Improvements in hip arthroplasty - did they work?

Evaluation of different articulations and fixation concepts

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To Erika,

Ebba and Arvid

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Evaluation of different articulations and fixation concepts

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ABSTRACT

Today, total hip arthroplasty (THA) is one of the safest and most efficient surgical treatments. New materials, surgical techniques and design concepts intended to improve THA have not always been successful. Thorough preclinical and early clinical investigations can detect some aspects of under-performing, while continuing surveillance is recommended to detect and analyze reasons for any later appearing flaws. In this thesis, several ways to monitor and assess THA performance are explored and carried out, using survival analysis in registry studies, radiostereometry (RSA), radiology and clinical outcome.

In Paper I, a study using the Nordic Arthroplasty Register Association (NARA) registry shows that HRA had an almost 3-fold increased early non-septic revision risk and that risk factors were found to be female sex, certain HRA designs and units having performed few HRA procedures. Papers II and III contain comparisons of highly cross-linked polyethylene (XLPE) and conventional polyethylene (PE). XLPE had a considerably lower wear rate up to 10 years but showed no obvious improvements regarding implant fixation, BMD or clinical outcome. In the NARA registry, in 2 of 4 studied cup designs the XLPE version had a lower risk of revision for aseptic loosening compared to the PE version. Paper IV describes that stem subsidence and retrotorsion measured with RSA at 2 years predicted later aseptic stem failure in an unfavorably altered, previously well-functioning cemented femoral stem. In Paper V and VI, a novel approach to measure articulation wear with RSA in radiodense hip arthroplasty articulations was presented and evaluated. Subsequently, a comparison between ceramic-on-ceramic (COC) and metal-

on-conventional PE uncemented THA displayed a considerably lower wear rate, smaller periacetabular bone lesions and a relatively high squeaking rate, the latter with unknown long-term consequences, in the COC hips. Implant fixation, heterotopic ossification and clinical outcome did not differ between articulation types.

In conclusion, it was confirmed that implant surveillance can be done with RSA, also in radiodense THA. Early migration predicts later aseptic implant failure. Prolonged surveillance can confirm long-term material and design performance, verify or contradict anticipated advantages as well as detect unanticipated long-term complications.

Keywords: total hip arthroplasty, innovation, outcome

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SAMMANFATTNING PÅ SVENSKA

Höftledsprotes har från 1970-talet och framåt visat sig vara en av de mest säkra och effektiva kirurgiska behandlingsmetoderna med i genomsnitt mindre än 10 % risk för omoperation på 10 år. Cirka ca en miljon operationer görs årligen världen över. Då det fortfarande finns komplikationer, framför allt i form av proteslossning, vanligast i yngre åldrar (>60 år), pågår det en kontinuerlig utveckling av material, protesutformning och kirurgiska tekniker. Flera av dessa innovationer har på kortare eller längre sikt visat sig fungera sämre och innebära en större risk för omoperation jämfört med tidigare, välfungerande protestyper. Inom modern utveckling av material och protesutformning används omfattande laboratorie-, simulerings- och djurstudier innan proteserna opereras in på människor. Även om prekliniska studier visar lovande resultat kan man ändå inte vara säker på att den nya protesen eller det nya materialet kommer att fungera i klinisk praxis, vare sig på kort eller lång sikt. Man bör därför följa en specifik arbetsordning när nya material, protestyper och även operationstekniker införs i klinisk verksamhet.

Efter genomförande av prekliniska studier genomförs en pilotstudie där ett mindre antal patienter opereras, som härefter följs upp med metoder som tidigt kan ge en uppfattning om potentiella för- och nackdelar. En sådan metod är radiostereometri, med vilken man kan upptäcka rörelser mellan protes och ben eller slitage i protesdelar med en upplösning ner till 0.1 mm, förutsatt att protesdelarna syns tydligt på röntgenbilder. Vi vet sedan tidigare att så kallade mikrorörelser mellan protes och ben ökar risken för senare proteslossning. Slitage i kontaktytan mellan ledkula och ledskål kan orsaka uppluckring av benvävnad runt protesen eftersom mikroskopiska partiklar, som av slitageprocessen lossnat från ledytorna, aktiverar celler som bryter ner benvävnad. Förutom radiostereometri bör man följa de opererade patienterna med röntgenundersökningar och kliniska undersökningar samt ta reda på hur patienterna mår.

Om de tidiga utvärderingarna ger tillfredställande resultat, kan man förutom att fortsätta uppföljningen utöka antalet opererade fall för att förbättra underlaget och i större utsträckning täcka in individuella variationer. Multicenterstudier och protesregister med hög täckningsgrad är en effektiv metodik i utvärderingens senare skede. Till registren rapporteras vilken protes som använts vid operation och hur operationen gjorts. Dessutom registreras eventuella omoperationer, inklusive vad som gjorts vid och även orsaken till omoperationen. Numera samlar också vissa register information om patientens hälsa och utvalda symptom före och efter operationen, samt hur nöjd patienten blir med den inopererade protesen. Genom att sammanställa stora mängder data från många patienter med inopererade

proteser kan man utvärdera i vilken utsträckning som protesen ger förväntat resultat på kortare eller längre sikt.

I denna avhandling har vi studerat olika aspekter på samt utfört uppföljning av innovationer inom höftproteskirurgi och funnit att:

Sammantagna omoperationsrisken av icke-infektiös orsak vid två år är nästan tredubblad för en ytersättningsprotes jämfört med en vanlig höftprotes. Ytterligare riskfaktorer för omoperation är kvinnligt kön, vissa protestyper (fabrikat) och sjukhus/enheter som opererat få ytersättningsproteser.

Höggradigt korsbunden plast som utvecklats för att motverka ledprotesslitage slits mycket mindre än en äldre typ av plast när de 2 plasterna studeras i två grupper av patienter som opererats med samma utformning på ledskålen och under en period på 10 år. Vi kan dock inte påvisa någon skillnad beträffande protesernas fixation till ben, omgivande bentäthet eller patienternas funktion och aktivitet. När man i en registerstudie jämför utfallet för de båda plasttyperna i samma typ (fabrikat) av ledskål ser man en minskad risk för omoperation för icke-infektiös proteslossning i 2 av de 4 typer av ledskålar som studerades.

Ökade mikrorörelser uppmätta med radiostereometri vid 2 år ökar risken för senare icke-infektiös lossning av en väl fungerande cementerad protesstam, som efter smärre förändringar visade sig utveckla ökad risk för icke-infektiös lossning.

Vi har utvecklat och utvärderat en ny metod för att mäta ledslitage med radiostereometri på proteser där protesledens delar inte syns på en röntgenbild. Med hjälp av den metoden kan vi konstatera att en protesled med ledhuvud och ledskål av keramik slits mycket mindre än en led med ledhuvud av metall och en ledskål av den äldre typen av plast. Storleken på benuppluckringar runt ledskålen är mindre i en keramikled. Varierande förekomst av missljud (”gnissel”) från höftproteser med keramikled har tidigare rapporterats. Den protestyp som vi studerade uppvisade en relativt hög frekvens av missljud. De långsiktiga följderna av detta problem är okänt.

Sammanfattningsvis konstaterar vi att radiostereometri kan användas för att följa upp höftproteser på kort eller lång sikt, även där protesleden är skymd på röntgenbilder. Vi bekräftar återigen att tidiga mikrorörelser i en protes ökar risken för senare icke-infektiös lossning. Lång uppföljning kan belysa den långsiktiga funktionen hos en innovation, bekräfta eller förneka förväntade fördelar samt upptäcka eventuella okända nackdelar.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Johanson PE, Fenstad AM, Furnes O, Garellick G, Havelin LI, Overgaard S, Pedersen AB, Kärrholm J. **Inferior outcome after hip resurfacing arthroplasty than after conventional arthroplasty. Evidence from the Nordic Arthroplasty Register Association (NARA) database, 1995 to 2007.** Acta Orthop. 2010 Oct;81(5):535-41. doi: 10.3109/17453674.2010.525193.

II. Johanson PE, Digas G, Herberts P, Thanner J, Kärrholm J. **Highly crosslinked polyethylene does not reduce aseptic loosening in cemented THA. 10-year findings of a randomized study.** Clin Orthop Relat Res. 2012 Nov;470(11):3083-93. doi: 10.1007/s11999-012-2400-x.

III. Johanson PE, Furnes O, Ivar Havelin L, Fenstad AM, Pedersen AB, Overgaard S, Garellick G, Mäkelä K, Kärrholm J. **Outcome in design-specific comparisons between highly crosslinked and conventional polyethylene in total hip arthroplasty.** Acta Orthop. 2017 Aug;88(4):363-69. doi: 10.1080/17453674.2017.1307676.

IV. Johanson PE, Antonsson M, Shareghi B, Kärrholm J. **Early Subsidence Predicts Failure of a Cemented Femoral Stem With Minor Design Changes.** Clin Orthop Relat Res. 2016 Oct;474(10):2221-9. doi: 10.1007/s11999-016-4884-2.

V. Johanson PE, Shareghi B, Eriksson M, Kärrholm J. **Wear measurements with use of radiostereometric analysis in total hip arthroplasty with obscured femoral head.** In manuscript.

VI. Johanson PE, Shareghi B, Eriksson M, Kärrholm J. **Ceramic-on-ceramic versus metal-on-polyethylene articulation in uncemented hip arthroplasty. A prospective randomized study with 7 years follow up.** In manuscript.

CONTENT

ABBREVIATIONS

AOANJRR	Australian Orthopaedic Association National Joint Replacement Registry
CI	Confidence interval
COC	Ceramic-on-ceramic
CoCr	Cobalt-Chromium
CT	Computed tomography
FH	Femoral head
HA	Hydroxyapatite
HHS / HPS	Harris Hip Score / Harris Pain Score
HO	Heterotopic ossification
ME-RBF	Mean error of rigid body fitting
MOP	Metal-on-polyethylene
NARA	Nordic Arthroplasty Register Association
OA	Osteoarthritis / osteoarthrosis
PE	Non-crosslinked up to medium-crosslinked polyethylene
PJI	Periprosthetic joint infection
PMMA	Polymethylmetacrylate
ROI	Region of interest
RSA	Roentgen stereophotogrammetric analysis / radiostereometric analysis
SD	Standard deviation
SE	Standard error

SHAR	The Swedish Hip Arthroplasty Register
THA	Total hip arthroplasty
UHMWPE	Ultra-high molecular weight polyethylene
XLPE	Highly cross-linked polyethylene

DEFINITIONS IN SHORT

Articulation	Contact point or area, natural or artificial, between two skeletal parts that can move with respect to one another.
Biomaterial	Material used in devices that replace a part or a function in the body, in short or long term
Etiology	Medical term describing the reason for a disease or condition
Hardinge approach	A surgical approach to the hip joint, performed with the patient in supine or lateral position. The incision is made lateral to the greater trochanter and the hip joint is accessed by detachment of the anterior part of the glutaeus medius and minimus insertions.
Oxidation	Chemical reaction where a compound loses one or more electrons. Oxidation reactions within organic polymers cause chain scission and change of mechanic properties.
Ra	Classical measure of surface roughness / asperity defined as the average of individual heights and depths from the mean level of a surface profile
Radiology	Collection of diagnostic and treatment methods that utilize images of tissues and implants/instruments
Statistical power	The ability for a statistical method to detect an effect in a population, if the effect exists

1 INTRODUCTION

Hip osteoarthritis in its endstage is a severely debilitating condition that causes limited mobility, impaired social life and decreased overall quality of life. Hip OA normally presents with pain upon movement and decreased range of motion. Inflammatory symptoms occur more frequently as the disease progresses. It affects gait function and in advanced forms also decreases quality of sleep due to pain at rest.

The biological etiology of OA is a focus of intense investigation but still much is unknown about the molecular events leading to OA (1). Joint trauma, malformations and growth disturbances are known to be associated with OA (2). Such OA is labeled as secondary. On the other hand, primary OA has no obvious external or internal cause for the joint disease. Certain occupations (heavy manual workers e.g. farmers (3)) and activities (some contact sports on elite level (4)) have been associated with hip OA. Also, increasing age and body weight as well as heredity increases the risk for developing hip OA (2, 5).

Main treatment for hip OA is exercise, weight reduction, activity modification, pain medication and walking supports. Patients benefit from education on their condition (6). However, if the disease progresses or presents as a radiologically advanced disease with severe pain and disability, total hip replacement surgery has become an extremely successful treatment, enabling patients to regain quality of life and lost functionalities.

1.1.1 A brief early history

Based on post-mortem and early radiological findings of damage to cartilage and subchondral bone in OA, it has since long been conceptualized that removing the osteoarthritic joint or separating joint surfaces decrease OA pain. Based on this assumption several surgical treatments for hip OA have been developed.

Hip arthrodesis was described in the early twentieth century for unilateral cases of hypertrophic OA, OA secondary to childhood disease, joint infections and trauma (7). The procedure is still considered to be suitable for young patients with a unilateral non-inflammatory OA, provided that the patient is well-informed and that the surgeon is familiar with surgical techniques allowing for later conversion to a THA (8).

Osteotomies for ankylosed hips and joint amputations had some success in the early nineteenth century even if peri- and postoperative mortality was extremely high (9). Joint amputation was further improved by G Robert Girdlestone, who described a technique for a femoral head excision arthroplasty (10).

Interposition arthroplasty, separating degenerated joint surfaces with biological or artificial material, gained interest in the nineteenth century and continued into the following century. Adipose tissue, fascia lata, pig bladder and gold foil were some materials used with varying success (9).

In 1923, Marius Smith-Petersen further refined the concept of interposition arthroplasty by introducing the mold arthroplasty (11). He initially used glass molds, but due to their brittleness turned to Vitallium, an alloy of mainly cobalt, chromium and molybdenum. The Vitallium mold arthroplasty was the first joint implant that had any kind of systematic follow-up in larger numbers, reaching about 45 % of excellent or good results at two years (12).

The first artificial joint replacement is assigned to professor Themistocles Glück in the late nineteenth century (13).

1.1.2 Cemented hip arthroplasty

History

Professor Glück used a kind of bone cement, based on plaster of Paris and pumice, to achieve intramedullary fixation. His early attempts with arthroplasty failed due to inferior materials and deep infection (9).

The first documented use of acrylic bone cement in a hip arthroplasty was reported in 1952 by Sven Kiaer (14).

A modified Thompson stem was adopted into the McKee-Farrar arthroplasty, paired with a Vitallium metal cup, utilizing the concept of metal-on-metal bearings (15). Initially the stem was just inserted into the bone without any additional fixation and the cup was fixed to the acetabulum with a screw. Due to loosening problems and Charnley's early experience with cemented fixation, the developers started to use acrylic bone cement fixation for both stem and cup (15).

John Charnley was successful in creating his low friction total hip arthroplasty in the early sixties. In the previous decade, he had experimented with cemented fixation of a metallic stem and polytetrafluoroethylene (Fluon) cup, but abandoned Fluon due to inferior wear and creep properties (16). With UHMWPE as the cup bearing material and small femoral heads, Charnley

presented the first THA with a success rate anywhere near modern hip arthroplasty (16).

1.1.3 Uncemented hip arthroplasty

Despite trials with "cemented" fixation, Glück is considered to have designed and inserted the first uncemented joint replacement fixed with nickel-plated screws (9).

In 1938 Philip Wiles made early, mainly unsuccessful attempts to design a stainless steel hip arthroplasty using screw-fixated components and the first recorded use of a metal-on-metal articulation (17).

In 1946, the Judet brothers invented a hip hemiarthroplasty, that replaced the femoral head with an PMMA femoral head attached to the femoral neck with a PMMA rod extension. Because of frequent breakage, the implant was reinforced with a metal rod (18). The implant gained much attention but continued to perform poorly due to implant fracture and wear and was abandoned (9).

In 1940, Austin Moore used for the first time his self-locking hemiarthroplasty with stem fenestrations to allow for bony ingrowth (19). Frederick Thompson developed a hemi-arthroplasty stem in the early 1950ies (20). Both stems were made of Vitallium, supplied with a proximal collar and were initially intended for uncemented fixation.

The first versions of the McKee-Farrar prosthesis were cementless but suffered from severe loosening problems and hence cementless fixation was abandoned (15). The Ring prosthesis, also having a metal-on-metal articulation, had a modified uncemented Austin-Moore stem and a screw-fixed cup (21).

In the seventies it was perceived that cemented hip implants were prone to loosening due to the bone cement itself ("cement disease") (22) and therefore a multitude of uncemented implants were developed. The concept of porous surfaces emerged and immediate intraoperative stability was identified as crucial for subsequent fixation. Stem shapes were designed to achieve a diaphyseal or metaphyseal fit, or both.

