

Wear and Migration in Cemented Total Hip Arthroplasty

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1. SCIENTIFIC ENVIRONMENT

This study was carried out at the Department of Orthopaedic Surgery, Kysthospitalet i Hagevik and Department of Radiology, Haukeland University Hospital, Bergen, Norway, during the period 2004-2014. Scientific support has also been given by the staff at the Norwegian Arthroplasty Register, Department of Orthopaedic Surgery, Haukeland University Hospital, Bergen, Norway and the Department of Orthopaedic Surgery, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway.

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3. LIST OF ABBREVIATIONS

ANOVA	Analysis of Variance
AP	Antero-posterior
BMI	Body mass index
BPs	Bisphosphonates
CI	Confidence interval
CN	Condition number
CoCr	Cobalt Chromium
CoC	Ceramic-on-Ceramic bearing
CPE	Conventional Polyethylene
EtO	Ethylene oxide
GUR	Granular, UHMWPE and Ruhrchemie. Designation of UHMWPE resin
HHS	Harris hip score
ME	Mean error
MoM	Metal-on- Metal bearing
MoP	Metal-on-Polyethylene bearing
OA	Osteoarthritis
PE	Polyethylene
RCT	Randomised controlled trial
RSA	Radiostereometric analysis
THA	Total hip arthroplasty
TNF	Tumor necrosis factor
UHMWPE	Ultra high molecular weight polyethylene
HXLPE	Highly cross-linked polyethylene

4. LIST OF PUBLICATIONS

This thesis is based on the following papers, which will be referred to by their Roman numbers in the text.

- I. Kadar T, Hallan G, Aamodt A, Indrekvam K, Badawy M, Skredderstuen A, Havelin LI, Stokke T, Haugan K, Espehaug B & Furnes O. **Wear and Migration of Highly Cross-linked and Conventional Cemented Polyethylene Cups with Cobalt Chrome or Oxinium Femoral Heads: A Randomized Radiostereometric Study of 150 Patients.** *J Orthop Res* 2011;29 (8):1222-9
- II. Kadar T, Hallan G, Aamodt A, Indrekvam K, Badawy M, Havelin LI, Stokke T, Haugan K, Espehaug B & Furnes O. **A randomized study on migration of the Spectron EF and the Charnley flanged 40 cemented femoral components using radiostereometric analysis at 2 years.** *Acta Orthop* 2011;82 (5):538-544
- III. Kadar T, Furnes O, Aamodt A, Indrekvam K, Havelin LI, Haugan K, Espehaug B & Hallan G. **The influence of acetabular inclination angle on the penetration of polyethylene and migration of the acetabular component: a prospective, radiostereometric study on cemented acetabular components.** *J Bone Joint Surg Br* 2012;94 (3):302-307

5. ABSTRACT

Background: In THA the aim is to offer lasting functional improvement and pain relief. Several variables affect the longevity in THA. New materials in the acetabular cup and femoral head components have been developed to reduce wear, and thus improve longevity. Several different designs have been introduced to optimize implant fixation. Component orientation has been suggested as a variable influencing wear in THA. The purpose of this thesis was to compare new and traditional materials and design features used in cemented THA. We also wanted to investigate whether the acetabular cup inclination angle affected wear.

Methods: 150 patients were randomized to receive five different articular bearings with two different femoral stems. Wear and fixation of the components was evaluated with radiostereometric analysis (RSA) at 2 years follow-up.

Results: The use of HXLPE instead of conventional PE substantially reduced wear at 2 years. The use of oxidized zirconium femoral heads did not reduce wear compared to CoCr. The Charnley Ogee cup was not outperformed by the more recently introduced implants in our study. The Spectron EF femoral stem was more stable than the Charnley flanged 40 stem in our study when evaluated at 2 years. We found no relationship between the inclination angle of the acetabular component and wear or cup migration.

Interpretation: Further follow-up is required to discern differences between CoCr and Oxinium heads with respect to wear, implant durability, and clinical benefits. Based on concerns of the mechanical properties and the lack of long-term clinical follow-up studies, we recommend the use of Oxinium to be restricted to clinical studies. Our results of the HXLPE cup confirm the results of other reports. Initial femoral stem stability is not invariably related to good long-term results. Our results emphasize the importance of prospective long-term follow-up of prosthetic implants in clinical trials and national registries, and stepwise introduction of implants. Concerns other than polyethylene wear and migration must be considered in conjunction with the inclination angle of cemented all-polyethylene acetabular components. An optimal angle of inclination for the acetabular component may be of greater importance with hard-on-hard bearings. We conclude that the Charnley prosthesis still represents a standard against which new implants can be measured.

6. INTRODUCTION

6.1 Osteoarthritis of the hip

The hip joint, or the femuroacetabular joint, is a synovial joint formed by the femoral head and the acetabular socket. Both joint surfaces are covered with articular hyaline cartilage. For further containment there is a ring-shaped fibrocartilaginous lip on the acetabular side, called the labrum. Outside the labrum, on the acetabular side, a capsule attaches and reaches to the base of the femoral neck. There are extra-articular ligaments and muscles to facilitate both stability and movement. All in all the hip joint is only second to the shoulder joint with regard to range of movement and yet, supports the majority of bodyweight. Thus, disease of the hip joint potentially not only causes pain, but also strongly interferes with an individual's function.

The most common chronic disorder of the hip joint is osteoarthritis (OA), due to destruction of the joint cartilage. OA can be either primary, with largely unknown causes or secondary, often caused by, but not limited to earlier injuries or infections, congenital malformations or diseases in the hip joint during growth, or systemic inflammatory disease, such as Rheumatoid Arthritis. As breakdown products from the cartilage are released into the synovial space, inflammation of the surrounding joint capsule can occur. Potentially osteophytes form on the margins of the joints (1-3). Ultimately the joint gets painful and stiff, resulting in limitation of walking range, work disability and reduction in quality of life.

The diagnosis of OA in the hip is usually quite straightforward and based on history and clinical examination. A conventional anteroposterior X-ray of the hip and/or pelvic confirms the diagnosis with typical findings of joint space narrowing, subchondral sclerosis and cyst formation and adjacent joint spurs/ osteophytes (4).

The prevalence of OA in the hip in the general population is not known for certain, and depends on factors like age and gender, but overall representative figures are in the range of 10-15% and increases with age (5-7).

6.2 Treatments of osteoarthritis of the hip

When the diagnosis of osteoarthritis has been established the first-line treatment is conservative. This includes unloading of the affected hip with crutches or soft footwear, and analgesics such as Paracetamol and NSAIDS, with the occasional use of stronger analgesic medication. Exercise therapy is an often recommended treatment of OA of the hip, although previous literature has been evasive on the clinical benefit (8;9).

If pain and disability is severe, and the conservative treatment has failed, the standard treatment is joint replacement surgery with total hip arthroplasty (THA). Other diagnoses treated with THA are e.g. hip fracture and avascular necrosis of the femoral head.

6.3 Total hip arthroplasty (THA)

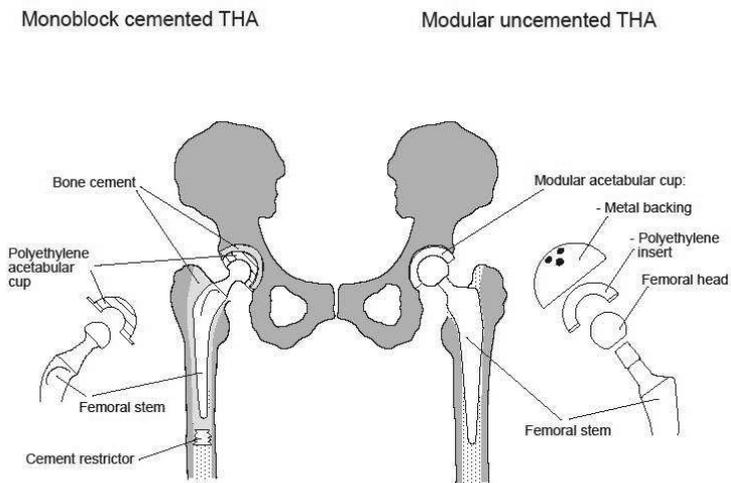
6.3.1 Basic principles

Already in the late 19th century the idea of replacing an articulation with foreign material was born as surgeons explored the possibility of replacing diseased hip joints with foreign materials such as ivory (10). Also, soft tissue interpositional arthroplasties with organic materials such as tendons and muscles were tested in susceptible patients. Teflon prostheses were eventually introduced on a large scale (11). However, the results regarding function and longevity were rather disappointing. It was not before the introduction of the Low Friction Arthroplasty (12) by Sir John Charnley in the 1960s, that the quality of THA became acceptable according to contemporary criteria. Since then, the Low Friction Arthroplasty concept has prevailed and THA in the 21st century has been considered as one of the most successful interventions in modern medicine (13). It offers lasting functional improvement and pain relief.

The overall concept of modern THA is relatively straightforward: the diseased joint is replaced with an artificial joint consisting of an acetabular cup, and a femoral stem with a femoral head. Although the concept of THA seems quite simple, there is a vast range of different materials, designs, principles, surgical techniques and combinations in THA.

The implants are either fixed with bone cement or by bony ingrowth without the use of cement. The stem / head entity is either modular, in which the head is attached to a taper on the metal femoral stem, or non-modular, meaning that the femoral head and femoral stem is a monoblock construction. Similarly, the acetabular cup is also either modular, with a liner inserted inside a metal shell or non-modular, where the construct is in one piece.

Figure 1. The basic concepts in THA (used with permission from Geir Hallan)



6.3.2 Cemented vs. uncemented THA

There is an ongoing debate about the choice of optimal implant fixation in THA: uncemented or cemented fixation. In Norway, Sweden and the United Kingdom cemented fixation has been the dominant fixation method until recently. Worldwide however uncemented fixation has been preferred for the last 10 or 15 years. In Norway uncemented fixation is used increasingly, and in the year 2012 30 % of the primary THAs were cemented, 26.5 % were uncemented and 43.5 % hybrids with one component cemented and the other uncemented(14). The introduction of uncemented THA evolved from the belief that the cement itself was the main cause for failure in THA (15). In general, cemented THA is used in older patients, whereas the uncemented alternative is more commonly used in younger patients.

