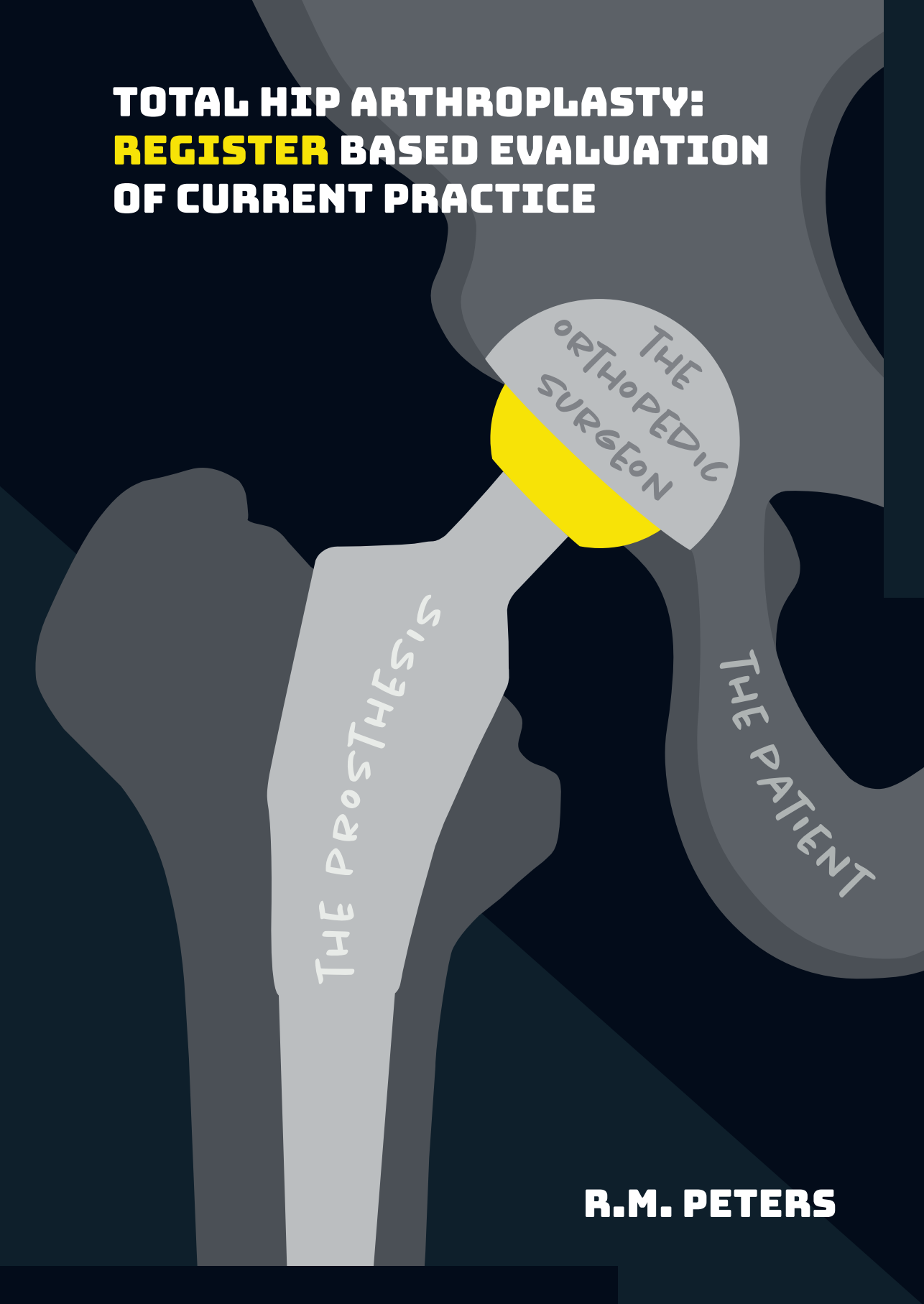
TOTAL HIP ARTHROPLASTY: REGISTER BASED EVALUATION OF CURRENT PRACTICE



R.M. PETERS

TOTAL HIP ARTHROPLASTY: REGISTER BASED EVALUATION OF CURRENT PRACTICE

PROEFSCHRIFT

RINNE MARIJN PETERS

Work performed at University Medical Center Groningen and Medical Center Leeuwarden.

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Total Hip Arthroplasty: register based evaluation of current practice

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GENERAL INTRODUCTION

Total hip arthroplasty (THA) is considered a successful treatment for end-stage osteoarthritis (OA) of the hip joint. The number of THAs has grown globally in recent decades and is ranked among the top-5 most frequently performed inpatient surgical procedures in the United States (Fingar, 2012). In the Netherlands, the number of THAs performed annually exceeded 31,000 in 2017 and grew by 26% since 2010 (LROI, 2019). This increase can be explained by a growing population of elderly and obese patients, as well as by changing thresholds for arthroplasty surgery. Indications for total hip replacement used to be largely restricted to elderly patients with disabling osteoarthritis (OA). To date, the procedure is also performed in younger patients aiming to restore quality of life, which for them typically includes physically demanding activities.

HISTORY OF THA

The THA procedure as it is performed today, is the result of gradual development of biomechanical concepts, prosthetic materials, antiseptic measures and surgical techniques over the last century (Habermann, 1986). In the course of the evolution of THA, major failures have been described such as implant breakage, periprosthetic fractures, poor component design, wear related complications such as osteolysis and component loosening, peri-prosthetic infections, sepsis and thromboembolic events. An overview is given below of this staged development of hip arthroplasty.

Hip-affecting disorders are not new pathology. Palaeopathologists have found OA in ancient skeletons (Learmonth, 2007). In the late 19th century, interpositional arthroplasties were performed with the intention of mobilising ankylosed joints. Neighbouring soft tissue (e.g. fascia lata) and foreign substances (plastic materials, submucosa of pig's bladder) have been placed between the articular surfaces of the osteoarthritic or ankylosed hip in an attempt to restore motion, relieve pain and prevent repeat fusion. This technique was adopted by multiple surgeons and early results seemed promising, yet failure rates were relatively high and functional results disappointing (Wiles 1958, Habermann 1986). In 1923 the idea of mould arthroplasty was conceived. A mould of some inert material, interposed temporarily between the affected femoral head and the acetabulum, would guide formation of fibrous tissue and regeneration of articular cartilage (Smith-Peterson, 1948). Due to early breakage before removal, the original glass and heavier Pyrex glass moulds were abandoned (Smith-Peterson, 1948). In 1938, Smith-Peterson first performed a vitallium mould arthroplasty after his dentist suggested vitallium (an alloy of cobalt, chromium and molybdenum) as an ideal inert and strong material that should be robust enough to allow weight bearing (Smith-Peterson, 1948) (Fig. 1).

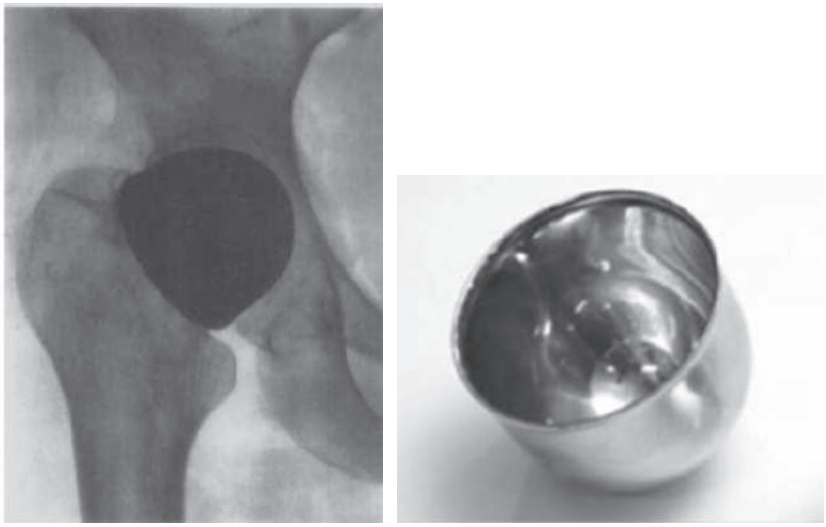

FIGURE 1. Vitallium mould arthroplasty (cobalt-chromium-molybdenum alloy) after 5-year follow-up. Resorption of the femoral neck (Wiles 1958, Hernigou 2014).

Hereafter, the first 'hip replacement surgery' was performed by Philip Wiles in 1938 by replacing the femoral head with a stainless steel ball-and-cup arthroplasty (Fig. 2). In contrast to mould arthroplasty, where the mould is placed freely between the articular surfaces in order to initiate regeneration of articular cartilage, replacement surgery has a more mechanical rather than physiological function (Wiles, 1958). In the late 1940s, brothers Jean and Robert Judet in Paris replaced the proximal femur with a polymethyl-methacrylate (PMMA) hemispherical femoral head component (Charnley, 1961) (Fig. 3).

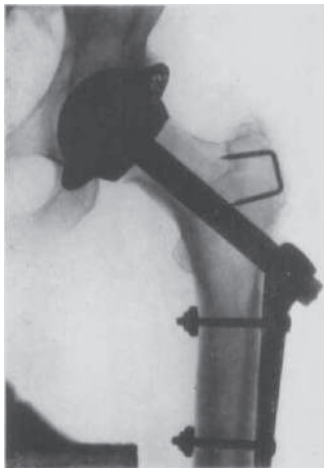

FIGURE 2. Pre-formed stainless steel acetabulum and femoral head with a round stem fitted into a round hole into a plate at the lateral aspect of the proximal femur. The smaller gluteal muscles were re-attached with a staple (Wiles, 1958).

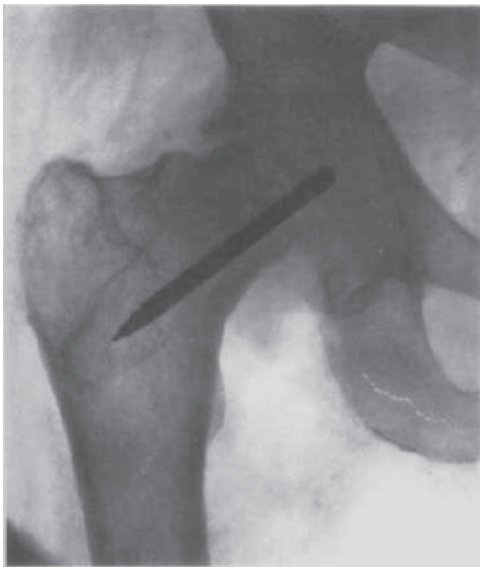

FIGURE 3. Judet arthroplasty: replacement of the proximal femoral head with a poly-methyl-methacrylate (PMMA) femoral head component (Wiles, 1958).

In the 1950s McKee and Watson-Farrar used a metal-on-metal (MoM) prosthesis with components made of cobalt-chromium. In the late 1950s and 1960s, Sir John Charnley made important contributions to the development of THA by introducing the concept of low friction arthroplasty. Charnley used a high-density polyethylene acetabular component with a metal femoral head as bearing surface (Fig. 4). He was also the first to use acrylic cement for component fixation (Charnley, 1961).

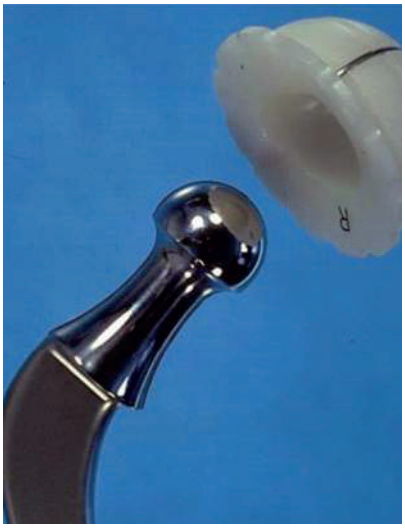

FIGURE 4. Charnley's metal-on-polyethylene THA (Rieker, 2017).

As the results of Charnley's low-friction arthroplasty became apparent, cemented fixation became the standard fixation method. However, the first generation of

cemented THAs showed premature loosening of components due to periprosthetic osteolysis. In the 1970s, histological examination of periprosthetic tissue harvested during revision procedures evidenced a local inflammatory response that was attributed to the fixation technique and described as 'cement disease' (Jones 1987, Learmonth 2007). As a result, the use of cementless, press-fit implants gained popularity. In the late 1970s, similar problems of osteolysis and subsequent aseptic loosening were encountered in uncemented implants. Wear-generated polyethylene (PE) particles were now recognised as the main cause for bone resorption and component loosening. It was found that PE debris can initiate a pro-inflammatory response, promoting differentiation of macrophages into bone-resorbing osteoclasts (Purdue, 2006).

Further endeavours to improve longevity of THAs focused on the development of alternative bearing surfaces with reduced wear properties (e.g. ceramics, oxidised zirconium, highly crosslinked polyethylene), new implant designs and improved cementation techniques. Advances in bone-cement and cement-prosthesis interface attachment included meticulous cleaning and drying of the reamed bony surfaces, vacuum mixing and enhanced pressurisation techniques (Habermann 1986, Jones 1987, Learmonth 2007).

FAILURES AND THE NEED FOR REGISTERS

As described above, a wide variety of surgical techniques and implants have been implemented over the past decades in order to improve the procedure, yet not all innovations resulted in improved outcome. Throughout the history of orthopaedic surgery, some implants were introduced to the market without known long-term results. One example from the early 1990s is Boneloc bone cement (Biomet, Warsaw, IN, USA), designed to decrease the risk of aseptic loosening compared to traditional polymethyl methacrylate (PMMA) bone cement thanks to improved physical (less exothermic polymerisation temperature) and chemical characteristics (lower toxicity). Despite the biological advantages of Boneloc, clinical trials demonstrated unacceptably high short-term failure rates compared to traditional PMMA cement (Abdel-Kader, 2001). There is also the case of large-diameter metal-on-metal THAs, which were later found to have significantly higher revision rates compared to conventional bearings after initial excellent in vitro results (Rieker, 2017). Use of these articulations has been associated with wear-related adverse events, e.g., soft tissue inflammatory reactions to metal debris that include inflammatory pseudotumors and aseptic lymphocytic vasculitis-associated lesions (Drummond, 2015).

Ideally, decision-making in orthopaedic surgery should be based on diligent assessment of the evidence available. Failures such as implant breakage, loss of fixation and wear-related periprosthetic osteolysis often become clear years after an initial, successful introduction (Malchau, 2018). A stepwise introduction of new devices and surgical techniques is necessary to increase the use of evidence-based care while exposing as few patients as possible to the potential risk of failure (Malchau, 2000). Malchau suggested a standardised method to introduce new devices and surgical procedures. A stepwise clinical introduction was advocated starting with pre-clinical testing, followed by (preferably randomised) prospective trials, e.g. radiostereometric analysis (RSA). Lastly, registry studies based on large cohorts should be used to reveal potential clinical complications (Malchau 1995, Malchau 2000).

In this development of THA, local, regional and national arthroplasty registers have played an important role. The purpose of an arthroplasty register is to systematically collect data in order to detect patient-, implant- or procedure-related risk factors for good or poor outcome, aiming to improve the quality of orthopaedic care delivered at institutional, regional or national level. A major benefit of national arthroplasty registers is that they can provide early warnings on such major problems with new implants or methods (Robertsson, 2014). These registers allow identification of suboptimal implant performance after their introduction and can therefore be used as post-market surveillance and long-term tracking of patients or implants.

NATIONAL ARTHROPLASTY REGISTERS WORLDWIDE

The first national arthroplasty register was the Swedish Knee Arthroplasty Register (SKAR), established in 1975. The SKAR was shortly followed by the Swedish Hip Arthroplasty Register (SHAR), initiated by Peter Herberts in 1979. The initial objective of SHAR was to register all re-operations after THA in Sweden, to document complications associated with revision surgery and improve long-term outcome. The register gained early acceptance, and compliance of orthopaedic surgeons to register revision procedures was high. Over the years the register expanded. SHAR started to register all primary THAs in 1992, subsequently adding more prosthetic characteristics (1999) and collecting patient-reported outcome measures (PROMs) (2002) (Malchau, 2018).

Detailed data on implant survival, reasons for revision and complications for each orthopaedic department are available on a confidential basis. These figures are not publicly shared; they are presented against the national average and provide a strong incentive to reflect on daily practice and adopt successful practices. As a result of these efforts, in recent decades the incidence of major complications

and revision surgery have decreased drastically in Sweden (Malchau, 2018). The reports from the Swedish hip and knee arthroplasty registers created international interest and resulted in the establishment of other registers. The Finnish National Arthroplasty Register was initiated in 1980, followed by the Norwegian Arthroplasty Register (1987), the Danish Hip Arthroplasty Register (1995) and other registers (Table 1). In the Netherlands, the Dutch Arthroplasty Register (LROI) was initiated in 2007.

TABLE 1. Timeline of onset of national arthroplasty registers with full ISAR membership.

National Arthroplasty Registers
1975 Swedish Knee Arthroplasty Register (SKAR) (first national knee register)
1979 Swedish Hip Arthroplasty Register (SHAR) (first national hip register)
1980 Finnish Arthroplasty Register (FAR)
1987 Norwegian Arthroplasty Register (NAR)
1995 Danish Hip Arthroplasty Register (DHR)
1997 New Zealand National Joint Register (NZJR)
1999 Australian Orthopaedic Association National Joint Replacement Register (AOANJRR)
2001 Romanian Arthroplasty Register (RAR)
2001 Kaiser Permanente National Total Joint Registry
2003 National Joint Register for England, Wales, Northern Ireland and Isle of Man (NJR)
2003 Slovak Arthroplasty Register (SAR)
2007 Dutch Arthroplasty Register (LROI)
2011 Lithuanian Arthroplasty Register (LSER)
2012 Swiss National Joint Register (SIRIS)

In 2007 the Nordic registers joined forces by initiating the Nordic Arthroplasty Register (NARA), a combined database for hip and knee arthroplasty from Sweden, Finland, Denmark and Norway, aiming to further improve outcome and cooperation in arthroplasty research.

INTERNATIONAL SOCIETY OF ARTHROPLASTY REGISTERS (ISAR)

In 2004 ISAR, a global network of implant registers, was created. ISAR was founded after a consensus meeting, aiming to utilise the strength of cooperation and information-sharing, and further enhance the capacity of individual registers to meet their own goals and objectives. The society is involved in the development of new registers and frameworks to foster collaboration between its members (Mission statement ISAR). Currently, the society has 14 full members and 23 associate members. A full membership requires over 90% of procedures being recorded with data collection validated. Full members of ISAR are registries from Australia

(AOANJRR), Denmark (DKAR), Finland (FAR), New Zealand (NZJR), Norway (NAR), Sweden (hip (SHAR) and knee (SKAR)), Lithuania (LAR), Romania (RNE), Slovakia (SAR), the Netherlands (LROI) and Kaiser Permanente National Total Joint Registry. Associate membership includes developing registries with completed organization structures but less than 90% data coverage or no complete validation, as well as regional registries that receive at least 90% of data from a state/ province/ region with a specified country.

The worldwide distribution of arthroplasty registers with full ISAR membership is displayed in Fig. 5. Regional or institutional hip registers, as frequently seen in the United States, are not displayed. Due to financial, legal and regulatory issues there is no single national, multi-institutional arthroplasty register in the United States (Hughes, 2017). Major institutional (Mayo Clinic and Massachusetts General Hospital) and regional (HealthEast, Kaiser Permanente, and Michigan Arthroplasty Registry Collaborative Quality Initiative (MARCQ1)) registers cover hospitals across the United States (Hughes, 2017).

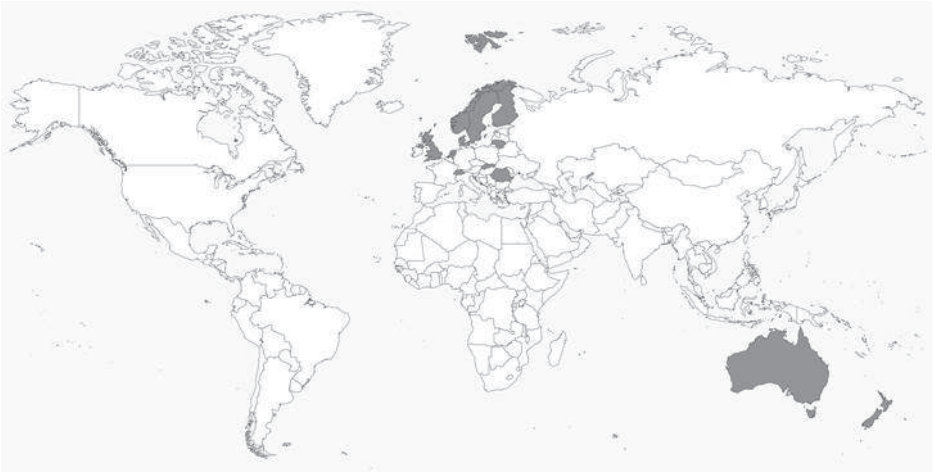

FIGURE 5. National arthroplasty registers with full ISAR membership (14).

DUTCH ARTHROPLASTY REGISTER (LROI)

LROI was initiated in 2007 by the Dutch Orthopaedic Association (NOV). LROI is a nationwide population-based register that prospectively collects data on primary and revision arthroplasties in the Netherlands, aiming to improve the quality of orthopaedic care. LROI covers all Dutch hospitals, which has resulted in a completeness of more than 98% for primary THAs and 88% for revision THAs (van Steenbergen, 2015). Key objectives for the register are enhancing traceability of implants, quality assessment of care delivered, identification of outlier results,

informing the public and society, and supporting scientific research (Strategic Plan LROI 2014-2016). Hip and knee replacement procedures have been included since the start of the register. During the course of the years data on ankle, shoulder, elbow (2014), wrist, finger and thumb (2016) joint replacement procedures have been added to the database. The register contains information on patient characteristics such as age, gender, ASA score, body mass index, smoking status, Charnley score, surgical history of the affected joint and preoperative diagnosis, as well as procedure and prosthesis information collected such as year of operation, surgical approach to the hip, femoral head size, bearing surface, fixation type and prosthesis characteristics (name and type, manufacturer). The vital status of all patients is obtained from the national insurance database on healthcare in the Netherlands. Outcome measurements are implant survival and patient-reported outcome measures (PROMs).

Joint-specific and general health-related PROMs are registered in LROI since 2015. For hip patients, a set of PROMs as recommended by the NOV is used to measure pain, functional outcomes and health-related quality of life (HRQoL). This consists of the short version of the Hip disability and Osteoarthritis Outcome Score (HOOS-PS), Oxford Hip Score (OHS), EuroQoL five-Dimensions questionnaire (EQ-5D-31) and EQ-5D thermometer, and a numeric rating scale (NRS) to measure pain both during activity and at rest.