Thigh pain and proximal stress shielding osteoporosis have been reported with stems that are osseointegrated along the whole stem surface as well as stems with a proximal fixation (23). Modern short stem designs with metaphyseal or even femoral neck fixation have currently been marketed. Studies with short- to midterm follow-up show good fixation (24-26), improved proximal bone stock preservation compared to conventional cementless THA (27), and a notable learning curve (28). Stem designs and hence also mechanical

properties can vary considerably (29) and therefore it may be inappropriate to extrapolate results between designs.

Early cementless cups were unsuccessful due to inappropriate surface texture and/or geometry, utilizing pegs, cylindrical or threaded shapes as well as simple smooth metal shells supporting polyethylene inserts (30-34). Subsequently, press-fit porous-coated designs have shown more reliable results (35). Most designs have screw holes to allow for intraoperative screw fixation in order to aid primary press-fit / friction fixation and increase the probability of osseointegration. The rationale for use of additional fixation with screws has however been debated (36). It has been a considerable development regarding polyethylene liner locking mechanisms in order to reduce PE wear between the cup shell and backside of the liner (37).

1.1.4 Cemented fixation

In cemented bony fixation, the two main interfaces (bone/cement and implant/cement) have some common prerequisites for optimal function. Generally, little or no movement is tolerated for the fixation to remain intact. Furthermore, the cement mantle has to be properly configured to remain intact and transfer loads adequately from the implant to the surrounding bone.

Bone cement

Contemporary bone cement is based on polymethylmetacrylate (PMMA) polymer, also used in constructional settings, e. g. acrylic glass, Plexiglas®. It has a good resistance to compression but is sensitive for tensional or shear stresses. In the body environment, bone cement has an apparent tendency to creep but also elastic properties enabling it to resist and compensate for repeated, cyclical compressive loading. However, cyclic tensional or shearing load may lead to fatigue fractures and especially if the cement layer is thin (38).

There are multiple commercial varieties of PMMA bone cement, with basically the same composition. In addition to PMMA polymer, inclusions of small amounts of methylmetacrylate monomer, clorophyll or other dyes, a radio-opaque substance like barium sulphate or zirconium dioxide, plasticizer as well as antiobiotic powder are present in the cement (39)

PMMA is the result of a polymerization of methyl-methacrylate (MMA) monomer in the presence of an initiating compound, benzoyl peroxide. The reaction starts when the mixture is heated to 100 ºC and is then exothermic. The reaction can be initiated at room temperature by adding an activator, usually DmpT (N,N-dimethyl-p-toluidine). In a clinical setting, bone cement is prepared by mixing powder containing PMMA powder, initiator, radiopacifier, antibiotic powder, dye and plasticizer with a liquid containing

MMA monomer, activator, stabilizer (hydroquinone, prevents premature polymerization) and dye. Prepolymerized PMMA powder decreases the polymerization heat generation and also diminish polymerization shrinkage from 21 % in pure monomer to an acceptable amount of 3-5 %. The curing of cement releases heat and local bone tissue temperatures up to 46 ºC have been recorded in vivo (40).

Handling and application is an important factor of bone cement performance. Successive introduction of techniques such as bone anchoring drill holes in the acetabulum, femoral distal cement restrictors, optimized bone-bed preparation including pulsatile lavage and cement pressurizers to improve cement penetration into cancellous bone, vacuum mixing in closed systems to reduce cement porosity, retrograde filling of the femoral canal to avoid air inclusions and stem centralizers and cup spacers to improve implant positioning and cement mantle quality have markedly improved results of cemented THA (41).

Bone - cement interface

In well-functioning cemented implants, minimal amounts of fibrous tissue are found at the junction between cement and bone. Bone cement is intercalated between viable bone trabeculae and revascularization has been observed close to the cement surface in animal studies. With decreasing thickness of surrounding cancellous bone and increasing local motion at the interface, the amount of fibrous tissue at the interface tends to increase (42).

Implant-cement interface

Implants are attached to bone cement in two principal ways.

In shape-closed (43) fixation, the implant has macroscopic dents and grooves to create a mechanic interlock with the cement. Polyethylene cups usually have coarse grooves and spikes whereas metal stems frequently are designed with a combination of more or less smooth shapes and a satin surface with an asperity (Ra) around 1-2 µm. Fixation in such an interface is dependent on interface stability and only minimal motion between implant and cement is tolerated (44). Motion at the stem-cement interface creates local shearing stresses that break the bond between implant and cement and increase the risk for abrasive wear and generation of cement and metal particles (45). A satin finish with surface roughness (Ra) around 1-2 µm has been associated with successful shape-closed designs but there is probably a considerable interaction between stem geometry and optimal surface finish (44). With smaller pores, interface motion increases due to less micro-interlock whereas larger pores increase the risk of abrasive wear.

Force-closed fixation (43) is associated with very slow and controlled movement between implant and cement combined with the plasticity of bone

cement. Stems are wedge-shaped in order to transfer weight-bearing load into compressional force within the cement mantle and highly polished (Ra<1, often much lower*)* to avoid abrasion against the cement surface (44). Slow and continuous progressive subsidence of the stem in the cement mantle has been demonstrated and is tolerated (46). Rapid subsidence will exceed the plasticity of bone cement, leading to cement fracture and stem loosening.

Cement mantle

The main purpose of the cement mantle is to keep the implant fixed while transferring loads between implant and bone. PMMA bone cement is sensitive to tensile and shearing forces and such forces need to be dispersed over some distance in order not to cause cement fracture. The cement mantle needs to be adequately thick to allow the force of load-induced micromovements to be transferred without creating local stress-concentration. Normally a cement mantle thickness of about 2-3 mm is required for sufficient load transfer and to avoid cement mantle breakage (47, 48). Concepts like centralizers on stem tips, PMMA distances on PE cup surfaces as well as anatomically shaped femoral stems have been shown to improve cement mantle quality when combined with a correct surgical technique (49-51). Areas with a thin or absent cement mantle, in particular around femoral stems, increase the risk of cement fracture, implant-cement debonding, local exposure to wear particles and subsequent loosening (52-54).

1.1.5 Uncemented fixation

Early uncemented implants had smooth surfaces and a geometry that did not allow for any efficient bone ingrowth and relied heavily on proximal collars for initial fixation (55, 56). Smooth or polished surfaces are now utilized in surface areas of contemporary uncemented implants where bone ingrowth is judged not to be desirable, e.g. on the distal part of some stem designs (57).

Cobalt-chromium and titanium surfaces with pore-sizes between 50-400 μm were found to be optimal for bony ingrowth (58). However, also implants with coarser (30, 59) or smoother surfaces (60, 61) have shown successful fixation.

The implant-bone interface in a stable uncemented fixation is characterized by close contact between living bone and the implant surface (62). No chemical bonds have been demonstrated between bone and implant. With increasing instability, the amount of fibrous tissue increases at the interface (58). However, some uncemented implants seem to be well-functioning despite thin radio-lucent lines found at the stem surface, interpreted as thin fibrous layers (63). Also, the fixation process of cementless implants seems to be associated with an initial seating into bone (64).

In the eighties, hydroxyapatite (HA) ceramic coatings were added to titanium implants in order to improve the osteoinductivity of implant surfaces (65). Some studies showed a favorable effect on implant migration (66) and osseointegration (67). However, the concept was also questioned due to concerns for third-body articulation wear from abraded HA particles (68). There is some evidence of no or even negative effects on implant survival (69-72). A great deal of contemporary commercially available uncemented stems and cups are HA-coated or have an HA-coated option.

Some cementless stem designs are anatomically shaped in order to achieve a more adequate proximal fit and initial stability. However, some of these stem designs have been prone to thigh pain (73).

1.1.6 Metals

A prerequisite for a biomaterial in order to function in an arthroplasty implant is mechanical properties good enough to endure relevant cyclical and non-cyclical loads without breaking while withstanding the corrosiveness of the physiochemical environment. In addition, it should be sufficiently biocompatible, i.e. not evoke a foreign body reaction or exert direct toxicity. Despite sometimes being toxic or irritable in solved or particulate form, certain metal combinations (alloys) have been proven useful for arthroplasty. In a stable situation, oxidation of these alloys forms a superficial oxide layer that seals the metal bulk from the corrosive environment, in a process called passivation (74). Passivation layers are able to prevent corrosion even when different metals in contact could create a Galvanic element. However, stability in such a contact is a prerequisite for corrosion resistance. Generally, corrosion progresses if the passivation layer is repeatedly broken (74).

Stainless steel

Stainless steel has been utilized in orthopaedic implants throughout the twentieth century due to corrosion resistance, mechanical stability and a relatively low price (75). It is included in a number of arthroplasty applications, mainly stems and femoral heads, including successful cemented implants like the Exeter stem. It has an elasticity similar to CoCr-alloys.

Cobalt-chromium alloys

Vitallium, a cobalt-chromium-based alloy initially used in dental implants, was identified as versatile and durable for arthroplasty devices, starting with the final version of the Smith-Petersen mold arthroplasty (11). Since then, cobalt-chromium-based alloys have become the most common metal alloys in hip arthroplasty. CoCr-alloys are mechanically relatively stiff and in some cases pronounced stress-shielding has been apparent when used in uncemented applications (30, 76). When used in cemented stems, CoCr-alloy stem designs include two of the most successful metal implants in THA, the Lubinus and

Spectron EF stems. CoCr femoral heads have been successfully combined with other types of metal alloys in the stem.

Titanium

Titanium alloys have been widely used for uncemented THA both at the femoral and acetabular side. Titanium has a good fatigue fracture resistance and is more elastic compared with stainless steel or CoCr alloys (77). It has been less used in cemented applications due to stem-cement debonding and loosening (44). Also, titanium alloys perform inferiorly in articulations due to high friction and wear. The titanium oxide passivation layer is mechanically weak and corrosion progresses at the articulating surface even when coupled with soft materials such as PE (78, 79)

1.1.7 Polyethylene

Polyethylene with the chemical formula $(C_2H_4)_n$ was discovered by mistake, in 1898. Similarly, an industrially practical synthesis method was revealed in 1933 (80). PE exists in a variety of types based on chain length and branching. Ultrahigh molecular weight polyethylene (UHMWPE) is currently widely used in industry, household and medical applications due to its ductility, elasticity, compression and creep resistance, toughness and relative chemical inertia. A typical UHMWPE molecule has a molecular weight of between 2 - 6 MDa, corresponding to 71,000 - 214,000 ethylene monomers (81). Like other PE forms, the basic microstructure of UHMWPE at room temperature is a mixture of amorphous and crystalline regions containing ethylene polymer chains (82). Also, an intermediate phase has been described. Crystallinity gradually decreases upon heating and reaches zero at the melting point at approximately 135 ºC (83).

Virgin UHMWPE resin is produced by polymerization of ethylene gas in the presence of hydrogen and a catalyst. PE powder is then compression molded or ram extruded into PE sheets or bars. After machining, the manufactured PE components are sterilized and packaged.

In addition to the mechanical properties, UHMWPE has low friction when articulated against a metal or ceramic surface. Until around the year 2000 it was the dominating type of soft articulation material in hip arthroplasty, despite clinically relevant susceptibility to wear (82). Attempts to improve wear resistance by adding carbon fibers (84) or high pressure recrystallization (85) failed. Also, the addition of calcium stearate may increase wear (86)

Early in the seventies, it was noticed that PE cups sterilized with gamma-rays had a better wear resistance due to PE chain cross-linking than cups sterilized with non-ionizing methods. Unfortunately, gamma-sterilizing in air also induced a strong tendency for the PE material to oxidize and degrade both

when stored in air and in vivo service. The proneness to oxidation was found to be caused by residual reactive free radicals created within the PE during irradiation. Free radicals within crystalline regions of the PE cause chain scission that gradually reduce molecular weight, turning the UHMWPE into a more brittle low-molecular, high-density type of PE. When gamma-sterilizing PE in an inert atmosphere, the proneness of oxidative degradation diminished but did not disappear (82)

In 1970, Oonishi and colleagues treated PE with gamma-irradiation up to 1,000 kGy (100 MRad) and used these cups in a small series of hip arthroplasties. A commercial device was launched but discontinued due to manufacturing problems. Despite no scavenging treatment for free radicals and thereby high levels of oxidizing agents, retrievals from the clinical trial showed unexpectedly low oxidative changes and low wear (87).

Based on early reports on the favorable results of Oonishi and colleagues, the development of highly cross-linked PE (XLPE) restarted in the nineties. XLPE was found to have reduced fracture toughness, fatigue strength and elasticity compared to virgin PE but also showed less creep (83). Wear was substantially reduced in wear simulator studies (88, 89). In commercially available varieties, virgin UHMWPEs have been irradiated with effective doses of 50-100 kGy (5-10 MRad). There has been a clear evolution of XLPE regarding methods to eliminate free radicals (90).

In the first XLPE generation, the irradiated PE was heated to just below (annealing) or above (remelting) the PE melting point, in order to eliminate reactive residuals. Crystalline regions unfold upon heat treatment, allowing for residuals to react and form additional cross-links.

Annealing does not completely unfold crystalline regions and has been shown to leave residual reactive compounds within the material. Oxidative changes in retrievals have been reported (90). Remelting further decreases fatigue crack propagation resistance (91) due to reduced size of crystals reformed after melting. Reactive residuals and oxidation have been found also in remelted XLPE retrievals, rising concerns for long-term oxidation (90).

Since annealed XLPE retain the physical properties of virgin PE better than remelted, two modifications to annealing was developed. Still, effective irradiation doses ranged between 50 and 100 kGy (5 - 10 MRad).

In sequential irradiation-annealing, the total cross-linking irradiation dose is divided in multiple irradiation - annealing cycles, which has been shown to improve radical elimination compared to first generation annealing (92). Also,

the outer 2-3 mm of surface XLPE layers having the highest oxidation index is removed before cup/liner machining (93).

In another modification, annealing is combined with a compression - deformation procedure, shown to further reduce the number of free radicals while introducing a slight anisotropy in the XLPE crystals. Theoretically, such an ordering of XLPE crystals can result in direction-dependent wear properties (94).

For both variants, laboratory tests show beneficial wear and mechanical properties as well as good oxidation resistance in accelerated ageing tests (92, 94, 95). Concerns remain whether free-radical elimination by annealing methods is efficient enough to prevent future oxidation in the XLPE material. Oxidative changes have been observed in sequentially irradiated XLPE (96).

A later approach to free radical elimination has been to introduce chemical scavengers into the PE, thereby eliminating the need for post-irradiation heat treatment. Alpha-tocopherol (vitamin E) has been found to be an efficient and non-toxic scavenger that can be incorporated into polyethylene (97).

In vitamin E-blended XLPE, alpha-tocopherol is mixed into virgin PE powder prior to consolidation. Due to the presence of a powerful anti-oxidant, irradiation doses are increased and well as vitamin E concentrations adjusted in order to achieve a cross-linking density equal to non-vitamin E XLPE (98). Several different formulations are present. In vitamin E-diffused XLPE, irradiated and machined PE cups are soaked in alpha-tocopherol. Due to the hydrophobic properties of both PE and vitamin E, the latter will diffuse into the former. A homogenization step with heating up to 120 ºC improves the spatial distribution of the infused anti-oxidant (97, 99).

Both varieties of vitamin E-XLPE have shown a good oxidation resistance as well as low wear in simulator tests (97). The long-term effects on mechanic properties and stability from adding a quite large chemical compound such as alpha-tocopherol in the XLPE chain framework is yet unknown.

Yet another approach to the reduction of oxidative potential is mechanical removal of XLPE surface layers containing high levels of free radicals after irradiation. By mechanically removing the superficial 5 mm layer of irradiated XLPE, oxidation propensity is claimed to be reduced (100). Laboratory wear and oxidation tests have shown low wear and good oxidative stability. To our knowledge, no clinical studies are published.

Major commercial XLPE brands are listed in Table 1.

Table 1. Examples of different XLPE brands used in THA (93, 100, 101).

