CI, 5.7–7.6) for the 32- and 36-mm groups respectively at 6 years.

RSA

20 hips in each group could be measured with RSA in order to estimate wear from the baseline scan taken postoperatively until 6-year follow-up (Figure 1). At 6 years, we found that wear (including "bedding in") in the proximal direction for 32- and 36-mm heads was 0.15 mm (95% CI, 0.08–0.21) and 0.06 mm (-0.002–0.12), respectively ($p = 0.015$). For the total 3D direction, wear in the same period for 32- and 36-mm heads was 0.29 mm (0.21–0.37) and 0.18 mm (0.14–0.22), respectively ($p = 0.015$) (Table 1) (Figures 2 and 3). From 3 months to 6 years, wear in the proximal direction was 0.10 mm (0.05–0.15) and 0.05 mm (-0.01–0.11) for 32- and 36-mm heads, respectively ($p = 0.12$). In the total 3D direction, wear from 3 months to 6 years was 0.09 mm (-0.02–0.20) and

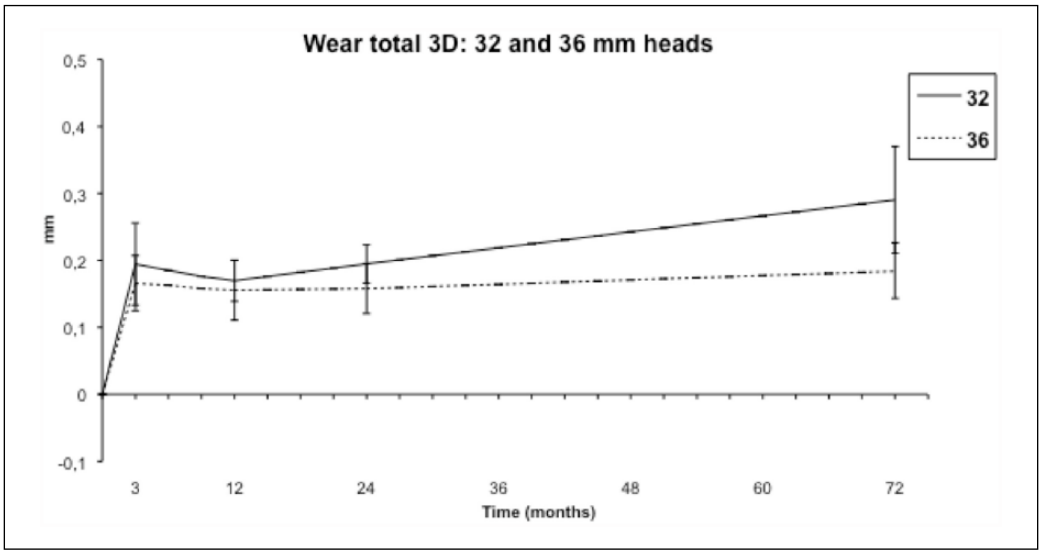

Figure 3. Wear for 32- and 36-mm heads in the total 3D direction.

Table 2. Wear (mm) from 3 months to 6 years follow-up for 32- and 36-mm heads in the proximal (y-axis) and the total 3D.

Wear direction	32-mm heads		36-mm heads		Mean difference (95% CI)	*p**
	Mean	SD	Mean	SD		
Proximal (y)	0.099	0.105	0.050	0.122	0.049 (-0.025–0.123)	0.27
Total 3D	0.090	0.229	0.023	0.114	0.067 (-0.053–0.187)	0.12

SD, standard deviation; CI, confidence interval.
*Non-parametric Mann-Whitney U-test.

0.02 mm (-0.03–0.08) for 32- and 36-mm heads respectively ($p = 0.27$) (Table 2). This corresponds to an annual wear rate in the proximal direction of 0.02 mm and 0.01 mm, from 3 months to 6 years, for 32- and 36-mm heads, respectively.