AIM AND OUTLINE OF THESIS

Gradual developments over the last decades have significantly increased the outcome reflected in improved implant survival and functional results in patients with a total hip replacement. National arthroplasty registers have been used to identify implant-related risk factors for (un)satisfactory outcome after THA (e.g. revision). Over time, the Dutch Arthroplasty Register has evolved from merely being a device register involved with safety to a quality register with an important scientific function – linking the outcome of arthroplasty not only to the prosthesis, but also to factors influenced by the patient (case-mix) and the orthopaedic surgeon. In addition, since the registration of PROMs, LROI can be used to evaluate functional results and health-related quality of life after THA. By identifying which modifiable patient-, procedure- and prosthesis-related factors influence arthroplasty outcome, efforts can be undertaken to positively influence these factors in order to obtain better outcomes (both risk for revision and functional results).

As the interplay between patient, surgically modifiable factors and prosthesis is only recently becoming clearer, many issues remain to be discovered thanks to the abundance of data that LROI is currently generating. Aim of this thesis is therefore

to provide insight into a number of current issues affecting outcome after THA in the Netherlands, by using the data from the Dutch Arthroplasty Register. For the sake of simplicity, we postulate that outcome of THA is the result of the interplay between three entities: 1) the patient, 2) the orthopaedic surgeon, and 3) the prosthesis. This thesis is accordingly divided into three sections. The first part examines the effect of patient characteristics (case-mix) on both survival (Chapter 2) and PROMs (Chapter 3) after primary THA. The second part focuses on factors predominantly determined by the orthopaedic surgeon (surgically modifiable factors). Chapter 4 examines effect of bearing type on revision after primary THA. We subsequently investigated the effect of surgical approach on PROMs (Chapter 5). The third part focuses on the prosthesis. Chapter 6 describes the incidence and risk for revision for THAs assembled of components from different manufacturers (mixed THA). In line with Chapter 6, in Chapter 7 we assessed the rules for mixed THAs based on European law. Lastly, a general discussion on the aforementioned studies is provided, including our main findings, the value of arthroplasty registry research, the use of PROMs in arthroplasty registry studies, and propositions for future research.

OUTLINE OF THESIS

Part 1 The patient | Patient characteristics

Chapter 2. Patient characteristics influence revision rates of THA.

Patient characteristics or case-mix are known to influence postoperative outcomes after primary THA. Case-mix is defined as the variation in the population, relating to factors such as American Society of Anesthesiologists (ASA) physical status or body mass index (BMI). The influence of these factors on outcome, will help surgeons identify patients at risk for revision surgery preoperatively, so that appropriate preventive measures can be taken.

Questions addressed:

- What is the effect of patient characteristics on the revision risk after primary THA in the Netherlands?
- Is there a difference in reason for revision among patients with differences in case-mix?

Chapter 3. Influence of patient characteristics on patient-reported outcome measures after primary THA.

Similarly to revision rates (Chapter 2), PROMs can be affected by patient characteristics and case-mix factors. When arthroplasty registry data are used to compare outcomes across providers and hospitals, it is important to have an accurate and standardized method to identify differences in case-mix. This study aims to determine the effect of case-mix on PROMs after primary THA.

Question addressed:

- What is the effect of patient characteristics (case-mix) on improvement of PROMs (physical functioning, health-related quality of life and pain) after primary THA in the Netherlands?

Part 2 The orthopaedic surgeon | Surgically modifiable factors

Chapter 4. Effect of bearing type on the outcome of total hip arthroplasty.

Hip arthroplasty articulation is differentiated based on the bearing surface of the femoral head and the acetabular component. Increased activity of patients and a younger age at the time of the primary procedure have sparked the development of alternative bearing surfaces in THA. Modern bearing surfaces such as ceramics, oxidized-zirconium, metal-on-metal and highly-crosslinked-polyethylene (HXLPE) were introduced in order to further increase implant survival after total hip replacement.

In this study we assessed whether these modern bearing surfaces were associated with improved survival compared to traditional metal-on-polyethylene THAs.

Questions addressed:

- What is the distribution of the different bearing surfaces in THA in the Netherlands?
- What is the effect of bearing type on risk for revision after primary THA?
- What is the effect of bearing type effect on reason for revision?
- Does risk for revision according to bearing type vary among THAs with different femoral head sizes?
- Is there a difference in revision rate for different bearing surfaces in patients younger than 60?

Chapter 5. Similar superior patient-reported outcome measures (PROMs) for anterior and posterolateral approach after THA.

The decision for a surgical approach is predominantly determined by the surgeon's preference and training. It is known that the surgical approach chosen to implant a total hip replacement affects implant survival as well as reason for revision. The different approaches have their advantages and disadvantages in terms of duration of surgery, exposure and risk for complications. Whether the surgical approach influences PROMs after primary THA in the Netherlands is subject to debate.

Question addressed:

- Is there a difference in postoperative improvement in self-reported physical functioning, disability and pain between THAs implanted using the posterolateral, direct lateral, anterolateral or, anterior approach?

Part 3 The prosthesis | Mix and match

Chapter 6. Nationwide review of mixed and non-mixed components from different manufacturers in total hip arthroplasty.

Mixed prostheses are defined as THAs (stem, head, cup) assembled of components produced by different manufacturers. National arthroplasty studies demonstrate that the use of mixed components is common practice worldwide.

Although often combined, manufacturers generally issue warnings and precautions regarding their products, cautioning against mixing components from different manufacturers. It has been hypothesised that mixing and matching of components can lead to adverse events due to unforeseen mismatch of the head and taper or the femoral head and cup. In this study we aim to examine the use of mixed components in primary THA in the Netherlands.

Questions addressed:

- What is the proportion of THAs used in the Netherlands assembled of components produced by different manufacturers?
- Is there a difference in revision rates between mixed and non-mixed THAs registered in the Dutch Arthroplasty Register?

Chapter 7. To mix or not to mix? Medical legal implications of mixed components in Total Hip Arthroplasty.

As described, use of mixed components in THA is frequent and provides medical benefits in specific situations. Several national arthroplasty registry studies have demonstrated that various combinations of cups, heads and stems produced by different manufacturers yield similar and for some combinations even better results in terms of survival compared to non-mixed THAs. However, this raises the question of whether there are legal implications. In this study we aimed to assess the legality of mixed THAs based on European law.

Question addressed:

- What are the legal implications of using mixed components in THA, based on European law?

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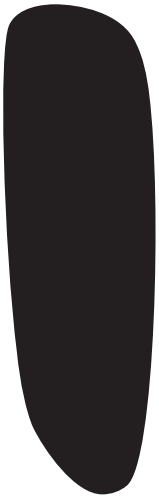
PART



THE PATIENT | PATIENT CHARACTERISTICS

PATIENT CHARACTERISTICS INFLUENCE REVISION RATE OF TOTAL HIP ARTHROPLASTY: ASA-SCORE AND BMI WERE THE STRONGEST PREDICTORS FOR SHORT-TERM REVISION AFTER PRIMARY THA

RINNE M. PETERS
LIZA N. VAN STEENBERGEN
ROY E. STEWART
MARTIN STEVENS
PAUL C. RIJK
SJOERD K. BULSTRA
WIERD P. ZIJLSTRA

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ABSTRACT

Background: Outcome and survival after primary total hip arthroplasty (THA) can be affected by patient characteristics. We examined the effect of case-mix on revision after primary THA using the Dutch Arthroplasty Register.

Methods: Our cohort included all primary THAs (n = 218,214) performed in patients with osteoarthritis in the Netherlands between 2007 and 2018. Multivariable logistic regression analysis was used to calculate the difference in survivorship in patients with different patient characteristics (age, gender, American Society of Anesthesiologists (ASA) score, body mass index (BMI), Charnley score, smoking, and previous operations to the hip).

Results: Case-mix factors associated with an increased risk for revision 1 year after THA were the following: a high ASA score (II and III-IV) (odds ratio (OR) 1.5, 95% confidence interval (CI) 1.1-2.0 and OR 3.0, 95% CI 1.7-5.3), a higher BMI (30-40 and >40) (OR 1.4, 95% CI 1.2-1.5 and OR 2.0, 95% CI 1.4-1.7), age ≥75 years (OR 1.5, 95% CI 1.1-2.0), and male gender (OR 1.3, 95% CI 1.2-1.4). A similar model for 3-year revision showed comparable results. High BMI (OR 1.9, 95% CI 1.3-2.9), a previous hip operation (OR 1.8, 95% CI 1.3-2.5), ASA III-IV (OR 1.2, 95% CI 1-1.6), and Charnley score C (OR 1.5, 95% CI 1.1-2.2) were associated with increased risk for revision. Main reasons for revision in obese and ASA II-IV patients were infection, dislocation, and periprosthetic fracture. Patients with femoral neck fracture and late post-traumatic pathology were more likely to be revised within 3 years, compared to osteoarthritis patients (OR 1.5, 95% CI 1.3-1.7 and OR 1.5, 95% CI 1.2-1.7).

Conclusion: The short-term risk for revision after primary THA is influenced by case-mix factors. ASA score and BMI (especially >40) were the strongest predictors for 1-year revision after primary THA. After 3 years, BMI and previous hip surgery were independent risk factors for revision. This will help surgeons to identify and counsel high-risk patients and take appropriate preventive measures.

INTRODUCTION

National arthroplasty registry data can be used to evaluate provider and device performance in orthopedic surgery. Both surgical outcome variables (e.g. survival) and Patient Reported Outcome Measures (PROMs) may be derived from these registries, in combination with patient characteristics and surgical factors. Registries allow identification of suboptimal performance or inequalities in health care and subsequently drive quality improvement (Burns 2016, Lekander 2017). When comparing health care outcomes, adequate risk adjustment for factors unrelated to the provider or device is warranted (SooHoo, 2016).

Patient characteristics (case-mix) are known to influence postoperative outcomes, and hence can influence cost as well. Case-mix is defined as the variation in the population, relating to factors such as age, sex, American Society of Anesthesiologists (ASA) physical status, Charnley score, diagnosis, previous operations to the affected joint, smoking status and body mass index (BMI) (LROI annual report, 2018). It is important to know preoperatively which patients are at risk for revision surgery. At present, tools are scarce to adequately identify these high risk patients. The aim of our study was to identify high risk patients, by determining the effect of case-mix on revision rates after primary total hip arthroplasty (THA) using the data in the Dutch Arthroplasty Register.

MATERIALS AND METHODS

Dutch Arthroplasty Registry
In 2007, the Dutch Arthroplasty Register (LROI) was started by the Dutch Orthopedic Society (NOV). The LROI is a national data cohort with coverage of all hospitals performing hip replacement surgery in the Netherlands. The level of completeness is more than 95% for primary THAs (van Steenbergen, 2015). LROI contains demographic information (e.g. as age, gender, ASA-score, diagnosis, previous surgery to the affected joint), surgical variables (e.g. surgical approach, fixation technique), prosthesis characteristics (e.g. femoral head size and bearing type), and survival of the prosthesis. Smoking behavior, orthopedic vitality (i.e. Charnley score) and body mass index (BMI) have been added in 2014. The LROI is linked to Vektis, the Dutch national insurance database for healthcare data (Vektis, 2017).

All primary hip arthroplasties performed in the Netherlands between 2007-2018 were incorporated in the dataset (n = 259,849). Patients with bilateral prosthesis were included. Metal-on-metal THAs were excluded (n = 6,635), because these are known to result in higher revision rates (Drummond 2015, Nederlandse Orthopaedische Vereniging 2015, Zijlstra 2017). Hereafter, the cohort contained 253,214 procedures.

Since pre-operative diagnosis may impact revision rates differently, only patients with osteoarthritis (OA) were included in our main analysis (n = 218,214). Baseline characteristics and operation details were categorized (Fig. 1). This was similar to previous studies using LROI-data (van Steenbergen 2015, Zijlstra 2017, Peters 2018-04, Peters 2018-06). Smoking status, BMI and Charnley score were registered since 2014 in the LROI. The median length of follow-up was 4.9 years, with a maximum of 12.0 years. The minimum length of follow-up was 1.0 year.

Demograpic data:

- age (<60, 60–74, and ≥75 years), gender (male/female), ASA-score (I, II, III-IV), diagnosis, previous operation to the affected hip (yes/no), smoking status (yes/no), BMI (<18.5, 18.5-25, 25-30, 30-40, and ≥40) and Charnley score (A, B1, B2, and C)

Surgical variables:

- surgical approach (direct anterior, anterolateral, straight lateral, posterolateral, other), fixation technique (cementless, cemented, reversed hybrid, hybrid)

Prosthesis characteristics:

- femoral head size (22-28 mm, 32 mm, 36 mm, ≥ 38 mm), bearing type (metal on PE, ceramic on PE, ceramic on ceramic, oxidized zirconium on PE)

FIGURE 1. Dutch Arthroplasty Register data: variable overview.

Statistics

Survival (with 95% confidence interval (CI)) was defined as time from primary THA to first revision procedure for any reason, death of the patient, or end of follow-up (January 1st 2019). The cumulative incidence of revision was calculated using competing risk analysis, where death was considered to be a competing risk (Putter 2007, Keurentjes 2012, Lacny 2015, Wongworawat 2015). Crude cumulative revision percentages within 1-, 5-, and 9 years were determined. In order to test for differences in revision rates between case-mix subgroups, multivariable logistic regression analyses were performed, based on 1-year and 3-year revision rate, while adjusting for confounders. The following confounding factors were entered into the model: age, gender, ASA score, previous operation to the affected hip. Since smoking status, Charnley score and BMI were registered since 2014, a subset of procedures performed in 2014-2017 with a follow-up of 1 year were used to calculate the odds ratios (OR) of revision within 1 year. For the 3-year revision rate procedures performed in 2014-2015 were selected to assure at least 3 year follow-up. Interaction was tested between age and respectively ASA, smoking and BMI. Goodness of fit was tested using Nagelkerke R square and the Hosmer and Lemeshow test (HL test) to examine how well the model fitted the data.

Furthermore, revision rates according to the reason for revision were provided. Group comparisons according to case-mix (dichotomous) were performed using

Chi-square tests. Categorical variables were made binary to simplify interpretation: age <60 or ≥60 year, ASA I-II versus ASA III-IV, Charnley A, B1, or B2 versus C, and BMI <30 versus BMI ≥30. P-values below 0.05 were considered statistically significant. All analyses were performed using SPSS version 23.0.

Ethical approval
Ethical approval for this study was obtained by the Medical Ethics Committee of University Medical Center Groningen (no. 154 METc2017/388).

RESULTS

Overall crude cumulative incidence of revision
In total, 218,214 THAs were included (Table 1 and Table 5 (appendix)), of which 6,552 were revised. The overall crude 1-, 3-, 5- and 9-year revision rates were respectively 1.4 (95% confidence interval: 1.4–1.5), 2.4 (2.4–2.5), 3.0 (2.9–3.1), and 4.2 (4.0–4.4) percent (Table 2 and Fig. 2).

Overall adjusted revision rates according to case-mix
Multivariable logistic regression analyses demonstrated that patients with osteoarthritis were more likely to have a revision within 1 year after primary THA when they had a high ASA-score (II and III–IV) (respectively OR =1.51 and 3.00) or high BMI (30-40 and ≥40) (respectively OR = 1.35 and 1.96). In addition, patients aged 75 years or older (OR = 1.50) or male (OR = 1.29) were more likely to have a revision within 1 year (Table 3). A similar model for 3-year revision showed comparable results. However, age was no longer associated with an increased risk of 3-year revision, whereas a previous operation to the affected hip joint and a Charnley score C were independent risk factors for enhanced 3-year revision rates. The interaction term between age and ASA was a statistically significant factor for 1-year revision rate, while this was no longer significant in the model for 3-year revision rate. The goodness of fit tests showed a rather good fit of the 1- and 3-year revision models (1-year revision model: HL test p = 0.16; Nagelkerke R-square 0.010; 3-year revision model: HL test p = 0.47, Nagelkerke R square 0.009).

TABLE 1. Patient characteristics of all patients with osteoarthritis who received a primary THA (n = 218,214) in the period 2007-2018 in the Netherlands.

Total Hip Arthroplasty (n = 218,214)		
	N *	(%)
Age		
<60	30,937	14.2
60-74	113,878	52.2
≥75	73,399	33.6
Gender		
Male	71,447	32.8
Female	146,489	67.2
ASA score		
I	47,114	22.3
II	136,082	64.3
III - IV	28,269	13.4
Previous operation		
Yes	4,495	2.2
No	203,742	97.8
Period		
2007-2010	53,458	24.5
2011-2014	88,132	40.4
2015-2017	76,624	35.1
Smoking		
Yes	11,248	5.2
No	90,149	41.3
Not registered; before 2014	116,817	53.5
Charnley score		
A	44,080	20.4
B1	30,267	14.1
B2	22,010	10.2
C	2,288	1.1
Not registered; before 2014	117,477	54.2
BMI (kg/m2)		
≤18.5	649	0.3
>18.5-25	33,998	15.6
>25-30	46,507	21.3
>30-40	25,453	11.7
>40	1,336	0.6
Not registered; before 2014	108,011	49.5

* Numbers do not add up to total due to unknown or missing values.

TABLE 2. Overall crude cumulative incidence of revision (non-casemix corrected) for THA.	
Revision for any reason	**Total Hip Arthroplasty**
	Proportion % (95%CI)
1 year	1.4 (1.4 – 1.5)
3 year	2.4 (2.4 – 2.5)
5 year	3.0 (2.9 – 3.1)
9 year	4.2 (4.0 – 4.4)

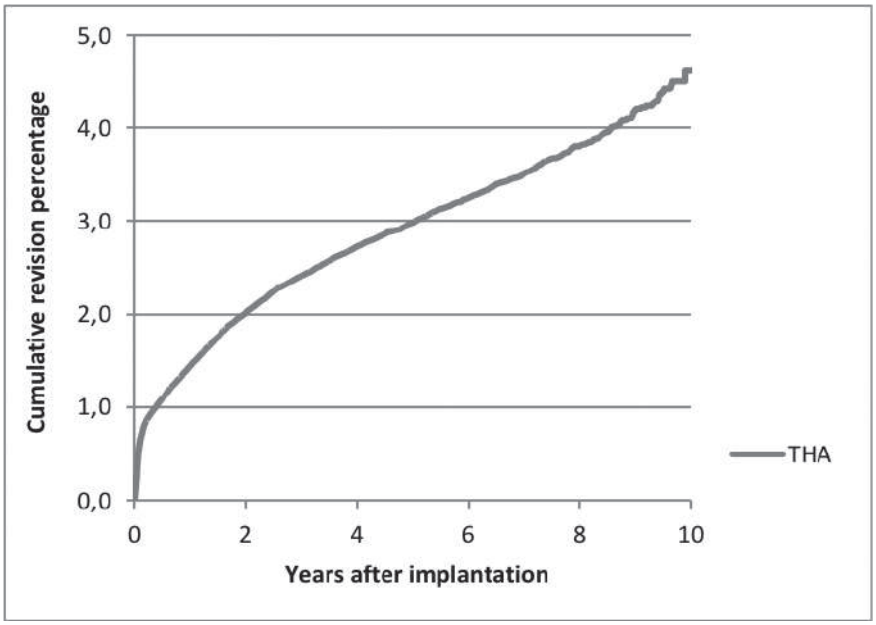

FIGURE 2. Overall crude cumulative incidence of revision (non-casemix corrected) for THA.

TABLE 3. Multivariable logistic regression analysis of 1- and 3 year revision percentages after primary THA in the Netherlands, in patients with osteoarthritis.

Total Hip Arthroplasty (n = 100,737) [a] Revised within 1 year: 1,737 (1.7%) 2014 - 2017			**Total Hip Arthroplasty** (n = 48,918) [b] Revised within 3 years: 1,227 (2.5%) 2014 - 2015		
1 YEAR	**Odds ratio (95% CI)**	**p-value**	**3 YEAR**	**Odds ratio (95% CI)**	**p-value**
Age (years)			**Age (years)**		
<60	0.72 (0.55 – 0.96)	0.02	<60	1.13 (0.95 – 1.34)	0.17
60-74	1.0		60-74	1.0	
≥75	1.50 (1.11 – 2.03)	0.01	≥75	1.02 (0.88 – 1.17)	0.82
Gender			**Gender**		
Male	1.29 (1.16 – 1.43)	<0.001	Male	1.25 (1.10 – 1.42)	0.001
Female	1.0		Female	1.0	
ASA score			**ASA score**		
I	1.0		I	1.0	
II	1.51 (1.13 – 2.00)	0.01	II	1.06 (0.90 – 1.25)	0.50
III - IV	3.00 (1.69 – 5.33)	<0.001	III - IV	1.24 (1.00 – 1.55)	0.05
Previous operation			**Previous operation**		
Yes	1.26 (0.91 – 1.75)	0.17	Yes	1.77 (1.27 – 2.47)	0.001
No	1.0		No	1.0	
Smoking			**Smoking**		
Yes	1.13 (0.97 – 1.32)	0.11	Yes	1.12 (0.93 – 1.34)	0.23
No	1.0		No	1.0	
BMI (kg/m2)			**BMI (kg/m2)**		
≤18.5	1.33 (0.74 – 2.37)	0.34	≤18.5	1.73 (0.94 – 3.20)	0.08
>18.5-25	0.86 (0.76 – 0.98)	0.02	>18.5-25	0.76 (0.65 – 0.88)	<0.001
>25-30	1.0		>25-30	1.0	
>30-40	1.35 (1.20 – 1.52)	<0.001	>30-40	1.15 (0.99 – 1.33)	0.07
>40	1.96 (1.42 – 2.72)	<0.001	>40	1.91 (1.27 – 2.86)	0.002
Charnley score			**Charnley score**		
A	1.0		A	1.0	
B1	0.98 (0.87 – 1.11)	0.78	B1	0.97 (0.84 – 1.12)	0.67
B2	1.12 (0.99 – 1.27)	0.08	B2	1.06 (0.91 – 1.24)	0.47
C	1.29 (0.97 – 1.72)	0.08	C	1.51 (1.06 – 2.15)	0.02
Interaction term					
ASA * Age	0.85 (0.75 – 0.97)	0.01			

[a] Adjusted for age at surgery, gender, ASA score, diagnosis, previous operation, smoking status, and BMI. [b] Adjusted for age at surgery, gender, ASA score, diagnosis, previous operation, smoking status, and BMI

A sub analysis focussing on osteoarthritis patients versus patients with other diagnoses (fracture, osteonecrosis, late posttraumatic changes, dysplasia, and other) demonstrated that patients operated for a fracture or for late posttraumatic pathology had a significantly higher risk for revision within 3 years compared to patients with osteoarthritis (respectively OR 1.5 (1.3-1.7) for fracture and OR 1.5 (1.2-1.7) for late posttraumatic) (data not shown). Furthermore, it was demonstrated that the influence of case-mix variables of revision rate varied among patients with different pre-operative diagnoses. Stratified analyses per diagnosis showed that patients with a hip fracture were more likely to undergo a revision procedure if they had a high ASA score (OR 2.7 (1.1-6.9)) or were male (OR 1.9 (1.1-3.2)) (data not shown). In patients with osteonecrosis, only smoking was associated with an increased 3 year revision rate (OR 2.0 (1.0-3.9)). In patients with late posttraumatic changes and dysplasia, a BMI above 40 (respectively 44.5 (2.3-858.5) and 29.7 (3.5-253.9)) was associated with an increased risk for revision (data not shown).

