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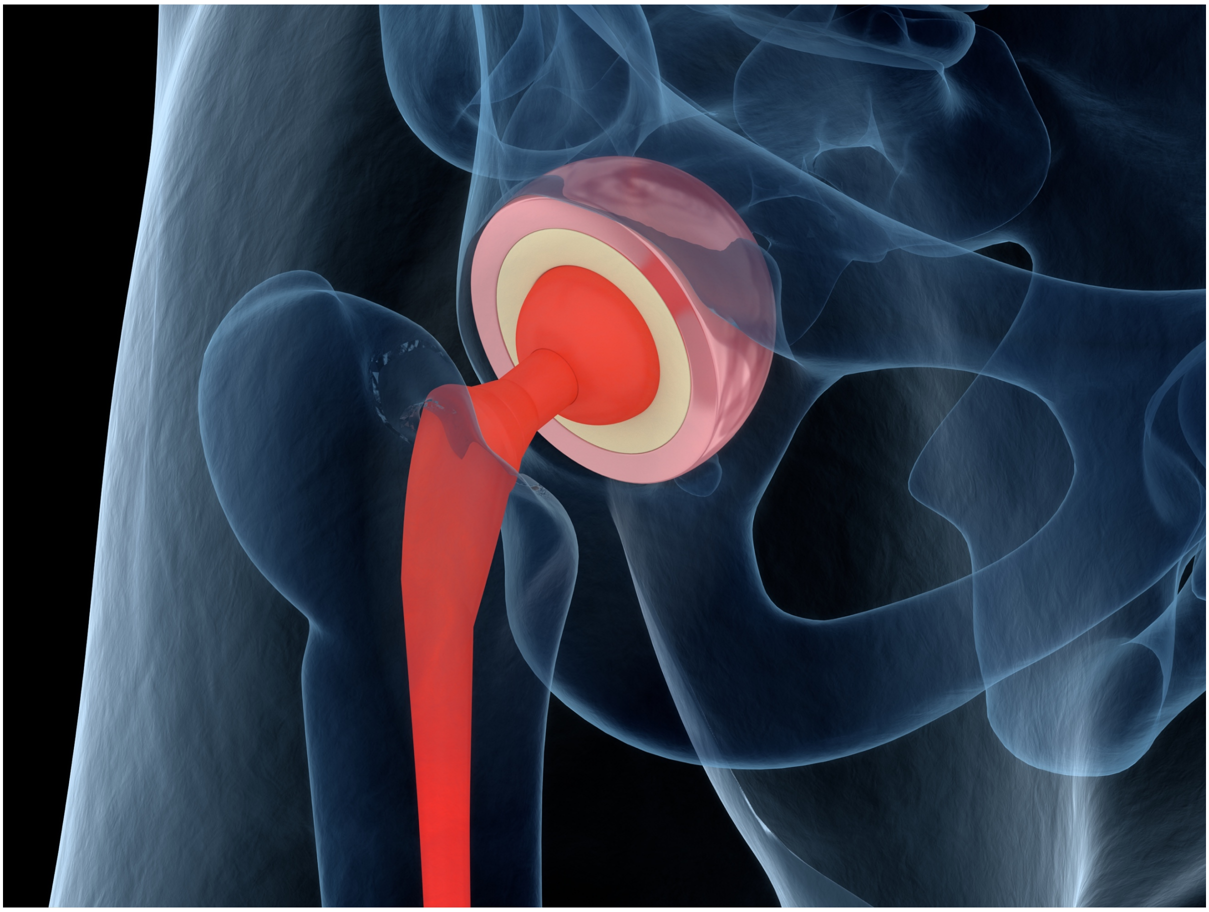

Michael Charles Wyatt

A dissertation submitted to the University of Bristol in accordance with the requirements for award of the degree of MD in the Faculty of Health Sciences

Bristol University, September 2019

(62,721 words)

Abstract

This thesis explores factors that affect successful primary total hip replacement (THR) surgery. Future success in THR will likely occur through reducing the incidence of adverse events and need for revision surgery. Such improvements rely on precision in addressing patient, implant and surgical factors and are essential as the demands on THR are ever higher. The key topics of contention in contemporary THR concern stem fixation, bearing surfaces and infection.

Stem fixation

Patient age and activity influence the longevity of THR. This thesis will examine the evidence for femoral stem fixation, i.e. cemented or uncemented, according to patient age group and the influence of femoral stem offset on the survivorship of cemented stems. Furthermore, the reliability of short cemented stems will be examined. Patients requiring THR often have bilateral disease and the surgeon may offer single-anaesthetic bilateral total hip replacements. This thesis investigates if this is safe when using cemented stems.

Bearing surface factors

This thesis will examine the New Zealand Joint Registry to determine the best performing bearing surface couple in THR. In addition, the evidence for the latest polyethylenes will be investigated.

Preventing and diagnosing infection

Prosthetic joint infection is a devastating complication of THR, its incidence is increasing and the success of diagnosis and treatment is time-critical. Prevention and early diagnosis are of paramount importance in improving THR outcomes. This thesis examines the evidence for the surgeon' decisions regarding operating theatre environment factors such as the use of laminar flow and modern spacesuits. The

evidence for the use of diagnostic biomarkers to improve diagnostic accuracy will be investigated.

Dedication

I dedicate this work to my loving family; in particular my wife Tanya, my daughter Anna and my father whose tireless work ethic in the face of uncertainty for many years I truly respect and admire. I also thank my mother for her unwavering love, support and wisdom and my brothers who though we live far from each other now are always close in spirit.

Acknowledgements

I would like to acknowledge the tremendous support and mentorship of both Professor Gary Hooper and Professor Martin Beck. I would also like to acknowledge my excellent supervisors Michael Whitehouse and Professor Ashley Blom who have patiently led me through a process of academic development and allowed me to do so whilst working with their world class unit.

Author's Declaration

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's *Regulations and Code of Practice for Research Degree Programmes* and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

SIGNED: [redacted] DATE: 23.4.2021

Table of Contents

List of Tables

List of Introduction Figures

List of Figures

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INTRODUCTION

Total Hip Replacement and Pathology Indicating Its Use

Total joint replacement is a surgical procedure whereby once nonoperative measures have failed a symptomatic, damaged joint is removed and replaced with prosthetic implants. The resulting prosthetic joint is designed to replicate the pain-free movement and function of a normal, healthy joint. Whilst Total Hip Replacement (THR) and Total Knee Replacement (TKR) are the most commonly performed joint replacements such surgery can also be performed on shoulder, elbow, ankle and wrist joints.

Several pathological conditions can cause not only joint pain but also functional disability and impediments to the patient's quality of life. In the majority of cases the pathology affects articular (hyaline) cartilage with other indications being less common (Dreinhöfer et al, 2006). Osteoarthritis (OA) is the commonest joint disease worldwide and affects 10% of males and 18% of females over the age of 60 (Woolf and Pflege 2003). The socioeconomic burden of OA in developed countries costs between 1 and 2.5% of the gross domestic product (Hiligsmann et al., 2013). Primary OA is the commonest indication for THR across all ages and the proportion of patients requiring THR for OA increases with age (New Zealand Joint Register 2018).

Articular cartilage itself is a matrix consisting of collagen bundles intertwined with non-collagenous proteins and negatively charged hydrophilic molecules. Collagen provides the tensile property of articular cartilage. Gel-like proteoglycan lies between the collagen fibrils thereby reinforcing the three-dimensional structure and protecting chondrocytes. The role of chondrocytes is to regulate the consistency of the extra-cellular matrix consisting of 65-80% water, 10-20% type 2 collagen and complex proteoglycan molecules known as aggregan. Aggregan contributes to the swelling pressure necessary to resist compressive forces imposed on articular cartilage (Rogers et al., 2006).

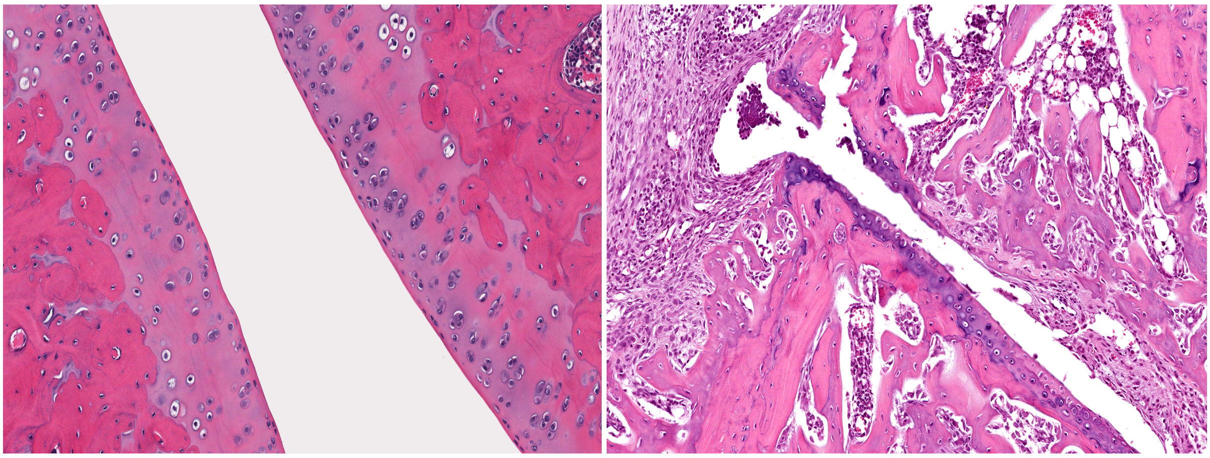

Figure Intro 1. Micrographic view of normal joint and articular cartilage (LEFT) and OA (RIGHT) with loss of articular cartilage, fibrosis and lymphocytic infiltrate (purchased stock image from shutterstock.com)

OA is a process that alters and culminates in damage and subsequent loss of articular cartilage (Hammerman, 1989) (Figure Intro 1). This is demonstrable on radiographs as loss of joint space signifying the loss of articular cartilage with other features being bone remodelling, formation of osteophytes, formation of subchondral bone cysts and the production of secondary deformity (Watt and Dieppe, 1990) (Figure Intro 2). A diarthroidal joint requires an even distribution of load across it to maintain integrity for the resilience of subchondral bone which, in turn, supports articular cartilage. The proper bone alignment, stability, biomechanics and biology for the hip joint are therefore essential (Felson, 2004). Abnormalities of bone alignment occur for example from previous trauma; abnormalities of biomechanics are encountered with hip dysplasia (Hasegawa et al., 1992) and femoroacetabular impingement (Ganz et al., 2003); pathological problems associated with subchondral bone (Shimizu et al., 1993) occur for example in disorders of bone turnover such as Paget’s disease, and abnormalities of associated soft tissues occur, for example, in ochronosis and crystal deposition diseases. Such processes may all predispose to secondary OA (Apley and Solomon’s System of Orthopaedics and Trauma 2017). Other pathology in order of frequency that indicates the need for THR comprises fractured neck of femur in high functioning patients (Figure Intro 3), inflammatory arthritis, avascular necrosis (AVN), the sequelae of paediatric hip conditions leading to secondary arthritis, tumour (primary or metastatic) and miscellaneous conditions such as pigmented villonodular synovitis (Vigorita, 2008).

Figure Intro 2. AP pelvic radiograph showing OA of LEFT hip with loss of joint space, osteophytes and a large supra-acetabular cyst (purchased stock image from shutterstock.com)

The History and Evolution of the Modern THR

THR involves the replacement of both the acetabulum and the femoral head. A metal stem is inserted into the femoral canal with a modular head and this then articulates with a prosthetic cup. THR has been described as “the operation of the 20th century” given its excellent clinical results, the predictably-high patient satisfaction and the improvement in the quality of life (Learmonth, Young and Rorabeck, 2007). THR today is not only clinically effective but it is also highly cost-effective (Garellick et al., 1998) . More than one million THRs are performed worldwide per year and according to National Joint Registry 796,636 THRs were performed between 2003 and 2015 (National Joint Registry for England. Wales, Northern Ireland and the Isle of Man, 13th Annual Report, 2016) and in the United States of America more than 2 million people live with an implanted THR (Maradit Kremers et al, 2015). Demand for THR is growing rapidly as a result of the ageing population and obesity epidemic (Pivec et al., 2012).

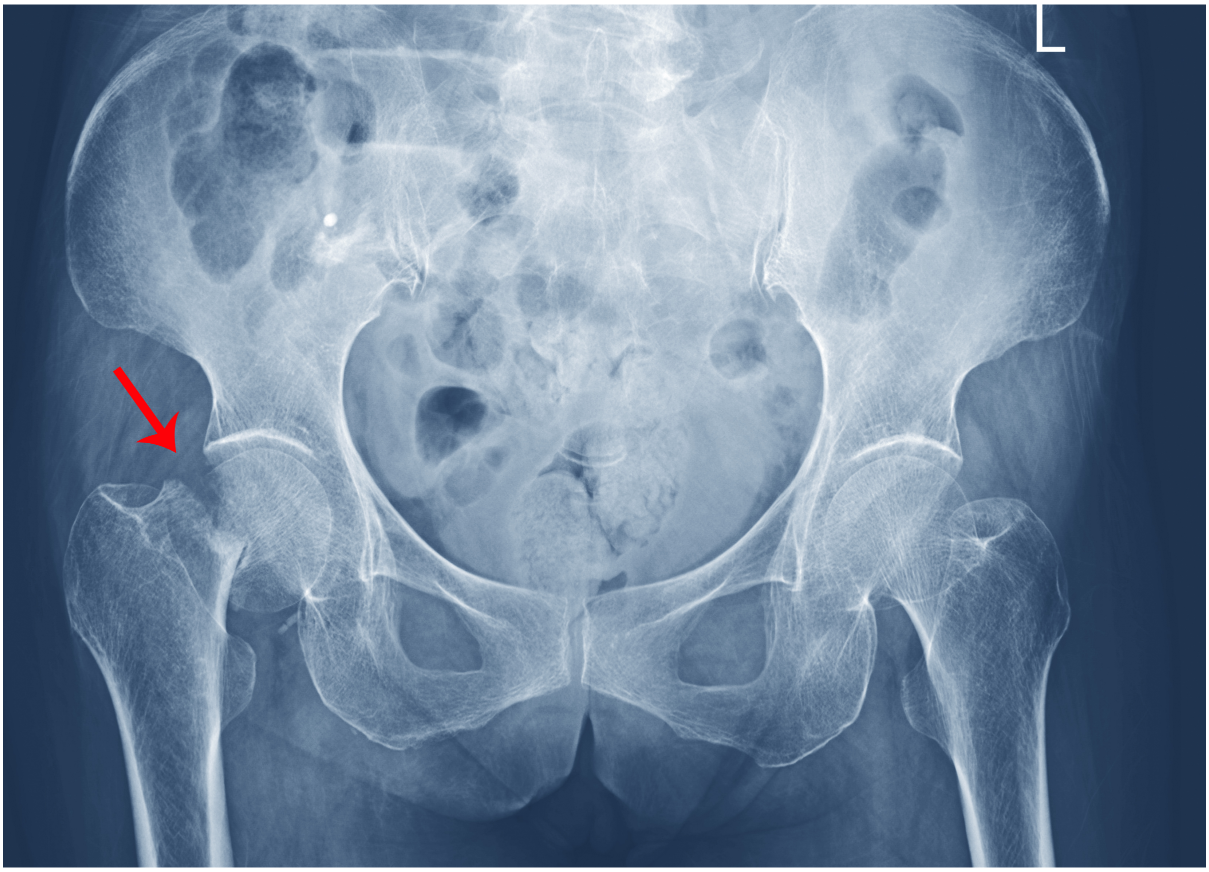

Figure Intro 3. AP Pelvic radiograph showing a displaced intracapsular fracture of the RIGHT hip (purchased stock image from shutterstock.com)

Origins of THR

The earliest recorded attempts at THR occurred in Germany in 1891 with the use of ivory to replace femoral heads destroyed by tuberculosis presented by Professor Themistocles Gluck (Eynon-Lewis, Ferry and Pearse, 1992). Subsequently surgeons experimented with interpositional arthroplasty in the 19th and 20th Centuries using a range of tissues including fascia lata (Lexer, 1908) and pig's bladder (Baer, 1909). Marius Smith-Petersen created a glass "mould arthroplasty" consisting of a hollow hemisphere that fitted over the femoral head and provided a new, smooth surface for articulation (Smith-Petersen, 1948). Whilst biocompatible and strong the brittle nature of this material lead to catastrophic failure from shattering. Wiles subsequently in 1938 introduced a stainless steel THR fitted to bone with bolts and screws (Wiles, 1957). In 1938 Judet developed his short-stemmed acrylic prosthesis (Judet and Judet, 1950) and then in 1939 Thompson (Thompson, 1952) and Moore introduced their monobloc femoral stems (Moore and Bohlman, 1983).

Other design evolutions emerged including the first metal-on-metal hip resurfacing by Haboush (1953). Mckee and Farrar (McKee and Watson, 1966) then introduced their cemented metal-on-metal THR but by the mid 1970s these and similar metal-on-metal designs such as the Ring prosthesis (Ring, 1971*)* were associated with high revision rates from aseptic loosening and osteolysis. Ceramic on ceramic articulations were first introduced in 1970 by Boutin (Boutin, et al., 1988) and this bearing surface combination is still favoured today by many Orthopaedic surgeons. Hip resurfacings continued to be developed with metal on polyethylene articulations such as by Freeman (Freeman and Bradley, 1983), Furuya (Furuya, Tsuchiya and Kawachi, 1978), Wagner (Wagner and Wagner, 1996). and Amstutz implants (Amstutz et al., 1981). Ultimately these designs displayed high rates of mechanical failure, fracture, wear, osteolysis and loosening.

Introduction of the Modern THR

In 1962, Sir John Charley pioneered and implanted the first “modern” cemented THR. Charnley’s “low friction arthroplasty” consisted of three parts: a metal femoral stem with a 22mm femoral head, an ultra-high molecular weight polyethylene (UHMWPE) acetabular component and acrylic bone cement (Charnley, 1979). The key advances with Charnley’s THR were firstly the concept of low frictional torque which was based on the finding that low friction depends mostly on the friction coefficient of the bearing surface materials rather than the hydrodynamic lubrication of intervening fluid. Secondly, Charnley adopted a new high molecular-weight polyethylene polymer which had long chains between 2 and 6 million atomic mass units. Thirdly, Charnley’s use of cement was revolutionary as he employed it as a grout rather than an adhesive between the components and bone.

Charnley not only worked with the local engineering department at the University of Manchester Institute of Science and Technology and dental school regarding his materials and acrylic cement but also developed a clean, enclosed operating theatre environment to diminish the risk of prosthetic infection with Howarth Air Conditioning, another local resource experienced in building air filtration systems. Charnley appreciated that another source of contamination was through the surgeon’s gown and therefore he also developed a full-body gown with a negative-pressure exhaust system.

At the Annual Meeting of the British Orthopaedic Association, London 1964 GK McKee (Norwich) presented his initial work with the McKee-Farrar metal-on-metal prosthesis (McKee and Watson-Farrar, 1965). At the same meeting Sir John Charnley (Wrightington) showed one of his patients walking normally across the stage having undergone a metal-on-polyethylene Low Friction Arthroplasty under his care (Charnley, 1972).

The results of THR displayed at this meeting were revolutionary compared to the experience of most surgeons with surgery for OA of the hip at the time namely upper femoral osteotomy, cup arthroplasty, Girdlestone's pseudoarthrosis and arthrodesis. The THR operation could apparently offer pain relief, restore mobility and function and be coupled with a short hospital stay and benign convalescence. Interest in THR escalated and spread globally and also led to the introduction of similar procedures in other joints. Multidisciplinary collaboration of surgeons, engineers, tribologists, pathologists and chemists accelerated. The long-term survival of these implants was encouraging with <81% of Charnley THR not requiring revision THR at 25 years (Learmonth ID et al., 2007.)

The evolution of THR occurred differently in different centres. In Exeter for example the McKee-Farrar prosthesis was introduced in 1969 and over 300 were implanted. Aseptic loosening and severe osteolysis were encountered which tempered enthusiasm for cemented THR. Many surgeons attributed this to the use of cement despite the excellent ongoing results from Wrightington. This suggested that it was the method of cementation rather than an inherent problem with the cement itself. Cementing technique evolved from "first generation" which did not involve washing or drying of the bone before unpressurised antegrade finger packing of cement with neither cement restrictor nor pressurisation. This technique was associated with cement lamination, the inclusion of blood clots and voids within the cement mantle and poor cancellous bone penetration of cement (Berry and Harmsen, 2002).

“Second generation” cementing technique with thorough cleaning and drying of cancellous bone, use of a cement gun and distal occlusion of the femoral canal increased the cement penetration of cancellous bone and thereby increased the mechanical interlock that provides shear strength at the cement-bone interface (Askew et al., 1984). Second generation cementing techniques reduced the incidence of femoral loosening (Barrack, Mulroy and Harris, 1992).

“Third generation” or contemporary cementing techniques focus on improved pressurisation of cement at all times to improve cement-bone microinterlock. Such techniques include the use of a rubber seal around the cement gun nozzle. Pulsed lavage is used to clean endosteal bone. In addition, vacuum mixing of cement in a centrifugal manner reduces porosity (Wixson, 1992). Using centralisers improves the likelihood of obtaining a uniform cement mantle. (Breusch et al., 2001).

The femoral stem component of THR should transmit torsional and axial load to the cement and bone without excessive stress or micromovement thereby allowing the stem to remain stable despite repetitive loading (Scheerlinck and Casetleyn, 2006). Two modes of achieving these goals were adopted: (i) the “force-closed” or “loaded-taper” and (ii) the “shaped-closed” or “composite beam”. The loaded-taper model epitomised by the Exeter stem subsides and wedges into the cement during axial loading reducing peak stresses within the cement mantle (Stefansdottir et al., 2004). In the composite-beam model the stem is bound rigidly to the cement itself and the stems in this concept are not meant to subside (Alfaro-Adrian, Gill and Murray, 2001). The original loaded-taper design of the Exeter polished cemented stem was introduced in collaboration with the University of Exeter Department of Engineering in 1960. Whilst the original Exeter cemented stem has evolved, the loaded-taper and polished stainless-steel stem concept has endured. This is the commonest femoral component implanted in New Zealand today (New Zealand Joint Registry 2018).

During the 1970s and 1980s concerns over what was considered “cement disease” i.e. implant loosening occurring in association with cement fixation (Jones and Hungerford 1987) drove the parallel development of uncemented THR components such the Engh (Engh, et al., 2001) and Zweymueller uncemented stems (Garcia-Cimbrelo et al., 2003). Uncemented stems rely on bony in-growth or on-growth which is permitted by the creation of micro-fractures during femoral canal reaming. Such early designs were associated with mismatch of the elastic modulus of implant versus bone which affected the stress distribution under applied loads (Engh, Bobyn and Glassman, 1987). The greater the mismatch then the greater the propensity for proximal bone stress shielding as biomechanically the stems transferred load directly to the femoral diaphysis. Cementless cup fixation evolved from smooth surfaces which had high rates of loosening to various methods including coatings, screw-in designs and press-fit. The press-fit concept involves implanting a slightly oversized component into the prepared acetabulum with or without the addition of accessory screw fixation (Yamada et al., 2009). The evolution of manufacturing of polyethylenes and the introduction of highly crosslinked polyethylenes have subsequently reduced wear-induced osteolysis and associated prosthetic loosening (Devane et al., 2017). The introduction of modular implants afforded greater surgical options and versatility. Current THR implants can use various femoral head sizes and have four main groups of bearing surface combination: metal-on-polyethylene, ceramic-on-polyethylene, ceramic-on-ceramic and metal-on-metal. Fixation techniques comprise fully cemented, fully uncemented, hybrid (when the femoral stem has been cemented and the cup uncemented) and reverse hybrid (cup cemented and stem uncemented). Whilst the concept “cement disease” has fallen from favour there is still little evidence that uncemented fixation is superior to cemented (Abdulkarim et al., 2013).

Outcomes of Interest After THR

It is imperative to use outcome measures to ascertain temporal changes and the results of THR not only to compare the patient value of the intervention but also to determine whether the incremental health benefits are worth the associated financial investment. Patient outcomes should be monitored closely and regularly to optimise surgical results. A plethora of outcome measures exist which can therefore make it difficult to not only apply evidence into clinical practise but also to compare the results from different studies (Clarke, 2007).

Outcome measures are artificial and an individual's health and well-being not only fluctuates but is influenced by many factors other than their diagnosis or treatment (Paterson et al., 2009). The "outcome" of a THR can be assessed by the patient, surgeon, relative or spouse and therefore can vary depending on perspective. Adverse events such as mortality and prosthesis failure (Wylde and Blom, 2011), whilst very important, have been accompanied by clinician-administered tools such as Harris Hip Score (Harris, 1969) and patient-completed outcome scores (PROMs) such as the Oxford Hip Score (Dawson et al., 1996), Hip disability and osteoarthritis outcome score (HOOS) (Nilsdotter et al., 2003) and the Western Ontario and McMaster Universities osteoarthritis index score (WOMAC) (Bellamy et al., 1988). Both clinician and patient reported scores are important given the dissonance between clinician and patient perspectives (Hewlett, 2003). PROMs allow patients to report their pain, function, health-related quality of life, mental health, satisfaction and social participation. Outcome measures may be generic or "joint-specific". Routine collection of PROMs occurs before elective THR surgery in the UK (Department of Health, 2009) since the Darzi report (Darzi, 2008). There are many different outcome measures and such tools must be validated, appropriate, responsive to change and have high validity.

Pain and Loss of Function

The predominant symptoms experienced by patients prior to a THR are pain and loss of function. The characterization and context of the pain and the types of functional loss may vary. (Blom et al., 2016); Lenguerrand et al., 2016). Whilst pain is subjective, function can be assessed in a number of ways including PROMs, performance testing (Senden et al., 2009) and gait analysis (Ornetti et al., 2010). In the ADAPT study HHS correlated well with PROMs such as the WOMAC and walk time in patients with hip pathology (Lenguerrand et al., 2016). In this study pain levels were closely associated with patient function. Age was associated strongly with performance tests, most likely related to sarcopenia, but not PROMs. Patient gender was associated strongly with disability in patients undergoing THR. Patient anxiety and depression was associated strongly with PROMs and clinician-administered scores but not performance-based assessments. Therefore, when comparing functional assessments pain, age and psychological status must be accounted for. This important study also suggested that patient function should be assessed with both PROM and performance tests.

Societal Participation and Quality of Life

Outcome measures can also reflect patient well-being, their ability to function in society and their quality of life (QoL). QoL can be regarded as a “utility” and patients’ QoL level can be assessed using generic patient-completed Health Related QoL questionnaires such as the EQ-5D, SF-12, SF-36 scores which can then be used to calculate Quality-Adjusted Life Years, a preferred outcome measure for cost-effectiveness analysis (Williams and Kind, 1992). 1 QALY is a year in perfect health whilst 0 is deceased. In a recent study of 5,463 THRs performed for OA the mean QALY at baseline was 0.6 QALY and the mean increase two years following THR was 0.25 QALY (SD 0.2) from baseline (Konopka et al., 2018).

Longevity of Implant

The risk of first revision surgery after THR for any reason, so-called “all-cause revision rate”, is highly relevant as this is what is experienced by the individual patient and any patient who has a THR is at risk of revision surgery. In an immortal cohort all THR would ultimately fail. In a recent study of 13,212 THRs the 25-year pooled survival for THR from National joint registries was 57.9% (95%CI 57.1 to 58.7) and from case series this was 77.6% (95%CI 76 to 79.2) (Evans et al., 2019). Further analysis of revision rates can be indication-specific e.g. aseptic loosening/wear or periprosthetic fracture. Revision rates may then be further quantified by relevant patient, implant or surgical factors to create hazards ratios comparing outcomes between groups. The increased risk of complications after THR is 40% for every decade above the age of 65 (Bayliss et al., 2017). In this study the lifetime risk of revision surgery was 5% in patients over the age of 70 with no difference between sexes. Conversely if THR was performed under 70 years of age the lifetime risk of revision increased and was 35% (95%CI 30.9 to 39.1) in men in their early 50s and the risk was 15% less for women of the same age.

Excess Mortality After THR

THR is associated with a short-term increase in mortality rate. Quantification of this risk and identification of modifiable factors allows risk-management strategies to reduce mortality. Quantification of mortality risk facilitates informed consent and aids shared decision making with patients making prior to surgery. The 90-day mortality after THR for OA has been reported at <1% (Hunt et al., 2013). This study also performed cumulative hazard estimates that showed that the mortality risk after THR plateaus at approximately 90 days following surgery which indicates that the mortality rate has likely returned to baseline risk at this stage. In modern series cardiovascular disease is the leading cause of death rather than pulmonary embolism (Berstock et al., 2014). In this systematic review of 32 studies comprising 1,139,330 patients the pooled incidence of mortality within 30-days was 0.3% (95%CI 0.22 to 0.38) and 90-days was 0.65% (95% CI 0.5 to 0.81). This study provided a benchmark to identify excess mortality rates. There was a strong trend for diminishing mortality rates despite increasingly comorbid patients. Early mortality was associated with the non-modifiable factors of increasing age and male gender. Modifiable risk factors for mortality after THR were patient comorbidity indices including ASA grade >3, Charlson comorbidity index >3 and prior cardiovascular disease. Cardiovascular disease has been shown to increase the risk of mortality after THR by an Odds Ratio 8.8 (95%CI 1.78 to 43.6) (Comba et al., 2012).

Current Modes of Failure in THR

Substantial demands are placed on modern THR implants as patients expect to remain active for longer. Furthermore, the global population is ageing, and patients have associated increased numbers of comorbidities and associated treatments which adds complexity to the overall operative situation. In New Zealand, as in many other countries, the ageing population and projected incidence of debilitating OA has seen the rate of THR increase to 363/100,000 in 2014, with projections of increasing to around 600/100,000 by 2026 (Hooper, 2016).

Current modes of failure of primary THR are multifactorial. Understanding why THRs fail is of great importance to surgeons given the high and increasing demand for this procedure, the healthcare funding costs and the potential to reduce the risk of revision rates (Liu et al., 2016). Improved insight into why a primary THR fails, when it fails, and what the relevant risk factors are, advantageous. This allows an Orthopaedic surgeon to address modifiable risk factors or mitigate against the risk of a certain complication or mode of failure. The overall rate of revision THR, both early and late, is increasing and the common modes of failure are wear, loosening, dislocation, instability and infection. All of these may cause the patient severe pain and disability (Kurtz et al., 2007). In 2017 of 8,589 revision THR procedures reported in the National Joint Registry of England, Wales and Northern Ireland and the Isle of Man 44% were for aseptic loosening, 16% for instability, 15% for periprosthetic fracture, 16% for infection. (National Joint Registry for England, Wales, Northern Ireland and the Isle of Man, 15th Annual Report 2018).

Patient factors that affect the risk of revision THR include age at surgery, underlying diagnosis, Body Mass Index (BMI) and comorbidities. Implant factors include design, modularity, bearing surfaces and fixation; surgical factors include the choice of surgical approach, number of operations performed i.e. surgical experience and theatre environmental factors that mitigate against the risk of the infection. The common current modes of failure are outlined briefly below.

(i) Wear, aseptic loosening and problems associated with bearing surface articulations

Particulate debris formation from various types of wear has been the principle underlying cause of osteolysis around THR. Wear debris from adhesive wear of THR bearing surfaces is the principal factor limiting long-term THR survival. Other types of wear include abrasive wear (i.e. the prosthesis scraping off wear particles), third body wear (i.e. particles within the articulation cause abrasion), linear wear (i.e. the femoral head penetrates into the liner of the articulating surface) and volumetric wear (which is affected by femoral head size and is the main determinant of the number of wear particles) (Bennett et al., 2002). Increasing the femoral head size increases volumetric wear. A metal or ceramic femoral head combined with a UHMWPE cup have been used in the majority of recorded THR. Wear leads to particulate debris formation which then triggers a cellular response. These particles are taken up by macrophages which then release osteolytic factors including TNF-alpha, osteoclast activating factor, hydrogen peroxide, acid phosphatase, interleukin 1 and 6 and prostaglandins. Further macrophages are recruited. Osteolytic factors activate osteoclasts which then differentiate. Osteoclasts increase RANK and RANKL gene transcripts and cause osteolysis and aseptic implant loosening (Jacobs et al., 2001; Harris, 1995; Broomfield et al., 2017).

UHMWPE is associated with osteolysis and implant loosening (Dumbleton, Manley and Edidin, 2002). To reduce wear-related failures PE was modified to Highly Crosslinked PE (HXLPE). Cross-linking increases the mechanical wear-resistance of the UHMWPE (Muratoglu et al., 1999; Muratoglu et al., 2001) yet the process of achieving this such as with gamma-irradiation produces free-radicals. The free-radicals potentiate oxidation and make PE more brittle and more likely to undergo wear. Annealing, remelting and the addition of antioxidants have been used to diminish the amount of residual free radicals in HXLPE (Zagra and Gallazzi, 2018). Prospective randomised controlled trials have shown that HXLPE use reduced both wear (Devane et al., 2017; Digas et al., 2004) and revision rates (Devane et al., 2017) compared to UHMWPE. The study by Devane et al. showed that HXLPE had higher rates of initial creep than UHMWPE. Patient-related risk factors for aseptic loosening in THR are young age at index surgery and male gender (Bayliss, 2017; Cherian et al., 2015; Munger, 2006) and BMI (Munger et al., 2006).

Hard-on-hard bearing surfaces were introduced to improve biomechanics and reduce wear rates. Ceramic-on-ceramic (CoC) articulations, at the expense of squeaking and requiring precise positioning to avoid edge-loading and breakage have achieved excellent long-term survivorship (Varnum, 2017). In a recent study of the National Joint Registry using multivariable flexible parametric survival models CoC articulations with larger femoral heads were associated with improved survival and a 5-year revision rate of 3.3% (95%CI 2.6 to 4.1) with 28mm and 2.0% (95% CI 1.5 to 2.7) with 40mm diameter heads for men aged 60 (Smith et al., 2012).

Metal-on-metal (MoM) articulations were reintroduced given optimism in advances in both metallurgy and tribology in the early 2000s (Zywiel et al., 2011). MoM have been used in firstly, hip resurfacings in which the acetabulum is replaced by a metal cup and the femoral head is rounded and a metal cap placed upon it, and secondly, in combination with a stemmed THR. The popularity of metal-on-metal resurfacings has diminished tenfold in a decade and was <1% in England and Wales in 2015 given the significant problems of early failures and metal ion release specifically Cobalt and Chromium. Metal ions can cause not only systemic toxicity but also affect local soft-tissue (Davies et al., 2005) and cause pseudotumours (Mahendra et al., 2009; Pandit et al., 2008) with bone loss, osteolysis and implant failure (Langton et al., 2011; Henegan, Langton and Thompson, 2012). The Depuy ASR metal-on-metal hip resurfacing and THR were recalled in 2010 (Cohen, 2011) by the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK and all metal-on-metal implants are recommended to be monitored closely along with screening of blood ion level (Medicines and Healthcare products regulatory agency, 2017; Gunther et al., 2013). When MoM was used in combination with conventional THR stems these issues were particularly problematic (Reito et al., 2017). In a study of the National Joint Registry of England and Wales, Smith et al. (2012) showed high failure rates for MoM THR and larger heads failed earlier: 6.1% (95%CI 5.2 to 7.2) for 46mm heads compared with 1.6% (95%CI 1.3 to 2.1) for 28mm MoP (Smith et al., 2012).

For MoM resurfacings the revision rate is >8 additional revisions in 100 cases by 10 years compared to contemporary THR alternatives (Hunt et al., 2018). In the study by Smith et al., 2012 multivariable flexible parametric survival models were used to estimate covariate-adjusted cumulative incidences of revision adjusting for the competing risk of mortality. In women, resurfacings had worse survivorship than conventional THR irrespective of femoral head size: in 55-year old women the predicted 5-year revision rate was 8.3% (95%CI 7.2 to 9.7) with a 42mm head resurfacing, 6.1% (95%CI 5.3 to 7.0) with a 46mm head and 1.5% (95%CI 0.8 to 2.6) for a 28mm metal-on-polyethylene cemented stemmed THR. In 55-year old men a 46mm resurfacing head had a 5-year survival rate of 4.1% (3.3 to 4.9), 2.6% (95%CI 2.2 to 3.1) with a 54mm resurfacing head and 1.9% (95%Ci 1.5 to 2.4) with a 28mm cemented metal-on-polyethylene stemmed THR (Smith et al., 2012). The risk of MoM failure is significantly higher than a conventional THR with no apparent benefit in terms of early revision rates, function, activity or pain relief (Costa et al., 2012) and purported benefits in lower mortality rates has been shown to be purely a function of healthy patient selection (Hunt et al., 2018). This thesis will examine the New Zealand Joint Registry to determine the most reliable bearing surface for a particular patient in terms of all-cause revision rate and aseptic loosening.

(ii) Instability

The incidence of postoperative dislocation in the USA after primary THR has been reported at 3.2% after a posterior approach, 2.2% after anterolateral approach and 1.27% after a transtrochanteric approach (Masonis and Bourne, 2002). In the UK there are similar results at 4.1% for the posterior approach and 3.4% for the anterolateral approach (Blom et al., 2008). In this study, with follow up for 8 to 11 years after surgery, 58.5% of dislocations were recurrent and the mean number of dislocations per patient was 2.81. Most dislocations occur within 2 months of surgery (Blom et al., 2008, Ullmark, 2017; Kunutsor et al., 2019). Dislocation following THR may be under-reported in National joint registries as the majority of dislocation events are managed with closed reduction and do not require revision THR (Devane, et al., 2012). In a recent systematic review and meta-analysis Kunutsor et al. synthesised data on 4,633,935 primary THR and 35,264 dislocations from 149 articles. The overall pooled incidence of instability was 2.1% (95%CI 1.83 to 2.38%) with a mean follow-up of 6 years. Dislocation rates have decreased between 1971 and 2015 (Kunutsor et al., 2019). The cost of dislocation is significant as the problem is often recurrent resulting in multiple hospital admissions. In the study by Sanchez-Sotelo, Haidukewych and Boberg, 2006, the hospital cost of each closed reduction was 19% of an uncomplicated THR. When a revision was performed for recurrent instability the cost was 148% of an uncomplicated THR (Sanchez-Sotelo, Haidukewych and Boberg, 2006).

The true incidence of postoperative instability varies depending on patient, implant and surgical factors (Bozic et al., 2009). Patient risk factors for instability are age >70 (RR 1.27; 95%CI 1.02 to 1.57) compared to patient age <70 but not female gender (RR 0.97; 95%CI 1.02 to 1.57), drug use disorder, social deprivation, BMI >30 kg/m^2

(RR 1.38; 95%CI 1.03 to 1.85) compared to patients with BMI<30 kg/m^2, neurological disorders, psychiatric disease, comorbidity indices, previous surgery including spinal fusion (Wyatt et al., 2020), underlying diagnoses of AVN, rheumatoid and other inflammatory arthritis (Kunutsor et al., 2019). Implant-related factors that decrease the ratio between the femoral head relative to the femoral neck increase the risk of instability. A larger femoral head increases the head-to-neck ratio, jump distance and functional range of motion without impingement and thereby increases construct stability (Girard, 2015). The use of lipped liners, dual-mobility implants and standard femoral neck lengths also reduce the incidence of instability (Kunutsor et al., 2019, Wyatt et al., 2020). Using a femoral head ≥36mm in diameter though, significantly increases the risk of corrosion at the head-neck junction - a process known as "trunnionosis" (Berstock et al., 2018). Surgical factors affecting instability include implant malpositioning, failure to recreate the requisite hip biomechanics such as femoral offset, leg-length or the use of a particular surgical approach (Ullmark, 2016). Surgical approaches that reduce the risk of dislocation are the direct anterior, lateral and the posterior approach if the capsule is repaired (Karachalios et al., 2018; Kunutsor et al., 2019). Surgeon experience and volume also significantly reduce the risk of dislocation (Kunutsor et al., 2019). Late instability is a function of not only the causes of early instability but also include polyethylene wear and subsequent trauma, neuromuscular dysfunction and subsequent spinal fusion procedures (Pulido et al., 2007; Stefl et al., 2017).

In recent years there has been research interest in examining the relationship of the pelvic tilt and resultant acetabular anteversion and its relationship to spinopelvic dynamics (Phan, Bederman and Schwarzkopf, 2015). Some surgeons advocate the use of preoperative sitting and standing radiographs to assess the functional acetabular anteversion as a means of planning precise implant positioning thereby reducing the risk of instability and wear (DiGioia, Hafez and Jaramaz, 2006; Pierrepont, et al., 2017). However, this practice has not yet been demonstrated to improve patient function, prevent instability or reduce wear rates in prospective clinical studies. This thesis will examine which bearing surface combination is most reliable at minimising all-cause revision rates for a patient, and specifically revision for instability.

(iii) Periprosthetic fractures

The incidence of periprosthetic fractures in THR in a recent systematic review and meta-analysis was 0.1% for men and 0.2% for women, odds ratio 0.82 (95%CI 0.52 to 1.27) (Deng, et al., 2019). Periprosthetic fractures may occur either intraoperatively (incidence 0.1 to 27.8%) or following trauma at some duration after THR (incidence 0.07 to 18%) (Sidler-Maier and Waddell, 2015). Such fractures are associated with disappointing clinical outcomes including high associated mortality rates (Miettinen et al., 2016; Sidler-Maier and Waddell, 2015). Risk factors for intraoperative fractures include osteoporosis, rheumatoid arthritis, surgical technique and the use of press-fit cementless implants (Sidler-Maier and Waddell, 2015). Postoperative fractures are more common in elderly females, patients with rheumatoid arthritis, osteoporosis, aseptic loosening, osteolysis and prior hip surgery (Karachalios et al., 2018). This thesis will examine the New Zealand Joint Registry comparing patient, implant and surgical factors in both cemented and uncemented stems.

(iv) Infection

In the 1970s there was a high rate of potentially lethal septic complications (Fitzgerald, 1992). Advances in surgical technique, the use of antibiotic prophylaxis and modern operating theatre environments mean that infection is <1% following primary THR (Blom et al., 2003; Lindgren et al., 2014; Springer et al., 2017). The annual volume of revision THR performed for Periprosthetic Joint Infection (PJI) however increased 2.6-fold between 2005 and 2013 and although the overall risk is low this increase coupled with the predicted increase in demand for THR represents a growing healthcare burden (Lenguerrand et al., 2017; Bozic et al., 2009). PJI has a profoundly negative impact on patients physically, emotionally, socially and economically (Kunutsor et al., 2017). PJI also has profoundly negative effects on the surgeon themselves (Mallon et al., 2018). PJI causes a significant increase in not only the hospital length of stay and cost, estimated to amount to up to 8 million dollars in New Zealand per year, (Gow et al., 2016).

The evolution of antibiotic-resistant biofilms forming on the implant surface, more complex patient comorbidities, increased BMI, diabetes or indeed the immunosuppressive effect of drugs used to treat chronic conditions contribute to the concerning trend of increasing PJI (Kurtz et al., 2008). In a systematic review Kunutsor et al., 2016 showed that increased BMI, diabetes, rheumatoid arthritis, depression, steroid use and previous surgery were all associated with an increased risk of PJI (Kunutsor et al., 2016). To compliment this study factors shown to be associated with PJI from a recent study of the National Joint Registry for England and Wales included younger age, male gender, elevated BMI, diabetes, previous infection, fractured neck of femur, not using antibiotics in the cement of cemented THR and use of the lateral surgical approach (Lenguerrand et al., 2018). This thesis will examine the impact of modern theatre environments on revision THR for deep infection and examine modern methods for early diagnosis and future prevention of this devastating complication.

Major Current Issues in Primary THR

Despite good results, many variations have been introduced during in THR with the stated aims of further improving patient outcomes. Firstly, the indications for THR have become broader and with this the optimal method of stem fixation remains disputed. Secondly, the techniques and devices have evolved as have the approaches, tissue preservation philosophy and tribological advances to diminish wear, osteolysis and subsequent loosening and need for revision surgery. Thirdly, the processes surrounding the patient journey have improved with renewed focus on perioperative management of patient expectations and goals, scaled digital templating, minimising blood loss, improved analgesia with minimal opiate use and postoperative protocols permitting Enhanced Recovery After Surgery (ERAS). Some variations are market driven and it is crucial to differentiate between “innovations that will improve patient outcomes” and “innovations that will improve market share and commercial profit”. Lastly, as the burden of periprosthetic joint infection increases, strategies to prevent and detect this terrible complication attract renewed attention.

Avoiding Complications and Poor Outcomes

Strict indications must be followed as younger age is associated with a higher risk of revision during the patient's lifetime (Bayliss et al., 2017). Patients after THR have diminished long-term PROMs, perform less well than the general population, but are much improved compared to those with untreated OA (Nilsdotter et al., 2003). The level of surgical satisfaction is high with 7% overall dissatisfaction reported after THR (Bourne et al., 2010). Adequate informed consent and managing patient expectation are important (Palazzo et al., 2014). Postoperative functional scores, pain relief, and restoration of function are factors associated with a good outcome whilst a major complication is not a predictor of dissatisfaction. The proportion of patients with long-term pain according to a systematic review of prospective studies was 7-23% following a THR (Beswick et al., 2012).

Choice of Surgical Approach to the Hip

The aim of any surgical approach to the hip is to provide safe, minimally traumatic and blood conserving access. An excellent, direct surgical view of the anatomical landmarks for implant positioning allow accurate referral to the preoperative template. The approach should be suitable for different types of implants whatever the fixation type. The approach should be extensile to address a complex situation or complication. The surgeon must avoid excessive force in retraction to protect surrounding soft tissues and also prevent intraoperative tilting of the pelvis which might compromise implant positioning. The rate of complications must be acceptable in association with the supposed advantages.

The posterior or "Southern" approach was popularised by Moore (Moore, 1957). The posterior approach divides the fibres of gluteus maximus to expose the short external rotators. The sciatic nerve is identified and protected, and the short external rotators and capsule are released from the posterior part of the proximal femur (Figure Intro 4). This approach does not disturb the abductor mechanism.

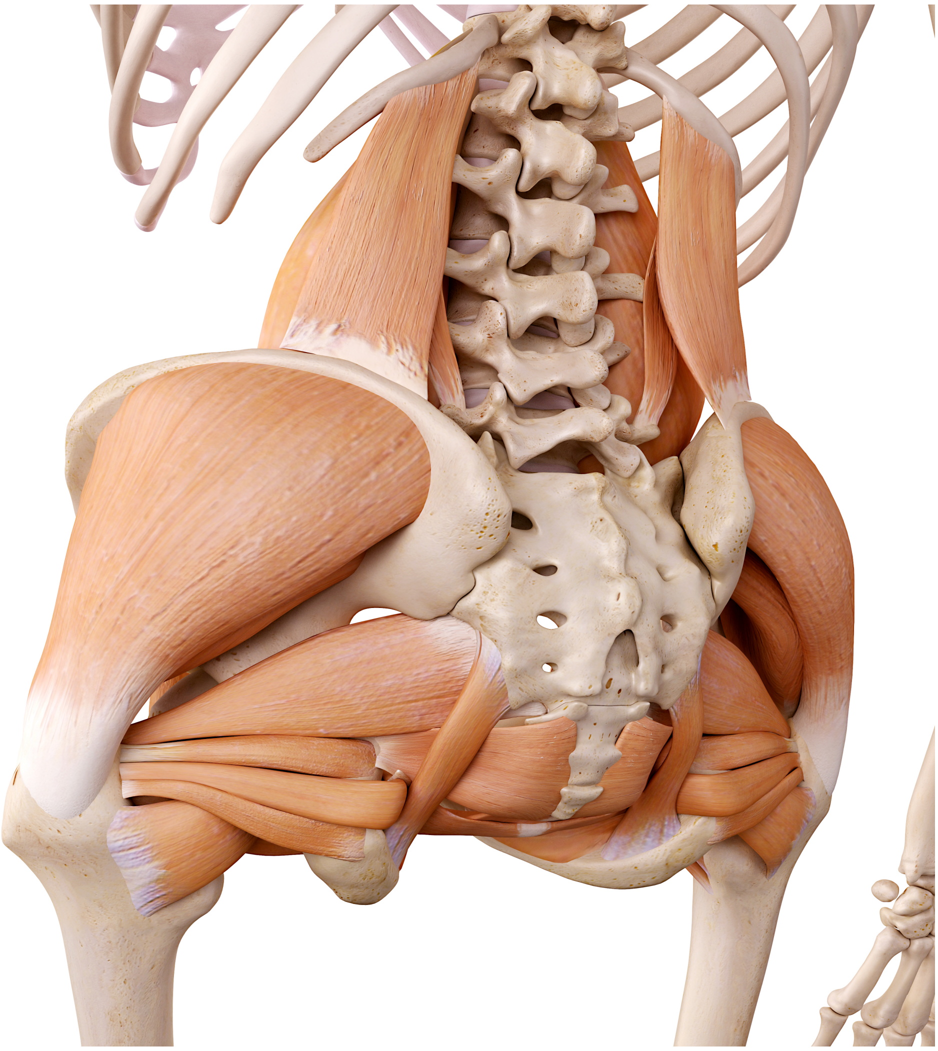

Figure Intro 4. Anatomical representation of the LEFT hip showing the gluteus medius and short external rotators inserting onto the proximal femur (purchased stock image from shutterstock.com)

The anterolateral approach exploits the internervous plane between tensor fascia lata and gluteus medius and this was first described by Watson-Jones (1936). It was subsequently modified by Charnley (1979), Harris (1967) and then Muller (1974) and involves at least partial detachment of the abductor mechanism.

Lateral approaches are subdivided into direct lateral and transtrochanteric techniques and both detach the entire abductor mechanism during the approach (Onyemaechi et al., 2014). The rationale for this approach is that the gluteus medius and vastus lateralis are in functional continuity through the periosteum covering the greater trochanter (McFarland and Osborne, 1954). Hardinge modified this approach subsequently to the transgluteal approach by incising the tendon of gluteus medius obliquely across the greater trochanter and leaving the posterior portion attached (Hardinge, 1982).

Berstock et al. compared the posterior approach with the lateral approach in a systematic review and meta-analysis. Compared to the lateral approach the posterior approach was less likely to have femoral stem malposition (Odds Ratio 0.24; p=0.02) and was less likely to have a Trendelenburg gait (Odds Ratio 0.31; p=0.0002) (Berstock et al., 2015). In another systematic review and meta-analysis a mini-posterior approach was superior to a standard posterior approach with less blood loss, shorter in-patient stay and better functional scores without compromising implant positioning, stability or thromboembolic risk (Berstock et al., 2014).