DEXA (dual energy x-ray absorptiometry)

The CV in ROI 1, ROI 2 and ROI 3 were 3.2 %, 1.7% and 2.0%, respectively. Comparing change in bone mineral density (BMD) around the cup in the 3 ROIs we found no difference between study groups at 6-year follow-up, and no statistically significant change in BMD between the baseline scan and 6-year follow-up. The BMD values at baseline and 6-year follow-up for the different ROIs are shown in Table 3.

Radiology

The groups were comparable regarding implant position at 2 years, with a mean inclination of the cup of 41° and 42° for the 32-mm and the 36-mm groups respectively.[13] All implants seemed to be well osseointegrated and well-fixed radiographically at both 2- and 6-year follow-up. There was no significant progression of lucent lines around the cup or around the stem for the total material from 2- to 6-year follow-up, and no difference between the study groups at 6 years.

Discussion

After 6 years, the wear of this vitamin E-infused highly cross-linked polyethylene is still low. We have not identified any adverse effects using this polyethylene. At mid-term follow-up, the remodelling of bone has not shown a decrease of BMD around the cup. Radiological analysis did not reveal progression of lucent lines around the cup and stem, and there was no difference between study groups at 6-year follow-up. The acetabular cups and femoral stems seemed to be well fixed without radiological signs of loosening. Therefore, the results so far are promising.

At 6 years follow-up we were able to measure 20 hips in each group (32- and 36-mm heads) with RSA. This is within the preclinical study power calculation. Baseline demographic data for the 2 study groups were comparable as described at 2-year follow-up.[13] There were no significant differences between the study groups using the UCLA activity score even at 6-year follow-up.

Table 3. BMD (Bone mineral density (g/cm^2) for the 3 ROIs at baseline and at 6 years follow-up. Mean difference between study groups regarding the difference of BMD at 6 years and baseline.

	Bone mineral density (BMD)				Difference of BMD at 6 years and baseline Mean difference between groups (95% CI)	*p**
	32-mm (*n* = 21)		**36-mm (*n* = 19)**			
	Post-op BMD Mean	6 years BMD Mean	Post-op BMD Mean	6 years BMD Mean		
ROI 1	1.43	1.42	1.63	1.55	−0.076 (-0.216-0.064)	0.555
ROI 2	1.46	1.42	1.46	1.39	0.031 (-0.090-0.153)	0.452
ROI 3	0.94	0.91	1.03	1.04	−0.037 (-0.106-0.033)	0.282

ROI, region of interest, CI, confidence interval.
*Non-parametric Mann-Whitney U-test.

In the previous published study at 2 years follow-up we noticed less "bedding in" for 36-mm heads compared to 32-mm heads at 3 months.[13] A recent *in vitro* study compared the effect of bedding in for UHMWPE and vitamin E-infused highly cross-linked polyethylene. They found that vitamin E-infused highly cross-linked liners showed greater resistance to creep than UHMWPE.[27] They found that the thickness and the internal diameter of the liner affected the creep behaviour of the polyethylene for both vitamin E-infused highly cross-linked polyethylene and UHMWPE. They showed that an increasing internal diameter, accommodating for larger heads, decreased the rates of creep strain significantly. This could partly explain why we found less bedding-in for 36-mm heads compared to the 32-mm heads.

RSA at 6-year follow-up revealed less wear for 36-mm heads than for 32-mm heads when compared with the baseline scan taken postoperatively. The increase in wear during the first 3 months is assumed to be the effect of "bedding in", seating of the liner into the metal shell, or tissue or blood interpositioned between the head and the liner.[13] Assuming that the initial 3 months is the "bedding in" period, wear could be analysed separately after this period. We therefore compared wear from 3 months to 6 years between study groups and again we found less wear for 36-mm heads, but not reaching statistical significance.