Reasons for revision

The reason for revision varied according to the length of the follow up. After 1 year the most frequently registered reason for revision was dislocation (33%), followed by infection (23%), and periprosthetic fracture (18%) (data not shown). After 5 years, THAs were most commonly revised due to dislocation (32%), loosening of the femoral- (22%) or acetabular (14%) component. At 9 year follow up, recurrent dislocation continued to be the most frequently registered reason for revision of primary THA in the Netherlands, followed by loosening of the femur (24%) or acetabulum (16%).

Revisions for infection were more common in patients with an ASA-score III-IV, a BMI over 30, aged under 60, and females (Table 4-1 and 4-2). Revision due to a periprosthetic fracture was more frequently registered in patients with ASA score III-IV, Charnley score C and in elderly and male patients. For dislocation, case-mix did not matter. Loosening of the femoral or acetabular component and liner wear as reason for revision was more common in the elderly. Loosening of the femoral component was observed more in patients with high BMI.

Table 4A. Reasons for revision in revised THAs in patients with osteoarthritis, performed between 2007-2018 in the Netherlands according to age, gender, and ASA-score.

Revision within follow-up Period	**Age <60** n = 30,937 of which 1,220 (3.9%) were revised	**Age ≥60** n= 187,277 of which 5,332 (2.8%) were revised	**Male** n = 71,447 of which 2,413 (3.4%) were revised	**Female** n = 146,489 of which 4,134 (2.8%) were revised	**ASA I-II** n = 183,196 of which 5,393 (2.9%) were revised	**ASA III-IV** n = 28,269 of which 887 (3.1%) were revised
Infection	199 (0.6)	977 (0.5)*	616 (0.4)	558 (0.8)**	921 (0.5)	220 (0.8)**
Periprosthetic fracture	93 (0.3)	845 (0.5)**	692 (0.5)	246 (0.3)*	769 (0.4)	143 (0.5)*
Dislocation	268 (0.9)	1,566 (0.8)	1,242 (0.8)	592 (0.8)	1513 (0.8)	258 (0.9)
Loosening of femur	300 (1.0)	1,116 (0.6)**	767 (0.5)	647 (0.9)**	1160 (0.6)	179 (0.6)
Loosening of acetabulum	168 (0.5)	669 (0.4)**	593 (0.4)	243 (0.3)*	711 (0.4)	87 (0.3)*
Cup/ liner wear	61 (0.2)	139 (0.1)**	145 (0.1)	55 (0.1)	167 (0.1)	14 (0.0)*
Periarticular ossification	23 (0.1)	79 (0.0)*	53 (0.0)	49 (0.1)*	81 (0.0)	10 (0.0)
Girdlestone	37 (0.1)	164 (0.1)	116 (0.1)	85 (0.1)*	157 (0.1)	28 (0.1)
Other	258 (0.8)	772 (0.4)**	670 (0.5)	360 (0.5)	865 (0.5)	120 (0.4)

[a] A patient may have more than 1 reason for revision. As such, the total may exceed the actual number of revisions.

* $p < 0.05$; ** $p < 0.0001$ for dichotomous patient characteristics (e.g. age <60 vs age >60)

TABLE 4B. Reasons for revision in revised THAs in patients with osteoarthritis, performed between 2007-2018 in the Netherlands according to BMI, Charnley-score and smoking status.

Revision within follow-up period	**Charnley A, B1 or B2** n = 96357 of which 2417 (2.5%) were revised)	**Charnley C** n = 2288 of which 79 (3.5%) were revised	**Smoker** n = 10337of which 303 (2.9%) were revised	**Non-smoker** n = 83459of which 2079 (2.5%) were revised	**BMI <30** n = 73986of which 1697 (2,3%) were revised	**BMI ≥30** n = 24495of which 799 (3,3%) were revised
Infection	701 (0.7)	22 (1.0)	78 (0.8)	627 (0.8)	417 (0.6)	305 (1.2)**
Periprosthetic fracture	354 (0.4)	19 (0.8)**	49 (0.5)	304 (0.4)	280 (0.4)	96 (0.4)
Dislocation	647 (0.7)	20 (0.9)	84 (0.8)	545 (0.7)	496 (0.7)	177 (0.7)
Loosening of femur	419 (0.4)	12 (0.5)	51 (0.5)	352 (0.4)	298 (0.4)	131 (0.5)*
Loosening of acetabulum	222 (0.2)	6 (0.3)	26 (0.3)	184 (0.2)	165 (0.2)	55 (0.2)
Cup/ liner wear	43 (0.0)	0 (0.0)	6 (0.1)	34 (0.0)	25 (0.0)	18 (0.1)*
Periarticular ossification	25 (0.0)	0 (0.0)	4 (0.0)	21 (0.0)	13 (0.0)	12 (0.0)*
Girdlestone	49 (0.1)	1 (0.0)	7 (0.1)	43 (0.1)	31 (0.0)	20 (0.1)*
Other	322 (0.3)	13 (0.6)	39 (0.4)	275 (0.3)	228 (0.3)	106 (0.4)*

[a] A patient may have more than 1 reason for revision or reoperation. As such, the total may exceed the actual number of revisions. * $p < 0.05$; ** $p < 0.0001$ for dichotomous patient characteristics (e.g. smoker vs non-smoker)

DISCUSSION

In this arthroplasty registry study, our primary goal was to identify high risk patients, by determining the effect of case-mix on short-term revision rates after primary THA in the Netherlands. We found higher revision rates one year after primary THA in patients with morbid obesity (BMI >40), high ASA-scores (III-IV), patients aged 75 or older or male patients. After 3 years, a high BMI, surgical history to the hip, Charnley score C, male gender, and a high ASA score, were independently associated with an increased risk for revision. Main reasons for revision in obese and ASAII-IV patients were infection and periprosthetic fracture. Furthermore, we found that patients with a femoral neck fracture and patients with late posttraumatic changes were more likely to undergo a revision, compared to osteoarthritis patients.

Adequate risk-adjustment is required in order to enable fair comparisons between hospitals and providers (SooHoo, 2016). Schilling (2016) developed a series of risk-adjustment models specific to 30-day morbidity and mortality following hip fracture repair, THA, and TKA procedures by using prospectively collected data in the United States. According to the results, regression models that account for differences in demographics, ASA classification, comorbidities, laboratory values, and vital signs can be used to make fair comparisons of outcome measures intended to characterize quality of care per provider. Similar case-mix adjustments were applied in the 12th annual report of the National Joint Registry of England, Wales, Northern Ireland and the Isle of Man. When comparing the observed numbers of revision surgeries of hip replacement for each hospital in the period 2003-2014 to the numbers expected, the data were corrected for age, gender and reason for primary surgery (NJR annual report, 2015). In the Netherlands, similar adjustments for case-mix factors were used for the annual quality performance indicator '1-year revision rate' defined by the Care Institute Netherlands, health insurance companies, the Netherlands Orthopaedic Association and the Patient Federation Netherlands. It is however debated, which specific case-mix factors should be used for these kinds of comparisons. The growing number of case-mix factors that have been added to the Dutch Arthroplasty Registry, especially since 2014, enabled us to perform new calculations with a broad set of case-mix variables. Based on the results of this study, registry outcomes of THA should be adjusted for age, gender, ASA-score, BMI, diagnosis, and previous operations, in order to make fare comparisons.

Patient characteristics

THA is consistently identified as a successful treatment for end-stage osteoarthritis of the hip joint with high survival rates and a significant improvement in quality of life after the procedure. Given the success of the surgery, it has been suggested that the focus of research should perhaps shift towards patient selection for these procedures to optimize outcomes and health resources (Wagner, 2016). Multiple

factors are known to influence the risk for revision after joint replacement surgery. Most patient factors cannot be modified, although smoking status and BMI can be modified.
A high ASA-score and severe obesity were the strongest predictors for short-term revision after a primary THA in patients with osteoarthritis. This is similar to previous studies. Wagner (2016) analyzed 21,361 consecutive THAs from their institutional database and demonstrated that reoperation and implant revision were strongly associated with BMI. Increasing BMI was significantly associated with increased rates of early hip dislocation, wound infection, and, deep periprosthetic infection (OR of 1.09 per unit of BMI >25)(Wagner, 2016). We also found higher rates of periprosthetic infection revisions in obese patients.

Diagnosis
Our data demonstrated that the preoperative diagnosis and indication for THA influenced short-term revision rates. Compared to osteoarthritis patients, those with an acute fracture or late posttraumatic hip pathology, showed increased short-term revision rates. In general, high BMI and high ASA scores increased the risks of short-term revision, but the influence of case-mix variables on revision rate varied with different pre-operative diagnoses. For instance, smoking was only associated with a higher risk for revision in patients with osteonecrosis.

Reason for revision
We demonstrated that the reason for revision differed among patients with differences in case-mix. Main reasons for revision were dislocation, infection and periprosthetic infection. Infection revisions were more common in obese patients and in patients with an ASA-score III-IV; smoking did not matter. Periprosthetic fracture revisions were performed more frequently in ASA III-IV, Charnley C and elderly patients. Dislocation revisions were common, but case-mix did not seem to matter based on our data. In literature however, advanced age, previous surgery, ASA III-IV and BMI>30 have been associated with increased risk of dislocation (Jones, 2019).

Based on the results of this study, patient characteristics can be used to help surgeons counsel patients and give a patient-tailored advice, in order to decrease the risk for short-term revision after THA. For example, the diagnosis is a non-modifiable risk factor which could be taken into account during pre-operative planning. In order to reduce the risk for dislocation in patients with an acute femoral neck fracture and late posttraumatic pathology, the use of a larger (e.g. 36 versus 32mm) femoral head component or a change of surgical approach could be considered, to reduce the risk for revision due to recurrent dislocation (Zijlstra, 2017). For obese patients, strategies to minimize infection should be optimized, for instance the dose of perioperative cefazolin should be adjusted to 3g instead

of 2g in case of BMI>40 or perhaps >35 (Löwik, 2019). Furthermore, for ASA III-IV patients, one might consider a cemented prosthesis, in order to reduce the risk of periprosthetic fracture (Zijlstra, 2017).

Limitations
Using registry data has the advantage of using national population-based routinely collected data. However, rather limited patient characteristics have been collected since the start of the registry in 2007. BMI, Charnley score and smoking status were only added to the registry in 2014, thus limiting the follow-up time. The Hosmer and Lemeshow tests proved that our model fitted the dataset well, but the predictive ability of our model, as shown by explained variance (R squared), was low, perhaps due to this limited set of patient characteristics. Furthermore, arthroplasty registry data are observational data, therefore residual confounding can remain and causality cannot be distracted from our data.

Conclusion
The short-term risk for revision after primary THA is influenced by case-mix factors. ASA-score and BMI (especially >40) were the strongest predictors for 1-revision after primary THA. After 3 years, BMI and previous hip surgery were independent risk factors for revision. Main reasons for revision in obese and ASAII-IV patients were infection, dislocation and periprosthetic fracture. This will help surgeons to identify and counsel high-risk patients and take appropriate preventive measures.

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Supplementary data
Tables 5 is available in the appendix of this article.

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APPENDICES

TABLE 5. Procedure characteristics all THAs (n = 218,214) performed in the period 2007-2018 in the Netherlands.

Total Hip Arthroplasty (n = 218,214)		
	N *	(%)
Fixation		
Cementless	135,909	62.8
Cemented	61,174	28.3
Reversed hybrid	8,821	4.1
Hybrid	10,318	4.8
Approach		
Direct anterior	28,028	13.0
Anterolateral	15,456	7.2
Straigt lateral	41,844	19.4
Posterolateral	130,003	60.2
Other	741	0.3
Femoral head size (mm)		
22-28 mm	63,834	31.2
32 mm	99,040	48.3
36 mm	40,609	19.8
≥ 38 mm	1,433	0.7
Articulation		
Metal on PE	63,225	29.0
Ceramic on PE	108,023	49.5
Ceramic on ceramic	16,314	7.5
Oxidized zirconium on PE	12,170	5.6
Other	18,482	8.5

PE: polyethylene. * Numbers do not add up to total due to unknown or missing values.

WHICH PATIENTS IMPROVE MOST AFTER TOTAL HIP ARTHROPLASTY? INFLUENCE OF PATIENT CHARACTERISTICS ON PATIENT REPORTED OUTCOME MEASURES (PROMS) OF 22,357 THA'S IN THE DUTCH ARTHROPLASTY REGISTER

RINNE M. PETERS
LIZA N. VAN STEENBERGEN
ROY E. STEWART
MARTIN STEVENS
PAUL C. RIJK
SJOERD K. BULSTRA
WIERD P. ZIJLSTRA

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ABSTRACT

Background: Patient Reported Outcome Measures (PROMs) after total hip arthroplasty (THA), can be influenced by patient characteristics (case-mix factors). We used the Dutch Arthroplasty Register (LROI) to determine the effect of case-mix on improvement of PROMs after primary THA.

Methods: We included all primary THAs (n = 22,357) performed in the Netherlands between 2014-2018. The Hip disability and Osteoarthritis Outcome Score Physical function short form (HOOS-PS), Oxford Hip Score (OHS), EQ-5D index score and thermometer, and Numeric Rating Scales (NRS) measuring pain during activities and in rest, were recorded. The difference between preoperative and 3- and 12 months postoperative scores was calculated (delta-PROM) and used as primary outcome variable. Multivariable linear regression was used to examine the association between patient characteristics (age, sex, ASA-score, BMI, Charnley-class, smoking, and previous operations to the affected hip) and PROMs. Cohens' d was used to measure effect size.

Results: Postoperative improvement (delta-PROM) on HOOS-PS, OHS, EQ-5D, and pain relief were significantly higher in patients younger than 60 years, in patients with female gender, a high ASA-score (3-4), a BMI >30 kg/m^2, and patients without a previous operation to the hip. Cohen's d indicated clinically small differences (0.2).

Conclusion: Patients benefitting most in terms of postoperative improvement of self-reported physical functioning, pain relief and quality of life after primary THA were young, female, with a high ASA or BMI-score, and without previous operations to the hip.

INTRODUCTION

In the Dutch healthcare system the need for transparency by reporting outcomes is increasing. Publication of outcome measures is compulsory, driven by the increasing influence of health insurance companies and market mechanisms (Siregar, 2011). The intended benefits are to drive quality improvement, demonstrate transparency, facilitate patient choice, and allow identification of poor performance (Burns, 2016).

Patient Reported Outcome Measures (PROMs) registered in national arthroplasty registers are increasingly being used to evaluate provider and device performance in orthopedic care. However, one of the primary criticisms is the lack of well-developed risk adjustment models that adjust for factors unrelated to the provider or device that are known to influence outcomes, generally known as patient characteristics or case-mix factors (SooHoo, 2016). Case-mix is the term used in surgical practice to describe variation in the population, relating to factors such as age, gender, American Society of Anesthesiologists (ASA) physical status, diagnosis, smoking and body mass index (BMI) LROI annual report, 2016).

PROMs can be affected by patient characteristics (case-mix factors). It is important to have an accurate, comprehensive, and standardized method to identify differences in case-mix, enabling fair adjustment in order to compare outcomes across providers and hospitals. This also benefits the integrity of public reporting of provider performance. Moreover, appropriate case-mix adjustment will decrease incentives that might otherwise encourage hospitals to minimize treatment of patients with comorbid conditions which might increase the risk for complications (SooHoo, 2016).

The influence of case-mix factors on PROMs after THA in the Netherlands is not well investigated. Therefore, our aim is to determine the effect of patient characteristics (case-mix: e.g. age, gender, BMI, ASA-score, and Charnley class, previous operations to the affected joint, and smoking status) on improvement of PROMs (measured as delta-PROM) after primary THA in the Netherlands. The future goal is to enable risk-adjustment models for outcome of THA that account for case-mix variation in the Netherlands.

MATERIALS AND METHODS

Dutch Arthroplasty Registry

A retrospective observational study was performed using data of the Dutch Arthroplasty Register (LROI). The LROI is a prospective database containing data derived from all hospitals performing hip replacement surgery in the Netherlands. The completeness is more than 95% for primary THA (van Steenbergen, 2015). The LROI contains demographic information, surgical variables, prosthesis characteristics, survival of the prosthesis and PROMs. Hip specific and general health-related PROMs have been collected since 2014. The vital status and, if applicable, date of death are obtained via access to the national insurance database on healthcare in the Netherlands (Vektis, 2017). PROM-data is not available for patients registered before 2014. Baseline characteristics were collected from the LROI and categorized similar to previous studies using LROI-data (van Steenbergen 2015, Zijlstra 2017, Peters 2018).

Patient Reported Outcome Measures

In order to determine the influence of case-mix factors on PROMs, our cohort was compiled of all, primary THAs (n = 22,357) performed in the Netherlands, for the diagnosis osteoarthritis, in the period 2014 until 2018. Health-related quality of life (HRQoL), pain and functional outcomes, were assessed using a set of PROMs as recommended by the Dutch Orthopedic Association (Nederlandse Orthopaedische Vereniging, 2012). This consist of the EuroQoL five-Dimensions (EQ-5D-3L) questionnaire with EQ-5D index score and thermometer to measure health perception and HRQoL, a Numeric Rating Scale (NRS) measuring pain during activity and rest, Oxford Hip Score (OHS), and the short version of the Hip disability and Osteoarthritis Outcome Score (HOOS-PS) to assess physical functioning and disability.

The EQ-5D-3L questionnaire asks patients to value their general health status in multiple dimensions. The index score range from -0.329 (poor health) to 1.0 (perfect health). The EQ-5D thermometer is a one question PROM which scores current health status on a scale ranging from 0 (worst imaginable health) to 100 (best imaginable health). Physical functioning was assessed using the HOOS-PS, a validated, joint-specific measure to assess activity during daily living, recreational activities and sports. This PROM ranges from 0-100 with zero representing no effort and 100 the most possible effort. HRQoL and disability in patients with osteoarthritis of the hip was measured using the OHS (range 12–60). Higher scores on the OHS indicate less disability. Lastly, a NRS is used to measure pain during activity and rest on a 11-point Likert scale with higher scores indicating more severe pain. The PROMs were filled in pre-operatively, at, 3 months and 1 year postoperatively (Peters, 2018). The preoperative PROMs were collected during consultation at the outpatient clinic. Postoperative PROM data were registered during the follow up visits by pen

and paper or using a web-based tool after invitation by email (LROI annual report 2016, Peters 2018). To measure changes, the differences between preoperative and postoperative scores were calculated and described as delta-PROM. This method was previously applied in a national cohort study comparing improvement of PROMs after primary THA for different surgical approaches (Peters, 2018).

Statistics

Baseline characteristics of all included patients were provided. Testing for differences in postoperative improvements in PROMs (delta PROM) was performed in a multivariable linear regression analysis. We entered the following confounders into the analysis: age, gender, ASA-score, smoking status, BMI, Charnley class, previous operation to the affected hip, fixation technique, femoral head diameter, surgical approach, and period of surgery. Previous operations was defined as a prior operation to the affected hip (e.g. osteosynthesis, arthroscopy). Categorical variables were made binary to simplify interpretation: age <60 or ≥60 years, ASA I-II versus ASA III-IV, Charnley A, B1, or B2 versus C, and BMI <30 kg/m^2 versus BMI ≥30 kg/m^2. Also surgical hospital volume can be expected to influence delta-PROM (Courtney, 2018). Hospital volume was divided into institutions in which 0-1000 procedures or institutions in which more than 1000 procedures were performed during our research period.

The outcome was presented as adjusted mean difference (AMD) with associated 95% confidence interval (CI). Post-hoc analysis to adjust for multiple comparisons was done using Bonferroni. Cohen's d was used as a standard measure of effect size. The effect size was calculated by dividing the difference between two means by the standard deviation of the data (small effect: 0.2–0.5; medium: 0.5–0.8; large: 0.8–1.3; very large: >1.3) (Cohen 1988, Amlie 2014). All analyses were performed using SPSS version 23.0.

Ethics

The study was approved by the board and scientific advisory committee of the LROI and the Medical Ethics Committee of University Medical Center Groningen (no. 154 METc2017/388).

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RESULTS

In total, 22,357 THAs were included in this study (Table 1). The majority of patients were aged between 60-74 years, female, ASA II, non-smoking, and had Charnley score A or B1.

TABLE 1. Descriptives for patients who received a primary THA in the period 2014-2018 with completed pre- and postoperative PROMs.

	THAs with 3- and 12 months follow-up (n = 22,357) *	
	N	Percentage
Age (years)		
<60	3,349	15.0
60-74	12,760	57.1
≥75	6,243	27.9
Gender		
Male	8,072	36.1
Female	14,276	63.9
ASA-score		
I	4,482	20.1
II	14,468	64.7
III- IV	3,398	15.2
Smoking		
Yes	2,075	9.5
No	19,792	90.5
Previous operation		
Yes	393	1.8
No	21,838	98.2
Charnley class		
A	9,975	44.8
B1	6,995	31.4
B2	4,707	21.2
C	569	2.6
BMI (kg/m2)		
≤18.5	114	.5
>18.5-25	7,259	32.6
>25-30	9,693	43.5
>30-40	4,994	22.4
>40	224	1.0

TABLE 1. Continued.

	THAs with 3- and 12 months follow-up (n = 22,357) *	
	N	Percentage
Hospital volume		
0 – 500 THAs	796	3.6
500 – 1000 THAs	8,428	37.7
1000 – 1250 THA	6,263	28.0
>1250 THAs	6,870	30.7
Approach		
Anterior	6,968	31.2
Posterolateral	12,253	54.8
Straight lateral	1,848	8.3
Anterolateral	1,098	4.9
Fixation		
Cemented	4,771	21.4
Cementless	15,917	71.5
Hybrid: stem cemented	858	3.9
Reversed hybrid: cup cemented	718	3.2
Articulation		
Metal-on-PE	5,537	24.8
Ceramic-on-PE	12,980	58.1
Ceramic-on-ceramic	1,492	6.7
Oxidized zirconium-on-PE	1,141	5.1
Femoral head size (mm)		
22-28	3,566	16.6
32	12,919	60.2
36	4,932	23.0
≤ 38	43	0.2

PE, polyethylene. Note: * Numbers do not add up to total due to unknown or missing values.

Physical functioning

The unadjusted delta-PROM data demonstrated higher postoperative scores (more improvement) on the HOOS-PS for young (<60 years) patients (respectively 32 after 3 months and 37 after 1 year), female patients (31 and 35), those with a high ASA-score (III-IV) (32 and 35), those without a previous operation to the affected hip joint (30 and 35), patients with a low Charnley class (30 and 35 for Charnley A, B1 and B2), or patients with a BMI ≥30 kg/m^2 (31 and 35) (Fig. 1). Adjusted analyses showed similar results for all examined case-mix factors, except Charnley score which was no longer statistically significant. Furthermore, high BMI and ASA-score were only associated

with more improvement in physical functioning at 3 months postoperatively (Table 2A-E and appendix Table 2F-H). All effect sizes were <0.2.