“New” surgical approaches such as the Direct Anterior Approach (DAA), have been promoted on the basis of a claimed reduction in THR instability and faster rehabilitation. Spaans et al. analysed their first 46 consecutive minimally invasive (MIS) anterior approaches matched *versus* 46 posterolateral approach THR. They reported: longer duration of surgery, greater blood loss, four intraoperative conversions to the posterior approach, more complications and the same length of stay in hospital with no functional difference (Spaans, van den Hout and Bolder, 2012). Higgins et al., in a systematic review and meta-analysis concluded that “current evidence comparing outcomes following anterior versus posterior THA does not demonstrate clear superiority of either approach. Until more rigorous, randomised evidence is available, it is recommended to choose a surgical approach based on patient characteristics, surgeon experience and surgeon and patient preference” (Higgins et al., 2015). Another systematic review and meta-analysis compared DAA with posterior approach showed early postoperative functional scores favoured DAA yet there was no difference at 1 year after surgery (Wang et al., 2018). Recently, Aggarwal et al. reported increased infection rates with the DAA compared to other surgical approaches in THR (Aggarwal et al., 2019). Less invasive posterior approaches such as the Spare Piriformis And Internus, Repair Externus (SPAIRE) approach may offer advanatges (Hanly, Sokolowski and Timperley, 2017).

New Technologies

Computer navigation and robotic surgery are currently expensive. There is some evidence that demonstrates greater precision of the acetabular cup placement (Domb et al., 2014) and improved functional outcomes compared to traditional methods (Bukowski et al., 2016). THR navigation does not improve mid-term functional outcome (Banchetti et al., 2018), bony ingrowth nor polyethylene wear. Randomised controlled studies with long-term follow-up are needed to ascertain whether navigation is cost-effective and of long-term clinical benefit to patients.

Methods Used in This Thesis and context

This thesis has made use of my particular access to data from the New Zealand Joint Registry (NZJR) for a number of studies as well as the Exeter Hip team database whilst a Ling Fellow in 2015. My affiliation with University of Bristol permitted excellent tuition and mentorship in formal systematic review and meta-analysis of high-quality studies. The use of a variety of sources and research methods permits triangulation of and substantiates research findings. This permits the broad application and generalisability of evidence to guide the delivery of healthcare. A brief discussion of the research methods and evidence follows.

Consent

The NZJR was established in 1998 and has a >96% data capture rate of all joint replacement surgeries. Prospective entry of data into the NZJR is a mandatory requirement of all members of the New Zealand Orthopaedic Association with all data secured in Christchurch, New Zealand. Patients consent to information concerning their joint replacements being recorded in the NZJR prospectively. Similarly, the Exeter Hip database records information concerning their joint replacements after prospectively obtained informed consent. The systematic reviews and meta-analyses performed in this thesis were done so with prospective registration with PROSPERO and followed PRISMA guidelines.

Systematic Review

This is a review conducted by a systematically applied process performed to minimise the risk of bias and random errors. The review has clear, explicit objectives and aims. A systematic review is carried out with the same scientific rigour as the RCT. Biases are considered and the quality of the evidence assessed objectively to understand their effect, magnitude and direction. The steps involved in a systematic review are (i) formulation of the question using the Patients, Intervention, Comparator and Outcomes (PICO) method (Chalmers and Altman, 1995), (ii) development of a protocol that defines both inclusion and exclusion criteria, outcomes of interest and publication of this protocol before the review commences for example with PROSPERO, (iii) perform the literature search (iv) application of the eligibility criteria (v) extraction of the data using standardised proforma (vi) assessment of the risk of bias (vii) synthesis. A systematic review may permit a meta-analysis to provide a single estimate of the treatment effect. Statistically meta-analysis can be performed using either a fixed-effects or random-effects model. A fixed-effects model assumes that all of the studies included are measuring the same treatment effect and this approach is advantageous when there is low heterogeneity between studies. A random-effects model assumes that the treatment effect varies between studies and is in fact normally distributed. The random-effects method accounts better for heterogeneity (Berstock and Whitehouse, 2019).

Registry Cohort Study

National joint registry data improve awareness and allow surgeons to make more informed choices and improve outcomes. The purported advantage of introducing a new prosthesis must be carefully scrutinised. A systematic review of Randomised Controlled Trial's (RCT's), comparative observational studies and registry data on new orthopaedic devices stated that "new technologies are being introduced to the commercial market without sufficiently high-quality evidence for improved benefit over existing, well proven, and safe alternatives. Moreover, the existing devices may be safer to use in total hip and knee replacement" (Nieuwenhuijse et al., 2014).

National joint registries provide simultaneous comparison of multiple treatments and include the effects of multiple factors that affect THR outcomes. Registry data however cannot infer causality but rather the strength of associations. The hierarchy of levels of clinical evidence is based on the ability of a study design to determine causality from data with respect to outcome and support a hypothesis. Registry studies in this hierarchy are therefore classified as observational studies and as such are considered to be less valuable that RCTs or systematic reviews. Unlike National Joint Registries however RCTs require adequate statistical power and they also have a defined endpoint. The focus of a registry is ongoing quality assurance and not determining causality. They have a different purpose than RCTs and therefore data collection and analysis are different from RCTs. When registry data analysis shows a difference, factors associated with that difference are identified. This information can guide surgeons in their choice of treatment options, and this can improve outcomes. This is without determining the specific question of causality which can subsequently be examined by other scientific means such as an RCT. RCTs require high internal validity yet this limits the wider applicability. In contrast a study of Registry data is likely to have high external validity (Graves, 2010). Registries can also, given the large number of patient data recorded within, determine rates of clinically rare events such as early mortality and revision following primary THR, both relatively rare but important events. When studying single-anaesthetic bilateral THR (SABTHR) in a RCT for example, if we assumed a 90-day mortality of 0.7% one would need 1,346 patients with SABTHR along with 13,460 controls to detect an increase in 90-day mortality by a factor of 2 (alpha=0.05; power=80%) (Wyatt et al., 2018). From a purely scientific perspective therefore prospective randomised controlled trials (RCTs) are the best way to investigate causation of revision rates and patient-reported outcome measures in performing THR. However, this is often not feasible from a logistical or financial standpoint (Sayers et al., 2017). Therefore, RCTs and registries provide different information and as such are complimentary.

A number of registry studies in this thesis use survival analysis using not only Kaplan-Meier but also Cox regression (Cox proportional hazards regression). This permits the investigation of multiple covariates upon the time a specific event such as revision THR takes to occur. This type of survival analysis assumes that the effects of predictor variables upon survival remain constant over time which is reasonable for say gender, ASA grade at surgery, BMI and diagnosis/indication for THR. Some covariates are time-dependent and can be considered in Cox proportional regression hazards providing they are considered as categorical variables.

Rationale for this thesis

The introduction therefore highlights three key areas of research focus regarding decision making in primary THR namely (i) the optimum femoral stem fixation, (ii) the optimal bearing surface combination and (iii) strategies for reducing the risk of periprosthetic joint infection. At the synthesis level this thesis aims to provide an evidence base and synthesis for the author's clinical practice in hip replacement surgery. In the following rationale I will describe why and how I embarked on this research and how the research story unfolded.

Section 1 Stem fixation

Background to Chapter 1

Firstly, it was apparent during my Higher Orthopaedic training that Consultant Orthopaedic Surgeons made choices of THR fixation based on their personal preference, i.e. a function of their experience, training, familiarity and local tradition. I do not believe that these factors, though relevant, were sufficient to justify fixation choices in THR. I wished therefore to determine the evidence-based **optimal type of fixation for femoral stems in primary THR** for a particular patient. At this stage of my career I had the opportunity to learn both uncemented and cemented techniques in centres of excellence and therefore wished to elucidate for my own practice an evidence-based approach for a particular individual patient.

In the wider context uncemented fixation has historically been preferred in North America and cemented stem fixation in Europe especially in the UK (Dunbar 2009, Murray 2011). Centres of excellence in the USA have published 98% 20-year Kaplan-Meier femoral stem survivorship with extensively porous-coated cylindrical stems for example (Belmont et al., 2008). In addition, metaphyseal porous uncemented or hydroxyapatite-coated uncemented stem series have been reported with approximately 99% survivorship at 20 years (Lombardi et al., 2009; McLaughlin and Lee 2010; Vidalain 2011). The use of uncemented stem fixation globally is also increasing despite national registries reporting superior survivorship with cemented stems especially in older patients (Troelsen et al., 2013). Excellent results with cemented stems such as the Exeter have also been reported in young patients by specialist centres (Lewthwaite et al., 2008).

Potentially there is therefore a danger that fashion and market forces would mean that cemented techniques would be forgotten at the detriment of patient care. I wished to determine an evidence-based decision-making reationale for stem-fixation. Furthermore, the question of which stem fixation type is optimum for the New Zealand patient population remains unanswered. To address these important questions it is logical to examine the large-volume datasets of the National Joint Registries. Therefore I addressed these issues in chapter one.

Chapter 1 research question: *Which type of femoral stem fixation should be adopted and is one type of stem more appropriate in a particular age of patient?*

The first chapter of this thesis examines the issue of THR failure related to the type of femoral stem fixation in the New Zealand Joint Registry. The primary question is which type of femoral stem fixation should be adopted and is there a pattern for example is one type of stem more appropriate in a particular age of patient. The findings will be interpreted in the context of other National Joint Registry findings.

Background to Chapter 2

Establishing the correct biomechanics for a THR is recognised as crucial to not only obtain a stable construct but also to promote its longevity and minimise the risk of failure from aseptic loosening secondary to wear (Charnley 1979). Femoral offset is defined as the distance between the centre of the femoral head and the central femoral medullary axis and is a key biomechanical concept that should be recreated during THR.

Offset affects clinical outcomes of THR and affects wear; an increased femoral offset may potentiate the function of the abductor muscles and in theory this is associated with reducing wear (McGory BJ et al., 1995; Sakalkale DP et al., 2001). However the effect of femoral offset on THR survivorshipor reasons for revision has not been examined at a national registry level. Moreover the effect of femoral component offset on these outcomes of interest have not been examined with regards to different types of fixation. Therefore I addressed these questions in chapter two:

Chapter 2 research question*: In patients undergoing primary THR does femoral offset affect the revision rates of cemented compared to uncemented stem prostheses?*

The second chapter explores the biomechanical concept of femoral offset and whether this factor affects the all-cause and cause-specific revision rates of primary cemented compared to uncemented stems. The NZJR is examined to compare diminished, normal and increased offset groups in both cemented and uncemented stems.

Background to Chapter 3

Short stems in THR have gained recent popularity and potentially permit less-invasive surgical exposures yet there are no long-term results published. In theory such stems potentiate bone-stock for the future revision scenario and minimise proximal stress-shielding and therefore are potentially “bone-preserving” compared to standard length femoral stems. In addition, short stems may promote more physiological loading of femoral bone and reduce the incidence of thigh pain. This rationale makes the use of these stems in the younger patient attractive. Short stems vary in their design and how they transfer load to the proximal femur and have been classified (Falez, Casella and Papaliaet, 2015). The majority of short stems are uncemented designs and in a recent systematic review short uncemented stems showed similar clinical and radiological outcomes compared with conventional length implants at the mid-term (Lidder, Epstein and Scott, 2019). In a recent registry study both short and conventional length uncemented stems had >90% survival at 15 years which is an excellent result compared to standard length stems (Giardina et al., 2018).

There is a relative paucity of published results regarding cemented short stems however. This is of great relevance as short cemented stems should in theory convey the same advantages as short uncemented stems in terms of bone preservation. Choy et al. 2013 reported on the medium-term results of the Exeter short stems in the Australian Joint Registry. Since then the Exeter cemented stem, which was identified in previous chapters to have excellent clinical outcomes, was modified in 2011 to include short stems with more available offsets, The outcomes of such Exeter short stems are unreported in the NZJR. The purpose of the next chapter was to examine the NZJR outcomes of short Exeter cemented stems:

Chapter 3 research question*: In patients undergoing primary THR does a shorter length of cemented stem affect outcomes compared to standard length stems?*

The third chapter touches on the topical issue of shorter femoral stems which have been purported to be “bone conserving”. The NZJR is used to compare the all-cause and cause-specific revision rates of standard cemented stems, short cemented stems with the normal offsets and short cemented stems with smaller offsets.

Background to Chapter 4

Symptomatic bilateral hip OA is not infrequently encountered and may be addressed by single-anaesthetic bilateral THR (SABTHR). Given the global trend for more uncemented fixation especially in younger patients it follows therefore that SABTHR is performed more commonly using cementless THR. Several series with uncemented stems have reported excellent results with SABTHR (Berend et al., 2005; Aghayev et al., 2010; Gondusky et al., 2015).

In Exeter, however, cemented stems have been used in SABTHR for mover 40 years yet concerns about embolic-associated complications remain (Christie et al., 1994; Pitto et al., 2002; Donaldson et al., 2009). The key questions to be addressed in the next chapter are whether SABTHR can be done safely using cemented Exeter stems.

Chapter 4 research question: *In patients requiring single-anaesthetic bilateral THR is it safe to use cemented stems?*

The fourth chapter examines the issue of bilateral THR which is most commonly performed in younger, higher demand patients compared to unilateral THR. The safety of this practice using cemented stems is examined.

Section 2 Bearing surfaces

(ii) Secondly this thesis will focus on the **optimal bearing surface combination** to be used in primary THR. Bearing surface combinations can be considered in two broad groups: “hard-on-soft” such as metal or ceramic femoral heads on polyeyhtlene or “hard-on-hard” such as metal-on-metal or ceramic-on-ceramic. Furthermore, the size of the femoral head in hard-on-soft combinations is highly relevant given its influence on polyethylene wear rates and THR stability.

Background to Chapter 5

Lopez-Lopez et al., 2017 showed in a systematic review of randomised controlled trials that there was little evidence that any bearing surface combination was superior to metal-on-polyethylene. However ceramic femoral heads have been shown to have improved wear rates compared to metal heads (Dahl et al., 2013). The evolution of polyethylene to highly-crosslinked has also been shown to improve survival rates (Devane et al., 2017).

Whilst metal-on-metal has fallen from favour in the UK (Smith et al., 2012) its performance in New Zealand remains unknown. Ceramic-on-ceramic has very low wear rates and excellent long-term survivorship (Petsatodis et al., 2010) yet comparative studies to other bearing surfaces in New Zealand are lacking. The next chapter therefore focused on the NZJR to identify which bearing surface combination has the best survival rates:

Chapter 5 research question***:*** *In patients undergoing THR which bearing surface combination has the lowest rate of revision?* The fifth chapter focuses on the NZJR evidence for the bearing surface combination with the lowest all-cause revision rate.

Background to Chapter 6

A recent prospective randomised controlled trial with 10 years of follow up compared UHMWPE to HXLPE in primary THR. The HXLPE group had significantly reduced wear and lower revision rates compared to the UKMWPE group (Devane et al., 2017).

The latest generation of HXLPE includes Vitamin E. The antioxidant effects of Vitamin E are purported to reduce wear rates compared to previous generations of HXLPE. A recently published study has reported linear wear rates of 0.02mm/year compared to UHMWPE at 0.058mm/year on RSA studies (Rochcongar et al., 2018). Whether Vitamin E HXLPE is superior in vivo compared to HXLPE is unknown. In this Chapter this assertion is examined through a formal systematic review and meta-analysis.

Chapter 6 research question: *In patients undergoing primary THR for osteoarthritis does the recently introduced Vitamin E highly crosslinked polyethylene convey advantage over more established highly crosslinked polyethylene?*

HXLPE has been advocated as a major advance in THR tribology. The latest evolution of HXLPE incorporates vitamin E. A systematic review and meta-analysis is performed to examine the evidence for this latest bearing surface.

Section 3 Periprosthetic infection

(iii) Thirdly this thesis will examine **issues related to preventing and diagnosing periprosthetic joint infection**.

Background to Chapter 7

Prosethtic joint infection (PJI) is a serious and devastating complication of THR. The Lidwell prospective multicenter randomised controlled trial found that the incidence of infection in laminar flow theatres was reduced when compared to the control group (Lidwell et al., 1987). This study foud that infection rates were reduced further when the ultraclean environment was combined with the practice of wearing body exhaust suits. However, there was no accounting for the use of antibiotic prophylaxis. Subsequent randomised controlled trials have not shown that laminar flow theatres offer greater protection from infection compared to non-laminar flow theatres (Marotte et al., 1987; Brandt et al., 2008). The NZJR is the only National Joint Registry that records surgeon use of laminar flow theatres and body exhaust suits. As the burden of PJI is increasing with considerable associated costs this Chapter will address whether using laminar flow and space suits is associated with lower deep infection rates.

Chapter 7 research question*: In patients undergoing primary hip and knee replacement does the use of laminar flow and modern space suits reduce the rate of periprosthetic infection?*

The seventh chapter examines the NZJR and the use of commonly adopted preventative theatre environmental measures against PJI.

Background to Chapter 8

The burdern of PJI is increasing (Padegimas et al., 2015) and from a patient's perspective the impact and experience of PJI should not be underestimated (Moore AJ et al., 2015). The surgical treatment for PJI can be, in ascending order of magnitude, Debridement, Antibiotics and Implant Retention (DAIR), a one-stage revision or lastly a two-stage revision. An early diagnosis of PJI may mean less invasive surgery can successfully address the PJI (Kunutsor et al., 2015).

Establishing the diagnosis of PJI swifltly therefore affects the patient outcome (Moojen et al., 2014). However, the classic clinical features may be absent and acquiring the diagnosis may be challenging. The Musculoskeletal Infection Society (MSIS) developed diagnostic criteria to standardise and facilitate this diagnostic process (Parvizi et al., 2011). The search for a single diagnostic test on synovial fluid with the requisite accuracy, sensitivity and specificity has yielded numerous biomarkers as potential candidates – the term biomarker meaning a biologically pertinent molecule that can be evaluated objectively to indicate the presence of a disease or biological state. The most promising biomarkers are alpha-defensin and leucocyte esterase. The next chapter will examine the efficacy of these tests for the diagnosis of PJI.

Chapter 8 research question: *In patients with a possible periprosthetic infection what is the optimal biomarker as a diagnostic tool: alpha-defensin or leucocyte esterase?*

The eighth chapter is a formal systematic review and meta-analysis that examines the diagnostic use of these two promising biomarkers.

STEM FIXATION

CHAPTER ONE

Survival outcomes of cemented compared to uncemented stems in primary total hip replacement

Reference: Wyatt, M., Hooper, G., Frampton, C. and Rothwell, A. (2014). Survival outcomes of cemented compared to uncemented stems in primary total hip replacement. *World Journal of Orthopaedics*, 5(5), pp.591–596.

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Wyatt M – data analysis, writing the paper, lead author
Hooper G – reviewing and editing paper
Frampton C – statistical analysis and data retrieval from Registry
Rothwell A – senior author, final editing

Abstract

Total hip replacement (THR) is a successful and reliable operation for both relieving pain and improving function in patients who are disabled with end stage arthritis. The ageing population is predicted to significantly increase the requirement for THR in patients who have a higher functional demand than those of the past. Uncemented THR was introduced to improve the long-term results and in particular the results in younger, higher functioning patients. There has been controversy about the value of uncemented compared to cemented THR although there has been a world-wide trend towards uncemented fixation. Uncemented acetabular fixation has gained wide acceptance, as seen in the increasing number of hybrid THR in joint registries, but there remains debate about the best mode of femoral fixation. In this article we review the history and current world-wide registry data, with an in-depth analysis of the New Zealand Joint Registry, to determine the results of uncemented femoral fixation in an attempt to provide an evidence-based answer as to the value of this form of fixation.

Introduction

The best mode of implant fixation in primary total hip replacement (THR) has long been a source of debate. Cemented implants achieve stability from cement-bone mechanical interlock once the polymethylmethacrylate has cured, whereas cementless fixation relies on primary press fit stability with long term stability occurring secondary to endosteal microfractures at the time of preparation and subsequent bone ongrowth or ingrowth. The optimum fixation choice should be guided by patient-based outcomes, in particular the implant survivorship as measured by revision for aseptic loosening, as this was a major reason for the introduction of uncemented implants.

Advocates of cemented implants cite the excellent and reliable long-term reported survivorship (Wroblewski, Siney and Fleming, 2007; Ling et al., 2010; Burston et al., 2012) whereas proponents of cementless fixation contend that this method is equally reliable (Gwynne-Jones et al., 2009; Engh and Massin, 1989; Ihle et al., 2008; McAuley et al., 1998) and in fact superior in younger, high-demand patients (Hooper et al., 2009; Kim et al., 2011). Furthermore, cementless implants provide a broader range of options especially for the acetabulum where liner exchange may be required for postoperative instability; the commonest cause for early re-operation in all primary THR (Ulrich et al., 2008). Modular cups offer the option for changing the femoral head diameter which may improve the functional outcome especially in the younger or more active patient, yet cemented cups also offer various internal diameters. A hybrid THR, where the stem is cemented and the cup uncemented, has been suggested to provide the benefits of both fixation methods (Clohisy and Harris, 1999; Pennington et al., 2013) although the reported results have been mixed (Horne et al., 2007; Swedish Hip Registry, 2011; Norwegian Joint Registry, 2011). Worldwide there has been an observed trend towards uncemented fixation with confirmatory joint registry results in Australia, New Zealand, England, Wales and Sweden. Both Canada and the USA have continued to have a predominant use of uncemented THR (Swedish Hip Registry, 2011; Norwegian Joint Registry, 2010; New Zealand Joint Registry, 2011; Australian Joint Registry, 2012; NJR Steering Committee report, 2013).

One of the traditional arguments against uncemented THR has been the increased cost with implants often being three to four times more expensive than the cemented variety. In the immediate future, the burden of an ageing population with the projected increase in demand for THR will put considerable strain on health funding agencies requiring balanced economic arguments for the use of THR implants. There is also likely to be an increase in the absolute number of revision procedures which are approximately four times more expensive than primary procedures, especially when both the femoral and acetabular components are revised. This has implications if one form of fixation is inferior to the other. Those that advocate uncemented implants suggest that following successful bonding of both the femoral and acetabular components to bone then future revision procedures may only involve exchange of articulating surfaces, which is likely to be a procedure whereby patients recover rapidly with a lower overall health cost (Briggs, 2012).

Uncemented acetabular implants are widely used in all age groups with registry results showing satisfactory early and mid-term results (Gwynne-Jones et al., 2009; Swedish Hip Registry, 2011; Norwegian Joint Registry, 2010; New Zealand Joint Registry, 2011; Australian Joint Registry, 2012; NJR Steering Committee report, 2013). However, uncemented femoral implants have been less widely accepted with several countries continuing to favour the cemented option as seen in the increasing number of hybrid THR performed in registries across the world (Norwegian Joint Registry, 2010; NJR Steering Committee report, 2013). We have reviewed the recent evidence supporting femoral implant fixation, in particular joint registry outcomes, in an attempt to provide sound recommendations for future practise.

History of fixation in primary total hip replacement

The British Orthopaedic Association meeting in London, September 1964 was a turning point for the treatment of patients with crippling osteoarthritis of the hip. McKee (Norwich) presented the results of the cemented metal-on-metal McKee-Farrar arthroplasty and Charnley (Wrightington) demonstrated the results of his cemented metal-on-polyethylene THR by having one of his patients walk normally across the stage. Widespread high rates of aseptic loosening of cemented THR during the 1960s and 1970s tempered enthusiasm and “cement disease” was widely held as the cause of this loosening. Many surgeons began to favour the use of cementless fixation as recommended by Ring with his metal-on-metal replacement (Ling, 2010). However excellent results with cemented fixation were maintained with the Charnley prosthesis. The Exeter group, who believed that poor cementing technique and not cement per se was the issue, developed their collarless, taper-slip cemented prosthesis specifically designed to subside into the cement mantle while providing even load. The early metal-on-metal design soon fell from favour with high failure rates, possibly related to poor manufacturing tolerances of the implant, and the improving results of cemented metal-on-polyethylene replacements.

The high rates of early loosening and failures observed in younger, active patients coupled with concerns regarding “cement disease” continued to drive a renewed interest in uncemented fixation (Dorr, Kane and Conaty, 1994; Joshi et al., 1993; Mulroy and Harris, 1997). Early failures of cemented implants in these younger patients were often associated with a varus positioning of the femoral stem whereas the acetabular component often failed after 12 years with polyethylene wear and loosening. The use of cementless components in this patient cohort initially established the wider use of these implants throughout the world in the hope that they would improve survivorship. Once it had been established that aseptic loosening was in fact due to the polyethylene debris and not ‘cement disease’ uncemented THR had become firmly established as a recognised and viable option for surgeons.

The modern primary femoral stem

Over the last 20 years significant attention has been paid to improving the cementing technique which has emphasised both the preparation of the femoral canal and the pressurisation of the cement on insertion. These changes have improved the cement-bone interface with more stable interlocking and as a result the intermediate survival rates of cemented stems have improved. Current joint registries record between 92% at 11 years and 86% at 22 years survival for these implants (Swedish Hip Registry, 2011; Norwegian Joint Registry, 2010; NJR Steering Committee report, 2013). These improved survival statistics have been interpreted as a cemented THR is likely to be a 'life-long' implant for patients aged 62 or older, whereas for a 58-year-old patient there is a 50:50 chance of undergoing a revision within their life time (Wainwright et al., 2011).

There are currently two philosophies of cemented femoral fixation: composite beam and polished, tapered wedge. The former is predominant in North America whereas the latter is more widely used in Europe. A composite beam relies on rigid bonding to the cement and is not intended to subside. This is in contrast to the loaded taper wedge which converts radial compression into hoop stresses within the cement mantle, and is expected to subside. The addition of cement around an implant provides an additional buffer that the surgeon can manipulate to control correcting leg length and version during insertion. Cement use has sporadically been reported as producing potentially fatal associated cardiovascular and embolic phenomena at implantation, especially in the elderly compromised patient (Parvizi et al., 1999).

Cementless stems rely on bone on-growth or ingrowth to provide stability. A roughened titanium stem has been shown to attract bone and provide early stability (Wieland et al., 2000) and most uncemented stems today have this type of surface. The addition of hydroxyapatite to this surface has been shown to also stimulate bony fixation (Vidalain, 2011) without the initial early concern of producing ceramic particles in the joint that could cause third body wear.

There are two major uncemented stem designs: proximal (metaphyseal) loading or fully coated. Proximal loading has been advocated to avoid the stress shielding that was observed with early 'distal fitting' implants (Chambers, St Clair and Froimson, 2007). Often these implants are bulky in the proximal metaphyseal region, which is responsible for the early resistance to subsidence and rotation, and smooth distally to prevent bone apposition. They are inserted following minimal reaming and are rarely associated with femoral fracture. On the other hand, fully coated stems rely on a graduated loading of the proximal femur, allow bone apposition throughout their length and provide stability by their wide, flat nature. Initial stability is achieved by either reaming the femur to accept a maximally sized implant which undergoes three-point fixation in the proximal femur or by compaction of cancellous bone. The former type of implants requires exact sizing and significant reaming and are associated with a higher incidence of femoral fracture (Yoshihara et al., 2006). The latter type, such as the Corail does not have the cancellous bone removed with broaching.

European Joint Registry outcomes and trends in femoral fixation

The Swedish Hip Registry reports a gradual trend for the increased use of uncemented fixation although cemented THRs were used in 64% of all patients in 2011 regardless of age (Swedish Hip Registry, 2011). Overall cementless stem fixation was more common in the younger, active patient whereas cemented fixation was favoured for patients over 70 years of age. Cemented THR had a 90% 16-year survivorship and was 30-80% less likely to be revised compared to uncemented and hybrid THRs during the first eight years, suggesting that early revision was more likely to be related to acetabular problems. After eight years the survivorship of the uncemented group tended towards that of the cemented group. Up to age 70 years the uncemented hips had fewer revisions attributed to loosening. The hybrid combinations did not convey a clear advantage over either group.

The Norwegian Hip Registry also reported an overall trend towards less cemented fixation but in Norway this was largely due to an increase in hybrid THR (Norwegian Joint Registry, 2010). Overall cemented THRs had a 20 year survival rate of 85% compared to 50% for uncemented total hips. Hybrids had no clear advantage over either cemented or uncemented THRs in terms of implant survival during the same time period. Uncemented or hybrid fixation were preferred in patients under the age of 60 years whilst cemented fixation was used in the great majority > 60 years old.

In the National Joint Registry of England and Wales cemented THRs represented only 33% of all primary THRs yet were used the majority of times for patients over 80 years of age (Briggs, 2012). Total cementless fixation was used in 43% of patients and was the major type of fixation for patients less than 70 years old. Hybrid THRs accounted for 20% of primary THRs. The cumulative percentage of revision (with 95% confidence intervals) at 9 years was 2.71% (2.57-2.87) for cemented, 6.71% (6.40-7.05) for uncemented and 3.42% (3.10-3.76) for hybrid THR.

Results from the New Zealand Joint Registry

The data from the world-wide joint registries portray a similar pattern for the survival of cemented THR compared to uncemented THR, and these results are supported by those of the New Zealand Joint Registry (Table 1 and Figure 1). On this basis it would be easy to dismiss the uncemented variety as inferior, but revision as an end point is a 'blunt tool' and needs to be interpreted in conjunction with several other factors. We have reviewed the results of the New Zealand joint Registry in detail to elucidate this and to look at cofounding variables which may contribute to these revision rates.

Table 1. Thirteen year NZJR revision rates vs fixation method

Fixation	Component years	Events	Rate/100 cy	95% CI
Cemented	14,9098	870	0.58	0.55 to 0.62
Hybrid	16,8604	117	0.66	0.62 to 0.70
Reverse hybrid	3124	19	0.61	0.37 to 0.95
Uncemented	14,8214	1313	0.89	0.84 to 0.94

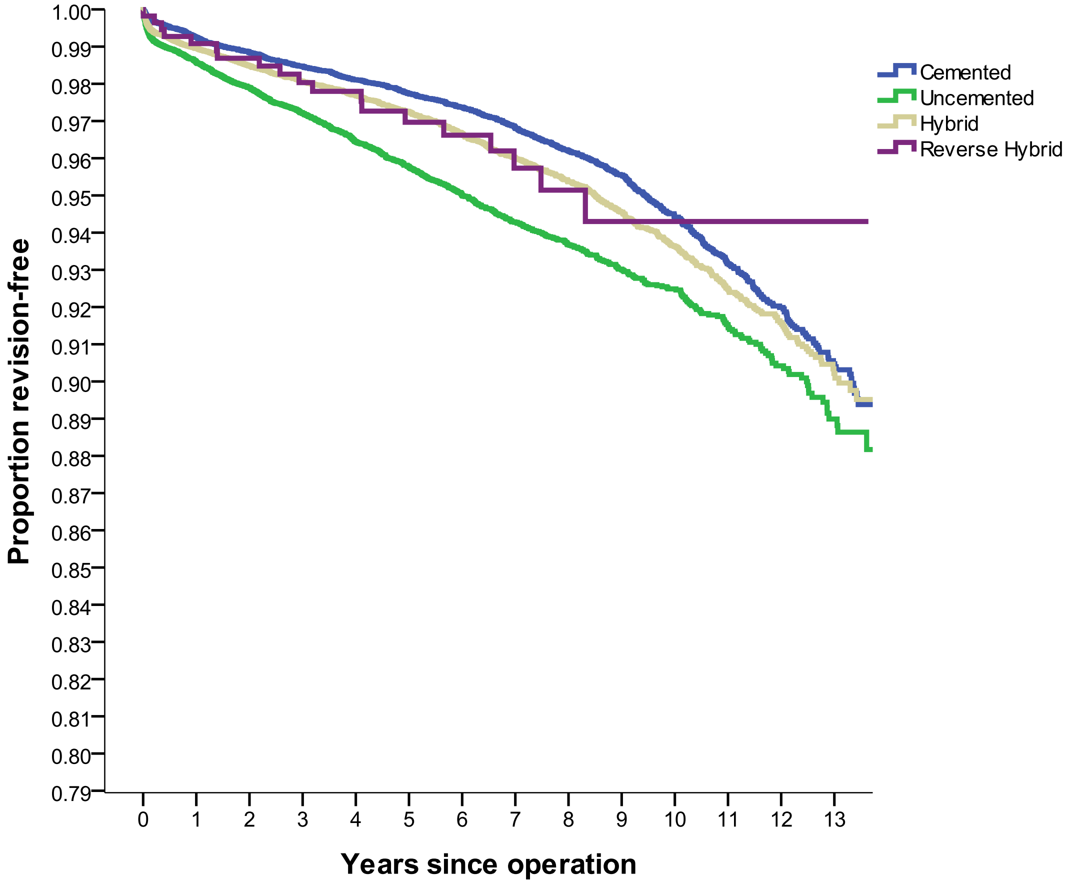

Figure 1. Thirteen NZJR Kaplan-Meier survival curve of THR by fixation type

One of the primary reasons for the introduction of the uncemented stem was to improve the outcome in younger, more active patients, particularly males. The New Zealand Joint Registry has shown a revision rate of 0.89/100 component years (cy) for uncemented THRs in patients under 55 years compared to 1.73/100cy for cemented THRs and 0.90/100cy compared to 0.98/100cy for those between 55 and 65 years ($p < 0.001$) (New Zealand Joint Registry 2013). Over 65 years this was reversed with the cemented THR surviving longer than the uncemented variety ($p < 0.001$). The overall revision rate was significantly higher ($p < 0.001$) in patients under 65 years (1.00-0.83/100cy) compared to those over 65 years (0.65-0.45/100cy) and an argument could be made that because of this the uncemented stem was more robust in a high demand patient. Hybrid fixation also showed poorer survival in the under 55 year age group compared to uncemented THR (1.03/100cy compared to

0.93/100cy, $p < 0.002$) suggesting that it may be the uncemented stem in this age group which has helped improve the survival statistics.

Early revision (within 90 days) was far more common ($p < 0.001$) in the uncemented THR (0.899%) compared to cemented THR (0.353%) which continued across all age groups but only reached significance in those over 65 years ($p < 0.001$) (See Table 2). When the reason for revision was analysed, the major cause for early revision in uncemented implants was either due to femoral fracture (30%) or dislocation (40%) whereas 75% of early revisions in the cemented group were secondary to dislocation. Femoral fracture with uncemented stems has been identified as an early cause for failure by others (Swedish Hip Registry, 2011). Femoral fracture was shown to be age dependent, with older patients and presumably those with poorer bone density having a much higher incidence of this complication (Figure 2). This complication may be due to surgical inexperience and/or attempting to 'over ream' the femur to insert the largest implant to avoid early subsidence or failure of bonding to the prosthesis. The early rate of femoral fracture did not continue beyond 90 days as the overall 13 year results showed, using Kaplan-Meier analysis and log rank testing, that there was no significant difference in revision for femoral fracture between the fixation methods ($p = 0.208$) (Table 3). This contradicts the Swedish registry results which show that uncemented stems are revised twice as frequently as cemented stems during the first 5 years and that cemented stems were ten times less likely to require revision for periprosthetic fracture.

Fixation/n	**Loose cup**	**Loose stem**	**Unstable**	**Deep infection**	**Pain**	**Femoral fracture**
Cemented/77	7.8% (6)	3.9% (3)	75.3% (58)	11.7% (9)	2.6% (9)	3.9% (3)
Hybrid/189	16.4% (31)	3.7% (7)	59.8% (113)	13.8% (26)	2.6% (5)	4.8% (9)
Reverse hybrid/2	0	50% (1)	0	0	0	50% (1)
Uncemented/270	8.5% (23)	8.5% (23)	40% (108)	9.6% (26)	1.9% (5)	30% (81)

Table 2. Thirteen year NZJR reasons for revision for loosening within 90 days

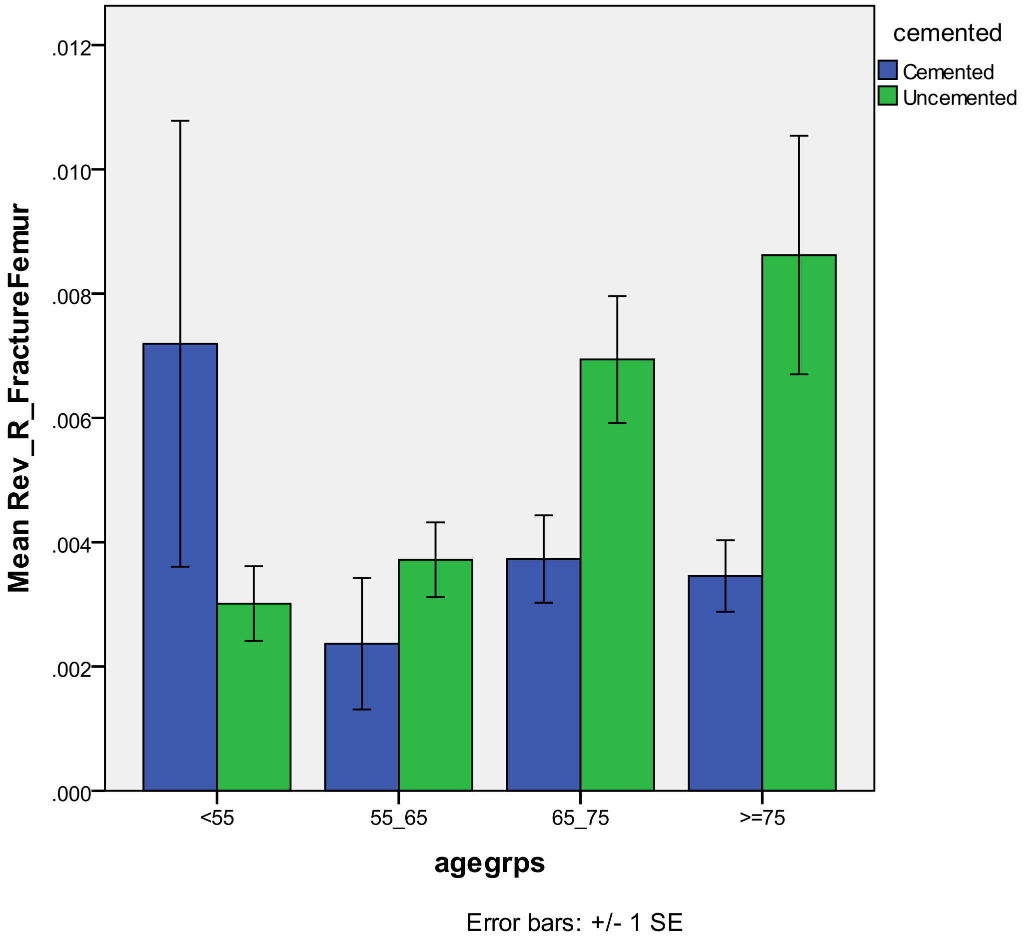

Figure 2. The NZJR results showing the comparison of the incidence of femoral fracture and age with cemented and uncemented stems (65-75 years p = 0.008, > 75 years p = 0.001)

Table 3. Thirteen year NZJR reasons for revision by fixation method

Fixation/n	**Loose cup**	**Loose stem**	**Unstable**	**Deep infection**	**Pain**	**Femoral Fracture**
Cemented/870	48% (415)	17% (148)	23% (200)	12% (105)	10% (86)	8.5% (74)
Hybrid/1117	14% (160)	21% (235)	34% (384)	14% (157)	12% (136)	11% (141)
Reverse Hybrid/19	21% (4)	5% (1)	26% (5)	21% (4)	11% (2)	16% (3)
Uncemented/1313	15% (198)	15% (192)	24% (307)	9% (124)	17% (222)	11% (141)
p-values	< 0.001	< 0.001	< 0.001	0.003	< 0.001	0.208

The rate of femoral loosening within 90 days was significantly higher in uncemented stems ($p < 0.009$) but decreased over the 13-year period to become essentially the same as cemented stems (0.62% compared to 0.66%). This early ‘loosening’ of uncemented stems is likely to be associated with surgical technique and under sizing of the component, whereas the longer results are more likely to reflect the true aseptic loosening rate. Figure 3 shows the increasing failure rate of cemented stems due to aseptic loosening compared to uncemented stems. The fact that failure of hybrid fixation secondary to femoral loosening was 0.77% ($p < 0.001$) adds evidence to the suggestion that the cemented femoral stem may be more likely to fail by this mechanism. These results are supported by the Swedish registry which showed that from 8 to 16 years cemented stems had a higher rate of revision over cementless stems and 80% of these were for loosening.

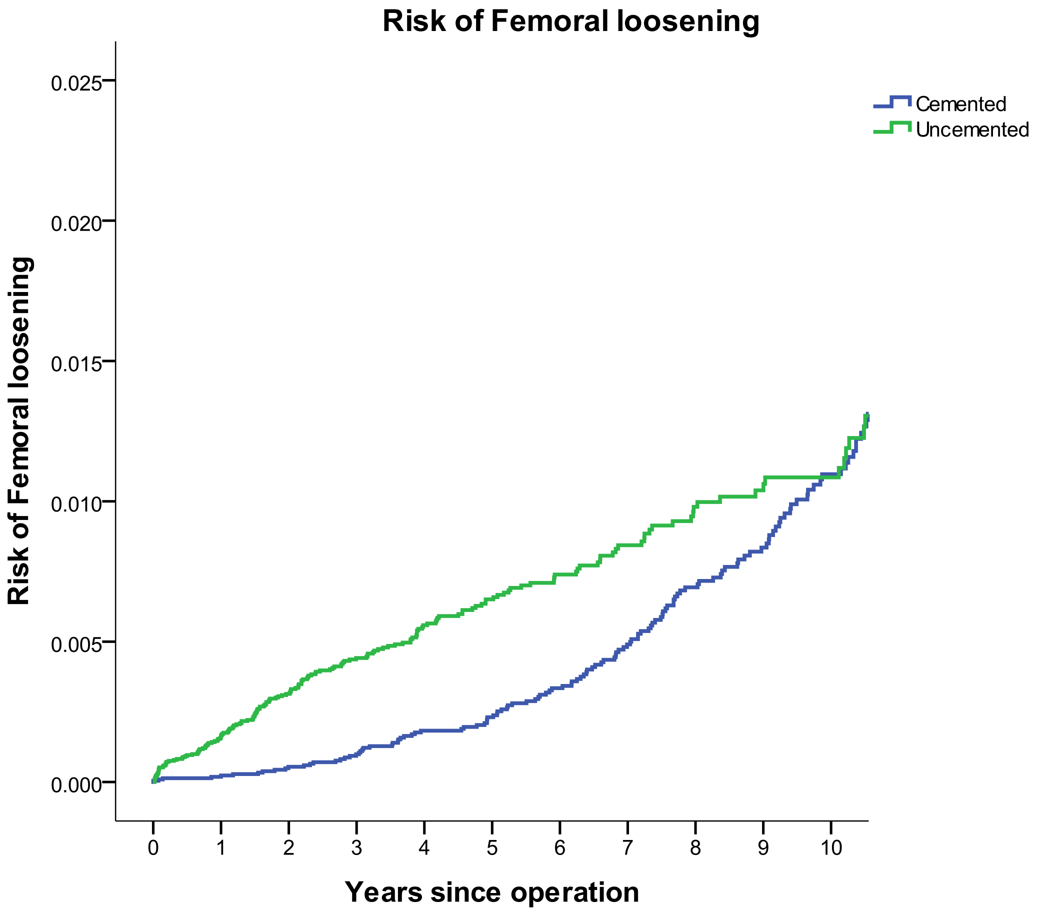

Figure 3. The NZJR results showing the comparison between cemented and uncemented stems and the incidence of revision for aseptic loosening

In the past there has been controversy over the use of antibiotic loaded cement and whether this would decrease revision for prosthetic infection. Most have accepted that it was unlikely to do any harm, however the results from the NZJR are interesting when you consider that the great majority (> 90%) of cemented implants are performed with antibiotic cement. The combined revision rate for infection for both cemented and hybrid THR was 0.50% compared to 0.40% for uncemented THR which suggests that antibiotic cement may not have the protective effect against infection that has been assumed. This result is similar to the Swedish registry which demonstrated that cemented stems were 1.4 times more likely to be revised for infection.

In the past, unexplained pain has been a feature of the uncemented femoral stem, but with a move away from distal fixation, the incidence of revision for this complication was low at 90 days, however by 13 years pain became the second commonest cause for revision surgery behind dislocation in this group of implants. Pain as a cause for revision was not specified and so may not have been due to femoral pain. Regardless, it is encouraging to find that pain was now a low cause for early revision of uncemented stems.

Another complicating variable which is unique to uncemented THR has been the ability to use different bearing surfaces in an attempt to improve the wear associated with a polyethylene articulation. Both metal-on-metal and ceramic-on ceramic surfaces however have been associated with early failures due to reasons not associated with cemented THR. However, most of these complications have arisen from the articulating surface itself, with ceramic fracture and excessive metal ion debris two of the primary reasons for early failure. These problems have not necessarily resulted in failure of the uncemented stem secondary to loosening and as a result have almost certainly skewed the overall revision rates in favour of cemented THR. The problem can be illustrated in the 14 year NZJR report where the revision rate for metal-on-metal articulations with femoral head size > 36mm was 3.08/100cy. The use of larger femoral head sizes is almost solely used in uncemented implants and those with a head size > 36mm had a combined revision rate of 2.75/100cy, irrespective of the articulating surface. This offers a potential explanation for the different revision rates between the two forms of femoral fixation.

Implant Cost

Although uncemented implants are more costly than cemented there have been studies suggesting that the overall cost differential between the two types of fixation is not dramatically different (Kallala et al., 2013; Yates et al., 2006). With the increasing use of hybrid fixation, the overall cost difference between a cemented and uncemented THR is even smaller and likely to be less relevant in the overall economic assessment. Determining the exact cost of a femoral stem can be difficult as the list price may be significantly different from the purchase price after discounting for bulk purchases and other company driven incentives. We cannot make a comment about pricing in other countries but are aware that companies in our country are required to price their implants in reasonable price bands to remain commercially viable and competitive.

Conclusions

Controversy continues to exist regarding the best form of fixation to use in THR. Often opinions are polarised by such factors as training, tradition, and personal preference with proponents of cemented fixation often citing the overall poorer revision rates for uncemented THR reported in the various national joint registries. This review has attempted to clarify the differences between cemented and uncemented THR, with the emphasis on femoral fixation, by analysing the reported joint registry data. There has been a world-wide trend towards uncemented THR over the last 10 years, and even countries who in the past have been the major proponents of cemented fixation have not been excluded from this trend.

Uncemented THR was introduced to address the poorer results observed with cemented THR in younger patients with higher functional requirements and to this end the registry results would confirm that inpatients < 65 years have a lower revision rate with uncemented fixation. In particular the uncemented stem has performed better in this age group with a lower rate of aseptic loosening compared to the cemented variety. Femoral fracture remains a significant reason for early revision with uncemented stems which is more likely to be related to surgical technique and potentially could be improved by increased exposure to this technique in surgical training.

Commentary

Critique

The optimum mode of implant fixation has long been debated. The previous chapter, essentially an editorial published in 2014, examined the NZJR 13-year report comparing patients undergoing cemented, hybrid, reverse hybrid and uncemented THR. The decision of which stem fixation to use is important however as this decision carries with it a prognosis of survival for that patient's THR. The choice of stem fixation should be based in principle on which type of fixation has the best chance of delivering to the patient a long-lasting, well-functioning hip, avoiding complications and minimising the risk of revision surgery. The methodology used in the previous chapter warrants further explanation and clarification. An update from the more recent literature and national joint registry findings is also warranted as more recent literature may have permitted new insights.

Methodology in previous chapter

When searching the literature to compose the previous chapter Web of Science, Pubmed and Google Scholar were searched using the following MESH terms: cemented, uncemented, total hip replacement. Examining the NZJR, all-cause revision rates were compared between fixation types with the lowest rate observed in cemented THR constructs. The reasons for revision for each fixation option were then compared and cemented cups were significantly more likely to require revision for aseptic loosening compared to uncemented constructs. Periprosthetic femoral fractures required revisions more commonly with uncemented rather than cemented stems. When patient ages were examined this difference was more pronounced with increasing patient age. Kaplan-Meier survival analysis was performed will all-cause revisions as the endpoint. Cemented THR had the lowest rate of all-cause revision at all time points following surgery. When revisions for aseptic loosening of the femoral stem were compared between cemented and uncemented stems there were significantly fewer revisions than cemented stems until 10 years following surgery. The other national joint registry reports were then examined to provide comparison. The key pertinent outcomes regarding stem fixation were therefore all-cause revision rates and the influence of patient age, rate of revision for periprosthetic femoral fracture, rate of revision for periprosthetic joint infection and relative cost-effectiveness. In terms of the statistical analysis used in Chapter 1, the lack of regression modelling is a potential limitation.

Up-to-date literature search

The following databases were searched from 2014 to 27.3.2020 using the programme Papers: ACM, ADS, arXiv, CERN DS, CrossRef DOI, DBLP, Espacenet, Google Scholar, Gutenberg, Highwire, IEEExplore, Inspire, JSTOR, OAIster, Pubget, PubMed, ScienceDirect, Scopus and Web of Science. Search terms related to: Cemented stem, Uncemented stem, Total hip.

299 references were identified of which 21 were collected as potentially relevant. The article described in this chapter was cited in 7 published articles, and these were examined. Journals with impact factors <2 were excluded. Any correspondence relating to the article described in this chapter was reviewed. In addition, the national joint registry reports of (i) Norway, (ii) Sweden, (iii) England, Wales, Northern Ireland and the Isle of Man, (iv) Australia and (v) New Zealand were revisited.

All-cause revision rates of stem fixation methods and patient age

The use of uncemented acetabular implants has remained popular in many countries with reliable survivorship data (Swedish Hip Arthroplasty Register, 2017; Norwegian Arthroplasty Register, 2018; National Joint Registry for England, Wales, Northern Ireland and Isle of Man 2018, New Zealand Joint Registry 2018). The trends for THR fixation however have changed in recent years, with cemented stem fixation the overall most preferred option in both Norway and Sweden, and uncemented stems more often inserted in New Zealand and the UK.