Several published studies, measuring wear of vitamin E-infused highly cross-linked polyethylene with RSA, have shown low wear at 2- to 3-year follow-up.[13–16] We have only been able to identify 2 studies using RSA and vitamin E liners with 5-year follow-up.[17,18] In the study by Nebergall et al.[17] they used 32-mm heads of cobalt chromium. The wear rate in the proximal direction was low and a total mean wear in this direction at 5-year follow-up (including "bedding in") was just 0.06 mm. This wear is comparable to the wear we found at 6 years for the 36-mm heads of Biolox Delta in the same direction. For the 32-mm heads, we found that wear in the proximal direction was somewhat higher, with a mean of 0.15 mm (95% CI, 0.08–0.21) between baseline and 6 years. This is comparable to the wear in the proximal direction found by Shareghi et al.[18] They found that the median proximal wear was 0.13 mm at 5 years follow-up with the use of 32-mm heads of cobalt-chromium.[18]

As we have discussed previously, there are some limitations to the current study.[13] A limitation of the UCLA activity score was that we used an English version on a cohort of Norwegian participants and some patients needed help with the translation and interpretation of this instrument. This may be a source for bias and lead to a less precise measurement of the activity level in each group. Furthermore, we used a validated markerless RSA method,[28] but the design of the Exceed cementless cup in our study made it difficult to measure. This cup has a rim flare and anti-rotational pegs securing the liner. These pegs protrude and make the marking of the periphery of the cup-opening somewhat difficult. This could influence accuracy as discussed previously.[13] Our precision published in the 2-year follow-up study was 0.17 mm in the proximal direction.[13] Even though the sample size was within the preclinical study power calculation, the sample size was small, particularly given that we assumed a better precision based on earlier RSA studies. Difficulties in marking the shells could theoretically make this method less accurate using this particular cementless shell, and with some measurements being outliers, this could influence the results. We also used ceramic Biolox Delta heads that might blur the exact contour of the femoral head, more than if cobalt chromium heads were used. However, if this resulted in a systematic measurement error, it would have been the same for all hips and at all time points.

In the current study we used ceramic heads and femoral stems from the same manufacturer (Depuy). The liner and the cup were manufactured by Biomet. There has been some concern regarding mixing components from different manufacturers.[29] However, in a study using data from

the National Joint Registry of England and Wales the authors found no increase in revision rates when mixing components unless heads and stems from different manufacturers were used together.[29]

RSA studies with 5 or more years of follow-up of highly cross-linked polyethylene have been published. Digas et al.[6] found mean wear in the proximal direction of 0.08 mm for Longevity liners and the use of 28-mm heads of cobalt chromium, at 5-year follow-up. Jonsson et al.[9], with 5-year follow-up, found wear of 0.10 mm and 0.12 mm in the proximal direction using cemented highly cross-linked polyethylene and 28-mm heads of cobalt chromium or oxidised zirconium, respectively. Röhrl et al.[8] analysed 8 hips with cemented Crossfire polyethylene and heads of metal. They found a proximal head penetration of 0.07 mm at 10-year follow-up. Nebergall et al.[7] analysed wear of Longevity liners at 13-year follow-up. Interestingly, they found a proximal wear of 0.10 mm and 0.03 mm using 28-mm and 36-mm heads of cobalt chromium, respectively. They could only analyse 5 patients in the 28-mm group and 6 in the 36-mm group with RSA at 13 years of follow-up.

However, the annual wear rates for both heads in the current study are low and we found no statistically significant difference between the 32- and 36-mm heads from 3 months to 6-year follow-up.

DEXA measurements around the acetabular cup did not reveal any significant bone loss compared to the scan taken postoperatively and no significant differences between study groups. Polyethylene wear, loosening and osteolysis have been major factors leading to revision when using conventional low or non-highly cross-linked UHMWPE in cementless cups.[3] A review of highly cross-linked polyethylene published by Kurtz et al.[10] found less wear and less osteolysis when using first generation highly cross-linked polyethylene compared to conventional UHMWPE. At mid-term follow-up, the current study shows both low polyethylene wear rates and no significant change in BMD around the cup.