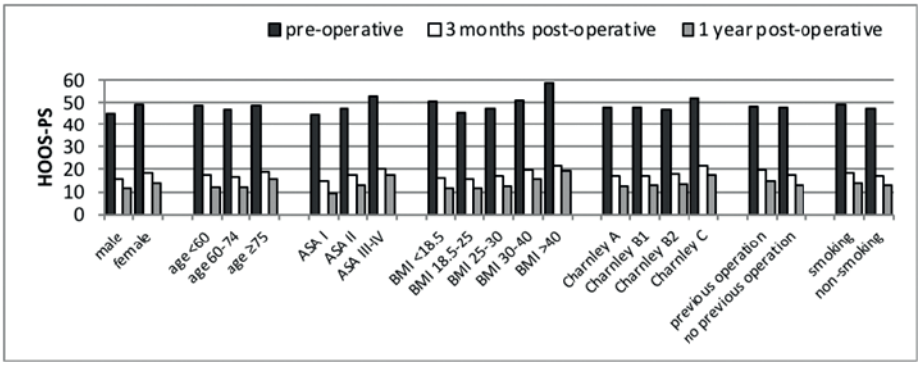

FIGURE 1. HOOS-PS for patients with a THA which completed the pre-operative and 3- and 12 months postoperative questionnaires (n = 22,357). Lower scores indicate higher physical function.

Health related quality of life and disability

Post-operative improvement after 3 and 12 months on the OHS was higher in female patients (17 and 19), young patients (17 and 20), a high ASA (18 and 20) or high BMI-score (17 and 20), patients without a previous operation to the hip (16 and 19), and a high Charnley class (C) (17 and 19) (Fig 2, appendix). The adjusted analyses demonstrated that higher improvement in HRQoL was associated with gender (female), age (<60 years), ASA (III-IV), and BMI (<30 kg/m^2), and hospital volume (low volume <1000) (Table 2A-E and appendix Table 2F-H). The Cohen's d effect sizes were smaller than 0.2.

Patient perception of health

Unadjusted post-operative improvement on the EQ5D index score, respectively 3- and 12 months postoperatively, was higher for female patients (0.27 and 0.30), young patients (<60 years) (0.29 and 0.33), and patients with high ASA-score (III-IV) (0.30 and 0.32) and high BMI (≥ 30 kg/m^2) (0.28 and 0.31) (Fig. 5, appendix). In the adjusted analyses these improvements remained significant, with an effect size <0.2. In addition, patients who smoked showed a larger improvement in HrQoL after 1 year compared to patients without a smoking habit in the adjusted analysis. Furthermore, young patients (<60 years), patients with a BMI above 30 kg/m^2 (only at 3 months), patients who smoked (only at 3 months) and patients with a Charnley score A, B1 or B2 (only at 1 year) had a larger improvement in health perception (Fig. 6 (appendix) and Table 2A-E and appendix Table 2F-H). Except for age, these differences had an effect size smaller than 0.2.

TABLE 2A. PROMs for patients who underwent THA: adjusted mean differences and CI according to gender (n = 22,357).						
	Male (n = 8,072; 36.1%)					
	Adjusted mean difference (CI)	p-value	Cohen's d	Adjusted mean difference (CI)	p-value	Cohen's d
Female (n = 14,276; 63.9%)	**3 MONTHS**			**12 MONTHS**		
Δ EQ5D index score	−0.03 (-0.04 to −0.02)	0.000	0.11	−0.03 (−0.04 to −0.02)	0.000	0.11
Δ EQ5D thermometer	−0.72 (−1.38 to −0.07)	0.02	0.03	−0.78 (−1.61 to 0.05)	0.07	0.03
Δ NRS (active)	−0.06 (−0.14 to 0.02)	0.21	0.01	−0.20 (−0.29 to −0.10)	0.000	0.07
Δ NRS (in rest)	−0.28 (−0.36 to −0.20)	0.000	0.10	−0.38 (−0.48 to −0.29)	0.000	0.14
Δ HOOS-PS	−1.40 (−1.98 to −0.81)	0.000	0.08	−1.71 (−2.41 to −1.00)	0.000	0.08
Δ Oxford Hip Score	−0.83 (−1.17 to −0.49)	0.000	0.09	−1.32 (−1.66 to −0.98)	0.000	0.14

[A] Adjusted for covariates: age, ASA-score, previous operations, fixation, articulation, femoral head size, BMI, Charnley class, smoking status, hospital volume, fixation technique, articulation and femoral head size. [B] Adjustment for multiple comparisons: Bonferroni

TABLE 2B. PROMs for patients who underwent THA: adjusted mean differences and CI according to age (n = 22,357).						
	Age < 60 (n = 3,349; 15.0%)					
	Adjusted mean difference (CI)	p-value	Cohen's d	Adjusted mean difference (CI)	p-value	Cohen's d
Age ≥ 60 (n = 19,003; 85.0%)	**3 MONTHS**			**12 MONTHS**		
Δ EQ5D index score	0.04 (0.03 to 0.05)	0.000	0.14	0.05 (0.04 to 0.06)	0.000	0.17
Δ EQ5D thermometer	2.70 (1.96 to 3.45)	0.000	0.15	4.18 (3.24 to 5.13)	0.000	0.20
Δ NRS (active)	−0.06 (−0.030 to 0.15)	0.19	0.05	0.14 (0.03 to 0.24)	0.01	0.04
Δ NRS (in rest)	0.48 (0.39 to −0.57)	0.000	0.21	0.52 (0.41 to 0.62)	0.000	0.18
Δ HOOS-PS	−0.89 (0.24 to −1.55)	0.01	0.08	2.80 (2.00 to 3.60)	0.000	0.14
Δ Oxford Hip Score	0.65 (0.26 to 1.04)	0.001	0.06	1.27 (0.88 to 1.66)	0.000	0.13

[A] Adjusted for covariates: gender, ASA-score, previous operations, fixation, articulation, femoral head size, BMI, Charnley class, smoking status, hospital volume, fixation technique, articulation and femoral head size. [B] Adjustment for multiple comparisons: Bonferroni

TABLE 2C. PROMs for patients who underwent THA: adjusted mean differences and CI according to ASA-score (n = 22,357).						
	ASA I – II (n = 18,950; 84.8%)					
	Adjusted mean difference (CI)	p-value	Cohen's d	Adjusted mean difference (CI)	p-value	Cohen's d
ASA III-IV (n = 3,398; 15.2%)	**3 MONTHS**			**12 MONTHS**		
Δ EQ5D index score	−0.04 (−0.05 to −0.03)	0.000	0.17	−0.04 (−0.05 to −0.03)	0.000	0.14
Δ EQ5D thermometer	−0.04 (−0.75 to 0.68)	0.92	0.03	0.25 (−0.69 to 1.18)	0.61	0.04
Δ NRS (active)	−0.15 (−0.24 to −0.07)	0.000	0.06	−0.08 (−0.18 to 0.03)	0.14	0.04
Δ NRS (in rest)	−0.05 (−0.13 to −0.04)	0.28	0.01	−0.03 (−0.14 to 0.08)	0.56	0.01
Δ HOOS-PS	−1.63 (−2.29 to −0.98)	0.000	0.10	−0.74 (−1.57 to 0.09)	0.08	0.02
Δ Oxford Hip Score	−1.36 (−1.74 to −0.97)	0.000	0.15	−0.99 (−1.38 to −0.61)	0.000	0.10

[A] Adjusted for covariates: age, gender, previous operations, fixation, articulation, femoral head size, BMI, Charnley class, smoking status, hospital volume, fixation technique, articulation and femoral head size. [B] Adjustment for multiple comparisons: Bonferroni

TABLE 2D. PROMs for patients who underwent THA: adjusted mean differences and CI according to BMI (n = 22,357).						
	BMI < 30 (n = 17,066; 76.6%)					
	Adjusted mean difference (CI)	p-value	Cohen's d	Adjusted mean difference (CI)	p-value	Cohen's d
BMI ≥ 30 (n = 5,218; 23,4%)	**3 MONTHS**			**12 MONTHS**		
Δ EQ5D index score	−0.02 (−0.03 to −0.01)	0.000	0.10	−0.02 (−0.03 to −0.01)	0.000	0.10
Δ EQ5D thermometer	−0.71 (−1.32 to −0.10)	0.02	0.02	−0.15 (−0.94 to 0.63)	0.70	0.01
Δ NRS (active)	−0.143 (−0.22 to −0.07)	0.000	0.08	−0.08 (−0.17 to 0.02)	0.10	0.03
Δ NRS (in rest)	−0.26 (−0.34 to −0.19)	0.000	0.10	−0.14 (−0.23 to −0.05)	0.003	0.07
Δ HOOS-PS	−1.02 (−1.58 to −0.47)	0.000	0.06	−0.38 (−1.05 to −0.30)	0.28	0.03
Δ Oxford Hip Score	−1.00 (−1.32 to −0.68)	0.000	0.13	−0.73 (−1.01 to −0.41)	0.000	0.10

[A] Adjusted for covariates: age, sex, ASA-score, previous operations, fixation, articulation, femoral head size, Charnley class, smoking status, hospital volume, fixation technique, articulation and femoral head size. [B] Adjustment for multiple comparisons: Bonferroni

TABLE 2E. PROMs for patients who underwent THA: adjusted mean differences and CI according to surgical history to the hip (n = 22,357).						
	Previous operation (n = 393; 1.8%)					
	Adjusted mean difference (CI)	p-value	Cohen's d	Adjusted mean difference (CI)	p-value	Cohen's d
No previous operation (n = 21,838; 98.2%)	**3 MONTHS**			**12 MONTHS**		
Δ EQ5D index score	0.01 (–0.03 to 0.04)	1.00	0.00	0.01 (–0.02 to 0.05)	1.00	0.04
Δ EQ5D thermometer	–0.01 (–2.46 to 2.44)	1.00	0.10	2.70 (–0.34 to 5.73)	0.10	0.10
Δ NRS (active)	–0.32 (–0.61 to –0.02)	0.03	0.11	–0.52 (–0.87 to –0.18)	0.001	0.18
Δ NRS (in rest)	–0.05 (–0.35 to 0.24)	1.00	0.00	–0.13 (–0.48 to 0.23)	1.00	0.04
Δ HOOS-PS	–3.12 (–5.32 to –0.92)	0.002	0.12	–0.79 (–3.42 to 1.84)	1.00	0.04
Δ Oxford Hip Score	–0.32 (–1.58 to 0.94)	1.00	0.03	–0.52 (–1.77 to 0.73)	0.95	0.06

[A] Adjusted for covariates: age, sex, ASA-score, previous operations, fixation, articulation, femoral head size, BMI, Charnley class, hospital volume, fixation technique, articulation and femoral head size. [B] Adjustment for multiple comparisons: Bonferroni

Pain during activity and rest
Larger improvement in pain reduction during activities was associated with female gender, young age (only after 1 year), a high ASA score or BMI (only at 3 months), no previous operation (only at 3 months), and smoking habit (only at 3 months) (Fig. 3 (appendix) and Table 2A-E and appendix Table 2F-H). All effect sizes were smaller than 0.2. Postoperative pain reduction in rest was best accomplished in patients aged younger than 60 years (0.48; 95% CI: 0.39 to -0.57, Cohen's d: 0.21 after 3 months and 0.52 (0.41 to 062), Cohen's d: 0.18) (Fig 4 (appendix) and Table 2A-E and appendix Table 2F-H).

DISCUSSION

In this arthroplasty register study, we identified the effect of patient characteristics (case-mix factors) on postoperative improvement of PROMs three months and 1 year after THA in the Netherlands. Gender, age, ASA-score, BMI, and surgical history of the affected joint were significantly associated with postoperative improvement of self-reported physical functioning, pain relief and health-related quality of life after primary THA. However, absolute differences were small.

SooHoo (2016) advocated that adequate risk-adjustment is required in order to enable fair comparisons after total joint arthroplasty. The California Joint Replacement Registry was used to report on predictors of adverse outcome after joint replacement surgery using the complication rate. Age and ASA-score were the strongest predictors of complication rates. It was stated that adequate risk adjustment plays an important role in objective comparison of providers, institutions, and implant devices using more traditional parameter to estimate the success rate of surgery based on, complication rate (SooHoo, 2016).
There is an increased interest in using PROMs, registered in national arthroplasty registries, to evaluate outcome after primary THA. In this study the influence of case-mix on post-operative improvement of physical function, pain and HRQoL after THA was determined. Improvement of physical outcome score after THA was strongly associated with surgical history of the hip joint: patients without a previous operation of the hip reported greater improvement in physical functioning as measured by the HOOS-PS.
Patients with an ASA-score III or IV had a larger improvement on physical functioning after primary THA. Based on the lower pre-operative score for these patients, this might be an effect of more advanced disease. A higher risk profile might make surgeons more reluctant to operate, causing a longer waiting period pre-operatively. In addition, patients with a BMI above 30 demonstrated higher post-operative improvement on HRQoL and physical functioning. Obesity in combination with advanced osteoarthritis of the hip might result in a lower level of physical

performance before joint replacement surgery. Severe obesity is widely associated with reduced cardiopulmonary capacity, metabolic abnormalities and decreased hemostasis which may predispose to morbidity and mortality after surgery (Onggo, 2020). These factors might lead to a higher threshold for orthopedic surgeon to progress with surgery.

Furthermore, young age was associated with a higher postoperative improvement on health perception and physical functioning. Osteoarthritis of the hip is not limited to people of advanced age, as it also affects patients participating in the labor process. Such patients aged younger than 60 years of age might be unable to fulfill their work responsibilities, especially in physically demanding jobs. Return to work after the procedure might result in a larger improvement of patient perceived outcome measures.

Another factor which resulted in more improvement in perceived health postoperatively was low hospital volume. Little is known about the effect of hospital volume on PROMs after THA. Laucis (2016) found that higher hospital volume resulted in lower surgical complication rate using the National Inpatient Sample (NIS) in the United States. However, the authors used different cut off points to indicate low (0-99 annually), intermediate (100-399) and high volume (≥400) hospitals. Based on the distribution of our data, only 3.6% of THAs were performed in low-volume hospitals, based on the above cut-offs. According to international standards, the majority of joint prostheses in the Netherlands is implanted in high volume hospitals. Although statically significant differences in PROM-improvement were found between patients with differences in case-mix characteristics, absolute differences between the groups were small. An effect size (Cohens' d) can be calculated. This method was used previously in studies from by the Norwegian and Dutch Arthroplasty Register (Amlie 2014, Peters 2018). An effect size of 0.2, implicates a small effect (Cohen, 1988). In our study, the largest effect size found measured 0.21, indication a small effect.

Limitations and possibilities

Arthroplasty registries are designed to identify and monitor differences in comparative outcomes, like revision rate or PROMs. This is being done by the collection of observational data reflecting clinical practice of the entire population without exclusions. Causality cannot be distracted from observational registry data and there might be (unmeasured) factors influencing the outcome of interest. Therefore, our finding that specific patient groups improve more on PROMs after a THA does not imply that these patient groups should receive a THA. Many more factors, like grade of osteoarthritis, health status, and shared decision making are of vital importance to decide whether a patient should undergo THA. In addition, we do not know the number of orthopaedic surgeons performing THAs per hospital. However, we do know the number of THAs per hospital.

Conclusion
In conclusion, a young age, female gender, a high ASA- or BMI-score, and no previous operations to the hip are independently associated with higher postoperative improvement of self-reported physical functioning, pain relief and quality of life (PROMS) after primary THA.

Supplementary data
Tables 2F-H and figure 2-6 are available in the appendix of this article.

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APPENDICES (TABLES)

TABLE 2F. PROMs for patients who underwent THA: adjusted mean differences and CI according to Charnley class (n = 22,357).

	Charnley A, B1 or B2 (n = 21,677; 97.4%)					
	Adjusted mean difference (CI)	p-value	Cohen's d	Adjusted mean difference (CI)	p-value	Cohen's d
Charnley C (n = 569; 2.6%)	**3 MONTHS**			**12 MONTHS**		
Δ EQ5D index score	−0.02 (−0.05 to 0.00)	0.08	0.07	−0.01 (−0.03 to 0.02)	0.70	0.03
Δ EQ5D thermometer	0.48 (−1.12 to 2.08)	0.56	0.05	2.27 (0.19 to 4.35)	0.03	0.11
Δ NRS (active)	−0.08 (−0.27 to 0.11)	0.41	0.01	0.07 (−0.17 to 0.30)	0.58	0.02
Δ NRS (in rest)	−0.27 (−0.46 to −0.07)	0.01	0.08	−0.17 (−0.41 to 0.07)	0.16	0.08
Δ HOOS-PS	−0.22 (−1.69 to 1.25)	0.77	0.02	1.33 (−0.51 to 3.18)	0.16	0.05
Δ Oxford Hip Score	−0.62 (−1.45 to 0.21)	0.14	0.07	−0.34 (−1.16 to 0.49)	0.43	0.04

[A] Adjusted for covariates: age, sex, ASA-score, previous operations, fixation, articulation, femoral head size, BMI, smoking status, hospital volume, fixation technique, articulation and femoral head size. [B] Adjustment for multiple comparisons: Bonferroni

TABLE 2G. PROMs for patients who underwent THA: adjusted mean differences and CI according to smoking status (n = 22,357).

	Smoking (n = 2,075; 9.5%)					
	Adjusted mean difference (CI)	p-value	Cohen's d	Adjusted mean difference (CI	p-value	Cohen's d
Non-smoking (n = 19,792; 90.5%)	**3 MONTHS**			**12 MONTHS**		
Δ EQ5D index score	0.02 (0.00 to 0.03)	0.07	0.03	0.02 (0.01 to 0.04)	0.002	0.07
Δ EQ5D thermometer	1.35 (0.28 to 2.42)	0.01	0.04	0.50 (−0.87 to 1.86)	1.00	0.02
Δ NRS (active)	−0.15 (−0.28 to −0.02)	0.02	0.04	−0.10 (−0.26 to 0.05)	0.35	0.03
Δ NRS (in rest)	0.04 (−0.08 to −0.17)	1.00	0.02	0.07 (−0.09 to 0.22)	0.96	0.02
Δ HOOS-PS	0.47 (−0.50 to −1.43)	0.74	0.02	0.65 (−0.53 to 1.82)	0.56	0.03
Δ Oxford Hip Score	−0.07 (−0.63 to 0.50)	1.00	0.01	0.35 (−0.21 to 0.91)	0.41	0.04

[A] Adjusted for covariates: age, sex, ASA-score, previous operations, fixation, articulation, femoral head size, BMI, Charnley class, hospital volume, fixation technique, articulation and femoral head size. [B] Adjustment for multiple comparisons: Bonferroni

TABLE 2H. PROMs for patients who underwent THA: adjusted mean differences and CI according to hospital volume (n = 22,357).						
	Hospital volume 0 - 1000 THAs (n = 9,224; 41.3%)					
	Adjusted mean difference (CI)	p-value	Cohen's d	Adjusted mean difference (CI)	p-value	Cohen's d
≥ 1000 THAs (n = 13,133; 58.7%)	**3 MONTHS**			**12 MONTHS**		
Δ EQ5D index score	−0.01 (−0.02 to 0.00)	0.05	0.04	−0.004 (−0.01 to 0.004)	0.34	0.00
Δ EQ5D thermometer	−0.06 (−0.59 to −0.47)	0.82	0.01	−0.02 (−0.71 to 0.67)	0.95	0.00
Δ NRS (active)	−0.003 (−0.07 to 0.06)	0.92	0.05	0.06 (−0.02 to 0.14)	0.15	0.01
Δ NRS (in rest)	−0.07 (−0.13 to −0.001)	0.05	0.03	0.01 (−0.08 to 0.09)	0.90	0.00
Δ HOOS-PS	−0.10 (−0.58 to 0.38)	0.69	0.04	−0.08 (−0.68 to 0.52)	0.78	0.01
Δ Oxford Hip Score	0.30 (0.01 to 0.58)	0.04	0.02	0.61 (0.33 to −0.90)	0.000	0.04

[A] Adjusted for covariates: age, sex, ASA-score, previous operations, fixation, articulation, femoral head size, BMI, Charnley class, smoking status, fixation technique, articulation and femoral head size. [B] Adjustment for multiple comparisons: Bonferroni

APPENDICES (FIGURES)

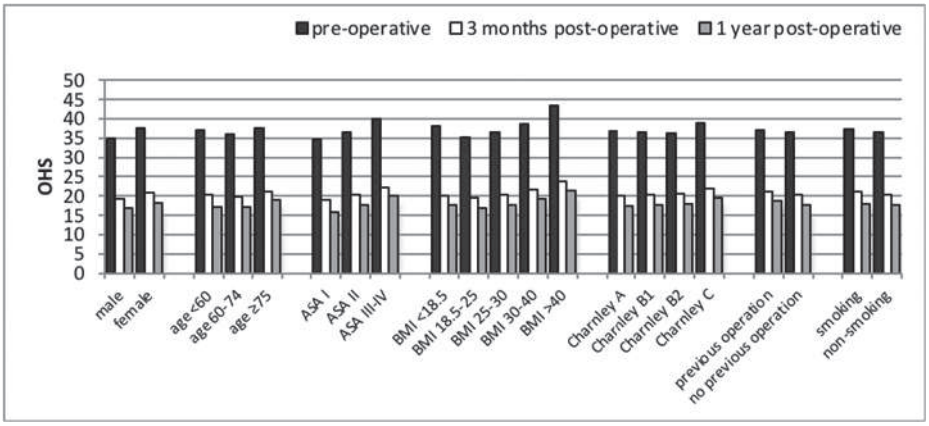

FIGURE 2. OHS for patients with a THA which completed the pre-operative and 3- and 12 months postoperative questionnaires (n = 22,357). Lower scores indicate higher physical function.

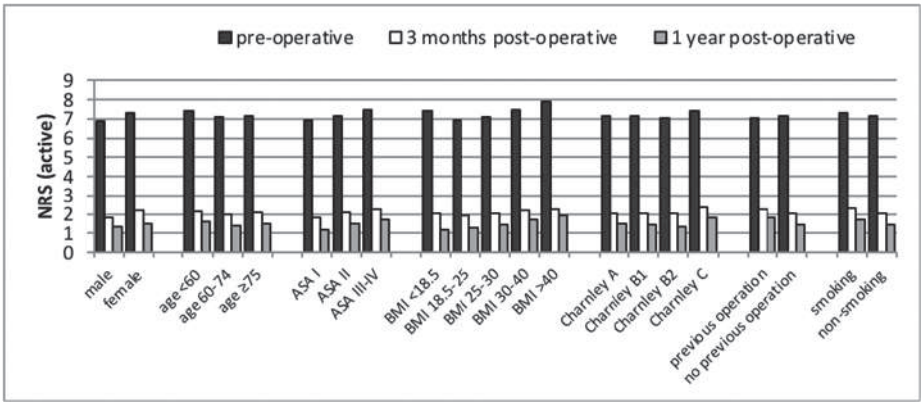

FIGURE 3. NRS (active) for patients with a THA which completed the pre-operative and 3- and 12 months postoperative questionnaires (n = 22,357).