According to the Norwegian Arthroplasty Register, in patients under the age of 65 there has been an increase in the use of reverse hybrid THR, i.e. an uncemented stem with a cemented cup, with this becoming the preferred choice in Norway (Norwegian

Arthroplasty Register, 2018). Those patients aged 65 to 75 years of age have good all-cause survivorship with all types of fixation methods whilst those > 75 years of age should receive cemented THR. In particular female patients > 75 years of age have a 54-60% increased risk of revision THR if uncemented fixation is used. Overall cemented THR, from 1987 to 2017, has the lowest rate of revision and uncemented fixation has a 1.29 relative risk of revision compared to cemented ($p < 0.001$). In the Swedish Hip Arthroplasty register 2017 report, cemented fixation is still the most commonly preferred fixation although in 2017 the proportion of cemented THR had fallen from 93% in 2000 to 60% (Swedish Hip Arthroplasty Register, 2017). Completely uncemented fixation in 2017 was 24% overall and this increase occurred predominantly in patients under 60 years of age. Hybrid THR has increased steadily and in 2017 was 1.5% of THR.

Conversely the National Joint Register of England, Wales, Northern Ireland and the Isle of Man, 2018 report showed that overall uncemented THR is the most often performed (38.9%) followed by all cemented (34.2%), and uncemented THR has been the preferred method of fixation since 2008 followed by hybrid THR. When the registry is examined for survivorship stratified by age group and gender the survivorship in cemented THR is equitable to uncemented stems in patients under 65 years of age. In the NZJR there has been a steady decline in the past 19 years in cemented THR with the uncemented fixation preferred closely followed by hybrid THR (NJR England, Wales, Northern Ireland and Isle of Man 2018, NZJR 2018).

Moskal et al., commented that cemented THR was more commonly performed in Europe whilst uncemented fixation was widely adopted in the USA although there is a worldwide trend for performing more uncemented THR. Uncemented fixation using anatomic medullary locking extensively porous coated cylindrical stems and some hydroxyapatite coated stems metaphysial porous fixation stems have reported <98% 20-year survivorship in series from the USA (Moskal et a;., 2016). These results may be prone to both publication and performance bias. At a society and economic level however, there is a strong incentive to use cemented stems over uncemented stems yet paradoxically there remains a lack of training and experience in using cemented stems especially in Northern America (Moskal et a;., 2016). Orthopaedic surgeons often make implant choices based on personal preference and familiarity, yet these healthcare decisions should be made based on scientific evidence. The authors of this article commented that a reasonable evidence-based approach including the use of registry data would be to adopt cemented fixation in patients >70 years of age and uncemented in younger patients given the all-cause revision rates and the high rate of periprosthetic femoral fractures in patients >70 years of age. Moreover, it is imperative that the excellent results of cemented fixation do not deteriorate due to a lack of technical skill in cementing.

Pursuing the same theme Liu et al., 2019 performed a retrospective review with a minimum 5 year follow-up of the South China Hip Arthroplasty database comparing cemented and uncemented THR in patients who had sustained a neck of femur fracture. The mean age was 68.7 years in each group and the cemented THR had better Harris Hip Scores and significantly fewer complications (revision surgery, loosening and periprosthetic fracture) compared to the uncemented THR group.

Dale et al., 2020 recently examined 66,995 primary THR in the Norwegian Arthroplasty Register and showed that uncemented stems, both in all uncemented and reverse hybrid THR constructs, had an increased all-cause risk of revision compared to cemented THR (RR 1.4; 95%CI 1.2 to 1.6) mainly due to the increased risk of periprosthetic fractures. Women had a much higher risk of revision for periprosthetic fracture after all uncemented THR (RR 12; 95CI 6 to 24). The increased risk of revision with uncemented fixation in women >55 years of age was mainly because of periprosthetic fractures and recurrent instability. Similar to the NZJR findings in this chapter the different risk of periprosthetic fracture observed between cemented and uncemented stems increased with patient age. The authors recommended therefore using cemented stems in females >55 years of age.

Tyrpenou et al., 2020 reported a 15 year minimum follow-up study of a metaphyseal fit-and-fill uncemented femoral stem inserted in patients mean age 49.6 (19 to 71 years). This single centre series from Toronto reported 97.7% all-cause survivorship with those cases that failed being revised for periprosthetic fractures and periprosthetic joint infection.

Keeling et al., 2020 reported on the use of cemented Exeter stems from Exeter in patients with mean age of 41.8 (17 to 50 years of age). Of 130 THR the 22 years all-cause revision rate was 25% and the survivorship for stem revision for aseptic loosening 96.3%. This series of THR were all performed by surgeons highly trained and experienced in cementing stems yet shows that with technical competence in cementing cemented stems can be performed reliably and successfully in patients <50 years of age.

Bunyoz et al., 2020 also reviewed the annual reports from the arthroplasty and hip registries comprised Australia, Denmark, England and Wales, Finland, the Netherlands, New Zealand, Romania, Norway, Sweden and Switzerland. All-cause revision rates were compared between cemented and uncemented fixation and in the various age groups (Dennmark <50, 50 to 59, 60 to 69, 70 to 79, >80 years of age whilst for Australia, New Zealand, England/Wales and Finnland <55, 55 to 64, 65 to 74 and >75 years of age). Risk estimates were presented as either hazard ratios, rate per 100 component years or as Kaplan-Meier estimates of revision.

This study showed that uncemented component use has increased in Australia, Norway, Denmark and Sweden whilst it has decreased in England/Wales, New Zealand and Finland. In patients >75 years of age the proportion of patients having uncemented fixation has remained stable in the Netherlands, Sweden, New Zealand and England/Wales. When compared with uncemented fixation, the all-cause revision risk for THR using cemented components was lower in patients >75 years of age in all registries except for the oldest males in the Finnish Arthroplasty register in which there was no difference between cemented and uncemented fixation.

Younger patient age is associated with a lower mortality yet better functional outcomes after THR but with a greater risk of revision during the patient's lifetime (Bayliss et al., 2017). In this important study of 63,158 patients who had undergone THR between 1991 and 2011 the 10-year survival rate was 96.1% and 20-year implant survival rate was 89.7%. The lifetime risk of requiring revision surgery for those over the age of 70 was 5% with no difference between genders. The lifetime risk for a patient in their 50s however was 35% (95%CI 30.9 to 39.1) and was 15% less if female. If the patient was younger than 60 the median time to revision was 4.4 years. This does not necessarily mean that a young patient should be denied THR but does mean that both surgeons and patients should be aware of these facts in order to facilitate appropriate shared decision making.

Periprosthetic joint infection and stem fixation

The issue of fixation in conjuction with the risk of periprosthetic infection has been addressed in more recently published research in the study by Lenguerrand et al., 2018. This study was a prospective observational study linking the NJR with Hospital Epsidoe Statistics data on 623,253 primary THR between 2003 and 2013. The study examined the association of risk factors for periprosthetic joint infection across the follow-up period using Poisson multilevel models. The incidence of infection per 1000 person-years was 0.85 (95% CI 0.8 to 0.9) for cemented THR and 0.97 (0.92 to 1.03) for uncemented THR. Moreover Trela-Larsen et al., 2018 using the same data source showed that there was no significant difference in observed revision rates between plain and antibiotic-loaded cement fixation in cemented THR. Kunutsor et al., 2019 in a systematic review and meta-analysis examined the evidence for risk of periprosthetic joint infection and implant fixation method. In pooled analyses uncemented THR was associated with decreased risks yet only after 6 months following surgery. Plain cement was associated with an increased risk of periprosthetic joint infection compared to antibiotic-loaded cement (RR 1.52 95%CI 1.36 to 1.70). The authors concluded that uncemented and antibiotic-loaded cemented fixations reduce the risk of periprosethetic joint infection in THR.

Cost-effectiveness

A recent study examining the NJR and Swedish Hip Arthroplasty Register showed that the greater the patient age the more likely that the cheapest implants, smaller headed metal-on-polyethylene implants were cost-effective. There was no evidence that uncemented, hybrid or reverse hybrid THRs were more cost-effective for any patient group. This important study is highly pertinent for both patients, surgeons and healthcare providers alike (Fawsitt et al., 2019).

To reflect therefore on the conclusions made in Chapter 1 the validity of preferred uncemented stem fixation in the younger patient, despite its increasing popularity, has been subsequently challenged in favour of cemented stem fixation both in terms of survivorship and cost-effectiveness by the findings of the UK Joint Registry NJR for England, Wales, Northern Ireland and the Isle of Man and the study by Keeling et al., 2020. Having established therefore that correctly implanted cemented stems are of great value in all ages and that uncemented stems are reliable in younger patients, what are the important biomechanical features that we must consider during the preoperative planning process?

Preoperative planning and templating may decrease iatrogenic complications such as leg length inequality, instability, incorrect implant sizing, pain and potentially therefore periprosthetic fractures (Alnahhal, Aslam-Pervez and Sheikh, 2019). Firstly, the detailed clinical assessment recorded in the out-patient clinic letter is scrutinised. The diagnosis, history of previous trauma or paediatric hip conditions, functional limitations, treatment to date and patient expectations should have been recorded. Risk factors for postoperative delirium, bleeding, thrombotic events and instability are noted. The current medical problems and treatments are recorded. The physical examination should commence with a general appreciation of the patient’s fitness to rehabilitate. The examination should exclude signs of infection, note previous scars and contractures, identify sources of leg length discrepancy and record neurovascular status. This permits consideration of soft-tissue releases, accommodation of previous incisions and metalware (possibly with the need to acquire prior operation notes and registry data) and anticipation of additional procedures. Both digital and acetate templating can be used. Using acetates applied to the viewing screen of a digital templating radiograph is also highly accurate and a viable alternative (Brew et al., 2012). Alternatiively digital templating with a templating marker allows for accurate scaling (Wimsey et al., 2006; Zhang et al., 2019). Using a systematic approach identifies the underlying condition (OA DDH, Perthes, Trauma, normal variants), the offset required, what change in leg-length is required and where the centre of rotation of both the femoral head and the acetabulum are situated and planned for. The position of intraoperatively identifiable anatomical structures are checked. The correct size and orientation of the implants is planned. The femoral canal geometry is noted.

This templating and planning process should be done well ahead of the day of surgery and once completed allows clear communication with the theatre team, implant company representatives and checking of implant inventories. Alternative operative reconstructive strategies are contemplated and mentally rehearsed well ahead of time and this permits a more fluid and less stressful operative workflow. This process is an excellent training discipline for junior surgeons. Furthermore, the preoperative template can then be used to compare the postoperative radiographs as a tool for audit and reflective practice.

In stance phase the centre of gravity is anterior to the S2 vertebra and posterior to the axis of the hip joints. The centre of gravity deviates as the torso moves with respect to the pelvis. The hip can be considered as a “first order lever” where the body weight moment is countered by the tension in abductor muscles. The joint reactive force (JRF) is the result of these two forces acting on the hip joint. The JRF varies depending on the patients’ activity. For example, the JRF is twice the patient’s body weight when they perform a straight leg raise and this in fact is a useful provocative diagnostic examination test in the out-patient clinic known as the Ling Test. The JRF varies during the gait cycle: at heel strike the JRF is 94% of total body weight, at mid-stance it is 345% of total body weight, at terminal stance phase it is 223% of total body weight and at toe off it is 80%. Thus there is considerable force acting on the hip joint during even simple activities of daily living and the correct restoration of hip biomechanics is crucial to minimise JRF and therefore wear (Terrier, Florencio and Rüdiger, 2014; Bonnin et al., 2011).

When considering common anatomical variants in bony hip morphology in coxa valga there is an increased neck/shaft angle, the tip of the greater trochanter lies lower than the centre of the femoral head and in a more medial position which thereby results in a shorter offset and abductor lever arm. The body weight lever arm remains unchanged but overall there is an increased JRF and more abductor force is required during swing phase. In coxa vara there is a decrease neck/shaft angle and the tip of the greater trochanter lies not only more lateral but also more distal than the centre of the femoral head. The abductor lever arm is increased but the abductor muscle length is less and therefore disadvantaged. There is a comparatively reduced JRF. In dysplastic hips, there may be a more proximal centre of hip rotation, a reduced abductor moment and a shortened abductor lever arm. The centre of rotation of the hip joint is more lateral and the body weight lever arm is increased. Global offset is the sum of femoral offset (centre of the femoral head to the midmedullary axis of the femur) and the acetabular offset (centre of the femoral head to the base of the acetabulum). Furthermore, increased femoral neck anteversion will reduce femoral offset.

The offset of the hip is therefore of great importance yet femoral offset can vary up to 4cm in individuals (Terrier, Florencio & Rüdiger, 2014). The centre of rotation of the acetabulum achieved during reaming and implantation of the acetabular component must be carefully considered along with femoral offset to achieve both the correct hip centre and global hip offset. When considering a femoral component, the resulting offset is a function of the offset of the stem component itself and that coming from the femoral head length. The next chapter of this thesis will examine the influence of femoral component offset on survivorship of THR with both cemented and uncemented stems.

CHAPTER TWO

Does the femoral offset affect total hip replacements? The results of a National Joint Registry

Reference: Wyatt, M., Kieser, D., Kemp, M., McHugh, G., Frampton, C. and Hooper, G. (2019). Does the femoral offset affect replacements? The results from a National Joint Registry. *Hip International May;29(3):289-298.* *https://doi.org/10.1177%2F1120700018780318*

Authors contributions:
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McHugh G – data analysis
Frampton C – statistical analysis and data retrieval from Registry
Hooper G – senior author, final editing

Abstract

Background

Femoral component offset influences the torque forces exerted on a femoral stem and may therefore adversely affect femoral component survival. This study investigated the influence of femoral component offset on revision rates for primary total hip replacements (THR) registered on the New Zealand Joint Registry (NZJR).

Methods

There were 106,139 primary THRs registered, resulting in 4,960 revisions for any cause. There were 46,242 THRs performed using the five commonest femoral components listed on the NZJR. A total of 41,100 were done for primary osteoarthritis of which 40,548 had all the offset information available for analysis. We defined low offset as <42mm, standard as 42-48mm and high offset as >48mm offset and examined revision rates according to the reasons for revision. We performed survival analyses for both cemented and uncemented femoral components grouped by the different offsets.

Results

The all-cause revision rate was 0.54/100cys. Stems with <42mm offset had a revision rate of 0.58/100cys (mean 0.58; 95%CI 0.53 to 0.63), 42-48mm offset 0.47 (95%CI 0.43 to 0.52) and >48mm offset 0.67 (95%CI 0.57 to 0.79).

There was no significant difference in all-cause revision rates between varying stem offsets in uncemented stems adjusting for age and gender. In cemented stems both high and low offset stems were more likely to be revised. Uncemented stems of all offsets were more likely to undergo revision for femoral fracture.

Conclusion

Femoral component offset affects the overall all-cause revision rate of the most commonly used cemented stem, but not uncemented stem designs. In cemented stems offset influences the rate of revision for loosening and periprosthetic fractures.

Introduction

Total hip replacement (THR) for hip osteoarthritis is one of the most successful and cost-effective operations in modern medicine (Garellick et al., 1998). THR is now performed in increasingly younger patients but this trend places growing demands on implant longevity. The most common mode of implant failure is aseptic loosening (Herberts and Malchau, 2000) primarily from osteolysis secondary to wear debris (Beksaç et al., 2009; Johanson et al., 2012; Kuzyk et al., 2011).

The femoral offset is defined as the horizontal distance between the neutral axis of the femur and the centre of the femoral head (Ling et al., 2010; Lecerf et al., 2009). It is an indicator of the abductor lever arm length, which, in principle, should be restored correctly in THR surgery to recreate normal anatomy and biomechanics. Restoration of the correct offset will, in theory, improve implant joint stability by optimising soft tissue tension and reducing the risk of impingement (Weber et al., 2014; Malik, 2007). Furthermore, the correct femoral offset should maximise the range of motion, abductor muscle strength (Tezuka et al., 2015) and decrease wear (Ling et al., 2010; Sakalkale et al., 2001).

Increasing the offset will increase the moment arm of the abductors which, in turn, reduces the abductor muscle force required during normal gait (Sariali et al., 2014). Secondarily, this reduces the transarticular hip forces (Davey et al., 1993) which should reduce articular surface wear. An association with trochanteric pain syndrome has also been described, however this is controversial (Ries, 2003; Sayed-Noor and Sjoden, 2006). An increased offset femoral component may also lead to increased bending moments and torsional forces in the proximal femur and potentially lead to premature failure of the femoral component by aseptic loosening (Thien and Kärrholm, 2010). However, it remains unknown how increased offset stems affect cemented or uncemented fixation in THR in the long-term. An increased femoral stem offset may potentiate earlier failure in cemented stems due to increased strain into varus and retroversion (Kleeman et al., 2003), but this is controversial (Davey et al., 1993).

A decreased offset of the reconstructed hip compared to the preoperative state can result from using a femoral component that has less offset than the anatomy of the patient, from using a more valgus femoral stem or from using a short-necked femoral component. In addition, acetabular malposition and excessive deepening and resultant medialisation can similarly reduce functional hip offset. Either way, a reduced functional hip offset decreases the abductor lever arm, increases joint reaction forces and increases the energy requirement for normal gait. This may manifest itself as an abductor lurch, limited range of motion and decreased stability.

The primary aim of this study was to examine the New Zealand Joint Registry (NZJR) to determine whether the offset of the femoral component affected the revision rates of primary THR and to compare the reasons for revision. The secondary aim was to determine whether this primary result was affected by the femoral component being cemented or not.

Materials and methods

We performed a retrospective cohort analysis of the 16 year results of the NZJR identifying primary THRs performed between 1 January 1999 and 31 December 2015 for osteoarthritis, ensuring a minimum 2 year follow-up. Our primary outcome measure was the all-cause revision rate for each of the stem types. The revision rates for the five most commonly implanted femoral stems which had both standard and high offset (CLS, Corail, Exeter V40, twinSys Cemented and twinSys Uncemented) registered on the NZJR, were compared. The addition of a collar to the Corail prosthesis to resist motion is unproven in finite element analysis (Al-Dirini et al., 2017) and we therefore did not examine the presence of a collar or skirted head as covariates. Using femoral component and head product codes, the true offset was measured explicity for each prosthesis, and revision rates were once again compared for low (< 42mm), standard (42 - 48mm) and high (> 48mm) offset groups.

Large metal-on-metal heads were excluded. A revision was defined as a new operation in a previous THR during which one of the components was exchanged, removed, manipulated or added. It included excision arthroplasty and amputation, but not soft tissue procedures. Bilateral THRs were considered independently for the purposes of this study.

The all-cause revision rate was chosen to provide the most conservative estimate of survivorship. The revision rate was expressed as the rate per 100-component-years (100cys) to give an average estimate of survival for each coupling, allowing for the variable number of years that each had been implanted. This estimate allows comparison of revision rates when analysing data with varying follow up times but does assume consistent revision rates over time. Kaplan-Meier survival curves and Cox-proportional hazards regression were therefore also performed to summarise the proportion of revision-free and to allow for confounders such as age at surgery, gender, surgical approach, surgeon volume, fixation and head size when comparing couplings.

The reason for revision as listed on the NZJR was compared between the couplings used and femoral offsets attained. Demographic data including age and gender as well as procedure specific data such as head size, fixation technique, surgical approach and surgeon volume were all compared between couplings using ANOVA and Chi-square tests as appropriate. All-cause revision rates were calculated with 95% confidence levels using a Poisson approximation. A p-value of less than 0.05 was deemed to be statistically significant.

Results

There were 106,139 primary THRs registered on the NZJR during the study period with 4,960 (4.7%) revision procedures performed on these implants, giving an overall revision rate of 0.74/100cys (0.72 to 0.76, 95% CI). 46,242 THRs were performed using the femoral components in question of which 41,100 were inserted for primary osteoarthritis and a study group of 40,548 of these had the offset information available for analysis combining both the femoral component and its associated head component.

Patient Demographics

There were no significant differences in gender distribution between implants used with 51.5% female and 48.5% male (Table 4). The mean age for patients in this study was 66.8 years (SD 10.6 years).

Table 4. Demographic data on THRs done for primary osteoarthritis.

Type of femoral stem			Sex F	Sex M	Total
	CLS	Count	2767	4220	6987
		%	39.6%	60.4%	100.0%
	Corail	Count	2489	2963	5452
		%	45.7%	54.3%	100.0%
	Exeter V40	Count	12254	9492	21746
		%	56.4%	43.6%	100.0%
	TwinSys cemented	Count	823	441	1264
		%	65.1%	34.9%	100.0%
	TwinSys uncemented	Count	2570	2565	5135
		%	50.0%	50.0%	100.0%
Total		Count	20903	19681	40584
		%	51.5%	48.5%	100.0%

Type of femoral stem	N	Mean age/yr	Std. Deviation	Minimum	Maximum
CLS	6987	59.16	9.141	18	92
Corail	5452	61.90	9.636	20	91
Exeter V40	21746	70.14	9.451	17	96
TwinSys cemented	1264	74.32	7.178	43	96
TwinSys uncemented	5135	66.38	10.859	19	94
Total	40584	66.80	10.596	17	96

Revision rates

The all-cause revision rate was 0.54/100cys. Stems with < 42mm offset had a revision rate of 0.58/100cys (mean 0.58; 95%CI 0.53 to 0.63), 42-48mm offset 0.47/100cys (95%CI 0.43 to 0.52) and > 48mm offset 0.67/100cys (95%CI 0.57 to 0.79) (Figure 4). Standard offset femoral components were significantly less likely to undergo revision than both small ($p = 0.002$) and higher offset stems ($p < 0.001$).

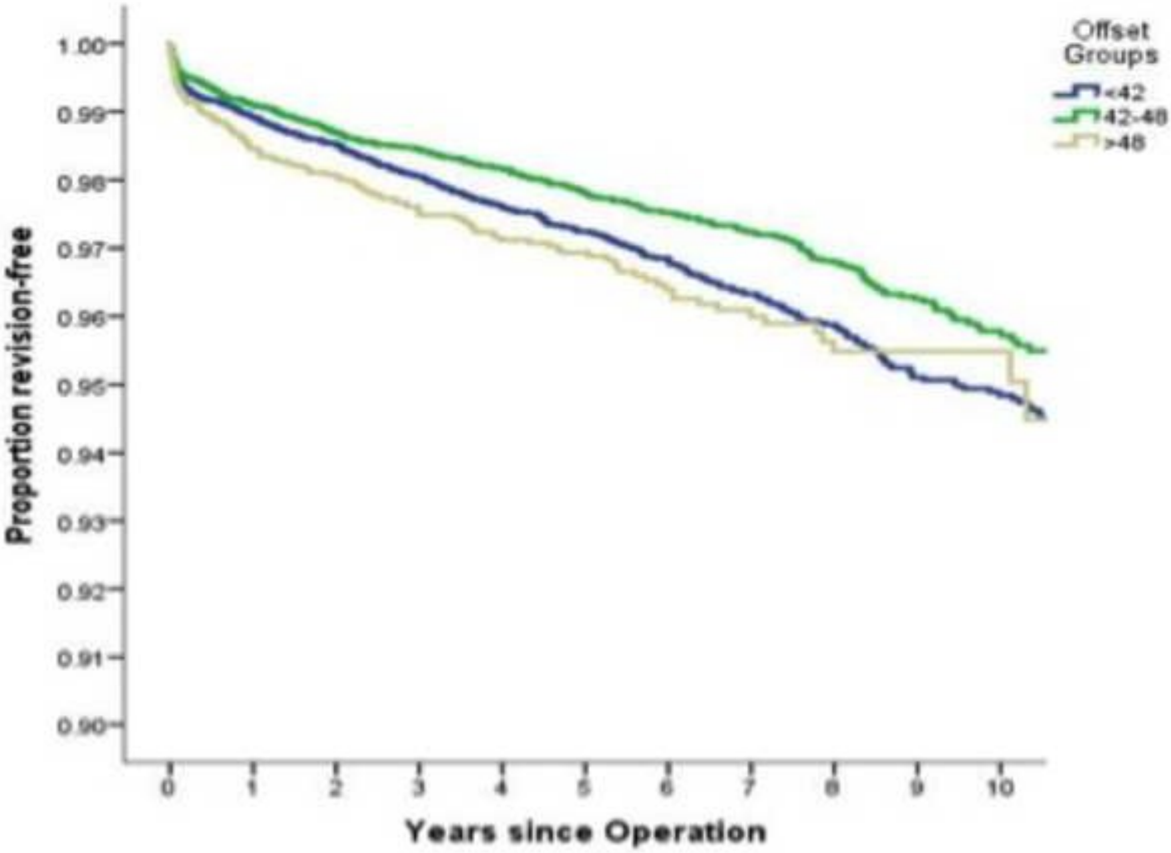


Figure 4. K-M curves for each offset overall

When examining uncemented and cemented stems there was no significant difference in all-cause revision rates between offsets in either groups in unadjusted analyses (Tables 5 and 6). However, when adjusting for gender and age while the uncemented group continued to show no difference across the various offsets, the cemented group had significantly higher rates of revision in low and high offset stems in contrast to standard offset stems (Tables 5 and 6). The all-cause survival for each stem type is shown in Kaplan-Meier plots in Figures 5-9.

Table 5. Influence of offset (mm) on revision rates in uncemented THR

		Unadjusted				Adjusted (age/gender)		
Offset group	Revision Rate/100py	Analysis of groups	HR	95%CI	P value	HR	95%CI	p value
<42mm	0.623	<42mm v >48mm	0.95	0.7-1.2	0.70	0.91	0.67-1.22	0.52
42-48mm	0.648	42-48mm v >48mm	0.96	0.7-1.3	0.78	0,94	0.69-1.3	0.69
>48mm	0.703	42-48mm v <42mm	1.01	0.8-1.2	0.88	0.86	0.86-1.25	0.69

Table 6. Influence of offset on revision rates in cemented THR.

		Unadjusted				Adjusted (age/gender)		
Offset group	Revision Rate/100py	Analysis of groups	HR	95%CI	P value	HR	95%CI	p value
<42mm	0.51	<42mm v >48mm	0.79	0.61-1.02	0.067	0.91	0.61-1.02	0.133
42-48mm	0.39	42-48mm v >48mm	0.61	0.48-0.77	0.000	0,94	0.48-0.77	0.000
>48mm	0.65	42-48mm v <42mm	0.77	0.64-0.94	0.011	0.86	0.63-0.94	0.012

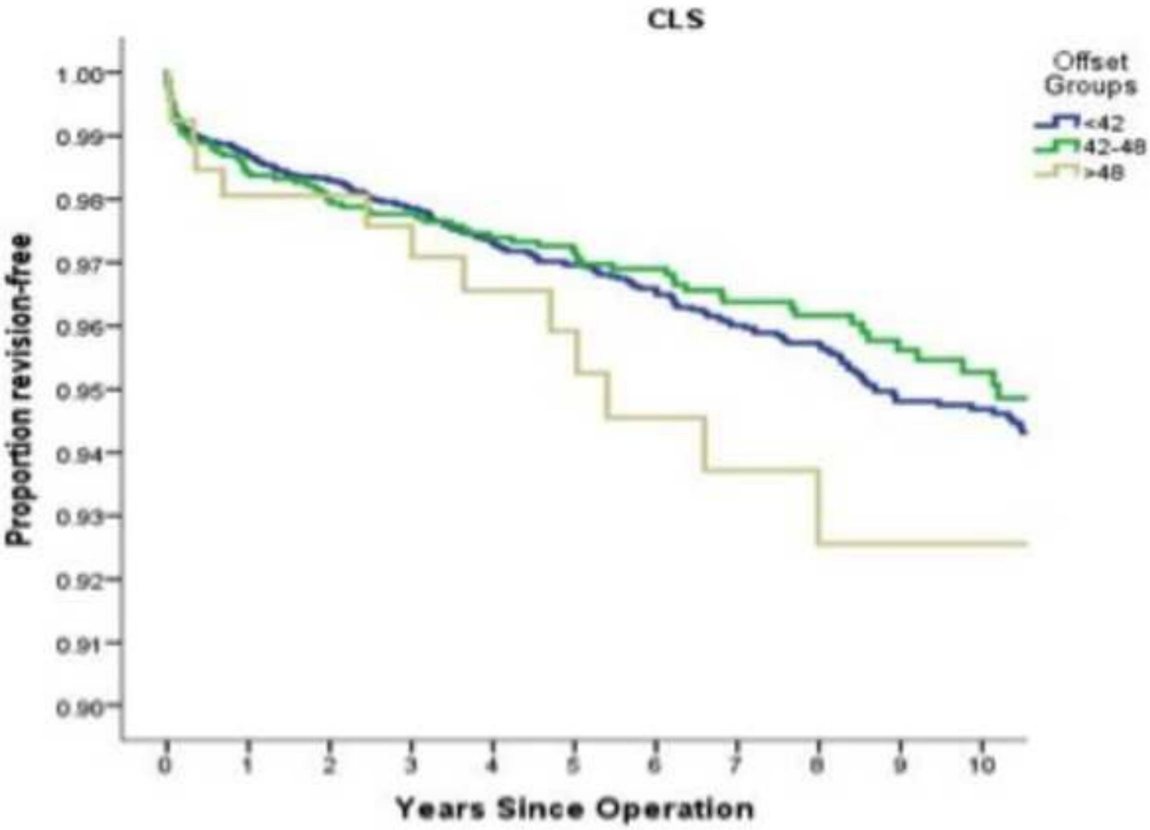


Figure 5. K-M curves for each offset in CLS uncemented stem

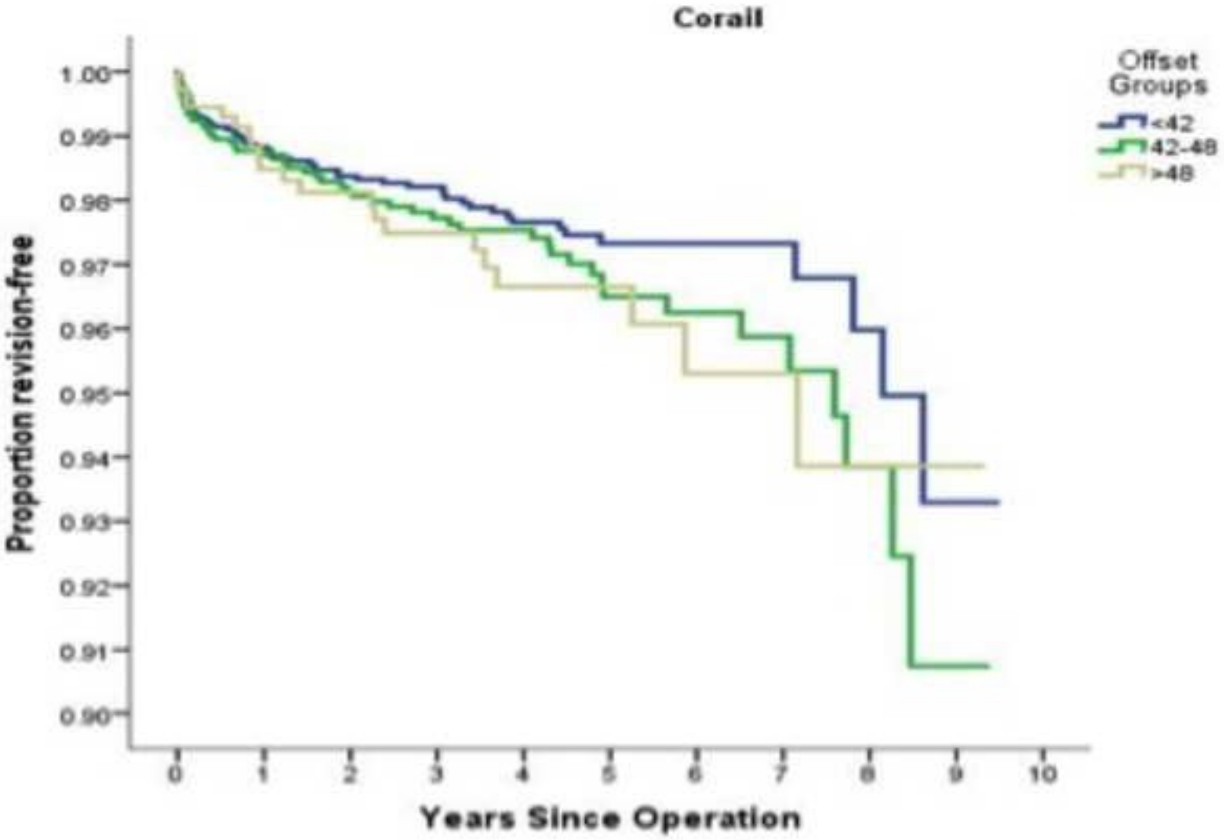


Figure 6. K-M curves for each offset in Corail uncemented stem

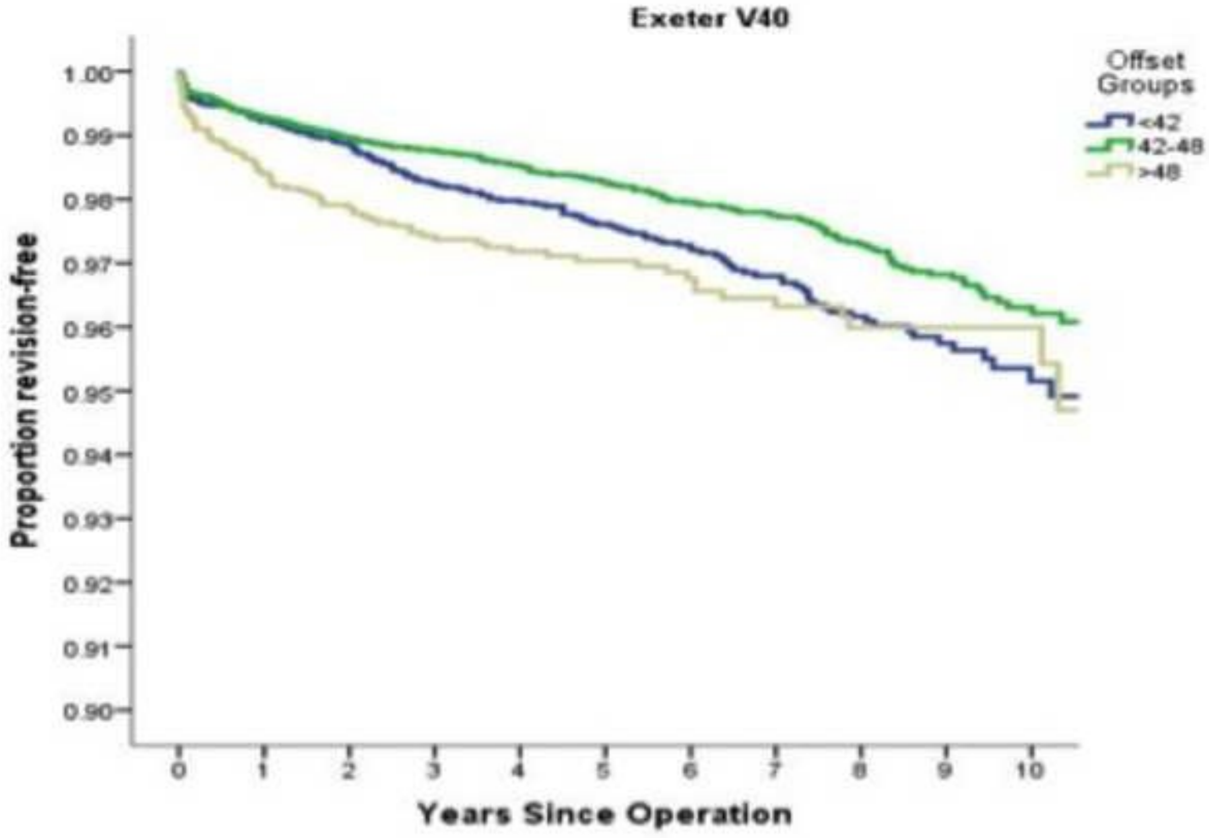


Figure 7. K-M curves for each offset in Exeter cemented stem.

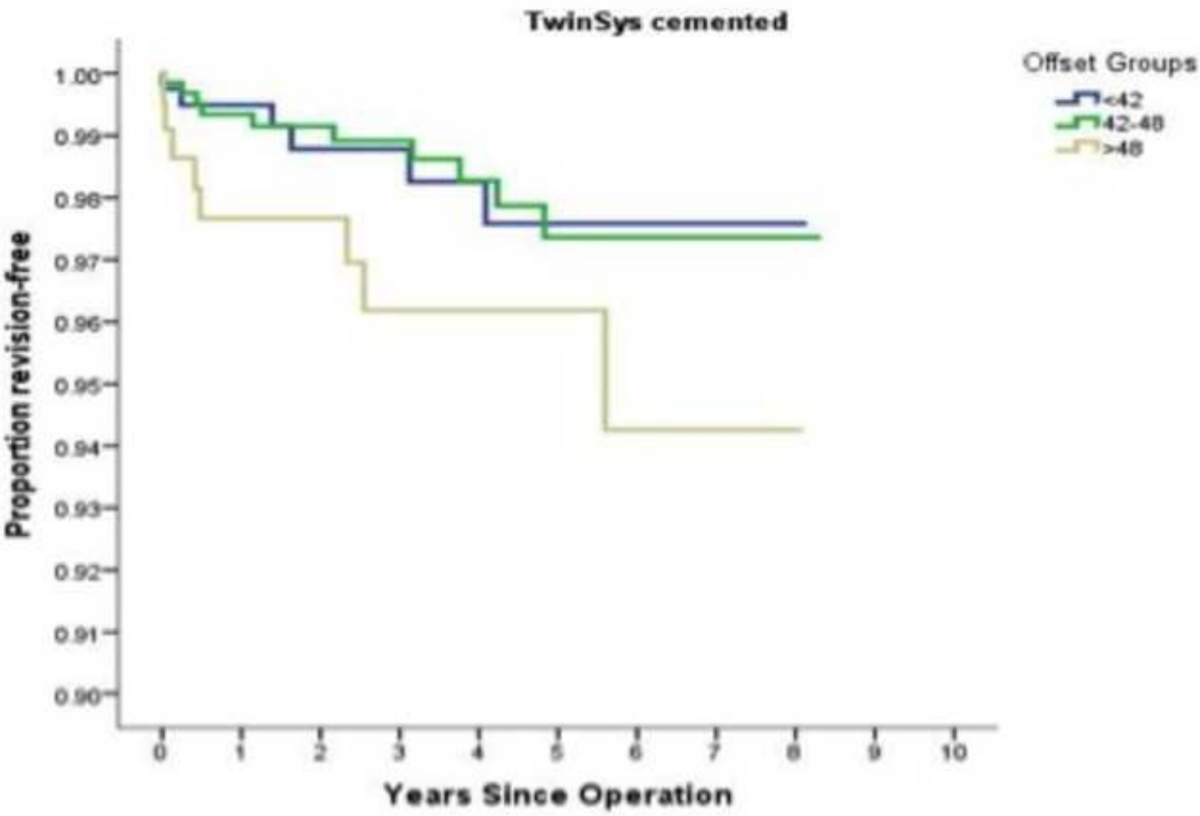


Figure 8. K-M curves for each offset in Twinsys cemented stem.

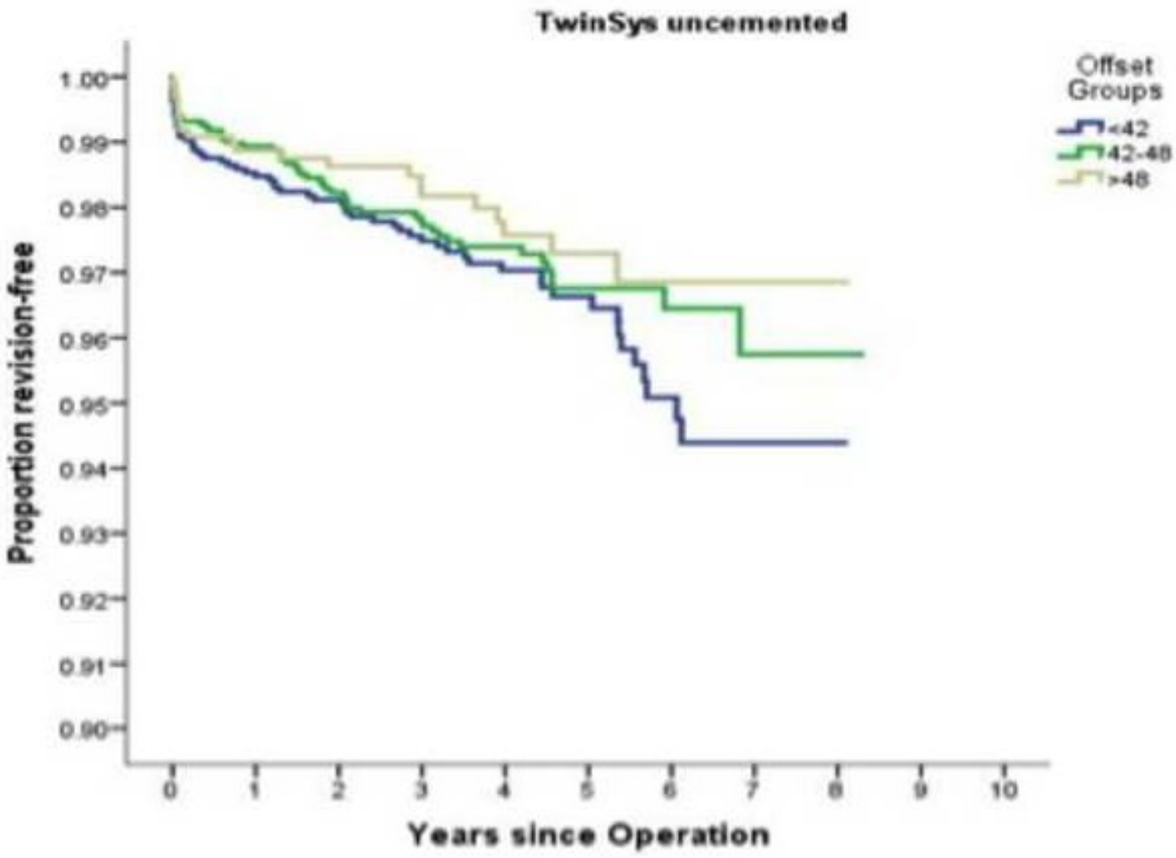


Figure 9. K-M curves for each offset in Twinsys uncemented stem.

Reason for revision

The most common revision performed was acetabular component revision. In the cemented stem group, cup revision was significantly less in those components with standard versus low offsets (Hazards ratio 0.551; 95%CI 0.366 to 0.829; p = 0.004). These differences were true in both unadjusted and analyses adjusted for age and gender alike. In the uncemented group there was no difference in the risk of acetabular component revision based on femoral component offset.

There was no significant difference in revision rates by offset for pain overall, or when sub-analysing cemented versus uncemented femoral components (Tables 7 and 8).

Table 7. Influence of offset on revision rates for pain in uncemented THR.

		Unadjusted				Adjusted (age/gender)		
Offset group	Revision Rate/100py	Analysis of groups	HR	95%CI	P value	HR	95%CI	p value
<42mm	0.072	<42mm v >48mm	1.41	0.49-3.96	0.52	1.13	0.39-3.29	0.82
42-48mm	0.077	42-48mm v >48mm	1.50	0.52-4.36	0.46	1.34	0.446-3.92	0.59
>48mm	0.051	42-48 v <42	1.61	0.63-1.81	0.81	1.18	0.63-2.05	0.55

Table 8. Influence of offset on revision rates for pain loosening in cemented THR

Unadjusted						Adjusted (age/gender)		
Offset group	Revision Rate/100py	Analysis of groups	HR	95%CI	P value	HR	95%CI	p value
<42mm	0.050	<42mm v >48mm	0.89	0.38-2.08	0.79	0.69	0.27-1.79	0.448
42-48mm	0.039	42-48mm v >48mm	0.71	0.32-1.58	0.41	0.62	0.27-1.44	0.267
>48mm	0.056	42-48 v <42	0.80	0.43-1.50	0.49	0.90	0.47-1.72	0.747

Revision for femoral periprosthetic fracture was higher in the uncemented group than the cemented group for all offset groups (Tables 9 and 10). The risk of revision for periprosthetic femoral fracture was 0.07/100cys (95%CI 0.06 to 0.08). However, when we examined the risk of revision for femoral fracture in cemented components high offset components (Hazards ratio 0.486; 95%CI 0.267 to 0.886, p = 0.019)) showed an increased risk of femoral fracture compared to standard components (Table 10). This was not observed in the uncemented group, where no significant differences in revision risk for fracture were observed amongst the offset groups (Table 9).

Table 9. Influence of offset on revision rates for periprosthetic femoral fracture in uncemented THR

		Unadjusted				Adjusted (age/gender)		
Offset group	Revision Rate/100py	Analysis of groups	HR	95%CI	P value	HR	95%CI	p value
<42mm	0.076	<42mm v >48mm	0.85	0.396-1.83	0.677	0.82	0.37-1.83	0.633
42-48mm	0.105	42-48mm v >48mm	1.11	0.51.2.42	0.797	1.11	0.50-2.42	0.798
>48mm	0.102	42-48 v <42	1.30	0.81-2.09	0.275	1.35	0.82-2.20	0.236

Table 10. Influence of offset on revision rates for periprosthetic fracture in cemented THR

		Unadjusted				Adjusted (age/gender)		
Offset group	Revision Rate/100py	Analysis of groups	HR	95%CI	P value	HR	95%CI	p value
<42mm	0.197	<42mm v >48mm	0.85	0.086-0.45	0.000	0.27	0.11-0.67	0.005
42-48mm	0.416	42-48mm v >48mm	1.11	0.23-0.74	0.003	0.49	0.27-0.88	0.019
>48mm	2.116	42-48 v <42	1.30	0.97-4.58	0.057	1.81	0.82-4.02	0.143

Revision rates for aseptic femoral component loosening were higher in uncemented femoral components than cemented components across all offset groups (Tables 11 and 12). Furthermore, offset did not influence aseptic femoral loosening revision rates in uncemented stems (Table 11). In the cemented group lower offset stems were revised more often compared to standard offset stems (Hazards ratio 0.321; 95%CI 0.15 to 0.736, p = 0.007) (Table 12).

Table 11. Influence of offset on revision rates for aseptic femoral stem loosening in uncemented THR

		Unadjusted				**Adjusted (age/gender)**		
Offset group	Revision Rate/100py	Analysis of groups	HR	95%CI	P value	HR	95%CI	p value
<42mm	0.067	<42mm v >48mm	0.89	0.37-2.12	0.789	1.07	0.44-2.62	0.885
42-48mm	0.098	42-48mm v >48mm	1.28	0.53-3.1	0.582	1.33	0.55-3.23	0.529
>48mm	0.077	42-48 v <42	1.44	0.87-2.38	0.149	1.25	0.74-2.01	0.404

Table 12. Influence of offset on revision rates for aseptic femoral stem loosening in cemented THR

		Unadjusted				Adjusted (age/gender)		
Offset group	Revision Rate/100py	Analysis of groups	HR	95%CI	P value	HR	95%CI	p value
<42mm	0.040	<42mm v >48mm	1.41	0.46-4.33	0.546	2.83	0.85-9.39	0.09
42-48mm	0.019	42-48mm v >48mm	0.66	0.21-2.05	0.473	0.91	0.29-2.85	0.87
>48mm	0.028	42-48 v <42	0.47	0.21-1.03	0.058	0.32	0.14-0.74	0.01

Revision for dislocation overall was 0.19/100cys (95%CI 0.17 to 0.21). Standard offset cemented femoral stems were significantly less likely to undergo revision for instability than high offset stems (Hazards ratio 0.59; 95%CI 0.399 to 0.872, p = 0.008). This is shown graphically in Figure 10.

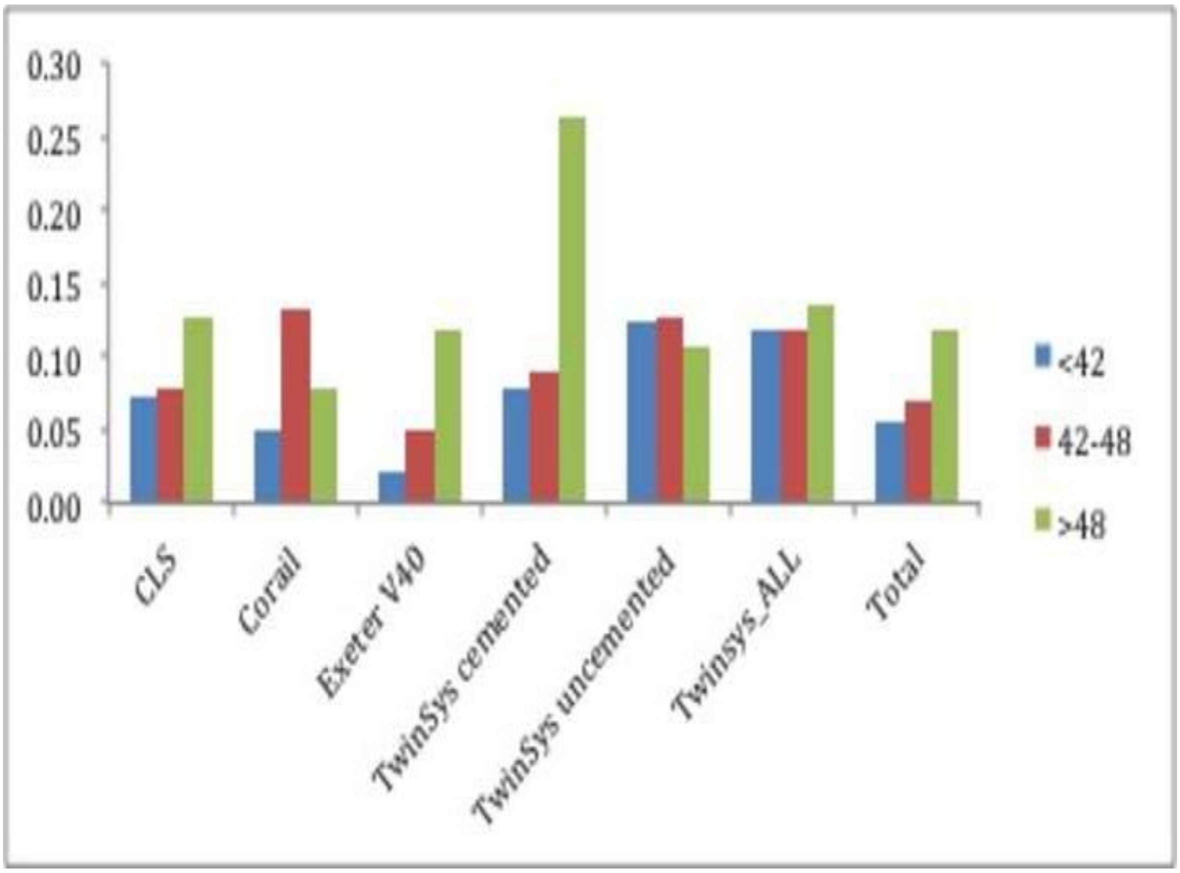


Figure 10. Revision rates for instability by offset for each femoral component

Discussion

Our study showed that in uncemented stems there was no significant difference in all-cause revision rates between varying stem offsets. However, in cemented stems both higher and lower offset stems were more likely to be revised than standard offset stems. This suggests that femoral component offset is potentially less critical in uncemented fixation.