In present literature the results of uncemented total hip arthroplasty are differing. An American meta-analysis from 2007 did not demonstrate overall superiority of either method of fixation, when measured as difference in implant survival. However, it is commented on that the results cannot be generalized to all subgroups of prostheses (16). A study from the Swedish Hip Arthroplasty Register found the survival of uncemented THA to be inferior to cemented THA (17). The authors concluded that the overall results may be related to the poorer outcomes of uncemented cups. Poor overall performance of uncemented cups, primarily caused by wear-related problems with conventional UHMWPE liners, was also reported in a study from the Norwegian Arthroplasty Register (18). Nevertheless, results from the above mentioned studies indicate that currently used uncemented THA implants perform better than earlier uncemented implants (16-18).

It is my view that femoral stem survival today is good, regardless of the method of fixation. However, cemented stems have longer follow-up. Furthermore, cemented cups perform better than the uncemented alternative with conventional polyethylene. Modern cross-linked polyethylene liners may have the capacity of improving uncemented cup performance since there is now emerging evidence of less osteolysis and loosening at above 10 years of follow-up compared to conventional PE.

The above controversies are not investigated in the present study in which fixation with bone cement was used in all patients. Some mechanisms of failure may to some extent be transferable to uncemented THA, particularly with regards to acetabular cup failure.

6.4. Contemporary challenges in cemented THA

Since the development of modern low friction THA further evolvments have been done to improve both the functional outcome after surgery and the longevity of the implants. Overall, implant survival of above 90 % at 10 years has been proposed as a benchmark criterion for the unrestricted use of it (19). Further development is still motivated based on changes in demographics of the population. In general people are getting older, demands of functional capacity, both at work and in private, are

becoming higher placing increasing demands on the performance of the THAs. This reality has led to further developments in the fields of THA.

There are several mechanisms of failure in THA. Early failure is often caused by complications such as postoperative deep infection (20) or dislocation (21), which may necessitate complicated and costly revision surgery with severe additional suffering for the patient. In the 1970s loosening of the femoral stem was the most common reason for THA revision (22). Since then substantial improvements in stem survival has been achieved, although the problem with stem loosening has not been eliminated. Aseptic loosening due to wear induced bone resorption (osteolysis) is today considered the most common cause for mid- to longterm failure of THAs (23-25).

6.4.1 Wear, osteolysis and acetabular cup loosening

The mechanical consequence of wear in THA, due to a progressive thinning of the polyethylene, is not the main clinical problem of wear, as one may believe. It is widely agreed that the clinical problems from wear mainly are caused by the release of wear debris particles into the biological environment, when the femoral head moves against the polyethylene acetabular cup. The ingress of polyethylene particles into the interface between cement and bone initiates an adverse biological response in which macrophages phagocytises the particles. As a response prostaglandins, TNF and cytokines are released and act as pro-inflammatory factors in the surrounding tissues and thus cause an inflammatory reaction (26).

Osteoclasts are activated, leading to bone resorption / osteolysis. The complex biological reaction on particles is also thought to decrease bone formation.

Increased resorption and decreased bone formation leads to osteolysis (27;28).

Eventually, with progressive periprosthetic bone loss, the implant loosens and fails (29). Although particles from polyethylene are considered the dominant culprit of osteolysis in THA, particle disease can also result from other particles originating from bone cement or metal.

Long-term success of THA depends on the wear resistance of the bearing materials and a lasting bond between the prosthesis and bone. Thus, material selection and implant design play an important role in the wear- and fixation-related performance

of THA. However, wear and osteolysis are multifactorial processes, not limited to material and design only.

Other factors than wear particles, possibly in conjunction with these, may facilitate acetabular cup loosening. Micromovement of the implant may lead to high fluid pressures in the periprosthetic tissue. High pressures in the periprosthetic tissue may induce further osteolysis, thus introducing a more mechanical explanation to loosening of an implant (30;31). Fluid pressure may induce osteolysis by causing bone cell death or by interfering with the bone formation or bone resorption on a cellular level (32;33).

Also, the presence of an acetabular prosthetic component may alter the physiological load distribution on the surrounding bone causing so-called stress shielding and osteopenia (34;35), which may enlarge the total effective joint space (36). Thus, wear debris particles and high pressurized joint fluid are allowed to propagate to a larger area at the implant-cement-bone interface, ultimately leading to further osteolysis.

Several variables can affect PE wear *in vivo*. These can be divided into factors related to the patient, the surgery and the implant. Patient related factors include gender; female gender has been associated with lower wear (37). High activity level is associated with high wear rates (38). Smaller diameter prosthetic femoral heads have shown to be beneficial due to shorter sliding distance on the PE as compared to larger femoral heads (29;39-41). A varus position of the femoral stem has been related to less polyethylene wear (37) but is normally not intended for other reasons. Acetabular component malposition is linked to higher bearing surface wear and osteolysis (42;43). Support of the cup by the rim of the acetabulum is believed to be beneficial in this context (37). Lateral displacement of the cup has been linked to higher wear rates possibly due to altered lever arm (44).

Also, contact stress of the femoral head on the polyethylene is associated with wear (45-47). Laboratory studies and finite element analyses have demonstrated that a high inclination angle of the acetabular cup increases stresses on the PE (48;49). However, previous literature on cemented THA has not been conclusive on the effect of the inclination angle of the acetabular cup *in vivo* (50-54).

A literature review of the association between wear rate and osteolysis concluded with increased risk of osteolysis when the annual two-dimensional cup wear rate exceeds 0.1 mm (55). Another study has reported a continuous dose-response relationship between wear and osteolysis (56). The magnitude of biological reaction is also reported to be dependent on particle size. Smaller polyethylene particles could be more likely to cause osteolysis (57-59). Therefore, osteolysis may not solely be an effect of the concentration of wear induced particles. Moreover, continuous migration or early proximal migration of the acetabular cup between 1 and 2 mm has indicated increased risk of early or intermediate term revisions (60).

It is clear that the loosening process of cemented acetabular cups involves a wide panorama of causes. Despite improvements in the field of tribology, particle disease still is the Achilles heel of THA. Therefore, contemporary and future research will be searching for innovative solutions to decrease PE wear.

6.4.2 Femoral stem loosening

Femoral stem loosening in cemented THA is a multifactorial process with different mechanisms (22;61). Factors that contribute to cemented femoral stem success, or failure, are material, implant geometry, surface roughness, surgical technique and patient selection (62;63). According to some authors the longevity of cemented femoral stems is related to the quality and endurance of the bonding between the femoral stem and cement (63;64).

In cemented THA there are mainly two fixation principles: the “loaded-taper” and the “composite-beam” fixation model. Loaded-taper designs become lodged as a wedge in the cement mantle during loading (i.e. the Exeter type stems), whereas composite-beam femoral stems rely on an early rigid fixation to the cement (i.e. the Link Lubinus stem). Both principles have examples of good clinical performance. In the composite-beam concept the rigidity of the stem-cement bond can be enhanced by the use of a rough surface finish (63). However, micromovement and subsequent debonding *in vivo* between the stem and cement seems to be inevitable (65). Therefore not only the bonding strength, but also the fail-safe mechanisms after debonding should be considered. Debonding starts at the tip and proximally and extends towards the middle of the stem (11). Debonding decreases the cement

implant conformity and can thus produce micro-motions at the cement-bone interface. In the presence of full thickness cement mantle defects, the micromotions of the femoral stem has the potential to facilitate loosening by forcing high-pressure fluid and particles through the defects onto the underlying bone (the femoral stem pump mechanism) (30;66).

Another failure scenario is based on the biological response to particle debris at the cement bone interface in the femur (cement, polyethylene and metal) from the articulation and from the stem-cement interface, similar to the failure scenario of acetabular cups (40). It has been reported that when rough surfaced femoral stems debonds they may produce more cement debris than polished ones (67;68) and provide routes to transport these wear products.

The degree of migration during the first years after surgery has been shown to correlate with the long-term performance of joint prostheses (69;70). There has also been suggested a limit for the magnitude of subsidence which is considered to be safe with respect to long-term performance. Continuous migration is a warning sign for failure. A square cross-sectional shape of the stem offers more rotational stability than oval stems and a medial collar can reduce the overall migration and optimize the stem-cement load (71). The use of a collar is however debatable (56-58). The use of a dorsal flange has been advocated to enhance the stability of cemented femoral stems.

Nonetheless, implant durability is difficult to predict based on different stem philosophies, due to the complexity of the interactions involved in the loosening of femoral stems. Still, new implants and designs are introduced to the market, without clinical documentation of superior properties.

6.5 Advances in tribology

It has become evident that UHMWPE quality and sterilization technique are related to wear (72). Sterilization of UHMWPE with gamma or electron beam irradiation breaks the polymer chains and generates free radicals in the polyethylene (PE). The free radicals can combine with each other and create cross-links between adjacent molecules, resulting in a restriction of chain mobility and reduced plasticity. The reduced plasticity is reported to improve wear resistance (73;74).

In addition to reacting with each other, free radicals in the PE entail the disadvantage of oxidative degradation of the PE when exposed to oxygen, e.g. during pre-implantation storage or in the body's environment. It is widely accepted that post-irradiation oxidative degradation is a dominant aging mechanism of PE that can have adverse effects on the wear resistance and mechanical properties of UHMWPE (75;76).

To address the problem with free radicals, sterilization methods in inert environments with ethylene oxide (EtO) or gas plasma, but without irradiation, were introduced (77). These methods do not create free radicals and therefore oxidative degradation is not a concern. However, these sterilization methods do not have the benefits of cross-linking.