The wear rate from 3 months up until 6 years was low and we found no differences between the 32-mm and 36-mm heads. The cementless implants seemed to be osseointegrated without signs of loosening and we found no statistically significant progression of lucent lines from 2 years to 6 years. Use of vitamin E-infused highly cross-linked polyethylene liners and 32- or 36-mm Biolox Delta heads in cementless total hip arthroplasty seems to yield good results up to 6-year follow-up. Still, further long-term evaluation and consideration are warranted regarding the mechanical properties and results of this polyethylene.

Declaration of conflicting interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: SMR: Educational course and travel expenses, 2011 from Biomet. LN: Has received earlier financial research funding for another study, and has lectured for Biomet Norway, Depuy and Ortomedic. Advisory board for Depuy and Biomet. EL and ØH: Reduced price of components used in the current study from Biomet, Norway.

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

F.nr. (11 sifre).....

Navn:.....

(Skriv tydelig ev. pasientklistrelapp – **spesifiser sykehus**.)

Sykehus:.....

HOFTEPROTESER

Alle totale hofteproteseoperasjoner og hemiproteser på annen indikasjon enn fraktur/fraktursekvele registreres her (hemiprotese for fraktur/fraktursekvele registreres på Hoftebruddskjema). Alle reoperasjoner skal registreres: skifte/fjerning av protesedeler, kantplastikk, bløtdelsdebridement, og operasjoner for protesenær fraktur eller gluteal svikt.

TIDLIGERE OPERASJON I AKTUELLE HOFTE (ev. flere kryss)
☐0 Nei
☐1 Osteosyntese for fraktur i prox. femurende
☐2 Hemiprotese pga. fraktur
☐3 Osteotomi
☐4 Artrodese
☐5 Totalprotese(r)
☐6 Annen operasjon .....

AKTUELLE OPERASJON (ett kryss)
☐1 Primæroperasjon (også hvis hemiprotese tidligere)
☐2 Reoperasjon (totalprotese tidligere)
☐3 Primær hemiprotese for annen indikasjon enn fraktur/fraktursekvele

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

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

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

A. Primæroper. pga (ev. flere kryss)
☐1 Idiopatisk coxartrose
☐2 Rheumatoid artritt
☐3 Sekvele etter frakt. colli. fem.
☐4 Sekv. dysplasi
☐5 Sekv. dysplasi med total luksasjon
☐6 Sekv. Perthes
☐7 Sekv. epifysiolyse
☐8 Mb. Bechterew
☐9 Akutt fraktura colli femoris
☐10 Annet.....
(f.eks caputnekrose, tidl. artrodese o.l)

B. Reoper. pga (ev. flere kryss)
☐1 Løs acetabularkomponent
☐2 Løs femurkomponent
☐3 Luksasjon
☐4 Dyp infeksjon
☐5 Fraktur i acetabulum
☐6 Fraktur av femur
Vancouverklassifikasjon, se bakside.
☐A ☐B1 ☐B2 ☐ B3 ☐C
☐7 Smerter
☐8 Osteolyse i acetab. uten løsning
☐9 Osteolyse i femur uten løsning
☐10 Implantatfraktur femurdel
☐11 Implantatfraktur caput
☐12 Implantatfraktur kopp
☐13 Implantatfraktur liner
☐14 Implantatfraktur annet: .....
.....
☐15 Gluteal svikt
☐16 Annet.....
(f.eks Girdlestone etter tidl. infisert protese)

REOPERASJONSTYPE (ev. flere kryss)
☐1 Bytte av femurkomponent
☐2 Bytte av acetabularkomponent
☐3 Bytte av hele protesen
☐4 Fjernet protese og satt inn sementspacer
☐5 Fjernet sementspacer og satt inn ny protese
☐6 Fjernet protese (Girdlestone eller fjerning av sementspacer)
Angi hvilke deler som ble fjernet.....
☐7 Bytte av plastforing
☐8 Bytte av caput
☐9 Bløtdelsdebridement
☐10 Ny protese etter Girdlestone
☐11 Resutur av muskel
☐12 Transposisjon av muskel
☐13 Osteosyntese for fraktur
☐14 Konvertering til hemiprotese
☐15 Andre operasjoner .....