When examining the causes of revision, lower offset cemented components had greater risk of revision for acetabular loosening than other offset classes. This may reflect the higher transarticular hip forces with a decreased offset with both higher torque forces applied to the acetabulum and increased wear. All uncemented stems were more likely to undergo revision for femoral fracture. We have previously reported on the revision for femoral fracture comparing cemented and uncemented stems where femoral fracture was much more likely to occur within the first year for the uncemented stem (Wyatt et al., 2014). This difference was not apparent after 1 year, with almost equal rates, suggesting that the early fracture rate was probably due to either perioperative fracture on stem insertion or subsidence secondary to stem undersizing. The difference in rates of periprosthetic fracture is unlikely to be due to the offset of the stem alone.

In our study both high and low offset cemented stems were at higher risk of revision than standard offset cemented stems, consistent with the results observed in the Swedish Hip Register (Thien and Kärrholm, 2010). For the higher offset stems the increased lever arm may potentiate abrasive wear between the stem and the cement mantle (Thien and Kärrholm, 2010; Harman et al., 2016). In a Norwegian Registry study, high offset cemented stems had a significantly greater risk of revision (relative risk 3.3; 95%CI 2.3 to 4.8) compared to standard offset stems ($p < 0001$) (Hallan et al., 2012).

The offset in uncemented stems did not show a correlation with risk of revision for aseptic femoral loosening in our study. This indicates that recreating the precise offset in uncemented THR may be less critical for the longer-term survival of the femoral component. This might be explained by higher offset cemented stems being more likely to be smaller sized stems than the uncemented equivalent (i.e. accommodated with the cement mantel), whereas in the uncemented component the femoral size is almost always reamed to accept the biggest stem size. In a study of the CLS, the uncemented stem 3-dimensional measurement of micromotions showed no difference between offsets which is in accordance with our findings (Fottner et al., 2011). Therefore, the concept that higher offsets, in uncemented components, cause excessive interface stresses could not be substantiated. Our findings also corroborate with those of Krushell and colleagues (Krushell, Fingeroth and Lehman, 2012), who examined a high offset hydroxyapatite-coated femoral implant in the revision scenario and found no evidence of aseptic loosening with this component. In the National Joint Registry study of England and Wales, Jameson and colleagues examined the Corail uncemented stem at 7.5 years follow-up (Jameson et al., 2013). They found no association with a higher revision rate and femoral offset.

The findings of our study did not show an increased rate of revision for pain in relation to femoral offset. This did not therefore extrapolate the functional results of Liebs and colleagues (Liebs et al., 2014) who showed a correlation between offset and pain after uncemented THR. However, our study only assessed revision for pain and therefore failed to identify pain scores in those not requiring revision. While it seems counter-intuitive that higher offset stems dislocated more than standard in cemented stems, the authors feel this reflects the common practice of increasing offset to achieve stability in those patients who are intraoperatively unstable and therefore there is a selection bias towards these patients. Furthermore, patients with a higher BMI may have larger offset stems as a strategy to reduced extra-articular soft-tissue impingement. Unfortunately, this registry study cannot determine implant alignment, leg length and soft tissue laxity to understand the cause of instability in these cases.

The strengths of this study relate to the quality data provided by the NZJR with a high capture rate of 98% across the whole country, and large data sets pertaining to THRs for the various femoral component offsets. This study is representative of a wide spectrum of Orthopaedic surgeons with varied clinical experience covering an entire nation. A potential weakness is that we have used all-cause revision as a surrogate marker for failure. This has the potential to not identify patients who are living with a painful hip, awaiting revision, or are too unwell for revision surgery. Furthermore, the NZJR does not include revisions for soft tissue procedures such as soft tissue tensioning and addressing trochanteric bursitis which are highly relevant to offset.

Whilst it has been suggested that restoring the correct offset and centre of hip rotation is advantageous, we have no information on whether this was achieved in our analysis. In our study the reason for offset chosen was not declared and the decision may have been done intraoperatively. One of the other differences between cemented and uncemented is stem positioning, and it may be easier to put a cemented stem in varus and thus increase offset than in an uncemented stem. Furthermore, the anteversion of the femoral component is not accounted for in our study. In cemented stems excessive cement stresses occur with highly anteverted stem positions as well as high offsets in finite element models (Harman et al., 2016). Some implant-related factors may be biased by other unknown influences. In uncemented stems the level of neck resection, for example, is much more critical than in cemented fixation. The level of neck resection can profoundly influence the flexibility to change the patient's offset intraoperatively without dramatic changes in leg length, anteversion and stability. One potential example may be that a THR operated on with a maximum femoral head length may represent a technically difficult case or one in which there was suboptimal preoperative templating.

Generally, surgeons select the offset based upon preoperative templating and intraoperative findings to reproduce leg length and offset. A large offset stem is often used if the hip was potentially unstable with the standard offset prosthesis. The limitations of a registry study preclude analysis of selecting standard offset stems in these patients, however surgeons should recognise a potentially higher revision rate, particularly in cemented higher offset components, and incorporate this knowledge into decision making when planning THR surgery.

Conclusion

This retrospective study of the New Zealand Joint Registry has identified that femoral component offset has an association with the overall all-cause revision rate of the most commonly used cemented stem, but not uncemented stem designs. This may be because the biomechanics become more critical with the additional interface of cement. In addition, this may be confounded for example by surgeon preference for a particular implant fixation. Furthermore, despite the risk of loosening and femoral fracture being higher in uncemented stems, only in cemented stems was offset associated with the rate of these complications.

Commentary

Critique

In this chapter the influence of the femoral component offset and how this affects the overall THR survivorship especially with cemented fixation was examined. This study suggests that accurate restoration of the correct femoral offset becomes of great importance when using cemented stems. In the previous chapter however, we acknowledge that the methodology of analysing a large observational data set precluded insight into whether templating occurred or not and there is potentially confounding in comparing cemented and uncemented stems using a proportional hazards model. We also did not have precise information on what the patients' true offsets were preoperatively. In addition, the data did not include soft tissue procedures such as fascia lata release which may have been performed to address trochanteric pain associated with increased femoral offset after THR. Finally, the anteversion of the stems inserted was not ascertained and this affects the functional offset. However, such imprecisions may have reasonably been countered by the large number of THR in the analysis and the nationwide capture of the dataset. In addition, regression modelling may have improved the strength of the results and conclusions drawn.

Up-to-date literature search

The following databases were searched from 2018 to 27.3.2020 using the programme Papers: ACM, ADS, arXiv, CERN DS, CrossRef DOI, DBLP, Espacenet, Google Scholar, Gutenberg, Highwire, IEEExplore, Inspire, JSTOR, OAIster, Pubget, PubMed, ScienceDirect, Scopus and Web of Science. Search terms related to: Offset, Total hip.

51 references were identified of which 2 were collected as potentially relevant. Articles that cited the study described in this chapter were examined. Journals with impact factors <2 were excluded. Any correspondence relating to the article described in this chapter was reviewed.

There were no other publications that examined the effect of femoral component offset on THR outcomes. One study compared short uncemented stems and standard length stems and suggested that whilst femoral offset was increased postoperatively in both groups there was less of an increase with the short stem group (Erivan et al., 2020).

Chapter 2 identified that both the Exeter V40 and the Twinsys cemented stems had lower revision rates for periprosthetic femoral fractures compared to uncemented stems. Palan et al., 2016 examined the National Joint Register for England, Wales and Northern Ireland and discerned that the type of cemented stem also influenced the rate of revision for periprosthetic fracture. In adjusted analyses controlling for age, gender and ASA grade, the CPT cemented stem had a hazards ratio of 3.89 (95% CI 3.07 to 4.93) compared to the Exeter V40 cemented stem. There was no significant difference between the Exeter V40 and the C-stem whilst the Charnley had a hazards ratio of 0.41 (95%CI 0.24 to 0.7) compared to the Exeter. Chatziagorou, Lindahl and Kärrholm (2019), examined the Norwegian Joint Arthroplasty Register and showed that the Exeter stem had a higher risk of Vancouver B (i.e.periprosethtic femoral fractures within the bed of the stem) fractures compared to the Lubinus cemented stem but not other fracture types.

Overall from Chapter 2 it is apparent that the offset of cemented stems is important for THR survivorship yet how important is cemented stem length? The increased indications for THR in younger patients and the higher risk of revision in this population provided the rationale for considering bone-preserving stems, able to transmit the load to the proximal femur, to avoid stress-shielding and thigh pain. Bone loss in revision THR is challenging and therefore strategies to preserve bone stock and/or facilitate femoral stem revisions such as using cement-in-cement revision or femoral impaction grafting are worthy of consideration.

Interestingly the cemented Exeter short stem, which is an identical design to the conventional Exeter stem except being 125mm rather than 150mm in length has shown promising results in the Austrarian National Joint Replacement Registry. This stem applies the same Exeter polished taper-slip philosophy and provides proximal femoral loading given the transferred hoop stresses through the low modulus cement mantle which may preserve not only proximal bone but also the femoral isthmus potentially providing options for revision in the longer term (Choy et al., 2013). Connor et al., 2016 reviewed a database of CT images of femora to evaluate the risk of the distal tip of the femoral rasp contacting the endosteal cortical surface. Standard rasps were significantly more likely to have the rasp in contact with the endosteal surface of the cortex and in theory such broach contact may compromise the cement mantle thickness. Short stems therefore may be suitable for a greater range of femoral anatomy, preserve bone and reduce proximal stress-shielding. In the next Chapter we will examine the NZJR experience of the Exeter short cemented stems compared to the standard 150mm Exeter stem.

CHAPTER THREE

How do cemented short Exeter stems perform compared to standard length Exeter stems? The experience of the New Zealand National Joint Registry.

Reference: Wyatt, M., Poutawera, V., Kieser, D., Frampton, C. and Hooper, G (2020). How do cemented short Exeter stems perform compare to standard length Exeter stems? The experience of the New Zealand National Joint Registry. *Arthroplasty Today 6;104-111. https://doi.org/10.1016/j.artd.2020.01.003*

Authors contributions:
Wyatt M – inception, data analysis, writing the paper, lead author
Poutawera V – editing the paper
Kieser D – writing the paper
Frampton C – statistical analysis and data retrieval from Registry
Hooper G – senior author, final editing

Abstract

Background

The standard Exeter cemented stem is 150mm long with standard offsets ranging from 37.5mm to 56mm. Exeter short stems of 125mm are also available in the offsets of 37.5mm, 44mm and 50mm. In addition smaller (125mm and shorter) Exeter cemented stems with offsets of 35.5mm or less are available. The aim of this study was to examine the New Zealand Joint Registry (NZJR) comparing survival rates and functional outcomes of standard-length stems with short Exeter stems of various offsets in patients undergoing primary total hip replacement (THR).

Methods

Using the New Zealand Joint Registry we reviewed the results of three separate groups of patients with Exeter stems. Patients with standard 150mm length Exeter stems (Standard), were compared with those with short 125mm stems with regular 37.5mm, 44mm, 50mm offsets (Short 37+) and short ≤ 125mm stems with offsets 35.5mm and below (Short 37-). The demographic data, preoperative diagnosis, patient reported outcome measures and reasons for revision were compared between groups. Kaplan-Meier survival analysis, Cox multi-variate regression analysis and proportional hazards ratios were used to examine implant survival and the influence of stem group on revision rates adjusting for gender, age and surgical approach.

Results

There were 43,427 Exeter cemented stems registered in the NZJR between 1st January 1999 and 31st May 2018: 1,501 were Short 37-, 657 Short 37+ and 41,269 Standard stems. In all three groups the posterior surgical approach was preferred (Short 37- 76.6%; Short 37+ 94.7%; Standard 76.1%; $p < 0.001$). In the Short 37- group, 94.1% were female whilst in the other two groups there was an equal gender ratio ($p < 0.001$). The Short 37- group was also significantly younger than the other two groups with 41.6% under 65 years of age compared to Short 37+ (37.2%) and Standard groups (36.9%) ($p < 0.01$). There was no difference in ASA grade between

groups. Body Mass Index (BMI) was significantly higher in the both the Short 37- and Short 37+ groups compared to Standard group (Short 37- 29.09, SD 7.07; Short 37+ 29.69, SD 6.67; Standard 28.71, SD 5.72; $p < 0.001$). The all-cause revision rate for standard stems was 0.55/100cy (95% CI 0.52 to 0.58). The Short 37- group had a higher rate of revision compared to the Standard group (Hazard Ratio 1.60 (95% CI 1.30 to 1.98; $p < 0.001$) whilst the Short 37+ group had a hazard ratio of 0.84 (95%CI 0.38 to 1.88; $p = 0.674$) compared to the Standard group.

The differences in Oxford Hip Scores between groups at 6 months were statistically significant (Standard 40.29, SD 7.61; Short 37+ 39.11, SD 7.83; Short 37- 39.28, SD 8.14; $p = 0.018$) and maintained at 5 years for Standard versus Short 37- stems (Standard 42.21, SD 7.06; Short 37- 40.2, SD 8.39; $p = 0.003$). However, these differences were below the mean clinically important difference for this functional score.

Conclusion

At 20 years there was a significant difference in all-cause revision rates with standard length Exeter stems out-performing short stems with offsets 35.5mm or less. Short stems with offsets of 37.5mm or greater performed similarly to standard length stems.

Key words: Exeter, short stem, registry, offset, survivorship, function

Introduction

Total hip replacement (THR) for hip osteoarthritis is one of the most successful and cost-effective operations in modern medicine (Garellick et al., 1998). THR is now performed in increasingly younger patients but this trend places growing demands on implant longevity. In New Zealand the Exeter stem is the most commonly used cemented femoral component and has been for the last 20 years.

The Exeter stem was first introduced in 1970 and despite small modifications the essential collarless, polished, dual tapered design has endured. This design transmits compressive load into circular hoop stresses which are then transmitted into the surrounding low modulus cement mantle and subsequently the surrounding bone (Ling et al., 2010). The standard Exeter stem is 150mm in length and is available in 37.5mm, 44mm, 50mm and 56mm offsets. To address smaller femoral canals such as those of the Asian population, patients with juvenile arthritis or hip dysplasia the 35.5mm offset 125mm long “CDH stem” was introduced in 2001. In addition, stems with smaller offsets of 33mm (115mm long) and 30mm offset (95mm long) were produced (Figure 11). Despite concerns about insufficient mechanical strength and premature stem breakage in short stems (Thien and Kärrholm, 2010) a recent study from the Australasian Orthopaedic Association National Joint Registry showed that at 7 years there was no significant difference in survival rates between standard length Exeter stems and short stems of offsets of 35.5mm or less (Choy et al., 2012). However, this study did not address how Exeter 125mm short stems of offsets 37.5mm, 44mm and 50mm, introduced in 2011, compared in terms of function or survivorship. Small changes in implant designs can lead to dramatic clinical failures (Thien and Kärrholm, 2010), (Rockborn and Olsson, 1993) therefore the performance of smaller Exeter stems of various offsets must be proven to at least be the equivalent of the established standard length stem.

Figure 11. Short and standard length Exeter cemented stems. Left to right: 95mm length with 30mm offset, 115mm length with 33mm offset, 125mm length with 35.5mm offset, 150mm length with 37.5mm offset

The purpose of our study was to examine the New Zealand Joint Registry (NZJR) to investigate the long-term survivorship of Exeter short stems (≤ 125mm) of offsets 37.5mm, 44mm and 50mm (Short 37+ group) with Exeter short stems (≤ 125mm) of offsets ≤ 35.5mm (Short 37- group) compared to Standard length Exeter stems (Standard).

Methods

Data source

The NZJR was established in 1998 and has a > 96% data capture rate of all joint replacement surgeries. Prospective entry of data into the NZJR is a mandatory requirement of all members of the New Zealand Orthopaedic Association with all data secured in Christchurch, New Zealand. One of the authors (CF) accessed the database to acquire data specifically for this study. Deidentified data of all patients undergoing primary THR from the NZJR inception to 31st May 2018 was available for analysis. We performed and reported this study in accordance with STROBE and RECORD guidelines (Benchimol et al., 2015).

Ethical approval

No formal Institutional Review Board (IRB) approval was required as this was a review of the NZJR which already has IRB approval for publication of results stored in its registry.

Patient demographics and diagnosis

We collected the following patient demographics: age, gender, Body Mass Index (BMI), American Society of Anesthesiologists class (ASA) and preoperative diagnosis. These factors were then compared between the three groups.

Operative cohort

We identified all Exeter stems used and divided these into three groups: Standard 150mm length Exeter stems (Standard), Short 125mm stems with offsets 37.5mm or greater (Short 37+) and Short ≤ 125mm stems with offsets 35.5mm and below (Short 37-). The surgical approach used in each of the three groups to access the hip was also examined.

Outcome measures

(i) Revision rates

We examined the all-cause rates of revision between study groups with revision recorded as the rate/100 component years (cy) with 95% confidence intervals. We define observed component years as the number of registered primary procedures multiplied by the number of years each component has been in place. The revision rate/100cy is equivalent to the yearly revision rate expressed as a percentage and is derived by dividing the number of prostheses revised by the total observed component years multiplied by 100. This estimate allows the comparison of revision rates when examining implant data with varying follow-up times but does assume consistent revision rates over time.

A revision was defined as a new operation in a previous THR during which one or more of the components was exchanged, removed, manipulated or added. It included excision arthroplasty and amputation, but not soft tissue procedures. The all-cause revision rate provides the most conservative estimate of prosthesis survivorship. In addition, we examined the reasons for revision and compared them within each group, in particular we examined revisions for stem-related reasons such as fracture and aseptic loosening.

(ii) Functional outcome scores

We examined the Patient Reported Outcome Measures (PROMs) collected from patients at 6 months and at 5 years post arthroplasty (Oxford 12 scores). This validated score consists of twelve domains which address pain, function and activities of daily living. Within each domain a score of 0 is the worst, whilst 4 is the best. The overall best possible total score is 48 and the worst is 0. These questionnaires were completed by the patients without medical assistance. In the first four years of the NZJR all patients were invited to complete these questionnaires and did so with a compliance rate of 70%. Since this time 28% of patients have been randomly selected and PROMs distributed to this group to ensure a 20% return rate.

Statistical analysis

All-cause revision rates were expressed as rate/100cy with 95% confidence intervals. Hazard ratios with 95% confidence intervals were examined and Kaplan-Meier survival analysis performed. Subsequently, Cox multi-variate regression analysis was used to examine the influence of stem group on all-cause revision rates and revisions due to stem-related failures such as aseptic loosening and fracture adjusting for gender, age, and approach. The Oxford 12 scores were compared between study groups using an ANOVA.

Funding

No funding was received for this study.

Results

There were 43,427 Exeter cemented stems reported in the NZJR between 1st January 1999 and 31st May 2018. There were 1,501 Exeter short stems with offsets of 35.5mm and below (Short 37-), 657 Exeter short stems with standard i.e. 37.5mm, 44mm and 50mm offsets (Short 37+) and 41,269 standard length stems (Standard).

Patient demographics and diagnosis

The Short 37- group was significantly younger than the other two groups with 41.6% under 65 years of age (mean 65.71, SD 12.97) compared to 37.2% (66.95, SD 10.96) (Short 37+ group) and 26.9% (69.97, SD 10.14) (Standard group) ($p < 0.01$). There was also a significantly higher proportion of female patients in the Short 37- group (1412; 94.1% female: 89; 5.9%; $p < 0.001$) whilst the gender distribution was equally split in both the Standard and Short 37+ groups.

Osteoarthritis was the primary diagnosis in 87.6% in the Standard group, 93.8% in the Short 37+ group and 79.3% in the Short 37- group. The proportion of patients undergoing THR for dysplasia was higher in the Short 37- group (6.9%) whilst it was only 1.5% and 1.1% in the Short 37+ and Standard groups respectively. The distribution across the other diagnoses was similar between the three groups (Table 13). There was no significant difference in ASA class between the groups however BMI was significantly higher in the both the Short 37- and Short 37+ groups compared to the Standard group (Short 29.09, SD 7.07; Short 37+ 29.69, SD 6.67; Standard 28.71, SD 5.72; $p < 0.001$).

Table 13. Comparison of diagnoses for patients undergoing primary THR for each of the three groups of Exeter stems

			Diagnosis										
			Osteoarthritis	Rheumatoid arthritis	Other Inflammatory	Acute fracture NOF	Post dysplasia	Old fracture NOF	Post dislocation	Avascular necrosis	Tumour	Other	Total
Short/ standard stem	Short	Count	1191	36	20	70	103	21	6	51	25	49	1501
		%	79.3%	2.4%	1.3%	4.7%	6.9%	1.4%	0.4%	3.4%	1.7%	3.3%	100.0%
	Short 37+	Count	616	2	2	13	10	3	0	17	1	8	657
		%	93.8%	0.3%	0.3%	2.0%	1.5%	0.5%	0.0%	2.6%	0.2%	1.2%	100.0%
	Standard	Count	36144	567	224	2061	364	566	76	1178	252	872	41926
		%	87.6%	1.4%	0.5%	5.0%	0.9%	1.4%	0.2%	2.9%	0.6%	2.1%	100.0%
Total		Count	37951	605	246	2144	477	590	82	1246	278	929	43427
		%	87.4%	1.4%	0.6%	4.9%	1.1%	1.4%	0.2%	2.9%	0.6%	2.1%	100.0%

Operative cohort

In all groups the posterior approach was the preferred surgical approach (Short 37- 76.6%; Short 37+ 94.7%; Standard 76.1%; $p < 0.001$). The distribution of femoral offsets used in our study is shown in Table 14.

Table 14. Distribution of femoral component offsets (mm) between groups of Exeter cemented stems

			Offset							Total
			30	33	35.5	37.5	44	50	56	
Short/standard stem	**Short**	Count	12	13	1476	0	0	0	0	1501
		%	0.8%	0.9%	98.3%	0.0%	0.0%	0.0%	0.0%	100.0%
	Short 37+	Count	0	0	0	245	326	86	0	657
		%	0.0%	0.0%	0.0%	37.3%	49.6%	13.1%	0.0%	100.0%
	Standard	Count	0	0	0	9061	27094	5010	95	41260
		%	0.0%	0.0%	0.0%	22.0%	65.7%	12.1%	0.2%	100.0%
Total		Count	12	13	1476	9306	27420	5096	95	43418
		%	0.0%	0.0%	3.4%	21.4%	63.2%	11.7%	0.2%	100.0%

All-cause revision rates and reasons for revision

The overall all cause revision rate for all Exeter stems at a maximum of approximately 19 years follow-up (289980.9cy) in the NZJR was 0.56/100cy (95%CI 0.53 to 0.59). The all-cause revision rate for standard stems was 0.55/100cy (95% CI 0.52 to 0.58). The low offset short stem (Short 37-) group had a higher rate of revision compared to the Standard group (all cause revision rate 0.92/100 cy (95%CI 0.74 to 1.13; Hazard Ratio 1.60 (95% CI 1.30 to 1.98; $p < 0.001$) whilst the Short 37+ group had an all cause revision rate of 0.80/100cy (95%CI 0.25 to 1.65; hazards ratio of 0.84 compared to the Standard group (95%CI 0.376 to 1.88; $p = 0.674$). These results are displayed in Figure 12.

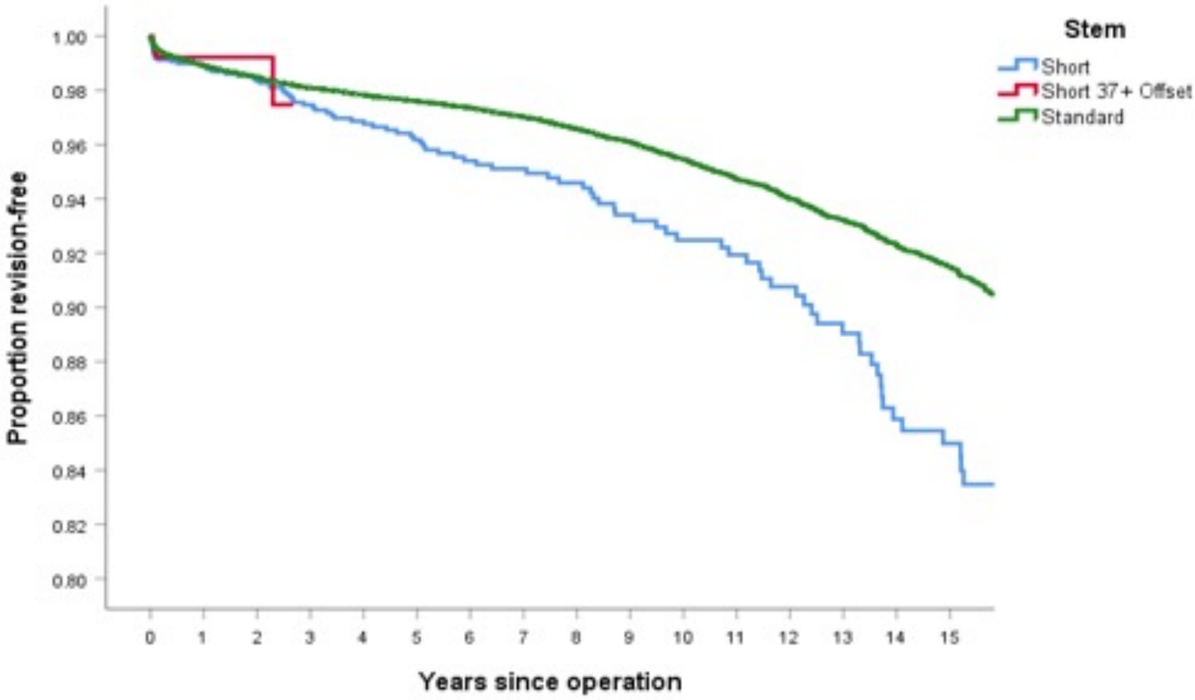


Figure 12. Kaplan-Meier survivorship curve of all-cause revision free survival rates compared between Exeter cemented stem groups

The comparison between groups of reasons for revision are shown in Table 15. There was a higher proportion of deep infection in the Short 37+ group and this is not attributed to the characteristics of this stem (5 deep infection, 83.3% of revisions in this group) whilst in the Standard group the most common cause of revision was instability (458, 29.9%) and in the Short 37- group it was acetabular loosening (39, 42.4%). Aseptic loosening of the femoral component was not seen in the Short 37+ group compared to 7.9% in the Standard group and 1.99% in the Short 37- group (Table 15; Figure 13).

Table 15. Comparison of reasons for revision between groups

Reason for Revision									
			Loosening Acetab	Loosening Fem	Dislocation	Pain	Deep Infection	Fracture Femur	Aseptic Loosening
Short/standard stem	**Short 37-**	Count	39	18	17	11	8	5	51
		%	42.4%	19.6%	18.5%	12.0%	8.7%	5.4%	55.4%
	Short 37+	Count	0	0	0	1	5	0	0
		%	0.0%	0.0%	0.0%	16.7%	83.3%	0.0%	0.0%
	Standard	Count	408	110	458	135	250	202	484
		%	26.6%	7.2%	29.9%	8.8%	16.3%	13.2%	31.6%
Total		Count	447	128	475	147	263	207	535
		%	27.4%	7.9%	29.2%	9.0%	16.1%	12.7%	32.8%

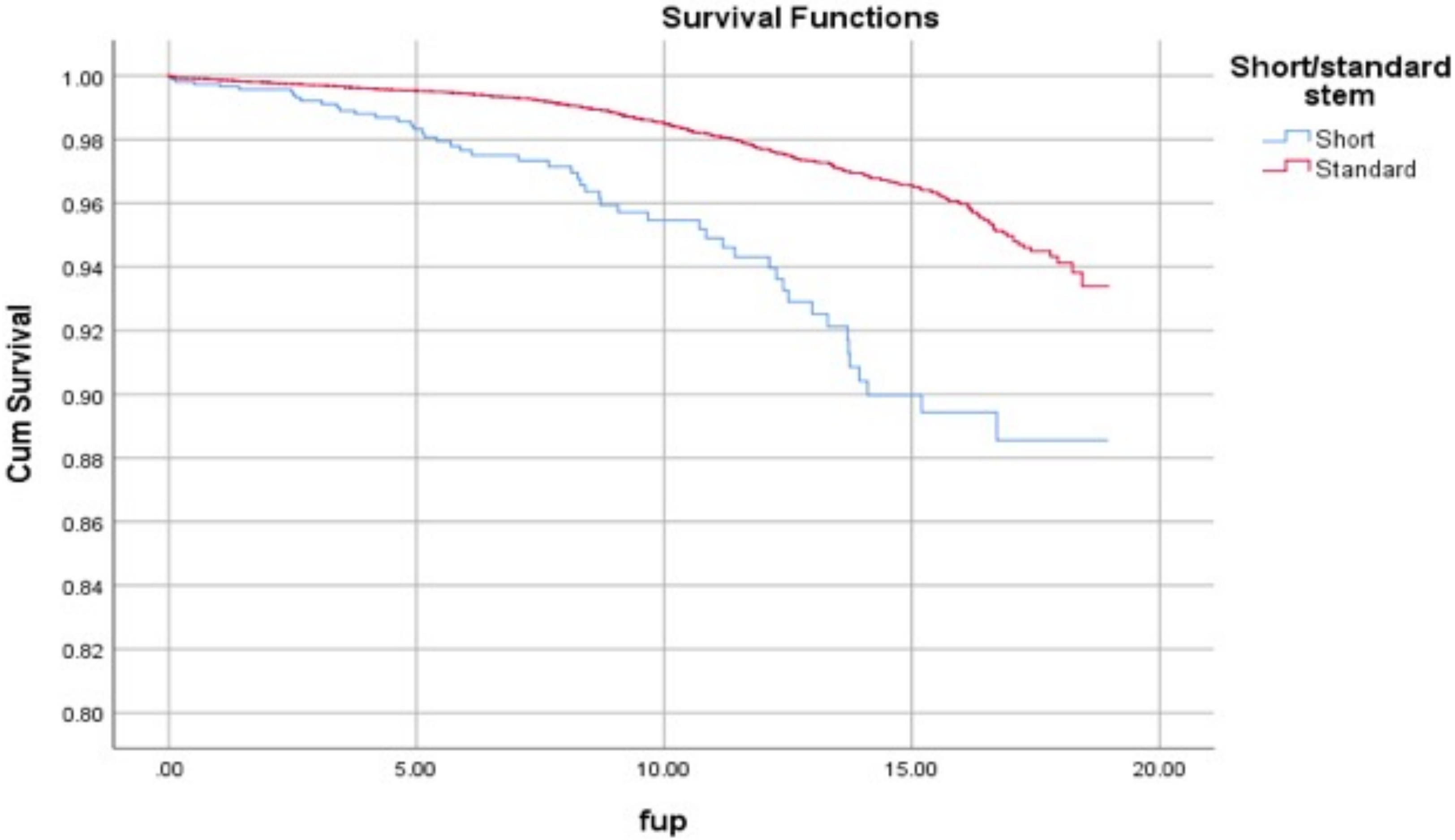


Figure 13. Kaplan-Meier survivorship curve of revisions of aseptic loosening compared between Exeter cemented stem groups. Given insufficient numbers in the Short 37+ group was excluded.

Cox multivariate regression analysis of all-cause revision rates is shown in Table 16. When regression analysis of all-cause revisions was performed, and adjustments made for gender, age and approach in the model, the statistically significant difference in revision rate between the Short 37- and the Standard groups persisted (Hazard Ratio 1.55 (95% CI 1.23 to 1.95; $p < 0.001$) (Table 16).

Table 16. Cox multivariate regression analysis (all cause revision rates)

	B	SE	Wald	df	Sig.	HR	95.0% CI for HR	
							Lower	Upper
Short/standard stem			15.167	2	0.001			
Standard stem v Short	0.439	0.116	14.472	1	0.000	1.552	1.237	1.946
Standard stem v short 37+	-0.350	0.449	0.605	1	0.437	0.705	0.292	1.701
Sex Female	-0.201	0.053	14.577	1	0.000	0.818	0.738	0.907
Age			78.441	3	0.000			
Age <55 v 55-64	-0.347	0.082	17.740	1	0.000	0.707	0.601	0.831
Age <55 v 65-74	-0.598	0.079	56.870	1	0.000	0.550	0.471	0.642
Age <55 v >=75	-0.686	0.087	62.297	1	0.000	0.503	0.425	0.597
Approach			6.705	3	0.082			
Approach Anterior v Posterior	-0.071	0.126	0.322	1	0.570	0.931	0.727	1.192
Approach Anterior v Lateral	-0.222	0.135	2.696	1	0.101	0.801	0.614	1.044
Approach Anterior v Troch-Osteo	0.265	0.464	0.327	1	0.568	1.303	0.525	3.235

Stem survival for aseptic loosening is displayed graphically in Figure 12. When the regression analysis focused on aseptic loosening as a cause of revision (Table 17), aspetic loosening was significantly higher in the Short 37- group compared to the Standard group (Hazards Ratio 2.72; 95%CI 2.04 to 3.633, $p < 0.001$) and this remained significant even after adjusting for age, gender and approach (Hazards Ratio 2.429, 95%CI 1.76 to 3.35, $p < 0.001$). There was no significant difference between Short 37- and Standard groups in both unadjusted comparisons (Hazards ratio 0.66; 95%CI 0.27 to 1.59, $p = 0.353$) and adjusting for age, gender and surgical approach (Hazards ratio 1.122; 95%Ci 0.41 to 3.07, $p = 0.82$).

Table 17. Cox regression analysis of stem revisions for aseptic loosening

	B	SE	WALD	DF	SIG.	HR	95.0% CI FOR HR	
							LOWER	UPPER
SHORT V STANDARD STEM	0.887	0.164	29.350	1	0.000	2.429	1.762	3.349
SEX	-0.114	0.094	1.489	1	0.222	0.892	0.743	1.072
AGEGRPS			45.064	3	0.000			
AGEGRPS(1)	-0.133	0.138	0.935	1	0.334	0.875	0.669	1.146
AGEGRPS(2)	-0.467	0.136	11.793	1	0.001	0.627	0.480	0.818
AGEGRPS(3)	-0.988	0.169	34.001	1	0.000	0.372	0.267	0.519
APPROAC			11.791	3	0.008			
APPROAC(1)	-0.506	0.183	7.645	1	0.006	0.603	0.421	0.863
APPROAC(2)	-0.329	0.196	2.826	1	0.093	0.720	0.490	1.056
APPROAC(3)	0.494	0.604	0.670	1	0.413	1.639	0.502	5.348

Functional outcome scores

The Oxford scores were significantly higher in the Standard group compared to the Short 37- group at both 6 months and 5 years. The Oxford score was also significantly higher in the Standard group compared to the Short 37+ group at 6 months. There was insufficient data for statistical analysis of the Short 37+ group at 5 years. The magnitude of the differences between groups was small and is unlikely to represent clinically relevant effects (Table 18).

Table 18. Oxford functional scores compared between groups at both 6 months and at 5 years

		Short	Short 37+	Standard	Total	
Oxford Score 6m	Mean	39.28	39.11	40.29	40.25	**p=0.018**
	Std. Deviation	8.14	7.83	7.61	7.63	
	Minimum	5	15	0	0	
	Maximum	48	48	48	48	
	N	378	72	9957	10407	
Oxford Score 5 years	Mean	40.20		42.27	42.21	**p=0.003**
	Std. Deviation	8.39		7.01	7.06	
	Minimum	14		5	5	
	Maximum	48		48	48	
	N	106	0	3614	3720	

Discussion

The results of this study show that the use of the Exeter stem for primary hip replacement in New Zealand provides excellent function and survivorship at 20 years. According to the most recent NZJR report overall primary hip replacements have an all-cause revision rate of 0.72/100cy (95%CI 0.71 to 0.74) therefore the Exeter stem overall, with a revision rate 0.56/100cy (95%CI 0.53 to 0.59), is a positive outlier for survivorship (7). Our results also show that patients who received a short Exeter stem with an offset 35.5mm or less were significantly younger and more likely female than those who received a standard-length Exeter stem. This lower offset group, perhaps predictably, also had a higher prevalence of dysplasia. We cannot comment on patient ethnicity from our study, nor the precise nature of femoral geometry. In our study the posterior approach was the preferred approach for implanting the Exeter stem and on multivariate analysis the surgical approach did not affect revision rates. The Exeter short stems of offset 35.5mm or less were significantly more likely to undergo revision compared to standard length Exeter stems. Short Exeter stems with regular 37.5-50mm offsets also had a higher revision rate compared with standard length stems, however it should be noted that the reasons for revision varied between groups and if deep infections were excluded the Short 37+ group displayed similar results to the Standard group. When we examined revisions for stem-related reasons the Short 37-stem had a higher likelihood of failure for aseptic loosening compared to standard Exeter stems. There was no difference between groups when examining revisions for stem fracture. This is noteworthy as one might suspect that a short Exeter cemented stem with a higher offset might have an increased varus moment that potentiates its failure by either aseptic loosening or fracture. There were no implant breakages. Whilst Oxford scores were superior in the Standard Exeter cemented stem group the difference observed is below the mean clinical important difference for this outcome measure and this clearly limits the clinical significance of this statically significant result.

In the Australian NJR study at 7 years there was no significant difference in survivorship rates between short stems with offsets less than 35.5mm (3.4% revised; 95%CI 2.4 to 4.8%) compared to standard length Exeter stems (3.5%; 95%CI 3.3 to 3.8%) (Choy et al., 2012). This contrasts with the findings of our study where the standard-length Exeter stems had lower revision rates in the NZJR (Figure 12). In the Australian NJR, short stems with offsets of 37.5mm, 44mm and 50mm were not included, however, our study's results suggest that these newer stems behave more like the standard-length Exeter stems. The findings of our study compliment a recent study that showed that low offset cemented femoral component offset was associated with a higher risk of revision (Wyatt et al., 2018). Moreover, the offset and shape of the proximal stem may be more critical than stem length with the cemented Exeter as rotational stability is provided by the proximal body (Wilson et al., 2012).

In this study cohort we have combined the standard-length Exeter Universal stems grouped with V40 stems of standard length. The Exeter Universal stem was introduced in 1988 and proved highly successful. With aseptic loosening as an endpoint the first 325 hips implanted demonstrated a 100% femoral component and 90.4% acetabular component survivorship (Carrington et al., 2009). As there were no published differences of altered survivorship with the change from the Universal to the V40 Exeter stems we feel that this combination is justified for the purpose of this study (Westerman et al., 2018).

This study is a retrospective analysis of prospectively, systematically and consecutively collected registry data with a > 96% capture rate. The revision rate of the Exeter stem is low therefore large datasets are needed to provide adequate statistical power for an intelligible comparison. Over 40,000 Exeter stems were available for the analysis provided in our study, which we feel substantiates this as an important and pertinent study. However, the study is limited by the relatively low numbers of Exeter stems ≤ 125mm length. The study is representative of a wide spectrum of Orthopaedic surgeons with varied clinical experience covering an entire nation. The inclusion of 43,427 Exeter cemented stems is the largest comparative series of Exeter short and standard length stems to our knowledge.

National Joint Registry data can support evidence-based practice, implant surveillance, hospitals, surgeons and PROMs. They can also identify subtle trends, which would not be logistically feasible through other methods. Such trends can be then investigated through other scientific means (Konan and Haddad, 2013). We were unable to allow for possible confounders such as severity of joint disease or the precise and increasing complexity of patient comorbidities or medications. We have used age and ASA as proxy indicators for comorbidities with the rationale that these are the best indices in recent research (Ondeck et al., 2018). All-cause revision rates do not capture patients too unwell to undergo revision surgery or for whom the joint replacement may be functioning poorly. The decision to revise a THR depends on patient factors such as comorbidity and choice, surgical factors such as perceived risk/benefit analysis, surgical skills and departmental resources. Furthermore, the NZJR does not include revisions for soft-tissue procedures. Moreover, no radiographic comparisons have been made in our study cohort and therefore we cannot critique cementing technique or implant alignment. The anteversion of the femoral stem is not accounted for in our study and excessive cement stresses can occur with highly anteverted stem positions in finite element models (Harman et al., 2016).

Shorter Exeter cemented stems were introduced to address femora which were either smaller or had fluted or narrower internal geometries. Accurate preoperative templating will allow the surgeon to predict the need for a shorter stem in most cases. During surgery the perceived inability to gently pass the larger T-handled fluted reamer can indicate that a short stem may be required. Whilst a short, low offset stem is undoubtedly desirable in order to recreate native hip biomechanics in dysplastic or small femora, the results of our study suggest that an Exeter stem of offset 37.5mm or greater should be used if possible.

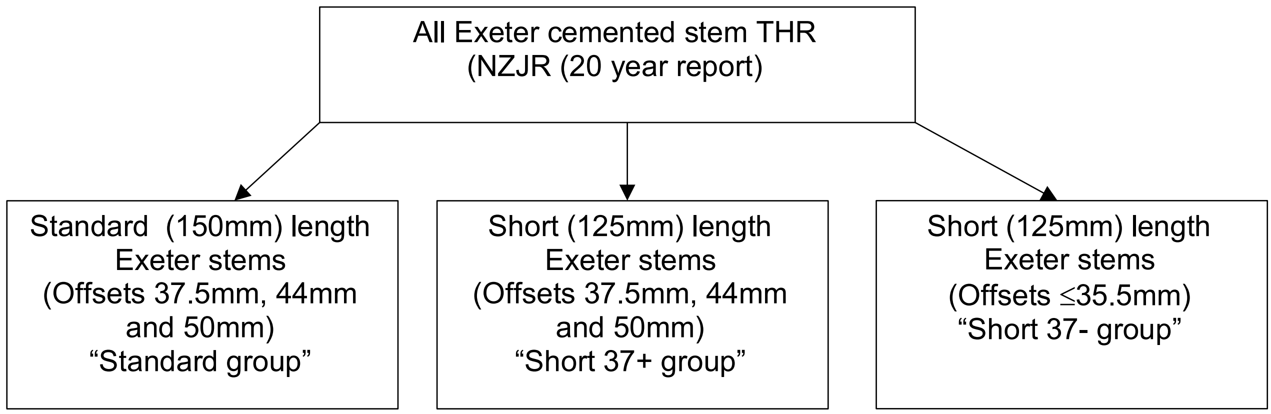
Conclusion

At 20 years there was a significant difference in all-cause revision rates with standard length Exeter stems out-performing short stems with offsets 35.5mm or less. In contrast, short stems with offsets of 37.5mm or greater performed similarly to standard length stems. This information should allow surgeons to council their patients accordingly.

Commentary

Critique

The previous Chapter showed that in the NZJR the Exeter short cemented stems with the most common offsets (i.e. 37.5, 44 and 50mm) had survivorships comparable to the standard-length Exeter stems with the same offsets. To clarify the three groups examined in this study a schematic diagram is shown below.



This study suggests that the length of the Exeter cemented stem *per se* is not the critical determinant of survivorship and that the short 37+ Exeter stems behave similarly to the standard Exeter stems. The findings in Chapter 2 indicated that femoral offset was an important factor in cemented stem survorship and we did not model this directly in Chapter 3 which is a potential weakness; instead we subdivided the Exeter stems into three categories i.e. we did not model for offset itself as a continuous variable in our analysis. In chapter 2 both low and high offset cemented stems were at greater risk of all-cause revision yet in chapter 3 this risk was attributed to the lower offset group only. In the previous Chapter we examined the Exeter cemented hip only whilst in Chapter 2 other cemented designs were included in the analysis. The study can also be criticised as there were no baseline Oxford hip scores which is therefore a potential confounder when comparing Oxford hip scores at 6 months and at 5 years between groups. Despite the methodology used and adjustments made during the analysis the influence of patient factors especially age and underlying diagnosis such as hip dysplasia may be highly pertinent to the observed results.

Up-to-date literature search

The following databases were searched from 2018 to 30.3.2020 using the programme Papers: were searched on 30.3.2020: ACM, ADS, arXiv, CERN DS, CrossRef DOI, DBLP, Espacenet, Google Scholar, Gutenberg, Highwire, IEEExplore, Inspire, JSTOR, OAIster, Pubget, PubMed, ScienceDirect, Scopus and Web of Science. Search terms related to: Short stem AND cemented AND Total hip.

25 references were identified of which 6 were collected as potentially relevant. Two articles that cited the study described in this chapter were examined. Journals with impact factors <2 were excluded. Any correspondence relating to the article described in this chapter was reviewed. There was no correspondence nor recent similar studies comparing cemented short stems to standard length cemented stems. Despite the potential weaknesses the Chapter 3 study does highlight the excellent results of Exeter cemented stems in the hands of many surgeons across the whole of New Zealand and therefore has high external validity.

Short stems with uncemented fixation have been compared to standard length uncemented stems (Giardina et al., 2018). In this Registry study from 2000 to 2016 short stems were defined as less than 12cm in length and were compared with conventional ones. The short stems were then classified according to the classification of Feyen and Shmimin 2014. Short stems were found to have been implanted into younger patients in this study. Similar to the results shown in Chapter 3 there were comparable survival rates in the short and conventional length stems and survival rates were >90% at 15 years (Giardina et al., 2018). Uncemented short stems therefore can achieve reliable long-term survival and longer-term studies will elucidate whether this applies to cemented short stems as well.

Let us now consider that 42% of patients presenting to an Orthopaedic surgeon with osteoarthritis of the hip have bilateral disease (Stavrakis, SooHoo and Lieberman, 2015). Should patients with bilateral hip disease receive single anaesthetic bilateral THR (SABTHR) and if so, what protocol should be followed? The potential advantages of SABTHR are a shorter overall anaesthetic time, shorter total length of hospital stay, quicker overall recovery, lower costs and a more expeditious recovery of function (Della Valle et al., 2003). However the key issue of contention in performing especially cemented SABTHR remains safety (Tsiridis, Pavlou and Charity, 2008) and specifically whether early mortality rates are increased. The next Chapter will focus on the 40-year experience of cemented Exeter stems in the context of SABTHR to address these questions.

CHAPTER FOUR

Is single anaesthetic bilateral total hip replacement using cemented femoral components safe and appropriate in specialist arthroplasty centres? A review of four decades of experience from Exeter

Reference: Wyatt, M.*, Charity, J.*, Jameson, S., Whitehouse, S., Wilson, M. and Gie, FG. (2018). Is single anaesthetic bilateral total hip replacement using cemented femoral components safe and appropriate in specialist arthroplasty centres? A review of four decades of experience from Exeter. *Hip International* 29(5):468-474

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Gie GA – senior author, final editing

Abstract

Symptomatic bilateral hip osteoarthritis can be surgically treated with either staged or single anaesthetic bilateral total hip replacement (BTHR). Today the younger, fitter patient with severe bilateral hip disease, the typical candidate for BTHR, is more likely to receive cementless rather than cemented implants. We present the Exeter experience of single anaesthetic bilateral fully cemented and hybrid THR performed through the posterior approach and, to our knowledge, the largest prospective single-centre series.

We performed a cohort study of all patients (319 patients: 638 hips) having BTHR at our institution between December 1977 and December 2015. No case was lost to follow-up. Data was collected prospectively but reviewed retrospectively. Lengths of stay and complication rates were assessed. Locally collected data were compared with Hospital Episode Statistics (HES) data for the operations carried out between March 2005 and June 2014 to confirm local database validity.

The rates for mortality, deep vein thrombosis (DVT), non-fatal myocardial infarction (MI) within 6 months were each 0.3% (1 episode) and non-fatal pulmonary embolism (PE) 0.6% (2 episodes). There were no intraoperative periprosthetic fractures or any readmissions within 30 days. Our study shows a low risk of complications when performing fully cemented and hybrid BTHRs for appropriately selected patients and the risk of complications compares favourably with published results. Overall complication risks of the single procedure are half that of the two operations otherwise required.

Introduction

Surgical management options of bilateral hip osteoarthritis comprise staged or single-anaesthetic bilateral total hip replacement (BTHR), the latter having been first described by Charnley (Stavrakis, SooHoo and Lieberman, 2015; Jaffe and Charnley, 1971). Advocates of BTHR over staged operations assert the benefit of a single anaesthetic providing shorter overall anaesthetic time, length of hospital stay and recovery period. A 30% saving in cost and further cost-savings for the patient from the perspective of time off work have been shown with BTHR (Della Valle et al., 2003). Those recommending staged operations may prefer the standard protocol of a unilateral procedure, avoiding the more prolonged surgical time of a BTHR. On the other hand, from the patient's perspective are the significant advantages of not having to face a second anaesthetic and major procedure along with its known risks. The key issue of debate in performing BTHR appears to be safety (Tsiridis, Pavlou and Charity, 2008; Haverkamp et al., 2010).

The National Joint Registries of England and Wales, Norway, Sweden, Australia and New Zealand all show an increasing trend for cementless fixation, particularly in younger, fitter patients who are the typical candidates for BTHR (Wyatt et al., 2014). A number of studies using cementless hip replacements have compared BTHR with staged procedures. These studies show, in general, excellent functional results and no difference in risk of complications and mortality between groups but show a higher transfusion risk with BTHR (Parvizi et al., 2006; Kim, Kwon and Kim, 2009; Hooper et al., 2008). Although studies reporting on cemented BTHR are uncommon, cemented BTHR has been performed at our institution since 1977, becoming routinely performed in selected cases since 1991. The aim of this study therefore was to examine whether cemented BTHR is safe and efficacious at our institution and how this method compared with published results in the literature.

Patients and Methods

Subjects of this study

The hip research team at the Princess Elizabeth Orthopaedic Centre, formerly the Princess Elizabeth Orthopaedic Hospital, has been collecting data prospectively from every elective hip arthroplasty patient prior the first BTHR, performed in December 1977. We searched our unit's database, patient records and hospital electronic record systems for all consecutive cases of BTHR until December 2015. Data was reviewed and analysed retrospectively. The database identified 319 patients (638 THRs) who received BTHR.