Highly cross-linked polyethylene (HXLPE) is increasingly used in inserts for uncemented modular metal-backed cups, and also in sockets intended for cemented fixation. The common denominator of HXLPEs is an increased cross-linking by high dosage irradiation and the reduction of oxidative degradation by eliminating the free radicals through post-irradiation thermal stabilization. Initially, re-melting of the HXLPEs represented the post-irradiation thermal stabilization process. However, the increased cross-linking and re-melting process decreases the resistance to ultimate tensile strength and fatigue crack propagation (73;78), which could ultimately lead to implant fracture. Ultimate tensile strength is the maximum stress that a material can withstand while being stretched or pulled before failing or breaking, while fatigue crack propagation is the progressive spread of a crack when a material is subjected to cyclic loading.

As a consequence attempts were made with annealing HXLPEs below the melting temperature which produce good resistance to wear and fatigue crack propagation. However, this process leaves the material susceptible to oxidation of the residual free radicals (79). The latter method of thermal stabilisation is the one most commonly used by current manufacturers. The adverse effects of this process may not become evident before long-term follow up. There are reports of late material failure of annealed highly cross-linked PEs (74). Moderate cross-linking combined with post-irradiation re-melting produces less resistance to fatigue crack propagation and wear, but good resistance to oxidative degeneration.

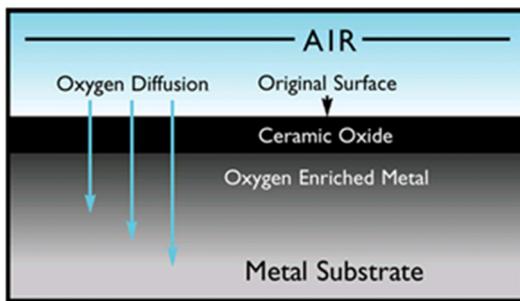
The differences in manufacturing processes of the HXLPEs currently available are not limited to irradiation dose and methods of thermal stabilization. Different UHMWPE resins (GUR) also affect the behaviour of the material (79). Differences between the available UHMWPE resins include the average molecular weight (80). GURs designated 1020 has a lower average molecular weight than GUR 1050, both of which are commonly used in orthopaedic applications. *In vitro* studies have proven no difference in wear between these two materials. However, with the same dose of radiation and thermal treatment, GUR 1020 showed a higher fatigue crack propagation resistance than GUR 1050 (79). These findings are not directly transferable to *in vivo* wear and to daily clinical practice, but they illustrate the wide diversity that ultimately can influence the wear and mechanical behaviour of an implanted prosthesis.

A reduction of wear with HXLPEs of 70 to 100 % as compared to conventional PE has been found in *in vitro* studies (73;81). Short-and midterm clinical studies also have proved a considerable reduction of wear rate compared to conventional PE (82-85). Studies with longer follow-up have confirmed low wear rates of HXLPEs (86-90). A meta-analysis showed consistently lower femoral head penetration and an 87 % lower risk of osteolysis with the use of highly cross-linked PE liners compared to conventional PE liners (91).

The concerns about PE wear have also been addressed by introducing alternative femoral head materials. The use of ceramics for the articulating femoral head offer the advantage of a smoother and harder surface and an improved resistance to scratching (92;93), which is thought to prolong the survival of a joint replacement. However, ceramics are brittle and susceptible to fracture (94-96). While the fracture rates of contemporary ceramic femoral heads are reported to be below 1 %, the consequences for the individual patients are devastating (97). With the intention to reduce the risk of fracture, but maintain the beneficial wear properties of ceramics, zirconia (ZrO₂/zirconium oxide) ceramic femoral heads were introduced. However, the zirconia compound did not perform well (98-102). The reason for this is suggested to be related to the fact that zirconia may go through a phase transformation *in vivo*, which is reported to result in inferior wear properties, due to increased roughness and altered sphericity of the head (103).

Oxidized zirconium femoral heads (Oxinium, Smith & Nephew, Memphis, USA) was introduced in the year 2003 for use in THA (104;105). It is marketed as having the fracture toughness of metals and the wear performance of ceramics. This compound has a metal core and a thin, approximately 5 μm thick, zirconia ceramic surface. The surface is not an externally applied coating. During the manufacturing process, heating to 500 ° Celsius causes oxygen to diffuse into the metallic zirconium alloy. This transforms the original metal surface into a ceramic oxide (zirconia) surface. (Figure 2)

Figure 2. Oxidized Zirconium (with permission from Smith and Nephew)



Niobium is alloyed with the zirconium metal to increase strength and improve mechanical properties. Oxidized zirconium femoral heads are formed directly in the stable phase and are thus theoretically not susceptible to phase transformation, as opposed to conventional zirconia femoral heads. Laboratory tests of oxidized zirconium femoral heads have shown less risk of fracture than traditional ceramic heads and superior scratch resistance over metal heads (104;105). It is more than twice as hard as conventional cobalt chrome (CoCr) femoral heads on the articular surface. It has been reported that when scratching appears valleys are produced instead of a buildup of counterface material above the articulating surface, resulting in less abrasion of the PE (106). Furthermore HXLPE articulating with oxidized zirconium femoral heads had undetectable wear rates in a hip simulator study (104).

The use of oxidized zirconium is also reported to have an impact on the biological response to the wear debris. An *in vitro* analysis under abrasive conditions indicated that oxidized zirconium produces 42 % fewer of the smaller PE particles than CoCr (107;108). Wear debris from oxidized zirconium showed low cytotoxicity and

inflammo-stimulatory effect in another study, suggesting good biocompatibility of the compound (109). Another *in vitro* study reported on low susceptibility of oxidized zirconium for bacterial adherence (110).

6.6 The stepwise introduction of new hip implant technology

The concept of stepwise introduction of new implants was introduced by Malchau in 1995 (111). The incentive of this was to identify inferior implants or techniques as early as possible and to prevent the widespread use of these. History has shown that interesting new technologies and designs in THA have been introduced and implanted in large scale, which later proved to perform inferiorly. A change is not invariably a progress. The importance of surveillance of new products is exemplified by the Boneloc cement disaster (112). Still, there is no formal governmental requirement of clinical studies before the release of new implants in any country as far as I know. One cannot ignore the fact that development ultimately is driven by market forces and the objective of profit. The aggregate influence of inherently self-interested patients and implant manufacturers can incite the introduction of prostheses that seems to be high quality products, but are inferior regarding documentation of being so (113).

The first step in the stepwise introduction is pre-clinical testing e.g. in hip simulators with load patterns and environments simulating *in vivo* use.

If the obtained results are adequate and there is no suspicion of possible adverse effects, a new implant can be tested in step I clinical studies, preferably by independent investigators. In this phase, the study population should be small and the new implant should be compared to an existing design with known good long-term results. For this purpose radiostereometric analysis is suited, because of its high accuracy and thus the need of few study patients to obtain reliable results. Thus, early wear and migration properties can be used as a surrogate end-point for longevity of an implant. There is however still an issue of how long one should follow a new implant, before going further to step II clinical studies (114).

With favourable results in step I clinical studies the new implant can be tested in multi-centre trials, step II clinical studies. The new implant will then be exposed to

different techniques, surgeons and hospital environments and thus any biases introduced by the design of the step I clinical trials can be ruled out.

The final step of the stepwise introduction is the continuous surveillance of joint replacement surgery in national (or international) registers after widespread implementation.

Recently, a study demonstrated the benefits of integrating a retrieval center into the workflow of national arthroplasty registers (115). Poorly performing implants are identified in the register, and retrievals are analysed to study the reasons for failures. The advantage of this concept is the possibility to establish a cause and effect relationship, introducing a further step to implant introduction and surveillance.

6.7 On the pertinence of the study

Patient inclusion in the present study started in 2004. In the years before, the Charnley prosthesis (DePuy International Ltd.) was used as a standard prosthesis at the Orthopaedic Department, Haukeland University Hospital. The Spectron EF Primary femoral stem, used with an EtO-sterilized, non-irradiated Reflection All-PE acetabular cup (Smith and Nephew) was used with older patients who needed a large femoral head to avoid dislocation. At Kysthospitalet i Hagevik the Spectron EF/ Reflection All-Poly combination had been used as a standard implant for some years.

The Spectron EF Primary stem is a modified version of the older satin-finish Spectron stem, which has been one of the best performing stems in the Swedish Hip Register (116). The Spectron EF Primary stem was introduced in 1989 with a proximally roughened surface to enhance stem-cement bonding. In 2007 the Spectron EF stem used with the Reflection All-PE cup was the most commonly used primary total hip prosthesis in Norway (24). Still, the Charnley prosthesis had the longest follow-up and the largest volume of documentation of implants used for primary THA (19). The latter was and by many still is regarded as the gold standard for THA.

In 2003 there were observations of accelerated wear with the non-irradiated EtO-sterilized Reflection All-PE (Smith and Nephew) cups causing concerns about long-

term outcome (52). At the same time HXLPEs were emerging onto the market. The highly cross-linked Reflection XLPE All-PE cup (Smith and Nephew) was introduced as an alternative to the non-irradiated Eto-sterilized Reflection All-PE cup, used at our department. However, the clinical experience of this compound was sparse.

Furthermore, at our department CoCr femoral heads were the primary choice in THA. Oxidized zirconium was introduced in the early 00's as an alternative bearing material with promises of having the fracture toughness of metals and the wear characteristics of ceramics.

In this context, we launched the present study to compare the new bearing materials with their contemporary counterpart and to compare them with the most extensively documented prosthesis, the Charnley prosthesis.

7. AIMS OF THE STUDY

The present study was an approach to a stepwise introduction of new implants used in THA. The main objective of this thesis was to determine wear and migration in different cemented THAs using radiostereometric analysis.

Based on a clinical, randomized, radiostereometric study the specific aims of the 3 papers were:

Paper I To compare wear of oxidized zirconium femoral heads with traditional cobalt chrome femoral heads.

To compare wear of a modern highly cross-linked PE acetabular cup with its non-irradiated and non-crosslinked counterpart.

To compare the cup migration of two different cup designs and to examine if bearing material influences migration.

The null hypothesis was that wear and migration were equal to the Charnley Ogee prosthesis.