Commercial name	Manufacturer	Irradiation type, dose (kGy)	Free radical reducing treatment	Sterilization	Clinical introduction
Crossfire	Stryker	Gamma 75	Annealing	Gamma 30 kGy / N2	1998
Durasul	Zimmer/Biomet	E-beam 95	Remelting	EtO	1998
Marathon	DePuy/JJ	Gamma 50	Remelting / annealing	Gas/plasma	1998
Longevity	Zimmer/Biomet	E-beam100	Remelting	Gas/plasma	1999
XLPE	Smith&Nephew	Gamma 100	Remelting	EtO	2001
X3	Stryker	Gamma 30 x 3	Annealing x 3	Gas/plasma	2005
ArcomXL	Zimmer/Biomet	Gamma 50	Compression / annealing	Gas/plasma	2005
AltX	DePuy/JJ	Gamma 75	Remelting / annealing	Gas/plasma	2007
E1	Zimmer/Biomet	Gamma 100	Vit E diffusion	Gamma 30 kGy / Ar	2007
Vitamys	Mathys	Gamma 100 (±10)	Vit E blending	Gas/plasma	2009
X-LINKed	Link	Gamma 75	Mechanical removal of layers with high levels of oxidation	EtO	2010
Vivacit-E	Zimmer/Biomet	E-beam, N.A.	Vit E blending	EtO	2012

1.1.8 Metal-on-polyethylene articulations

One of the main reasons for Charnley's success was the use of a small metal head and a cup made of UHMWPE creating a comparably durable low-friction articulation. The metal femoral head was highly polished to minimize abrasive wear and the head diameter was small (22 mm) in order to decrease sliding speed and thereby minimize friction and adhesive wear. The initial Charnley hip arthroplasty had an impressive durability (102, 103). Despite this, problems with polyethylene wear and loosening were identified and the combination of PE wear and a small femoral head diameter caused concerns for dislocation.

Larger FH diameters were found to generate more stable articulations due to an increased jumping distance, i. e. the distance the FH has to move from its seated position before it dislocates from the cup (104, 105). Larger FH, however, increase PE volumetric wear (106). In general, thin PE probably have greater contact stresses than thicker (107), and higher local stress concentrations are associated with increased wear (108). Polyethylene wear will with time remove sufficient amount of material to destroy the cup (109) or the liner, but will long before that have the potential to cause biologic reactions resulting in osteolysis and aseptic loosening, a problem already observed by Charnley, which later became more widely recognized (110).

XLPE has displayed little or no increase in volumetric wear with increased femoral head diameter, a finding that has entailed a revival of MOP articulations with large heads (>32 mm) in order to reduce the risk of dislocation (104). It remains to be seen if mechanical properties and wear resistance of XLPE will suffice to keep such articulations persistently intact.

1.1.9 Metal-on-metal articulations

McKee and Watson-Farrar (15) used metal-on-metal articulations based on cobalt-chromium alloy, initially probably based on availability. They later justified the use of a metal-on-metal articulation with the comparably low friction in a cobalt-chromium couple and the reported problems with early wear in metal-on-plastic articulations. Also, Ring used a similar metal-on-metal articulation (111). Due to articulation clearance mismatch, some of these early MOM hips malfunctioned due to equatorial head-cup contact and subsequent jamming (112). With the advent of Charnley's low friction arthroplasty and due to high rates of aseptic loosening, the use of MOM articulations dropped. However, hips where jamming did not occur were shown to have a long durability. Therefore, in the nineties, a renewed interest in MOM articulations emerged (113) due to their low articulation wear. The knowledge how to optimize articulation metallurgy, clearance and fluid film lubrication improved, which resulted in better wear characteristics (114). With MOM articulations, it was perceived that larger FHs could be used with no or very slight increase in wear (115). In the first decade of the twenty-first century, MOM articulations became increasingly popular introduced both as MOM versions of older implant designs as well as in hip resurfacings.

1.1.10 Ceramic-on-ceramic articulations

Ceramic materials were introduced into arthroplasty practice in the seventies (116). The problem with polyethylene wear was apparent at that time and the ceramic materials had an almost unmeasurable wear when tested in the laboratory (116). The first alumina-based ceramics were used in THA combining ceramic FH with cemented cups and were prone to both ceramic

fracture and aseptic cup loosening (117, 118). Refinement of the alumina ceramic material with smaller grain size and less porosity resulted in a less brittle and thus less fracture-prone alumina-matrix material (119). Also, uncemented titanium shells with ceramic inserts had better results with regards to cup loosening. However, liner rim fracture at liner insertion (chipping) emerged as a new mode of failure. Metal-ceramic composite inserts have been developed to eliminate this complication while adding another metal-to-metal interface with unknown consequences (120).

Phase-stabilized zirconia along with strontium was introduced into alumina ceramics around year 2000 in order to further increase fracture toughness (121). With this toughened ceramic, larger heads are commonly utilized in order to reduce dislocation risk (104).

1.1.11 Ceramic-on-polyethylene articulations

Coupling of alumina ceramic FH with PE cups has been shown to decrease PE wear compared to MOP articulations (122) and decrease risk for revision (123). Pure zirconium ceramic heads were introduced in the eighties for use with PE cups because of higher mechanical strength and further improvements in PE wear characteristics compared to alumina ceramics (124, 125). However, frequently the long-term PE wear increased because of material degradation due to Zr crystal phase transitions, causing roughened femoral heads (85, 126).

1.1.12 Hip resurfacing

Conventional hip arthroplasty requires resection of the femoral head and neck and utilize FH diameters smaller than normal anatomy. Due to stress-shielding, additional bone loss is noted during service and the small FH diameter increases the risk of dislocation.

Inspired by the concept of Smith-Petersen mold arthroplasty, early attempts with a hip resurfacing concept was made in the fifties by Charnley (127). He covered arthritic femoral heads with a metal cup and placed a thin Fluon cup in the prepared acetabulum. Postoperative pain relief and function were favorable but the Fluon cups failed within a few years. Subsequent attempts where Fluon was replaced with PE also failed because of excessive wear in large MOP articulations with thin and often poorly supported PE (114, 128). Additional complications noted at these early attempts were fracture in the remaining femoral neck and FH osteonecrosis (127).

Experience with conventional THA showed elevated wear, implant loosening and failure in younger patients compared to older. It was also realized that the MOM hips of McKee-Farrar and Ring that did not fail because of articulation clearance mismatch had a considerable long-term survival without apparent

complications (113, 114). Therefore, the concept of hip resurfacing became even more interesting for younger, active patients. Hip resurfacing is postulated to be an anatomically correct hip replacement with low dislocation risk and minimal bone loss due to the surgery method and subsequent stress-shielding (114).

Consequently, the current concept of hip resurfacing was developed, in most cases as a hybrid implant consisting of an uncemented acetabular cup combined with a cemented femoral head cap with a short guide pin. Several designs with slight variations in implant geometry, articulation clearance and metallurgy have been marketed and widely used.

1.2 Modes of failure

A well-functioning implant is appropriately fixed in the periprosthetic bone, does not cause its bearer any considerate pain neither at rest or at weight-bearing and also allows a functional range of motion without dislocation. In addition, it should be biochemically inert, i. e. not cause any local or systemic reaction. When failing, an implant usually displays one or more of the following failure mechanisms. In many, but not all cases, the symptoms of a failed implant can be relieved with revision surgery, partly or completely replacing the implant, sometimes combined with soft-tissue and/or bony procedures.

1.2.1 Implant wear

The concept of wear applies to material loss during normal and abnormal motion in an arthroplasty articulation. In normal THA joint motion, articular surfaces are sliding against each other without any intermittent articular separations. Any irregularity on one surface will rub off fragments of the opposite surface, giving rise to abrasive wear. During sliding motion, contacting parts of the surfaces tend to adhere to each other, with a bond sometimes strong enough to rip away adhered fragments, generating adhesive wear (129). In addition, abrasive particles that gain access to the articulation can cause additional abrasive wear (third body wear) (130). With neck-rim impingement and/or articulation surface separation, further wear can be generated due to high point contact stresses and possible fracturing or chipping of articulation surfaces. Articular surface separation can be caused by insufficient overall soft tissue tension, e g due to joint shortening, but possibly also by periarticular soft tissue imbalance. Neck-rim impingement is usually considered to be associated with malpositioning of stem and/or cup but could also be attributed to excessive joint range-of-motion (131).

Articulation wear can subsequently alter the geometry of the articulation and therefore give rise to dislocations and instability occurring several years after surgery (132). Extreme wear, described mainly in uncemented PE cups, can result in wear-through and thereby contact between metal parts of stem taper and the acetabular metal liner, leading to accelerated metal destruction and metallosis (133, 134).

Implant wear produces wear particles of varying number and size, depending on the type of articulation and material. Frequently such particles are biologically active. When presented to and ingested by immune cells, specific signal paths are activated leading to periarticular osteolytic activity (135) and/or local immunological tissue reactions (136). Particles produced within the prosthetic articulation, or at locations with abrasive wear, travel with the lymphatic system and have been found in histological samples throughout the body (137).

In MOP articulations without third body wear or rim impingement, PE particles are the sole wear product. Submicron PE particles activate macrophages and giant cells, that initiates a path-way leading to increased osteoclast activity and local osteolysis (138). Seemingly, there is an individual variation in PE particle susceptibility (139), and some patients never develop implant loosening or osteolysis despite obvious radiologically detectable wear. For susceptible patients with non- or moderately cross-linked PE implants, there seems to be a relation between PE wear and osteolytic activity (140).

Metal particles are generally smaller than their PE counterparts but hence have a high area-to-volume ratio. Therefore, despite low volumetric wear in MOM articulations, the biological particle effect can be considerable in the absence of radiologically detectable wear (141). Metal particles from CoCr alloys or stainless steel can activate macrophage osteolytic pathways (135). In addition, they can also activate lymphocytes that initiate ARMD (Adverse reactions to metal debris), which include metallosis (metal debris laden necrotic synovium), aseptic lymphocytic vasculitis-associated lesions (ALVAL) and formation of inflammatory pseudotumours (136).

Metal particles will dissolve and cause elevated levels of metal ions in body fluids such as blood and urine (142). Thus, unlike most other particles, metal particles are slowly eliminated through the renal pathway. Systemic toxicity has been reported due to implant produced metal ions (143). Elevated levels of serum cobalt and chromium are associated with ARMD but the adverse reaction can occur also with slightly elevated blood metal ion levels (144). Thus, there is no clearly defined threshold value for acceptable blood metal ion levels.

Alumina ceramic wear particles are scarce due to an extremely low volumetric wear and have also been shown to have weak biological effects (145). However, osteolysis associated with COC THA has been described (146-148). With ceramic fractures, the affected joint can be loaded with ceramic fragments of varying sizes. Often such ceramic debris is impossible to remove completely and may pose a third body wear problem to any subsequent implant with softer articulation surfaces (149).

Other particles occur that are not related to normal wear. Cement particles should normally not be generated in a stable fixed implant but can be produced, along-side metal particles, by abrasive processes around a stem loose within the cement mantle. Cement particles can activate osteolytic pathways, similar to PE and metal particles (135).

Hydroxyapatite ceramic coatings are dissolved and resorbed during the ingrowth process of uncemented implants (150) and thus normally create no particle problem during implant service. However, it is conceived that, during implantation, abrasive fragments of HA coating can be scratched off implant surfaces and cause third body wear (151).

1.2.2 Corrosion

Conditions that destroy the passivation layers of metal alloy implants can induce corrosion. Trunnion corrosion involving CoCr alloys have been identified as a cause of ARMD, despite normally displaying lower blood metal ion levels than for MOM articulations. The risk for trunnion damage and corrosion increases with larger FH diameters, especially for CoCr alloy heads and with multiple couplings, as in stems with modular necks (152, 153). Some reports from laboratory and retrieval studies state that current ceramic FHs may have a lower risk of trunnion corrosion (154, 155). Corrosion is also sometimes seen on the surface of stems intentionally or unintentionally migrating within cement mantles (156, 157). Pronounced corrosion with extensive metal defects may also lead to implant fractures (158).

1.2.3 Osteolysis

Osteolysis presents as linear or cavernous radiolucencies on plain radiographs. Pain can occur if the osteolysis is combined with implant instability, but isolated osteolysis with stable implants is usually symptom free. Small radiolucencies are common also in well-functioning and well-fixed hip implants and may in some cases represent bone voids remaining from surgery or representing remnants from arthritic bone cysts (159). A progressively growing bone void indicates an active osteolytic activity (140), which may lead to implant loosening or be an effect of the loosening process itself.

1.2.4 Implant loosening

Implant bone anchoring, whether cemented or uncemented, is crucial for long-time function and pain reduction in arthroplasty. In Sweden, implant loosening without signs of infection, i. e. aseptic loosening, is the main reason for THA revision (160).

Early instability, measured as micro-motion in newly implanted arthroplasty components, has repeatedly been shown to increase the risk of later implant loosening, both at individual implant level and for the implant design performance as a whole. Observed early migration rates vary between different cup and stem fixation concepts and attempts to establish group-level thresholds for acceptable early micro-motion based on multiple studies have been reported (161-163).

Excessive initial implant micromotion impair fixation by preventing bone healing and ingrowth in cementless fixation (164). Initial micromotions between bone and cement in cemented implants are also suggested to be caused by heat injury due to the intraoperative cement curing process (165). The produced heat causes periprosthetic bone necrosis that subsequently creates a fibrous layer inhibiting implant fixation. With modern cementing techniques for stems, the stem-cement interface seems to be the main interface of early micromotion (166, 167).

Loosening of a previously fixed implant involves a process that gradually weakens the fixation interface, eventually resulting in a complete and symptomatic loosening. In cemented implants, this is often a slow and gradual process with slowly worsening symptoms for stems, while cup loosening can be asymptomatic also with advanced radiologic loosening. In cementless implants, loose stems tend to present with symptoms while for cups, a large osteolysis may be mainly asymptomatic until fracture through a portion of remaining bone fixation causes a sudden onset of symptoms, associated with a small or non-existent trauma. A completely loose implant is usually painful and urges for revision surgery without unnecessary delay, both because of patient suffering and the often rapidly progressing bone loss caused by the unstable implant.

It is unclear whether aseptic loosening in cemented implants is initiated at primary surgery or has a later onset, and whether it is mainly biological or mechanical. In cemented fixation, on the femoral side the process may be mainly mechanical with secondary osteolytic reactions (168), while the opposite may be true for cemented cups (169).

In cementless fixation, migration patterns that show fixed stems becoming loose after several years (170, 171) indicate a fatigue process in surrounding

bone weakened by progressive osteolysis and/or stress shielding (172). Cementless cups are less well studied.

Several other mechanisms for aseptic loosening have been proposed. Most likely, multiple mechanisms act simultaneously (173). Micromotion occurring within and close to compartments in well-functioning implants can create local fluid pressure fluctuations that may damage bone either by direct pressure effects or by creating micro-jets of fluid that erode or otherwise destruct bone tissue (173). Bacterial endotoxins remaining at the surface of implants or bone, either introduced at manufacture or in surgery, have been shown to induce osteolytic cells and have also been proposed as contributor to loosening (173), still considered aseptic due to absence of active infection.

1.2.5 Dislocation

A THA dislocation event is a painful and traumatic experience for the patient. It often results in a distrust of the operated hip and thereby puts restraints on activity and function. Dislocation constitutes the most common reason for early (within two years) revision surgery (174). The dislocation rate for primary THA has been reported at between 0.3 - 3 % (175) but in some studies up to 10 % are encountered (176). Recurrent dislocations despite revision surgery are not uncommon (177). Hip function tend to deteriorate with repeated dislocations and successful revision surgery does not restore full functional scores (178). A majority of dislocations occur within months after primary surgery and the risk is elevated by female sex, prior hip surgery, neuromuscular disorders, joint laxity, alcohol abuse, dementia or other inabilities to comply with activity restrictions (179, 180). Late THA dislocations occurring after at least five years in service can be caused by change of the geometry of the inner surface in PE cups altered by wear, change of cup position due to loosening and acquired neuromuscular dysfunction (181). Periprosthetic infection and ARMD could probably also cause THA instability and dislocation due to joint effusion. Misaligned implants increase the risk of dislocation and “safe” zones of implant positions have been proposed, both combined stem and cup positioning and for cup position alone (131). However, dislocations occur also in well-aligned THA without concomitant joint inflammatory processes (182). Posterolateral surgical approach has been shown to increase the risk of dislocation compared to lateral or anterior approaches (183).

Smaller FH diameters are associated with increased risk of dislocation due to a short jump distance (105). Therefore, many authors recommend the use of larger articulation diameters to decrease the risk of dislocation (184) usually in combination with wear resistant materials such as XLPE, ceramics or metal.

1.2.6 Periprosthetic fracture

No currently used implant has an elasticity modulus as low as that of bone tissue. Because of this elasticity mismatch, stress concentrations arise at implant borders, most apparent around the tip of femoral stems. Any torsional or bending force acting across the stem will concentrate around the tip of the stem, increasing the risk of fracture compared to the physiological state. Furthermore, stress shielding caused by a stiff implant creates local bone remodeling with loss of BMD. In accordance to Wolff's law, bone tissue adapts structurally to its applied local load and consequently unloaded volumes become osteoporotic and weakened, further increasing the propensity for peri-implant fractures.