TILGANG (ett kryss)
☐1 Fremre (Mellom sartorius og tensor)
☐2 Anterolateral (Mellom glut. medius og tensor)
☐3 Direkte lateral (Transgluteal)
☐4 Bakre (Bak gluteus medius)
☐5 Annen .....

MINIINVASIV KIRURGI (MIS) ☐0 Nei ☐1 Ja
LEIE ☐0 Sideleie ☐1 Rygg
TROCHANTEROSTEOTOMI ☐0 Nei ☐1 Ja

BENTRANSPLANTASJON (ev. flere kryss)
Acetabulum ☐0 Nei ☐1 Ja ☐2 Benpakking
Femur ☐0 Nei ☐1 Ja ☐2 Benpakking a.m. Ling/Gie

BENTAP VED REVISJON (Paprosky's klassifikasjon se baksiden)
Acetabulum ☐1 I ☐2 IIA ☐3 IIB ☐4 IIC ☐5 IIIA ☐6 IIIB
Femur ☐1 I ☐2 II ☐3 IIIA ☐4 IIIB ☐5 IV

PROTESEKOMPONENTER (Bruk klistrelapp på baksiden, eller skriv REF.NR.)

Acetabulum
Navn/Type .....
ev. REF.NR. ... .
☐ Med hydroksylapatitt ☐ Uten hydroksylapatitt
☐1 Sement med antibiotika – Navn .....
☐2 Sement uten antibiotika – Navn .....
☐3 Usementert

Femur (+ ev. trokanterdel)
Navn/Type .....
ev. REF.NR. .. ..
☐ Med hydroksylapatitt ☐ Uten hydroksylapatitt
☐1 Sement med antibiotika – Navn .....
☐2 Sement uten antibiotika – Navn .....
☐3 Usementert

Caput (+ ev. halsdel)
☐1 Fastsittende caput
☐2 Separat caput - Navn/Type .....
ev. REF. NR. .. ..
Diameter .....

ANTIBIOTIKAPROFYLAKSE ☐0 Nei ☐1 Ja

	Navn	*Dosering*	*Varighet i timer*
Medikament 1	.....		.....timer
Medikament 2	.....		.....timer
Medikament 3	.....		.....timer

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

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

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

OPERASJONSSTUE
☐1 "Green house"
☐2 Operasjonsstue med laminær luftstrøm
☐3 Vanlig operasjonsstue

OPERASJONSTID (hud til hud) .....min

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

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

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

2025016 Bergen Grafisk AS 04.2016

RETTLEDNING TIL HOFTEPROTESER

Registreringen gjelder innsetting, skifting og fjerning av totalproteser i hofteledd, samt kantplastikk, bløtdelsrevisjon for infisert protese og hemiproteser på annen indikasjon enn fraktur/fraktursekvele. Hemiprotese for fraktur/ fraktursekvele registreres på Hoftebruddskjema. Ett skjema fylles ut for hver operasjon. Fødselsnummer (11sifre) og sykehusnavn må påføres. Aktuelle ruter markeres med kryss. På eget Samtykkeskjema skal pasienten gi samtykke til rapportering til Leddregisteret.

AKTUELLE OPERASJON

Primæroperasjoner: Første totalproteseoperasjon, og første hemiprotese hvis denne settes inn på annen indikasjon enn fraktur. Hemiprotese for fraktur/fraktursekvele registreres på Hoftebruddskjema.

Reoperasjon (totalprotese tidligere): Fjerning av protesedeler (f.eks. Girdlestone) må registreres. Kantplastikk (f. eks. PLAD), bløtdelsrevisjoner for infeksjon, osteosyntese, resutur av muskel og muskeltransposisjon registreres selv om protesedeler ikke skiftes.