Paper II To determine the migration patterns of the Spectron EF stem and to compare them with those of the Charnley stem, which differs with regards to geometry and surface finish.

The null hypothesis was that the migration of the Spectron EF stem was equal to that of the Charnley prosthesis.

Paper III To determine the effect of the inclination angle of the acetabular component on PE wear and component migration in cemented acetabular sockets.

The null hypothesis was that inclination angle did not affect wear and migration.

8. METHODS

8.1 Ethics and protocol

The trial was registered with ClinicalTrials.gov (NCT00698672). It was conducted according to the Helsinki Declaration and was approved by the Regional Ethical Committee. Each patient provided informed consent.

8.2 Patients and randomization

150 patients aged 59–80 years with primary or secondary osteoarthritis of the hip were included in the study between November 2004 and June 2007. The baseline characteristics are presented in the Papers. In bilaterally operated patients, only one hip was included in the study. Exclusion criteria were body mass index over 35, uncompensated cardiopulmonary disease, malignant disease, dementia, dysplasia with the need for bone grafts, Paget's disease, Charcot's disease, rheumatoid arthritis, or other serious systemic diseases.

The patients were randomized into five groups. Eight consultant orthopaedic surgeons and one resident surgeon either performed or supervised the operations. Block randomization was used to ensure that each surgeon operated an equal number of hips in each of the 5 groups. After randomization, there were no crossovers. Randomization was by sealed envelopes revealing study group. An equal number of envelopes from each study group were placed inside a larger envelope. The latter envelope was assigned to one surgeon. After inclusion of a patient, the surgeon drew one of the smaller envelopes from the larger one. After using all the smaller envelopes, the surgeon had included an equal number of patients in each group. The patients were blinded.

8.3 Intervention

The five groups of patients received one of the following cemented THAs:

- (1) Charnley flanged 40 femoral stem with a 22.2 mm head. It articulated with a cemented Charnley Ogee UHMWPE acetabular cup which was γ -sterilized to 2.5 Mrad in Nitrogen (DePuy International Ltd)
- (2) Spectron EF Primary femoral stem with a 28 mm CoCr femoral head and a Reflection All-Poly UHMWPE cup that was sterilized by EtO (Smith and Nephew)
- (3) Spectron EF Primary femoral stem with a 28 mm oxidized zirconium (Oxinium) femoral head and a Reflection All-Poly UHMWPE cup that was sterilized by EtO (Smith and Nephew)
- (4) Spectron EF Primary femoral stem with a 28 mm CoCr femoral head and a Reflection All-Poly XLPE cup irradiated with 10 Mrad, melted at 135°C, and subsequently EtO sterilized (Smith and Nephew)
- (5) Spectron EF Primary femoral stem with a 28 mm oxidized zirconium (Oxinium) femoral head and a Reflection All-Poly XLPE cup irradiated with 10 Mrad, melted at 135°C, and subsequently EtO sterilized (Smith and Nephew)

The Charnley flanged 40 is a monoblock, oval, stainless steel, vaquasheen surfaced (Ra 0.8 μm) femoral stem.

The Spectron EF is a modular, square, matte distal surfaced (Ra 0.7 μm), collared, cobalt chrome stem with a grit blasted roughened proximal surface (Ra 2.8 μm).

Both stems rely on the composite-beam fixation model, in which the stem needs to be firmly bound to the cement.

Only patients suitable to receive both the Spectron EF stem size 2–5 with a standard offset and the Charnley Flanged 40 stem were included. This was determined on preoperative x-rays. In the Charnley group the smaller acetabuli received a 40 mm outer diameter (OD) cup, and the larger acetabuli received a 43 mm OD cup. The details of the surgical technique are described in Paper I. Patients

were allowed partial weight bearing with crutches from the 1st post-operative day. Restrictions were discontinued 6 weeks post-operatively.

Figure 3. The Charnley flanged 40 (left) and the Spectron EF (right), with tantalum markers. (The different bearings with the Spectron EF stem are radiographically identical.)



8.4 Radiostereometric analysis (RSA)

The main objective in the present study was to measure *in vivo* wear and migration of different THAs. There are several different methods of measuring wear and migration in THA (117;118). In this study we used the RSA method, previously comprehensively described (60;119).

RSA is a refined and accurate method to measure wear and migration in prospective studies and is extensively used for this purpose in orthopaedic research. It enables measurement of relative *in vivo* motion in three dimensions in the range of 0.1 mm and 0.05°. Due to its high precision, few patients are needed to obtain satisfactory statistical power. It is suitable for determination of early wear properties in modern low-wear bearing surfaces and for the early detection of

inferior implants and designs, as the degree of component migration during the first years after surgery has been shown to correlate with the long-term performance of joint prostheses (69;70;120) .

The overall concept of RSA is not difficult: determination of location in space of two objects. However, it is considered more technical demanding and expensive than other methods, mainly because it is depended on the implantation of markers into the bone, cement and on the implants. As a consequence there has also been developed markerless so-called model based RSA methods which allows measurements without markers on the implant (121;122).

In this study we used the traditional method with the use of tantalum markers attached to the implants. Tantalum is a preferred material because of its biocompatibility and radio opacity. The manufacturer supplied the acetabular cups with spherical tantalum markers into the dome and periphery. Also, both femoral components were supplied with tantalum markers by the manufacturer. The Spectron EF stem was supplied with 3 tantalum markers, one of which was attached to a cone that had to be impacted preoperatively. The Charnley flanged 40 stem was only supplied with 2 tantalum markers and therefore the centre of the femoral head was used as a third point for the calculations of movements of the stem. Furthermore, at surgery tantalum markers were inserted into the periprosthetic pelvic bone and proximal femoral bone with an injector. Tantalum markers were also inserted into the femoral cement with cannulas with trocars. To be able to identify the different segments, the markers in each adjacent segment had different sizes. The markers in each segment defines a rigid body (cup, stem, cement mantle, femoral bone and pelvic bone).

After surgery the Index RSA examination was done with a median time after surgery of 11 (9-15) days. RSA examinations were repeated at 3, 6, 12 and 24 months after surgery. One radiographer did all the examinations with the same set-up.

The uniplanar RSA examination technique we used depends on the use of a calibration cage positioned under the roentgen examination table. In the cage tantalum markers are placed systematically to construct a system of coordinates. Thus, with the patient lying supine and simultaneous roentgen exposures by two X-

ray tubes, the markers in the patient and implant are projected onto the co-ordinates of the calibration cage. Further details of our RSA method is presented in Paper I.

The obtained RSA-radiographs were subsequently analyzed with a software program (UmRSA Digital measure version 5.0 software RSA Biomedical). In this manner the accurate three-dimensional positioning of each segment (stem, cup, cement and bone) relative to each other was calculated. With subsequent RSA examinations relative 3D motion of the segments can be measured. Point motion of the femoral head centre, using the tantalum markers in the PE as a fixed reference segment, represented femoral head penetration. Segment motion of the markers in the PE cup, using the periprosthetic pelvic bone markers as the fixed reference segment, represented cup migration. Similarly, segment motion of the femoral stem, with markers in the femoral bone as the fixed segment, represented femoral stem migration.

During marker insertion, radiographic imaging and analysis, one has to have cognizance of some pitfalls and potential error sources which can interfere with the reliability of the data.

During X-ray RSA examination, one has to be reassured that the image quality is adequate with high resolution and that there is no over projection of the markers.

In RSA, the spatial configuration, or spread in all three dimensions, of the markers beads within each segment is assessed by the so-called condition number (CN) and obtained through software analysis. A high CN reflects a narrow spread of markers close to a line and a low CN indicates a broad spatial distribution of the markers. If CN is high the accuracy is jeopardized (119). Therefore, during insertion of the markers, we tried to obtain well-scattered bone markers. We used 150 as an upper limit for the condition number, as suggested by others (123). Segments with CN above 150 were not be analysed.

Furthermore, the mean error of rigid body fitting (ME) is suggested to be below 0.35 mm. This parameter is also calculated by the software program and characterizes the relative motion, or stability, of the markers inside the bone. Thus, loosening of a marker inside each rigid body can be detected, which may influence the accuracy of the motion calculation (123).

Also, one has to evaluate the repeatability of the method, expressed as precision. It is a measure of the possibility that an exact repeat of a result can be obtained (123). The precision of the measurements is evaluated by double examinations taken within a short time interval of minutes. The motion detected in this short interval, in which the implant theoretically should not have moved, is the precision of the used RSA technique. The details of how we determined and calculated the precision of our RSA method are presented in Paper I.

The RSA examinations in this study were performed at the Department of Radiology at Haukeland University Hospital. The digitized radiographs were then sent to the Department of Orthopaedic Surgery at St. Olavs Hospital, Trondheim University Hospital.

8.5 Radiographic evaluation of cup inclination

In Paper III the angle of inclination of the acetabular component was measured on standard post-operative anteroposterior pelvic radiographs. It was measured as the angle between a line drawn along the opening of the acetabular component and one joining the ischial tuberosities. The measurements were performed directly with the Picture Archiving and Communication System (PACS)(Agfa) program.

8.6 Clinical evaluation

In Paper I and Paper II clinical outcome was evaluated with the widely used and validated Harris Hip Score which was performed preoperatively and at 3, 12, and 24 months (124). The preoperative scoring was done by the operating surgeon whereas the subsequent scoring was mainly done by the first author.

8.7 Statistics

Statistical evaluation was performed using SPSS software version 17.0. For power analysis and sample size calculation we used PASS (NCSS Statistical software).

Due to the precision of the RSA method relatively few patients, 15-25 subjects, are needed to obtain reliable results. In this study we calculated that 24 subjects were needed to obtain a power of 80 % for the Student's t-test to detect a 0.1 mm difference in mean proximal head penetration with a two-sided significance level of

0.0125. The adjusted significance level of 0.0125 (0.05 divided by 4) was calculated with the Bonferroni correction method to counteract the problem of multiple comparisons in Paper I. Because we anticipated some exclusions we included 30 subjects in each bearing group.