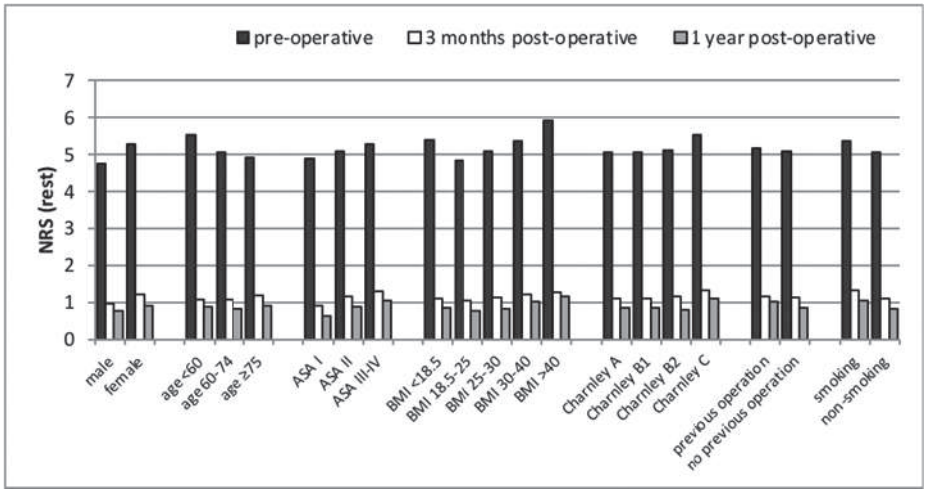

FIGURE 4. NRS (in rest) for patients with a THA which completed the pre-operative and 3- and 12 months postoperative questionnaires (n = 22,357).

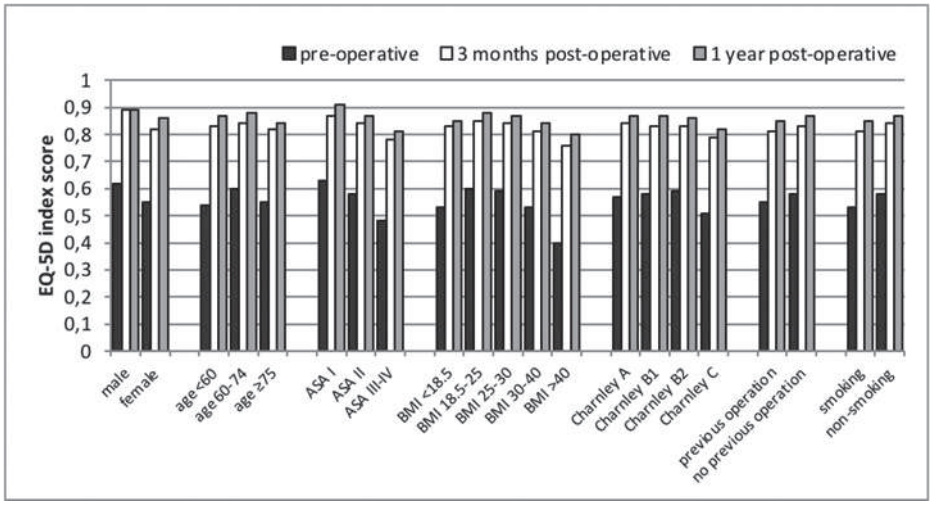

FIGURE 5. EQ-5D index score for patients with a THA which completed the pre-operative and 3- and 12 months postoperative questionnaires (n = 22,357).

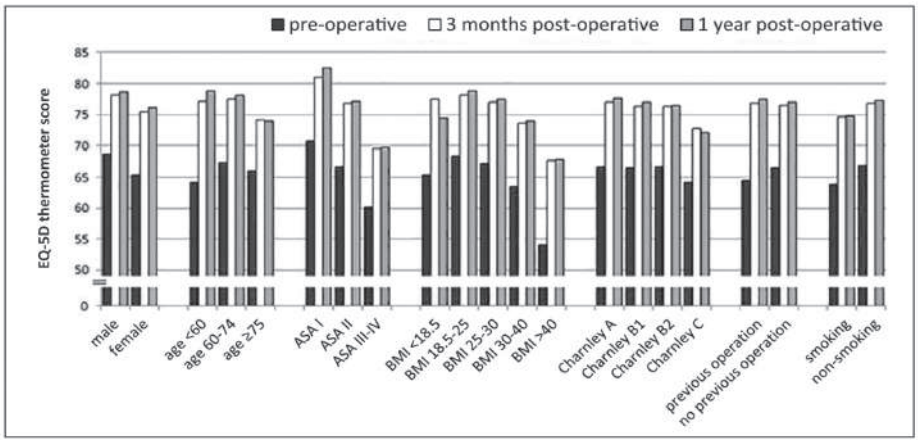

FIGURE 6. EQ-5D thermometer score for patients with a THA which completed the pre-operative and 3- and 12 months postoperative questionnaires (n = 22,357).

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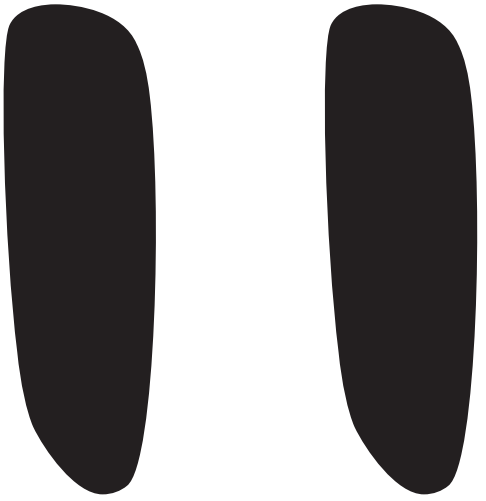

THE ORTHOPAEDIC SURGEON | SURGICALLY MODIFIABLE FACTORS

4

THE EFFECT OF BEARING TYPE ON THE OUTCOME OF TOTAL HIP ARTHROPLASTY

ANALYSIS OF 209,912 PRIMARY TOTAL HIP ARTHROPLASTIES REGISTERED IN THE DUTCH ARTHROPLASTY REGISTER

RINNE M. PETERS
LIZA N. VAN STEENBERGEN
MARTIN STEVENS
PAUL C. RIJK
SJOERD K. BULSTRA
WIERD P. ZIJLSTRA

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ABSTRACT

Background: Alternative bearing surfaces such as ceramics and highly-crosslinked-polyethylene (HXLPE) were developed, in order to further improve implant performance of total hip arthroplasty (THA). Whether these alternative bearing surfaces result in increased longevity, is subject to debate.

Methods: Using the Dutch Arthroplasty Register (LROI), we identified all patients with a primary, non-metal-on-metal THA implanted in the Netherlands in the period 2007-2016 (n = 209,912). Cumulative incidence of revision was calculated to determine differences in survivorship of THAs according to bearing type; metal-on-polyethylene (MoPE), metal-on-HXLPE (MoHXLPE), ceramic-on-polyethylene (CoPE), ceramic-on-HXLPE (CoHXLPE), ceramic-on-ceramic (CoC), and oxidized-zirconium-on-(HXL)polyethylene (Ox(HXL)PE). Multivariable Cox proportional hazard regression ratios (HRs) were used for comparisons.

Results: After adjustment for confounders, CoHXLPE, CoC, and Ox(HXL)PE resulted in a statistically significantly lower risk of revision compared to MoPE after 9-years follow-up (HR = 0.8-0.9 respectively, compared to HR = 1.0). For small (22-28mm) femoral head THAs, lower revision rates were found for CoPE and CoHXLPE (HR = 0.9). In the 36mm femoral head subgroup, CoC bearing THAs had a lower HR compared to MoHXLPE (HR = 0.7 versus 1.0). Crude revision rates in young patients (<60 years) for CoHXLPE, CoC, Ox(HXL)PE (HR = 0.7) were lower than MoPE (HR = 1.0). However, after adjustment for case-mix and confounders these differences were not statistically significant.

Conclusion: We found a mid-term lower risk of revision for CoHXLPE, CoC, and Ox(HXL)PE bearings compared to a traditional MoPE bearing surfaces.

INTRODUCTION

Increased activity of patients and a younger age at the time of the primary procedure have sparked the development of alternative bearing surfaces in Total Hip Arthroplasty (THA) such as ceramics, highly-crosslinked-polyethylene (HXLPE), and metal-on-metal articulations (MoM), in order to further improve survival and implant performance (Mihalko 2014, Varnum 2015). Currently, aseptic loosening of the acetabular component is the most frequent cause of revision after THA with a metal-on-polyethylene (MoPE) counterface (LROI annual report 2015, Norwegian Arthroplasty Register 2016). Osteolysis with subsequent loosening of components can be generated by polyethylene (PE) particles as a result of PE-wear (Varnum, 2015). Therefore, the use of alternative bearing surfaces has become more common over the last 2 decades. It is unknown whether the survivorship of these implants is better compared to the traditional MoPE bearings they sought to replace.

Studies which compared the survival of different bearing surfaces attained variant conclusions. The Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR) demonstrated superior results of HXLPE, ceramics, and ceramicised-metal (or oxidized-zirconium) in terms of increased longevity of the THA compared to standard PE (Annual Report AOANJRR 2016). A systematic review and network meta-analysis of randomized controlled trails demonstrated similar survivorship among ceramic-on-ceramic (CoC), ceramic-on-polyethylene (CoPE), ceramic-on-highly-crosslinked-polyethylene (CoHXLPE) and metal-on-highly-crosslinked-polyethylene (MoHXLPE) bearings, and inferior results for MoM and MoPE bearing implants (Yin, 2015).
Whether these alternative bearing materials, in combination with larger heads, have indeed resulted in increased survival rates however remains to be proven. Using nationwide data from the LROI, we assessed survivorship of CoC, CoHXLPE, MoHXLPE, CoPE, and oxidized-zirconium-on-(highly crosslinked)-polyethylene (Ox(HXL)PE) bearings in THA in the Netherlands, compared to MoPE.

MATERIAL AND METHODS

Data sources
The LROI, initiated by the Dutch Orthopaedic Association in 2007, is a nationwide population-based registry covering all hospitals in the Netherlands. This inter-institutional database has a completeness of 98% for primary THA and 88% for hip revision arthroplasty (van Steenbergen, 2015). The LROI contains prospectively collected data on primary and revision arthroplasty. Patients characteristics are recorded at the time of the primary procedure. In addition, surgical variables such as procedure- and implant information are registered in the LROI. Implant information

is supplied by all manufacturers, and is collected at the time of the procedure using stickers which could be attached to a registration form. Thereafter, prosthesis characteristics are derived from an implant library within the LROI, which contains several core characteristics of all prostheses used in the Netherlands, including name and type of the prosthesis, manufacturer, material, and femoral head size (van Steenbergen, 2015). Data from the LROI are matched with the national insurance database on healthcare (Vektis 2017), in order to obtain information on the vital status and date of death of registered patients.

Data collection
Eligible patients were registered in the LROI as having received a primary THA in a Dutch hospital, from the start of the registry in 2007 until the end of the follow-up period on December 31st, 2016 (n = 227,107). A patient can be registered twice, as having undergone a bilateral hip replacement. A primary THA is defined as the first implantation of a prosthesis, to replace a hip joint (van Steenbergen, 2015). Given their now known higher failure rates, THAs with a MoM bearing surface were excluded (n = 5,359) (Drummond 2015, Nederlandse Orthopaedische Vereniging 2015, Rieker 2017). Patients with unknown prosthesis components or patients for whom 1 of the components was not registered were excluded (n =11,836). The final cohort contained 209,912 THAs.

Types of bearing surface
Hip arthroplasty articulation was differentiated based on the bearing surface of the femoral head and the inlay or monoblock cup. Metal-on-standard-polyethylene was used as reference bearing type. All other bearing surfaces, except for ceramic-on-polyethylene, were considered as an alternative bearing type. The following groups were discerned; metal-on-polyethylene (MoPE), metal-on-highly-crosslinked-polyethylene (MoHXLPE), ceramic-on-polyethylene (CoPE), ceramic-on-highly-crosslinked-polyethylene (CoHXLPE), ceramic-on-ceramic (CoC), and oxidized-zirconium-on-(highly-crosslinked)-polyethylene (Ox(HXL)PE). Due to small group sizes, prostheses with an oxidized-zirconium-on-standard-PE (OxPE) and oxidized-zirconium-on-highly-crosslinked-polyethylene (OxHXLPE) were analyzed together. For demographics on all registered patients see Table 8, appendix. Categories for these explaining variables were classified similar to previous studies using data of the LROI (Peters 2016, Zijlstra 2017). Procedure and implant information (surgical variables) were retrieved, e.g. fixation technique, surgical approach and reason for revision.

Statistics
Group comparisons were made using chi-square-test to test for differences in patient and prosthesis characteristics. Survival time (with 95% confidence interval (CI)) was calculated as the time from primary THA to first revision arthroplasty for

any reason, death of the patient, or the end of follow-up. Cumulative crude incidence of revision was calculated using competing risk analysis, where death was considered to be a competing risk (Lacny 2015, Wongworawat 2015). The consequence of using Kaplan-Meier is that the probability of revision will be overestimated (Putter 2007, Keurentjes 2012). Crude cumulative revision percentages within 5 and 9 years were calculated. In addition, revision rates within 9 years according to the reason for revision were estimated for different bearing types. Differences were compared using chi-square test. In order to test for differences in revision rates between subgroups, hazard ratios were calculated using multivariable Cox proportional hazards regression analyses adjusting for possible confounding variables. The following confounders were entered into our analysis: age, gender, ASA-score, diagnosis, previous operation to the affected hip joint, fixation technique, femoral head diameter, surgical approach, and period of surgery. For all covariates added, the proportional hazards assumption was checked by inspecting log-minus-log curves (Jämsen, 2014). Differences in revision rate for the different bearing types in patients younger than 60 or with different sizes of the femoral head were assessed using a multivariable Cox proportional hazards regression analyses. Due to small numbers (1451 cases, 38 revision procedures) for the subgroup of 38mm femoral head components, multivariable regression analysis of this subgroup was not feasible. P-values <0.05 were considered statistically significant. All analyses were performed using SPSS for Windows version 23.0 (IBM Corp, Armonk, NY, USA).

RESULTS

The most frequently employed bearing surface between 2007-2016 was CoHXLPE (n = 70,175), followed by CoPE (n = 40,109), MoPE (n = 37,351), MoHXLPE (n = 32,867), CoC (n = 17,625), and Ox(HXL)PE (n = 11,785) (Table 8, appendix). The mean length of follow-up was 3.9 years, with a maximum of 9.9 years.

Reasons for revision

The most common reason for revision was dislocation (31%), followed by femoral loosening (21%), and infection (17%) (Table 1). Revision due to dislocation was more frequently registered in THAs with a MoPE bearing surface (38%) compared to other bearing types, but less frequent in CoC and Ox(HXL)PE. Revision due to femoral loosening was more frequently registered in CoC (25%), and Ox(HXL)PE (26%). Periprosthetic fractures which necessitated revision were less frequently registered in MoPE (10%), CoPE (10%) and CoC (9%) THAs compared to other bearings (Table 1).

TABLE 1. Reasons for revision or reoperation in revised THAs performed in the period 2007-2016 in the Netherlands (n = 5,464).

Revision within follow-up period	**Metal on PE** (n = 1,023)		**Metal on highly crosslinked PE** (n = 890)		**Ceramic on PE** (n = 1,186)		**Ceramic on highly crosslinked PE** (n = 1,649)		**Ceramic on ceramic** (n = 454)		**Oxidized zirconium on (highly crosslinked) PE** (n = 262)		**Total** [b] (n = 5,464)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Dislocation	391	38	248	28	393	33	498	30	91	20	60	23	1681	31[a]
Loosening of acetabulum	190	19	97	11	171	14	162	9.8	46	10	39	15	705	13[a]
Infection	163	16	165	19	180	15	330	20	51	11	35	13	924	17[a]
Loosening of femur	145	14	213	24	262	22	323	20	112	25	69	26	1124	21[a]
Periprosthetic fracture	106	10	166	19	118	9.9	283	17	42	9.3	59	23	774	14[a]
Cup/ liner wear	27	2.6	17	1.9	30	2.5	29	1.8	15	3.3	9	3.4	127	2.3
Girdlestone	35	3.4	32	3.6	44	3.7	52	3.2	14	3.1	9	3.4	186	3.4
Periarticular ossification	12	1.2	19	2.1	36	3.0	23	1.4	8	1.8	2	0.8	100	1.8
Other	158	15	133	15	182	15	249	15	133	29	39	15	894	16[a]

[a] $p < 0.05$ between different bearing types; [b] A patient may have more than 1 reason for revision of re-surgery. As such, the total is over 100%.

Overall crude cumulative incidence of revision

In total, 5464 THAs, were revised within the follow-up period. The overall, unadjusted 5- and 9-year cumulative incidence of revision for traditional MoPE THAs were respectively 2.7% (95% confidence interval 2.5-2.9) and 3.9% (3.6-4.2) (Table 2, Fig. 1). After 5 years, MoHXLPE showed a higher cumulative incidence of revision compared to MoPE. At 9 years, there were no differences in crude revision rate between the various bearings (Table 2). For MoHXLPE, crude hazard ratio (HR) for revision was higher than for MoPE (HR = 1.18; CI: 1.08-1.29) (Table 3). Other bearing couples did not display improved crude revision rates over MoPE.

TABLE 2. Crude cumulative incidence of revision for different bearing types for THA (non case-mix corrected) (n = 209,912).

Revision for any reason	**Metal on PE** (n = 37,351)		**Metal on highly crosslinked PE** (n = 32,867)		**Ceramic on PE** (n = 40,109)		**Ceramic on highly crosslinked PE** (n = 70,175)		**Ceramic on ceramic** (n = 17,625)		**Oxidized zirconium on (highly crosslinked) PE** (n = 11,785)	
	%	CI	%	CI	%	CI	%	CI	%	CI	%	CI
5 year	2.7	2.5-2.9	3.3	3.1-3.5	3.0	2.8-3.2	2.9	2.7-3.0	2.8	2.5-3.0	2.5	2.2-2.8
9 year	3.9	3.6-4.2	4.2	3.8-4.6	4.0	3.7-4.3	4.0	3.6-4.4	4.1	3.4-4.9	3.5	3.0-4.1

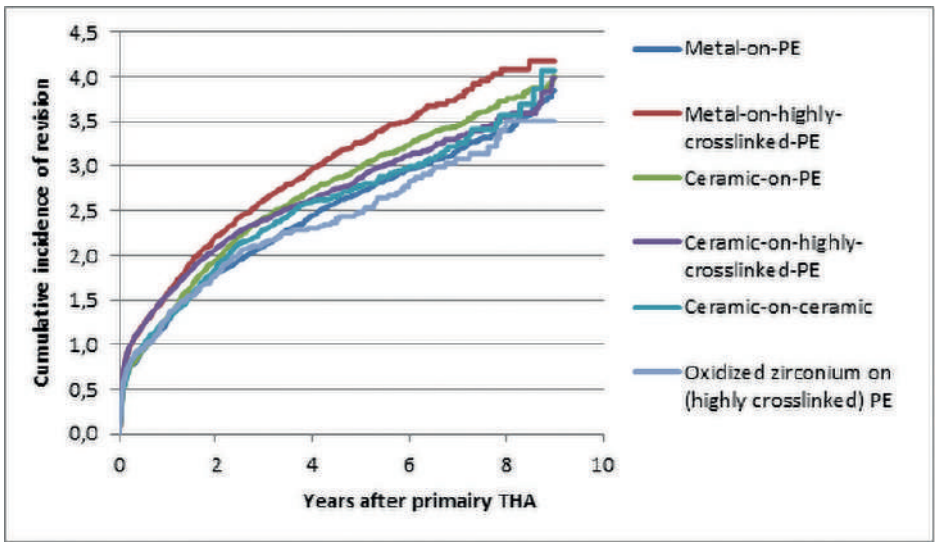

FIGURE 1. Cumulative incidence of revision according to bearing type in the Netherlands in 2007-2016 (n = 209,912).

Overall multivariable (case-mix adjusted) revision rates
Since the risk of revision can be influenced by case-mix, prosthesis and operation characteristics, we performed multivariable survival analyses, adjusted for age, gender, ASA, diagnosis, previous operation, fixation, head diameter, surgical approach, and period of surgery. These analyses showed that CoHXLPE, CoC, and Ox(HXL)PE had a 13-19% lower risk of revision compared to MoPE (respectively HR = 0.87; CI: 0.8–1.0, HR = 0.82; CI: 0.7–0.9, and HR = 0.81; CI: 0.7–0.9) (Table 3).

TABLE 3. Multivariable survival analysis of patients who underwent THA in the period 2007-2016 in the Netherlands (n = 209,912).

	Crude hazard ratio for revision (95% CI)	Adjusted hazard ratio for revision [a] (95% CI)
Articulation		
Metal on PE	1.0	1.0
Metal on highly crosslinked PE	1.18 (1.08 – 1.29) [c]	0.98 (0.88 – 1.09)
Ceramic on PE	1.08 (0.99 – 1.17)	0.99 (0.90 – 1.08)
Ceramic on highly crosslinked PE	1.08 (1.00 – 1.17)	0.87 (0.79 – 0.96) [b]
Ceramic on ceramic	1.01 (0.91 – 1.13)	0.82 (0.71 – 0.94) [b]
Oxidized zirconium on (highly crosslinked) PE	0.94 (0.82 – 1.08)	0.81 (0.70 – 0.94) [b]

[a] Adjusted for age at surgery, gender, ASA score, diagnosis, previous operation, fixation, head diameter, surgical approach, and period. [b] $p < 0.05$. [c] $p < 0.001$

Revision rate in young patients (<60 years)
In patients under 60 years, THAs with a CoHXLPE, CoC, and Ox(HXL)PE bearing surface, were less frequently revised compared to traditional MoPE THAs (respectively HR = 0.73; CI: 0.60–0.88, HR = 0.68; CI: 0.55–0.85, and HR = 0.74; CI: 0.56– 0.98 versus HR = 1.0) (Fig. 2). However, after adjustment for case-mix and confounders, revision rates were similar (Table 4).

Revision rates and femoral head size
Subgroup-analyses for different femoral head sizes were performed (Table 9A-C, appendix). For small femoral head components (22-28mm), the adjusted analyses demonstrated statistically significant lower revision rates for CoPE and CoHXLPE compared to MoPE (HR = 0.9 vs 1.0) (Table 5). Furthermore, CoC and Ox(HXL)PE demonstrated numerically lower revision rates, which however were not statistically significant. For 32mm femoral heads the adjusted analyses showed a higher risk for revision for patients with CoPE bearing surface (HR = 1.3, CI: 1.1-1.6) (Table 5). In the 36mm femoral head subgroup, CoC bearing THAs had a significantly lower hazard ratio compared to MoHXLPE (HR = 0.7 vs. 1.0) (Table 4). The hazard ratios and associated CI for the MoPE and CoPE articulation were not applicable due to small numbers (number of revisions: MoPE 0, CoPE 1). The overall risk of revision

with 22-28mm heads was 18% higher than 32mm heads (HR = 1.2; CI: 1.1-1.3), and 36mm heads yielded a 11% higher risk over a 32mm head (HR = 1.1; CI: 1.0-1.2) (data not shown in Table).