Stem designs with elastic properties equal to bone in order to reduce stress shielding have been tried, but with disappointing results (185, 186).

Abdel et al report 3.5 % cumulative fracture rate at 20 years in an American registry study (187). There is an increased risk for uncemented stems and possibly also force-closed cemented stems (187, 188).

1.2.7 Intra-prosthetic fracture

Fatigue fracture is described in several biomaterials used for hip implant manufacturing. Cyclical loading with increased local stress concentrations constitutes a major risk factor along with internal properties of the biomaterial (189). PE cups and liners subjected to edge loading may fracture at the cup opening edge especially along elevated rims with PE parts poorly supported by a surrounding metal rim (190, 191). For metal parts, cyclical loading of an implant segment unsupported by surrounding bone, cement, metal or other material, may induce a fatigue fracture at the level where implant support increases (192, 193). Corrosion and high loads could increase the risk of implant fracture (158) and any irregularity at the tension side will also concentrate tensile stresses and act as an initiation site for crack propagation (193). Such irregularities can be caused by corrosion crevices but also by intra-operative denting or inappropriate manufacturing (194, 195)

A special case of implant fracture is burst or chip fracture of ceramic heads and liners. Ceramic FH fracture was fairly common with the first generation of alumina ceramics (120), but has been successively more infrequent as ceramic materials have been refined (117). The reported fracture rate of a modern Zr-doped Biolox Delta® ceramic is 0.003 % for ceramic heads and 0.03 % for liners (196). Surgical technique and proper handling of implants during primary surgery is important to avoid this complication, whose treatment may be complicated by the difficulty to remove very abrasive ceramic debris at the time of revision (117).

1.2.8 Periprosthetic joint infection (PJI)

Early attempts of arthroplasty surgery were unsuccessful due to inferior biomaterial properties but also suffered from extremely high infection rates. Professor Glück used his implants for tuberculous arthropathies resulting in a 100% chronic infection rate (13). Later, Charnley initially saw infection rates up to 9 % but was able to decrease infection rates down to about 1-2 % by using specialized operating theatres with exhaust gowns. With the addition of antibiotics into bone cement infection rates dropped further (197). Currently reported infection rates in THA are approximately 1 %. The real infection rate might be somewhat higher due to underreporting. Male sex, high age, increased ASA (American Society of Anesthesiologists) grade, diabetes mellitus, malnutrition, diseases associated with immunodeficiency, obesity, smoking and substance abuse increase the risk of PJI (198).

A PJI is a disastrous complication that in most cases requires at least one, but often multiple, surgeries ranging from soft tissue debridement with exchange of modular parts to total implant exchange in one or two stages (199). Reported infection eradication rates for surgical treatments vary between 70 - 90 % (200).

Basically, bacteria enter the artificial joint either at the primary surgery or by hematological spread from a separate infection site.

Bacteria exposed to surfaces like implants or dead organic material create and embed themselves in a biofilm layer that consists of proteins and carbohydrate-based compounds. During the process, they enter a semi-dormant stage where they are less susceptible to several antibiotics efficient for active bacteria in a planktonic stage. The ability for creating and sustaining biofilms as well as virulence vary widely between different bacterial species and strains. A periprosthetic infection with a highly virulent species such as Staph aureus may cause rapid sepsis and death while less virulent species like Staph epidermidis, the most common THA infecting agent, tend to cause low-grade, sometimes subclinical infections that create a low-grade inflammatory reaction and progressive implant loosening (200).

The treatment of a PJI includes thorough removal of bacteria-laden tissues as well as biofilms while securing bacterial cultures allowing for identification of the infectious agent and analyzing patterns of antibiotic resistance. Subsequent antibiotic treatment is prolonged (200).

1.2.9 Noise

Different types of noise can arise from a THA. Fairly common are dull clunks, pops or clicks in slightly unstable hips, presumably when the FH detaches and

then reseats into the cup cavity. Also grinding and crunching sounds can be experienced (201).

Squeaking denotes another type of noise arising in hard-on-hard articulations. Somewhat differing definitions have been proposed, but currently, squeaking is described as a high-pitched, audible sound experienced on movement of the affected joint and is rarely associated with pain (202). Mostly, the noise arises in flexion under load or at normal gait stance phase, either occurring after prolonged walking or immediately at the start of walking. It has been suggested that cup position in COC hips affects the precipitating type of movement. Neutral or retroverted cups tend to produce bending-related squeaking or delayed gait squeaking whereas anteverted cups squeak at normal walking (203). Squeaking rates in COC hips have been reported between 0.3 % (204) and 25 % (205). Squeaking in MOM hips are less well described but squeaking rates are reported between 2.9 % (206) and 10 % (127).

The mechanism of squeaking is not completely understood. Fluid film lubrication is crucial for low friction and low wear in hard-on-hard bearings. In circumstances where the fluid film is interrupted, as in edge-loading and/or separation between articular surfaces, as well as articulation clearance mismatch in MOM hips, squeaking is believed to be caused by stick-slip friction and thereby repeated catch-release between articular surfaces (207). The sound is then amplified by the attached implant(s). In COC hips, metal debris in the articulation as well as ceramic fracture may produce squeaking. Certain implant designs have been reported more prone to squeaking than others, perhaps due to acoustic resonance (202). Patient factors such as increased BMI and body height as well as male sex may increase the risk of squeaking but some studies fail to reproduce such a correlation (202).

Owen et reported a 0.2 % incidence of revision because of squeaking in COC hips al (205). In another work by the same group, 10/17 patients with squeaking hips described embarrassment, harassment and anxiety due to the prolonged noise (208) and one patient was scheduled for revision. Thus, squeaking in COC hips can cause their bearers varying degrees of discomfort. No other complications, such as loosening or osteolysis, have been associated with squeaking. However, retrieved components of squeaking COC hips frequently show signs of edge loading and stripe wear as well as neck-rim impingement and increased volumetric wear (209). The clinical long-term implications of these findings are still unknown.

A recent study comparing noises between MOP and COC THA indicated squeaking also in MOP THA (201). This is surprising and will have to be confirmed in further studies.

1.2.10 Heterotopic ossification

Heterotopic ossification (HO) is thought to be caused by inappropriate differentiation of pluripotent stem cells during healing of the surgical trauma (210). HO incidence is 5 - 90 % following THA, but the incidence of clinically relevant HO is considered to be 3 - 7 %. Early post-operative radiotherapy or NSAID/indomethacin therapy may be used as HO prophylaxis and could be considered if a high propensity for HO is suspected or established (211).

HO is classified according to Brooker (212). Brooker class 1 and 2 are most common and rarely cause any symptoms, whereas Brooker class 3 and 4 usually causes joint stiffness and sometimes also pain. Treatment include physiotherapy and in severe cases excision of ectopic bone (211).

1.2.11 Pain

Pain is normal in the early postoperative period up and will normally decrease gradually (213). Early persistent pain may be associated with complications such as periprosthetic infection or soft tissue ruptures but can also be neuropathic due to surgical damage to local nerves. Late occurring pain may be related to temporary overexertion and thus does not imply implant failure. However also implant complications like loosening, osteolysis, late occurring periprosthetic infections and ALTR may cause sudden or slow onset of pain (214).

Normally, persistent or recurring pain prompt for a thorough clinical and radiological work-up to reveal any condition that can be treated (215). However, when the etiology of pain is unclear, surgery is rarely if ever indicated due to poor results (214).

Patients with pain after THA are often concerned and bothered, and should not be dismissed since a sense of negligence will usually worsen the patient's symptoms and anxiety (216).

1.3 Concepts evaluated in this thesis

1.3.1 Hip resurfacing

Hip resurfacing arthroplasty has been widely adopted and used, mainly for younger active patients with primary and secondary OA. Early registry reports revealed elevated risk for revision for HRA compared to conventional THA (217). Concerns were expressed regarding MOM wear related complications as well as the classic and unique complications of femoral neck fracture and FH collapse due to osteonecrosis.

1.3.2 Highly cross-linked polyethylene

XLPE has been used extensively in THA from the end of the nineties. Early laboratory and RSA studies showed consistently reduced wear rates compared to non- or moderately cross-linked PE (82). In early studies, mainly on uncemented THA, in vivo wear and osteolysis were found to be reduced in XLPE compared to PE (218), and in a registry report the risk of revision was reduced for XLPE (219). Later registry studies showed inconsistent results (220, 221).

Cemented MOP articulations with XLPE are less well studied. Also, there are concerns regarding the long-term stability of the first generation of XLPE, due to oxidative degradation and fatigue failure (222).

1.3.3 Modification of a well-functioning implant

The Spectron® stem (Smith&Nephew, London, UK) is a shape-closed design cemented stem that was launched in its first version 1983. It was then a monoblock stem made of forged cobalt-chromium alloy and had a uniform satin surface finish with Ra 0.76 µm, a trapezoidal cross-sectional shape and longitudinal grooves at the anterior and posterior stem to facilitate rotational stability. FH diameter was 32 mm. The implant survival rate was 96% at 11 years in a randomized study (223).

In 1989, femoral head modularity was added along with a roughened proximal surface (Ra: 2.8 µm) and a distal finish somewhat smoother than previously (Ra: 0.7 µm). The altered implant was renamed Spectron EF (Enhanced Fixation). In the 2010 report from the Swedish Hip Arthroplasty Register, the 10 year risk for stem revision for aseptic loosening was 1% (174).

In 1995, a further design change was made, introducing distal centralizers, smaller trunnions and high offset option as well as two smaller sizes that are shorter and thinner than the previous version. The new stem, denoted Spectron EF Primary, replaced the preceding EF version more or less instantaneously. Inferior results have been reported with the new design, with revision risk for any cause up to 28 % at 11 years (224, 225).

There is some inconsistency in the reporting of failure rates for Spectron EF and EF Primary, apparently because several authors have not distinguished the two designs. However, Spectron EF stems operated after 1995 can be identified as Spectron EF Primary due to the manufacturer's complete exchange of assortment. These two designs were also separated in the SHAR when the Primary version was introduced.

Two RSA studies have reported comparably low subsidence and retroversion for Spectron EF Primary stems, but did not evaluate the correlation between early migration and subsequent loosening (226, 227). It is unclear whether the increased failure rate of the Spectron EF Primary stem could have been predicted by RSA.

1.3.4 Ceramic-on-ceramic uncemented THA

The majority of COC THA has been uncemented, due to aseptic loosening in early cemented ceramic cups. It has been hypothesized that the rigidity of the ceramic head and liner causes increased stress at the bone-implant interface and this could theoretically lead to increased migration also in uncemented components. However, a small randomized study by Zhou et al (228) did not reveal any significant difference in cup migration between MOP and COC articulations in an uncemented cup. Likewise in a more recent retrospective RSA study, the type of articulation, including COC, did not influence the migration pattern of short uncemented stems (229).

Retrieval studies of COC articulations with first generation alumina ceramics have occasionally revealed gross COC articulation wear after varying period of service (230-232). Corresponding studies with more recent alumina ceramics did not reveal any cases with excessive wear (233-235). Walter et al report overall low volumetric wear but increased wear in retrievals of squeaking compared to silent COC articulations (209).

Due to difficulty of radiographically delimitating the contour of ceramic FH in a COC articulation, there are currently no RSA studies reporting in vivo wear of COC articulations.

A previous review implies a lower osteolysis rate in COC THA compared to MOP THA (236). The included studies used plain radiographs. We are not aware of any studies comparing osteolysis in MOP and COC THA using computed tomography.

1.4 Tools of evaluation

1.4.1 Randomized studies

A randomized controlled study (RCT) is considered the ideal study design to detect or reject a causal relationship between phenomena. Prospectively randomizing each study subject (e. g. patient or hip) to either treatment or control groups is, when properly done, the safest way to create comparable study groups and thereby minimize selection bias. Ideally, to eliminate patient and observer bias, both patients and evaluators should be blinded, following

the concept of concealed assignment. In implant studies, total blinding is rarely possible due to practical and ethical reasons. However, there are reported exceptions (237).

RCTs usually demand considerable amounts of resources, thereby limiting the possible number of participants. Therefore, when large study groups are required to gain statistical power, as in studies of rare phenomena or outcomes with a large variation, the RCT design is unfeasible. In addition, external validity may be hampered by the fact that RCTs are frequently performed by highly specialized surgeons and address limited patient categories due to the need for extra appointments and lengthy follow-up.

1.4.2 Registry studies

Observational studies normally utilize data collected based on treatments not controlled by the investigator, often in large databases. Outcomes from different treatments can be analyzed and compared using appropriate statistical techniques adjusting for group differences. However, there is no method to completely eliminate confounding and hence observational studies at their best can detect possible correlation, not causality.

Large datasets can be created that, provided that data are collected correctly with minimized registration errors and missing data, are suitable for efficient analysis of unusual phenomena with low level of bias. Larger numbers also increase the ability to detect statistical correlations, i. e. increase study power.

The outcome of implant surgery is highly multi-factorial and multiple outcomes are relevant. Traditionally, time to revision surgery has been the most commonly measured outcome. However, not all failed implant will be revised, due to doctor and patient factors. Some cases where surgery have failed to improve or even have worsened the initial symptoms might thus not become revised, making the definition of implant failure difficult to delineate. Therefore, nowadays patient reported outcome measures (PROMs) are collected along with classic baseline patient and implant data as well as revision/reoperation and death/emigration. In addition, comorbidity and thereby preoperative quality of health may affect the outcome of arthroplasty surgery (238), even if a later study could not confirm (239). In Sweden, it has been increasingly common to link different health registries to analyze broader correlations between implant outcome and comorbidities (239-241)

The first orthopaedic implant registry, the Swedish Knee Arthroplasty Register, started in 1975. The Swedish Hip Arthroplasty Register was founded in 1979 and contains nearly 413,000 hip arthroplasties up to 2015 (160). Subsequently, numerous implant registries have emerged world-wide. The Australian Orthopaedic Association National Joint Replacement Registry

(AOANJRR) began data collection in 1999 and has rapidly grown to include a total of over 1,120,000 joint replacement procedures, including close to 500,000 hips (242). The Nordic Arthroplasty Register Association was initiated 2007 as a collaboration between hip and knee arthroplasty registries in Denmark, Norway and Sweden (243). Finland joined 2010 (244). Registry data from each participating country are anonymized and merged into a common database. The 2013 database contains over 620,000 hip arthroplasties performed since 1995.

1.4.3 Radiostereometry (RSA)

RSA is a radiographic method capable of measuring implant migration (translation and rotation) and wear with submillimeter precision and accuracy. Radiographic applications of stereo-photogrammetry methods had been previously evaluated but the RSA system as a total was developed by Göran Selvik (245).

Precision is defined as the variance around zero for double examinations performed at the same occasion (246, 247). Precision is determined for each mode of migration and is commonly expressed as a 95 or 99 % confidence interval distance from zero, indicating that a measured change exceeding the precision interval is likely to be a true difference.

Accuracy is the agreement between RSA measured migration or wear compared to a gold standard method with higher precision (247). Commonly, RSA phantoms mounted to a micrometer device are used to evaluate accuracy at different translation distances (246).

Based on stereo-photogrammetry methods, RSA utilizes simultaneously exposed X-ray images taken at an angle from each other. An object of interest is depicted together with a calibration device called cage, a radio-translucent construct that contains radiodense markers, usually made of tantalum, at well-defined three-dimensional positions. The two-dimensional positions in the pairwise images for each cage marker are measured. Since the marker positions are known, an image coordinate system can be defined which is then used to determine the position of identifiable features in depicted objects. The two-dimensional position of bony structures and irregular implant parts are normally not unambiguously possible to define on radiographs and thus some kind of position marking is required (marker-based RSA), both for bone and implants. However, if geometrical properties are known, positions of implant parts or whole implants can be determined without specific marking (model-based RSA).

In the standard RSA coordinate system, the x-axis runs horizontally from right to left, y-axis vertically from caudal to cranial and the z axis horizontally from posterior to anterior.

Marker-based RSA

In marker-based RSA, bony parts and implants are marked with tantalum beads. Marking of metal implants is normally done on manufacturing while marking of soft parts such as cement, polyethylene or bone tissue is done intraoperatively. No adverse reactions to tantalum markers have been recorded so far.