In Paper I one-way analysis of variance (one-way ANOVA) and *t*-tests for independent samples were used to detect differences among the groups in mean values of HHS, femoral head penetration and cup migration at 24 months. When comparing femoral head penetration and migration at different points in time we used the paired *t*-test.

In Paper II longitudinal effects of the different prostheses on the RSA migration data were investigated in a linear mixed-effect model, which took into account any correlation in outcome measures introduced by the repeated-measures design. Assumptions for these analyses were assessed based on residual plots and normal probability plots of the residuals. One-way ANOVA was used to determine any differences in mean migration at 2 years among the 4 different articulations in the Spectron EF group. Differences in paper II (and paper III) were regarded as being statistically significant if the two-sided *p*-value was less than 0.05.

In Paper III we used linear regression analysis to determine the relationship between the inclination angle of the acetabular component and femoral head penetration and migration of the acetabular component. Further analysis with adjustment for gender and BMI was also performed. We also investigated a possible interaction (effect modification) by the different types of acetabular component and femoral head. We compared the mean femoral head penetration at two years between the two different acetabular components using Student's *t*-test for independent samples. Assumptions for the use of linear regression were evaluated and regarded as satisfactory. A sample size of 95 achieved 87 % power to detect a difference in slope between the null hypothesis value 0 and the alternative hypothesis value 0.01 when the standard deviation (SD) of the inclination angle was 5.5; the SD of the penetration was 0.18 and the two-sided significance level was 0.05.

9. SUMMARY OF PAPERS I-III

Paper I

Kadar T, Hallan G, Aamodt A, Indrekvam K, Badawy M, Skredderstuen A, Havelin LI, Stokke T, Haugan K, Espehaug B and Furnes O. **Wear and Migration of Highly Cross-linked and Conventional Cemented Polyethylene Cups with Cobalt Chrome or Oxinium Femoral Heads: A Randomized Radiostereometric Study of 150 Patients.**

Background: Highly cross-linked polyethylene acetabular cups and oxidized zirconium femoral heads were developed as an approach to reduce wear debris induced osteolysis. The present RSA-study was performed to compare these new materials in vivo with conventional bearing materials used in articulations in total hip arthroplasty.

Methods: The patients were randomized to receive either a Charnley femoral stem with a 22.2 mm head or a Spectron EF femoral stem with a 28 mm head. The Charnley articulated with a γ -sterilized Charnley Ogee acetabular cup. The Spectron EF was used with either non-cross-linked polyethylene (Reflection All-Poly) or highly cross-linked (Reflection All-Poly XLPE) cups, combined with either CoCr or oxidized zirconium femoral heads. The patients were followed with repeated RSA measurements for 2 years.

Results: After 2 years, the non-cross-linked Reflection All-Poly cups had higher proximal penetration than its highly cross-linked counterpart. There was no difference between the Charnley Ogee cups and the highly cross-linked cups. Use of oxidized zirconium femoral heads did not affect penetration at 2 years compared to heads made of CoCr. We found no significant difference in migration between the cups.

Interpretation: Further follow-up is needed to evaluate the benefits, if any, of Oxinium femoral heads in the clinical setting. The Charnley Ogee was not outperformed by the more recently introduced implants in our study. We conclude that this prostheses still represents a standard against which new implants can be measured.

Paper II

Kadar T, Hallan G, Aamodt A, Indrekvam K, Badawy M, Havelin LI, Stokke T, Haugan K, Espehaug B and Furnes O. **A randomized study on migration of the Spectron EF and the Charnley flanged 40 cemented femoral components using radiostereometric analysis at 2 years.**

Background: Design and surface finish is of fundamental importance for the long-term performance of cemented femoral hip implants. The satin Spectron femoral stem has been performing well according to National Arthroplasty registers. A modified, proximally roughened version of the Spectron stem, the Spectron EF, was introduced to enhance stem-cement bonding. We performed a randomized study to determine the migration patterns of the Spectron EF femoral stem and to compare them with those of the Charnley stem, which is regarded by many as the gold standard for comparison of implants due to its extensive documentation.

Methods: 150 patients with a mean age of 70 years were randomized, single blinded to receive either a cemented Charnley flanged 40 monoblock, stainless steel, vaquasheen surface femoral stem with a 22.2 mm femoral head (n=30) or a cemented Spectron EF modular, matte, straight, collared, cobalt-chrome femoral stem with a 28-mm femoral head and a roughened proximal third of the stem (n=120). The patients were followed with repeated radiostereometric analysis for 2 years to assess migration.

Results: At 2 years, stem retroversion was 2.3° and 0.7° ($p < 0.001$) and posterior translation was 0.44 mm and 0.17 mm ($p = 0.002$) for the Charnley group (n = 26) and the Spectron EF group (n = 74), respectively. Subsidence was 0.26 mm for the Charnley and 0.20 mm for the Spectron EF ($p = 0.5$).

Interpretation: The Spectron EF femoral stem was more stable than the Charnley flanged 40 stem in our study when evaluated at 2 years. In a report from the Norwegian arthroplasty register, the Spectron EF stem had a higher revision rate due to aseptic loosening beyond 5 years than the Charnley. Initial stability is not invariably related to good long-term results. Our results emphasize the importance of prospective long-term follow-up of prosthetic implants in clinical trials and national registries and a stepwise introduction of implants.

Paper III

Kadar T, Furnes O, Aamodt A, Indrekvam K, Havelin LI, Haugan K, Espehaug B & Hallan G. **The influence of acetabular inclination angle on the penetration of polyethylene and migration of the acetabular component: a prospective, radiostereometric study on cemented acetabular components.**

Background: Previous literature has been equivocal on the correlation of acetabular cup inclination angle and polyethylene wear and cup migration in vivo. In the present prospective study we assessed the effect of cup inclination angle on femoral head penetration and cup migration in cemented acetabular sockets using radiostereometric analysis.

Methods: A total of 120 patients received either a cemented Reflection All-Poly ultra-high-molecular-weight polyethylene or a cemented Reflection All-Poly highly cross-linked polyethylene acetabular component, combined with either cobalt-chrome or Oxinium femoral heads. Femoral head penetration and migration of the acetabular component were assessed with repeated radiostereometric analysis for two years. The inclination angle was measured on a standard post-operative anteroposterior pelvic radiograph. Linear regression analysis was used to determine the relationship between the inclination angle and femoral head penetration and migration of the acetabular component.

Results: We found no relationship between the inclination angle and penetration of the femoral head at two years' follow-up ($p = 0.9$). Similarly, our data failed to reveal any statistically significant correlation between inclination angle and migration of these cemented acetabular components ($p = 0.07$ to $p = 0.9$).

Interpretation: We found no correlation between the angle of inclination of the acetabular component and either penetration of the femoral head or migration of the acetabular component. Concerns other than polyethylene wear and migration must be considered in conjunction with the inclination angle of cemented all-polyethylene acetabular components. An optimal angle of inclination for the acetabular component is notably of greater importance in prostheses with metal-on-metal articulations, such as hip resurfacing prostheses

10. DISCUSSION

10.1 Methods

10.1.1 Study design

The study was performed as a prospective, randomized controlled trial (RCT) which is considered to be the most reliable form of scientific evidence because it reduces bias and can conclude on causality (125).

When planning the study we performed a power analysis. This is important in statistics to prevent so called type II error which is the failure to reject a false null hypothesis. A type II error is most commonly caused by an insufficient number of patients. Moreover it is important to restrict the cost and timeline of the study. The number of subjects in RCTs depends on the magnitude of difference one has the intention to examine. In THA the differences are generally small, with some exceptions. Thus, the number of subjects required to study the differences usually are high. In this study we used the previously described RSA-method (119;126). Due to the high precision of the method, a relatively small number of subjects are needed when performing an RCT.

The patients in the present study were randomly assigned to treatment groups, minimizing allocation bias. The method for allocation concealment is described in the papers. To avoid the influence of surgeon, block randomization was used. The patients were blinded to prevent study participants from knowing which intervention was received. It was not possible to blind the surgeons and investigators to be blinded since the implants had different designs and instruments for implantation.

Although the RCT is regarded as the gold standard for a clinical trial, with the strongest level of evidence, it has some limitations. Among the most frequently mentioned drawbacks is the external validity. Thus, in the context of the present study, the results are not directly transferable to e.g all hospitals, surgeons and patients. However, I believe that the patients in our study and the hospital in which the procedures were performed do represent a quite common clinical environment in Norway.

Furthermore, small randomized controlled trials cannot detect any rare events unless they comprise very large number of patients.

Finally, outcomes from randomized controlled trials often are surrogate end-points that are supposed to correspond to some other end-point that you want to assess. In this particular study, we mainly based our conclusions of wear and migration from early RSA-results at 2 years. We cannot know for certain the long-term performance of an implant, due to the vast amount of factors contributing to the wear and migration behaviour. Therefore we can only provide facts and results and liaise these with present evidence. We can, based on similar studies predict the longevity of an implant, but we cannot estimate implant survival as an end-point. It is a meaningful insight that short-term data has limitations. Therefore, further follow-up is needed of the subjects in our study, and we plan RSA-examinations at 5 years and 10 years. A problem that we anticipate is the loss of follow-up and the resulting possibility of type II errors. However, the results after 5 years will tell us more about the examined properties of the implants, due to the nature of the issues involved, e.g. gradually increasing roughening of the femoral head.

For the purpose of longer follow-up of THAs (10-15 years) registry-based observational studies should be considered. Among the advantages of such studies are the improved external validity and applicability over RCTs. The numbers of patients usually are higher than in other study models, and the results represent a national mean. Moreover, it gives better insight in the assessment of safety. However, to obtain unbiased and accurate results from a register study it is necessary with a high degree of registration completeness (127).

When the numbers of revisions are small, differences should be interpreted with caution. Variables such as patient activity, skill of the surgeon, and indication for revision surgery usually cannot be controlled for and may introduce bias.