ÅRSAK TIL AKTUELLE OPERASJON

Kryss av under A ved primæroperasjoner og under B ved reoperasjoner. I B må du krysse av for alle årsakene til reoperasjon, eller forklare med fritekst.

REOPERASJONSTYPE

Fjerning av protesedeler (f.eks. Girdlestone) må registreres. Kantplastikk (f. eks. PLAD), bløtdelsrevisjoner for infeksjon, osteosyntese, resutur av muskel og muskeltransposisjon registreres selv om protesedeler ikke skiftes.

BENTRANSPLANTASJON Benpropp som sementstopper regnes ikke som bentransplantat. Vi skiller mellom benpakking og transplantasjon.

PROTESEKOMPONENTER: Acetabulum - Femur - Caput - Trokanterdel og hals hvis disse er separate deler

Bruk klistrelappene som følger med protesen. Lim disse på baksiden av skjema. Alternativt, skriv inn protesenavn + REF.NR., materiale, overflatebelegg og design. Sementnavn må anføres (bruk klistrelapp).

KOMPLIKASJONER Også operasjoner hvor pasienter dør på operasjonsbordet eller rett etter operasjon skal meldes. Ved stor blødning, angi mengde.

ASA-KLASSE (ASA=American Society of Anesthesiologists)

ASA-klasse 1: Friske pasienter som røyker mindre enn 5 sigaretter daglig.

ASA-klasse 2: Pasienter med en asymptomatisk tilstand som behandles medikamentelt (f.eks hypertensjon) eller med kost (f.eks diabetes mellitus type 2) og ellers friske pasienter som røyker 5 sigaretter eller mer daglig.

ASA-klasse 3: Pasienter med en tilstand som kan gi symptomer, men som holdes under kontroll medikamentelt (f.eks moderat angina pectoris og mild astma).

ASA-klasse 4: Pasienter med en tilstand som ikke er under kontroll (f.eks hjertesvikt og astma).

ASA-klasse 5: Moribund/døende pasient.

MINIINVASIV KIRURGI (MIS = Minimally Invasive Surgery**)** når det er brukt spesialinstrument laget for MIS.

ANTIBIOTIKAPROFYLAKSE Før på antibiotikum som er benyttet i forbindelse med operasjonen, f.eks.: Medikament 1: Keflin 2g x 4, med varighet 4,5 timer.

TROMBOSEPROFYLAKSE

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

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

BEINTAP VED REVISJON

Femur (Paprosky`s klassifikasjon)

Type I: Minimalt tap av metafysært ben og intakt diafyse.

Type II: Stort tap av metafysært ben, men intakt diafyse.

Type IIIA: Betydelig tap av metafysært ben uten mulighet for proximal mekanisk støtte. Over 4 cm intakt corticalis i isthmusområdet.

Type IIIB: Betydelig tap av metafysært ben uten mulighet for proximal mekanisk støtte. Under 4 cm intakt corticalis i isthmusområdet.

Type IV: Betydelig tap av metafysært ben uten mulighet for proximal mekanisk støtte. Bred isthmus med liten mulighet for cortical støtte.

Acetabulum (Paprosky`s klassifikasjon)

Type I: Hemisfærisk acetabulum uten kantdefekter. Intakt bakre og fremre kolonne. Defekter i forankringshull som ikke ødelegger subchondral benplate.

Type IIA: Hemisfærisk acetabulum uten store kantdefekter, intakt bakre og fremre kolonne, men med lite metafysært ben igjen.

Type IIB: Hemisfærisk acetabulum uten store kantdefekter, intakt bakre og fremre kolonne, men med lite metafysært ben igjen og noe manglende støtte superiort.

Type IIC: Hemisfærisk acetabulum uten store kantdefekter, intakt bakre og fremre kollonne, men med defekt i medial vegg.