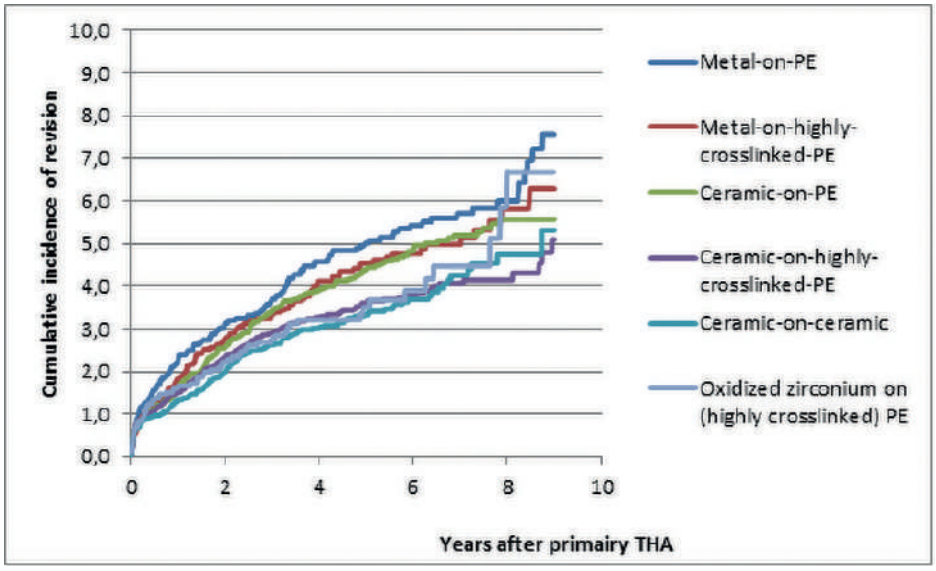

FIGURE 2. Cumulative incidence of revision according to bearing type for patients aged younger than 60 in the Netherlands in 2007-2016 (n = 34,204).

TABLE 4. Crude cumulative incidence of revision for different bearing types for THA for patients under 60 years (non case-mix corrected) (n = 34,204).

Revision for any reason	**Metal on PE** (n = 3,375)		**Metal on highly crosslinked PE** (n = 4,503)		**Ceramic on PE** (n = 4,718)		**Ceramic on highly crosslinked PE** (n = 14,166)		**Ceramic on ceramic** (n = 4,984)		**Oxidized zirconium on (highly crosslinked) PE** (n = 2,458)	
	%	CI	%	CI	%	CI	%	CI	%	CI	%	CI
5 year	5.0	4.3-5.9	4.5	3.9-5.4	4.4	3.8-5.1	3.6	3.2-4.0	3.3	2.8-3.9	3.5	2.7-4.6
9 year	7.6	6.1-9.4	6.3	5.0-8.0	5.6	4.8-6.5	5.1	4.1-6.3	5.3	4.0-7.0	6.7	4.4-10.4

TABLE 5. Multivariable survival analysis of patients with different femoral head components.

	N (revisions)	Crude hazard ratio for revision (CI)	Adjusted hazard ratio[a] (CI)
	FEMORAL HEAD 22-28 mm (n = 73,114)		
Articulation			
Metal on PE	27,423 (843)	1.0	1.0
Metal on highly crosslinked PE	7,236 (256)	1.3 (1.2 – 1.5) [c]	1.1 (1.0 – 1.3)
Ceramic on PE	22165 (660)	1.0 (0.9 – 1.1)	0.9 (0.8 – 1.0) [b]
Ceramic on highly crosslinked PE	14188 (367)	1.1 (1.0 – 1.2)	0.9 (0.7 – 1.0) [b]
Ceramic on ceramic	1406 (42)	1.0 (0.7 – 1.4)	0.8 (0.6 – 1.1)
Oxidized zirconium on (HXL) PE	696 (17)	0.8 (0.5 – 1.4)	0.7 (0.5 – 1.2)
	FEMORAL HEAD 32 mm (n = 96,330)		
Articulation			
Metal on PE	9908 (179)	1.0	1.0
Metal on highly crosslinked PE	17248 (377)	1.4 (1.1 – 1.6) [b]	1.1 (0.9 – 1.3)
Ceramic on PE	17888 (525)	1.5 (1.3 – 1.8) [c]	1.3 (1.1– 1.6) [b]
Ceramic on highly crosslinked PE	40496 (877)	1.3 (1.1 – 1.6) [b]	1.0 (0.9– 1.2)
Ceramic on ceramic	3279 (99)	1.5 (1.2 – 1.9) [b]	1.2 (0.9– 1.5)
Oxidized zirconium on (HXL) PE	7511 (158)	1.1 (0.9 – 1.4)	0.9 (0.8– 1.2)
	FEMORAL HEAD 36 mm (n = 39,017)		
Articulation			
Metal on PE	13 (0)	n.a [d]	n.a [d]
Metal on highly crosslinked PE	8124 (253)	1.0	1.0
Ceramic on PE	56 (1)	n.a. [d]	n.a [d]
Ceramic on highly crosslinked PE	15490 (405)	1.0 (0.8 – 1.1)	0. 9 (0.8 – 1.1)
Ceramic on ceramic	11756 (280)	0.8 (0.6 – 0.9) [b]	0.7 (0.6 – 0.9) [b]
Oxidized zirconium on (HXL) PE	3578 (87)	0.9 (0.7 – 1.2)	0.9 (0.7 – 1.1)

[a] Adjusted for gender, ASA score, diagnosis, previous operation, fixation, surgical approach, and period. [b] $p < 0.05$. [c] $p < 0.001$. [d] n.a. = not applicable; hazard ratios and confidence intervals for the MoPE and CoPE articulation were not applicable due to small number of revisions

Conventional versus highly-crosslinked-polyethylene

Adjusted overall hazard ratios were similar between THAs with highly-crosslinked-polyethylene acetabular components compared to standard PE (Table 6). However, revisions due to loosening of the acetabular component or liner wear were less frequently observed with HXLPE THAs compared to traditional PE (respectively 10% and 1.8% versus 17% and 2.7%). Revision due to recurrent dislocation was performed more frequently in THAs with conventional PE (35%) versus HXLPE (29%) (Table 7).

TABLE 6. Multivariable survival analysis according to the type of polyethylene.

	N (revisions)	Crude hazard ratio for revision (CI)	Adjusted hazard ratio for revision[a] (CI)
Articulation			
Standard polyethylene	81389 (2270)	1.0	1.0
Highly-crosslinked polyethylene	110898 (2740)	1.09 (1.03 – 1.15) [b]	0.95 (0.89 – 1.02)
Ceramic-on-ceramic	17625 (454)	0.99 (0.90 – 1.10)	0.88 (0.78 – 1.00)

[a] Adjusted for age at surgery, gender, ASA score, diagnosis, previous operation, fixation, head diameter, surgical approach, and period. [b] $p < 0.05$.

TABLE 7. Reasons for revision or reoperation in revised THAs performed in the period 2007-2016 in the Netherlands, according to type of polyethylene (n = 5464).

Revision within follow-up period	**Conventional PE** (n = 2,270)		**Highly-crosslinked PE** (n = 2,740)		**Non-PE / other** (n = 454)		Total [c] (n = 5,464)	
	n	%	n	%	n	%	n	%
Infection	356	16	517	19	51	11	924	17[b]
Periprosthetic fracture	231	10	501	18	42	9.3	774	14[b]
Dislocation	798	35	792	29	91	20	1681	31[b]
Loosening of femur	422	19	590	22	112	25	1124	21[a]
Loosening of acetabulum	383	17	276	10	46	10	705	13[b]
Cup/ liner wear	62	2.7	50	1.8	15	3.3	127	2.3[a]
Periarticular ossification	48	2.1	44	1.6	8	1.8	100	1.8
Girdlestone	83	3.7	89	3.2	14	3.1	186	3.4
Other	342	15	419	15	133	29	894	16[b]

[a] $p < 0.05$ between different bearingtypes. [b] $p < 0.001$. [c] A patient may have more than one reason for revision of re-surgery. As such, the total is over 100%.

DISCUSSION

There is an ongoing interest in alternative bearing surfaces in THA in order to further improve survivorship and reduce the risk of revision surgery. We found a statistically significant benefit in mid-term revision rates for CoHXLPE, CoC, and Ox(HXL)PE bearings compared to a traditional MoPE bearing surface. Furthermore, stratified analyses for small femoral heads (22-28mm), demonstrated lower revision rates for CoPE and CoHXLPE bearings. For THAs with a 36mm femoral head, CoC resulted in a lower risk for revision.

It has been hypothesized that modern bearing surfaces such as ceramics, oxidized-zirconium, and HXLPE articulations can decrease revision rates compared to traditional MoPE THAs. Historically, aseptic loosening is the most frequent cause of revision in THA (LROI annual report 2015, Norwegian Arthroplasty Register 2016). Over time, wear of the polyethylene liner in a traditional MoPE counterface can generate an adverse local host response which can result in periprosthetic osteolysis and subsequent aseptic loosening of components (Hu 2015, Varnum 2015). This process is even more relevant in young patients with increased activity demands. Alternative bearing surfaces were introduced in order to reduce PE-wear. Ceramic is harder and offers more scratch resistance than cobalt-chrome, which improves lubrication through a low friction coefficient, resulting in excellent wear resistance and low osteolysis rate (Wang 2013, Hu 2015). A meta-analysis of RCTs reporting on the comparison between CoC and MoPE bearing surfaces concluded that CoC resulted in lower revision rates, osteolysis, loosening of components and dislocation, despite more squeaking (Hu, 2015).

Well-documented drawbacks for ceramic components include high cost and adverse events, such as intra- or postoperative ceramic fractures, and audible squeaking (Hu 2015, Wyles 2015). In the Danish Arthroplasty Registry incidences of ceramic head and liner fractures of respectively 0.28% and 0.17% have been reported (Varnum, 2015). In addition, treatment of a fractured CoC THA could be challenging and the choice of the bearing surface in case of a revision is important. In the first appendix, we have described a case of systemic cobalt toxicity following revision of a failed CoC THA. In case of a fractured ceramic component, both surgeon and patients may be reluctant to choose for a ceramic-on-ceramic bearing again. In order to anticipate for a re-fracture, they may opt for revision to a metal-on-polyethylene THA. However, if ceramic particles remain present locally, they may become embedded in the PE inlay, causing abrasive wear of the relatively softer CoCr femoral head (Matziolis, 2003, Hasegawa, 2006). This could potentially lead to metallosis locally, and in more severe cases to systemic cobalt toxicity.

Ceramicised-metal or oxidized-zirconium (Oxinium, Smith & Nephew, Memphis, Tennessee) for femoral heads has been developed during the 1980s in an attempt to reduce PE-wear. Oxidized-zirconium femoral head components consist of a 5 µm-thick ceramic layer on the metal alloy core, which makes it more resistant to fractures compared to alumina ceramic heads (Jassim, 2015). Data from the AOANJRR demonstrated the lowest revision rates for ceramicised-metal-on-HXLPE with a 10-year follow-up. The cumulative incidence of revision was 3.2% (2.9-3.7) compared to 6.3% (6.1-6.6) for traditional MoPE bearing after 10 years. However, these results need to be interpreted with caution since the ceramicised-metal-HXLPE bearing is a single company product with a small number of femoral stem

and acetabular component combinations, which may have a confounding effect on the outcome (Annual Report AOANJRR 2016).

HXLPE was developed to decrease wear in traditional PE liners and subsequently decrease the incidence and severity of osteolysis. Mall (2011) compared the incidence of osteolysis in conventional PE versus HXLPE in young patients (under 50 years of age) undergoing primary THA using radiographs and computed tomography: HXLPE diminished the incidence of osteolysis by 92% compared to conventional PE. The AOANJRR demonstrated that HXLPE had a lower rate of revision compared to non-HXLPE. The difference increased with time and at 15 years the cumulative percentage of revision is 5.6% for HXLPE and 10.5% for non-HXLPE THAs. Fewer revisions for loosening and dislocation were observed. Other registries, e.g. Kaiser Permanente and NJR did not report on differences in survival between THAs with conventional and highly-crosslinked PE components, but did also show advantages of ceramics. In the Netherlands, we found a similar overall risk for revision for HXLPE and conventional PE THAs with a short-term follow-up. A similar shift in reasons for revision was observed in the Netherlands. Revisions due to loosening of the acetabular component or liner wear were less frequently observed in HXLPE THAs compared to traditional PE. Revision due to recurrent dislocations was performed more frequently in THAs with conventional PE compared to HXLPE. This can be explained by a preferential use of larger femoral head components in THAs with HXLPE (data not shown). In addition, Jassim (2015) found that the effect of using a HXLPE liner was more important in reducing component wear the material of the femoral head component (either ceramic or cobalt-chromium).

In the Netherlands, revision due to dislocation was more frequently encountered in MoPE THAs (38%) compared to other bearing types, which could be related a high proportion of small femoral head components (22-28mm) in this group (73%) (Table 8, Supplementary data). Femoral loosening as reason for revision was more frequently registered in CoC (25%) and Ox(HXL)PE (26%) THAs. Theoretically, this could be associated with the large proportion of uncemented THAs in these bearing type groups (respectively 89% and 55%). Periprosthetic fractures which necessitate revision were less common in MoPE (10%), CoPE (10%) and CoC (9%) THAs compared to other bearings. Theoretically, this could be explained by a large proportion of cemented fixation in THAs with MoPE and CoPE bearings.
In our dataset, metal-on-metal THAs were excluded. National Arthroplasty Registry data have demonstrated inferior results for large diameter MoM THAs. The use of these articulations have been associated with wear-related adverse events, e.g. soft tissue inflammatory reactions to metal debris, including inflammatory pseudotumours and aseptic lymphocytic vasculitis associated lesions (Drummond 2015, Nederlandse Orthopaedische Vereniging 2015, Rieker 2017).

We performed a detailed analysis in order to assess the influence of bearing surface on survival of the THAs in young (<60 years), generally more active patients (n = 34,204). We found a statistically significantly lower crude cumulative incidence of revision for advanced bearing surfaces such as CoHXLPE, CoC, and Ox(HXL)PE, over MoPE. However, after adjustment for confounding variables, no statistically significant differences at mid-term follow-up were found. This trend favoring the use of ceramics, HXLPE and oxidized-zirconium components, was consistent with results in patients aged under 55 years in the AOANJRR (Annual Report AOANJRR 2016).

We performed further subgroup analyses to assess the influence of bearing type in THAs with different femoral head components. Our results from patients with a small femoral head component demonstrate a reduced risk of revision for CoPE, CoHXLPE, CoC, and Ox(HXL)PE, compared to MoPE after correction for confounding variables. Although this phenomenon was visible for all alternative bearing surfaces, only CoPE and CoHXLPE demonstrated statistically significant differences.
In the large femoral head component (36mm) subgroup, significantly lower revision rates for CoC THAs were determined compared to the MoHXLPE reference bearing surface. Theoretically, the benefits of advanced bearing surfaces with more wear resistant characteristics would increase by an increasing size of the femoral head components since large femoral heads might cause more PE-wear and taper corrosion. Respectively, the use of HXLPE and ceramic or oxidized-zirconium heads may presumably lead to less wear and taper corrosion (Ries 2005, Zijlstra 2017).

Our study should be interpreted with its limitations in mind. Possible differences in survival are expected to be found on the long-term. Our study has a limited follow-up with a mean follow-up of 3.9 years and a maximum of 9.9 years. We acknowledge that variation in bearing type may result in possible differences in survival due to wear or loosening of components that will not be detected within our follow-up. Secondly, national registry studies are based on observational data and therefore cannot infer causality. Furthermore, our data limit the ability to comment on the effect of individual components which may be an unknown confounder. However, a prosthesis-specific analysis of frequently registered stem components did demonstrate a similar trend of superior results for THA with advanced bearing surfaces. Lastly, comparing different bearing surfaces inherently results in a confounding by indication bias which cannot be discounted. This phenomenon was also present in our data, but was statistically corrected for by multivariable Cox proportional regression analysis.

In summary, based on nationwide arthroplasty registry data, the use of a ceramic-on-highly-crosslinked-polyethylene (CoHXLPE), ceramic-on-ceramic (CoC), and oxidized- zirconium-on-(highly-crosslinked)-polyethylene (Ox(HXL)PE) bearing

surfaces resulted in significantly better mid-term survival rates compared to traditional MoPE in the Netherlands.

SUPPLEMENTARY DATA

Tables 8 and 9 are available in the appendix of this article.

The text in this chapter slightly differs from the published manuscript due to the introduction of a case description which was added as appendix to this thesis; see appendix.

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SUPPLEMENTARY DATA

TABLE 8. Descriptive and clinical data on all patients who received a primary THA in the period 2007-2016 in the Netherlands (n = 209,912).

	Metal on PE (n = 37,351; 17.8%)		**Metal on highly crosslinked PE** (n = 32,867; 15.7%)		**Ceramic on PE** (n = 40,109; 19.1%)		**Ceramic on highly crosslinked PE** (n = 70,175; 33.4%)	
	n	(%)	n	(%)	n	(%)	n	(%)
Age								
<60	3375	9.1	4503	13.7	4718	11.8	14166	20.2
60-74	15380	41.3	16973	51.7	20272	50.6	38575	55.0
≥75	18520	49.7	11352	34.6	15039	37.6	17361	24.8
Gender								
Male	10597	28.5	11276	34.4	11829	29.6	24580	35.1
Female	26638	71.5	21497	65.6	28176	70.4	45459	64.9
ASA score								
I	6263	17.7	6290	19.6	8635	22.9	17008	24.7
II	22424	63.5	19942	62.1	23912	63.5	44628	64.9
III- IV	6624	18.8	5873	18.3	5090	13.5	7178	10.4
Diagnosis								
Osteoarthritis	31696	85.9	28349	86.7	34978	88.3	61100	87.8
Non-osteoarthritis	5222	14.1	4358	13.3	4630	11.7	8526	12.2
Previous operation								
Yes	2337	6.5	1586	5.0	1814	4.8	3268	4.8
No	33253	92.4	29873	93.9	35783	94.5	63495	94.0
Unknown	387	1.1	371	1.2	261	0.7	750	1.1
Fixation								
Cemented	27357	74.1	5982	18.3	15253	38.7	8594	12.3
Cementless	5288	14.3	23449	71.7	18984	48.1	58054	83.0
Reversed hybrid	3247	8.8	728	2.2	3636	9.2	1226	1.8
Hybrid	986	2.7	2540	7.8	1525	3.9	2064	2.9
Unknown	61	0.2	27	0.1	64	0.2	44	0.1
Approach								
Straight lateral	8140	22.1	7112	21.8	11118	28.3	13193	18.9
Posterolateral	22932	62.3	20467	62.7	23672	60.2	41476	59.5
Anterolateral	2946	8.0	1917	5.9	3230	8.2	5972	8.6
Direct anterior	2597	7.1	2934	9.0	1159	2.9	8711	12.5
Other	169	0.5	238	0.7	153	0.4	328	0.5

TABLE 8. Continued.

	Metal on PE (n = 37,351; 17.8%)		**Metal on highly crosslinked PE** (n = 32,867; 15.7%)		**Ceramic on PE** (n = 40,109; 19.1%)		**Ceramic on highly crosslinked PE** (n = 70,175; 33.4%)	
	n	(%)	n	(%)	n	(%)	n	(%)
Head size								
22-28 mm	27423	73.4	7236	22.0	22165	55.3	14188	20.2
32 mm	9908	26.5	17248	52.5	17888	44.6	40496	57.7
36 mm	13	0.0	8124	24.7	56	0.1	15490	22.1
≥ 38 mm	7	0.0	259	0.8	0	0.0	1	0.0
Period								
2007-2010	16474	44.1	7135	21.7	16832	42.0	9612	13.7
2011-2013	11579	31.0	10448	31.8	13191	32.9	23531	33.5
2014-2016	9298	24.9	15284	46.5	10086	25.1	37032	52.8

TABLE 8. Continued

	Ceramic on ceramic (n = 17,625; 8.4%)		Oxidized zirconium on (highly crosslinked) PE (n = 11,785; 5.6%)		Total (n = 209,912)	
	n	(%)	n	(%)	n	(%)
Age						[a]
<60	4984	28.3	2458	20.9	34204	16.3
60-74	9547	54.3	6035	51.2	106782	50.9
≥75	3064	17.4	3285	27.9	68621	32.7
Gender						[a]
Male	6927	39.4	3966	33.7	69175	33.0
Female	10649	60.6	7806	66.3	140225	67.0
ASA score						[a]
I	5413	32.4	2598	22.5	46207	22.9
II	9653	57.8	7266	63.0	127825	63.2
III- IV	1639	9.8	1661	14.4	28065	13.9
Diagnosis						[a]
Osteoarthritis	15277	87.7	10391	88.6	181791	87.4
Non-osteoarthritis	2147	12.3	1343	11.4	26226	12.6
Previous operation						[a]
Yes	729	4.4	658	5.7	10392	5.2
No	15741	94.4	10830	94.2	188975	93.8
Unknown	212	1.3	13	0.1	1994	1.0
Fixation						[a]
Cemented	203	1.2	3744	32.1	61133	29.4
Cementless	15484	88.6	6441	55.3	127700	61.3
Reversed hybrid	13	0.1	453	3.9	9303	4.5
Hybrid	1767	10.1	1004	8.6	9886	4.7
Unknown	12	0.1	13	0.1	221	0.1
Approach						[a]
Straight lateral	2291	13.3	985	8.5	42839	20.7
Posterolateral	9243	53.6	9692	83.2	127482	61.5
Anterolateral	853	5.0	591	5.1	15509	7.5
Direct anterior	4721	27.4	198	1.7	20320	9.8
Other	122	0.7	177	1.5	1187	0.6
Head size						[a]
22-28 mm	1406	8.0	696	5.9	73114	34.8
32 mm	3279	18.6	7511	63.7	96330	45.9
36 mm	11756	66.7	3578	30.4	39017	18.6
≥ 38 mm	1184	6.7	0	0.0	1451	0.7
Period						[a]
2007-2010	4481	25.4	2885	24.5	57419	27.4
2011-2013	7801	44.3	3638	30.9	70188	33.4
2014-2016	5343	30.3	5262	44.6	82305	39.2

[a] $p < 0.0001$. PE: polyethylene. Numbers do not add up to total due to unknown or missing values.

TABLE 9A. Crude cumulative incidence of revision for different bearing types for THA for patients with femoral head size 22-28 mm (non case-mix corrected) (n = 73,114).