Each analysis entity, such as an implant and its surrounding bone, should each have minimum three measurable markers that are mathematically coupled to form a RSA segment. Motion between segments at different time points can be analyzed by comparing the calculated three-dimensional positions of segments from sequential RSA examinations. Markers in a segment must be sufficiently fixed in order to minimize the inter-examination three-dimensional error of the segment geometry, named mean error of rigid body fitting (ME-RBF). Normally, an acceptable ME-RBF is considered to be <0.35 mmm (246). Since progressive marker loosening with increasing time since implantation is common, an excess of markers is often inserted, up to ten per segment.

In order to obtain sufficient precision both for translation and rotation, markers in a RSA segment must have a proper spatial dispersion in all three dimensions, denoted by the condition number (CN). CN=1 denotes that all markers are perfectly spread, i e can be positioned on the surface of an imaginary sphere while an infinite CN is assigned markers in perfect linear configuration. CN=150 has been recommended as an acceptable upper limit but this requirement can sometimes be relaxed depending on the marker stability of the measured segment and direction of migration (246).

Marker-less RSA

Three-dimensional position of radiodense bodies with known geometry can be analyzed without RSA markers. Spheroid femoral heads and semi-spherical uncemented acetabular cups are available for marker-less (model-based) RSA provided that contours are clearly visible on both images in a RSA examination. The three-dimensional position of the center of a FH can be calculated by analyzing the ellipsoid contour on the two radiographs with regards to the calibration cage coordinate system (248). The center of a hemispherical cup can be calculated in a similar fashion. In addition, cup rotation parameters, except for around the cup pole axis, can be determined by analyzing the elliptical contour of the cup opening (248). The accuracy of

marker-less RSA can be enhanced by combination of marker-based and marker-less methods (249).

The most advanced form of marker-less RSA is based on the analysis of contours of irregular implants, where the geometry is known either by standardization in manufacturing and utilizing CAD models or preoperative 3D-scanning (reverse engineering) of individual implants. For hip and knee implants, the precision is somewhat worse compared to marker-based RSA (250, 251). Despite this, the method can be motivated since RSA marker insertion upon manufacturing is expensive and can be criticized for altering implants in unpredictable ways. In addition, markers in implants are frequently difficult to identify.

Migration

Migration of a segment is measured in six dimensions, translation and rotation along the x-, y- and z-axes. In some instances, also the Pythagorean sum of translations are presented, 3D-migration, which represents the absolute value of the maximum vector of movement (246). In marker-based RSA, translations and rotations are calculated at the geometrical center of the segment.

Migration between an implant and surrounding bone is commonly used to evaluate early and late fixation. It has been repeatedly shown that early migration of an implant can predict later aseptic loosening (161, 162, 252, 253).

Wear

THA wear is estimated by analyzing migration of the femoral head center, measured with marker-less geometrical shape RSA, with regards to markers in the cup/liner polyethylene or the cup shell measured with marker-less RSA. 3D-wear is commonly reported in accordance to 3D-migration.

1.4.4 Dual energy X-ray absorptiometry (DXA)

Periprosthetic bone mineral density (BMD) changes can be caused by several factors, such as stress concentration, stress shielding and osteolysis. If pronounced, these changes are visible on conventional radiographs, but in milder cases soft tissues obscure bone X-ray attenuation. In order to measure small or moderate changes in BMD, prior to clinical manifestation, more sensitive methods are needed.

With DXA, two different X-ray frequencies are used to produce an image where soft tissues can be subtracted from the image by its differing attenuation at the two frequencies (254). For THA, analyses are based on AP views. Results are mainly given as percentage change compared to a direct postoperative examination.

For femoral stems, analysis is divided according to Gruen regions (255). In multiple studies of conventional uncemented femoral stems, bone resorption was invariably observed in the proximal periprosthetic bone whereas for some stems, BMD was increased around and below the stem tip (27, 186). For short uncemented and neck preserving uncemented stems, proximal BMD loss was also observed but to a lesser extent. Occasionally in some regions in certain implants, BMD recovered to directly postoperative values with time (27). Cemented stems have shown a proximal bone loss pattern most prominent in the calcar region, with variations due to stem stiffness and design (256-258).

Studies on acetabular cups are rare and also frequently utilize variably defined regions of analysis. Uncemented cups tend to be associated with bone loss cranially and craniomedially combined with a tendency to gain BMD medially and inferiorly (259, 260). One DXA study on cemented cups (259) report an overall tendency to gain BMD cranial and caudal to the cup and to lose BMD medially at two years.

1.4.5 Radiology - fixation and bone deficiencies

Besides monitoring a patient's function and symptoms, radiographic examination is a crucial tool for the analysis of the state of an implant and its fixation. In some cases, as aseptic loosening of cemented cups or osteolytic bone resorption around a well-fixed uncemented cup, severe bone resorption can be seen on radiographs while the patient still has no or mild clinical symptoms.

Conventional plain radiographs are accessible, cheap and safe. They are useful for general clinical follow-up but have weaknesses regarding precision and detection ability. In a clinical setting, series of radiographs starting from the postoperative examination can and should be used to analyze initial implant positioning and any subsequent migration, quality of cement mantles, possible developing changes at interfaces, implant fixation and possible changes in surrounding structures including periprosthetic ossification, bony sclerosis and osteolysis. Relevant findings often motivate the use of other methods such as computerized tomography, magnetic resonance imaging and ultrasound imaging.

Implant fixation

Radiological signs of loosening have been widely described and several studies have correlated preoperative radiographs with findings at revision surgery.

For cemented cups, increasing extent of a radiolucent line in the bone-cement interface increases the probability that the cup is loose (261). The same authors concluded that a cemented cup that has migrated is always loose.

Harris et al proposed a staged definition of cemented stem loosening (262). A possibly loose stem has 50-99 % radiolucency between bone and cement. A complete bone-cement radiolucency indicates a probably loose stem, whereas migration at stem-cement or bone-cement interface, stem or cement fracture marks a 100% probability of loosening. For shape-closed stems, practically no migration is acceptable. Force-closed stems are found to slowly subside into the cement mantle and a small proximal-lateral debonding between stem and cement is normal for this type of stem design (46). Any cement fracture, however, indicate stem failure and need for future revision surgery (263).

Hodgkinson et al observed that a radiolucency in Charnley-DeLee zone 1 (264) of a cemented cup was associated with an increased risk of later aseptic cup loosening (265). This finding has been repeatedly confirmed (266-269).

Uncemented components are considered stable when showing signs of osseointegration.

On the femoral side, absence of radiolucent lines, occurrence of spot-welding and signs of local stress-shielding indicate osseointegration and a stable implant (63). A proximally fixed stem can be stable even if radiolucent lines are observed around the distal, non-coated part. Distal pedestals are associated with stem loosening only if concomitant radiolucent lines occur (263).

According to Moore and coworkers, 97% of uncemented, porous-coated cups are ingrown if they display three or more of five criteria more than two years after surgery: Absence of radiolucent lines, cortical thickening superolaterally and inferomedially, superomedial stress-shielding and radial trabeculation in Charnley-DeLee zones 1 and 2 (270). Radiolucent lines exceeding 1 mm and especially if progressive have also been regarded to indicate loosening (263).

Osteolysis

Osteolysis around a cemented cup is normally clearly visible on plain radiographs. It is generally associated with signs of aseptic loosening and often constitutes a ballooning appearance with a distinct sclerotic border (271). However, computed tomography is frequently required to assess the severity of periacetabular bone loss, such as pelvic dissociation and deficiency of anterior or posterior pillars.

Osteolysis around cemented femoral stems usually also have a distinct radiographic appearance (272), but computed tomography is usually needed to assess bone loss and to delineate any secondary fractures caused by severe bone destruction.

Periacetabular osteolysis around uncemented cups is localized and normally associated with a stable, osseointegrated cup. Larger and expansive lesions in contact with the articular cavity either at screw holes or implant rims are considered to be lesions with actual osteolytic activity (140, 273). Small, non-expanding lesions with distinct sclerotic borders could also be remnants of osteoarthritic bone cysts. Pelvic osteolysis around uncemented cups is frequently not readily visible on plain radiographs (274). Multiple radiographic projections may be helpful, but regardless of technique used the inter-observer variation can be considerable (275).

Computerized tomography offers better detectability and in addition, lesion volume can be measured (276). Still, distinguishing between active osteolysis and inert bone cysts remains a problem. Generally, osteolysis is defined as a volume with clearly decreased attenuation, delineable with slightly or markedly sclerotic borders. Some authors have also proposed a lower lesion volume threshold of 10 cm3 for osteolysis (277).

1.4.6 Statistics

The statistical methods used are presented separately for each study below.

2 AIM

This thesis aims to answer the following questions:

I. Is the risk for non-septic revision within two years for a hip resurfacing equal to that of a conventional THA? Are there specific risk factors for non-septic revision at two years in hip resurfacing?

II. Does a cemented THA with a remelted XLPE cup provide less wear, better fixation, less osteolysis, less BMD loss and better clinical function compared to the same THA design with a conventional PE cup? Is the relative risk for cup revision due to aseptic loosening lower for the XLPE compared to conventional PE version when used in the same cup design?

III. Can early migration measured with radiostereometry predict later revision or radiographic failure for a modified version of a previously well-functioning cemented stem, presumed to primarily fail at the stem-cement interface?

IV. Can radiostereometry be used to measure proximal articulation wear in THA with an obscured femoral head by mathematically transforming stem displacements to the position of the femoral head?

V. Is the vivo wear lower for one and the same uncemented THA when used with a ceramic-on-ceramic compared with a metal-on-PE-articulation? Does the choice of articulation influence implant migration, rate and volume of periacetabular bone lesions, revision rate, heterotopic bone formation and clinical function?

3 PATIENTS AND METHODS

3.1 Paper I

1,638 HRA and 172,554 conventional THA hips with corresponding age intervals (12 - 73 years) were identified in the NARA database. Patients were operated between 1995 and 2007 for primary or secondary osteoarthritis. Case selection sequence and demographics at surgery are presented in Figure 1 and Table 2.

We compared the risk for non-septic revision up to two years adjusted for age at surgery (classified as ≤49, 50 - 59 or ≥ 60 years), sex, diagnosis (primary/secondary OA), operated side and nationality. In the same population, we also performed an age-stratified subgroup analysis, dividing the study group at age 50 years corresponding to the mean age at surgery in the HRA group.

Within the HRA group, we analyzed risk of early non-septic revision up to two years with regards to HRA design, hospital production volume (<70 or ≥70 HRA operations in total), age at surgery (≤49 or ≥50 years), sex and diagnosis (primary/secondary OA).

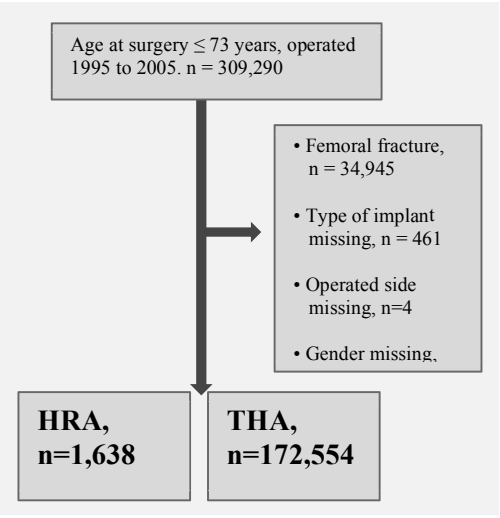

Figure 1. Case selection sequence

Table 2. Study group demographics

	HRA n=1,638	THA n= 172,554
Percentage males	68	43
Mean age, years (range)	51 (15-73)	62 (12-73)
Age groups, %		
< 30	2.1	0.6
30 - 39	8.9	1.8
40 - 49	31	6.1
50 - 59	42	23
60 - 73	17	69
Operated side, % (no.) Right	53 (861)	54 (93,866)
Diagnosis, %		
Primary OA	89	85
Inflammatory arthritis	2.2	4.3
Childhood diseases	6.5	6.1
Idiopatic femoral head necrosis	0.9	2.7
Other	1.0	2.1

In all analyses, we used Cox regression and calculated relative risk of revision with 95 % confidence intervals.

3.2 Paper II

60 patients (61 hips) suffering from primary or secondary hip osteoarthritis were randomized to receive a cemented Weber® cup (Centerpulse Orthopedics Ltd, Winterthur, Switzerland) made of either conventional PE, Sulene® (Zimmer, Warzaw, IN, USA), or highly cross-linked PE, Durasul® (Zimmer). One bilaterally operated patient had sequential surgeries and received the opposite type of PE in the contralateral hip. All patients received a cemented Spectron EF Primary® (Smith&Nephew, Memphis, TN, USA) stem with a 28 mm CoCr head. Hips were followed up to 10 years with radiostereometry, plain radiographs, dual energy x-ray absorptiometry and Harris Hip / Pain Score. 27 PE and 25 XLPE hips could be evaluated at 10 years, demographics are presented in Table 3.

Table 3. Demographics and implant data at surgery

	Included hips		Excluded hips	
	PE	XLPE	PE	XLPE
Number of hips (no.)	27	25	3	6
Age at surgery (years) †	56 (41-70)	55 (42-68)	55 (48-58)	51 (35-64)
Male / female (no.)	15/12	12/13	1/2	2/4
Primary/secondary OA (no.)	22/5	22/5	3/0	5/1
Weight (kg) †	83 (58-120)	82 (47-116)	72 (60-79)	78 (53-99)
Cup size (mm) ††	54 (48-60)	54 (48-60)	52 (50-52)	53 (46-60)
Stem size 1/2/3 (no.)	5/15/7	1/14/10	1/2/0	3/2/1
Standard / High offset (no.)	17/10	19/6	2/1	4/2
Charnley Group A/B/C (no.)	16/7/4	16/2/7	2/0/1	3/2/1
Preoperative HHS (points) ††	46 (18-68)	44 (18/78)	61 (45-66)	57 (29-68)
Preoperative HPS (points) ††	10 (0-30)	10 (0-30)	20 (10-30)	20 (0-20)

†mean (range), ††median (range)

Polyethylene wear and implant migration were evaluated with RSA. We investigated AP and lateral plain radiographs for extent and width of radiolucent lines in the bone-cement interface around cups divided into Charnley-DeLee regions and around stems using Gruen regions. For stems, a similar region classification was used for evaluating bone mineral density with DXA. For cups, we analyzed five regions of interest (ROIs), two superior, one medial and two inferior (259). Harris Hip and Pain Scores (HHS, HPS) were examiner-derived and obtained at each follow-up occasion. Revisions were recorded.

Implant migration and wear, bone mineral density change, width of linear osteolysis as well as Harris Hip/Pain Scores were compared between PE groups using Mann-Whitney's test. The extent of radiolucent lines and crude revision rates were similarly compared with Fischer's Exact test.

3.3 Paper III

We searched the 2013 NARA database for THA cup designs where PE and XLPE versions are similar or nearly similar and had been used in more than 500 cases each. PE usage preceded that of XLPE and, since THA outcome varies with time, the earliest included year was when the yearly use of XLPE

cups exceeded 100 cases for cemented (2006) and uncemented (2003) cups respectively. The study group selection sequence is shown in Figure 2.

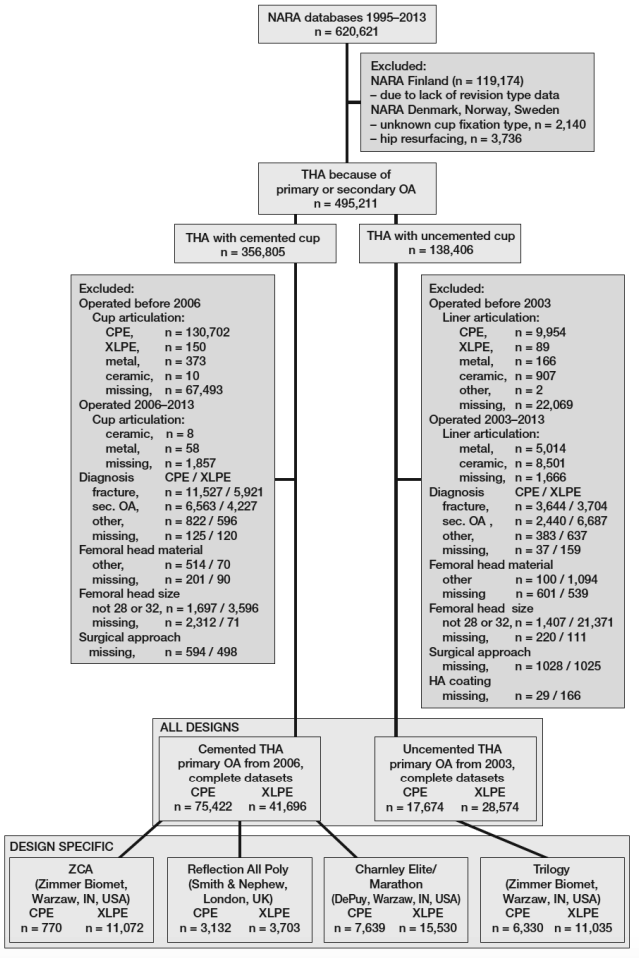

Figure 2. Study group selection sequence

We compared the revision risk for any reason and for aseptic loosening of the cup between PE and XLPE versions of each selected design and also compared revision risks for all cemented and uncemented cups in corresponding time intervals.