We offered BTHR to patients aged 70 years or younger with American Society of Anesthesiologists (ASA) grade 1. Early in the series BTHR was selectively offered to fit and healthy patients irrespective of age. The perioperative management of these patients has evolved over four decades of practice. Our current practice mandates that all patients undergo thorough preoperative assessment, led by specialist nursing staff, in a specific outpatient clinic at one to 2 weeks prior to surgery and includes consultation with a hip surgeon. A consultant anaesthetist is available to review cases on request in advance of surgery. Prior to the introduction of this clinic (April 2009) patients were admitted the night before surgery with an anaesthetic assessment that evening on the ward. The anaesthetic technique most commonly used in this series was an epidural blockade and sedation, enabling top-up analgesia requirements for the first 36 to 48 hours and mobilisation the day following surgery. In the last 5 years spinal anaesthesia combined with either general anaesthesia or sedation, along with periarticular local anaesthetic infiltration, has become the technique of choice, allowing all patients to start mobilisation from the first postoperative day and still providing adequate analgesia. Blood conservation measures of intravenous tranexamic acid (15mg/kg IV) at the time of induction of anaesthesia and use of a cell salvage system have been incorporated as routine practice for the last 5 years. This is in keeping with the recommendations of recent studies (Babis et al., 2011; Lindberg-Larsen et al., 2013; Rasouli et al., 2014). The transfusion threshold depends on an individualised assessment that takes into account preoperative haemoglobin levels, but largely is of a haemoglobin level of 80 g/l. Since 1995, thromboprophylaxis has included mechanical prophylaxis (foot or calf pumps), early mobilisation, prophylactic use of low molecular weight heparin starting 6 hours postoperatively and continuing for 6 weeks following surgery, either with the same drug or oral anticoagulation. Prior to this, thromboprophylaxis comprised of TED stockings, aspirin or hydroxychloroquine in combination with mobilisation.

Surgical care

The first 4 patients (8 hips) received a monoblock matt surfaced Exeter stem (Howmedica) with the remainder receiving a polished modular Universal Exeter stem (Stryker Orthopaedics, Mahwah, NJ) The type of socket fixation (cemented or uncemented) varied according to surgeon preference. All operations were performed by a consultant level surgeon or an arthroplasty fellow / senior registrar under direct supervision. The more symptomatic side was replaced first.

Routine practice is to inform the anaesthetist when cement is about to be introduced into the acetabulum or femur. In the acetabulum, thorough high pressure irrigation is performed and the bony surface then dried, prior to hand insertion and then pressurisation of the cement. On the femoral side, specific technical measures to minimise embolic potential are high pressure saline irrigation and suctioning of the canal prior to each instrumentation (Timperley and Whitehouse, 2009). Before the cement gun nozzle is introduced, the canal is suctioned by a small diameter catheter and is cleaned and dried with ribbon gauze. (Until January 2015, the ribbon gauze was routinely soaked in 1.5% hydrogen peroxide solution for all primary THRs at our institution. However, due to regulations set by The Medicines and Healthcare products Regulatory Agency [MHRA 2014], peroxide has since been replaced by 0.9% saline solution.) The suction catheter is left in position until blocked by the retrograde insertion of cement, when it is removed. As soon as the canal is full of cement, it is pressurised as per modern practice, followed by insertion of the implant to the planned and trialled position required to restore the anatomy of the hip.

Postoperative care and follow-up

Patients followed a uniform perioperative care pathway. Follow-up was routinely made in the outpatient department at 6 to 8 weeks postoperatively, which included an aftercare physiotherapy review, and then at 6 months, 2 years, 5 years and every 5 years thereafter for clinical and radiographic assessment (The Exeter Hip. 40 years of innovation in total hip arthroplasty, 2010).

Outcome measures

Data collected prospectively included: age at operation; diagnosis; operating surgeon grade; duration of in-hospital stay; mortality at 6 months; cardiorespiratory and thromboembolic complications at 6 months; periprosthetic fractures; 30 day readmission rates and reasons for revision up to the most recent follow-up. The extended time point of 6 months after surgery for assessment of mortality, cardiorespiratory and thromboembolic complications was chosen to ensure enough time for complete recovery and return to usual activities for the entire cohort, considering the difference in rehabilitation protocols from the initial cases in the series to our current practice. National Health Episode Statistics (HES) data were used to capture complications that may have been missed by the local database or occurred elsewhere. HES data was available from March 2005 to June 2014 and matching was carried out using anonymised datasets linking age, sex and operation date. We were able to apply this to 240 patients (75% of the cohort) having their complication rates also captured by HES, serving as a validation tool for data obtained from our institution.

Statistical analysis

Demographics and complication rates were calculated. Data was analysed using SPSS for Windows (version 23, SPSS Inc., IBM Corporation, Armonk, New York).

Results

The mean age in the study group was 58.6 (range 21-83; 95% Confidence Interval (CI) 57.3 to 59.8) years. BTHR was performed infrequently before the senior author was appointed as consultant to the Hip Unit in 1991, as shown in Figure 14. Diagnoses for each hip are shown in Table 19. There were 32 different surgeons recorded as first surgeon, 16 of which were consultant level. All operations were either performed by a consultant level surgeon or a senior registrar / arthroplasty fellow under direct supervision. A total of 319 patients were included for review, with no BHTR exclusions. A fully cemented THR was used in 412 hips (65% of series) and a hybrid combination in 226 hips (35%). Although the majority of patients underwent standard primary procedures, five patients had at least one side performed as a complex or revision procedure (Table 20). The median length of stay for the overall series was 7.0 days (range 3 to 49, interquartile range (IQR) 5), decreasing to a median of 5.0 days in the last 5 years (range 3 to 11, IQR 2) (Figure 15).

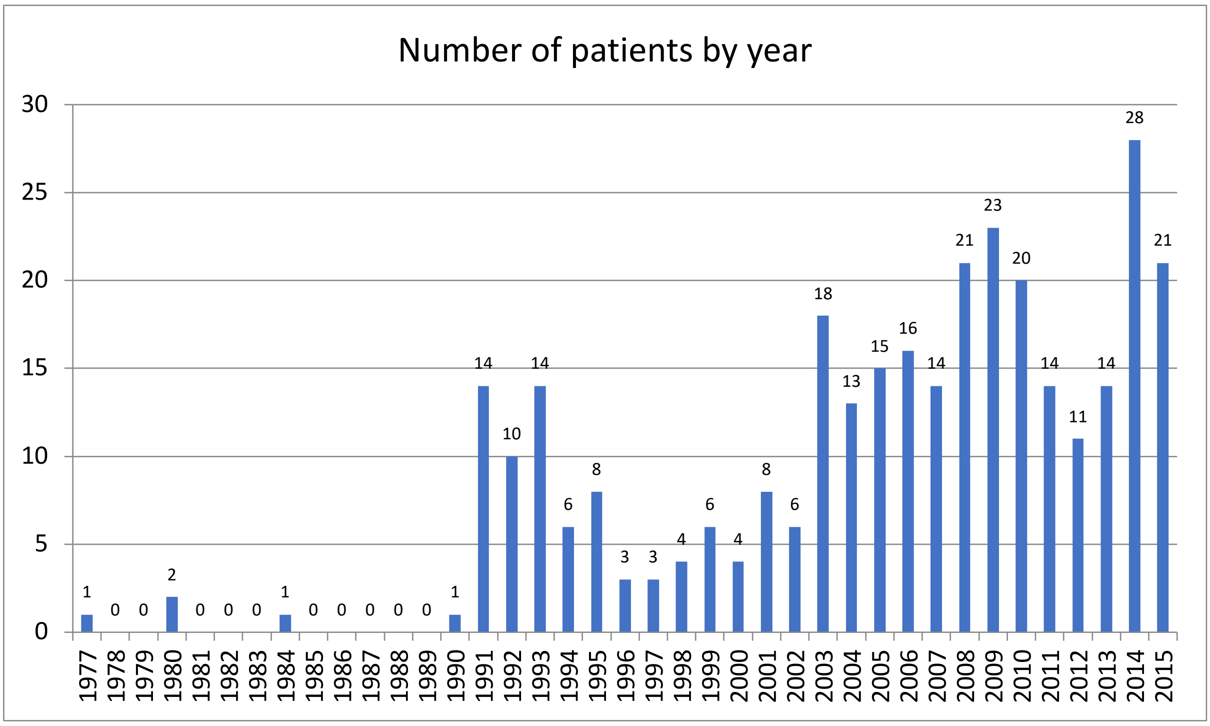

Figure 14. Bar chart showing increasing frequency of BTHR with time (years)

Table 19. Diagnosis of patients having BTHRs

Diagnosis	Hips (n = 638)
OA	530 (83%)
Osteonecrosis	24 (3.8%)
Protrusio	17 (2.7%)
Dysplasia	16 (2.5%)
Rheumatoid arthritis	15 (2.4%)
Epiphysiolysis	12 (1.9%)
Ankylosing spondylitis	6 (0.9%)
Other inflammatory arthritides	6 (0.9%)
Perthes	5 (0.8%)
Failed THR	4 (0.6%)
Failed osteotomy	2 (0.3%)
Failed hemiarthroplasty	1 (0.2%)
TOTAL	638

Table 20. Details of patients submitted to at least one complex or revision procedure as part of a BTHR

Patient	Year	First side	Second side
1	1991	Primary THR	Revision THR for acetabular loosening and cemented femoral revision
2	1999	Primary THR	Revision THR for acetabular loosening and in-cement femoral revision
3	2001	Complex THR with acetabular impaction grafting	Complex THR with acetabular impaction grafting
4	2004	Revision THR with acetabular impaction grafting for socket loosening and in-cement femoral revision	Revision THR with in-cement acetabular revision to a constrained liner
5	2005	Removal of sliding hip screw and complex THR in single setting	Primary THR

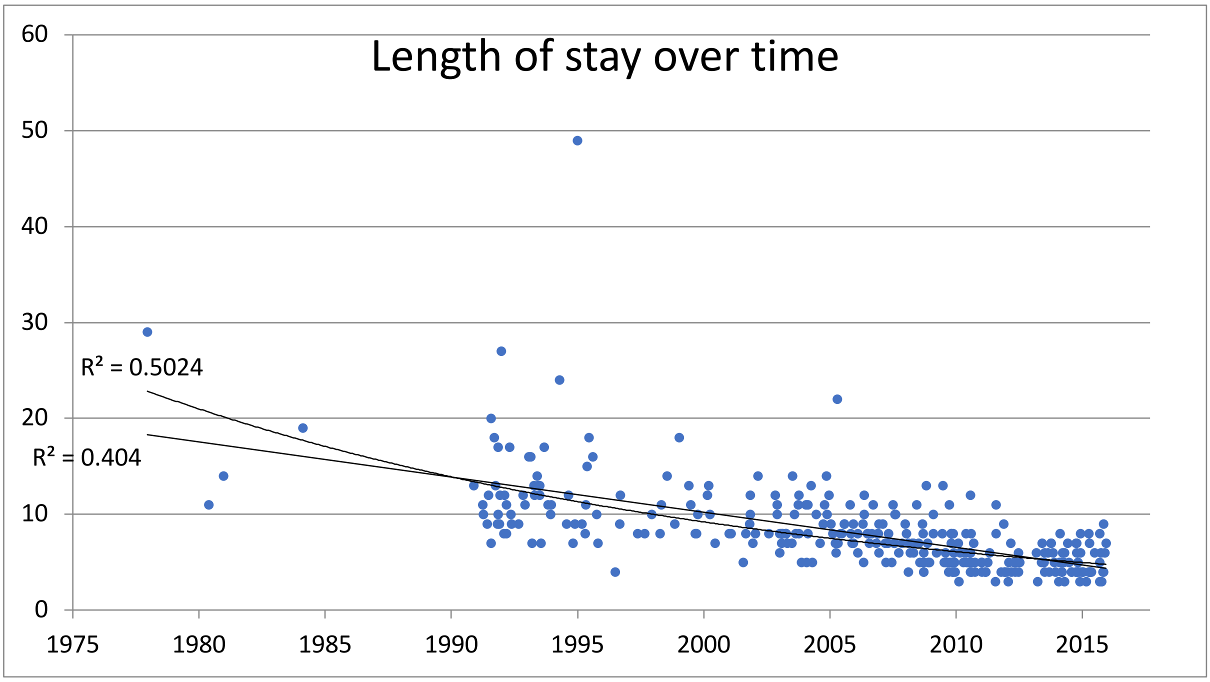

Figure 15. Scatterplot showing length of stay (days) versus time (years)

Medical complications within the first 6 months

In 1992, one death (0.3% of series) was recorded at 62 days postoperatively, a likely but unconfirmed myocardial infarction following readmission of a 73 year old patient under the general surgical team.

In 2009 one patient (0.3% of series) suffered a non-fatal myocardial infarction in the recovery room immediately after surgery. This patient had a previous history of hypertension and thyroid dysfunction.

In 2009 and 2010 there were two cases of pulmonary embolism (0.6% of series) on days 6 and 89, respectively, treated with full anticoagulation for 6 months. Both patients had a body mass index (BMI) of over 30 kg/m2 and were not mobilised until the second postoperative day due to epidural catheterisation. Chemoprophylaxis with low molecular weight heparin for one of these patients was started only once the epidural catheter was removed 24 hours postoperatively.

In 2014 one patient (0.3%) sustained unilateral deep vein thrombosis that was treated with full anticoagulation for 12 weeks. There were 19 (2.97%) revisions in the entire series. The reasons for any revision for the entire series are shown in Table 20. There were no intraoperative periprosthetic fractures or any readmissions within 30 days. No discrepancy was found when comparing our database with available HES data.

Revisions

The most common cause for revision was aseptic loosening of the acetabular component (Table 21).

Table 21. Reasons for revision THR

Patient	Year	First side	Second side
1	1991	Primary THR	Revision THR for acetabular loosening and cemented femoral revision
2	1999	Primary THR	Revision THR for acetabular loosening and in-cement femoral revision
3	2001	Complex THR with acetabular impaction grafting	Complex THR with acetabular impaction grafting
4	2004	Revision THR with acetabular impaction grafting for socket loosening and in-cement femoral revision	Revision THR with in-cement acetabular revision to a constrained liner
5	2005	Removal of sliding hip screw and complex THR in single setting	Primary THR

Two patients (three hips) required revision for sepsis: one patient treated with a first stage revision on the right side in 1993 at 17 months after surgery with no subsequent surgery and the other patient with a background of Hepatitis C having a two-stage revision on the right side in 2013 at 9 years after surgery and a first stage revision on the left hip at 12 years after surgery with no subsequent procedure since then.

Discussion

This non-randomised, prospectively collected study of consecutive patients with bilateral hip disease is the largest single-centre series with the longest follow-up of BTHR where only cemented femoral components were used. A similar study by Gaston et al., 2006 examined 49 cemented bilateral THRs and compared them with 215 unilateral cemented THR. In that study there was no difference in mortality rates, complications, instability or function but an increased transfusion rate was noted in the BTHR group. Age and underlying diagnoses were similar to those of our study. There was a trend for patients receiving BTHR to be younger with no patients greater than 70 years of age for the last 5 years. The length of stay in our study showed an expected trend towards more expeditious discharge from hospital over time with a mean stay of 5 days over the last 10 years.

This series suggests a mortality risk at 6 months of 0.3% and compares favorably to a large data-set study of the Swedish Hip Registry (0.3% at 90 days) (Garland et al., 2015). The overall 90 day mortality rate for unilateral THR is 0.29% in the National Joint Registry of England and Wales (Hunt et al., 2013), being therefore higher than that of our study where patients were submitted to 2 total hip replacements at a single setting. The mortality rate in our study is not higher than that of several uncemented series (Stavrakis, SooHoo and Lieberman, 2015; Wyatt et al., 2014; Parvizi et al., 2006; Aghayev et al., 2010; Lamo-Espinosa et al., 2015; Berend et al., 2005; Martin et al., 2016; Gondusky et al., 2015).

There were 2 cases (0.63%) of pulmonary embolism (PE) within 6 months in our series, both with BMI > 30. PE rates of 0.45% have been reported in larger cohorts of uncemented bilateral THRs performed in the United States (Timperley and Whitehouse, 2009) and other uncemented series (Aghayev et al., 2010; Lamo-Espinosa et al., 2015; Martin et al. 2016; Gondusky et al., 2015).

Three hips in 2 patients were revised for deep infection in our series. The patient with bilateral deep infection was found to be Hepatitis C positive at preoperative screening for bone donation and subsequently required a two-stage revision on the right side and a first stage revision to an articulating spacer on the left, not requiring further interventions after that. The rate of deep infection reported by Stavrakis, SooHoo and Lieberman (2015), was 0.54% infection rate. We feel important points of relevance are strict patient selection, careful surgical technique, avoidance of prolonged surgical time and hypothermia, thorough haemostasis and irrigation, meticulous wound closure, timely administration of prophylactic IV antibiotics according to an agreed local protocol and the use of antibiotic-loaded cement (pre-mixed by the manufacturer) that in conjunction may confer additional prophylactic effect.

Our study has some limitations and did not examine transfusion rates, although these issues have been addressed in previous studies (Parvizi et al., 2013; Romagnoli et al., 2013). It is a retrospective analysis of prospectively, systematically and consecutively collected data. Another potential criticism is whether or not the findings of this study can be generalised. However, this series comprised those operated on by 32 different surgeons of which seven were specialist hip surgeons. Macaulay et al. in 2002 recommended that BTHR should be best performed in dedicated centres and we support this recommendation. Furthermore, we could not identify how many patients were initially intended to have bilateral THR and then had staged surgery because of anaesthetic concerns following completion of the first side. However, there was only one such case recalled by the senior author (GAG). Overall our study showed a low rate of complications for cemented BTHR in patients with very few or no risk factors. There were no revisions for early instability.

We conclude by endorsing the use of cemented and hybrid BTHR in fit and well patients of 70 years or less with no known comorbidities in specialist centres that follow safe cementing techniques. We advocate appropriate patient selection through strict preoperative assessment, use of anaesthetic techniques that enable mobilisation from the first postoperative day, use of blood conserving strategies and meticulous surgical technique.

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Commentary

Critique

In the previous chapter performing cemented SABTHR using Exeter stems in a specialist centre was shown to be safe in appropriately-selected patients using a strict care protocol ie patients less than 70 years of age and ASA 1 or 2. Whether the excellent outcomes demonstrated are generalisable to other centres or with other cemented implants is unknown however. Another potential confounder to acknowledge in this study was the potential influence of tariff and renumeration for single versus bilateral THR and whether there might be a financial incentive for the surgeon or healthcare provider to do staged operations.

Up-to-date literature search

The following databases were searched from 2018 to 30.3.2020 using the programme Papers: ACM, ADS, arXiv, CERN DS, CrossRef DOI, DBLP, Espacenet, Google Scholar, Gutenberg, Highwire, IEEExplore, Inspire, JSTOR, OAIster, Pubget, PubMed, ScienceDirect, Scopus and Web of Science. Search terms related to: Bilateral AND Total hip.

306 references were identified of which 4 were collected as potentially relevant. Those 2 published articles that cited Chapter 4 were also examined. Journals with impact factors <2 were excluded. Any correspondence relating to the article described in this chapter was reviewed.

With regards the mortality associated with SABTHR a recent publication by Partridge et al., 2020 examined the HES data from the entire UK and 2507 SABTHRs. In accordance to Chapter 4 patients in this study were younger and more likely male than patients having unilateral THR. SABTHR was however shown to have a greater risk of thromboembolism, myocardial infarction, renal failure and in-hospital mortality. Patients at particular risk had a higher Charlson score. This study however did not show patients only operated on in specialist centres nor was the same strict care pathway adhered to with every patient. Patient selection bias may partially explain the difference in findings to Chapter 4.

A recent paper published online by Villa et al., 2020 reported a single centre retrospective series of 670 primary staged bilateral THR and TKR between 2010 and 2016. Patients who waited >12 months from the first operation had shorter in-hospital length of stay and lower overall transfusion rates than those who had their second operation <12months from the first. The study did not show a benefit in delaying surgery by a shorter time period than this.

Delaying the second THR in staged bilateral THR by 90 days to allow the mortality risk to return to baseline is justified, however, by Hunt et al., 2013. In this study of 409,096 THR recorded in the National Joint Registry of England, Wales, Northern Ireland and the Isle of Man between 2003 and 2011 linking data to the national mortality database and the Hospital Episode Statistics database examining details on mortality, comorbidity and sociodemographics were examined. Mortality rates within 90 days of surgery were examined using Kaplan-Meier analysis and the role of patient and treatment factors by Cox proportional hazards model. The type of prosthesis, in accordance with the findings of the previous 2 chapters was not related to mortality. The factors that reduced mortality were using a posterior approach (Hazards ratio 0.82; 95%CI 0.73 to 0.92, p = 0.001), the use of thromboprophylaxis (both mechanical and chemical) and spinal versus general anaesthetic (Hazards ratio 0.85; 95%CI 0.74 to 0.97; p = 0.019).

Wyatt et al., 2018 examined the NZJR between 1999 and 2015 and compared the 90 day mortality rate, all-cause revision risk and Oxford Hip scores between single-anaesthetic bilateral THR, unilateral THR and staged bilateral THR in three groups: second THR within 90 days, 90 days to 12 months and >12 months. Single-anaesthetic bilateral THRs were performed in younger and predominantly male patients with significantly lower BMI and ASA grades. The mortality risk for the single-anaesthetic bilateral group was 0.26%. The hazards ratio compared to unilateral THR was 0.25 (95%CI 0.3 to 0.41; p<0.001) in both unadjusted analyses and adjusting for age, and ASA grade. In staged bilateral THR the lowest mortality risk was observed when the second side was delayed at least 90 days after the first THR. The all-cause revision rate was not increased in the single-anaesthetic bilateral group compared to the unilateral group. The functional scores were significantly greater in the single-anaesthetic bilateral group.

This study though used Kaplan-Meier analysis and this warrants careful consideration. The use of competing risk models has been widely promoted in the literature as Kaplan-Meier estimates are perceived to be biased. Sayers et al., 2018 explored these issues and their impact on describing implant failure by simulating the differences in the two analyses. Competing risk estimates crude failure rates and tends to underestimate implant failure whilst conversely the Kaplan-Meier method estimates net failure. Kaplan-Meier is appropriate therefore for describing implant survival whilst competing risk estimates the risk of revision as the latter is a function not only of implant survival but also patient mortality (Sayers et al., 2018). If describing solely a single implant failure then when comparing groups of implants the Kaplan Meier is appropriate; if concerned with resource planning, health economics or patient informed consent about the likelihood of requiring a revision an estimation of crude failure is more desirable. In the analysis of the NZJR it could be countered that a competing risk model would have been more appropriate. When assessing our functional outcome scores in staged bilateral THR we should interpret the 6 month Oxford scores with some caution as we did not control for baseline differences between groups. We also assumed that a patient having unilateral THR did not have a hip problem on their other side and used the Oxford scores 6 months after the second surgery was completed. SABTHR therefore appears safe and surgeons should remain confident in continuing their practise using the same indications, but the results of our study suggest there may well have been an element of selection bias. Whilst there were statistically significant differences in Oxford scores between groups these were less than the mimimum clinically important difference and, to be more circumspect, the previous chapter showed that SABTHR patients are no worse than those having unilateral THR. Wyatt et al., 2018 also did not examine clustering of surgical practices within New Zealand which may have had a confounding effect. The two national joint registry studies complement one another and permit triangulation of the results to substantiate the research conclusions regarding a delay of second THR by >90 days.

SABTHR is most often contemplated in younger patients. In young patients strategies to mitigate against the risk of revision are important not least as the survivorship of subsequent revision THRs diminish over time (Swedish Hip Arthroplasty Register, 2017). Minimising aseptic loosening from bearing-surface wear is one such strategy. There is little evidence comparing effectiveness of various hip implant bearings (Lopez-Lopez et al., 2017). RCTs show similar short- to mid-term survivorship among ceramic-on-ceramic (CoC), ceramic-on-highly cross-linked polyethylene (HLXPE) and metal-on-HLXPE in patients younger than 65 years. Standard ultra-high molecular weight polyethylene (UHMWPE), sterilised in Ethylene Oxide and with correct packaging, can show good clinical results even in the long-term (Lopez-Lopez et al., 2017).

Large datasets from national joint registries show that metal-on-conventional PE has a higher risk of revision compared with metal-on-HXLPE. A minimum HXLPE thickness must be preserved as breakage of the XLPE liners has been described especially in steeply inserted cups with elevated rims and poor locking mechanisms. Osteolysis is seldom perceived with wear rates < 0.1mm per year (Dumbleton, Manley and Edidin, 2002).

The head size that can be used is linked to the bearing material couple. For HXLPE the range should be from 28mm to 36mm in large acetabular cups with enough thickness of the HXLPE liner and for CoC from 32mm to 36mm with 40mm heads only for selected cases of big acetabulae with good thickness of the metal back. There is a lack of long-term analysis of cost-effectiveness on the use of different bearings. Long-term follow-up data is required in order to explore the association of different bearing couples with the risk of revision and other outcomes. The use of big metal-on-metal heads is no longer considered justified and has been abandoned by most surgeons. CoC is not cost-effective in the older population but may be considered for young active patients and perhaps, at the same price, ceramic-on-HXLPE could be preferable to metal-on-HXLPE. The next chapter examines the NZJR evidence for the most reliable bearing surface couple in terms of all-cause revision rates with the influence of femoral head sizes as part of the analysis.

BEARING SURFACES

CHAPTER FIVE

Which is the best bearing surface for primary total hip replacement? A New Zealand Joint Registry study

Reference: Sharplin, P*., Wyatt, M*., Rothwell, A., Frampton, C. and Hooper, G. (2017). Which is the best bearing surface for primary total hip replacement? A New Zealand Joint Registry study. *Hip International*, 71, pp.1-6.

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Authors contributions:
Sharplin P – writing the paper, joint lead author
Wyatt M – inception, data analysis, writing the paper, joint lead author
Rothwell A – editing the paper
Frampton C – statistical analysis and data retrieval from Registry
Hooper G – senior author, final editing

Abstract

Background

We have investigated the revision rates of all bearing surface combinations for primary total hip replacement (THR) registered on the New Zealand Joint Registry (NZJR) to determine which coupling has been the most durable and successful over the last 16 years.

Methods

There were 106,139 primary THRs registered, resulting in 4,960 revisions for any cause. We examined all-cause revision rates, reasons for revision and performed survival analyses.

Results

Ceramic-on-highly cross-linked polyethylene (CoPx) had the lowest all-cause revision rate of 0.54/100-component-years (cys) (95% confidence interval 0.48 to 0.61). This was superior to all other hard-on-soft bearing combinations in unadjusted analysis. Furthermore, the age of patients receiving CoPx was significantly lower than for metal-on-polyethylene (mean 62.9; standard deviation [SD] 10.1 vs. 69.1; SD 9.6; $p < 0.001$). Acetabular loosening was the reason for revision in 14.5% of CoPx, compared to 33% of MoP THRs ($p < 0.001$). Metal-on-metal bearings had the highest revision rate of 1.43/100cys and were significantly inferior to CoPx ($p < 0.001$). Kaplan-Meier analysis and Cox regression analyses were performed and we adjusted the analyses to control for age, femoral head size, surgical approach and fixation.

Conclusions

CoPx remained the most durable and successful coupling used in primary THR in New Zealand irrespective of age, gender or size of femoral head.

Keywords: Bearing surfaces, Primary total hip replacement, Revision rates and causes

Introduction

The most common mode of implant failure in Total hip replacement (THR) is aseptic loosening (Herberts and Malchau, 2000; Beksaç et al., 2009; Johanson et al., 2012) from osteolysis secondary to wear (Beksaç et al., 2009; Johanson et al., 2012; Kuzyk et al., 2011). Interest in reducing wear has driven the development of alternative bearing surfaces to improve the results of the traditional metal on ultra-high-molecular-weight polyethylene articulation (MoP). These include metal (MoPx) or ceramic (CoPx) heads on highly cross-linked polyethylene, ceramic-on-ceramic (CoC), metal-on-metal (MoM) and ceramic-on-metal (CoM) articulations. Each of these combinations has their own unique characteristics.

MoP has been used for more than 40 years as a bearing surface in THR but the macrophage-mediated reaction to polyethylene particles has caused osteolysis and limited the implant survival. Highly cross-linked polyethylene has improved wear characteristics compared to ultra-high-molecular-weight polyethylene (Beksaç et al., 2009; Johanson et al., 2012; Kuzyk et al., 2011; Campbell, Shen and McKellop, 2004) but has altered the mechanical strength of the polyethylene and also produces smaller particle debris, the fate of which remains unknown. Ceramic heads are smoother, harder, more scratch resistant with greater wetability than metal heads and have shown improved *in vivo* wear profiles (Campbell, Shen and McKellop, 2004; Wroblewski et al., 1996; Urban et al., 2001; Dahl et al., 2013) but are brittle and may fracture.

CoC articulations can demonstrate even lower rates of wear compared to both MoP and CoP (Campbell, Shen and McKellop, 2004; Jazrawi et al., 1999; Hernigou et al., 2009; Nikolaou et al., 2012; D'Antonio and Sutton, 2009) but require very precise cup positioning and have risks of stripe wear and squeaking, plus a small but significant risk of catastrophic failure with subsequent limitations in salvage bearing options (Campbell, Shen and McKellop, 2004). CoC is the most likely bearing to achieve true fluid-film lubrication due to their high λ ratio (Heisel, Silva and Schmalzried, 2003).

MoM articulations have had recent high failure rates secondary to metal ion production and “pseudotumour” formation. CoM theoretically reduces the risk of squeaking and fracture associated with CoC but has not been shown to reduce metal ion levels compared to MoM articulations (Schouten et al., 2012). The aim of this study therefore was to use the 16 year results of the New Zealand Joint Registry to identify which bearing surface had the lowest rate of revisions and qualify this by surgeon practice, approach, head size, age, gender and reason for revision, to provide surgeons with an evidence-based approach for choosing the best coupling for THR.

Materials and methods

We performed a retrospective cohort analysis of the 16 year results of the New Zealand Joint Registry (NZJR) identifying primary hip arthroplasty surgeries performed between 1st January 1999 and 31st December 2015 (The New Zealand Joint Registry, 2016). The analysis consisted of four hard-on-soft bearing combinations (MoP, MoPx, CoP and CoPx) and 3 hard-on-hard combinations (CoC, MoM and CoM).

Our primary outcome measure was the all-cause revision rate for each of the 7 bearing couples studied. A revision was defined as a new operation in a previously replaced hip joint during which one of the components was exchanged, removed, manipulated or added. It included excision arthroplasty and amputation, but not soft tissue procedures (New Zealand Joint Registry, 2016). Bilateral THRs were considered independently for the purposes of this study. The all-cause revision rate was chosen to provide the most conservative estimate of survivorship. The revision rate was expressed as the rate per 100-component-years (cys) to give an average estimation of the survival of each coupling over all follow-up by allowing for the number of years that the THR had been implanted. This estimate allows comparison of revision rates when analysing data with varying follow-up times but does assume consistent revision rates over time. Kaplan-Meier survival curves and Cox-proportional hazards regression were therefore also performed to summarise the proportion revision-free and to allow for confounders such as age at surgery, gender, diagnosis, surgical approach, surgeon volume, fixation and head size when comparing couplings. In order to exclude historical problems with locking mechanisms in uncemented cups we examined the revision rates for CoPx, CoC and MoPx over the last 10 years in THRs performed with 32mm and 36mm femoral heads.

The reason for revision as listed on the NZJR was compared between the couplings used. Demographic data including age and gender as well as procedure specific data such as head size, fixation technique, surgical approach and surgeon volume were all compared between couplings using ANOVA and chi-square tests as appropriate. All-cause revision rates were calculated with 95% confidence levels using a Poisson approximation. A p value < 0.05 was deemed to be statistically significant.

Results

There were 106,139 primary THR registered on the NZJR during the study period with 4,960 (4.7%) revision procedures performed on these implants, giving an overall revision rate of 0.74 (0.72 to 0.76, 95% CI)/100 cys. The traditional MoP bearing combination was the most common coupling at 33.6% (35,647) followed by MoPx at 29.8% (31,579). Ceramic on polyethylene combinations were less commonly utilised with 13.6% CoPx (14,382) and 6.4% CoP (6,833). The most frequently used hard-on-hard bearing was CoC with 10.6% (11,235), followed by MoM at 5.6% (5,989) and infrequently CoM at 0.4% (474).

Patient demographics

The mean age of patients varied widely when comparing the group of hard-on-hard with hard-on-soft bearings, with the youngest patients in the MoM group and the oldest in the MoP group (Table 22). The MoM patients were significantly younger than the other hard-on-hard bearing patients (mean age 54.1; standard deviation [SD] 9.8; $p < 0.001$). Of those receiving hard-on-soft bearings there was a significantly lower mean age of those with CoPx (mean age 62.9 years; SD 10.1; $p < 0.001$) and a higher mean age for those with MoP bearing (mean age 72.1 years; SD 9.6; $p < 0.001$).

Table 22. Patient age by bearing surface

Surface	Mean Years (sd)	% Female
CoC	56.5 (9.9)	48.8%
CoM	56.5 (9.1)	36.9%
CoP	63.2 (10.7)	49.6%
CoPx	62.9 (10.1)	48.4%
MoM	54.1 (9.8)	35.8%
MoP	72.1 (9.6)	59.3%
MoPx	69.1 (10.1)	54.5%

There was a relatively equal split in gender for CoP, CoPx and CoC but males were much more predominant in both MoM and CoM articulations, whereas females were predominant when a metal head was used with a polyethylene liner/cup (MoP and MoPx) (Table 22).

Surgical features

Fixation

Across all, the most common fixation technique was uncemented at 39.1%, followed by hybrid (cemented femur and uncemented cup) with 38.6% and cemented at 22.3% (Table 23). Hard-on-hard bearing combinations favoured uncemented fixation in 79% of CoC, 99% of CoM and 90% of MoM. Within the hard-on-soft bearing groups MoP was the only bearing combination that favoured cemented fixation at 58%, with hybrid also commonly used at 30%. CoP bearings were predominantly uncemented at 55% or hybrid at 39%, which was similar for CoPx with uncemented 70% and hybrid 28%. For MoPx, hybrid fixation was more common at 65% compared with uncemented at 27%.

Table 23. Surgical features by bearing surface

		Bearing surfaces													
		CoC		CoM		CoP		CoPx		MoM		MoP		MoPx	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Type of fixation	**Cemented**	0	0	0	0	421	6.2	220	1.5	7	0.1	20593	58	2434	7.7
	Uncemented	8855	79	467	98.5	3776	55	10866	70	5382	90	4390	12	8520	27
	Hybrid	2380	21	7	1.5	2636	38	4076	28	600	10	10664	30	20625	65
Surgical approach	**Anterior**	200	2	18	4	265	4	505	3.8	233	4.2	1654	5	914	3.1
	Posterior	9301	87	336	79	4117	64	9878	74	4176	75	20489	61	19514	66
	Lateral	1106	10	70	16.5	2023	31	2969	22	1181	21	11296	34	9004	30.5
	Trochanteric osteotomy	6	0.1	0	0	6	0.1	13	0.1	7	0.1	43	0.1	50	2
Surgeon volume per annum	**<10**	34	0.3	0	0	51	0.7	60	0.4	24	24	0.4	661	440	1.4
	10-24	655	6	1	2	760	11.1	1302	9	498	8.4	4365	12	3930	12.5
	25-49	3555	32	210	44	2577	38	6179	43	1759	29	16458	46	14321	45
	50-74	2175	19	60	12	1846	27	4796	33	1372	23	9354	26	6492	20
	75-99	1716	15	117	24	173	2.5	1404	9.8	850	14	2859	8	3959	12
	>100	3100	27	84	18	1424	21	637	4	1461	25	1934	5	2400	8
Femoral head size (mm)	**<28**	733	6	23	5	6347	93	4254	30	2855	47	30539	85	13733	44
	32	3308	29	0	0	484	7	6855	48	481	8	5088	14	15387	49
	36	5836	52	443	94	2	0	3257	23	1002	17	8	0	2425	8
	>36	1337	12	7	1	0	0	1	0	1649	28	2	0	32	0.1

Head size

Head size varied across all groups, but hard-on-hard bearings tended to use a larger head size, with CoC and CoM using ≥ 36mm heads in 64.0% and 95.1% of cases respectively (Table 23). MoM bearings were inserted in 2 major head sizes: 47.7% receiving 28mm heads, while the next most common was > 36mm at 27.5%. Size 28mm heads were most frequently used in CoP at 92.9% and MoP at 85.7%. There was a tendency to use larger heads (≥ 32mm) when using highly cross-linked polyethylene, with MoPx at 56.5% and CoPx at 70.4%.

Surgeon volumes and approach

12.1% of the joint replacements performed were by surgeons who averaged < 25 joints per year (Table 23). They were relatively evenly distributed across all bearing types with a tendency to use hard-on-soft couplings. The most common surgical approach was posterior at 68.3% followed by lateral at 27.8%. There was no significant association between bearing type and approach used.

Revision rates

The all-cause revision rate was lowest for the CoPx which was significantly better than CoP ($p < 0.001$), MoPx ($p = 0.003$) CoM ($p = 0.019$), MoM ($p < 0.001$), CoC ($p = 0.005$) and MoP ($p = 0.008$) (Table 24). The poorest performing bearing surface was MoM. Furthermore, MoPx had a significantly lower revision rate than CoP ($p<0.001$) suggesting the major benefit was from the polyethylene rather than the ceramic head. MoP and MoPx bearing combinations had higher rates of revision for component loosening when using ≤ 28mm femoral head (Figure 16).

Table 24. All-cause revision rates for each bearing coupling studied

Bearing Surface	Primary Procedures	Total Component-Years	Revision Procedures	Rate / 100-component-years (95% CI)
CoC	11235	58591.1	355	0.61 (0.54 - 0.67)
CoM	474	2601.6	21	0.81 (0.50 - 1.23)
CoP	6833	65690.0	486	0.74 (0.68 - 0.81)
CoPx	14382	52521.9	283	0.54 (0.48 - 0.61)
MoM	5989	55702.6	797	1.43 (1.33 - 1.53)
MoP	35647	295137.1	2143	0.73 (0.70 - 0.76)
MoPx	31579	142306.0	875	0.61 (0.57 -0.66)

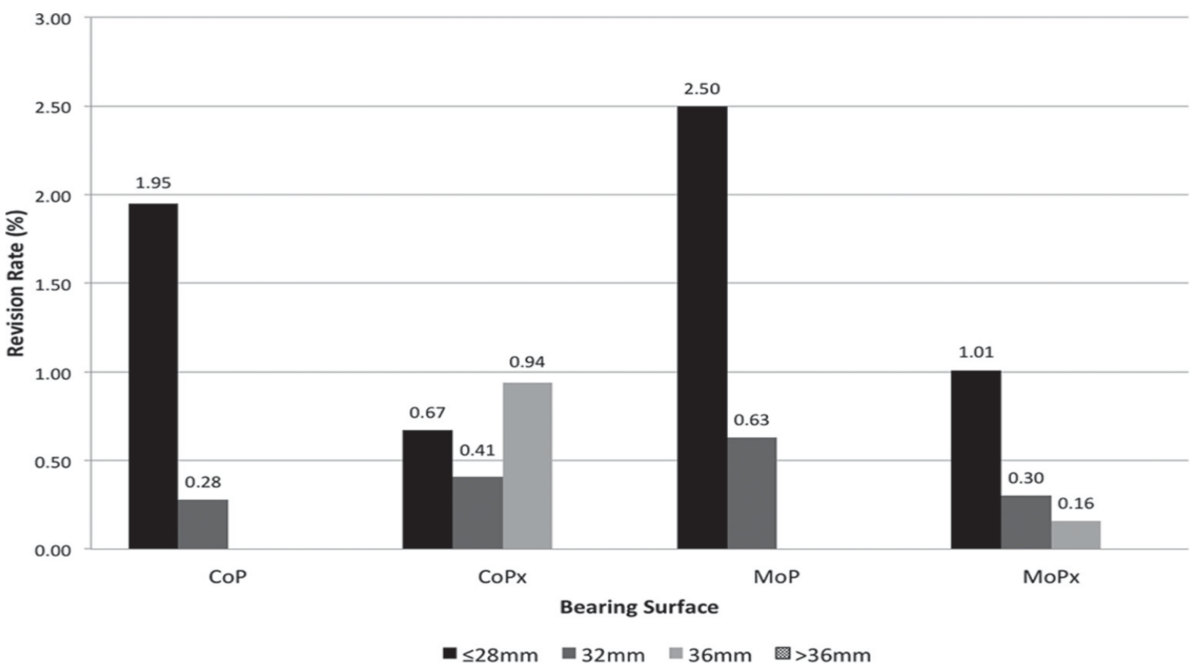

Figure 16. All-cause revision rates by bearing surface combination and femoral head size

When the analyses were adjusted to control for age, gender, femoral head size, surgical approach, surgeon volume and fixation, CoC bearings were better than all other couplings closely followed by CoPx which in turn was significantly better than the others (Table 25), significances both adjusted and unadjusted are shown in Table 24. The Kaplan-Meier survivorship analyses (Figure 17) demonstrated that the unadjusted all-cause revision-free survivorship was highest for CoPx and lowest for the MoM bearings when we analysed the last 10 years' results looking specifically at CoC, CoPX and MoPx with 32mm and 36mm femoral heads, however CoPx had a significantly lower revision rate ($p < 0.05$) (Table 26).

Table 25. P values from pairwise log-rank tests between bearing surfaces, values in brackets are from adjusted+ comparisons.

	CoC	CoM	CoP	CoPx	MoM	MoP
CoC						
CoM	0.217 (0.155)					
CoP	0.026*(< 0.001)*	0.295 (0.201)				
CoPx	0.005*(0.011)*	0.019*(0.626)	< 0.001*(0.001)			
MoM	< 0.001*(< 0.001)*	0.005*(0.161)	< 0.001*(0.755)	< 0.001*(< 0.001)*		
MoP	0.515 (< 0.001)*	0.062 (0.020)*	0.629 (0.001)*	0.008*(< 0.001)*	0.003*(< 0.001)*	
MoPx	0.638 (< 0.001)*	0.116 (0.373)	< 0.001*(0.127)	0.003*(< 0.001)*	< 0.001*(0.083)	0.039*(< 0.001)*

* Denotes statistically significant ($p < 0.05$) result.
+ Values adjusted for age, gender, head size, approach, surgeon volume, and fixation.
CoC = ceramic-on-ceramic; CoM = ceramic-on-metal; CoP = ceramic-on-polyethylene; CoPx = ceramic-on-highly cross-linked polyethylene; MoM = metal-on- metal; MoP = metal-on-polyethylene; MoPx = metal-on-highly cross-linked polyethylene.

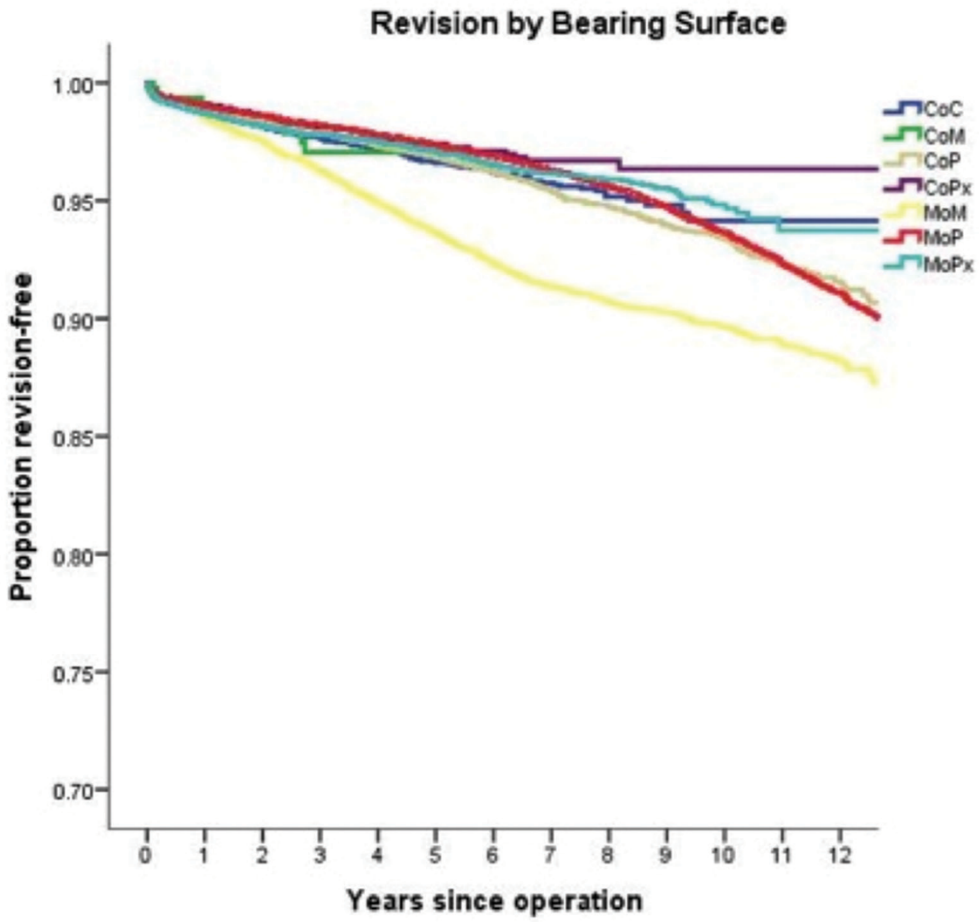

Figure 17. Kaplan-Meier analysis of revision rates by bearing surface combination

Table 26. Analysis of total hip replacements with larger femoral heads over the last 10 years

2008 onwards – cementless and size 32 or 36mm								
					Lower 95% CI			p values
Surface	**Ops**	**Cpyrs**	**Revised**	**Rate/100-component-years**		**Upper 95% CI**	**vs. CoPX**	**vs. MoPX**
CoC	5,587	22,167.4	158	0.71	0.61	0.83	0.017	0.743
CoPX	6,886	19,146.9	115	0.60	0.5	0.72		0.005
MoPX	4,965	15,449.7	126	0.82	0.68	0.97		
Total	17,438	56,764.1	399	0.70	0.63	0.77		

CoC = ceramic-on-ceramic; CoPx = ceramic -on-highly cross-linked polyethylene; MoPx = metal-on-highly cross-linked polyethylene.

Reasons for revision

Loosening of components was the commonest cause for revision surgery across all articulations (Table 27) with acetabular loosening (22.2%, rate of 0.17/100 cys [95% CI 0.16-0.18]) more common than femoral loosening (16.7%, rate of 0.12/100cys [95% CI 0.11-0.13]). The lowest rate of acetabular component loosening was with CoPx and MoPx with MoPx being significantly better than CoC ($p = 0.013$), CoP ($p < 0.001$), MoM ($p = 0.001$) and MoP ($p < 0.001$) whereas CoPx was significantly better than MoM ($p < 0.001$) and MoP ($p < 0.001$). MoP had the highest revision rate for acetabular loosening. Femoral loosening was lowest in CoC and CoPx but this was only significant when compared to MoM ($p = 0.001$ and $p = 0.004$ respectively).

Table 27. Summary of Reason for Revision (note that each revision surgery can have more than one reason for revision)

	Bearing surfaces															
Reason for revision	CoC		CoM		CoP		CoPx		MoM		MoP		MoPx		**Total**	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Acetabular loosening	55	15	2	9	89	18	41	14.5	117	14	708	33	1102	22	1102	22
Femoral loosening	47	13	3	14	81	16	46	16	82	10	436	20	8520	27	828	17
Instability	60	17	3	14	140	28	76	27	58	7	543	25	266	30	1146	23
Pain	56	16	5	24	49	10	26	9	229	29	270	13	86	10	721	14
Deep infection	40	11	7	33	42	8	49	17	57	7	217	10	178	20	590	12
Femoral fracture	32	9	1	5	45	9	44	16	33	4	213	10	147	17	515	10
Ceramic head fracture	9	2.9			6	2	1	1							15	0.4
Ceramic liner failure	34	11													34	0.5
Ceramic noise	24	7.8													24	0.6
Metallosis related									112	23					112	3.5
ASR implant									61	12					61	1.9
PE wear					30	8.4					56	3.7	3	0.6	89	2.8
Miscellaneous	34	15	4	19	50	12	20	15	49	10	140	9	62	13	358	11
Total revisions	**355**		**21**		**486**		**283**		**797**		**2143**		**875**		**4960**	

Dislocation was the most commonly recorded reason for revision surgery of CoP (28.8%), CoPx (26.9%) and MoPx (30.4%) hips (Table 27). For all bearing combinations except CoM, femoral heads of size 28mm or less were more commonly associated with dislocation (Figure 18). All hard-on-hard bearings had lower dislocation rates than hard-on-soft bearings. CoPx was the best hard-on-soft bearing, being significantly better than MoP ($p < 0.001$), MoPx ($p = 0.005$) and CoP ($p < 0.001$).

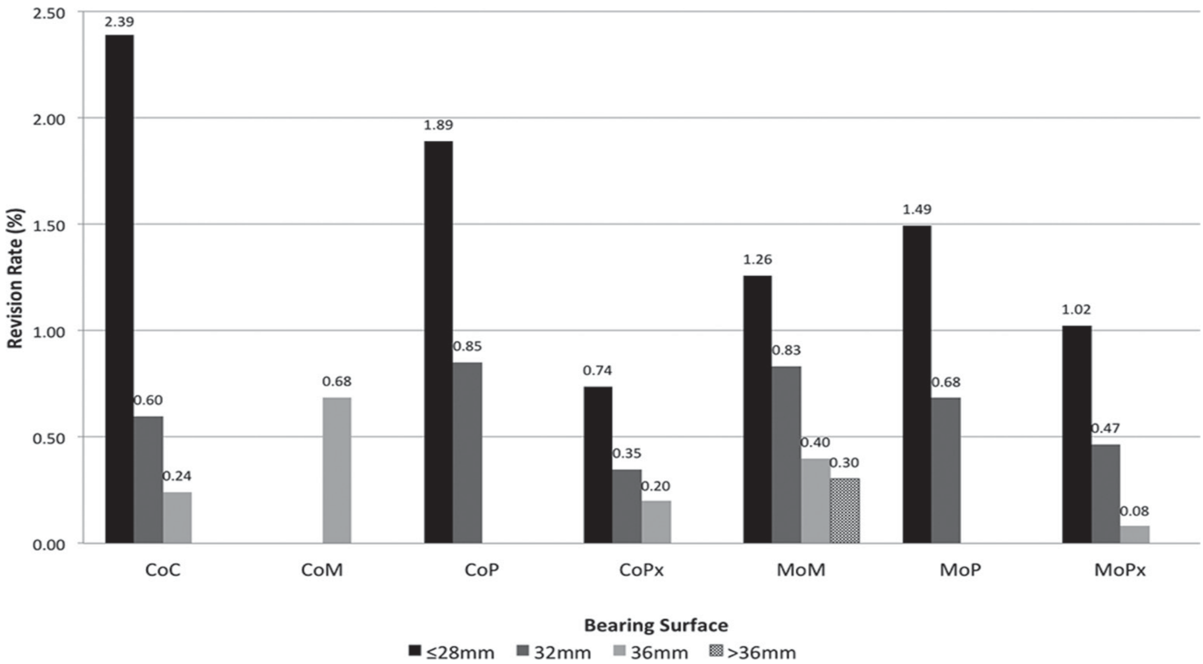

Figure 18. Revision rates for instability by bearing surface combination and femoral head size

Revision for periposthetic infection was least common in CoC (0.07/100cys, 95% confidence interval [CI] 0.05-0.09), CoP (0.06/100 cys, 95% CI 0.05-0.09) and MoP (0.07/100cys, 95% CI 0.06-0.08) and highest in CoM (0.27/100cys 95% CI 0.11-0.55) and MoPx (0.13/100cys 95% CI 0.11-014).