In conclusion RCTs are prominent in the hierarchical approach to study design. The results of our single RCT trial should however be interpreted with some caution (125). Evidence from other trials and from well-designed observational trials should be evaluated together with our results. However, observational trials are limited in their ability to establish a cause and effect relationships. For this, retrieval analysis

of failed implants may be used, as a supplement to both observational studies and RCTs.

10.1.2 Radiostereometric analysis and follow-up

RSA is a validated method to measure wear and migration in THA . Short-term follow-up (e.g. 2 years) can provide a surrogate outcome for long-term survival. Due to its high precision a relatively small numbers of patients, 15-25 subjects, are needed to obtain adequate statistical power (123).

Still, the RSA method is technically difficult to perform and will probably remain a research tool. Knowing about the difficulties, we planned our study to allow for exclusions. The RSA follow-up of all included patients was however above 80 % at 2 years. The most frequent cause of excluded RSA examinations was poor visibility of markers in the acetabular cup. In the group using the Spectron EF stem with Oxinium femoral head on Reflection All-Poly the RSA follow-up rate at 2 years was somewhat inferior. We could not find any other reason for this than coincidence.

The tantalum markers are bio-inert and there are no reports of adverse reaction of these. Loosening of the tantalum markers may theoretically constitute a risk of third-body wear if released into the joint space. There have been no reports on this problem in the literature, and the prevalence of this is not known. The prolongation of operation time and the possibly increased tissue trauma may increase the risk of infection (128). The double examinations for the calculation of precision expose the patient for additional radiation. However the radiation dose is low. To my knowledge there are no reports on side effects of the method. On some radiographs we found a displaced markercone. Analysis of some of the first implanted Spectron EF stems showed a high value of mean error of rigid body fitting. This lead us to the suspicion of insufficient fixation of the markercone on the Spectron EF stem. After identification of this problem, we were cautious when impacting the cone onto the neck of the Spectron EF stem and the problem was solved. I am not aware of any patient related morbidity as a consequence of this.

The RSA examinations in our study were done with the patients supine and non-weight bearing. There has been some controversy as to whether supine radiographs underestimate penetration values. Another RSA study found no

clinically relevant differences between supine and weight-bearing radiographs (129). Therefore I consider supine radiographs, as used in our study, to be adequate for the measurement of penetration.

The patients in the present study were operated at two geographically separate units. The RSA radiographs were however taken in one unit. Thus, 110 of the 150 patients included in the study had to travel to the other unit when discharged. For this reason, the index RSA examinations were performed between nine and 15 days post-operatively. At this point some patients may have been mobilised and others not. This may have lead to different degrees of non-elastic deformation of the PE (creep) before the index RSA examination, which can affect the starting point for the measurements. However, there is no reason to believe that the degree of weight-bearing differed in the study groups.

With RSA being a 3-D method one has the possibility to calculate mean total point motion (MTPM). MTPM represents the magnitude and direction of maximal penetration. We chose proximal penetration as the main outcome, because the magnitude of the penetration occurs cranially. Also, several other studies to which we compare our results, report the two-dimensional femoral head penetration.

In summary I believe that our RSA method was of high standards with values of precision comparable with those presented by others. We have presented our method with transparency. Thus, our RSA results can be regarded reliable, in concordance with the idea of a stepwise introduction of new implants in THA (111).

10.1.3 Radiographic evaluation of cup inclination

Computerized tomography (CT) is the most accurate tool for the measurement of acetabular cup inclination (130). However, measurement of orientation of component orientation on plain radiographs is also considered a reliable and accurate method. This is a more ubiquitous method than CT, with lower costs and lower radiation dose exposure. It is by far the most widely used method (130;131).

Acetabular cup inclination was assessed with the PACS program. Cup inclination was measured on all 120 radiographs of the Reflection All-Poly cups by the first author. One of the senior authors did the measurements on 20 radiographs in order

to assess inter-observer agreement. The intraclass correlation (ICC) between the two observers was strong (ICC= 0.9). The mean difference between the two observers was 0.56°. Intra-observer agreement was assessed by repeating 20 measurements with an interval of at least two weeks. The intraclass correlation was strong (ICC= 0.99) and the mean difference between the observations was 0.14°.

10.2 Results

10.2.1 Wear and cup migration

The non-elastic deformation of the PE (creep) explains part of the femoral head penetration during the first 12 months after implantation. After that, creep becomes negligible (29;132). Therefore, penetration of the femoral head into the PE is not entirely attributed to the actual removal of substance.

An interesting literature review indicates that osteolysis is rarely observed at a wear rate of less than 0.1 mm/y (55). Others suggest a continuous dose–response relationship between PE wear rate and periprosthetic osteolysis (55).

Either way, the high femoral head penetration rate of the of the non-irradiated and non-crosslinked Reflection All-Poly cups constitutes a great concern. Our findings are in accordance with previous reports (52;133).

10.2.2 Oxidized zirconium

We found no differences in femoral head penetration between oxidized zirconium and CoCr heads, regardless of the PE type. Another study has also found that short-term wear with oxidized zirconium were comparable to CoCr heads articulating with highly cross-linked polyethylene (107). Our findings thus do not support the *in vitro* results found earlier showing reduced wear with oxidized zirconium heads (104). This illustrates that caution should be used upon transferring laboratory results to clinical performance of the implant.

Retrieval studies have reported cracking, gouging, and delamination of the oxidized zirconium femoral head after hip dislocation (134-136). The ceramic layer on a more elastic metal substrate was apparently unable to resist the high contact stresses, resulting in a damaged surface with higher roughness than CoCr and alumina

femoral heads (137). This problem is probably of greater importance when oxidized zirconium heads are used with metal backed cups instead of cemented all-PE cups. Others have reported on extensive wear following PE liner dislocation (138). There has also been a report on damage of an oxidized zirconium femoral head with metal transfer due to a metal foreign body (139). Thus, despite expected to be more scratch resistant, metallic foreign bodies can damage oxidized zirconium femoral heads.

Regarding clinical outcome at 2 years none of the femoral heads were superior to the other, which is equivalent to the findings of another study (140). This is also expected, because the basic principle and design of both implants were identical.

Our results might be a consequence of the short follow-up. CoCr femoral heads can be roughened with time because of third bodies of bone cement and metallic or bone debris (141). One study concluded that alumina and zirconia ceramics were more resistant to simulated third-body damage than metal alloys (142). Another study has reported on better wear properties with alumina ceramic heads than with CoCr at 10 years follow up with uncemented sockets (143). An *in vitro* study demonstrated that the ceramic surface of oxidized zirconium resists roughening, resulting in less abrasion of the PE, as compared with CoCr femoral heads (104). Also, the biological response to the particles generated in bearings with oxidized zirconium may be favourable compared with CoCr (108;109;144). Therefore differences may become evident with a longer follow-up period. In 2012 The Australian Orthopedic Association National Joint Registry reported of 97.8 % survival at seven years for Oxinium used with highly cross-linked polyethylene, which was the highest survivorship of all bearing categories (145). However, as stated by the Australian Joint registry, the results should be interpreted with caution, mainly because the confounding effect of limited numbers of implants.

In summary, further follow-up is required to discern differences, if any, between CoCr and oxidized zirconium femoral heads with respect to wear, implant durability and clinical benefits. Based on concerns of the mechanical properties of this material and the lack of long-term clinical follow-up studies we recommend the use of oxidized zirconium to be restricted to clinical studies.

10.2.3 Highly cross-linked PE

We found low wear of the highly cross-linked Reflection All-Poly XLPE cups, which is consistent with earlier reports with cemented HXLPE (82;146). After the bedding-in period the proximal femoral head penetration was below the suggested osteolysis-threshold of 0.1 mm/year (55).

Care should be taken to generalize our results to other highly cross-linked PEs, as the available implants differ in the manufacturing process. The Cold Irradiated Subsequent Melt (CISM) sterilization process of the Reflection XLPE involves a relatively high radiation dose of 10 MRad (147). After irradiation the PE is subsequently heated above melt temperature to eliminate the retained free radicals to prevent oxidation. Indeed, laboratory tests have shown very low oxidation of the Reflection XLPE (148;149). However, cross-linking and the post-irradiation melting step may, as mentioned before, change the amorphous and crystalline regions of the polymers. The loss of plastic deformation and concomitant reduction in fracture resistance and crack propagation (148;150) may yield HXLPEs more susceptible to fracture. This is especially a concern in patients with high physical demands or other factors providing high stresses on the material (151). Because of these reasons some authors have proposed that lower degrees of cross-linking of PE may be more appropriate in total joint replacements (151). In my view, this is presumably a greater concern with modular HXLPE liners where e.g. high stress rim loading may initiate propagating cracks.

Others have proposed that the mechanical properties in the highly cross-linked PE may compromise the periprosthetic bone remodelling, jeopardizing socket fixation (152). The degree of migration during the first years after surgery has been shown to correlate with long term performance of acetabular cups (60). In our study we found no differences in migration between the two different Reflection cups.

The results of our study suggest that the amount of PE wear particles is substantially reduced in the presence of highly cross-linking. Several studies with longer follow-up show a considerable reduction of osteolysis with the use of HXLPEs (87;88;153;154). However, there are still reports of osteolysis being observed 5-7 years after THA with the use of highly cross-linked bearings (155-

157), thus indicating that the problem with osteolysis has not been eliminated. HLXPEs produce smaller wear debris particles (158). Smaller wear debris particles may be more biologically active and are thus presumably be more likely to cause osteolysis (159-161).

Our results regarding PE wear cannot directly be transferred to uncemented sockets using PE-liners. Several studies with non-crosslinked PE have shown higher wear rates with the use of metal-backed uncemented PE liners compared to all-PE cemented cups (162-164). A systematic literature review reported on equal or increased wear rate with uncemented fixation (165). There are several possible explanations for this. Some suggest that the cement absorbs some of the stresses on the PE (166). Another explanation may be the backside wear, which is only present in uncemented sockets (167). Furthermore, PE-liner thickness of at least 6-8 mm is recommended due to increased wear with thinner PE-liners (11;168).