We used Cox regression adjusted for age at surgery, sex, femoral head size (28 or 32 mm), diagnosis (primary/secondary OA), femoral head material (CoCr/ceramic), stem fixation (cemented/uncemented), surgical approach

(posterolateral approach/other) and, for uncemented cups, presence or absence of HA coating. We reported relative risk of revision with 95 % confidence intervals.

3.4 Paper IV

247 hips in 209 patients with a valid two year RSA examination were identified from 4 different RSA studies where all patients received a cemented Spectron EF Primary® stem (Smith&Nephew, London, UK) with a 28 mm CoCr femoral head. Selected hips had a complete follow-up until stem failure, revision, death or end of follow-up period. Patient demographics are shown in Table 4.

Table 4. Demographic and implant data

	Non-failed stems (n=215)	Failed stems (n=32)	All stems (n=247)
Age, years; median (range)	62 (29-80)	57.5 (34-75)	62 (29-80)
Sex, male/female *	69/146 (31/69)	17/15 (53/47)	86/161 (35/65)
Diagnosis *			
Primary OA	164 (76)	25 (78)	189 (77)
Secondary OA	40 (19)	6 (19)	46 (18)
Subcapital femoral neck fracture	11 (5)	1 (3)	12 (5)
Stem size, 1/ 2/ 3+/ missing *	46/100/67/2 (21/47/31/1)	19/12/1/0 (59/38/3/0)	65/112/68/2 (26/45/28/1)
Femoral offset, normal/high/missing *	174/40/1 (81/18/1)	19/13/0 (59/41/0)	193/53/1 (78/21/1)
Cup type *			
Cemented			
Weber PE	24 (11)	5 (16)	29 (12)
Weber XLPE	25 (12)	2 (6)	27 (11)
Reflection All Poly	90 (42)	13 (41)	103 (42)
Uncemented			
Trilogy PE	51 (24)	7 (22)	58 (23)
Trilogy XLPE	25 (12)	5 (16)	30 (12)
Cement type, Palacos/Other *	170 / 45 (79/21)	24 / 8 (75/25)	197 / 53 (80/20)

*) Numbers (percent)

Stem failure was defined as revision of a loose femoral stem or radiological failure with significant osteolysis in Gruen regions 2 to 6.

Cox regression adjusted for age, sex, stem size, FH offset (standard/high) and PE type (PE/XLPE) was used to evaluate if stem subsidence and rotation measured with RSA at two years could predict later stem failure.

Additional analysis

We report overall mean stem subsidence as well as mean subsidence for the novel stem sizes introduced with Spectron EF Primary compared to the larger sizes (sizes 1, 2 and >3,) at two and five years.

3.5 Paper V

We identified two available ongoing RSA studies with two different uncemented stems having suitable stem marker positions and MOP uncemented cups. For MOP cups, we could perform direct RSA measurements of FH positions and FH translations as well as indirect calculations of FH positions and translations using stem marker positions and the point transfer function of the UmRSA suite. Four different stem marker configurations were used (all available scattered along a stem were used, the three most proximal, three with maximum spread, and three markers in an elongated configuration with a condition number of median 277, range 257 – 297 indicating poor spread, Figure 3. The FH position was calculated indirectly using each selected marker configuration and available measurements up to seven years follow-up.

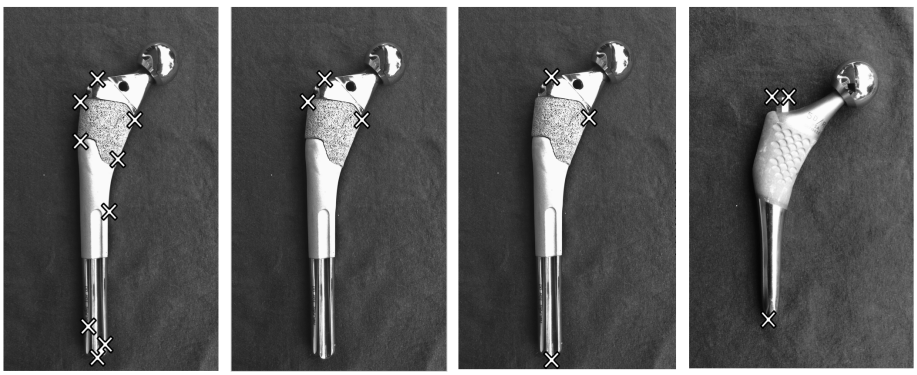

Figure 3. Four stem marker configurations examined in the study: a) all available scattered, b) three proximal markers, c) three maximally spread markers, d) three markers, high CN

At first, we calculated stem-wise scatter of calculated FH positions along the three principal axes and also compared measured and calculated FH positions for all 4 marker configurations. Scatter was evaluated using standard deviation centered on the mean value for each stem. The difference between directly and indirectly measured positions was presented as mean and SD.

For the principal axis with the least scatter, we constructed a Bland-Altman plot for each marker configuration, comparing measured and calculated FH

translation in relation to the acetabular cup. We also presented the agreement between measured and calculated FH translation with 95 % CI.

Finally, we used the stem with an elongated stem marker configuration (two shoulder markers and one tip marker) to evaluate the translation of a ceramic FH into an acetabular cup with a ceramic insert. We presented the mean linear translation rate calculated from individual regression slopes for each analyzed hip. We also present the 99 % precision limits calculated from available double examinations.

3.6 Paper VI

104 hips (97 patients) were included in a randomized study comparing MOP and COC articulations in an uncemented THA design (ABG-2®; Stryker, Mahwah, NY, US). Patient demographics are shown in Table 5. Hips were randomized with closed envelopes. Bilateral cases were operated sequentially and the contralateral hip received the opposite type of articulation. All hips had 28 mm femoral heads.

Hips were followed up to seven years with stem and cup migration measured with RSA, Harris Hip and Pain score, activity level and occurrence of pain, discomfort and squeaking. In addition, at seven years we analyzed heterotopic ossification on plain radiographs according to Brooker (212) and the occurrence and size of periacetabular bone lesions using CT. Revisions were registered.

Stem and cup migration for MOP and COC hips, HHS/HHP, heterotopic ossification and activity levels were compared using Mann-Whitney's U-test. Fischer's Exact tests were used for analysis of pain/discomfort.

Occurrence and volume of periacetabular osteolysis were analyzed with a zero-inflated negative binomial regression adjusted for age at surgery, body weight and sex.

Additional analyses

For the MOP hips in Paper VI we also used marker-based RSA to measure mean linear vertical translation rate of the FH in relation to the acetabular cup up to seven years as well as 99% precision based on available double examinations. Proximal PE wear rate in the MOP hips was compared to proximal wear rate for COC hips obtained in Paper V using Mann-Whitney U-test.

Additionally, in an explorative approach, we analyzed the association between proximal wear rate and occurrence/size of osteolytic lesions, heterotopic ossification and hip noise, for MOP and COC hips separately.

Table 5. Demographics at surgery.

	Full follow-up		Discontinued at 7 years	
	MOP n=39	COC n=47	MOP n=10	COC n=8
Age at surgery (years)[1]	53 (33–63)	54 (32–63)	47.5 (32-58)	50 (39-63)
Sex (woman/man)[2]	18 / 21	27 / 20	6 / 4	4 / 4
Weight at surgery(kg)[1]	79 (56–108)	80 (60–117)	87 (52–142)	90 (69–140)
Charnley class [2]				
A	24 (62)	26 (55)	6 (60)	2 (25)
B	14 (36)	21 (45)	4 (40)	6 (75)
C	1 (2)	0	0	0
Diagnosis [2]				
Primary OA	25 (64)	36 (77)	8 (80)	7 (88)
Secondary OA	14 (36)	11 (23)	2 (20)	1 (12)
Preop Harris Hip Score[1]	54 (25 - 64)	52 (28 - 73)	56 (39 - 70)	53 (29 - 59)
Preop Harris Pain Score[1]	20 (10 - 20)	20 (10 - 30)	20 (10 - 30)	20 (10 - 20)

1) median (range)
2) number of hips (percent)
3) 2 patients (2 MOP hips) deceased, 3 patients (2 MOP, 2 COC hips) revised, 11 patients (6 MOP, 6 COC) declined

4 RESULTS

4.1 Paper I

In general, hip resurfacings had an increased risk ($RR_{HRA/THA}$ = 2.7, 95 % CI 1.9 - 3.7) for aseptic revision at two years. The difference was much less pronounced for men aged <50 years at surgery but was, on the contrary, increased for women of the same age interval (Table 6). Hospital production volume > 70 procedures, certain HRA designs and male sex significantly decreased the risk of aseptic revision at two years whereas age and OA type did not (Table 7).

Table 6. Age- and sex-stratified relative risk of aseptic revision within 2 years after primary operation.

	Adjusted revision risk (95% CI)				Number of cases (No of revisions)		
	HRA / THA	p-value	HRA/all c-THA	p-value	HRA	THA	All c-THA
Age < 50 years							
Males	1.9 (1.0-3.9)	0.07	2.4 (1.1-5.3)	0.04	460 (9)	7,183 (109)	1,782 (18)
Females	4.7 (2.6-8.5)	<0.001	7.4 (3.7-15)	<0.001	221 (13)	7,486 (114)	2,242 (21)
Age 50-73 years							
Males	1.7 (0.9-3.1)	0.1	2.1 (1.1-3.9)	0.02	653 (10)	67,134 (807)	43,725 (387)
Females	3.2 (1.6-6.5)	0.001	4.0 (2.0-8.1)	<0.001	304 (8)	90,751 (924)	64,308 (482)

Table 7. Relative risk of aseptic revision up to 2 years (RR) with 95 % CI in 1,611 hip resurfacings (35 revisions). Data are based on a Cox regression model adjusted for age, sex, diagnosis, hospital production volume, and the 4 most common HRA design with BHR as reference.

	RR	95 % CI	p-value
Hospital production volume:			
<70 / ≥70procedures	3.7	1.5 - 8.9	0.003
HRA design:			
BHR (reference)	1	-	-
Durom	3.1	1.2 - 7.8	0.02
ASR	2.7	1.0 - 7.4	0.06
ReCap	5.4	1.8 - 16	0.003
Male / female	0.5	0.2 - 0.9	0.03
Age (<50 / 50-73 years)	1.5	0.8 - 3.1	0.2
Primary / secondary OA	1.0	0.4 - 2.8	0.9

4.2 Paper II

Between two and ten years, XLPE articulations had a lower proximal steady state wear rate (0.005 mm/year (SE 0.002) vs 0.055 mm/year (SE 0.009)) and 3D steady state wear rate (0.005 mm/year (SE 0.002) vs 0.056 mm/year (SE 0.009)), both p>0.001 (Figure 4). We detected no differences regarding cup migration but a trend towards less stem subsidence and varus rotation for stems in XLPE articulations (Table 8). We found no significant differences in periprosthetic bone mineral density, Harris Hip and Pain Score and revision rate.

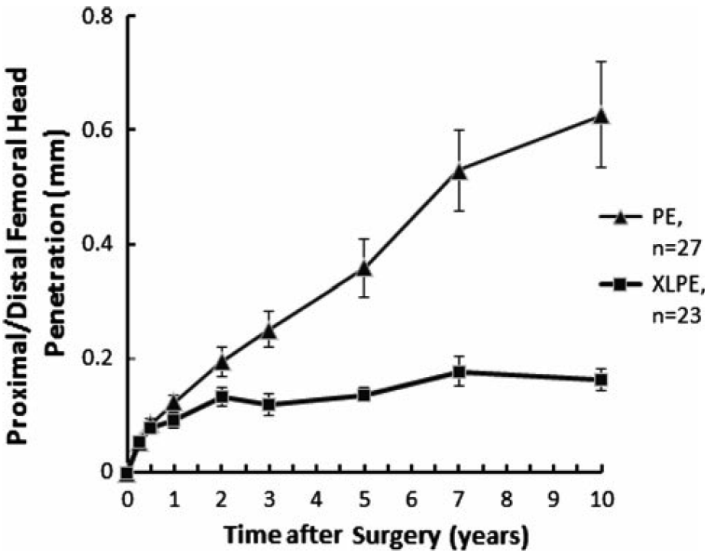

Figure 4. Proximal (+) femoral head penetration up to ten years in XLPE and PE articulations.

Table 8. Cup and stem rotation and translation at ten years

Variable	PE	XLPE	p-value*
Cup rotation (º)	n=26	n=24	
x-axis (forward tilt +)	0.05 (0.10)	-0.06 (0.13)	0.55
y-axis (anteversion +)	-0.02 (0.14)	-0.17 (0.14)	0.53
z-axis (increased inclination +)	0.60 (0.58)	0.24 (0.10)	0.51
Cup translation (mm)	n=26	n=24	
x-axis (medial +)	-0.29 (0.22)	-0.15 (0.05)	0.71
y-axis (proximal +)	0.29 (0.17)	0.22 (0.08)	0.61
z-axis (forward +)	-0.003 (0.08)	-0.13 (0.07)	0.32
Stem rotation (º)	n=26	n=20	
x-axis (forward tilt +)	-0.06 (0.05)	-0.15 (0.07)	0.81
y-axis (anteversion +)	-0.80 (0.35)	-0.55 (0.24)	0.65
z-axis (valgus +)	-0.15 (0.05)	0.03 (0.04)	0.005
Stem migration (mm)	n=27	n=23	
y-axis (proximal +)	-0.51 (0.14)	-0.15 (0.06)	0.05

Values are expressed as mean (SE)

* Mann-Whitney U-test

4.3 Paper III

For cemented cups in general, we found no significantly different adjusted revision risks for PE vs XLPE regarding any reason or aseptic loosening of the cup (Table 9). The length of follow-up was eight years.

3 specific cemented cup designs met the inclusion criteria; the ZCA, Reflection AllPoly and Charnley Elite Ogee/Marathon.

ZCA cups made of PE had eight years follow-up and a higher adjusted risk of revision compared to the XLPE version. The difference was non-significant for all causes of cup revision but significant for revision of the cup due to aseptic loosening (Table 9). In Reflection AllPoly cups with 7.5 years follow-up, the PE versions had significantly increased adjusted risk of revision both for all causes and aseptic loosening (Table 9). Charnley Elite Ogee/Marathon cups had a shorter follow-up of five years. The adjusted risks of revision did not differ between these two designs for neither of the two outcomes studied (Table 9).

Uncemented cups of all designs had 11 years follow-up. PE cups showed similar all-cause adjusted revision risk and no certain increased risk for revision caused by aseptic loosening (Table 9), compared to XLPE cups.

One uncemented cup design, Trilogy, met our inclusion criteria. The follow-up time was 11 years. Revision risk was similar in PE and XLPE cups for all causes and aseptic loosening (Table 9).

Table 9. Relative risk for revision between PE and XLPE

	Reason for revision	
	All	Aseptic loosening
	$HR_{PE/XLPE}$ (95% CI), p-value	
Cemented cups:		
All designs	0.94 (0.81 - 1.1), p=0.4	1.2 (0.89 - 1.6), p=0.2
ZCA	1.6 (0.94 - 2.6), p=0.09	6.1 (2.3 - 16), p<0.001
Reflection AllPoly	0 - 4 years: 1.8 (1.1 - 3.0), p=0.03 4 - 7.5 years: 7.8 (3.0 - 20), p<0.001	5.3 (2.8 - 10), p<0.001
Charnley Elite Ogee/Marathon	1.1 (0.74 - 1.5), p=0.8	1.4 (0.67 - 2.8), p=0.4
Uncemented cups:		
All designs	1.0 (0.86 - 1.2), p=0.9	1.5 (0.93 - 2.3), p=0.1
Trilogy	0.91 (0.73 - 1.2), p=0.5	0.89 (0.45 - 1.7), p=0.7

4.4 Paper IV

Both stem subsidence and stem retroversion at two years turned out to be associated with later stem failure. In addition, males, hips with small stem sizes, and in two of three analyses also stems with high offset had a significantly higher risk for stem failure (Table 10).