Revision for any reason	**Metal on PE** (n = 27,423)		**Metal on highly crosslinked PE** (n = 7,236)		**Ceramic on PE** (n = 22,165)		**Ceramic on highly crosslinked PE** (n = 14,188)		**Ceramic on ceramic** (n = 1,406)		**Oxidized zirconium on (highly crosslinked) PE** (n = 696)	
	%	CI	%	CI	%	CI	%	CI	%	CI	%	CI
5 year	2.9	2.7-3.1	3.9	3.4-4.5	2.8	2.6-3.1	3.1	2.8-3.5	3.0	2.2-4.1	2.2	1.3-3.8
9 year	4.1	3.8-4.5	5.2	4.4-6.2	3.7	3.3-4.0	4.4	3.5-5.7	4.0	2.8-5.6	3.3	2.0-5.6

TABLE 9B. Crude cumulative incidence of revision for different bearing types for THA for patients with femoral head size 32 mm (non case-mix corrected) (n = 96,330).

Revision for any reason	**Metal on PE** (n = 9,908)		**Metal on highly crosslinked PE** (n = 17,248)		**Ceramic on PE** (n = 17,888)		**Ceramic on highly crosslinked PE** (n = 40,496)		**Ceramic on ceramic** (n = 3,279)		**Oxidized zirconium on highly crosslinked PE** (n = 7,511)	
	%	CI	%	CI	%	CI	%	CI	%	CI	%	CI
5 year	2.1	1.8-2.5	2.8	2.5-3.1	3.3	3.0-3.6	2.6	2.4-2.8	3.1	2.5-3.8	2.3	1.9-2.7
9 year	2.7	2.1-3.6	3.2	2.8-3.7	4.6	4.1-5.3	3.7	3.2-4.1	5.1	3.6-7.1	3.2	2.7-4.0

TABLE 9C. Crude cumulative incidence of revision for different bearing types for THA for patients with femoral head size 36 mm (non case-mix corrected) (n = 39,017).

Revision for any reason	**Metal on PE** (n =13)		**Metal on highly crosslinked PE** (n = 8,124)		**Ceramic on PE** (n = 56)		**Ceramic on highly crosslinked PE** (n = 15,490)		**Ceramic on ceramic** (n = 11,756)		**Oxidized zirconium on highly crosslinked PE** (n = 3,578)	
	%	CI	%	CI	%	CI	%	CI	%	CI	%	CI
5 year	n.a	n.a	3.6	3.1-4.1	0.0	n.a.	3.4	3.0-3.7	2.7	2.4-3.0	3.1	2.5-4.0
9 year	n.a.	n.a.	4.6	3.9-5.3	2.9	0.4-19.7	4.0	3.5-4.6	3.8	2.8-5.2	4.0	3.0-5.3

SIMILAR SUPERIOR PATIENT REPORTED OUTCOME MEASURES (PROMS) FOR ANTERIOR AND POSTEROLATERAL APPROACH AFTER TOTAL HIP ARTHROPLASTY

POSTOPERATIVE PROM-IMPROVEMENT AFTER 3 MONTHS IN 12,774 PRIMARY THA'S USING THE ANTERIOR, ANTEROLATERAL, STRAIGHT LATERAL OR POSTEROLATERAL APPROACH

RINNE M. PETERS
LOES W.A.H. VAN BEERS
LIZA N. VAN STEENBERGEN
JULIUS WOLKENFELT
HARMEN B. ETTEMA
BAS L.E.F. TEN HAVE
PAUL C. RIJK
MARTIN STEVENS
SJOERD K. BULSTRA
RUDOLF W. POOLMAN
WIERD P. ZIJLSTRA

JOURNAL OF ARTHROPLASTY. 2018;33(6):1786-1793.

ABSTRACT

Background: Patient Reported Outcome Measures (PROMs) are used to evaluate the outcome of total hip arthroplasty (THA). We determined the effect of surgical approach on PROMs after primary THA.

Methods: all primary THAs, with registered pre-operative and 3 months postoperative PROMs were selected from the Dutch Arthroplasty Register (LROI). Based on surgical approach, 4 groups were discerned: (direct) anterior, anterolateral, direct lateral and posterolateral approach. The following PROMs were recorded: Hip disability and Osteoarthritis Outcome Score Physical function Short form (HOOS-PS), Oxford Hip Score (OHS), EQ-5D index score and EQ-5D thermometer, Numeric Rating Scale (NRS) measuring pain, both active and in rest. The difference between pre-operative and post-operative scores was calculated (delta-PROM) and used as primary outcome measure. Multivariable linear regression analysis was performed for comparisons. Cohen's d was calculated as measure of effect size.

Results: All examined 4 approaches resulted in a significant increase of PROMs after primary THA in the Netherlands (n = 12,274). The anterior and posterolateral approach were associated with significantly more improvement in HOOS-PS scores compared to the anterolateral and direct lateral approach. Furthermore, the posterolateral and anterior approach showed greater improvement on NRS pain scores, compared to the anterolateral approach. No relevant differences in delta-PROM were seen between the anterior and posterolateral surgical approach.

Conclusion: Anterior and posterolateral surgical approaches showed more improvement in self-reported physical functioning (HOOS-PS) compared to anterolateral and direct lateral approaches in patients receiving a primary THA. However, clinical differences were only small.

INTRODUCTION

Total Hip Arthroplasty (THA) is a successful treatment for end-stage osteoarthritis of the hip joint. Several surgical approaches are used to insert a THA. The decision for a surgical approach is predominantly determined by the surgeon's preference and local hospital standards (Amlie, 2014). In the Netherlands, there has been a shift in the surgical approach for primary THA over the last few years. The use of direct lateral and anterolateral approaches diminished, while the posterolateral and anterior approaches were employed more frequently (LROI report, 2015).

From recent research, it is known that surgical approach influences survival of THA, as well as reasons for revision. The posterolateral approach is associated with more revisions for dislocation due to inherent weakness of the posterior capsule, but has the least revisions for other reasons compared to anterior and anterolateral approaches, in a recent nationwide registry study in the Netherlands (Zijlstra, 2017). The direct lateral approach is associated with post-operative limping secondary to abductor weakness (Jameson 2014, Petis 2015). The anterolateral approach, theoretically facilitates early patient recovery and low dislocation rates (Watson-Jones, 1936). However, damage to the femoral shaft and malalignment of the femoral component have been reported (Bernasek, 2010). The direct anterior or anterior approach may provide potential benefits in early reported pain and function, post-operative length of stay, less dislocations and post-operative narcotic consumption (Petis, 2015, Higgins, 2015), perhaps because of diminished muscle trauma (Amlie 2014, Graves 2016). However, the anterior approach is a technically demanding procedure, associated with a steep learning curve (Den Hartog, 2016) and seems to be associated with increased femoral loosening at medium term (Zijlstra 2017, Janssen 2017).

Patient Reported Outcome Measures (PROMs) are increasingly being used to assess outcome after THA. Whether surgical approach influences outcome parameters such as PROMs, is subject to debate. Previous studies using data of national joint registries from England and Wales, and Sweden have demonstrated superior PROM scores for the anterior approach compared to direct lateral approach (Jameson 2014, Lindgren 2014). Amlie (2014) demonstrated inferior PROM scores for the direct lateral approach compared to the anterior and posterolateral approach using the Norwegian Arthroplasty Registry. To the best of our knowledge, literature is lacking a study comparing PROMs outcomes after primary THA, for the anterior, anterolateral, direct lateral and posterolateral approach, in a large national cohort. Furthermore, not all studies corrected for differences in femoral head size, fixation, and case-mix factors such as ASA, BMI, and Charnley score. We aim to determine the effect of surgical approach on PROMs after primary THA in the Netherlands.

MATERIALS AND METHODS

The Dutch Arthroplasty Register (LROI) prospectively collects data on primary and revision arthroplasty and covers all hospitals in the Netherlands. This nationwide registry was established in 2007 by the Dutch Orthopaedic Association. In 2015 the completeness of registered procedures was 98% for primary THAs (van Steenbergen, 2015). Patients characteristics such as age, gender, general health (ASA score), previous operation to the hip, body mass index (BMI), smoking status, Charnley score, hospital of surgery, and operation date have been recorded at the time of the index procedure. In addition, surgical variables such as procedure- and implant information are registered. Data from the LROI is matched with the national insurance database on healthcare in the Netherlands (Vektis, 2015), in order to obtain information on the vital status and date of death of registered patients (van Steenbergen, 2015).

Patient Reported Outcome Measures (PROMs)
Hip specific and general health related PROMs, are registered in the LROI since 2015. Patients were asked to complete the pre-operative PROM survey during the outpatient visit. Postoperative PROM-data were registered using a web-based tool after invitation by e-mail or by pen and paper. To measure health related quality of life (HRQoL), pain and functional outcomes, a set of PROMs as recommended by the Dutch Orthopedic Association (NOV) is used. This consist of the short version of the Hip disability and Osteoarthritis Outcome Score (HOOS-PS); a validated, hip-specific, 5-item measure of physical functioning derived from the items of activity during daily living (ADL), sports and recreational activities (Nilsdotter 2003, Davis 2008). The HOOS-PS is measured on a scale from 0-100. Lower scores indicate a higher level of physical function. The Oxford Hip Score (OHS) is recorded to measure HRQoL and disability (Dawson 1996, Murray 2007). Scores of this 12-item questionnaire range from 12-60, with higher scores indicating greater disability. The general health status was assessed using the EuroQoL five-Dimensions questionnaire (EQ-5D-31) and EQ-5D thermometer, a one-question for health status. The EQ-5D includes patients perception of health in 5 dimensions; mobility, self-care, usual activities, pain/discomfort and anxiety/ depression. The EQ-5D index scores range from 0.0 (poor health) to 1.0 (perfect health). The EQ-5D thermometer asks patients to value their current health status on a thermometer scale from 0 (worst imaginable) to 100 (best imaginable) (EuroQol group, 1990). Furthermore, a Numeric Rating Scale (NRS) is used to measure pain both during activity and rest. The NRS scoring system uses an 11-point Likert scale ranging from 0 (no pain) to 10 (severe pain). The PROMs are measured pre-operatively, 3 months and 1 year postoperatively. In order to measure changes, the difference between pre-operative and post-operative scores (3 months) were calculated and described as delta-PROM.

Patients

Since the PROM follow-up program has been introduced recently in the Netherlands, some clinics are just starting to implement the PROM-registration (Rolfson, 2011). Therefore, we have chosen to include data supplied by hospitals in which at least 25 patients completed the pre-and postoperative PROMs questionnaires (62 hospitals). All patients that received a primary THA for the indication osteoarthritis, with completed pre-operative and 3 months postoperative PROM-surveys, were selected from the LROI (n = 12,614). Patients can be registered twice, as having undergone a bilateral hip replacement (n = 1,822). Due to their known higher revision rates, the NOV advised against the use of large head metal-on-metal (MoM) THAs and resurfacing hip arthroplasties (Drummond 2015, Nederlandse Orthopaedische Vereniging 2015, Rieker 2017). Therefore, MoM THAs were not included in our dataset.

Surgical approach was classified as anterior, anterolateral, direct lateral and posterolateral. THAs with another approach, mainly trochanter osteotomy, were excluded (n = 340). Hereafter, 12,274 patients met the inclusion criteria. After selection of patients, demographic data were retrieved. Frequencies are described for the explanatory variables, e.g. age (<60, 60–74, and ≥75 years), gender (m/f), ASA classification (I–IV), smoking status (y/n), BMI (<18.5, 18.5-25, 25-30, 30-40, and >40), previous operation to the affected hip joint (y/n). The severity of the associated conditions was assessed using the Charnley classification (A, B1, B2, C) (Charnley, 1972). Furthermore, surgical variables were retrieved, namely type of fixation (cement, cementless, hybrid, and reversed hybrid), and femoral head size (22-28mm, 32mm, 36mm, ≥38mm).

Statistics

Descriptive statistics were provided for the subgroups based on surgical approach. Group comparisons for baseline characteristics were made using chi-square-test. Pre-operative and 3 months post-operative, as well as delta-PROM scores were presented as mean and standard deviation. Since baseline characteristics (case-mix variables) can be expected to influence delta-PROM, these factors were tested for confounding influences and included in the multivariable model. Testing for differences in delta-PROM scores between the surgical approaches was established using multivariable linear regression analyses. Outcome is presented as adjusted mean difference with associated 95%-confidence interval (CI). Post-hoc analysis to adjust for multiple comparisons was performed using Bonferroni. Cohen's d was used as a standard measure of effect size and was defined as the difference between two means divided by the standard deviation of the data (small effect: 0.2–0.5; medium: 0.5–0.8; large: 0.8–1.3; very large: >1.3) (Cohen 1988, Amlie 2014). All analyses were performed using SPSS 23.0.

Ethics

This study was approved by our local Medical Ethics Committee (no. METc2017/388).

RESULTS

In total, 12,274 THAs were included in the analyses. The most frequently performed surgical approach was the posterolateral approach (n = 7,286; 59.4%) (Table 1). The anterior, direct lateral and anterolateral approach were used in respectively 3,363 (27.4%), 1,052 (8.6%), and 573 (4.7%) of THAs. In the anterior approach subgroup a relatively large proportion of young patients, or patients with low ASA, Charnley, and BMI scores were encountered. Furthermore, a large proportion of cementless fixation (89,0%) was used in the anterior subgroup. In the subgroup operated thought an anterolateral approach, a relatively large proportion of patients aged 75 year or older (31.4%) or with high ASA scores (II-IV in 83.3%) were seen. In addition, small femoral head components (28.1%) and a ceramic-on-polyethylene (CoP) (74.7%) bearings surface were relatively frequently employed in this subgroup. In patients operated using a direct lateral approach a large proportion of 32mm femoral head (65.4%) components were encountered. The distribution of smoking status was similar between all subgroups. Mean pre- and postoperative PROM scores and subsequent differences (delta-PROM) for different approaches are shown in Fig. 1 – 6.

TABLE 1. Descriptives of independent variables (surgical approaches) for all included patients who received a primary THA in the period 2015-2016 in the Netherlands (n = 12,274).

	Anterior approach (n = 3,363; 27.4%)		**Anterolateral approach** (n = 573; 4.7%)		**Direct lateral approach** (n =1,052; 8.6%)		**Posterolateral approach** (n = 7,286; 59.4%)		**Total** (n = 12,274)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	%
Age										[a]
<60	557	16.6	90	15.7	145	13.8	1101	15.1	1893	15.4
60-74	1989	59.1	303	52.9	591	56.2	4116	56.5	6999	57.0
≥75	817	24.3	180	31.4	316	30.0	2066	28.4	3379	27.5
Sex										[a]
Male	1083	32.2	213	37.2	362	34.4	2712	37.3	4370	35.6
Female	2280	67.8	360	62.8	690	65.6	4566	62.7	7896	64.4
ASA score										[a]
I	835	24.8	96	16.8	209	19.9	1413	19.4	2553	20.8
II	2208	65.7	389	67.9	671	64.0	4675	64.2	7943	64.8
III - IV	320	9.5	88	15.4	169	16.1	1191	16.4	1768	14.4
Previous operation										[a]
Yes	31	0.9	6	1.0	29	2.8	150	2.1	216	1.8
No	3314	99.1	567	99.0	1019	97.2	7130	97.9	12030	98.2

TABLE 1. Continued.

	Anterior approach (n = 3,363; 27.4%)		Anterolateral approach (n = 573; 4.7%)		Direct lateral approach (n =1,052; 8.6%)		Posterolateral approach (n = 7,286; 59.4%)		Total (n = 12,274)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	%
Smoking										
Yes	327	9.8	78	13.7	107	10.3	701	10.0	1213	10.1
No	3016	90.2	492	86.3	932	89.7	6306	90.0	10746	89.9
Charnley score										
A	1575	46.8	250	43.6	504	48.3	3346	46.5	5675	46.6
B1	1065	31.7	199	34.7	326	31.2	2149	29.8	3739	30.7
B2	669	19.9	115	20.1	195	18.7	1542	21.4	2521	20.7
C	53	1.6	9	1.6	19	1.8	166	2.3	247	2.0
BMI										[a]
≤18.5	26	0.8	4	0.7	5	0.5	37	0.5	72	0.6
>18.5-25	1250	37.2	176	30.7	327	31.5	2203	30.3	3956	32.3
>25-30	1431	42.6	245	42.8	423	40.8	3189	43.9	5288	43.2
>30-40	638	19.0	141	24.6	268	25.8	1744	24.0	2791	22.8
>40	17	0.5	7	1.2	14	1.4	89	1.2	127	1.0
Fixation										[a]
Cementless	2993	89.0	368	64.2	590	56.1	4684	64.3	8635	70.4
Cemented	223	6.6	168	29.3	383	36.4	1914	26.3	2688	21.9
Reversed hybrid	97	2.9	14	2.4	44	4.2	303	4.2	458	3.7
Hybrid	43	1.3	21	3.7	34	3.2	372	5.1	470	3.8
Unknown	7	0.2	2	0.3	1	0.1	7	0.1	17	0.1
Articulation										[a]
Metal on PE	812	24.1	55	9.6	307	29.2	2281	31.3	3455	28.2
Ceramic on PE	1818	54.1	428	74.7	631	60.0	4089	56.2	6966	56.8
Ceramic on ceramic	642	19.1	48	8.4	60	5.7	298	4.1	1048	8.5
Oxidized zirconium PE	24	0.7	33	5.8	9	0.9	508	7.0	574	4.7
Other	67	2.0	9	1.6	45	4.3	106	1.5	227	1.9
Head size										[a]
22-28 mm	689	20.7	160	28.1	208	19.9	1277	17.6	2334	19.2
32 mm	1642	49.4	284	49.9	683	65.4	4260	58.8	6869	56.4
36 mm	995	29.9	125	22.0	146	14.0	1692	23.4	2958	24.3
≥ 38 mm	0	0.0	0	0.0	8	0.8	12	0.2	20	0.2

[a] $p < 0.0001$. Numbers do not add up to total due to unknown or missing values.

HOOS and OHS

The delta-PROM scores demonstrated higher postoperative improvement for the anterior and posterolateral approach (respectively 30.85 and 31.26) compared to the anterolateral and direct lateral approach (respectively 26.40 and 26.42) on the HOOS-PS (fig. 1). The anterior approach demonstrated the highest improvement (16.69) on the OHS, followed by the posterolateral (16.10), direct lateral (15.30) and anterolateral approach (15.27) (fig. 2).

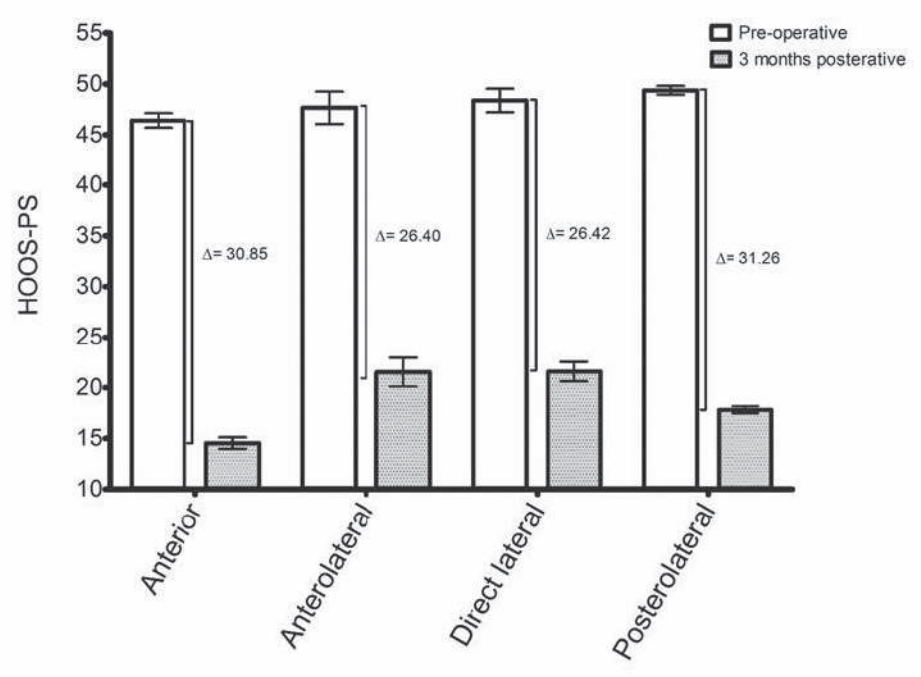

FIGURE 1. Crude (non-casemix corrected) pre-operative and postoperative HOOS-PS scores for different approaches.

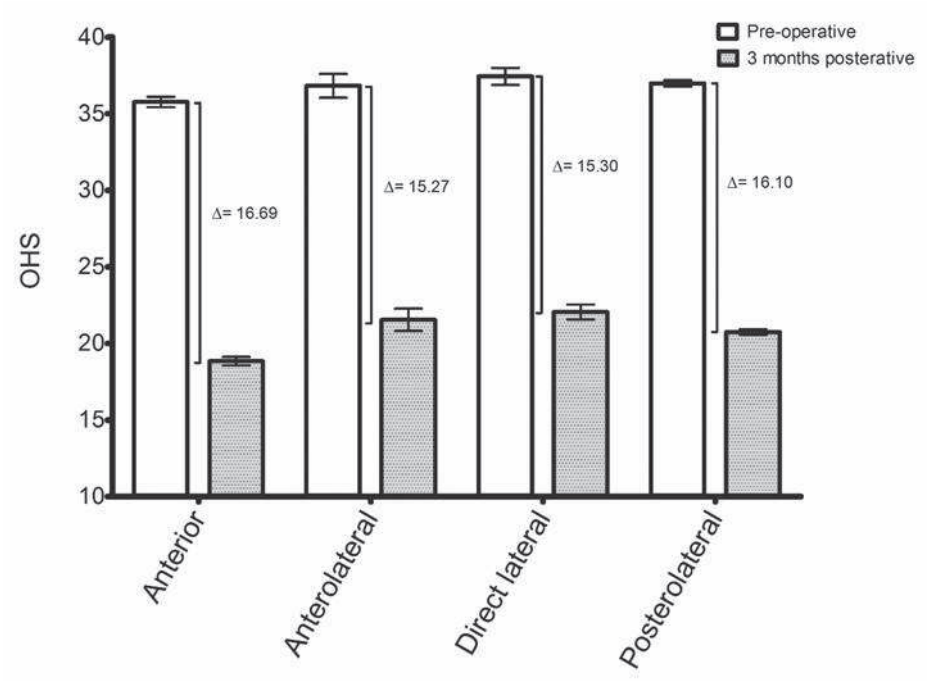

FIGURE 2. Crude (non-casemix corrected) pre-operative and postoperative OHS scores for different approaches.