Within the "other" causes for revision, ceramic component fracture was identified as the reason for 9.6% of CoC, 1.2% of CoP and 0.4% of CoPx revisions. This represents a rate of ceramic fracture of 0.30% (34/11,235) for CoC, 0.09% (6/6833) for CoP and 0.01% (1/14382) for CoPx. Of the 12 ceramic head fractures, 11 were size 28mm heads and one size 32mm. Revision for bearing-generated noise was undertaken in 8.2% of CoC hips, which was a rate of 0.22% (18/11235). Metal-on-metal bearings experienced metallosis-related complications for 23.2% of their revisions, while 12.6% of revisions were undertaken for complication with recalled ASR prosthesis.

Discussion

Our findings indicate that in New Zealand, CoPx bearing surfaces have the lowest all-cause revision rate for THR. This combination outperformed all others but failed to reach statistical significance over the traditional MoP combination and also CoC. The K-M analysis clearly shows an increasing rate of revision for both MoP and CoP after 8 years compared to CoPx and MoPx which have relatively flat curves after this time point. The best performing hard-on-hard bearing was CoC, whilst the poorest was MoM, which was not unexpected given the recent publications of metallosis-related failures and product recalls of these implants (Hunt et al., 2018). When these revision rates were adjusted for age, gender, approach, fixation method and surgical volumes the CoC couplings were superior followed by the CoPx, which were significantly better than all others. When looking at the last 10 years in THRs using 32mm and 36mm heads we therefore excluded the historical uncemented cups with poor locking mechanisms. CoPx was the significantly superior bearing surface in this group. Previous studies have shown that polyethylene wear is related to the level of activity of the patient. Older patients are quoted to have a reduction in their level of activity in the order of 15-20% for every decade of life (Howcroft, Head and Steele, 2008). Battenberg et al. (2013), studied a cohort of THR patients and found that over a decade of observation, a 16% reduction in gait cycles and 8.8% reduction in walking speed resulted in a reduction in cross-linked polyethylene wear rate of 40%. In our study, there was a significantly lower mean age ($p < 0.001$) for patients receiving CoPx bearings (62.9 years) compared with patients receiving MoP (71.8 years). However, despite patients in the ceramic group being almost a decade younger than their metal group counterparts, the ceramic cohort’s revision rate remained lower. A recent study comparing registry outcome data across 6 registries, not including the NZJR, showed no increased revision rate of MoPx compared to MoP in those patients aged between 45 to 64 years who had cementless implants (Paxton et al., 2014).

As anticipated, each of the bearing surfaces had an unique revision profile. Of interest was the percentage of revision due to aseptic loosening in both the CoP and CoPx combinations when compared to MoP (Table 31). This was not unexpected given that ultra-high-molecular-weight polyethylene has a poorer wear profile than highly cross-linked polyethylene, but it does support the lower wear rates reported when utilising ceramic heads (Campbell, Shen and McKellop, 2004; Kuzyk et al., 2011) with a subsequent lower rate of revision for aseptic loosening. Polyethylene wear has been the major cause of osteolysis and aseptic loosening with numerous studies supporting the use of CoP bearings, citing up to 50% reduction in polyethylene wear *in vitro* when compared with metal-on-polyethylene (Campbell, Shen and McKellop, 2004; Urban et al., 2001; Howcroft, Head and Steele, 2008). *In vivo* studies have supported these *in vitro* results showing improved wear profiles for ceramic heads compared with metal heads in THR with hard-on-soft articulation. Dahl et al. (2013), demonstrated that ceramic heads had more than a 50% reduction in polyethylene wear compared to chromium-cobalt heads at 10 year follow-up. Despite the reduction in polyethylene wear, they were unable to identify a significant difference in osteolysis or revision between their 2 study groups. Wang et al. 2013, also showed significantly reduced polyethylene wear rates for ceramic-on-polyethylene at 10-year follow-up in 22 simultaneous bilateral primary THR with a metal head on one side and ceramic on the other. The authors describe no evidence of aseptic loosening of components in any of their study subjects. We have shown that CoP and CoPx couplings have a rate of aseptic loosening closer to hard-on-hard bearings with a lower rate of aseptic loosening compared to MoP.

Femoral head size is an important consideration in bearing choice. The main concern with larger heads is the potential for increased volumetric wear (Cross, Nam and Mayman, 2012; Rajpura, Kendoff and Board, 2014), in combination with the requirement for a thinner acetabular liner for any given cup size. Although some have shown no increase in linear penetration between 28mm and 32mm metal heads on highly cross-linked polyethylene at either 7 or 10 years (Bragdon et al., 2013), others have found that although linear wear rates for smaller femoral heads (32mm or less) were similar to those of larger heads (36mm or more), there was greater volumetric wear with the larger femoral head sizes. Although the rates were below the suggested osteolysis threshold, wear with 36mm heads and partially irradiated polyethylene continues to be a concern, particularly with younger patients (Selvarajah et al., 2015). One systematic review concluded that based on currently available literature, large diameter metal heads (> 32mm) or ceramic heads of any size are not proven to reduce femoral head penetration or osteolysis risk (25). Allen, Hooper and Frampton (2014), found no relationship between increased femoral head size and an increase in functional outcome at 1 year follow-up, but did identify a trend toward reduction in dislocation rate with 36mm heads. They concluded that there was little advantage in using heads > 36mm in patients undergoing THR (Alllen, Hooper and Frampton, 2014). Analysis of the National Joint Registry for England and Wales found that there was a hazard ratio of 1.5 ($p = 0.005$) for revision with smaller head sizes < 28mm when compared with 28mm heads, but there was no significant difference in revision rate between hips with 28mm and 32mm heads (Jameson et al., 2012). There remains a balance between reduced dislocation with a larger head size and increased volumetric wear which is likely to be patient related, and the decision on head size needs to be individualised for each clinical situation, as our results indicate that smaller head sizes of ≤ 28mm are associated with higher rates of revision for dislocation, ceramic head fracture and loosening when used in combination with polyethylene bearings.

When looking at the last 10 years in THRs using 32mm and 36mm heads we therefore excluded the historical uncemented cups with poor locking mechanisms. CoPx was the significantly superior bearing surface in this group. Previous studies have shown that polyethylene wear is related to the level of activity of the patient. Older patients are quoted to have a reduction in their level of activity in the order of 15-20% for every decade of life (Howcroft, Head and Steele, 2008).

Prior to 2007 all ceramic implants were either Forte ceramic or Mathys ceramic. Following that, delta ceramic was introduced and all changed to this except Mathys who continue to use their own ceramic. All ceramic liners that fractured were forte components, 3 of which were associated with dislocation events. All ceramic head fractures were with 28mm heads or smaller except 1 (32mm), evenly spread across the different generation ceramics, often associated with traumatic events e.g. dislocation. Of note is the fact that 7 of the fractured heads were in CoP or CoPx couplings with only 5 in CoC joints. Although revision for infection was lowest with CoC bearings there did not seem to be any correlation with other ceramic bearing surfaces combinations (CoP and CoPX) to suggest that there was a protective effect from its use. These results have been reported previously and caution has been advocated in the interpretation because of a number of other cofounders, such as body mass index (BMI) and American Society of Anesthesiologists (ASA) score, which are likely to play a significant role in the incidence of infection (Pitto and Sedel, 2016).

Bearing generated noise was the reason for 8.2% of ceramic-on-ceramic revisions in this study. Stanat and Capozzi's meta-analysis found a mean rate of 2.4% (0.7% to 20%) for CoC bearing generated noise and they noted that the underlying causes of this included edge-loading, as well as 3rd body ingress and subluxation (Stanat and Capozzi, 2012). Ceramic fracture has been another potential mode of failure for ceramic bearings. In our study CoPx performed the best with a fracture rate of 0.01%, whereas CoC implants were at greatest risk (0.33%). The very nature of a CoC coupling exposes 2 hard, brittle surfaces that are potentially vulnerable to injury, particularly in the presence of implant malposition (Campbell, Shen and McKellop, 2004; Dahl et al., 2013; Howcroft, Head and Steele, 2008; Battenberg et al., 2013). Smaller femoral heads (28mm or less) were prone to fracture and the current trend towards larger femoral heads, partly to reduce the risk of dislocation, has resulted in head sizes > 32mm with a lower risk of fracture. The current production of ceramics, with better resistance to crack propagation, has decreased head fracture rates to 0.004% and 0.002% for 3rd and 4th generation alumina heads respectively (Rajpura, Kendoff and Board, 2014). A recent systematic review of THR in patients under 30 years of age showed that ceramic-on-ceramic bearings in combination with cementless implants still hold great promise for longevity in this patient population (Walker et al., 2016).

The debate is ongoing over which surgical approach for THR is superior but a recent systematic review and a cohort study both favour the posterior approach (Berstock, Blom and Beswick, 2015; Smith et al., 2012). Few studies report on aseptic loosening as an outcome measure when comparing approaches; however, a recent Swedish Registry study found that when compared to the posterior approach, an anterolateral transgluteal surgical approach resulted in an increased risk of revision for aseptic loosening for the Lubinus SPII (relative risk [RR] 1.3, 95% CI 1.0-1.6) and Spectron EF Primary stems (RR 1.6, CI 1.0-2.5) (Lindgren et al., 2012). The same study found no difference in revision for aseptic loosening between lateral and posterior approaches for the Exeter stem. Others looking at the Norwegian Registry found that the Charnley femoral stem had lower overall rates of revision when using a lateral approach with a trochanteric osteotomy, compared to either a posterior or a lateral approach without trochanteric osteotomy (Arthursson et al., 2007). The same study identified increased risk of revision for dislocation (RR 1.9, $p = 0.02$) when using the Charnley stem with the posterior approach, compared to a lateral approach without osteotomy. Palan et al. (2009), found no differences in Oxford Hip Score, dislocation or revision rates between anterolateral and posterior approach THR at 5 year follow-up of 1,089 hips. We found no difference between the 2 commonest approaches used in New Zealand (posterior and lateral) but did not compare approach to implant used. Interestingly, we also found no significant difference in the revision rates for those surgeons who performed < 25 THR per year compared to the rest.

The strengths of this study relate to the quality data provided by the NZJR with a high capture rate of 98% across the whole country (Hooper, 2013), and large data sets pertaining to THRs for the various bearing surfaces. A potential limitation is the choice of all revision rates between CoPx and MoP which may be due to the relatively low numbers of CoPx, with CoPx representing less than 10% of the total component years recorded in the NZJR. The numbers of CoPx have increased over the last 5 years and with time, and the accumulation of component years, statistical significance may yet be identified. It is also important to note that there are multiple other factors which impact on prosthesis wear, including cup positioning, implant fixation technique, implant materials and implant coating. Other patient factors may also play a significant role including weight and level of activity. Not all of these factors can be accounted for in this study. Another weakness is that we have used all-cause revision as a surrogate marker for failure. This has the drawback of not identifying patients who are living with a painful hip, awaiting revision, or who are too unwell for revision surgery. Finally, we have not assessed the different groups of implants used with these articulations as some groups are small and achieving adequate power would be unlikely.

Conclusion

In New Zealand, the lowest all-cause revision rate in THR was found with ceramic femoral heads in CoPX bearing combinations. This coupling was used in patients who were on average almost a decade younger than those receiving MoP bearings ($p < 0.001$). It is early days for follow-up in CoPx hips, but these data indicate that this is the most promising option for young and active patients requiring hip arthroplasty.

Commentary

Critique

In our study of the 16 year results of the New Zealand Joint Registry CoPx has the lowest all-cause revision rate for THR in unadjusted analyses. This finding remained when examining the last decade of practice and using 32mm and 36mm femoral heads. The next best and best performing hard-on-hard bearing was CoC and this was best in analyses adjusted for age, gender, head size, approach, surgeon volume, and fixation. CoC has its own unique problems as they require very precise positioning to avoid stripe wear, edge loading and squeaking. The superiority of CoPx however did not reach statistical significance over the traditional MoP combination and also CoC which therefore remain viable options in terms of bearing surface combinations and warrant further examination. A valid criticism of our study was that in order to exclude cups with locking mechanisms prone for locking liner ring breakage and failure Chapter 5 examined uncemented cups over the last 10 years. Harris-Galante II cups, for example, had a propensity for breakage of the locking mechanism (Matsuno, Yudoh and Kimura, 2002; Yamada et al., 2009). This method therefore can be criticised, as an alternative method would have been to reanalyse the dataset removing known implants that displayed this problem. Another weakness is that the influence of implant fixation was not accounted for by regression analyses in our study. MoM was the worst performing bearing surface combination in the NZJR analysis in the previous chapter. This is in keeping with the UK National Registry studies (Reito et al., 2017; Hunt et al., 2018) and does not support its implantation. The issue of cobalt and chromium metal ion release and toxicity associated with MoM bearing surfaces is well recognised (Davies et al., 2005).

Up-to-date literature search

To update the context of the findings of Chapter 5 the following databases were searched from 2017 to 30.3.2020 using the programme Papers: ACM, ADS, arXiv, CERN DS, CrossRef DOI, DBLP, Espacenet, Google Scholar, Gutenberg, Highwire, IEEExplore, Inspire, JSTOR, OAIster, Pubget, PubMed, ScienceDirect, Scopus and Web of Science. Search terms related to: Bearing surface AND Total hip.

341 references were identified of which 13 were collected as potentially relevant. Those single published articles that cited Chapter 5 were also examined. Journals with impact factors <2 were excluded. Any correspondence relating to the article described in this chapter was reviewed.

Choice of surgical approach

The commest hip approaches in the previous chapter were the posterior and the lateral approaches. In a recent publication by Lenguerrand et al. (2018), there was an increased risk of revision for deep infection when using the lateral compared to the posterior approach (relative risk 1.3; 95%CI 1.2 to 1.4). Aggarwal et al. (2019) showed that the posterior approach was associated with fewer complications overall, with the DAA having the highest incidence of complications (8.5%) compared to posterior approach (5.85%). Interestingly the DAA had a higher rate of postoperative instability compared to the posterior approach in this study. Hunt et al., (2013, 2018) showed a decreased risk of mortality with the posterior approach compared to other approaches (Hazards ratio 0.82; 95%Ci 0.73 to 0.92; p=0.001). Complications aside Lindgren et al. (2014), showed that in the Swedish Hip Arthroplasty Register the lateral approach had inferior patient reported outcome measures compared to the posterior approach.

Which bearing surface is superior?

The results of Chapter 5 at first sight differ from the findings of a systematic review and network meta-analysis of prospective randomised controlled trials (Lopez-Lopez et al., 2017). This evidence synthesis showed that there is little evidence that any bearing surface combination is in fact surperior to MoP bearings in terms of all-cause revision rates. This study focused on high-quality prospective RCT's trials but many included studies were small and focused on clinical outcomes other than revision surgery. When considering MoP linear wear is typically 100 to 300 μm/year (Semlitsch and Willert, 1997) and this has been shown to not vary significantly between 22mm, 28mm and 32mm femoral heads (Rieker, 2017). Volumetric wear of UHMWPE has been shown to vary between 5 and 50mm^3/year. Ceramic heads have been shown to reduce polyethylene wear by 50% when used with UHMWPE (Meftah et al., 2013). Stambough JB et al. (2018), reported a prospective cohort study of 123 patients who had THR at <50 years of age; although there was incomplete follow up with 101 THA in 84 patients mean 17,1 year FU (14.7 to 19.6). The outcomes reported were linear and volumetric wear, clinical outcome scores, implant survivorship and patient mortality. The median linear wear was 0.206mm/yr (95%Ci 0.079 to 0.133mm) and volumetric wear 43.58 mm^3/year (95%CI 33.4 to 53.75). With all-cause revision as the endpoint the survivorship was 79.2%. The majority were revised for wear-related causes. This study concluded that there are significant concerns for traditional MoP bearings at 15 years in young, active patients and alternate bearing surfaces should be considered.

Ceramic-on-ceramic

CoC bearings have achieved excellent long-term clinical results with an 84.4% survival rate at 21 years (Petsatodis et al., 2010). This bearing couple permits larger femoral head sizes (< 48mm) and thinner acetabular shell sizes. The bearing surface has very low wear rates but is very sensitive to component positioning. The registry analysis of risk factors associated with a higher risk of revision for infection showed that CoC had a relative risk of 0.6 (95%CI 0.4 to 0.7) compared to MoP at > 24 months; CoP had a relative risk of 0.7 (95%CI 0.5 to 0.9) compared to MoP at > 24 months (Lenguerrand et al., 2018).

Wyatt et al. (2014), showed that the phenomenon of noise from CoC bearings is more common than in CoP bearings and has significant patient impact. These findings may or may not be generalisable to all implants. There was an element of “mix-and-matching” with the implants used in this study as they were manufactured by a variety of implant companies in the previous study which may be relevant. Mathys ceramic heads in combination with Mathys cups were used rather than Biolox Delta femoral heads comprising zirconia (17%)/alumina (82%) composite heads. The Mathys ceramic is a zirconia (80%)/alumina (20%) composite and there is no literature to suggest any difference in noise generation between these and Biolox Delta types of ceramic. There remains however a potential for different manufacturer tolerances between Zimmer and Mathys that may have influenced the findings of this study.

HXLPE

HXLPE was originally developed in the 1990s and cross-linking for polyethylene polymer chains permitted modulation of its molecular structure and a higher resistance to both abrasive and adhesive wear. Cross-linking is produced by using irradiation and the subsequent formation of free radicals. Once cross-linking has occurred the elimination of free radicals is important to diminish the risk of oxidation and this is achieved by annealing, remelting or in latter HXLPE generations by adding antioxidants. HXLPE has been shown to have linear wear rates ranging between 2 and 20μm/year and volumetric wear rates <1mm^3/year for 28mm femoral heads (Rieker, 2017). Volumetric wear is proportional to the size of the femoral head therefore a larger femoral head should only be considered where the benefits of reducing instability outweigh the increased volumetric wear rate. Osteolysis thresholds are dependant on volumetric wear and the biological activity. Biological activity is higher in HXLPE than UHMWPE. De Steiger, Lorimer and Graves, 2018 analysed the Australian NJR for all patients having THR in Australia between 1999 to 2016 comparing HXLPE and conventional polyethylene. HXLPE was significantly less likely to be revised (6.2%; 95%CI 5.7 to 6.7%) compared to conventional polyethylene (11.7%; 95% CI 11.1 to 12.3). The hazard ratio at 9 years was 3.02 (p=0.001).

The use of ceramic femoral heads with HXLPE

Ceramic femoral heads have a low friction coefficient, are scratch resistant and harder than metal heads, have high wettability and do not undergo senescence *in vivo*. Volumetric wear of HXLPE using ceramic heads has been shown to be in the range 0.1mm to 1mm^3/year (D'Antonio and Sutton, 2009). The original Alumina ceramic heads were superseded by Biolox Delta (CeramTex; Plochingen, Germany) in the early 2000s. This comprised 82% alumina and 17% zirconia and has half the risk of crack propagation compared to all alumina heads (Reiker, 2017) and a fracture rate *in vivo* of 0.003% (Massin et al., 2014). Ceramic heads with short neck lengths are more at risk of fracture likely explained as shorter ceramic heads may have thinner ceramic between the corner on the inner surface of the female trunnion and the bearing surface (Callaway et al., 1995; Koo et al., 2009).

Ceramic heads are becoming increasingly popular compared with metal heads (NZJR report, 2018; Norwegian Arthroplasty Register, 2018; Swedish Hip Arthroplasty Register 2017) due to trunnionosis reports at the level of the head-neck junction. It must be evaluated when considering the cause of failure of a THR (Berstock, Whitehouse and Duncan, 2018). Using a ceramic head may avoid fretting and corrosion from the modular head-neck taper and diminish metal ion release when compared to metal heads. It is interesting that femoral stems made of stainless steel and coupled with either stainless steel or ceramic femoral heads have no reported incidence of trunnion corrosion (Westerman et al., 2018). Furthermore there have been recent concerns regarding intra-capsular fibrosis associated with the CoC bearing surface combination (Bertrand et al., 2018).

Femoral head size

Revision rates for aseptic loosening for 36mm heads are higher than 32mm femoral heads (NJR England, Wales Northern Ireland and Isle of Man, 2018) and the increased volumetric wear is proportional to sliding distance. Increasing the size of the femoral head beyond the threshold benefit for reducing instability risk is unjustified (National Joint Registry for England, Wales, Northern Ireland and the Isle of Man, 15th Annual Report, 2018) and femoral head sizes over 32mm increase the risk of trunionosis and does not improve the primary arc range of motion (Berstock, Whitehouse and Duncan, 2018). Fawsitt et al. (2019) performed a cost-effectiveness analysis of the UK and Swedish hip joint registries. A <36mm MoP cemented THR is most cost-effective in adults >65 years of age and a <36mm ceramic-on-polyethylene-cemented THR is most cost-effective in patients <65 years of age. >36mm heads were not cost-effective.

THR in young patients

Two recent registry studies examined the outcomes of THR in patients less than 20 years of age. The first, Pallante et al. (2020), reported the results from a single institution registry involving 91 primary THR performed in 78 patients < 20 years old (1998 to 2016). The bearing surfaces used were CoC (53 THA; 58%), MoPx (28 THA;

31%) and CoPx (10 THA; 11%). Outcome measures included revisions or reoperations, complications, clinical outcomes and bearing-surface wear. At a mean follow-up 8 years (2 to 18) the average modified HHS was 92 (54 to 100); survivorship at 10 years was 97.2% for all-cause revision. The commonest complication was recurrent instability (3%), aseptic loosening (2%) and foot-drop (2%). Linear wear was 0.019mm/yr. There was no difference in linear wear amongst these bearing surfaces. There were no correlations between age, gender, BMI, bearing surface, femoral head size, fixation method, operative time and survivorship. Secondly Metcalfe et al. (2018) reported the results of the National Joint Registry for England, Wales, Northern Ireland and the Isle of Man between 2003 and 2017. The primary outcome was all-cause revision. 769 THRs were done in 703 patients with median follow-up 5.1 years (IQR 2.6 to 7.8). 35 THRs were revised (survivorship 96% at 5 years (95%CI 94 to 98%). Better survival was seen in CoC and CoPx bearing surfaces couples compared to MoM and MoP and in higher volume surgeons.

Highly cross-linked polyethylenes vary in their modes of manufacture. The latest generation of HXLPE contains Vitamin E as an antioxidant in order to reduce wear rates. The infusion of vitamin E in HXLPE reduces oxidation *in vivo* with the aim of improving the mechanical strength of HXLPE. Even if attractive from a theoretical point of view promising early results have been shown with very low wear even for 36mm heads. The next chapter examines whether Vitamin E HXLPE conveys greater advantage over older HXLPE in primary THR.

CHAPTER SIX

Does vitamin E Highly cross-linked polyethylene convey an advantage in primary total hip replacement? A systematic review and meta-analysis

Reference: Wyatt, M., Roberton, A., Foxall-Smith, M., Beswick, A., Kunutsor, S. and Whitehouse, MR 2019. Does vitamin E Highly cross-linked polyethylene convey an advantage in primary total hip replacement? A systematic review and meta-analysis. *Hip International Jun 18:1120700019858335. doi: 10.1177/1120700019858335. [Epub ahead of print]*

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Wyatt MC – data analysis, writing the paper, lead author
Roberton A – writing the paper, construction of tables
Foxall-Smith M – writing the introduction
Beswick AD – Search strategy and construction of Excel spreadsheet
Kunutsor SK – meta-analysis
Whitehouse MR – Senior author, final editing

Abstract

Background

Vitamin E highly cross-linked polyethylene (HXLPE) was developed to reduce wear in total hip replacement (THR). This study aimed to provide independent synthesis of wear characteristics of Vitamin E treated HXLPE compared to HXPLE/UHMWPE. Secondary outcome measures were differences in revision rates and functional scores.

Methods

We performed a systematic review; literature searches were conducted on 14th November 2017 (MEDLINE, Embase on Ovid, and the Cochrane Library). We included randomised controlled trials, analyses of joint registries, and case-controlled studies of primary THR comparing cups with a Vitamin E HXLPE bearing with bearing surfaces made from other types of polyethylene. Initial screening was performed by two independent assessors; disagreement resolved in discussion with a third reviewer. Studies were evaluated using the Cochrane risk of bias tool. Data extraction permitted meta-analysis.

Results

372 studies were identified on initial screening; 5 studies met the eligibility criteria. There was no significant heterogeneity between studies. There was variable risk of bias. At a mean of 35 months (range 20 to 60), Vitamin E HXLPE had significant advantages over highly cross-linked polyethylene with regards total femoral head penetration ($p = 0.004$). Given the RSA measurement errors this may not be clinically significant. There were neither significant differences in revision rates nor Harris Hip Scores ($p = 0.06$).

Conclusion

At a minimum of 3 years this bearing surface does not as yet have clinically significant advantages in terms of revision rates or patient function over HXLPE.

Keywords: Vitamin E, meta-analysis, total hip replacement

Introduction

Many bearing materials have been utilised in total hip replacement (THR) including ivory, silver, rubber, celluloid, glass and wood (Kurtz et al., 1999). Ultra-high molecular weight polyethylene (UHMWPE) has been in used for nearly 60 years (Del Prever et al., 2009). According to National Joint Registry of England and Wales (NJR) data from 2016, it is used in 88% of THRs (NJR accessed 2017). Wear and aseptic loosening are common causes of revision in THR (NJR accessed 2017), wear of UHMWPE is predisposed to by oxidative degradation which decreases wear resistance and leads to increased osteolysis; a major cause of implant failure (Kurtz et al., 1999; NJR accessed 2017; McKellop et al., 2000; Besong et al., 1998; Harris, 2001).

The sterilisation process is a major contributor to degradation of UHMWPE (Yu et al., 1999; Costa et al., 1998). High-energy radiation, used in sterilisation processes, induces oxidation. Bond scission occurs with the formation of free radicals (Del Prever et al., 2009; Yeom et al., 1998). This reduces molecular mass and alters the mechanical properties of the UHMWPE. The oxidation continues during storage and *in vivo* once implanted (Costa et al., 1998). Since 1998, highly cross-linked and thermally treated polyethylenes (HXLPEs) were introduced to improve wear resistance. It was theorised they would reduce the incidence of revision. Cross-linking results in an increased molecular mass; improving wear resistance and mechanical properties compared to UHMWPE (Pruitt, 2005; Kuzyk et al., 2011). Following irradiation, the HXLPEs are thermally treated to remove residual free radicals. Two different processes, remelting and annealing, are used. Only remelting treatment effectively removes residual free radicals (Harris, 2004; Gomoll, Wanich and Bellare, 2002). Other processing methods have been considered but have not been able to eradicate free radicals meaning oxidative degradation can occur (Kurtz et al., 2006).

Vitamin E (VE) is an antioxidant that can be added to the HXLPEs to combat oxidative degradation and improve fatigue properties by avoiding post-irradiation melting (Oral 2004). *In vitro* studies have demonstrated a protective effect of VE on oxidative degradation, with improved mechanical and wear properties (Bracco et al., 2007; Oral et al., 2006; Oral et al., 2006). Additionally, *in vitro* and animal studies have not demonstrated adverse reactions (Jarrett et al., 2010). Despite this, there is currently limited clinical evidence to support the use of Vitamin E HXLPE.

There are 2 methods of adding Vitamin E: the first is by blending UHMWPE powder with vitamin E prior to consolidation and cross-linking (blended Vitamin E HXLPE); the second is by doping the consolidated and cross-linked material in a hot Vitamin E solution, allowing vitamin E to diffuse into the material (diffused Vitamin E HXLPE) (Tanino et al., 2017). The purpose of this study is to provide an independent synthesis of the wear characteristics of Vitamin E treated HXLPE compared to HXPLE or UHMWPE. Secondary outcome measures were differences in revision rates and functional scores.

Materials and Methods

Before commencing the review, the study protocol was registered with PROSPERO (CRD42017074141) as recommended by the Quality of Reporting of meta-analyses (QUOROM) statement (Moher et al., 1999). We used a rigorous and systematic approach conforming to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and a PRISMA checklist is included in Appendix 1.

Search Strategy

We searched the electronic databases MEDLINE and Embase on the OVID platform, and The Cochrane Library using the search strategy shown in Figure 19. Searches were conducted from database inception to 15th November 2017. We did not limit the search to English language publications. We also evaluated the grey literature with hand searches of conference abstracts published in 6 major Orthopaedic journals in the 5 years before the search date. Bibliographies of relevant articles were checked and key citations tracked in Web of Science.

1. Hip Prosthesis/ or Arthroplasty, Replacement, Hip/ or hip replacement.mp.
2. Vitamin e.mp.
3. Tocopherol.mp. or Tocopherols/
4. Tocotrienol.mp. or Tocotrienols/
5. 2 or 3 or 4
6. 1 and 5

Figure 19. Search strategy

Eligibility Criteria

We included all randomised controlled trials (RCTs), analyses of joint registries and case-controlled studies including patients of all age groups receiving primary total hip replacement using Vitamin E HXLPE compared to any other type of polyethylene.

Screening

Title and abstracts were screened by 2 independent assessors with any disagreements resolved in discussion with a third reviewer. If any uncertainties relating to inclusion occurred, we planned to contact authors for clarification.

Data Extraction

Two of the authors worked independently to extract the data using standardised forms. We extracted data on: study country; recruitment dates; setting; participant characteristics; duration of follow-up; acetabular and femoral head bearing material and size; outcomes relating to primarily the degree and measurement of femoral head penetration; secondarily the revision rates, Harris Hip Score, patient reported outcome measures; and risk of bias. An electronic spreadsheet was constructed to summarise the findings of relevant studies.

Study Quality

Potential sources of bias in RCTs were assessed using the Cochrane risk of bias tool (Higgins and Green, 2008). This method assesses selection, performance, detection, attrition, and reporting biases. Summary assessments of risk-of-bias (high, low or unclear) for each outcome in each trial are reported. We planned to use alternative risk of bias assessment methods for assessment of non-randomised studies.

Statistical Analysis

Data were combined in meta-analysis using Review Manager software (Review Manager (RevMan) 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration; 2014). Heterogeneity was assessed using the I2 statistic representing the proportion of variability across studies not due to chance or random error. Pre-specified subgroup analysis was performed relating to different polyethylene comparators and femoral head materials.

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Results

A total of 372 records were identified by literature searches. The titles and abstracts were screened to identify potentially useful articles for inclusion. After screening, 16 articles were assessed for eligibility. A flow diagram of the progression of studies through the systematic review is provided in Figure 20.

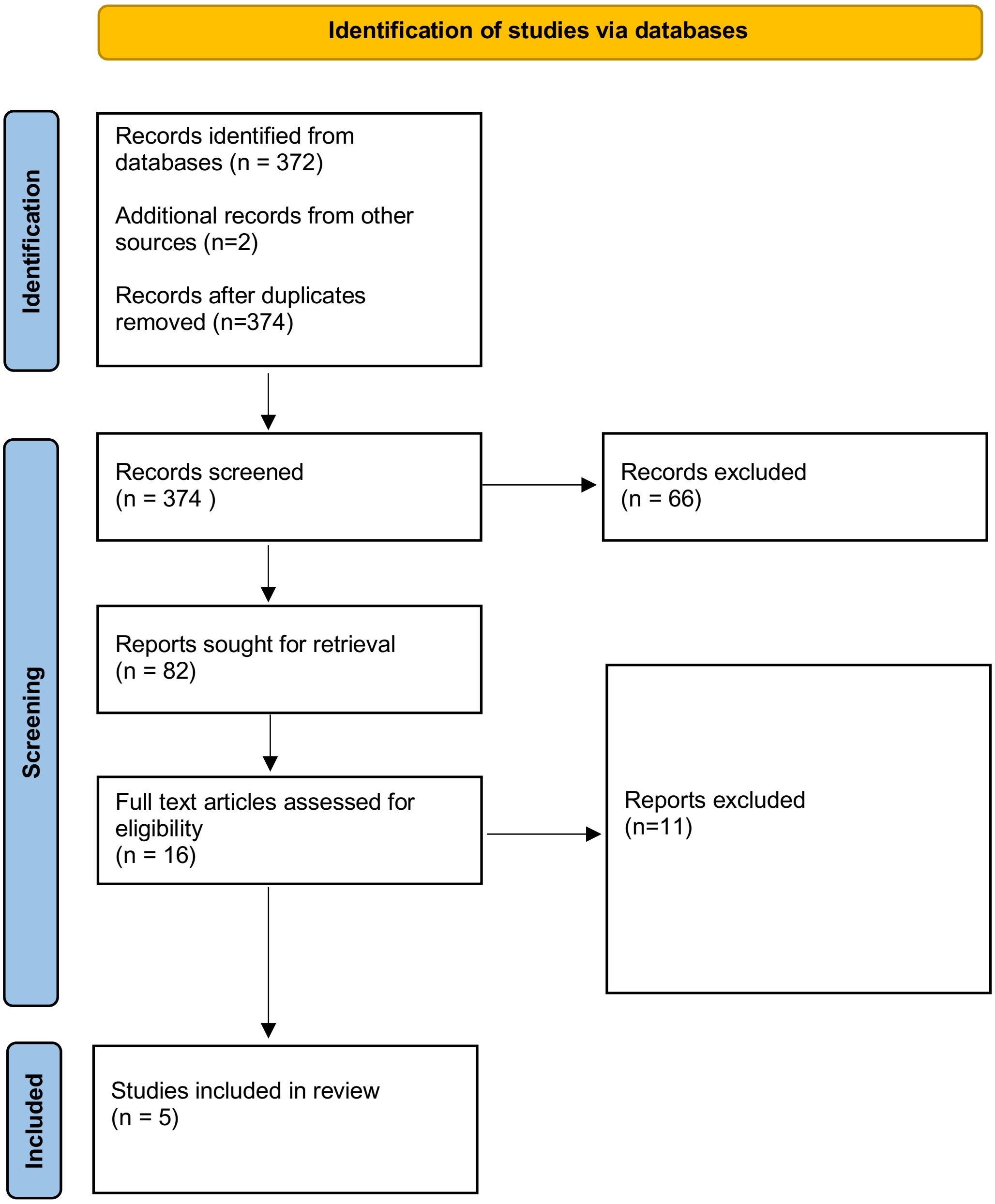

Figure 20. PRISMA flow diagram

There were 5 articles that contributed to our estimates of femoral head penetration, revision and functional outcome. There were 4 prospective randomised controlled trials (RCTs), all from Europe with recruitment from 2008, of which 3 examined diffused Vitamin E HXLPE compared to HXLPE (Salemyr et al., 2015; Nebergall et al., 2016; Shareghi et al., 2015). The remaining RCT compared Vitamin E blended HXLPE to conventional UHMWPE (Scemama et al., 2017). Study characteristics are summarised in Table 28. There was a low risk of bias amongst RCTs when we examined sequence generation, allocation/concealment, blinding, completedness of data and reporting (Table 29). One other study from Japan had a case-control design and compared blended Vitamin E HXLPE and HXLPE. Although the authors reported propensity matching, we considered the study to be at high risk of bias because under a quarter of the 348 patients recruited were followed up (Tanino et al., 2017).

Table 28. Study characteristics

Study Country Baseline dates Setting	Inclusion Number randomised: intervention; control Mean age (SD) % female	Groups compared Common treatments	Key outcomes Longest follow up	Overall risk of bias Key results
RCTs: Vit E diffused HXLPE vs HXLPE				
Salemyr et al. 2015 Sweden 2009-2013 1 hospital	Primary OA 51: 25: 26 (24; 26 received allocated intervention) 62 (6); 62 (5) 58%; 56%	Vit E diffused HXLPE liner vs standard HXLPE liner Uncemented acetabular shell. Uncemented stem with 32mm cobalt chrome head	Radiography, RSA, HHS, EQ-5D, complications 24 months	Low risk of bias Included in meta-analysis Head penetration in transverse x (p = 0.004) and vertical y (p = 0.035) axes were lower in Vit E group. Similar in anteroposterior z axis (p = 0.629). Total penetration similar between groups (p = 0.09). Revisions: 1; 1 HHS (p = 0.295) and EQ-5D (p = 0.173) similar between groups. Overall number of complications similar between groups.
Nebergall et al 2017 Denmark 2009-2011 1 hospital	Primary OA 82: 41; 41 (32; 35 received allocated intervention) Median (range) 67 (43, 76); 65 (40, 73) 50%; 54%	Vit E diffused HXLPE liner vs medium cross-linked PE liner Uncemented acetabular shell. Uncemented stem with 32mm ceramic head	Radiography, RSA, HHS, PROMs, osteolysis 5 years	Unclear risk of bias due to uneven loss to follow up at 5 years (4; 9) Included in meta-analysis Head penetration in mediolateral x, proximodistal y and anteroposterior z axes similar between groups. Revisions: 2; 3 No differences between groups in HHS, UCLA activity, SF-36 physical function, EQ-5D, VAS pain and satisfaction. No osteolysis observed
Shareghi et al. 2017 Sweden 2008-2010 1 hospital	Osteoarthritis 61 (70 hips): 38; 32 hips Median (range) 58 (20, 73)	Vit E diffused HXLPE liner vs heat-treated HXLPE Uncemented acetabular shell. Uncemented stem with 32mm CoCr head	Radiography, RSA, HHS (self-reported), pain score 5 years	Unclear risk of bias due to uneven loss to follow up (1; 6) and randomisation method Included in meta-analysis Total head penetration and head penetration in proximal y axis lower in Vit E group than heat treated group (p = 0.004 and p < 0.001 respectively). Revisions: 0; 1 No difference in HSS between groups (p = 0.90) or pain score (p = 0.80).
RCT: Vit E blended HXLPE vs UHMWPE				
Scemama et al. 2017 France 2010-2011 1 hospital	Primary or secondary OA 100 (50; 50) Median (range) 67 (32, 74); 66 (49, 75) 48%; 56%	Vit E blended HXLPE vs UHMWPE Monoblock cementless acetabular component. Cemented stem with 28mm CoCr head	Radiography, Martell, Merle d'Aubigné grade, adverse events 3 years	Unclear risk of bias due to high losses to follow up (13; 11). No suitable data for meta-analysis Total head penetration lower in Vit E HXLPE group compared with UHMWPE (p = 0.04). No differences between groups in Merle d'Aubigné grade (p > 0.99). No adverse events related to Vit E HXLPE
Case control study: Vit E blended HXLPE vs HXLPE				
Tanino et al. 2017 Japan 2013-2015 1 centre	170; 178 (180; 193 hips). 44; 41 (45; 45 hips) followed up 61.1 (range 42, 89) Sex not reported	Blended Vit E HXLPE liner vs conventional HXLPE liner 32mm CoCr head	Radiography, 2 years	High risk of bias. Propensity matched but only partial follow up No differences between femoral head penetration (p = 0.161). Dislocation 1; 2. Infection 1; 0.

Table 29. RCT risk of bias assessment.RCT risk of bias assessment

	Sequence generation	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Overall
Salemyr et al. 2015	Low. Block randomisation	Low. Opaque sealed envelopes	Low. Patients blinded	Low. 1 patient did not receive vit E HXLPE as allocated. 1;1 patients died	Low. None apparent	Low. HHS higher in Vit E HXLPE group but not significantly	Low
Nebergall et al 2017	Low. Pre-assigned	Low. Sealed envelopes	Low. “Blinded”	Unclear. Uneven loss to follow up at 5 years (4; 9)	Low. None apparent	Low. Vit E group older than comparison group	Unclear
Shareghi et al. 2017	Unclear. Unequal distribution of patients to groups due to method of allocating bilateral replacements	Low. Closed envelopes	Unclear. Blinding of patients and outcome assessment not described	Unclear. Uneven loss to follow up at 5 years (1; 6)	Low. None apparent	Low	Unclear
Scemama et al. 2017	Low. Computer generated	Low. Based on order of presentation	Low. Radiography by blinded observer. High. Clinical follow up by operating surgeon	High. Loss to follow up excluding 2 deaths high (13; 11)	Low. None apparent	Low. Similar baseline characteristics	Unclear
Tanino et al. 2017	Propensity matched case control study	Not applicable		High loss to follow up		High: partial follow up	High

Vitamin E HXLPE compared to HXLPE

All RCTs used radiostereometry (RSA) to examine femoral head penetration. In 2 studies with 187 patients followed up for 2 and 5 years (Salemyr et al., 2015; Shareghi et al., 2017), total reported femoral head penetration was presented. In the meta-analysis shown in Figure 21, total reported femoral head penetration was significantly less in the Vitamin E diffused HXLPE groups compared with conventional HXLPE, mean difference 0.08mm (95%CI 0.13, 0.02; p = 0.004) and no heterogeneity was evident (Figure 21). However, the RSA measurement errors in these 2 studies were 0.13mm and 0.14mm respectively therefore this numerically significant difference is unlikely to be clinically significant. Furthermore, only one study was at low risk of bias (Salemyr et al., 2015) and in this study with 51 patients followed up, the difference between groups was not statistically significant (p = 0.09). In one case-control study there was no difference between patients in femoral head penetration between Vitamin E blended HXLPE and HXLPE liners (p = 0.161) but risk of bias was high due to the reporting of interim follow up of 24% of patients (Tanino et al., 2017).

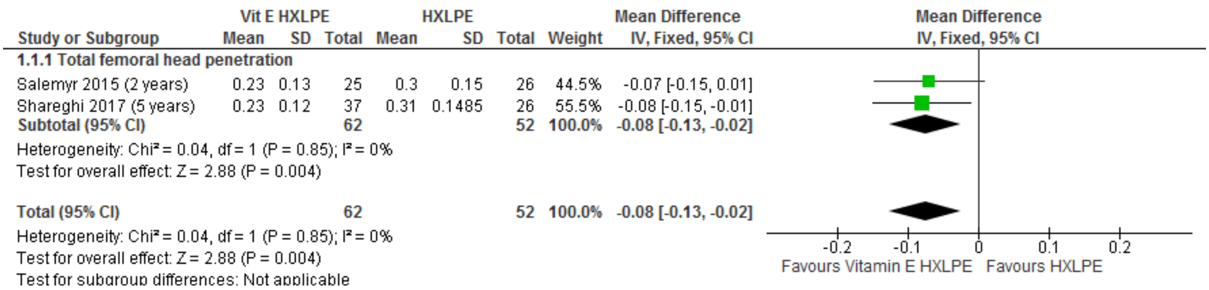

Figure 21. Meta-analysis of total femoral head penetration

Meta-analyses of femoral head penetration by vector are shown in Figures 22-24. Transverse femoral head penetration was reported in 2 RCTs with data from 104 patients followed up for 2 (Salemyr et al., 2015) and 5 years (Nebergall et al., 2017). In the meta-analysis shown in Figure 22 transverse femoral head penetration was lower in patients receiving a Vitamin E diffused HXLPE liner, mean difference 0.08mm (95%CI 0.03, 0.14; p = 0.003) with no heterogeneity evident. In the one study at low risk of bias (Salemyr et al., 2015), the difference was statistically significant (p = 0.004).

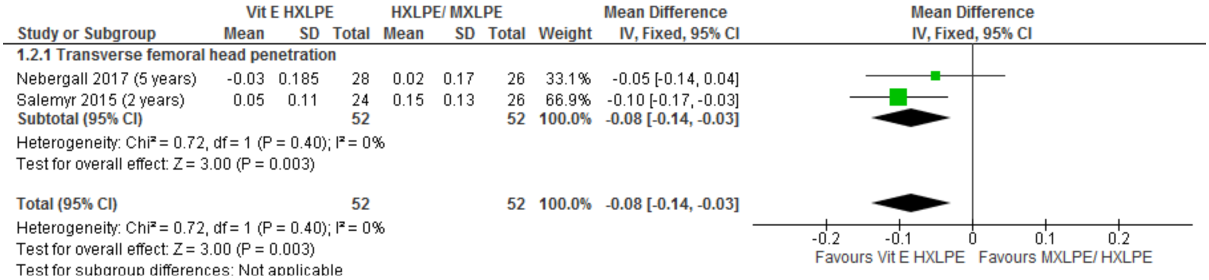

Figure 22. Meta-analysis of transverse femoral head penetration

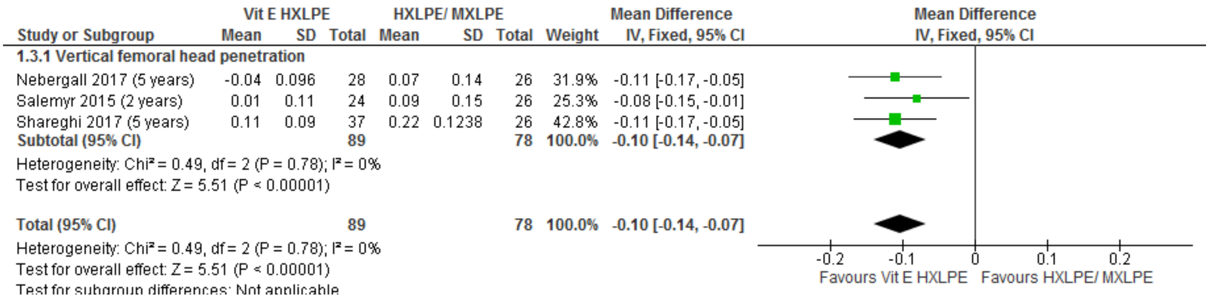

Figure 23. Meta-analysis of vertical femoral head penetration

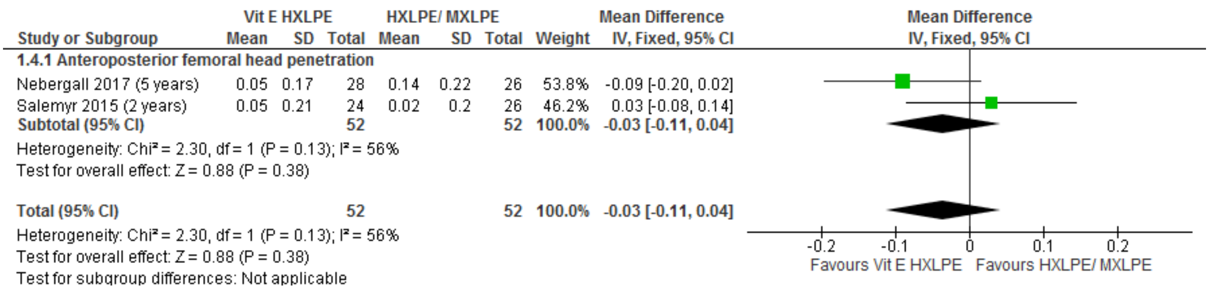

Figure 24. Meta-analysis of anteroposterior femoral head penetration

Three RCTs with 167 patients followed up for 2 (Salemyr et al., 2015) or 5 years (Nebergall et al., 2017) reported vertical femoral head penetration. In the meta-analysis shown in Figure 23, vertical head penetration was lower in patients receiving a Vitamin E diffused HXLPE liner, mean difference 0.10mm (95%CI 0.07, 0.14; $p < 0.00001$) and there was no heterogeneity between studies. In the one study with low risk of bias (Salemyr et al., 2015), the difference was statistically significant, p = 0.035.

Two RCTs with 104 patients followed up reported anteroposterior femoral head penetration at 2 and 5 years (Salemyr et al., 2015; Nebergall et al., 2017). The meta-analysis in Figure 24 showed a high level of heterogeneity between the studies, I2 = 56% and we only show the results for completeness. One study showed a trend favouring the group that received a Vitamin E diffused HXLPE liner (Nebergall et al., 2017) and the other a trend favouring the control group receiving HXLPE (Salemyr et al., 2015). Neither trend was statistically significant and only the latter study was at low risk of bias.

Revision rates

Study sample sizes were small and revision rates low. Overall there were 3 revisions in the Vitamin E diffused group and 5 revisions in the control HXLPE group. Two revisions for dislocations occurred in patients receiving Vitamin E diffused HXLPE and 1 in control patients receiving HXLPE but all were in a study with unclear risk of bias due to uneven losses to follow up between groups at 5 years (Nebergall et al., 2017). In the case control study with high risk of bias, there was 1 dislocation in patients receiving blended vitamin E HXLPE liners compared with 2 in those receiving an HXLPE liner.

Patient reported outcomes

Two RCTs with 104 patients and data suitable for meta-analysis reported the Harris Hip Score at 2 years (Salemyr et al., 2015) and 5 years (Nebergall et al., 2017) follow up. As shown in Figure 25, heterogeneity between studies was high. One study with low risk of bias showed no statistically significant difference between groups at 2 years ($p = 0.295$). One RCT with data suitable for meta-analysis (Nebergall et al., 2017) and another only reporting medians and ranges (Shareghi et al., 2017) had unclear risk of bias due to uneven loss to follow up. In neither was there a statistically significant difference in Harris Hip Score between groups.