Mean stem subsidence at two years was 0.14 mm (SD 0.32). For stem sizes 1, 2 and 3 or larger, mean subsidence was 0.16 mm (SD 0.21), 0.12 mm (SD 0.23) and 0.15 mm (SD 0.51) respectively (n=65, 112 and 68). Corresponding figures at five years are 0.30 mm (SD 0.60), 0.51 mm (SD 0.92), 0.26 mm (SD 0.47) and 0.17 mm (SD 0.23); n=60, 104 and 60.

Table 10. Cox regression analysis of stem subsidence and rotation with associated hazard ratios.

Covariates/factors	Stem subsidence at 2 years as continuous variable (n = 244; 32 stem failures)		Stem subsidence at 2 years dichotomized at 0.15 mm (n = 244; 32 stem failures)		Stem rotations at 2 years as continuous variables (n = 221; 31 stem failures)	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Subsidence at 2 years (mm)	6.0 (2.5–15)	< 0.001				
Subsidence at 2 years (≥ 0.15/< 0.15 mm)	–	–	5.1 (2.2–12)	< 0.001	–	–
Anterior(+)/posterior(−) tilt	–	–	–	–	0.90 (0.37–2.2)	0.82
Retro(+)/ante(−)torsion					1.7 (1.1–2.5)	0.018
Valgus(+)/varus (−) tilt (degrees)					0.27 (0.03–2.6)	0.26
Age (years)	0.99 (0.95–1.0)	0.39	0.98 (0.95–1.0)	0.26	0.99 (0.96–1.0)	0.56
Sex (men/women)	6.9 (2.9–17)	< 0.001	7.4 (2.9–19)	< 0.001	8.0 (3.0–21)	< 0.001
Stem size						
1	8.0 (3.3–19)	< 0.001	7.8 (3.1–20)	< 0.001	9.8 (3.6–27)	< 0.001
2 (reference)	1 (reference)	–	1 (reference)	–	(reference)	–
3 or larger	0.06 (0.004–0.82)	0.035	0.12 (0.02–0.93)	0.043	0.11 (0.01–0.98)	0.048
High/standard offset	3.1 (1.4–6.7)	0.005	2.2 (0.96–4.8)	0.062	2.3(1.0–5.3)	0.044
Highly crosslinked/ conventional polyethylene	Stratifying		Stratifying		Stratifying	

CI = confidence interval.

4.5 Paper V, VI and Additional Analyses

The variation between measured and calculated FH positions was lowest along the vertical axis for all four stem marker configurations, centered standard deviations ranging from 0.14 to 0.20 mm. Also, differences between measured and calculated FH positions as well as directly and indirectly measured FH translation was lowest along the vertical axis. 95 % CI of agreement between direct and indirect vertical translation was -0.42 to 0.51 mm (Figure 5A) for the stem with the least optimal stem marker configuration (elongated marker configuration, ABG-2 with CN 257 - 297). Direct and indirect measures of conventional MOP wear correlated well up to seven years but variance was increased (Figure 5B). 99 % precision of vertical translation in an ABG-2 COC articulation was 0.34 mm (73 double examinations), compared to 0.16 mm (45 double examinations) in the corresponding MOP articulation.

There were no significant differences in cup and stem fixation, Harris Hip and Pain scores, heterotopic ossification, activity level or presence of pain/discomfort. There were four revisions within three weeks postoperatively (2 MOP, 2 COC hips) for reasons not related to articulation material. The frequency of periacetabular bone deficiencies did not differ in MOP and COC hips but the lesion volume was larger in PE hips (p=0.002, adjusted zero-inflated negative binomial regression). Six patients (12 % of COC hips) reported squeaking from their COC hip and none from their MOP hip. Of the

six squeaking COC hips, five patients reported squeaking at flexion, in four cases occurring sometimes and one case often. The sixth patient experienced pronounced squeaking when having walked for a while and was annoyed with the sound, but did not want to have the hip revised.

In the uncemented ABG-2 MOP articulation, mean proximal wear rate between six months and seven years (direct marker-based RSA) was 0.08 mm/year (SD 0.06) compared to -0.003 mm/year (SD 0.021) obtained with indirect RSA in the corresponding COC articulation, $p<0.0001$ (Mann-Whitney).

We found a weak positive association between degree of heterotopic ossification and MOP articulation wear rate ($p=0.03$, Spearman's rho), but not COC articulation wear rate ($p=0.26$, Spearman's rho). There were no statistically significant associations between wear rates in MOP or COC articulations and hip noise / squeaking, frequency or size of periacetabular bone voids.

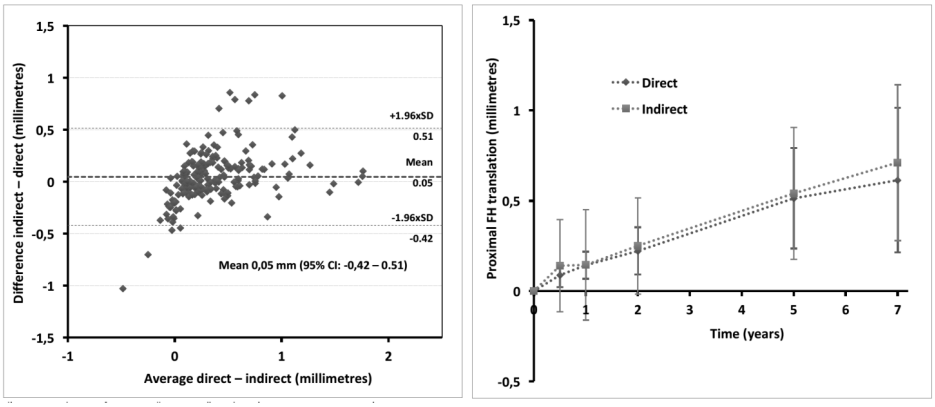

Figure 5. A. Bland-Altman plot on 204 examination pairs in 38 hips showing the accuracy of indirect compared to indirect measure of FH penetration. B. Graph showing directly and indirectly measured FH penetration in a MOP articulation up to seven years.

5 DISCUSSION

Prior to Charnley's low friction total hip arthroplasty, the development of hip implant technologies was pioneering and experimental. If there is no efficient treatment available for a debilitating disease, such an approach and inferior results may be accepted, provided that there is a theoretical base for the new treatment and patients are well-informed and adequately followed.

In the post-Charnley era, experimental approaches to hip implant design are not justified (278). Ten-year implant survival rates are with few exceptions 90 % or more, and the best performing implant combinations will have a >95 % probability to last more than ten years in healthy older patients. This success limits the possibility of further improvement (279). Implant survival is worse in younger, active patients, especially males. Current implant design development is to a large extent focused on this patient group. The difficulty to improve is however demonstrated in a study from the Australian registry, where hip and knee components introduced between 2003 and 2007 with at least one year follow-up were compared to their top performing predecessors. In the hip implant group, no new component performed better, 20 performed equally and 13 performed worse than their predecessors (280). Early learning curve could impair early results, concealing a better performing implant. In a review by Nieuwenhuijse et al, the authors found that five established hip and knee implant concepts did not improve functional or patient reported outcome (281). The 12 years' survival rate were no better, for some implants even worse than for earlier implant designs. Furthermore, they could not find convincing evidence of high quality for the introduction and use of these concepts.

For over 20 years it has been argued that innovations and intended improvements in joint arthroplasty surgery should be introduced with structure and care (278, 282). The most well-defined and well-structured model is the stepwise introduction of new hip implant technology described by Malchau (283).

The various proposals condense into the following steps:

- Innovations should be theoretically well motivated and based on previous knowledge documented in the scientific literature.
- New implants and concepts should undergo a thorough preclinical evaluation using applicable methods like laboratory bench testing, mathematical methods like finite element analysis, toxicological testing and animal studies.
- When a new implant or concept is introduced clinically, in order to minimize exposition, it should be done in a limited

number of patients that are followed thoroughly, to detect any proneness to early failure.
- Finally, after a wider market introduction, implants or concepts should be continuously followed in order to capture any increased tendency to late failure.

The studies within this thesis explore aspects and effectuate parts of the two last steps.

5.1 Hip resurfacing

In Paper I, we found that use of a hip resurfacing implant was associated with an almost three-fold increase for risk of non-septic revision at two years, compared to a conventional THA. This finding corresponds to registry reports published previous to our work as well as later studies (284). For men, the HRA disadvantage was much less evident than for women. Later studies have established that men, especially below 50-60 years at surgery, could still be considered suitable for hip resurfacing surgery (285-287).

Consequently, within the HRA group, women had a higher risk of early non-septic revision compared to men. Several studies including registry reports have identified female sex as an independent risk factor for HRA complications, but also smaller femoral head size is associated with increased HRA failure. Most likely there is a covariation between the two variables (288).

We did not detect any significantly increased revision risk from older age at surgery nor secondary vs primary OA, although other studies have shown such associations (286). The majority of our HRA patients, however, were younger and had primary OA so we might lack power in these subgroups.

Osteoporosis is more abundant at old age and it is reasonable that poor bone stock decreases especially femoral component fixation and increases the risk of femoral neck fracture. Hip dysplasia increases the risk of component malposition and thus the risk of edge wear and impingement (286). Femoral head osteonecrosis could impair the femoral head fixation due to insufficient quantity of viable bone (286). Malformed femoral heads after childhood disease also poses a challenge for implant fixation and positioning and data on outcomes are scarce (289, 290).

It has been established that HRA has a steep learning curve (291) and this was reflected in our results on the unit level. We are not able to identify the individual surgeon's results in the NARA database. However, considering the

complexity of the procedure, it is likely that HRA, if at all, is performed by a limited number of surgeons at each site.

Four individual designs, BHR, Durom, ASR and Recap, could be analyzed. Among these, BHR had a lower risk of non-septic early revision compared to the others. This relationship is concomitant with other registry reports (292) and the three latter implants have been withdrawn from the market.

The orthopedic surgeons in the Nordic countries cautiously used HRA in low numbers. Therefore, despite the relatively extended time interval for study group inclusion, the HRA group in the comparative analysis is relatively small, 1638 HRA including 40 revisions. The analysis involving HRA only comprises even smaller numbers, 1611 and 35 respectively. This is certainly a limitation with regards to power of detection and may impair the performance of the statistical method. However, in the main analyses, the number of events per variable are sufficient for Cox regression (293).

The first comprehensive reports regarding HRA came from the Australian registry. In 2002, they reported an increase in HRA use for the previous year (294) and the 2004 report showed increased revision risk compared to conventional THA, especially for older patients (217). In 2005, it was noted that HRA because of primary OA has lower revision risk than for secondary OA and that women had a higher risk for revision compared to men (295). Different outcome based on design was reported in 2007 (292) and dependence on articulation size the following year (296). The high number of HRA arthroplasties performed during a comparatively short period enabled this fast delivery of mainly inferior results and any delay was in part due to temporal variation in implant selection. However, the response to these results was slow, ending up in that still more HRAs were implanted worldwide.

It can be argued that a coordinated observation effort from multiple registries could have produced these results a few years earlier and perhaps also could have carried greater leverage across the world.

Still, HRA is advocated for younger men, preferably with primary OA, using successful implant designs (285, 286, 297). HRA studies with up to ten-years follow-up have showed persisting increase in blood cobalt and chromium levels (298), with uncertain long-term effects. A positron emission tomography study with 3 - 6.5 years follow-up on symptom-free and radiologically normal HRA that previously had displayed osteonecrosis under the femoral component showed progressive osteonecrosis in 5 cases out of 11 (299). Certain HRA designs used on selected patients have shown implant survival comparable or perhaps even better than conventional non-MOM THA (300, 301). A randomized study is announced but to our knowledge not reported.

The long-term benefit of HRA even in limited patient groups remains to be proven and until then HRA usage should be minimized or paused, considering the risks at stake.

5.2 Highly cross-linked polyethylene

In Paper II and III we evaluated XLPE with regards to wear, implant migration, clinical and radiological outcomes as well as design-wise comparisons of cup revision risk in the medium and long-term perspective. Wear was undoubtedly reduced with use of XLPE compared to PE, but other proposed advantages of XLPE could only be partly detected during the observation time.

The steady state wear rates between two and ten years, both in proximal direction and for the 3D vector, were reduced by 90 % for XLPE compared to PE. A relatively recent review of available RSA studies (302) as well as an older review including also other methods to measure wear (218) confirm our result. Considering the biological theory of cemented implant loosening (169), a reduced polyethylene wear could be expected to improve fixation. However, we could not detect any significant difference regarding cup fixation, between PE and XLPE hips. There was a tendency towards an increased stem subsidence and varus rotation in the PE group. Most of this subsidence probably takes place within the cement mantle as indicated by debonding of the stem at the cement-stem shoulder region and the proportionality between the magnitude of this separation and measured stem subsidence (Paper II). Longer follow-up will be needed to verify the differing subsidence between groups. However, if true, the reason may be that a larger PE particle burden within the joint may prevent a slowly subsiding stem to gain new stability within the cement mantle.

Bone mineral density did not seem to be significantly affected by the choice of polyethylene. To our knowledge, there are no other published studies that compare BMD for PE and XLPE cups.

We found no significant difference regarding HHS and HPS between the two polyethylene types.

We have found three published clinical studies that concern cemented XLPE cups. Kadar et al report similar HHS but a significantly lower proximal and 3D total wear as measured with RSA at two years in XLPE cups compared to their PE counterpart (303). In a small RSA study, Röhrl et al reported that eight cemented THA with an annealed XLPE had a steady-state linear wear less than 0.002 mm/year up to ten years, showed no signs of osteolysis and were stable except from a non-significant tendency towards increasing cup inclination beyond five years (304). Finally, Langlois et al used the Martell suite (305) to

evaluate polyethylene wear in PE vs XLPE and found a linear wear rate of 0.14 mm/year and 0.0002 mm/year respectively at a minimum of eight years follow-up (306). There were no radiographic signs of loosening or osteolysis and no difference in Merle D'Aubigné or activity score. There were no reports of wear-related revisions in the three studies.

Our study group was comparably young and that may limit the external validity of this study. On the other hand, wear resistant articulations primarily address this population and our observations have validity due to randomization.

Another potential confounder could be our use of the Spectron EF Primary stem. Even if this stem was used in all hips, it has a higher failure rate than the cemented standard stems used in Sweden today. As a possibly potent metal and cement particle generator, it may have influenced all study variables, tending to conceal group differences. However, distinct XLPE advantages or disadvantages should probably be visible at least as trends.

For both cemented and uncemented cups, there was a general discrepancy between the all-design and the design-specific analyses of risk for revision due to all reasons and aseptic loosening. The reason is probably that confounding at the implant level cannot be adjusted for unless there are a sufficient number of implants and events within both groups for each specific cup design. Such bias may account for some of the inconsistency in previous registry studies, some indicating a lower revision risk for XLPE (221, 307), and some report no detectable difference (220). A design-specific comparison is a more adequate method to analyze revision risk ratio for PE and XLPE cups.

For the ZCA cup, the benefit of XLPE compared to PE was more obvious for revision due to aseptic loosening than revision for all reasons. The ZCA cups has been reported to be generally prone to dislocation (308), probably due to cup geometry. An increased dislocation frequency in both groups may explain a diluting effect. Since we have not analyzed different reasons for revision in depth, we are not able to determine if this is the case. We have not found any other design-specific comparisons regarding PE and XLPE for the ZCA cup.

Interestingly, for Reflection AllPoly cups, the risk ratio for all-cause revision between PE and XLPE increased with time. Also for this cup, dislocations may explain the discrepancy between risk ratio for all-cause revision and revision due to aseptic loosening. The conventional PE in these cups is sterilized in ethylene oxide and has been reported to have higher wear rates than gamma-irradiation sterilized PE (303, 309). Therefore, late dislocations may in addition to aseptic loosening be more frequent in the PE group due to progressive wear. A design-specific analysis from the Australian Registry also showed that the XLPE version cemented Reflection AllPoly cup had a lower

risk of all-cause revision compared to the PE version from 1 year and forth (242). The shape of the cumulative all-cause revision graph is quite similar to the inverse of our corresponding Kaplan-Meier graph (Paper III).

For both ZCA and Reflection AllPoly cups, revision due to aseptic loosening was less common for the respective XLPE version at 7.5-8 years follow-up, conforming to the PE wear particle theory.

Aseptic loosening becomes more common with increasing time in service and it has been suggested that any beneficial effect regarding revision rate of XLPE vs PE for that reason will be detectable no sooner than five (310) to seven (311) years after surgery.

The Charley Elite Ogee / Marathon cup had a follow-up of five years. The short follow-up may at least partly explain that no significant difference in revision risks could be detected for all-cause or aseptic loosening revision. Also, the Marathon XLPE is irradiated with 50 kGy (5 MRad) which is a lower dose compared to the two other studied XLPE brands.