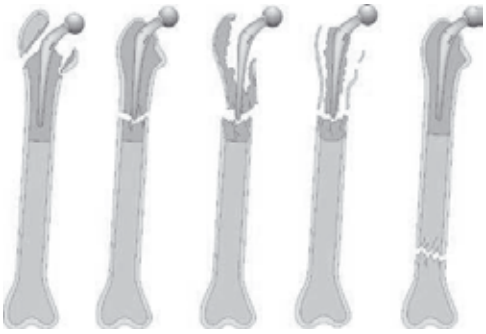
Type IIIA: Betydelig komponentvandring, osteolyse og bentap. Bentap fra kl.10 til 2.

Type IIIB: Betydelig komponentvandring, osteolyse og bentap. Bentap fra kl. 9 til 5.

Kopi beholdes til pasientjournalen, originalen sendes Haukeland universitetssjukehus.

PROTESENÆR FRAKTUR

Vancouverklassifikasjon



Type A Type B1 Type B2 Type B3 Type C

Kontaktpersoner vedrørende registreringsskjema er

Seksjonsoverlege Geir Hallan, tlf. 55 97 56 81 og overlege Ove Furnes, tlf. 55 97 56 90
Ortopedisk klinikk, Haukeland universitetssjukehus. Besøksadresse: Møllendalsbakken 11.
Sekretærer i Nasjonalt Register for Leddproteser, Ortopedisk klinikk, Helse Bergen:
Merete Husøy, tlf. 55 97 37 43 og Randi Furnes, tlf. 55 97 37 42
Epost nrl@helse-bergen.no Internett: http://nrlweb.ihelse.net/
Skjema revidert i november 2015.

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	(a) Yes, both in Title and Abstract (b) Yes	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	1.1: Yes, both in Title and Abstract 1.2: Yes, in Abstract 1.3 Not applicable (N.A.)
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	Yes, in Introduction		
Objectives	3	State specific objectives, including any prespecified hypotheses	Yes, in Abstract and Introduction		
Methods					
Study Design	4	Present key elements of study design early in the paper	Yes, in Abstract and Patients & Methods		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Yes, in Patients & Methods and Results		

Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case	(a) Yes, in Patients & Methods (b) Not applicable (N.A.)	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	6.1: Yes, in Patients & Methods 6.2: Not applicable (N.A.) 6.3 Not applicable (N.A.)
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	Yes, in Patients & Methods	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Yes, DAG (directed acyclic graph). Described confounders in which we were not able to adjust for.
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Yes, in Patients & Methods		

Bias	9	Describe any efforts to address potential sources of bias	Yes, in DAG (directed acyclic graph)		
Study size	10	Explain how the study size was arrived at	Not applicable (N.A.)		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	Yes, time periods (1-3)		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	(a) Yes, in Patients & Methods (b) Yes, in Patients & Methods (c) Missing data reported as missing (d) Not applicable (N.A.)		
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	12.1: Relevant data extracted and analysed.

				RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	12.2: Data were assessed per protocol (national based register study)
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	12.3: Person-level, no linkage
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	(a) Yes (b) Yes (c) Yes, used a Flowchart	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Yes, Flowchart provided
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	(a) Yes (b) Not applicable (N.A.) (c) Yes, follow-up time was described (0-1 years – endpoint: revision due to dislocation within 1 year after primary THA)		

Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures	Yes		
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	(a) Yes (b) Yes (c) Not applicable (N.A.)		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Yes		
Discussion					
Key results	18	Summarise key results with reference to study objectives	Yes		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes, in Discussion section	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over	Yes, addressed in the Discussion section

				time, as they pertain to the study being reported.	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Yes		Yes, addressed in in detail in the Discussion section
Generalisability	21	Discuss the generalisability (external validity) of the study results	Yes		Yes, addressed in Strength and Limitations section
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Yes		No funding (National based registry study)
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	References provided in manuscript

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.