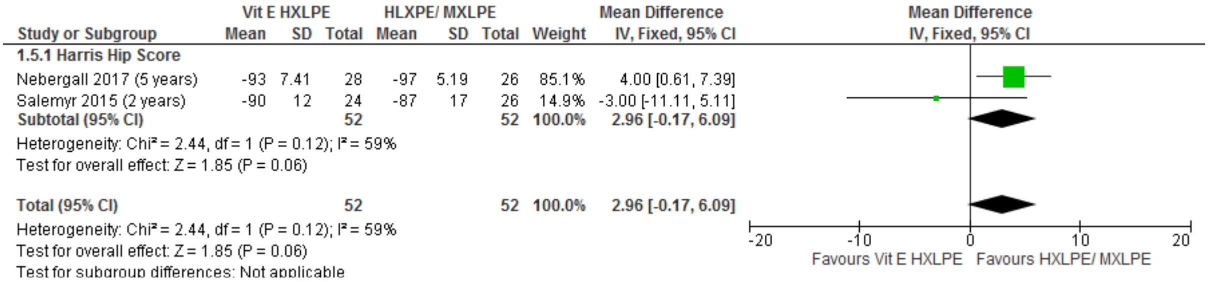

Figure 25. Meta-analysis of Harris hip scores

In two RCTs, patient reported health related quality of life was assessed using the EQ-5D (Salemyr et al., 2015; Nebergall et al., 2017). There were no differences between outcomes in either study, including one at low risk of bias (Salemyr et al., 2015).

Vitamin E blended HXLPE compared to UHMWPE

In one RCT with 100 patients randomised and followed up for 3 years, vitamin E blended HXLPE liners were compared with UHMWPE liners (Scemama et al., 2017). Total head penetration was lower in the vitamin E HXLPE group (p = 0.04) but the study was at unclear risk of bias due to high losses to follow up. There was no difference in functional outcome measured using the Merle d'Aubigné score (p > 0.99).

Discussion

Total hip replacement is a clinically effective and cost-effective intervention (Garellick et al., 1998). Any improvement in the outcome of THR is likely to arise through reducing the incidence of adverse events or reducing the need for subsequent revision surgery. This systematic review and meta-analysis have shown that Vitamin E HXLPE has reduced femoral head penetration over highly cross-linked and conventional polyethylenes. However, the differences are small in comparison with the measurement error of the techniques used to measure it and there is no evidence from our rigorous systematic review to show a clinically significant benefit of Vitamin E HXLPE over HXLPE in terms of revision rate or function at this early stage. The lack of difference in functional scores is perhaps not surprising as Harris Hip Score is a score to assess the effect of THR as an intervention and not to tell the difference between patients undergoing THR with different types of bearing surface. Ceramic-on-HXLPE in primary total hip replacement has been shown to have the lowest all-cause revision rates in a large National Joint Registry study (Sharplin et al., 2017) and the reduced wear evident with the use of Vitamin E HXLPE may lead to further reduction in revision rates. A reduction in revision rates has not been shown in this study.

The findings of our study should be interpreted with caution. A recent high-quality systematic review and network meta-analysis of 3,177 THRs concluded that there was currently insufficient evidence to recommend any bearing combination over a traditional metal on UHMWPE THR (Lopez-Lopez et al., 2017). A prospective RCT of 122 patients at 10 years follow-up not included in this systematic review and network meta-analysis showed that HXLPE liners have a significantly reduced wear and greater survival rate compared to UHMWPE liners (Devane et al., 2017). Furthermore, although *in vitro* evidence has shown increased bacterial resistance with Vitamin E HXLPE (Banche et al., 2015), there was no evidence in our study to support a decreased rate of revision for periprosthetic infection with this bearing surface.

Systematic review and meta-analysis with assessment of risk of bias can help clinicians to interpret results of studies in diverse settings with different outcome measures. There are limitations to this study however. There are a limited number of randomised controlled trials all of limited follow-up from which to extract data and there were only 187 patients contributing to the meta-analysis of total femoral head penetration. Further RCTs examining Vitamin E HXLPE are underway however (Jäger et al., 2014; Sköldenberg et al., 2016). We did not perform a network meta-analysis to compare blended and diffused Vitamin E HXLPE especially given the high risk of bias determined in the only study that examined the latter. There were a variety of femoral head sizes used in the studies and both metal and ceramic femoral heads were included. However, we extracted data using rigorous selection criteria and there was low heterogeneity for total femoral head penetration.

Long-term follow-up, high-quality independent RCTs involving large numbers of patients and using consistent outcome reporting or large generalisable observational cohorts with comprehensive coverage are required to determine if lower wear results in lower revision rates. Such studies should be undertaken however before guidance can be provided on clinical effectiveness of new technologies in THR.

Conclusions

This systematic review and meta-analysis showed that there were numerically but not clinically significant wear advantages in terms of femoral head penetration for Vitamin E HXLPE over HXLPE. There was no improvement in revision rates or functional outcome at this stage. However, there were few high quality studies and longer-term follow-up is required. This bearing surface has encouraging early results in terms of wear.

Commentary

Critique

In the previous chapter the systematic review and meta-analysis showed that Vitamin E HXLPE, at least at this stage, has no clear clinical advantage over HXLPE in terms of all-cause revision rates despite the theoretical advantages of increased resistance to oxidation. The RSA studies did not show Vitamin E HXLPE to be inferior to HXLPE in terms of wear which suggests that Vitamin E HXLPE may prove advantageous in the future.

If we accept an average life expectancy for a male aged 55 is 32 years and females is 34 years then THR ideally should last for 40 years before revision. Bone and soft-tissue preservation are crucial concepts to permit this and to potentiate the ease with which a revision THR can be performed. In theory, these goals can be achieved by excellent surgical techniques and sensible implant choices that have minimal stress-shielding with bearing surfaces, and that have wear rates beneath the osteolysis threshold of 0.05mm/year (Dumbleton, Manley and Edidin, 2002) or cumulative osteolysis threshold of 670mm^3 (Elke and Rieker, 2018). In recent studies a monoblock pressfit Vitamin E HXLPE cup showed linear rates of 0.02mm/year compared to UHMWPE at 0.058mm/year (Rochcongar et al., 2018, Wyatt et al., 2017) on RSA studies. This is in concordance with the results of Chapter 6. Vitamin E HXLPE with a 32mm head should therefore last more than 40 years before osteolysis threshld. Vitamin E HXLPE cups may be more forgiving in terms of the angle at which they are inserted as there was no demonstrable increase in wear rates between 45 degrees and 80 degrees in terms of wear rates (Halma et al., 2014). Long term registry studies will determine whether these benefits are realised.

Up-to-date literature search

To update the context of the findings of Chapter 6 the following databases were searched from 2019 to 30.3.2020 using the programme Papers: ACM, ADS, arXiv, CERN DS, CrossRef DOI, DBLP, Espacenet, Google Scholar, Gutenberg, Highwire, IEEExplore, Inspire, JSTOR, OAIster, Pubget, PubMed, ScienceDirect, Scopus and Web of Science. Search terms related to: Vitamin E AND Total hip.

111 references were identified of which 6 were collected as potentially relevant. Those single published articles that cited Chapter 6 were also examined. Journals with impact factors <2 were excluded. Any correspondence relating to the article described in this chapter was reviewed.

Galea et al. (2019), reported the 7 year results of their RCT for Vitamin E HXLPE liners in conjunction with uncemented shells. In this small RCT, RSA wear rates were were low at <0.1mm/yr in patients receiving botha Vitamin E HXLPE or a moderately cross-linked polyethylene liner. Interestingly Skoldenberg et al. (2019) performed a double-blind noninferiority RCT with cemented Vitamin E HXLPE liners in reverse hybrid THR constructs. 42 patients (mean age 67) were included. The total RSA migration and proximal migration of the Vitamin E HXLPE cemented cups were significantly higher than standard polyethylene at 2 years. There were no differences in clinical outcomes. Therefore, there was no evidence of non-inferiority but the early proximal migration the authors suggested is a reason for ongoing monitoring of Vitamin E HXLPE.

When performing this systematic review other properties and outcomes of interest concerning Vitamin E HXLPE became apparent. Vitamin E HXLPE has, in some studies, been shown to reduce the adhesive abiliity of bacteria commonly involved in periprosthetic joint infections including Staphylococcus epidermidis, Staphylococcus aureus and Escherichia (Banche et al., 2011; Banche et al., 2014). A decreased adhesion of blended Vitamin E HXLPE has also been found for *Candida albicancs*. Vitamin E-blended HXLPE did not however reduce the attachment or formation of bacterial biofilms of a clinically relevant strain of methicillin resistant *Staphylococcus aureus* compared to conventional UHMWPE or highly cross-linked UHMWPE. Some authors have shown that Vitamin E blended with UHMWPE (not HXLPE) decreased *in vitro* the adherence ability of some of the most common bacteria involved in periprosthetic joint infections (*Staphylococcus epidermidis, Staphylococcus aureus* and *Escherichia coli*) in comparison with untreated UHMWPE. In addition, a decreased adhesion on Vitamin E blended UHMWPE has been also found for *Candida albicans*. These studies therefore suggest that it is the addition of Vitamin E that produces the anti-adhesive effect and not the type of polyethylene potentially limiting the extent of bacterial adhesion and subsequent biofilm formation (Williams et al., 2015). This property of Vitamin E HXLPE may therefore inhbit the potential for periprosethetic joint infection and long-term studies will elucidate this (Banche et al., 2015).

Whilst periprosthetic THR infection is rare it remains a devastating complication. It costs at least 4 times the cost of the primary THR to address, and these costs are climbing (Mistry et al., 2017; Blom et al., 2003). The incidence of infected THR is increasing (Kurtz et al., 2008). A periprosthetic infection after THR also has extremely negative effects on the physical, emotional, social and economic aspects of a patient's life (Beswick et al., 2012). The annual incidence is 1 to 2.5% (Bozic et al., 2014). The key strategies to address this problem therefore are primary prevention of infection and should it occur early diagnosis and effective management by a multi-disciplinary team (Zimmerli, 2014).

Preventing periprosthetic infection comprises numerous methods employed preoperatively, intraoperatively and postoperatively. Preoperative skin cleaning with chlorhexidine cloths lower the incidence of infection in patients undergoing THR for example (Kapadia et al., 2013). Intraoperatively the patient's skin is ideally shaved with clippers and then prepared with 2 treatments of chlorhexidine gluconate (Mistry et al., 2017). The use of woven drapes is inferior to disposable plastic drapes and the bacterial penetration rate is > 100,000 times higher if the drapes are wet (Blom et al., 2000; 2002). Increased staff traffic volume is associated with an increased risk of infection and the use of antibiotic prophylaxis is mandatory. In a recently published systematic review however there was no evidence to support a difference between reusable or disposable drapes to reduce the riks of surgical site infection in orthopaedic surgery (Kieser et al., 2018). Intraoperative measures to prevent infection can also include management of the theatre environment which was first recognised and pioneered by Sir John Charnley. Such measures included the use of laminar flow and wearing space suits which will be explore in the next chapter as these factors are recorded routinely in the NZJR.

ADDRESSING INFECTION

CHAPTER SEVEN

Does the use of laminar flow and space suits reduce early deep infection after total hip and knee replacement? The 10-year results of the New Zealand Joint Registry

Reference: Hooper, G., Rothwell, A., Frampton, C. and Wyatt, M. (2011). Does the use of laminar flow and space suits reduce early deep infection after total hip and knee replacement?: the ten-year results of the New Zealand Joint Registry. *Journal of Bone and Joint surgery, British volume,* 93(1), pp.85-90.

Authors contributions:
Hooper G – lead author, final editing
Rothwell Ag – editing the paper
Frampton C – statistical analysis and data retrieval from Registry
Wyatt M – data analysis, writing the paper, Senior author

Abstract

We have investigated whether the use of laminar-flow theatres and space suits reduced the rate of revision for early deep infection after total hip (THR) and knee (TKR) replacement by reviewing the results of the New Zealand Joint Registry at 10 years.

Of the 51,485 primary THRs and 36,826 primary TKRs analysed, laminar-flow theatres were used in 35.5% and space suits in 23.5%. For THR there was a significant increase in early infection in those procedures performed with the use of a space suit compared with those without ($p < 0.0001$), in those carried out in a laminar-flow theatre compared with a conventional theatre ($p < 0.003$) and in those undertaken in a laminar-flow theatre with a space suit ($p < 0.001$) when compared with conventional theatres without such a suit. The results were similar for TKR with the use of a space suit ($p < 0.001$), in laminar-flow theatres ($p < 0.019$) and when space suits were used in those theatres ($p < 0.001$). These findings were independent of age, disease and operating time and were unchanged when the surgeons and hospital were analysed individually.

The rate of revision for early deep infection has not been reduced by using laminar flow and space suits. Our results question the rationale for their increasing use in routine joint replacement, where the added cost to the health system seems to be unjustified.

Background

Deep infection after total joint replacement is a devastating complication. Although the incidence of recurrent infection after a revision procedure is low (Biring et al., 2009) it still remains a significant complication which may require several procedures at considerable expense (Bannister, 2002). The estimated financial cost of revision for infection is four times that of the initial procedure (Dreghorn and Hamblen, 1989).

Early infection is predominantly secondary to intraoperative contamination (Charnley, 1964; Whyte, Hodgson and Tinkler, 1982). The prophylactic use of antibiotics both systemically and within cement has reduced the rates of early infection but the development of resistant bacteria continues to be a major concern (Ericson, Lidgren and Lindberg, 1973).

Airborne contamination can be decreased by limiting the number of personnel and their movement within the operating room, and also by changing the ventilation within it (Fitzgerald and Washington, 1975; Ritter, 1999; Lidwell, 1998). The creation of a clean-air environment by the use of laminar-flow systems was introduced by Charnley 1979 and resulted in a significant reduction in his rates of early infection. The 'cleanliness' of the air within an operating theatre can be further improved by increasing the rate of exchange of air within the room. Conventional plenum ventilation theatres have rates of air exchange of 30 times per hour, whereas laminar-flow theatres exchange the total volume of air in the room over 300 times an hour. This clean air delivered at a positive pressure should result in a maximum of 10 colony-forming units per cubic metre (cfu/m^3), but with values as low as 1 cfu/m^3. The Medical Research Council trial (Lidwell, 1998) confirmed the value of laminar-flow theatres in the reduction of cfus.

Protective suits with hoods and self-contained exhaust systems (space units) have been used to improve sterility further. The cfus/m^3 can be reduced to a value as low as 1.0 with the combined use of both laminar flow and space suits (Lidwell, 1998; Davis et al., 1999). This reduction in bacteria has been assumed to be associated with a lower risk of contamination of the wound and subsequent early infection. Although the combined use of laminar flow and space suits make intuitive sense there have been limited studies investigating early rates of infection after total joint replacement using these methods (Davis et al., 1999).

Since the overall rate of infection in joint replacement is extremely low and there are a multitude of factors potentially responsible (Willis-Owen, Konyves and Martin, 2010) conducting randomised trials with sufficient statistical power is unrealistic. Joint registries allow the study of large prospective data bases in a reliable manner and are able to produce powerful data for rare complications such as infection. We have studied the use of laminar flow and space suits and related this to the rate of early deep infection in revision arthroplasty by using data over 10 years from the New Zealand Joint Registry. This registry captures 98% of both primary and revision arthroplasties performed in New Zealand and records revision procedures secondary to deep infection. Our hypothesis was that both laminar flow and the use of space suits would result in a lower rate of early deep infection requiring a revision procedure following total hip (THR) and knee (TKR) replacements.

Patients and Methods

We retrospectively analysed the data from the New Zealand Joint Registry between 1999 and 2008 to record the early rates of revision for infection for all registered primary THRs and TKRs. We defined revision due to early infection as any such procedure performed within 6 months of the initial operation for infection.

The Joint Registry collects information on all revision procedures performed and documents the reason for the revision. It also captures information on whether the initial procedure was performed within a conventional or laminar-flow operating room and whether space suits were used at the time of the operation.

The rate of infection was recorded as a percentage of all the THRs or TKRs performed over the 10 years with a minimum follow-up of 6 months from these operations. The rate was compared between those procedures performed in a conventional operating room with those undertaken in a purpose-built laminar-flow operating room, and between operations using space suits with those without. Operations using both laminar flow and space suits were compared with those using neither.

In order to minimise associated variables such as the operating time, the use of antibiotics and the surgical technique, we then compared the revision rates for those surgeons who had experience in both conventional and laminar-flow operating theatres and who had performed at least 50 procedures in both. We also compared the revision rates of those surgeons who had used space suits in both surgical settings and who had completed at least 50 procedures in each. We made the assumption that these surgeons were likely to have maintained similar surgical practices between the differing operating environments. This was further investigated by sending a questionnaire on their surgical practice to all the surgeons who fulfilled the above criteria. These results were further evaluated by reviewing the data, the patient's clinical details and the duration of the operation in the Joint Registry for each surgeon. The questionnaire also requested information from the surgeons on the frequency of use of space suits, which members of the surgical team wore them, whether their practice changed depending on the operating theatre or surgical team and whether they wore full suits or just a hood with a fan system.

In order to decrease the impact of variables associated with individual hospitals, we analysed each hospital to see whether there was any difference among hospitals for those surgeons who used space suits and laminar flow compared with those who operated without them in conventional theatres. Finally, we asked all the hospitals to confirm which theatre ventilation system they used, the rate of air exchange and the maintenance programme of the filters.

Statistical Analysis

The percentages with revision for deep infection were compared between groups using the chi-squared test or Fisher's exact test when expected frequencies were low. A p-value of < 0.05 was considered significant.

Results

There were 51,485 primary THRs and 36,826 primary TKRs registered on the New Zealand Joint Registry during the period of study with full information on the theatre environment. The most common diagnosis before the initial procedure was osteoarthritis (94% for both THR and TKR) with a low incidence of inflammatory arthritis (3% THR, 4% TKR). Laminar-flow theatres were used for 33% of all THRs compared with 38% of all TKRs. Space suits were used in 21% of all THRs and in 26% of all TKRs. There was a steady increase in the use of laminar-flow theatres and the use of space suits between 1999 and 2008 (Table 30) and in 2008 almost half of these procedures were performed in laminar-flow theatres with space suits.

Table 30. The increase (%) in use of laminar-flow theatres and space suits over the last ten years recorded on the New Zealand Joint Registry for total hip and knee replacements

Year	Laminar flow (%)	Laminar flow (%)	Space suits (%)	Space suits (%)
	THR	TKR	THR	TKR
1999	21	21	9	12
2004	36	40	21	24
2008	49	53	42	44

Total hip replacements (Figure 26)

There were 46 (0.089%) patients who required early revision for deep infection. There was a significant increased association with the rates of early revision for deep infection for those procedures performed with the use of a space suit (0.186%) when compared with those without (0.064%, $p < 0.0001$) (Figure a) and for operations performed in a laminar-flow theatre (0.148%) compared with a conventional theatre (0.061%, $p < 0.003$) (Figure b). There was also a significant increase in the rates of revision for deep infection in procedures performed in a laminar-flow theatre with a space suit (0.198%) compared with those in a conventional theatre without a space suit (0.053%, $p < 0.001$) (Figure c). These results were independent of age and the diagnosis at the time of the initial procedure.

There were 43 surgeons who performed more than 50 procedures in both operating environments. These operations had an infection rate of 0.110% in the laminar-flow theatre compared with 0.028% in the conventional theatre ($p < 0.03$).

There were 33 surgeons who sometimes did and sometimes did not wear a space suit. The incidence of infection was 0.082% with a suit compared with 0.057% without ($p = 0.755$). Additionally, 30 surgeons had operated both with a space suit and laminar flow and without a space suit in a conventional environment. The operations performed in a conventional theatre without a suit had no infections from 3598 procedures, compared with 0.1035% carried out in a laminar-flow theatre with a suit ($p = 0.09$) The clinical details of the patients were similar in both groups with no significant difference in age, preoperative diagnosis or the length of the operation in the different environments.

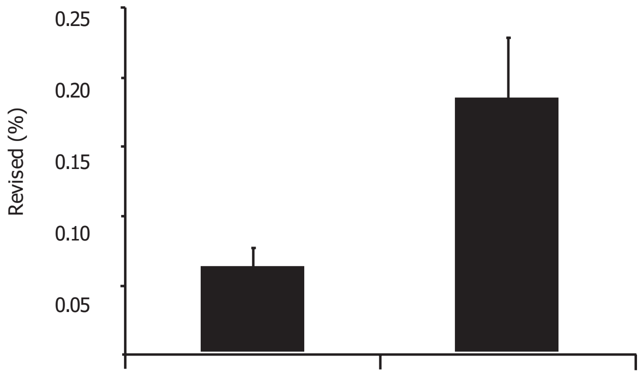

Figure a

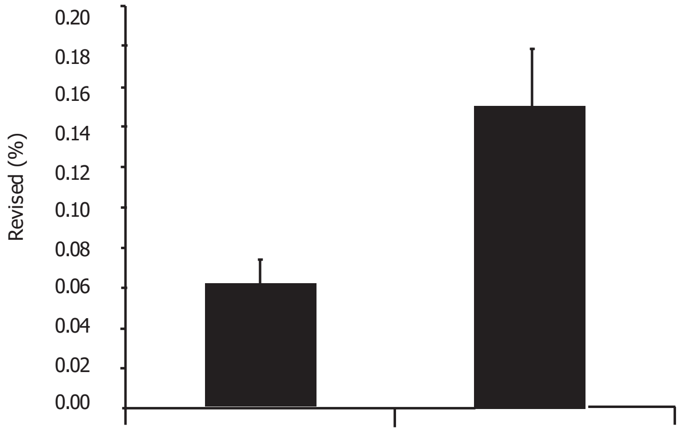

Figure b

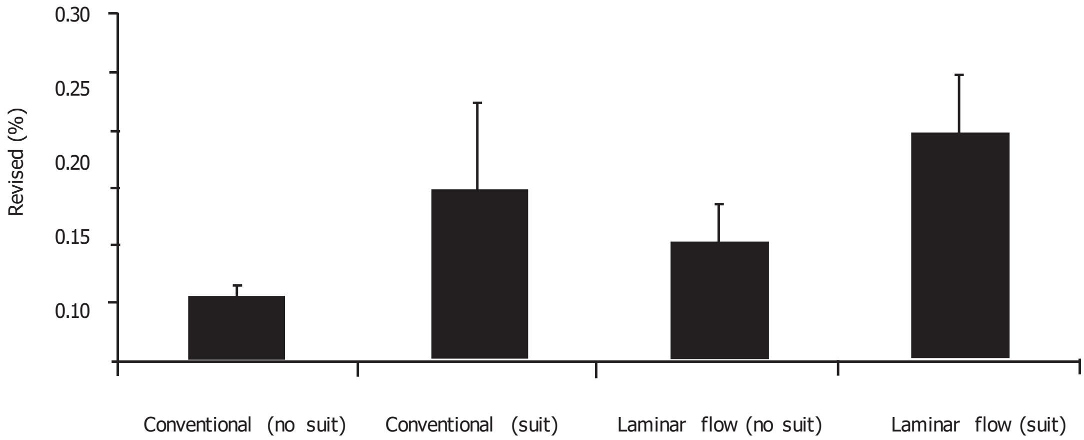

Figure c

Figure 26. Graphs showing the percentage of total hip replacements requiring revision for deep infection within six months comparing a) the use of a space suit with no suit, b) the use of laminar flow with a conventional operating theatre, and c) the use of laminar flow or conventional theatre with or without a space suit

There were 50 (0.136%) patients requiring early revision for deep infection.

There was a significant increase in early revision, similar to THR, for those TKRs performed with the use of a space suit (0.243%, $p < 0.001$) compared with those without (0.098%, $p < 0.001$) (Figure d), when laminar-flow theatres (0.193%) were compared with conventional theatres (0.100%, $p < 0.019$) (Figure e), and when laminar flow and space suits (0.25%) were used compared with no space suits and conventional theatres (0.087%, $p < 0.001$) (Figure f). Again, these results were independent of the patients' age and diagnosis at the time of the initial procedure.

There were 23 surgeons who performed at least 50 TKRs with or without a space suit. There was almost a tenfold increase in the rate of early revision because of deep infection in those who used a space suit (0.251% compared with 0.028%, $p = 0.016$). There were 32 surgeons who operated in both laminar-flow and conventional theatres, but in contrast to THR there was no significant difference in the revision rate for deep infection (0.147% compared with 0.189%, $p = 0.597$). Again, as with THR, there was no difference in the patients' clinical details between the groups and the duration of operations was similar.

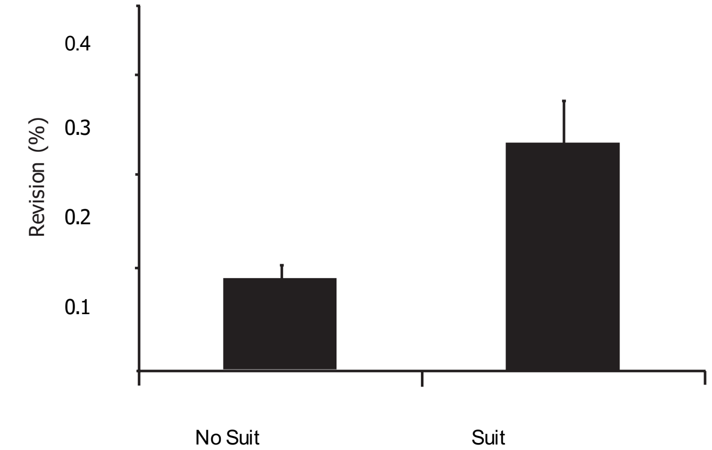

Figure d

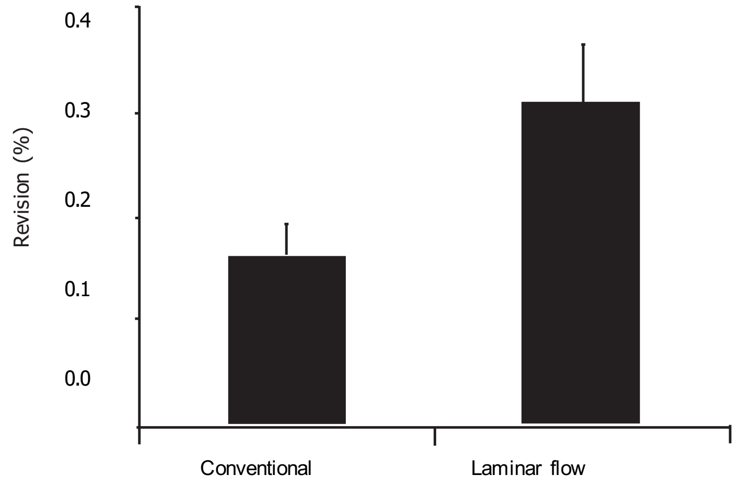

Figure e

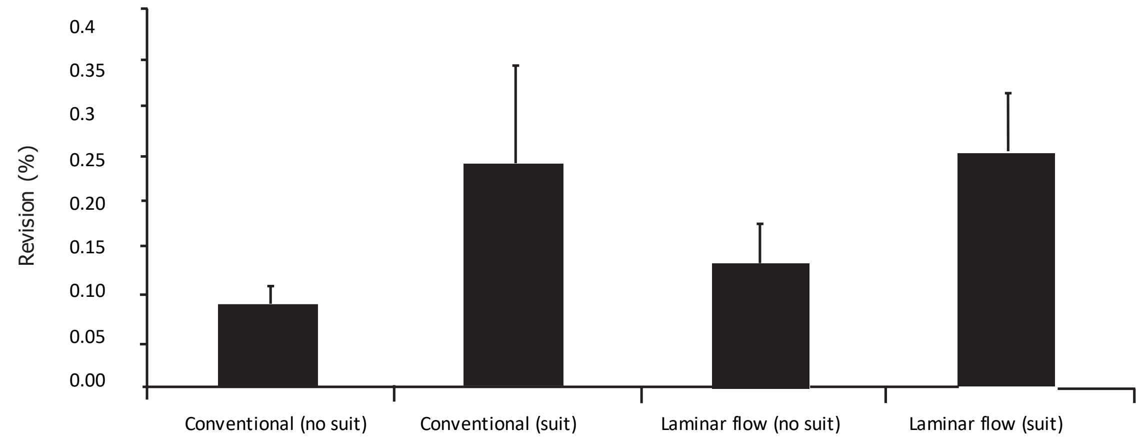

Figure f

Figure 27. Graphs showing the percentage of total knee replacements requiring revision for deep infection within six months comparing d) the use of a space suit with no suit, e) the use of laminar flow with a conventional operating theatre, and f) the use of laminar flow or conventional operating theatre with or without a space suit

The infection rate compared with the operating theatre

There were 64 hospitals that supplied data to the registry. Only one was identified as having a significantly increased rate of revision for early deep infection when the use of a conventional theatre and no space suit was compared with laminar flow with a space suit. This hospital contributed only a small number to the database and when these were removed from the analysis there was no change in the significance of the results.

All hospitals confirmed that they had a regular maintenance programme for filters. There were no hospitals which used laminar flow combined with a complete surgical enclosure.

Surgeon questionnaire

There were 35 responses from the 60 surgeons who had been sent a questionnaire, giving a response rate of 58.3%. All respondents currently use a space suit in all of their replacement procedures, and all stated that they used the same surgical technique regardless of the theatre environment. Most (28 of 31) used full suits for the surgeon, assistant and scrub nurse. All the suits were contemporary in design and no surgeon worked in a fully enclosed space. No surgeon worked with all the staff in the operating theatre wearing suits. In particular, no anaesthetist or technician wore a space suit.

Discussion

Our study has shown that the combined use of laminar flow and space suits did not protect against infection requiring revision within 6 months of the primary joint replacement and may have increased the risk. These results are surprising considering that the microbiological evidence suggests that their combined use should decrease the total number of colony-forming units within the operating theatre which should reduce the rate of infection (Bannister, 2002). To date, there have been no studies which have shown conclusively that a decreased number of colony-forming units relates to a lower rate of wound contamination and infection.

Although ultraclean air environments using laminar flow have been widely accepted as reducing the risk of wound contamination, there has only been one other major multicentre study which has examined the effect of laminar flow on wound infection in orthopaedic procedures (Lidwell, 1998). Lidwell et al., 1987 published the Medical Research Council's prospective trial and concluded that the incidence of confirmed sepsis was higher in conventional theatres. However, this study included only 8,052 procedures up to 4 years after surgery, with a mean of 2.5 years, and hence all may not have been due to intraoperative contamination. This trial has also been widely criticised because of the variable and uncontrolled use of perioperative prophylactic antibiotics. In New Zealand prophylactic antibiotics are given for most THR and TKR operations. The Joint Registry shows a use of prophylactic antibiotics of 96% and of antibiotics in the cement of 60% (NZJR report, 2010). We do not feel therefore that this is a significant confounding variable in our study.

Brandt et al. (2008), reviewed the German experience with surgical site infection in 99,230 general surgical and orthopaedic procedures. They concluded that laminar flow did not reduce surgical site infection and may have contributed to a higher rate of infection in THR. Others have found that bacterial contamination of the wound in THR was not reduced with laminar-flow ventilation (Clarke et al., 2004).

In order to be effective, laminar flow requires no obstructions to the path of the high flow of air. Obstructions cause eddies which in turn can produce areas of risk for increasing contamination and infection (Taylor and Bannister, 1993; Salvati et al., 1982). The layout of operating theatres varies considerably between hospitals. Our study could not control this variable, but by comparing surgeons in different theatre environments we believe that we have minimised such variables as the position of the surgeon and staff with respect to the patient and the individual surgical setup, all of which may interfere with the flow of air within an operating theatre.

The removal of airborne particles including bacteria and spores requires the use of high-efficiency particulate air filters, which in turn require regular maintenance. All the hospitals confirmed that they complied with these maintenance programmes and the observations that there were no hospitals using laminar flow which skewed the results suggests that this potential source of contamination was unlikely to be a factor.

The shedding of bacteria from the skin of the surgical team has been implicated as a major potential source of wound contamination (Ritter, 1999). The large air flows from laminar systems are commonly vertical and push air and debris from the ceiling to the floor. These flows pass the head and upper body of the surgeon and assistants and can potentially contaminate the wound from this source. The ears, which are not covered by the traditional hood and mask, are the most common part from which bacteria are shed. The use of enclosed hoods and exhaust systems combined with occlusive gowns should decrease wound contamination from this source. However, it has been shown that disposable hoods and masks are as effective as helmet aspirator systems (Friberg et al., 2001). Charnley, 1979 reported the lowering of infection after THR from 10% to 1% with the use of laminar flow and full-body exhaust suits. Our study has shown that the rate of infection in both theatre environments was increased with the use of space suits. Surgeons who returned a questionnaire made comments about the current space suits used, indicating that at times their spatial awareness was limited by the hood. Others suggested that it was easier to contaminate themselves while wearing a space suit since there was an apparent false sense of security within it. Observers who have been present during operations using space suits have noted that surgeons often adjust the suit or hood during the procedure and subsequently unknowingly contaminate their gloves. Another possible cause of contamination may be the exhaust systems of the space suits. There is no information as to the flow of the expelled air from exhaust systems and whether the air is concentrated with debris and significant numbers of colony-forming units close to the surgical site.

The causes of wound infection are multifactorial. We have tried to limit confounding variables in our study by including a group of surgeons who had operated in a variety of environments. Our assumption was that their operating procedures would not differ between different hospitals. Therefore, such factors as the duration of the operation, the patient mix, surgical technique, the use of antibiotics, the movement within the theatre and the general sterile procedures, would be similar. This was confirmed by the questionnaire which was sent to these surgeons, although a response rate of 58.3% could be regarded as low. Analysis of the patients registered on the New Zealand Joint Registry confirmed that there was no difference in the patient's clinical details between the hospitals for these surgeons. In particular, there was no difference in the number of patients perceived to have a higher risk of infection, such as those with inflammatory arthritis. The duration of the operation was the same in the 2 groups suggesting that the complexity of the operations was similar.

We also studied each individual hospital and in particular looked at those that had both a laminar flow and conventional theatre. We found only one hospital in which the trend towards revision for infection was increased in a conventional theatre. This was a provincial hospital and performed only a small number of procedures. When they were removed from the analysis the results were unchanged. We believe that this removed any bias which may have occurred because of a particular 'rogue' hospital. We defined early joint infection as that requiring a revision procedure within 6 months of the initial operation. It is generally accepted that any deep infection which develops within this timeframe is most likely to be due to bacterial contamination at the time of the replacement (Antti-Poika et al., 1990; Tsukayama, Estrada and Gustilo, 1996) but we acknowledge that not all joint infections will be captured by this method. Not all early deep infections would have had a revision procedure within this timeframe, especially those in older and infirm patients who may have been treated with suppressive antibiotics. Subacute infections which presented after 6 months were not captured by our study. However, we believe that including infections outside this period would be more likely to confuse the data with increasing numbers of infections from a secondary source. We accept that our study only captures those patients with severe deep infections who require a revision procedure. However, we believe that this is the most important group of patients since they suffer the most severe morbidity and are a large drain on health resources (Dreghorn and Hamblen, 1989).

Previous studies (Hooper et al., 2009; Rothwell et al., 2010) have shown the value of national joint registries which record large numbers of procedures and produce valuable data for rare complications which would be extremely difficult to produce in prospective, randomised trials. In response to the surgeon questionnaire, several surgeons made the comment that they monitored their infection rate and thought that their results were acceptable. However, the rates of early revision for infection were small (0.08% for THR and 0.13% for TKR). Therefore, an individual surgeon would have extreme difficulty in observing any change over time in their rate in relation to the use of laminar flow or space suits.

In conclusion, our study has shown that there is no benefit in the use of laminar flow or space suits in reducing the rate of revision for early deep joint infection in total joint replacement and questions the added cost of their use.

Commentary

Critique

The estimated costs of revision surgery for periprosthetic joint infection are escalating (Haddad, Ngu and Negus, 2017; Sousa et al., 2018). Our study of the NZJR in the previous chapter showed an increased rate of early deep infection with the combined intra-operative use of vertical laminar flow and modern positive-pressure helmet suits in patients undergoing both THR and TKR surgery. The Lidwell prospective multicenter randomised controlled trial in 1982 found that the incidence of infection in laminar flow theatres was reduced when compared to the control group. This study found that infection rates were reduced further when the ultraclean environment was combined with the practice of wearing body exhaust suits. However there was no accounting for the use of antibiotic prophylaxis. Subsequent studies that did control for the use of antibiotics did not demonstrate a significant difference in infection rates between traditional theatre environments and laminar flow theatres (Marotte et al., 1987). Brandt et al. (2008) also found that laminar flow did not convey an advantage in reducing infection rates although strictly this study was not specifically focused on orthopaedic procedures. Further consideration on the details of both laminar flow and space is warranted however, as Chapter 7 did not deduce any mechanism for these observational findings nor does it in itself permit triangulation with more recent published research to substantiate its validity. Our study chose revisions for deep infection within 6 months to likely be due to intraoperative contamination however Zimmerli, Trampuz and Ochsner (2004) suggested that intraoperative contamination was responsible for deep infections occurring up to 24 months following surgery. Another criticism of the previous chapter is that there was no regression analysis performed and adjustment for potential confounders.

Up-to-date literature search

To update the context of the findings of Chapter 7 the following databases were searched from 2010 to 303.3.2020 using the programme Papers: ACM, ADS, arXiv, CERN DS, CrossRef DOI, DBLP, Espacenet, Google Scholar, Gutenberg, Highwire, IEEExplore, Inspire, JSTOR, OAIster, Pubget, PubMed, ScienceDirect, Scopus and Web of Science. Search terms related to: Laminar flow OR Suits AND Infection.

215 references were identified of which 12 were collected as potentially relevant. Those 149 published articles listed in PubMed that cited Chapter 7 were also examined. Journals with impact factors <2 were excluded. Any correspondence relating to the article described in this chapter was reviewed. The NZJR reports since 2010 were examined.

National joint registries update

In every annual NZJR report (2011-2019) since the publication of Chapter Seven there has remained a significant difference in revision rates for deep infection within 6 months of surgery between conventional (lower) and laminar flow theatres. There has been 2.1 to 2.4 times increased risk in using a suit in either laminar flow or conventional theatres. In addition the risk of revision for deep infection within 6 months for laminar flow and suit has been 1.7 to 3.2 times that of a conventional theatre combined with no suit. In another NZJR study Tayton et al. (2016) showed no evidence that modern surgical helmet systems reduce the risk of PJI and that laminar flow may increase the risk of revision for deep infection within six months of surgery. In addition, Smith et al. (2018) examined 91,585 THRs in the NZJR between 2000 and 2014. Multivariate analysis again showed a significant association of PJI with the use of laminar flow (OR 1.98; 95%CI 1.01 to 4.6).

Evidence synthesis

Bischoff et al., 2017 performed a systematic review and meta-analysis of 12 observational studies concerning orthopaedic, general and vascular surgery. The role of the operating room's ventilation system in the prevention of surgical site infections was examined. Laminar flow was compared with conventional ventilation systems to assess their effectiveness in reducing the risk of surgical site infections. Laminar flow made no difference to the rate of surgical site infections (>300,000 THR) OR 1.29 (p=0.07) The study concluded that the added expense of laminar flow systems was therefore unjustified and that this equipment should not be installed in new operating theatres.

Young et al., 2016 performed a systematic review examining the evidence for modern positive pressure surgical helmet systems and the Charnley type negative pressure exhaust suits. This systematic review showed that positive-pressure surgical helmet systems did not reduce contamination or deep infection during arthroplasty in contrast to Charnley-type body exhaust suits.

Proposed mechanisms for findings of registry and evidence syntheses

Laminar flow

Our study did not include details on the type of laminar flow theatres reported and this may have a confounding effect. Ventilatory systems were purported to reduce the airborne bacterial contamination through the production of positive air pressure that displaced contaminated air away from the operation site. Air is taken in at ceiling level of the theatre through a series of fans and bacteria are removed most commonly using "High-efficiency particulate air" (HEPA) filters. Three types of ventilatory systems are available: plenum, ex-flow system (Howarth enclosure), laminar flow. Plenum relies on the pressure being greater in the operating theatre compared to the outside. Clean air enters through diffusers via the wall/ceiling and exits through vents at floor level. As air can also exit through open doors plenum is less reliable as an aseptic environment. Ex-flow system allows the flow of clean air from the theatre in the shape of an inverted trumpet with air moving down and outwards. This system therefore prevents the phenomenon of peripheral entrainment which is problematic with vertical laminar flow. Laminar flow is achieved when the entire body of air from the theatre suite moves with equal velocity in parallel flow lines, Ultraclean air from HEPA filtering achieves < 10 colony-forming units per metre cubed of bacteria. Laminar flow can operate by either a horizontal or a vertical system and in New Zealand the latter only are used. Peripheral personal at the edge of laminar flow can disrupt its efficacy however and promote entrainment of contaiminated air into the sterile field (James et al., 2015).

McGovern et al., 2011 using neutral buoyancy bubbles found that forced air warming used in conjunction with laminar flow may be detrimental and increase infection rates. In addition Refaie et al., 2017 showed, in their experiment with neutrally buoyant helium bubbles, that laminar flow was affected negatively by operating lights. Smith et al., 2013 showed that the laminar flow was affected negatively by theatre personnel traffic. Similarly Cao et al., 2018 showed that laminar air flow is disrupted by the presence of medical staff and the position of equipment such as the operating lamp. Traversari et al., 2019 in a study from the Netherlands showed how performances of different airflow systems compared between the operating room and the instrument preparation room. A number of factors affected the laminar flow of air and included the height of the canopy screen, position of the air exhaust terminals, the size of the canopy and the type of system.

Space suits

The original body exhaust suit of Charnley created a negative pressure inside the gown using intake/outflow tubing whilst the modern "space suit" systems incorporate helmet-based intake fans which use the hood material as a filter and create a positive pressure inside the gown. These newer devices, which are the ones used in New Zealand, drive convection currents and with them bacteria down from the head area and out of the glove/cuff interface which likely potentiates the incidence of PJI and is a potential rationale for the findings of our study (Young, Chisholm and Zhu, 2013). Vijaysegaran et al., 2018 compared particle emission rates of space suits and standard surgical clothing. This study found that space suits caused higher rates than standard clothing and therefore provide a mechanism to support the observational evidence in clinical studies.

Findings in other types of orthopaedic surgery

In a nationwide UK study linked to HES data of trauma surgeries surgical infection within 90 days was examined by Pinder et al., 2016 There was no difference in outcomes between plenum and laminar flow theatre i.e. laminar flow did not convey an advantage. Din et al., 2020 reported a single centre comparative study of both laminar flow and conventional theatre ventilation in 259 fractured neck of femur patients. There was no significant difference in infection rates between the 2 groups. Teo et al., 2020 reported a single-surgeon series of 1028 procedures and concluded that laminar flow was of no benefit compared to conventional theatres when performing primary total knee replacement. Furthermore Shirley et al., 2017 investigated the use of positive -pressure helmet systems in primary TKR surgery. This randomised controlled trial found, conversely, that there was no difference in wound contamination between standard gowns and helmet systems.

International consensus, guidelines and implementation strategies to reduces SSI and PJI

Graves et al., 2016 performed a cost-effectiveness study and concluded that systematic antibiotics, antibiotic-impregnated cement and conventional ventilation would be the optimum cost-effective strategy for the NHS to prevent PJI in THR. The implementation of Total Joint Replacement in developing countries is expensive and the considerable costs of laminar flow theatre construction has been justifiably questioned by Pedneault, St George and Masri, 2020. Finally, the World Health Organisation have recommended that laminar flow systems should not be used to reduce the risk of SSI for patients undergoing Total Joint Replacement. The International Consensus Meeting on Musculoskeletal Infection concluded that the Orthopaedic literature did not support the requirement for laminar flow systems when performing Total Joint Replacement surgery. Similarly the use of body exhaust suits remains controversial with no published evidence to show any benefit (Goswami, Stevenson and Parviz, 2020). We shall now consider other riskfactors for PJI.

Addressing other risk factors for PJI

In a recent systematic review and meta-analysis Kunutsor et al., 2019 showed that antiobiotic cement was associated with lower rates of prosthetic joint infection compared to cement fixation without antibiotics. Uncemented implants had the lowest rates of infection overall when compared to cemented implants and hybrid combinations. Interestingly this superiority was reversed during the first 6 months when antibiotic-cemented fixation was superior (Kunutsor et al., 2019).

A recent large registry cohort study by Lenguerrand et al., 2018 examined the risk factors associated with revisions for PJI after THR. Several modifiable (male gender, younger age, BMI > 30, diabetes, use of the lateral approach over the posterior approach, use of ceramic rather than metal femoral heads) and non-modifiable factors (dementia, previous septic arthritis, THR being performed for a fractured neck of femur) were associated with the risk of revision for deep infection after THR. Interestingly the risk of revision for deep infection was not influenced by the grade of operating surgeon or surgical volume/experience. The authors advocated the identification of modifiable risk factors and the use of targeted intervention ro reduce the incidence of PJI. The effect of non-modifiable risk factors is also important to consider when counselling patients during the process of informed consent.

Diagnosis of PJI

Accurate diagnosis diagnosis of periprosthetic infection is of paramount importance yet may be very challenging as the classic clinical features may be absent. An early precise diagnosis may mean that the infection can be addressed by a less radical treatment with debridement and retention of the implants instead of a 1- or 2-stage revision. The search for a single diagnostic test on synovial fluid with the requisite accuracy, sensitivity and specificity to determine whether a THR is infected or not is attractive. The search for such a test has yielded numerous biomarkers as potential candidates – the term biomarker meaning a biologically pertinent molecule that can be evaluated objectively to indicate the presence of a disease or biological state. In a recent systematic review and meta-analysis, the search for a standard reference test for determining periprosthetic infection through analysis of synovial fluid yielded numerous candidates. These comprised synovial leucocyte count, synovial C-reactive protein (CRP), alpha-defensin, leucocyte esterase, interleukin (IL)-6, IL8, IL-10, IL-1β, vascular endothelial growth factor (VEGF) and granulocyte-colony stimulating factor (G-CSF). The overall sensitivity of these biomarkers for diagnosing PJI was 0.85. Synovial fluid leucocyte count, CRP, alpha-defensin, leucocyte esterase, Il-6 and Il-8 demonstrated high sensitivity for diagnosing PJI with alpha-defensin the best synovial marker with the highest log diagnostic odds ratio (Lee et al., 2017). Given this apparent superiority of alpha defensin and the readily available alternative leucocyte esterase which is detectable on colormetric strips that detect a colour change the next chapter of the thesis compares, in detail, not only the sensitivity but also the specificity and diagnostic accuracy of these biomarker tests.

CHAPTER EIGHT

The Alpha-Defensin Immunoassay and Leucocyte Esterase Colorimetric Strip Test for the Diagnosis of Periprosthetic Infection – A Systematic Review and Meta-Analysis

Reference: Wyatt, M., Beswick, A., Kunutsor, S., Wilson, M., Whitehouse, M. and Blom, A. (2016). The Alpha-Defensin Immunoassay and Leukocyte Esterase Colorimetric Strip Test for the Diagnosis of Periprosthetic Infection: A Systematic Review and Meta-Analysis. *Journal of Bone and Joint Surgery, American Volume,* 98(12), pp.992-1000.

Authors contributions:
Wyatt MC – lead author, inception, writing the paper
Beswick AD – systematic review methodology
Kunutsor SK- meta-analysis
Wilson MJ – editing final version
Whitehouse MR – editing the paper
Blom AW – Senior author

Abstract

Background

Synovial biomarkers have recently been adopted as diagnostic tools for prosthetic joint infection (PJI), but their utility is uncertain. The purpose of this systematic review and meta-analysis was to synthesise the evidence on the accuracy of alpha-defensin immune-assay and leucocyte esterase colorimetric test strip for the diagnosis of PJI, compared to the Musculoskeletal Infection Society diagnostic criteria.

Methods

We performed a systematic review to identify diagnostic technique studies evaluating the accuracy of alpha-defensin or leukocyte esterase in the diagnosis of PJI. MEDLINE and Embase on Ovid, ACM, ADS, arXiv, CERN DS, Crossref DOI, DBLP, Espacenet, Google Scholar, Gutenberg, Highwire, IEEExplore, Inspire, JSTOR, OAIster, Open Content, Pubget, PubMed and Web of Science were searched from inception until 30th May 2015 along with grey literature. Classification of studies and data extraction were performed independently by 2 reviewers. Data extraction permitted meta-analysis of sensitivity, specificity with construction of receiver operator characteristic curves for each test.

Results

We included 11 eligible studies. The pooled diagnostic sensitivity and specificity of alpha-defensin (six studies) for PJI were 1.00 (95% CI 0.82-1.00) and 0.96 (95% CI 0.89-0.99) respectively. The Area Under the Curve (AUC) for alpha-defensin and PJI was 0.99 (95% CI 0.98-1.00). The pooled diagnostic sensitivity and specificity of leucocyte esterase (five studies) for PJI were 0.81 (95% CI 0.49-0.95) and 0.97 (95% CI 0.82-0.99) respectively. The AUC for leucocyte esterase and PJI was 0.97 (95% CI 0.95-0.98) There was substantial heterogeneity between studies for both diagnostic tests.

Conclusions

The diagnostic accuracy for PJI was high for both tests. Given the limited number of studies, more independent research on these tests is warranted given the large cost difference between the tests.

Level of Evidence

Level 2 Testing of previously developed diagnostic criteria with consistently applied reference standards.

Introduction

Periprosthetic joint infection (PJI) is a rare complication affecting between 0.7 and 2.4% of patients receiving joint arthroplasty (Blom et al., 2004; Blom et al., 2003; Ong et al., 2009; Kurtz et al., 2012; Huotari, Peltola and Jamsen, 2015; Dale et al., 2012; Achermann et al., 2011; Henricson, Nilsson and Carlsson, 2011; Padegimas et al., 2015). PJI after hip and knee arthroplasty in particular has extremely negative effects on physical, emotional, social and economic aspects of a patient's life (Andersson et al., 2010). Early diagnosis can lead to less radical treatment with debridement and retention of prostheses instead of one- or two-stage revision. Establishing a diagnosis of infection promptly (Moojen et al., 2014) is therefore of paramount importance, yet may be challenging as the classic clinical features may be absent and a painful joint replacement may be caused by other pathologies. The Musculoskeletal Infection Society (MSIS) has developed diagnostic criteria to standardise and facilitate this diagnostic process (Table 31) (Parvizi et al., 2011). The search for a single diagnostic test on synovial fluid with the requisite accuracy, sensitivity and specificity has yielded numerous biomarkers as potential candidates – the term biomarker meaning a biologically pertinent molecule that can be evaluated objectively to indicate the presence of a disease or biological state. Alpha-defensin (Deirmengian et al., 2014) and leucocyte esterase (Parvizi et al., 2011) are currently among the most promising.