In HXLPEs there are also concerns that higher internal stresses with the use of thin liners may increase wear (169), in addition to the possibility of catastrophic liner fracture. This has become further actualized in the way that the beneficial wear properties of HXLPEs have stimulated the interest in using larger femoral heads to avoid dislocation. A laboratory study on thin PE liners with increased cross-linking and larger femoral heads did not report on increased wear and only moderate internal stress elevation (169). In another clinical study wear of HXLPE liners at 8 years were the same irrespective of 26 - or 32 mm femoral head size (170), thus confirming *in vitro* findings (171). This suggests that the use of larger femoral heads with HXLPEs and concomitant greater stability does not come at the expense of increased wear, at least up to 32mm head diameters.

Despite the concerns about mechanical properties and not fully understood biological response to wear debris particles, the overall clinical performance of the highly cross-linked PE compounds is promising.

10.2.4 The Charnley Ogee cup

The Charnley Ogee cup was superior to the non-irradiated Reflection All-Poly cup, regarding femoral head penetration. There was no difference in femoral head penetration between the Charnley Ogee cup and the irradiated, highly cross-linked Reflection All-Poly cup after 2 years of follow-up.

The Charnley Ogee cup is gamma irradiated in the sterilization process, but with a lower radiation dose (2.5 MRad) than HXLPEs. The result is some cross-linking, but to a lesser extent than in HXLPEs. One would therefore expect higher penetration results for the PE used in the Charnley Ogee cup. However, the femoral head in the Charnley Ogee group was smaller than in the other groups. This may explain the similar penetration results, despite the lower degree of PE cross-linking of the Charnley Ogee cup compared to the highly cross-linked version of the Reflection cups (39;41). In THA there is a tradeoff situation with regard to femoral head size (172-174). A smaller diameter femoral head increases the risk for dislocation, but potentially offers lower wear. A larger head diameter reduces the risk for dislocation, but wear- and mechanical properties of the cup may be inferior (41). Moreover, there is a possibility that the low penetration of the Charnley Ogee is due to differences in surface characteristics and materials (steel vs. CoCr) of the femoral heads. Thus, the findings are not only attributable to the different PE-materials. The results are however directly relevant for a comparison of the prostheses *in toto*. We found no difference in HHS at 2 years between the groups. With a similar penetration rate the anticipated total wear debris load (volumetric wear) is lower with smaller femoral heads (172). This may lead to decreased osteolysis and improved longevity.

The overall penetration rate measured for the Charnley Ogee cup in our study is lower to those reported in other studies. Penetration rates between 0.07 mm/year-0.2mm/year have been reported earlier (175-177). The reasons for our lower wear rate are unclear, but may be explained by methodological differences. Furthermore, wear in the above mentioned studies was calculated as a mean over several years, with some reports not considering creep. It is possible that wear rates of the Charnley Ogee cup will accelerate after some years because of roughening of the articulating surfaces or aging changes to the polyethylene. The most adequate

explanation may be that the Charnley Ogee cups in the earlier reported studies were gamma sterilized in air, as opposed to our study in which it was gamma sterilized in inert environments. The manufacturing process does not involve elimination of free radicals. During and after implantation the acetabular cups are exposed to oxygen. This could facilitate oxidative degradation of the Charnley Ogee cup with time. Our early wear results may therefore not predict the later clinical performance due to the risk of progressive oxidative degradation of the Charnley Ogee compound *in vivo*. A report has however concluded that the effect of progressive oxidation *in vivo* of gammasterilized UHMWPE does not appear to affect wear (175).

The proximal migration of the Charnley Ogee and the cemented Reflection cups were comparable to other reports at 2 years (60;178). Both cups migrated initially, but after 6 months component fixation was stable. In our study all groups of cups had a migration that was within the limits of what is considered safe with respect to long-term performance (60).

There are concerns of adverse reaction to metal debris with Metal-on-Metal hip replacements (MoM) (179). Recently, wear at the trunnion of THAs (“trunnionosis”) has become an area of interest, due to the fear of similar adverse reactions to metal debris as seen with MoMs (180). Metal debris involved in “trunnionosis” may be more biologically active than wear debris from the articulating surface (181). The Charnley Ogee cup in our study articulated against a monoblock Charnley flanged 40 femoral stem. Because “trunnionosis” is not a concern with this prosthesis it may exhibit a favorable total wear debris load, compared to the other groups in this study with CoCr and oxidized zirconium modular femoral heads.

In conclusion, the Charnley Ogee has the longest follow-up and the largest volume of documentation of prostheses used in THA and it was not outperformed by the more recently introduced implants in the present study.

10.2.5 Femoral stem migration

The stability of the cement mantle was measured with the Spectron EF stem. Because it has a relatively thin cement mantle and the stem design is rectangular and voluminous, the identification of the markers in the cement was difficult. At 2 years only 26 THA could be measured.

A subsidence of more than 1 to 2 mm during the first two years has been reported to imply an increased risk of later revision (60). The subsidence of the prostheses in this study was in the range of 0.2-0.26 mm. Thus, both stems subsided within the limits of what is considered to be safe with respect to long-term performance. However, the Charnley flanged 40 was less stable for retroversion and posterior translation than the Spectron EF stem. The higher stability of the Spectron EF stem may be explained by its proximally roughened surface and rectangular cross-sectional shape (63;182).

We encountered difficulties with identifying RSA markers in the femoral cement and only 26 patients in the Spectron EF group were eligible for analysis. In those eligible for analysis, migration of the cement segment relative to the bone was of minor magnitude at 2 years. These results are similar to another study on the Spectron EF stem (183). Also, a previous study reported on a stable cement mantle with the Charnley stem (184). I therefore believe it is adequate to attribute most of the measured migration, to micromovement of the stem relative to the cement mantle.

An earlier study reported on a low early revision rate for the Spectron EF stem (185). In coherence with the anticipated prognostic value of RSA studies, one may also expect favourable long-term results for the Spectron EF stem. Contradictory, the Norwegian Arthroplasty Register reported a six times higher revision rate due to aseptic loosening for the Spectron EF stem beyond five years, when compared to the Charnley (24). Our short-term results are therefore not consistent with the medium-term results presented in the register study.

The discrepancy between our RSA results and the findings from the Norwegian Arthroplasty Register may be due to different mechanism of failure in the long term. Another RSA study showed that many Spectron EF stems eventually debond from the surrounding cement mantle (186). Debonding of the proximally roughened

Spectron EF stem may produce more abrasion debris, than the Charnley prosthesis that has a smoother surface (182). Retrieval analyses of failed Spectron EF stems have shown consistent failure mechanisms (187;188). Debonded stems cause fretting between the cement and the rough metallic stem and thus generate metallic and cement particles, with concurrent polishing of the stem surface. To my knowledge, these observations have not been reported with the satin finish-surfaced older version of the Spectron stem.

A study on cemented Müller-type stems reported on inferior long-term survival of the rougher surfaced version of this prosthesis, as compared to the polished version (189). This suggests that the coherence between surface roughness and loosening is not limited to the design of the Spectron EF femoral stem.

The failure mechanism of debonding and eventual loosening is gradual and evolves over many years. Presumably, this may explain the inconsistency of the short-term RSA findings and the longer-term results of the register study on the Spectron EF stem. However, the results for the Spectron EF stem in the register study may have been affected by the results of the poor performing Reflection cup. The non-irradiated and non-cross-linked Reflection All-PE cup was used together with the stem in the greater number of cases in the register study. Therefore, some stem revisions were probably done to facilitate the removal of acetabular components. Also, some stems may have been found to be loose at surgery, although not radiologically or clinically suspected to be loose before surgery. In other words, the non-cross-linked Reflection cup may have distorted the stem-results.

In conclusion *in vivo* migration patterns at 2 years should be considered in combination with the surface finish and design of the implant, as these factors influence the modes of failure. Initial stability is not constantly related to good long-term results. Our results emphasize the importance of prospective long-term follow-up of prosthetic implants in clinical trials and national registries, and use of a stepwise introduction of implants.

10.2.6 Acetabular cup angle of inclination

We found no relationship between the inclination angle of the acetabular component and the femoral head penetration or cup migration.

An *in vitro* study has showed increased penetration with increased inclination angle (49). Most *in vivo* studies on the influence of the inclination angle on wear have been performed on uncemented cups (43;49;131;190-196). Most of these studies report on higher wear rates with higher inclination angles. In cemented THA the results have been equivocal (50-54). Although no certain conclusion can be made, our results suggest that cemented all-PE cups are less sensitive to higher angles of inclination, than uncemented cups. Furthermore, our findings suggest that *in vitro* results not invariably are in agreement with *in vivo* results.

One study has reported on reduced peak contact stresses with an increased anteversion angle and implied less wear with more anteversion of the component (49). In the present study we did not account for the effect of anteversion. However, the literature on this issue is not comprehensive and any correlation has still to be resolved. There is presumably no association between anteversion and inclination of the acetabular cup.

Furthermore, restoration of femoral offset may have an effect on wear (193). Under-restoration of offset is reported to increase wear (197). In the present study we did not analyse the effect of femoral offset. Before randomization X-rays were examined with a template, and only subjects who were suitable to receive the Spectron EF stem size 2-5 (or the Charnley flanged 40) were included. BMI and gender can influence offset. These factors were equally distributed between the groups. Therefore, a systematic difference in femoral offset between the groups in this study is unlikely.

One study on cemented cups suggested that it is better to accept a vertical orientation of the cup and obtain full bony coverage than the contrary (198). Completely contained acetabular components had a lower incidence of complete cement-bone radiolucency. However, a high inclination angle increases the risk for dislocation (199). On the other hand, less abduction of the cup with some acetabular and femoral anteversion limits the range of motion of the joint (200). Thus, several

other factors than wear and migration should be considered when positioning cemented all-polyethylene acetabular components.

We found no effect of the inclination angle on migration of the acetabular component, which contrasts with the results with uncemented metal-backed components from another study (43). Our findings suggest that the stability of cemented components is less sensitive to the angle of inclination than that of uncemented metal-backed components. This might be explained by the different distribution of stresses on the surrounding bone and differences in the polyethylene thickness (201).