The Trilogy cup had 11 years of follow-up and displayed no significant different revision risks for PE and XLPE versions, neither for all causes or aseptic loosening. Considering the results for the cemented designs, this is somewhat unexpected. A design-specific subanalysis of two cementless cups (Duraloc and Reflection) in a study by Paxton et al with at least seven years follow-up showed a clearly decreased risk for all-cause and aseptic loosening revision for XLPE compared to PE (221). However, in a design-specific comparison of five cement-less cups with ≥7-years follow-up, two designs showed no difference regarding risk for all-cause revision (242).

Due to design philosophies and patent regulations, XLPEs are manufactured in various ways which may affect outcomes. Also, conventional PEs are highly heterogeneous, as exemplified by high wear rates of EtO-sterilized compared to gamma-sterilized PE (303, 309). Other factors may interact with PE type and sometimes perhaps counterbalance the probable benefit of XLPE with regards to revision risk. It may be that the conventional PE in a Trilogy cup is unusually well-functioning in that particular design, or conversely that the remelted XLPE have a design-related disadvantage.

All the analyzed XLPE brands in this section are irradiated and remelted. Since manufacturing methods vary, the results may not be fully generalizable to XLPE manufactured in other ways. However, XLPE as a group has hitherto shown relatively small variations regarding wear and mechanical properties, despite the effects of different oxidative residual elimination methods.

Several other XLPE have been analyzed with regards to wear, both with RSA and other methods, showing low wear rates (83, 302, 312). Preferably, since XLPE manufacturing methods differ, all types of XLPE should be evaluated with RSA and radiological studies at long follow-ups.

5.3 Modification of a well-functioning implant

In our study in Paper IV, increased early stem subsidence and/or retrotorsion were associated with later stem failure, as previously shown (161, 163, 313). Previous studies have established within-group cutoff values that can distinguish an individual stem or cup prone to later aseptic loosening. The latter study aimed at establishing a prospective group-based threshold value for acceptable early migration. It was based on a meta-regression combining two large reviews, one regarding RSA migration outcomes and the other regarding implant survival data from various registries. Based on these reviews the authors suggest a subsidence threshold of 0.15 mm at two years for shape-closed stem designs, predicting >95% 10-year stem survival. In our study the overall mean stem subsidence is 0.14 mm at two years, and if evaluated prospectively this stem design would be judged as safe using the suggested threshold.

Our results support the need for refined prospective migration thresholds, perhaps including intermediate intervals that call for increased vigilance and extended follow-up.

Another approach could be to analyze the distribution of migration estimates, in addition to mean and median values (314).

Although being one of the largest RSA studies with ten-years follow-up, in order to obtain statistical power, we had to include THAs from several studies where the Spectron EF Primary stem was combined with several different cup concepts. Even with 247 hips and 32 stem failures, the study size allows adjustment for only a limited number of possible confounders. Also, we lack knowledge of comorbidities, BMI, bone quality and activity levels. In addition, our arbitrary radiological definition of stem failure may have underestimated the true failure rate. Despite these limitations, our study currently provides the currently best available knowledge for this particular implant.

It should be noted that when the Spectron EF was modified to Spectron EF Primary the changes performed were intended to increase the usefulness of this stem and these changes were regarded to be harmless. One main design alteration of Spectron EF Primary compared to the older version was the introduction of two smaller and shorter size options and a small increase in length (130 to 135 mm) for the larger size implants. Several of these changes

probably facilitated debonding and subsequent inducible displacements between the stem and the cement mantle. The two smallest sizes turned out to be responsible for almost all failures. Therefore, it may be more adequate to perform subgroup analyses based on specific design changes especially if alterations of well-functioning implants are considered. Subgroup analysis may call for somewhat larger study groups but still a limited number of patients need to become exposed due to the high precision and accuracy of RSA.

A comparison of the mean subsidence between stem size subgroups at two years showed highest mean subsidence for size 1 followed by size 3 or larger and lowest for size 2. At five years, however there was an obvious trend to decreasing subsidence with increasing stem size with highest subsidence for size 1 and lowest for size 3 and larger. Thus, it might be that for cemented stems that fail because of cement-stem debonding and subsequent stem subsidence, the observation period with RSA should be extended beyond two years.

5.4 Ceramic-on-ceramic cementless THA

In Paper V, VI and Additional analyses, in summary, we demonstrated the possibility to measure in vivo implant wear in articulations where the femoral head is obscured or otherwise is impossible to depict on a radiograph, as exemplified with the COC articulation. Furthermore, we showed that the mean steady state wear rate in the analyzed COC articulation is close to zero and clearly lower than in a MOP articulation. The COC articulations had smaller cystic bone lesions than the MOP articulation and also a substantial rate of squeaking.

FH center positions were adequately calculated from stem marker positions along the vertical (y) axis for all four examined stem marker configurations, but with increased variance compared to direct model-based position estimation. Variance increases since the calculated virtual point representing the FH is situated far from the stem segment center of gravity at which translation and rotation are projected. Therefore, small measurement errors for the stem segment are amplified in the calculation of the FH position.

Geometrically, it is not surprising to find that the least variance is found along the vertical axis for positions calculated from elongated stem marker segments aligned with the vertical axis. If elongated stem segments are sufficiently vertically aligned on radiographs, also the normally worse precision of y axis rotation (due to less precision for marker positioning along the z axis) induce only minor increase of variation along the vertical axis. In addition, the combined high precision along the x- and y-axes minimizes varus-valgus rotation error (z axis rotation) that otherwise could increase the vertical axis

error due to the FH offset. For highly elongated stem segments with high condition number, the angle between stem long axis and the vertical axis of the RSA coordinate system must be minimized and measurements of individual markers need to be increasingly precise to avoid unacceptable errors in calculating the virtual point of interest.

Proximal FH translation relative markers in an acetabular cup or contour of an acetabular shell can be interpreted as articulation wear provided that the cup position measurement represents the true position of the acetabular articulation surface. Preferably this is achieved by using RSA markers implanted into the cup polyethylene but also the contour of a geometrically defined metal shell can be used provided that the polyethylene liner is fixed to the shell. Shareghi et al demonstrated a good agreement between marker-based and model-based measured wear at two years for the ABG-2 cup (315).

In our study, the 95 % confidence interval of agreement between direct and indirect wear measurement in a MOP articulation with an elongated stem marker segment was relatively wide and from the Bland-Altman plot it can be suspected that agreement decreases with FH penetration distance. Nevertheless, plots of directly and indirectly measured progressive wear in a conventional MOP articulation agreed well up to a proximal penetration of 0.6 mm at seven years follow-up, although with increased variance for indirect measures as expected. This magnitude of penetration will relatively rarely be encountered with modern articulation materials (316).

The precision of proximal FH penetration in a COC articulation was roughly half as good as the corresponding measure with directly measured wear in a MOP articulation. Therefore, indirect wear measurements may be of limited value for individual cases but can still be used on a group level.

Troelsen and coworkers have designed another RSA method for estimating proximal wear in radio-opaque hip articulations (317). The authors utilize the two most proximal stem markers and a prospectively established geometrical relationship between the FH and the markers for all combinations of stem sizes and necklengths available. By mathematically restricting the virtual FH position to the frontal plane of the cup center, they can calculate FH translation using the two stem markers. The authors do not provide any precision measures but report a slightly better agreement between the marker-based and the novel method, compared with our results. However, we believe our method is well justified due to the reasonable precision and because it requires no predefined geometrical relationships and also allows for variations in stem marker patterns.

The precision of the method can be expected to improve by using less elongated stem segments and high quality RSA radiographs. Another limitation is that due to overprojection of RSA markers, some stems will not be analyzable due to high measurement errors. Marker overprojection can be avoided with well dispersed marker configurations as well as awareness of the problem at manufacturing a marked stem. If possible, insertion of RSA markers in implants should be avoided. The method can be transferred to a completely model-based setting, provided that the accuracy and precision of model-based stem migration estimation improves and equals that of marker-based RSA.

The in vivo wear in a COC articulation is clearly reduced compared to a MOP articulation in the same THA design. This result and the very low COC proximal wear rate is by no mean surprising since multiple retrievals of the same Biolox Forte ceramic have displayed very low wear (233, 234). The wear rate in our conventional PE articulation compares well with an earlier report for this conventional PE (318). In addition, previous studies that compare MOP and COC articulations using methods less precise than RSA have shown similar results (319, 320).

We found no significantly differing cup or stem migration up to seven years when comparing MOP and COC hips. Likewise, in another randomized RSA study comparing implant migration in MOP and COC THA, Zhou et al studied a hybrid THA with either a COC or a metal-on-XLPE articulation and found no significant differences regarding cup migration at two years (228).

No significant HHS difference between COC and MOP articulations have been described in comparative studies (236), consistent with our results. We also found non-differing activity levels at seven years with a patient-reported UCLA-score, in contrast to Vendittoli et al who report a significantly higher unadjusted UCLA score for a COC hybrid THA compared to MOP (319). Experience of pain and discomfort were equally distributed between the COC and MOP groups. Similar findings are previously reported (320-322).

In our study, we did not detect any difference regarding periprosthetic heterotopic ossification in COC compared to MOP hips. A previous study using the same ceramic (Biolox Forte) with different cementless implants have shown non-differing rates of HO in the two groups (323). Another study also reported equal occurrence of HO in COC and metal-on-XLPE cementless THA but it is unclear what ceramic type and HO definition they used (321). Finally, a study by Higo et al in a Japanese THA population, detected COC articulations as an independent risk factor for HO of any Brooker class within one year from surgery (324). Further studies will be needed to detect any negative effects of COC articulations with regards to HO.

A small meta-analysis has detected a decreased overall revision risk for COC THA compared to MOP THA, based on three RCTs with mean follow-up between 4.2 and 12.3 years (236). Also two registry reports have a similar outcome (242, 325). We did not have any revisions beyond the early postoperative period but some large osteolyses in the PE group will probably call for surgery with longer follow-up.

Previous studies using conventional radiography have shown lower osteolysis rates in COC vs MOP cementless THA (319, 323). In contrast, with a CT based method we found equal lesion frequency but acetabular bone lesions in MOP hips were larger than in COC hips. CT is a more sensitive method to detect periprosthetic bone lesions (274) and several of the small lesions found by us in both groups could be residual osteoarthritic bone cysts. It has previously been suggested that lesion size is indicative of an ongoing osteolytic activity (140) and in that context, we suggest that acetabular osteolytic activity is higher in MOP than COC THA. Without comparative early postoperative CT scans, we cannot be certain if small lesions actually are new emerging active lesions.

We report a relatively high squeaking rate, compared to many studied COC THA combinations (120). In five of six cases, patients experienced squeaking as acceptable even if it occurred in a regular pattern. Our study design does not allow for direct comparison but other investigators have reported up to 50% of patients with squeaking hips to be seriously concerned (208). Our study is too small to analyze possible risk factors for squeaking. It has previously been reported that certain implant combinations can be more prone to squeaking than others (326, 327), but no such data exist for the ABG-2 THA. Squeaking in COC articulations may be associated with increased wear (209) but we could not detect such a correlation.

Limitations in general

The outcome measures in this thesis are based on revision rates, measures of implant wear and migration, radiological evaluations and simple clinical function and activity measures, representing a classical way of evaluating implant surgery. Our clinical studies were initiated between 1996 to 2003, which is partly mirrored in their design.

It is well known that not all non-revised, or even radiologically or otherwise complication-free implants are experienced as success by the patient. It has been repeatedly shown that the doctor's and patient's estimation of a joint arthroplasty outcome often show low agreement, especially in subjective domains (328, 329). Furthermore, revision of a problematic implant may be

hampered by doctor's or patient's delay or simply because medical comorbidities cause unacceptable perioperative risks. Classical scores for measuring clinical function, including HHS and HPS used in this thesis, have been extensively used but have also been criticized for having ceiling effects that cause low resolution in the upper part of the scale (330).

In the last decade, there has been an increased focus on patient-reported outcome measures (PROMs) with improved patient relevance, validity and resolution compared to earlier instruments. PROMs and related measures such as patient's satisfaction rating have broadened and deepened the knowledge of joint arthroplasty outcomes and prerequisites (331). General and specified recommendations on PROM selection, administration and interpretation for registries have been published (332) and the need for extended incorporation into clinical practice has been emphasized (331).

The clinical studies in this thesis were initiated prior to the general use of more sophisticated PROM instruments and the NARA database used in the two registry studies contains no PROM data. Certainly, patient-centered outcomes measured with appropriate tools should be included in modern study designs.

Patient-reported activity measurement tools have known disadvantages. Recall bias can affect detailed recall questionnaires and activity diaries filled in by patients are associated with high patient burden and thereby non-compliance (333). Measuring devices as pedometers and accelerometers are often recommended to obtain reliable data but their validity depends on the type of activity and where the device is attached to the body (333). The UCLA score has been widely used, is easy to apply and have been validated and recommended for activity measurements in multiple studies (334-336). Also, VAS activity rated by the investigator is highly correlated to activity measured with a pedometer (334).

6 CONCLUSION

I. Hip resurfacing has an almost three-fold increased risk of non-septic revision within two years compared to conventional THA. The revision risk is more pronounced for women, certain implant designs and for units having performed few procedures.

II. Remelted XLPE has a steady and low linear wear rate up to ten years, significantly lower than for conventional PE. The low wear did not correlate to improved cup fixation nor to lower BMD loss, less osteolysis or better clinical function for XLPE compared to conventional PE in a cemented THA up to ten years. When comparing revision risk for aseptic loosening between XLPE and PE versions of the same cup design an advantage was observed for XLPE in two of four analyzed cup designs.

III. Increased stem subsidence and retrotorsion at two years are associated with later risk for aseptic stem failure in an unfavorably modified, previously well-functioning cemented stem. However, mean early stem subsidence was comparably low compared to other cemented stems with a high failure rate.

IV. Radiostereometry can be used to measure proximal articulation wear in THA with an obscured femoral head by mathematically transforming stem displacements to the position of the femoral head.

V. A ceramic-on-ceramic articulation in a cementless THA has a very low and stable wear rate up to seven years, significantly lower than the corresponding metal-on-polyethylene articulation. Bone lesion volume is decreased while no difference in bone lesion rate, implant migration, articulation-related revision rate, heterotopic ossification or clinical outcome were detected in the ceramic-on-ceramic compared to the metal-on-polyethylene version of the same implant. The rate of squeaking was relatively high but the noises were in most cases limitedly annoying to patients.

7 FUTURE PERSPECTIVES

From a patient and community perspective it is imperative that the introduction and evaluation of innovations can be further improved with regards to quality and adherence to principles that have been highlighted since two decades. Preferably this should be done in cooperation with manufacturers but if not possible, regulatory measures are necessary.

RSA can and should be used to prospectively evaluate implant wear and fixation for new implants and articulations both in short and long time perspectives. The methodology can be made more available and less costly if model-based methods and automated procedures continue to improve. Ideally, simplified RSA follow-ups for limited groups of patients within an implant category under surveillance could be administered and scheduled by arthroplasty registries.

Due to the complex nature of implant fixation it will be difficult to define definitive thresholds for early migration valid for a whole implant category, (e. g. all cemented stems) and even less likely to establish any general guidelines across categories. Interval-based thresholds for more specific implant groups may be possible to establish, but this will probably require better and less costly access to RSA as well as coordinated efforts within and between arthroplasty registries.

Radiological methods to discriminate between inert bone cysts and active, progressive osteolysis need to be improved. As for today, repeated computed tomography, associated with high radiation doses, is utilized clinically to detect lesion growth.

Early registry studies regarding new implants should preferably be coordinated across registries in order to increase the efficiency of early analysis of revision patterns and PROM outcomes. The individual orthopedic surgeon's confidence in reported results may improve from such an arrangement. Further research is needed on how research results are perceived and implemented in the orthopaedic community.

Several properties of first generation, remelted XLPE seems beneficiary at long-term follow-up and no harmful effects are observed in our studies. However, continued surveillance is needed based on preclinical and sparse clinical data. It should also be noted that XLPE is a heterogeneous group with a multitude of different manufacturing procedures. Surveillance of different, preferably all, XLPE types is needed, since outcome for one particular type is not necessarily possible to extrapolate to other types.

Ceramic-on-ceramic THA seems to be a safe option in a mid-term time perspective. Articulation noise and its possible consequences are of concern and patients receiving COC THA need to be informed of the risk for squeaking. Results from valid studies comparing COC and metal-on-XLPE articulations will be needed to further establish the need for continued use of COC articulations in THA.

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PAPERS I-VI