Table 31. MSIS criteria for periprosthetic infection

Definition of Periprosthetic Infection

Based on the proposed criteria, a definite PJI exists when:

1. There is a sinus tract communicating with the prosthesis, or
2. A pathogen is isolated by culture from two or more separate tissue or fluid samples obtained from the affected prosthetic joint, or
3. When four of the following six criteria exists:

a. Elevated serum erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP) concentration,

b. Elevated synovial white blood cell (WBC) count

c. Elevated synovial polymorphonuclear percentage (PMN%)

d. Presence of purulence in the affected joint

e. Isolation of a microorganism in one culture of periprosthetic tissue or fluid, or

f. Greater than five neutrophils per high power field in 5 high power fields observed from histological analysis of periprosthetic tissue at 400 times magnification

Alpha-defensin is an antimicrobial peptide that is released naturally from activated neutrophils. The peptide then integrates into, and destroys, the pathogens' cell membrane (Lehrer and Ganz, 1992). The alpha-defensin immunoassay was developed from both genomic and proteomic studies and provides a qualitative result specific for synovial fluid. The advantages of this test include its simplicity and standardisation whilst a disadvantage is its relatively high cost of £500 per test ($760 US) (CD Diagnostics, Wynnewood, Pennsylvania).

Leucocyte esterase is an enzyme secreted by activated neutrophils recruited to areas of infection. Detection of leucocyte esterase has been used for many years in urinalysis to diagnose urinary infection (Leighton and Little, 1985). The leucocyte esterase colormetric strip test is performed by applying fluid to a reagent test strip. A detergent on the strip lyses the neutrophils within the fluid and this releases esterase which catalyses a reaction leading to formation of a violet dye. Advantages of this test are that it is quick, easy and inexpensive at 11 pence (17 cents US) per test (Combur-7, Roche Diagnostics, Indianapolis, Indiana). A potential disadvantage is the invalidation of the result by blood contamination (Deirmengian et al., 2015) although this has been addressed by centrifugation prior to application of the fluid (Tischler, Cavanaugh and Parvizi, 2014).

The purpose of this systematic review and meta-analysis was to synthesise the available evidence on the accuracy of alpha-defensin and leucocyte esterase in the diagnosis of PJI.

Materials and Methods

We used a rigorous and systematic approach conforming to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (Moher et al., 2009) (Appendix) and the critical evaluation of studies relating to diagnosis of PJI (Buntinx, Aertgeerts and Macaskill, 2009).

Protocol

A protocol was registered online with PROSPERO (CRD42015023704) before commencing the review as recommended by PRISMA.

Search strategy

We searched all studies indexed in MEDLINE and Embase on the Ovid platform, ACM, ADS, arXiv, CERN DS, Crossref DOI, DBLP, Espacenet, Google Scholar, Gutenberg, Highwire, IEEExplore, Inspire, JSTOR, OAlster, Open Content, Pubget, PubMed and Web of Science from inception until 30th May 2015 using the search strategy shown as applied in MEDLINE and Embase in Table 32. We also evaluated the grey literature with hand searches of 6 major Orthopaedic journals over the last 5 years. The bibliographies of the relevant articles were then cross-checked for articles not identified in the search. Studies in patients of all age groups were included. No language restrictions were applied, which is an important consideration with the perceived international interest in treatment of infected hip prostheses. The screening of studies was performed by 2 independent assessors with any disagreements resolved by a third reviewer. A spreadsheet was constructed to summarise the findings of relevant studies.

Table 32. Search strategy

Defensin/ leucocyte esterase search **MEDLINE 130715** 1. neutrophil antimicrobial peptide.mp. or alpha-Defensins/ 2. alpha defensin.mp. or alpha-Defensins/ 3. alpha-Defensins/ or peptide neutrophil antimicrobial.mp. 4. beta-Defensins/ or defensin.mp. or alpha-Defensins/ or Defensins/ 5. Arthroplasty, Replacement/ or Knee Joint/ or Arthroplasty, Replacement, Knee/ or Arthroplasty, Replacement, Hip/ or Hip Prosthesis/ or joint replacement.mp. or Joint Prosthesis/ 6. Arthroplasty, Replacement, Knee/ or Arthroplasty, Replacement, Elbow/ or Arthroplasty, Subchondral/ or Arthroplasty, Replacement, Ankle/ or arthroplasty.mp. or Arthroplasty, Replacement, Finger/ or Arthroplasty, Replacement/ or Arthroplasty/ or Arthroplasty, Replacement, Hip/ 7. Bacterial Infections/ or Prosthesis-Related Infections/ or prosthetic joint infection.mp. or Surgical Wound Infection/ 8. 5 or 6 or 7 9. 1 or 2 or 3 or 4 10. 8 and 9 11. leukocyte esterase.mp. 12. leucocyte esterase.mp. 13. 11 or 12 14. 8 and 13 15. 10 or 14 **Embase 130715** 1. alpha defensins.mp. or alpha defensin/ 2. neutrophil antimicrobial peptide.mp. or defensin/ 3. beta-Defensin/ or defensin.mp. or alpha-Defensin/ or Defensin/ 4. joint replacement.mp. or joint prosthesis/ 5. shoulder arthroplasty/ or knee arthroplasty/ or finger arthroplasty/ or ankle arthroplasty/ or elbow arthroplasty/ or reverse shoulder arthroplasty/ or arthroplasty.mp. or arthroplasty/ or hip arthroplasty/ 6. prosthesis infection/ or prosthetic joint infection.mp. 7. 4 or 5 or 6 8. 1 or 2 or 3 9. 7 and 8 10. leukocyte esterase.mp. 11. leucocyte esterase.mp. 12. 10 or 11 13. 7 and 12 14. 9 or 13 **Each part was specifically adapted for searching alternative databases.**

Eligibility criteria

We included all diagnostic studies that enrolled patients with true diagnostic uncertainty in the setting of PJI. Tests of interest were alpha-defensin assay and leucocyte esterase test scoring ++. Eligible studies had a reference standard for diagnosing prosthetic joint infection using the MSIS diagnostic criteria.

Screening

A total of 1,797 records were identified from searching the literature. The titles and abstracts were screened to identify potentially useful articles for inclusion in this systematic review. After initial screening, 30 full articles were assessed in detail for eligibility against criteria. A PRISMA flow diagram of the progression of studies through this systematic review is provided in Figure 28.

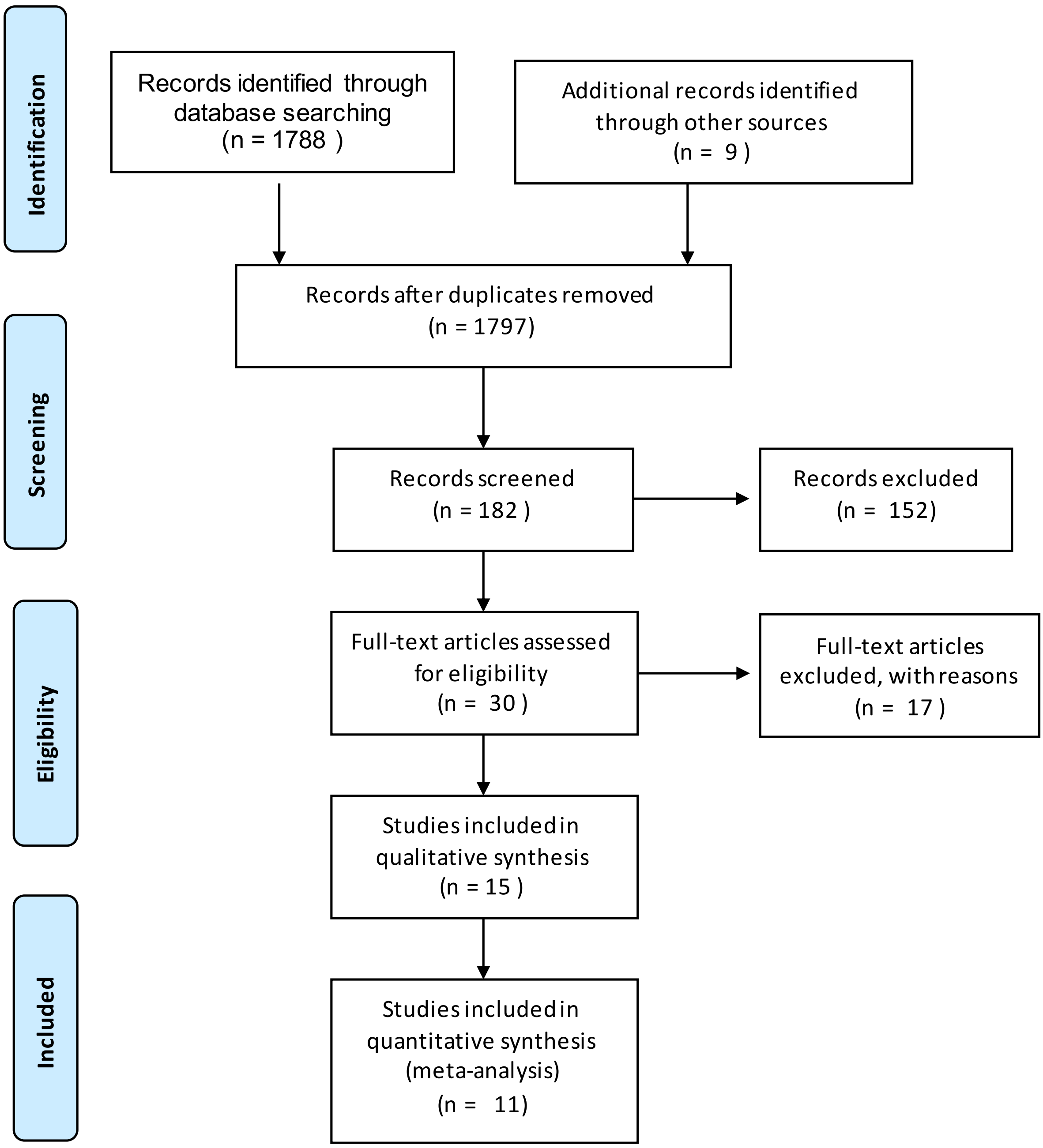

Figure 28. PRISMA flow diagram

Data extraction

Two of the authors (MCW and SKK) worked independently to extract the data using standardised forms. We extracted data on sensitivity, specificity, likelihood ratios, participants, joint involved, diagnostic test performed, cut off or range definitions of the tests, whether the cut-offs were derived with the use of receiver operator characteristic curves or predetermined by the study authors plus the nature and characteristics of the reference standard test. Quality assessment of each study was also performed using the QUADAS-2 tool (Whiting et al., 2011).

Statistical analyses

Overall sensitivity and specificity values for the diagnosis of PJI were pooled using the bivariate meta-analysis framework (Reitsma et al., 2005). The bivariate model is an improvement and extension of the traditional summary receiver operating characteristic (sROC) and jointly models sensitivity and specificity as the starting point of the analysis and hence may be more reliable for estimating diagnostic accuracy (Harbord et al., 2008; Kriston, Harter and Holzel, 2009). The sROC curve shows the consistency of results across studies and therefore whether there was a uniform Receiver Operator Curve (ROC) curve over all studies. The sROC curve data-points come from regression analysis of each study whilst the ROC curve data-points come from each threshold. In addition the area under the curve (AUC) depicts the accuracy of the test. The bivariate model employs a random effects approach, which takes into account the heterogeneity beyond chance between studies. In addition, it also accounts for between-study correlation between underlying sensitivity and specificity, caused by the use of different thresholds across studies. I2 was used to assess inconsistency between studies. An I2 statistic is the proportion of variability across studies due to patient population variability rather than to sampling error. I2 lies between 0% and 100%. A value of 0% indicates no observed heterogeneity, and values greater than 50% may be considered to indicate substantial heterogeneity. A priori hypotheses to explain potential heterogeneity included site of the prosthesis and diagnosis of infection occurring at different time points.

Pooled positive and negative likelihood ratios were calculated using the summary estimates of sensitivity and specificity. Potential sources of heterogeneity across studies could not be investigated because of the limited number of studies. In addition, tests for publication bias (e.g. Egger's test) require at least 10 studies and lower heterogeneity to be useful and valid, therefore we were unable to investigate for publication bias. All analyses were conducted using Stata version 14 (Stata Corp, College Station, Texas) and the "midas" and "metandi" commands were used for all analyses.

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Results

There were 10 articles reporting 11 evaluations (Deirmengian et al., 2014; Parvizi et al., 2011; Deirmengian et al., 2015; Tischler, Cavanaugh and Parvizi, 2014; Bingham et al., 2014; Deirmengian et al., 2014; Frangiamore et al., 2015; Colvin et al., 2015; Wetters et al., 2012; Deirmengian et al., 2015) contributing to our estimates of diagnostic accuracy for both tests. Six studies explored the diagnostic accuracy of alpha-defensin for PJI (Deirmengian et al., 2014; Deirmengian et al., 2015; Bingham et al., 2014; Deirmengian et al., 2014; Deirmengian et al., 2015), while the remaining 5 studies explored the diagnostic accuracy of leucocyte esterase for PJI (Parvizi et al., 2011; Deirmengian et al., 2015; Tischler, Cavanaugh and Parvizi, 2014; Colvin et al., 2015; Wetters et al., 2012). Study characteristics are summarised in Table 33. All of the included studies were published within the last 5 years and originated from the USA. The largest contribution for the alpha-defensin test was from Deirmengian and colleagues (Deirmengian et al., 2014; Deirmengian et al., 2015; Deirmengian et al., 2014; Deirmengian et al., 2015) but there was no overlap in patients within these studies.

Table 33. Characteristics of included studies

Study Country, date	Site	Inclusion criteria Number of patients/ (patients with infection) Mean age in years (range or SD); % male	Method
alpha-defensin			
Deirmengian 2014 USA, not specified	Total hip or knee arthroplasty	Pain at site of total hip or knee arthroplasty 149 (37) 65 years (range 41-89); 47% male	Citrano Medical Laboratories (CD Diagnostics)
Deirmengian 2015 USA, 2012-2014	Hip, knee or shoulder	Samples from patients in the setting of a workup for prosthetic joint infection 1937 (244) No patient details described	Synovasure, Citrano Medical Laboratories (CD Diagnostics)
Bingham 2014 USA, 2013	Hip or knee	Failed or painful hip or knee arthroplasty, or undergoing second-stage reimplantation 61* (19) No patient details described	Synovasure, Citrano Medical Laboratories (CD Diagnostics)
Deirmengian 2014 USA, 2009-	Hip or knee	Patients being evaluated for possible infection of a hip or knee arthroplasty 95 (29) 67 years (range 41-86); 488% male	CD Diagnostics
Frangiamore 2015 USA, 2012-2013	Shoulder	All patients evaluated for a painful shoulder arthroplasty by 2 surgeons 33 (11) 61.7 years (SD 12.4); 43% male	Synovasure, Citrano Medical Laboratories (CD Diagnostics)
Deirmengian 2015 USA, 2012	Hip or knee	Patients being evaluated for possible infection of a hip or knee arthroplasty 46 (23) Mean age 65 years; 43% male	CD Diagnostics
leucocyte esterase			
Tischler 2014 USA, 2009-2013	Hip or knee	Patienty with revision total knee or hip arthroplasty for either aseptic failure or periprosthetic infection 189 (52) 63 years (range 21-90); 48% male	Chemstrip 7 urine test strip (Roche)
Colvin 2015 USA, 2013-2014	Hip, knee, elbow or ankle	Unexplained painful hip, knee, elbow or ankle arthroplasty, routine implant testing, or clinical	Chemstrip 10 UA or Chemstrip 7 urine test strips (Roche)

		suspicion of periprosthetic infection or septic arthritis 52 (19) 69.1 years (range 31-91); 47% male	
Parvizi 2011 USA, 2007-2010	Knee	Patients undergoing revision knee arthroplasty or workup for possible periprosthetic knee infection 108 (30) 64 years (range 28-89); 44% male	Chemstrip 7 urine test strip (Roche)
Wetters 2012 USA	Hip or knee	Patients with suspicion of periprosthetic joint infection after hip or knee arthroplasty 158 (39) 63.3 years (range 33-88); 45.5% men	Chemstrip 7 urine test strip (Roche)
Deirmengian 2015 USA, 2012	Hip or knee	Patients being evaluated for possible infection of a hip or knee arthroplasty 38 (11) Mean age 65 years; 43% male (includes 8 patients with samples excluded due to blood interference)	Chemstrip 7 urine test strip (Roche)

*Aspirations

Five studies of alpha defensin included patients with hip or knee arthroplasty (Deirmengian et al., 2014; Deirmengian et al., 2015; Bingham et al., 2014; Deirmengian et al., 2014; Deirmengian et al., 2015) and 2 studies included patients with shoulder arthroplasty (Frangiamore et al., 2015; Deirmengian et al., 2015). When details were provided, the mean ages of patients in these studies ranged from 61-67 years and 43-47% were male. In the studies of leucocyte esterase, all studies included patients with knee arthroplasty (Parvizi et al., 2011; Deirmengian et al., 2015; Tischler et al. 2014; Colvin et al., 2015; Wetters et al. 2012), four studies included patients with hip arthroplasty (Deirmengian et al., 2015; Tischler, Cavanaugh and Parvizi, 2014; Colvin et al., 2015; Wetters et al., 2012), and one study also included patients with elbow or ankle arthroplasty (Colvin et al., 2015). The mean ages of patients ranged from 63-69 years, and 43-48% were male. Only one study reported the time since the index arthroplasty, 42.7 months (range 7 days to 458 months) (Wetters et al., 2012). The total numbers of patients contributing to the meta-analyses of alpha-defensin and leucocyte esterase were 2,321 and 545 respectively with 363 and 151 patients with PJI.

Quality assessment

In Table 34 the QUADAS-2 assessments for each study are reported. Using the QUADAS-2 tool had a mean score of 13.3 (range 12 to 14) where a maximum score is 14. This indicates that the studies used in this meta-analysis were of good quality.

Table 34. QUADAS-2 evaluation

Study	QUADAS score													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total
Alpha-defensin															
Bingham 2014	1	1	1	1	1	1	1	1	1	1	1	1	1	0	13
Deirmengian 2014	1	1	1	1	1	1	1	1	1	1	1	1	1	1	14
Deirmengian 2014	1	1	1	1	1	1	1	1	1	1	1	1	1	0	13
Frangiamore 2015	1	1	1	1	1	1	1	1	1	1	1	1	1	1	14
Deirmengian 2015	1	1	1	1	1	1	1	1	1	1	0	1	1	0	12
Deirmengian 2015	1	1	1	1	1	1	1	1	1	0	1	1	1	0	12
Leucocyte esterase															
Tischler 2014	1	1	1	1	1	1	1	1	1	1	1	1	1	1	14
Wetters 2012	1	1	1	1	1	1	1	1	1	1	1	1	1	1	14
Parvizi 2011	1	1	1	1	1	1	1	1	1	1	1	1	1	1	14
Colvin 2015	1	0	1	1	1	1	1	1	1	1	1	1	0	0	11
Deirmengian 2015	1	1	1	1	1	1	1	1	1	0	1	1	1	0	12

QUADAS scores
1. Was the spectrum of patients representative of the patients who will receive the test in practice?
2. Were selection criteria clearly described?
3. Is the reference standard likely to correctly classify the target condition?
4. Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the 2 tests?
5. Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?
6. Did patients receive the same reference standard regardless of the index text result?
7. Was the reference standard independent of the index test (i.e., the index test did not form part of the reference standard)?
8. Was the execution of the index test described in sufficient detail to permit replication of the test?
9. Was the execution of the reference standard described in sufficient detail to permit its replication?
10. Were the index test results interpreted without knowledge of the results of the reference standard?
11. Were the reference standard results interpreted without knowledge of the results of the index test?
12. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?
13. Were uninterpretable/intermediate test results reported?
14. Were withdrawals from the study explained? Yes

Diagnostic value of alpha-defensin for prosthetic joint infection

The pooled diagnostic sensitivity and specificity of alpha-defensin for PJI were 1.00 (95% CI: 0.82 to 1.00) and 0.96 (95% CI: 0.89 to 0.99) respectively (Figure 29). There was substantial heterogeneity between studies; I2 (95% CIs) for sensitivity and specificity values were 98.2 (95% CI: 97.5 to 98.9) and 98.8 (95% CI: 98.4 to 99.2) respectively. The pooled Positive Likelihood Ratio (PLR), Negative Likelihood Ratio (NLR), and diagnostic score were 27.0 (95% CI: 9.0 to 80.6), 0.00 (95% CI: 0.00 to 0.22), and 8.94 (95% CI: 4.73 to 13.15) respectively. The AUC for alpha-defensin and PJI was 0.99 (95% CI: 0.98 to 1.00) (Figure 30).

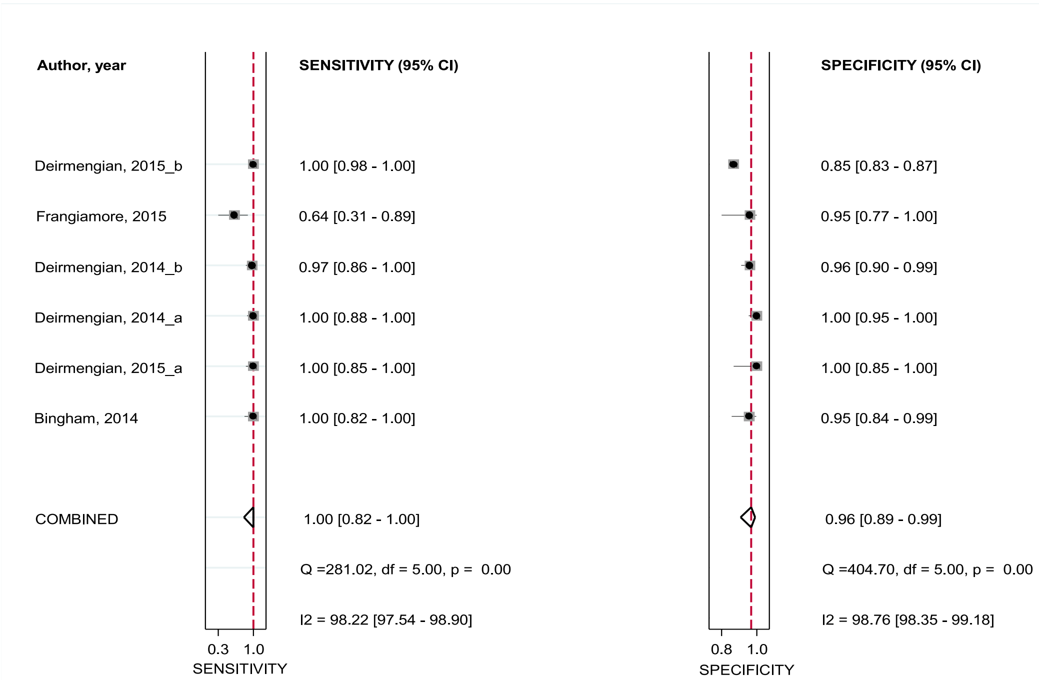

Figure 29. Sensitivity and specificity of Alpha Defensin in the diagnosis of prosthetic joint infection

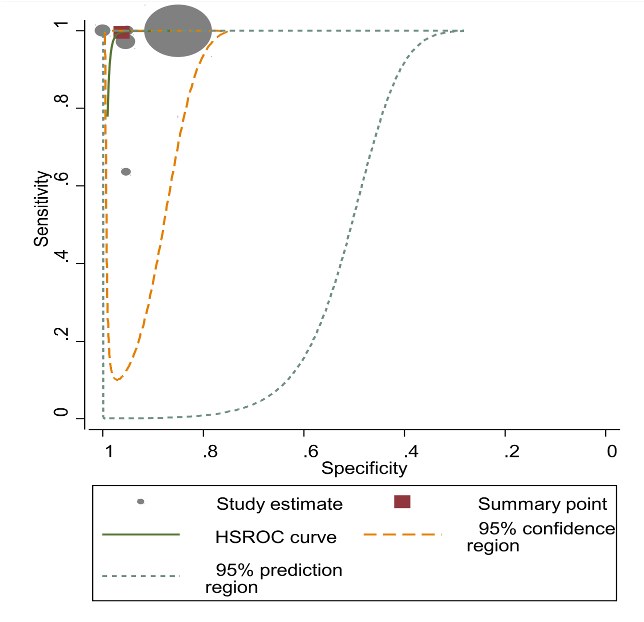

Figure 30. Summary receiver operating characteristic curves of Alpha Defensin in the diagnosis of prosthetic joint infection; HSROC = Hierarchical summary receiver-operating characteristic curve for the diagnostic performance of Alpha Defensin; Summary point= The summary sensitivity and specificity; 95% confidence region = 95% confidence region around the summary sensitivity and specificity; 95% predicted region=used to illustrate the extent of statistical heterogeneity (This is the region within which, assuming the model is correct, there is 95% confidence that the true sensitivity and specificity of a future study will lie in)

Diagnostic value of leucocyte esterase for prosthetic joint infection

The pooled diagnostic sensitivity and specificity of leucocyte esterase for PJI were 0.81 (95% CI: 0.49 to 0.95) and 0.97 (95% CI: 0.82 to 0.99) respectively (Figure 31). There was substantial heterogeneity between studies, I2 (95% CIs) for sensitivity and specificity values were 94.6 (95% CI: 91.4 to 97.9) and 93.3 (95% CI: 89.0 to 97.6) respectively. The pooled PLR, NLR, and diagnostic score were 23.9 (95% CI: 3.8 to 152.1), 0.19 (95% CI: 0.06 to 0.66), and 4.82 (95% CI: 2.27 to 7.36) respectively. The AUC for leucocyte esterase and PJI was 0.97 (95% CI: 0.95 to 0.98) (Figure 32).

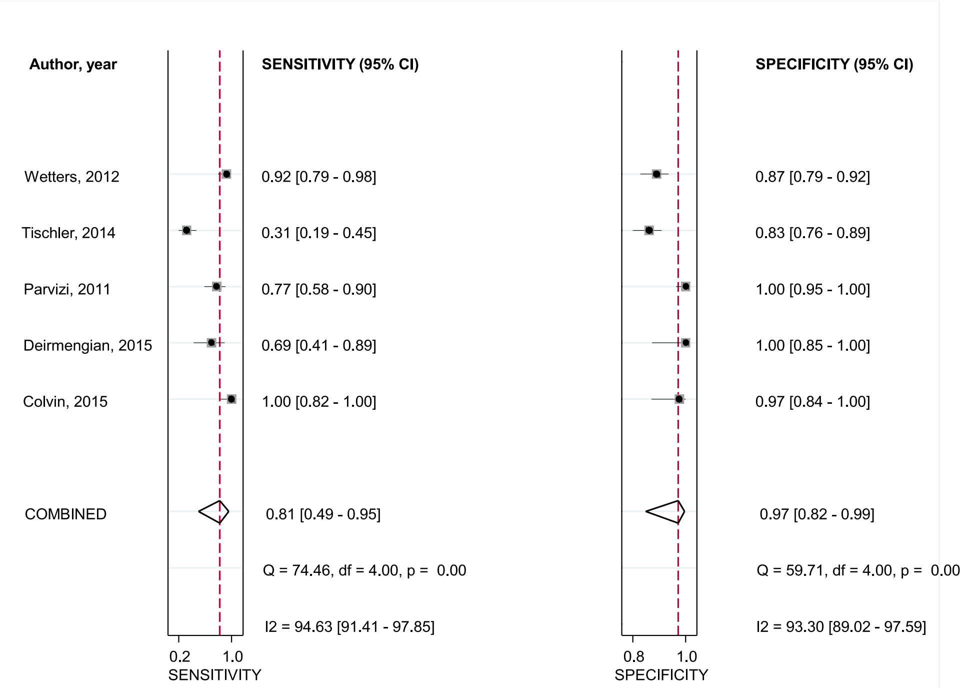

Figure 31. Sensitivity and specificity of leucocyte esterase in the diagnosis of prosthetic joint infection

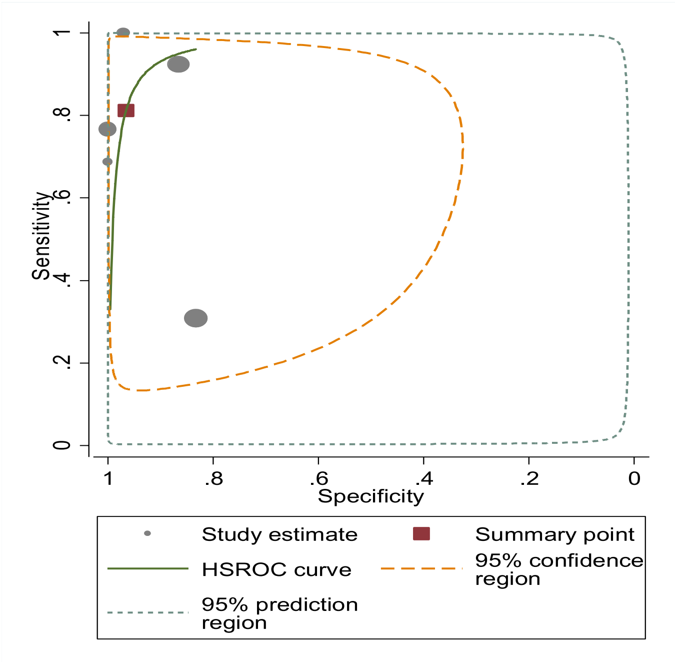

Figure 32. Summary receiver operating characteristic curves of leucocyte esterase in the diagnosis of prosthetic joint infection. HSROC = Hierarchical summary receiver-operating characteristic curve for the diagnostic performance of Alpha Defensin Summary point = The summary sensitivity and specificity; 95% confidence region = 95% confidence region around the summary sensitivity and specificity; 95% predicted region = used to illustrate the extent of statistical heterogeneity (This is the region within which, assuming the model is correct, there is 95% confidence that the true sensitivity and specificity of a future study will lie in)

Discussion

The prompt diagnosis of PJI remains a clinical challenge due to the diverse clinical presentations of patients suffering from this complication and the overlap of some of these features with other diagnoses and causes of failure of joint arthroplasty. The distinction between PJI and other causes of failure is important as the surgical management and chance of a successful outcome differs according to the mode of failure and thus the treatment strategy employed.

This systematic review has shown that alpha-defensin is extremely sensitive and specific in identifying PJI and that leucocyte esterase is slightly less sensitive, but also extremely specific. Both are therefore good candidates for diagnostic biomarkers. Traditional tests to diagnose PJI are less effective. In a study examining diagnostic accuracy for inflammatory serological markers in PJI (Berbari et al., 2010) the pooled sensitivity and specificity for the erythrocyte sedimentation rate were 88% (95% CI: 86% to 90%) and 70% (95% CI: 68% to 72%) respectively. The pooled sensitivity and specificity for C-reactive protein were 97% (95% CI: 93% to 99%) and specificity 91% (95% CI: 87% to 94%). However, this study did not use the MSIS criteria as its gold standard.

Several other synovial biomarkers have been investigated in relation to PJI. The synovial white blood cell count typically shows sensitivity of 84-93% and specificity of 51-100% (Lenski and Scherer, 2015; Zmistowski et al., 2012; Bedair et al., 2011; Yi et al., 2014). The proportion of synovial white blood cells that are polymorphonuclear and thus concerned with fighting infection typically shows sensitivity of 81-93% and specificity of 69-83% (Lenski and Scherer, 2015; Zmistowski et al., 2012; Bedair et al., 2011; Yi et al., 2014). While C-reactive protein in serum may have high sensitivity and poor specificity for PJI, measurement in synovial fluid shows sensitivity of 96-97% and specificity of 90-93% (Deirmengian et al., 2014; Omar et al., 2015). In one study included in our review, a broad range of synovial biomarkers were investigated and several in particular including neutrophil elastase, bactericidal/ permeability-increasing protein, neutrophil gelatinase-associated lipocalin and lactoferrin merit further study (Deirmengian et al., 2014).

The strengths and potential limitations of this analysis deserves mention. Our meta-analysis is the first of its kind and it examined nearly 2,000 in studies that were performed to a very high standard. All studies included in the review used the MSIS criteria, thereby minimising classification bias by using a common and widely accepted reference standard (Parvizi et al., 2011). The studies in our meta-analysis mainly included patients with hip and knee arthroplasty though some studies included patients with shoulder, ankle and elbow arthroplasty. The age ranges and proportions of male patients were similar between studies but information on the time since arthroplasty was highly limited. This may be important as some biomarkers may have different diagnostic accuracy in the early postoperative period (Yi et al., 2014) Future studies should aim to assess differences in diagnostic accuracy relating to potential sources of heterogeneity including arthroplasty site, time since index surgery and patient characteristics.

A number of the studies of alpha-defensin came from the same research group, which could hamper the generalisation of our findings; however, these findings were replicated by other groups. The limited number of studies precluded the ability to explore for publication bias, an important issue in diagnostic accuracy studies where results of new tests with poor sensitivity and specificity may remain unpublished. None of the studies reported on blinding, which potentially may have introduced selection bias. Further large-scale, independent and rigorous studies are warranted to evaluate the use of these synovial markers as diagnostic tools for PJI.

Alpha-defensin is substantially more expensive (£500 GBP per test) than leucocyte esterase (£0.11 GBP per test) though the latter may require the initial capital cost of a centrifuge and costs associated with its use. However, alpha-defensin may be more specific in diagnosing PJI and both tests may have clinical roles as biomarkers. We recommend that further comparisons are made between these 2 promising biomarkers and traditional diagnostic tests to assess their relative effectiveness and cost effectiveness.

Commentary

Critique

Chapter 8 is a formal systematic review and meta-analysis of the diagnostic properties of alpha-defensin and leucocyte esterase. A critism of this study not mentioned in the Discussion is the large confidence intervals for both sensitivity and specificity of leucoctye esterase shown in the summary receiver operating characteristic curve Figure 32. Since the publication of Chapter 8 the MSIS diagnostic criteria of PJI have evolved and further research into synovial biomarkers has been published and therefore at the time of publication both the diagnosis and management of PJI were not standardised worldwide. Since publication of Chapter 8 further clinical research has focused on synovial biomarkers to advance the potential complex task of PJI diagnosis.

Up-to-date literature search

To update the context of the findings of Chapter 8 the following databases were searched from 2016 to 8.4.2020 using the programme Papers: ACM, ADS, arXiv, CERN DS, CrossRef DOI, DBLP, Espacenet, Google Scholar, Gutenberg, Highwire, IEEExplore, Inspire, JSTOR, OAIster, Pubget, PubMed, ScienceDirect, Scopus and Web of Science. Search terms related to: Alpha defensin OR Leucocyte esterase AND Infection.

237 references were identified of which 11 were collected as potentially relevant. Those 23 published articles listed in PubMed that cited Chapter 8 were also examined. Journals with impact factors <2 were excluded. Any correspondence relating to the article described in this chapter was reviewed.

Diagnosis of PJI

The Musculoskeletal Infection Society (MSIS) published the original diagnostic approach consisting of 2 major and 6 minor criteria (Parvizi et al., 2011). The diagnosis of PJI required the presence of either one of the major or ≥4 minor criteria. The

Internation Consensus Group on Periprosthetic Joint Infection meeting in Philidelphia modified the MSIS criteria in 2013 by removing purulence of synovial fluid as a minor criterion and added the leucocyte esterase test as a potential option to assess synovial White Blood Cell count. Different thresholds for the minor criteria were clarified and PJI was determined as present if >1 major or ≥3 minor criteria are present (Parvizi, Gehrke and Chen, 2013). The MSIS diagnostic criteria were then amended again in 2018 to improve the sensitivity and specificity to 97.7% (from previously 79.3%) and 99.5% (from previously 86.9%) as follows: 2 positive cultures or the presence of a sinus tract were considered major criteria; a serum CRP elevated >1mg/dL, D-dimer >860ng/mL, ESR >30mm/h were awarded 2, 2 and 1 points respectively. An elevated synovial WBC>3000 cells/μL, alpha-defensin (signal to cutoff ratio >1), leucocyte esterase (++) PMN percentage >80% and synovial CRP >6.9mg/L received 3, 3, 2 and 1 points respectively. An aggregate score ≥6 indicates PJI whilst a score 2 to 5 requires the inclusion of intraoperative findings to confirm or refute the diagnosis (Parvizi et al., 2018). Therefore, the latest consensus defining criteria of PJI now includes both alpha-defensin and leucocyte esterase.

Alpha-defeinsin immune assay

The ELISA for alpha-defensin is performed in the laboratory. This immunoassay method is more time consuming that the lateral flow “Synovasure” test. The findings of Chapter 8 showed high pooled diagnostic sensitivity (100%) and specificity (96%) of the immunoassay. In another systematic review by Li et al., 2017 these results were reaffirmed. The leucocyte esterase test and alpha-defensin lateral flow tests are influenced by the sample quality in this review. Bonanzinga et al., 2017 performed a prospective study and demonstrated that the alpha-defensin immunoassay had a sensitivity and specificity of 97%; negative predictive value 99% and positive predictive value 88%.

Alpha-defensin lateral flow test

Lateral flow devices can be used to test for synovial levels of alpha-defensin comparatively swiftly both intraoperatively and at the bedside. Gehrke et al., 2018 assessed the accuracy of the Synovasure lateral flow test to the MSIS criteria. In this study of 195 joint aspirations the overall sensitivity was 92.1% and specificity 100%. The positive predictive value was 100% and negative predictive value 95.2%. Despite these results the lateral flow test is not as accurate as the laboratory immunoassay (Suen et al., 2018) yet its high specificity and relatively rapid response time makes it useful for “ruling in” infection for example intraoperatively which may well avoid unnecessary treatments. The lateral flow test has therefore been suggested as a confirmatory rather than a screening test (Renz et al., 2018).

Synovial biomarkers such as alpha-defensin and leucocyte esterase should therefore be used as adjuncts to synovial white cell count and microbiological culture. Both form part of the latest MSIS diagnostic recommendations. Ultimately the increased commercial costs associated with such biomarkers must be balanced by the potential savings in duration of hospital stay, shorter duration of antibiotic use and the associated positive effect regarding bacterial resistance rates. Further research will clarify cost-effective diagnostic algorithms for PJI than incorporate these tests.

SUMMARY

Synopsis/implications of the results from this thesis

This thesis aimed to focus on the pertinent issues of femoral stem fixation, optimal bearing surface and reducing the risk of infection.

Section 1 Stem fixation

With regards to stem fixation I had identified that the optimal mode of stem fixation for a particular patient in New Zealand within the clinical literature was unknown. I proposed to address this in Chapter 1 and examined which fixation of femoral stem was the most reliable for a particular patient undergoing primary THR comparing results from the national joint registries with the NZJR. The answer to the first chapter's research question, interpreted in the context of recent results and trends, was that cemented stem fixation is preferable in terms of all-cause revision rates – the singular most important outcome of interest for an individual patient. This type of stem can be used in any type of patient assuming the surgeon is well trained in their technique (Keeling et al., 2020) although uncemented stems also have excellent results in younger patients (Tyrpenou et al., 2020). The results of Chapter 1 remain valid therefore in the context of more recent literature. In fact, the practice of choosing cemented stems has, in recent research, set the benchmark for all other types of stem fixation (Deere et al., 2019). The use of a non-inferiority trial permits an implant performance to be compared to the accepted range of performance compared to a reference implant. The type of benchmarking study performed by Deere et al., 2019 for THR using UK NJR data using the NZJR would be valuable. This type of analysis of the NZJR would also provide useful information to guide patients, surgeons and healthcare funders. This is the topic of current further research I am undertaking.

Moreover, the influence of femoral offset on THR survival and whether this differed between cemented and uncemented stem fixation was unknown within the clinical literature. Chapter 2 therefore examined the NZJR for the effect of femoral offset on THR survivorship or reasons for revision. Moreover, the effect of femoral component offset on these outcomes of interest have not been examined with regards different types of fixation. The answer to the research question investigated in the second chapter was that there was a greater association with stem offset and outcomes in cemented versus uncemented stems. This implies that precise attention to surgical planning and templating may be of greater importance when using cemented stems. Whilst the methodology precluded modelling of offset as a continuous variable and has the potential weaknesses of analysing observational data the findings convey an important principle. This study has not been repeated elsewhere therefore clinicians should consider these results carefully in assisting decision making. Future research that applies the methodology of Chapter 2 to other National Joint Registries would be of interest. In addition, it would be interesting to record whether the THRs in question were preoperatively templated and to compare templated and untemplated THR results.

The literature concerning the influence of cemented stem length on THR survival remained inconclusive. Therefore Chapter 3 examined the outcomes of short cemented Exeter stems in the NZJR compared to standard length cemented Exeter stems. This chapter showed that the standard Exeter stem is a positive outlier for survivorship compared to the overall mean revision rate 0.72/100 cy (95%CI 0.71 to 0.74) compared to 0.56/100 cy (95%CI 0.53 to 0.59). The length of a cemented Exeter stem within the typical offsets of 37.5mm, 44mm and 50mm from the results of Chapter 3 is perhaps not as critical with short stems displaying similar results to standard length Exeter stems. The lower offset short stem group had poorer results which is most likely attributable to confounding from a higher proportion of patients with OA secondary to hip dysplasia in this group. This confounding is one of the inherent weaknesses of an observational study. Whilst the NZJR records Oxford scores these are not recorded preoperatively, and this is a further weakness of the study. There are currently no other published articles on survivorship of the Exeter short cemented stem with these offsets. Future validation of our NZJR findings in other National Joint Registries would be of interest and support clinical application of our research findings.

The safety of performing bilateral THR under a single-anaesthetic using cemented stems was contentious. Chapter 4 therefore examined the safety of single-anaesthetic bilateral THR with cemented stems in Exeter. The answer to the research question addressed in Chapter 4 was that during 4 decades of performing SABTHR using cemented stems in Exeter this practise was safe in terms of mortality and compared favourably with the published literature. However I would caution the interpretation of our results which were achieved with strict patient selection (i.e. ASA grade 1 or 2) and adherence to a rigorous perioperative protocol. Exeter is an academic centre of excellence for cemented THR. The technical aspects of canal irrigation/evacuation and meticulous cementing technique were followed for all patients in our study. The rigour achieved in Exeter and therefore the results of Chapter 4 may limit the wider application of our results. This study remains the largest published series of SABTHR with cemented stems and clinicians may consider applying the protocols and techniques described when performing cemented SABTHR. Whether SABTHR using uncemented stems can be performed in a greater variety of patients with higher ASA/comorbidities than this series would be of great interest for further research.

Section 2 Bearing surfaces

I had identified that the optimum bearing surface combination for a patient having had THR in New Zealand remained unknown. Therefore Chapter 5 examined the NZJR to detetermine which bearing surface combination had the best all-cause revision rate. CoPx had the lowest all-cause revision rate for THR in unadjusted analyses. In adjusted analyses CoC and CoPx were the best performers. When examining 32mm and 36mm femoral head sizes in THR for the previous decade CoPx was superior. The findings of this chapter support therefore the use of 32mm ceramic femoral heads in combination with a HXLPE acetabular component as the bearing surface combination least likely to require revision in New Zealand. These results compliment those of a recent study (Metcalfe et al., 2018). This finding should be interpreted in the context of cost-effectiveness as shown by Fawsitt et al., 2019. A metal-on-polyethylene cemented THR using a femoral head < 36mm in diameter was the most cost-effective option for men and women older than 65 years of age. In accordance with this thesis, which therefore substantiates the validity of the results, a ≤ 36mm diameter ceramic femoral head in combination with cemented fixation THR was the most cost-effective choice for men and women under the age of 65. There was no evidence to support the use of uncemented, hybrid or reverse hybrid THR in any patient group on the basis of cost-effectiveness. Clinicians may consider choosing CoPx in younger, more active patients undergoing THR. Future research may examine how different generations of HXLPE perform to refine such surgeon choices.

Given the findings in the previous chapter the use of new Vitamin E HXLPE as a superior alternative to HXLPE was of interest. Chapter 6 therefore examined the performance of Vitamin E HXLPE compared to previous generations of HXLPE and also UMWPE. At this relatively early stage the systematic review and meta-analysis did not show a clinical superiority in terms of revision rate however longer-term results may elucidate this. The in vivo analysis of wear for Vitamin E HXLPE is promising on RSA studies. This research cannot therefore provide an evidence-based direction for clinical practise. Further examination into the longterm performance of Vitamin E HXLPE compared to HXLPE is warranted. An interesting potentially advantageous property of Vitamin E HXLPE is the reduced bacterial adhesion noted in several studies which may hinder the formation of biofilms which are an important factor in periprosthetic joint infection (Banche et al., 2014). This is an interesting area for further research.

Section 3 Periprosthetic infection

Total hip replacement is a successful operation for addressing the pain and limited function associated with end-stage degenerative conditions of the hip as well as restoring mobility to selected patients who sustain a hip fracture. Despite its success, problems can occur and one of the most devastating is prosthetic joint infection (PJI). Patients who experience this complication and their surgeons face a difficult and protracted course of treatment and prolonged recovery periods. The patient’s perspective of PJI has been characterised by recent qualitative research and PJI simply ruins patients’ lives (Moore et al, 2015).

The prevalence of revision THR for PJI after primary THR in a recent UK NJR study was 0.4/100 procedures and during the 10 years observed in this study (2003 to 2014) the burden of PJI requiring revision rose 2.6 fold (Lenguerrand et al, 2017). In a recent prospective observational study the risk factors for PJI were male sex (rate ratio (RR) 1.7, 95%CI 1.6-1.8), elevated BMI (≥30 c.f. <25 RR 1.9, 95%CI 1.7-2.2), diabetes (RR 1.4, 95%CI 1.2-1.5), previous septic arthritis (RR 6.7, 95%CI 4.2-9.8), hip fracture (RR 1.8, 95%CI 1.4-2.3) and use of the lateral surgical approach compared to posterior approach (RR 1.3, 95%CI 1.2-1.4) (Lenguerrand et al., 2018). Ceramic containing bearings had a lower risk of revision for PJI than metal containing bearings and these effects were generally seen from 3 months onwards. The risk of revision for prosthetic joint infection following primary hip replacement is affected by multiple factors and is mainly driven by patient and surgical factors. The risk of developing an infection after hip replacement varies with the time period of follow up. The modifiable factors identified should be considered by clinicians when preparing patients for hip replacement surgery. It is equally important for them to consider the non-modifiable factors and the factors that exhibit time-specific effects on the risk of prosthetic joint infection, to counsel patients appropriately preoperatively (Lenguerrand et al., 2018).

The influence of the operating theatre environment factors of laminar flow and space suits was contentious in the literature. Chapter 7 therefore explored if deep infection could be prevented with regards the operative environment. As the NZJR is unique in that it records information on the use of laminar flow and space suits in the theatre environment, this thesis explored the association with these widely adopted practices and revision for early deep infection. The results of this chapter showed that laminar flow and space suits were in fact associated with higher infection rates in THR which contrast the findings of the study of Lidwell et al. (Lidwell et al., 1987). Laminar flow theatre environments do not convey the reduction in deep infection rates that they were purported to do so, and these findings are supported by other more recent studies in the literature. This thesis also focused on the use of space suits and from its results and additional research the differences between the classic body exhaust suit adopted by Charnley and the modern space suits have been elucidated (Young et al., 2013; Vijaysegaran et al., 2018). The findings of this chapter have been validated in every subsequent NZJR report. With regards to the clinical application of our research the WHO has, cogent with our research findings, recommended against the cost of installing laminar flow theatres (Pedneault et al., 2020) and there remains little evidence to support modern space suits (Goswami et al., 2020). Our study is potentially affected by confounding and we did not perform regression analysis. Further research could be directed towards understanding the differences in theatre ventilation systems combined with the physical dimensions of the operating theatre and personel within. Furthermore a New Zealand study that replicates the work of Din et al., 2020 examining trauma patients would be interesting.

The use of synovial biomarkers as potential diagnostic tools for PJI was unproven in the literature yet these were being adopted into clinical practise with alacrity. There was therefore a lack of evidence synthesis on the diagnostic accuracy of these biomarkers. Chapter 8 therefore examined the diagnostic accuracy of the 2 most promising synovial biomarker tests namely the alpha-defensin immunoassay and the leucocyte esterate calorimic strip test. Both were found to have excellent sensitivity and specificity. Leucocyte esterase is considerably cheaper yet remains vulnerable to blood contamination. Subsequent studies have shown the alpha-defensin immunoassay to be superior to the alpha-defensin lateral flow test (Suen et al., 2018). The application of the test results from these biomarker tests have evolved and the most recent MSIS criteria now include their results (Parvizi et al., 2018) in the decision-making algorithm. A pragmatic approach may be to use the leucocyte esterase test first and the alpha-defensin test as a second line investigation.

Strengths and Weaknesses of the Studies Presented

Whilst prospective randomised-controlled trials remain the gold-standard evidence judicious use of large data sets is warranted from a practical perspective. The methodology used in this thesis has centred around the results of the New Zealand Joint Registry. This was the only national joint registry to record patient reported functional scores from its inception and at 96% has a high data capture rate. The NZJR fortuitously captured data on laminar flow and space suits which permitted the association of these theatre environment choices to be examined with respect to deep infection rates. The analysis of large datasets reflects the practice of an entire nation and has the potential, despite adjusting for various covariates, for the introduction of confounders which can bias the results. The ability to interpret the analyses from a causal perspective is therefore compromised. In the study of the Exeter short stems for example, the impact of the underlying diagnosis i.e. the primary indication for THR surgery, is difficult to control for.

The use of formal systematic review and, where possible statistical meta-analysis, permits a structured unbiased review of the available literature (Berstock and Whitehouse, 2019). The first systematic review was in essence performed by James Lind in 1753 who examined scurvy afflicting the Royal Navy. The systematic approach to minimising biases and random errors in a strict step-wise process with clearly stated *a priori* objectives allows a measured synthesis of the available evidence. The systematic review on alpha-defensin and leucocyte esterase was the first to use summary receiver operator curves to examine diagnostic tests in this way. As the medical literature expands at a high rate the aggregation and appraisal of the available evidence so that it is both intelligible and useful to clinicians. A systematic review may act as the foundation for future research in terms of attracting funding and research initiatives.

Conclusions

The continued debate around issues such as fixation and bearing surfaces generates tension and tremendous tribal rivalries. A professional, candid and openly audited approach with scientifically-based willingness to change personal practice, are the appropriate ways to justify surgical advances. In summary the results of this thesis endorse the practise of precise execution of a surgical plan with a proper cemented stem that results in the correct biomechanics. An evidence-based rationale in the context of the recent literature is provided for type of stem, cup and bearing surface, safe practise concerning bilateral OA and raised awareness of prevention of periprosthetic infection. At a synthesis level this thesis and the adjoining commentaries provide an evidence-base for the authors' Hip Replacement practise.

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