With a high inclination angle, there is a possibility of edge loading and high local tensile stresses. The more brittle HXLPE compounds may therefore be prone to mechanical failure and fracture (202). Thus, a high inclination angle may be a greater concern in HXLPEs than in the mechanically more robust CPEs.

The effort to achieve an optimal angle of cup inclination is notably of greater significance in prostheses with metal-on-metal articulations (MoM), such as hip resurfacing prostheses (203;204). This has been further actualized by the concerns of soft tissue reactions and metal ion release into the circulation seen with MoM – bearings (205). Creep explains part of the penetration at two years (29;132). Longer follow-up is therefore warranted to evaluate any association between acetabular cup inclination and steady-state penetration rate. Our results should therefore be considered as preliminary.

11. CONCLUSIONS

Paper I

- The use of oxidized zirconium femoral heads did not affect penetration at 2 years follow-up compared to heads made of CoCr.
- We found that the highly cross-linked version of the Reflection all-polyethylene cup substantially reduced wear at 2 years compared to its EtO-sterilized, non-irradiated counterpart.
- All groups of cups had a migration that was within the limits of what is considered safe with respect to long-term performance.
- Further follow-up is required to discern differences between CoCr and Oxinium heads with respect to wear, implant durability, and clinical benefits. Based on concerns of the mechanical properties and the lack of long-term clinical follow-up studies, we recommend the use of Oxinium to be restricted to clinical studies.
- The Charnley Ogee was not outperformed by the more recently introduced implants in our study. We conclude that this prostheses still represents a standard against which new implants can be measured.

Paper II

- The Spectron EF femoral stem was more stable than the Charnley flanged 40 stem in our study when evaluated at 2 years follow-up.
- Initial stability is not invariably related to good long-term results.
- Our results emphasize the importance of prospective long-term follow-up of prosthetic implants in clinical trials and national registries, and the use of a stepwise introduction of implants.

Paper III

- We found no relationship between the acetabular inclination angle and cemented acetabular component polyethylene wear at two years' follow-up.
- We found no statistically significant correlation between acetabular inclination angle and migration of the cemented Reflection all-polyethylene acetabular components.

12. IMPLICATIONS AND FUTURE RESEARCH

Longevity, function, risk and patient satisfaction- these are the issues that have to be addressed in future research on THA. The “perfect THA” is everlasting, has the same function as a normal hip, is implanted with virtually no risk of infection or cardiovascular adverse events and results in 100 % patient satisfaction. A meaningful insight is that the above mentioned outcome is unrealistic and that one in search for great leaps in the science of THA, may oversee more pragmatic and realistic solutions. A change may not be an improvement-history has proved. I therefore concur with those who propose a careful and investigative stepwise introduction of new implants and techniques in THA.

Several alternatives to conventional THA have been introduced. Contemporary MoM resurfacing and large head THA gained huge popularity because of their proposed and assumed advantages regarding function, wear and safer revision surgery. However, despite being implanted in large scale, crude data do not support continued use of large head MoM-prostheses and there are serious concerns about adverse tissue reactions (206;207). The wide use of these prostheses could have been prevented with a more careful introduction to the market. Further research in the field of MoM bearings must lie in the field of damage control and careful surveillance of the patients who have received such a prosthesis. It seems that modern MoM -prostheses represent a change, not an improvement.

Another alternative to conventional metal-on-poly THA is the ceramic-on-ceramic bearing (CoC). The wear characteristics are favourable (208;209) and followers encourage the use in younger, active patients who may wear out conventional metal-on-PE bearings. Some authors state that ceramic-on-ceramic is a safe bearing coupling with excellent survivorship at 10 years follow-up (209-211). One study reported on fewer revisions for any reason and less osteolysis for ceramic-on-ceramic than metal-on-polyethylene at 10 years (212).

Others however, have a less supportive view. There are reports on a high rate of fractures of the liners. One study reported on 5.3 % non-traumatic liner fractures at a mean 32 months (213). Another study reported on 2% non-traumatic liner fractures at a mean of 4.3 years (214).

Another complication that is more or less specific to CoC bearings is squeaking. In one study 24.6 % reported at least one instance of squeaking, occurring on average at 34.2 months in one study (215). One more study reported on a high incidence, 21 %, at an average of 26.4 months (216).

Because of possible negative outcomes associated with the ceramic material, the ceramic-on-ceramics are by some regarded as too unpredictable to use regularly (217). One fairly recent report showed that neither CoCs nor MoMs improved midterm results when compared with the results of conventional bearings (218). Still, we do not know the long-term survival of CoCs. Further research and follow-up seems to be warranted before CoCs can be regarded as an improvement.

Our group and others have shown substantially reduced short-term wear with HXLPEs. Data on longer follow-up is increasing. The 2012 John Charnley Award paper "*Clinical Multicenter Studies of the Wear Performance of Highly Crosslinked Remelted Polyethylene in THA*" by Bragdon et al. (154) reported that the initial low HXLPE wear with the use of metal femoral heads remained unchanged over time. Furthermore, the authors reported on no clinical adversity with the use of larger femoral heads and concluded: "*The introduction of this HXLPE (irradiated and melted) substantially improved the prognosis of patients after THA up to 13 years as judged by clinical scores, incidence of osteolysis, and polyethylene wear measurements.*" The XLPEs are already used in large scale and there is today no evidence suggesting that they should be discontinued. No widespread deleterious effects have been seen. Although continued longer term follow-up is warranted, in general, the material seems to be more of an improvement than merely a change. However, the THA patients are getting younger and the physical demands are getting higher. Thus, not only the wear properties have to be considered, but also the mechanical strengths of the compounds. It may be that one has to differentiate patients with regard to activity, weight, age and demands in a more comprehensive way than today.

We will continue to follow the subjects included in our study and have plans to analyse wear and osteolysis at five years.

In second generation HXLPEs sequential annealing is used to reduce the oxidative potential of retained free radicals, while maintaining material toughness (219). An

alternative approach to this is stabilization of the free radicals with vitamin E, instead of post-irradiation thermal treatment (220). At present, due to the sparse clinical experience, the use of this compound should be restricted to clinical studies.

In the present study we investigated the short-term wear properties of the oxidized zirconium femoral head introduced in the year 2003. In general, at the femoral head side of the bearing in THA, few new implants have been introduced aside oxidized zirconium. BioloX Delta (CeramTec, Plochingen, Germany) was introduced to the marketplace in the year 2000 and is a zirconia-toughened alumina composite that was developed to increase the fracture resistance of alumina femoral heads. However, the documentation of clinical performance of this compound is sparse and should be further investigated before widespread use.

In our study, we showed that oxidized zirconium did not have wear performance that was superior to the conventional CoCr femoral heads. We cannot deduct the reason(s) for these findings. *In vitro* studies did confirm the theoretical advantage of the compound (104), opposite to our findings. Retrieval studies may give better insight to the cause of these contradictory results. There are presently not published any reliable *in vivo* data on this topic with longer follow-up. We will follow our subjects further and present our results at five years in due time. Furthermore, a register study on survival will possibly give insight to the performance of this compound. At present, one has to acknowledge the fact that there is no proof whatsoever that oxidized zirconium represents an improvement regarding longevity in THA. Therefore the use of it should still be restricted to clinical studies.

Our and other author's findings (154) imply that the emerge of HXLPEs may connote the departure of alternative femoral head materials. Is there really a need for another femoral head material than metal?

Also, with the emergence of HXLPEs, the main issue interfering with the long-term outcome of THA may change towards femoral stem fixation longevity again, as in the 1970`s. There is no doubt that there have been substantial improvements since then, but, as mentioned earlier, the demographics are changing. It may be that we will encounter new and unforeseen challenges. I want to emphasize that small changes in e.g. design and surface roughness, may interfere with the outcome of the prosthesis and that early RSA results is not consistently predictive of the long-

term outcome of stem fixation. Therefore, each different prosthesis or change in prosthesis design should be considered isolated.

Other fields that are to be further investigated to decrease aseptic loosening are surgical technique and component positioning. We concluded that the acetabular angle of inclination did not affect the wear after 2 years follow-up in cemented THA. However, it certainly affects outcome of MoM resurfacing arthroplasties, as discussed earlier. The importance of stem positioning and cement mantle thickness are other issues to be addressed (212;212). The wide scope of recommendations and literature on this topic, suggests that the endeavour to obtain comprehensiveness may obscure the fact that each prosthesis and each patient has to be evaluated individually.

Nonsurgical treatment of osteolysis may open another approach to improve outcome after THA. Bisphosphonates (BPs) have been shown to decrease osteolysis secondary to particle debris *in vitro* and *in vivo* (221;222), suggesting the possibility of pharmacological inhibition of osteolysis seen in aseptic loosening of THAs (223;224). However, the clinical efficacy of BPs to inhibit wear-related inflammatory bone loss is still debated (225).

Further investigation is certainly necessary, but due to the small extent of adverse effects with the use of BPs, the use may be indicated when osteolysis is seen around an implant. Thus, bisphosphonates may have a clinical role in THA by decreasing aseptic loosening and prolonging implant longevity.

Other drugs, e.g. erythromycin, have also proven the ability to inhibit particle induced osteolysis, opening for a wide field of future research (226).

Also, genetic factors may influence implant failure caused by osteolysis after THA (227). Susceptibility to osteolysis may vary between individuals (228). Further research in the field of gene expression and gene carriage rate is necessary, and future results can have implications for developing therapies to inhibit progression of osteolysis after THA and individualise implant choice (227).

Despite all new approaches for the surgical treatment of arthritis in the hip, the original concept of Low Friction Arthroplasty, as introduced by Sir John Charnley in the 1960s, still stands the test of time. The cemented Charnley prosthesis has the

most comprehensive and best documentation of all prostheses (19;24;229-236). It still represents a standard against which new implants can be measured.

In conclusion the answer of one question should be considered with the introduction of new implants in THA: *Is this an improvement or merely a change?*

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