Since delta-PROM can be influenced by case-mix and confounding variables, we performed a multivariable linear regression analyses, adjusted for gender, age, ASA classification, smoking status, Charnley score, BMI, fixation technique, articulation and femoral head size. The adjusted analyses demonstrated that the posterolateral and anterior approach were associated with significantly higher improvement in HOOS-PS after 3 months compared to the anterolateral approach and direct lateral approach (Table 2). The adjusted mean differences for the anterior approach compared to respectively anterolateral and direct lateral approach were: 4.35 (CI: 1.71–6.99) and 4.54 (CI: 2.46–6.62). The adjusted mean differences for the posterolateral approach compared to the latter two approaches on HOOS-PS scores were respectively 4.35 (CI: 1.83–6.87) and 4.53 (CI: 2.64–6.42). The effect size of all differences above, indicated a small effect (Cohen's d: 0.23-0.24) (Table 3). In addition, the adjusted mean difference in OHS was found to have a statistically significantly larger improvement for the anterior approach compared to the direct lateral and posterolateral approach. However, the effect size was smaller than 0.2 (Table 2 and 3).

TABLE 2. Patients Reported Outcome Measures: adjusted mean differences and CI in outcome for patients who underwent THA through anterior versus anterolateral, direct lateral and Posterior surgical approaches (n = 12,274).

HOOS-PS						
	Anterior approach (n = 3,363; 27.4%)		**Anterolateral approach** (n = 573; 4.7%)		**Direct lateral approach** (n = 1,052; 8.6%)	
	Adj mean diff (CI), p-value		Adj mean diff (CI), p-value		Adj mean diff (CI), p-value	
Anterolateral approach	4.35 (1.71 – 6.99)	0.000				
Direct lateral approach	4.54 (2.46 – 6.62)	0.000	0.18 (-2.82 – 3.19)	0.999		
Posterolateral approach (n = 7,286; 59.4%)	0.00 (-1.28 – 1.29)	0.999	-4.35 (-6.87 – -1.83)	0.000	-4.53 (-6.42 – -2.64)	0.000

Oxford Hip Score						
	Anterior approach (n = 3,363; 27.4%)		**Anterolateral approach** (n = 573; 4.7%)		**Direct lateral approach** (n = 1,052; 8.6%)	
	Adj mean diff (CI), p-value		Adj mean diff (CI), p-value		Adj mean diff (CI), p-value	
Anterolateral approach	1.14 (-0.16 – 2.44)	0.122				
Direct lateral approach	1.57 (0.53 – 2.60)	0.000	0.43 (-1.03 – 1.88)	0.999		
Posterolateral approach (n = 7,286; 59.4%)	0.73 (0.09 – 1.37)	0.017	-0.41 (-1.63 – 0.80)	0.999	-0.84 (-1.75 – 0.08)	0.093

EQ5D index score						
	Anterior approach (n = 3,363; 27.4%)		**Anterolateral approach** (n = 573; 4.7%)		**Direct lateral approach** (n = 1,052; 8.6%)	
	Adj mean diff (CI), p-value		Adj mean diff (CI), p-value		Adj mean diff (CI), p-value	
Anterolateral approach	0.00 (-0.03 – 0.04)	0.999				
Direct lateral approach	0.01 (-0.02 – 0.04)	0.999	0.01 (-0.03 – 0.05)	0.999		
Posterolateral approach (n = 7,286; 59.4%)	-0.01 (-0.02 – 0.01)	0.999	-0.01 (-0.04 - 0.03)	0.999	-0.01 (-0.04 – 0.01)	0.999

EQ5D thermometer						
	Anterior approach (n = 3,363; 27.4%)		**Anterolateral approach** (n = 573; 4.7%)		**Direct lateral approach** (n = 1,052; 8.6%)	
	Adj mean diff (CI), p-value		Adj mean diff (CI), p-value		Adj mean diff (CI), p-value	
Anterolateral approach	1.12 (-1.89– 4.12)	0.999				
Direct lateral approach	1.53 (-0.85 – 3.92)	0.540	0.42 (-3.01 – 3.84)	0.999		
Posterolateral approach (n = 7,286; 59.4%)	0.733 (-0.73 – 2.20)	0.999	-0.38 (-3.25 – 2.48)	0.999	-0.80 (-2.98 – 1.38)	0.999

NRS (active)						
	Anterior approach (n = 3,363; 27.4%)		**Anterolateral approach** (n = 573; 4.7%)		**Direct lateral approach** (n = 1,052; 8.6%)	
	Adj mean diff (CI), p-value		Adj mean diff (CI), p-value		Adj mean diff (CI), p-value	
Anterolateral approach	0.62 (0.27 – 0.97)	0.000				
Direct lateral approach	0.20 (-0.08 – 0.47)	0.361	-0.42 (-0.82 – -0.03)	0.030		
Posterolateral approach (n = 7,286; 59.4%)	0.04 (-0.14 – 0.21)	0.999	-0.58 (-0.92 – -0.25)	0.000	-0.16 (-0.41 - 0.09)	0.556

NRS (in rest)						
	Anterior approach (n = 3,363; 27.4%)		**Anterolateral approach** (n = 573; 4.7%)		**Direct lateral approach** (n = 1,052; 8.6%)	
	Adj mean diff (CI), p-value		Adj mean diff (CI), p-value		Adj mean diff (CI), p-value	
Anterolateral approach	0.36 (0.01 – 0.72)	0.043				
Direct lateral approach	-0.08 (-0.36 – 0.20)	1.000	-0.45 (-0.85 – -0.04)	0.022		
Posterolateral approach (n = 7,286; 59.4%)	-0.17 (-0.35 – -0.00)	0.046	-0.54 (-0.88 – -0.20)	0.000	-0.09 (-0.35 – 0.16)	0.999

Adj mean diff: Adjusted mean difference; CI: 95% confidence interval [A] Adjusted for covariates: age, gender, ASA-score, previous operations, fixation, articulation, femoral head size, BMI, Charnley score, smoking status. [B] Adjustment for multiple comparisons: Bonferroni

TABLE 3. Cohen's D standard measure of effect size.						
	Anterior vs Anterolateral	**Anterior vs Direct lateral**	**Anterior vs Posterolateral**	**Anterolateral vs direct lateral**	**Anterolateral vs Posterolateral**	**Direct lateral vs Posterolateral**
HOOS-PS						
Cohen's d	0.23	0.23	0.02	0.00	0.24	0.24
Oxford Hip Score						
Cohen's d	0.15	0.15	0.06	0.00	0.09	0.08
EQ5D index						
Cohen's d	0	0	0.04	0	0.04	0.04
EQ5D thermometer						
Cohen's d	0.06	0.09	0.05	0.03	0.01	0.04
NRS (active)						
Cohen's d	0.21	0.06	0	0.15	0.21	0.06
NRS (in rest)						
Cohen's d	0.12	0.05	0.08	0.17	0.20	0.04

Thresholds for measured differences: Cohen's d >0.2 (small); Cohen's d >0.5 (medium); Cohen's d >0.8 (large); Cohen's d >1.30 (very large) (Cohen, J. 1988).

EQ5D index, EQ5D thermometer and NRS pain

Postoperative improvement on the EQ-5D index score was similar for all approaches (0.26-0.27) (fig. 3). The EQ-5D thermometer demonstrated the highest improvement for patients operated by the anterior approach (fig. 4). Postoperative pain reduction during activities (NRS active) was best accomplished in patients operated using the posterolateral and anterior approach (5.18) (fig. 5). After adjusting for confounders the posterolateral approach was associated with greater improvement on NRS pain during activity (–0.58, CI: –0.92 to –0.25) and pain in rest (–0.54, CI: –0.88 to –0.20), compared to the anterolateral approach (Cohen's d = 0.21 and 0.20). Similarly, the anterior approach was associated with greater improvement on NRS pain during activity (0.62, CI: 0.27 to 0.97), compared to the anterolateral approach (Cohen's d = 0.21) (Table 2 and 3). Furthermore, the anterior approach was associated with a larger improvement in NRS pain, in rest, compared to the anterolateral approach (Fig. 6). The anterolateral approach was associated with significantly lower improvement in NRS pain during activity and pain in rest compared to the direct lateral approach. Finally, the posterolateral approach resulted in larger improvement in NRS pain in rest compared to the anterior approach. These differences measured an effect size lower than 0.2 (Table 3).

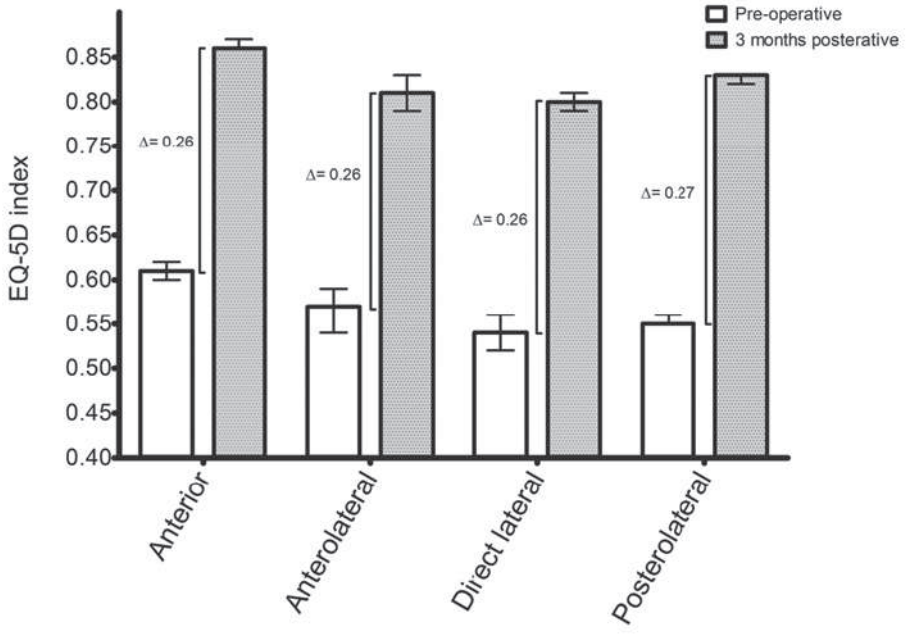

FIGURE 3. Crude (non-casemix corrected) pre-operative and postoperative EQ-5D index scores for different approaches.

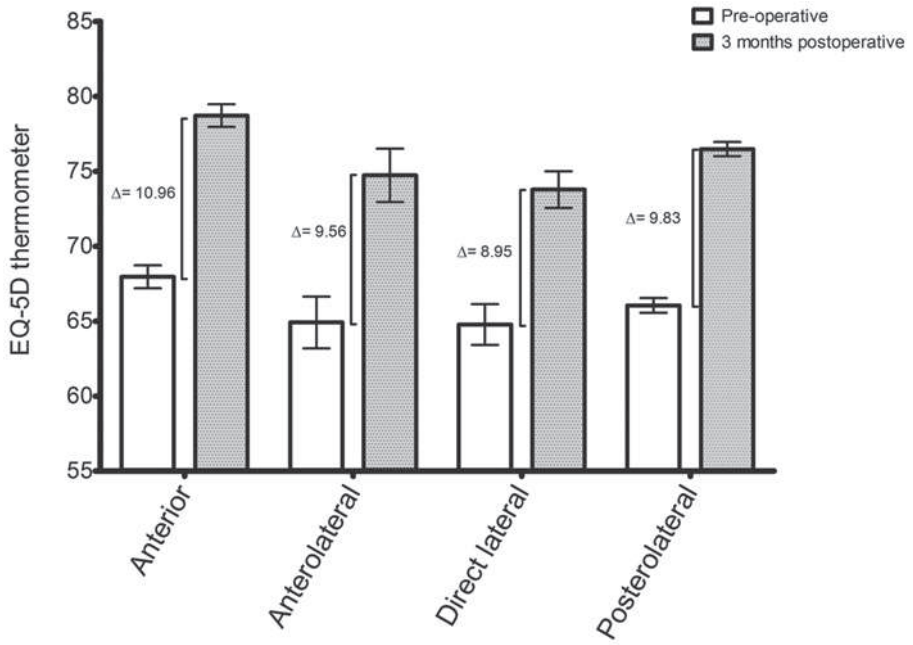

FIGURE 4. Crude (non-casemix corrected) pre-operative and postoperative EQ-5D thermometer scores for different approaches.

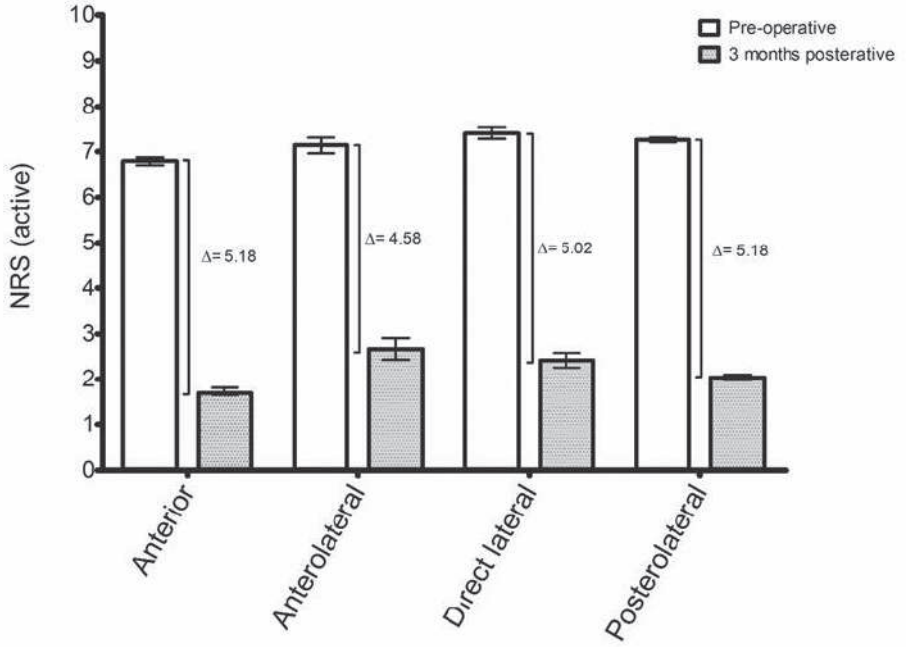

FIGURE 5. Crude (non-casemix corrected) pre-operative and postoperative NRS (active) scores for different approaches.

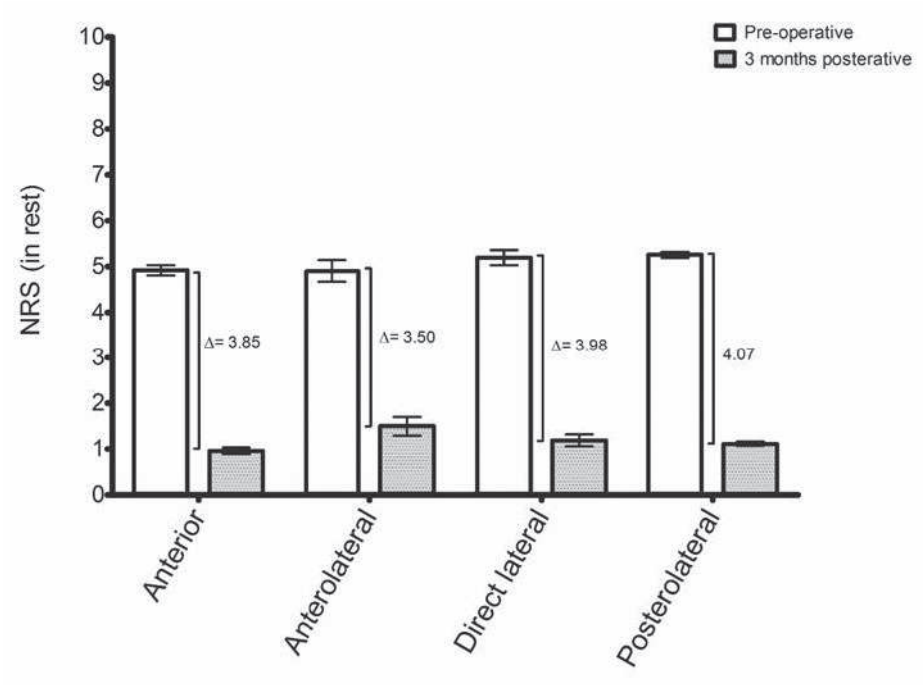

FIGURE 6. Crude (non-casemix corrected) pre-operative and postoperative NRS (in rest) scores for different approaches.

DISCUSSION

Development of implant designs, advanced bearing surfaces, enhanced surgical techniques (e.g. minimal invasive approaches, enhanced closure techniques), and peri-operative care improvements are continuously debated in order to optimize outcome of THA. Another subject that continues to stimulate debate is the surgical approach selected (Graves, 2016). In this prospective arthroplasty registry study, we found a larger improvement in self-reported physical functioning measured after primary THA using the anterior and posterolateral approach compared to the anterolateral and direct lateral approach. In addition, better pain relief after 3 months was observed in patients operated through a posterolateral (pain during activity and in rest) and anterior approach (only active) compared to the anterolateral approach. Furthermore, we found no relevant differences in PROM improvements between the anterior and posterolateral approach.

These findings are in accordance with previous studies. Using PROM-data from 1,476 patients, registered in the Norwegian Arthroplasty Register, Amlie (2014) found worse outcomes 1-3 years after primary THA performed with the direct lateral approach rather than the anterior and posterolateral approach. Patients operated

though the direct lateral approach reported more pain, less satisfaction, lower HRQoL, and twice the risk of limping, compared to the anterior and posterolateral approach. No statistical differences in postoperative PROMs were found, between patients who underwent THA via a posterolateral or an anterior approach (Amlie, 2014). Lindgren (2014) demonstrated that patients operated through a posterolateral approach perceived less residual pain and greater satisfaction after elective THAs compared to the direct lateral approach. This study was based on a prospectively collected cohort of 42,233 patients registered in the Swedish Hip Arthroplasty Register. Differences observed between the groups persisted after 6 years of follow-up. The authors state that although most patients, operated through the posterolateral and direct lateral approaches, perceived great improvement in pain, HRQoL, and hip function after THA, a clear effect of surgical approach was indicated.

Although a statistically significant benefit of the anterior and posterolateral approach in terms of perceived physical function 3 months postoperatively was found in our population, absolute differences were small and might therefore be of limited clinical relevance. A minimally clinical important difference (MCID) is defined as a change or difference in the outcome measure that would be perceived as important and beneficial by the clinician or the patient, assuming the absence of serious adverse effects and excessive costs. A MCID is therefore a threshold value for such change (Erdogan, 2016). Large ranges of MCID values, calculated for commonly used PROM-instruments such as OHS and EQ5D, for various diseases, were found. In patients with osteoarthritis the MCID of the OHS was calculated between 2 and 7 (Murray 2007, Jameson 2014, van der Wees 2017). The MCID for the HOOS-PS is determined at 23 (Paulsen, 2014). Given the limited clinical differences between the approaches in PROMs the decision to switch approaches should be balanced with possible complications and the learning curve of a new approach (den Hartog 2016, Zijlstra 2017).
In addition to the MCID, an effect size (Cohens' d) can be calculated. This method was adopted previously by the Norwegian Arthroplasty Register (Amlie, 2014). An effect size of 0.2, implicates a small effect, meaning that 58% of the target group will have an outcome above the mean of the comparison group (Cohen, 1998).

Furthermore, baseline analyses were performed and revealed that patients operated through an anterior approach reported lower pre-operative NRS, HOOS-PS and OHS, and higher quality of life (EQ-5D index) compared to the other approaches (data not shown). Differences in pre-operative PROM values, implicate an unequal potential for postoperative improvement. Therefore, differences based on postoperative outcome alone have to be interpreted with caution. Variance in baseline characteristics of the population (e.g. lower ASA, Charnley or BMI scores) may also influence pre-operative PROM scores and subsequently affect postoperative outcome. Our data demonstrate that patients who receive a THA

using the anterior approach are younger, slimmer and have lower Charnley scores. Postoperative outcomes score are largely dependent on the preoperative level of functioning. Preoperative group differences may form a confounding influence on the postoperative results. To account for differences in pre-operative PROM values between the different approaches, we used the delta-PROM as primary outcome variable. Delta-PROM is an objective parameter to measure improvements within the individual patient to account for population differences, instead of using post-operative values.

This study should be considered in light of its limitations. In the Netherlands, nationwide collection of PROMs after THA started in 2014. This implicates that at the end of our follow-up, preoperative and 3 months scores were available for a vast amount of patients, but 1-year scores were relatively scarce. Therefore we cannot state whether the differences found, will persist after 3 months follow-up. However, Lindgren (2014) found that differences found at 3 months postoperative were likely to persist over a 6-year period, indicating a long-term benefit. Another limitation is that early postoperative PROMs were not collected. Differences in PROMs during the first weeks after the procedure can therefore not be observed. Furthermore, the known limitations and risks for bias for cross-sectional observational studies are present for this study. Possible confounding variables might be omitted, which may have influenced our findings (Jameson, 2014). Causality cannot be distracted from our data. Finally, the prospective nature of the study entails that changes in treatment strategies might be implemented during the course of the data collection, for example multimodal pain control, liberal hip precautions, tranexamic acid and regional anesthesia. These adaptations might be adopted by surgeons utilizing different approaches at different points of time and might therefore confound the data. However, our data has been collected during a restricted period of time (2 years).

In conclusion, all examined approaches (anterior, anterolateral, direct lateral and posterolateral) resulted in a significant improvement of PROMs (delta-PROM) 3 months after primary THA in the Netherlands. No relevant differences in postoperative improvement in PROMs were seen between the anterior and posterolateral approach. Both the anterior and posterolateral approach showed more improvement in self-reported physical functioning (HOOS-PS) compared to anterolateral and direct lateral approach. Less pain in rest and during activities was perceived by patients operated thought a posterolateral approach compared to the anterolateral approach. However, clinical differences were only small.

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PART

THE PROSTHESIS | MIX AND MATCH

NATIONWIDE REVIEW OF MIXED AND NON-MIXED COMPONENTS FROM DIFFERENT MANUFACTURERS IN TOTAL HIP ARTHROPLASTY: A DUTCH ARTHROPLASTY REGISTER STUDY

RINNE M. PETERS
LIZA N. VAN STEENBERGEN
SJOERD K. BULSTRA
ADELGUNDE V.C.M. ZEEGERS
ROY E. STEWART
RUDOLF W. POOLMAN
ANTON H. HOSMAN

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A LETTER TO THE EDITOR REGARDING THIS STUDY IS ADDED AS AN APPENDIX TO THIS THESIS: RINNE M. PETERS, LIZA N. VAN STEENBERGEN, RUDOLF W. POOLMAN. CORRESPONDENCE: NATIONWIDE REVIEW OF MIXED AND NON-MIXED COMPONENTS FROM DIFFERENT MANUFACTURERS IN TOTAL HIP ARTHROPLASTY. ACTA ORTHOPAEDICA 2016; 87 (6): 651–652

ABSTRACT

Background: Combining components from different manufacturers in total hip arthroplasty (THA) is common practice worldwide. We determined the proportion of THAs used in the Netherlands that consist of components from different manufacturers, and compared the revision rates of these mixed THAs with those of non-mixed THAs.

Methods: Data on primary and revision hip arthroplasty are recorded in the LROI, the nationwide population-based arthroplasty register in the Netherlands. We selected all 163,360 primary THAs that were performed in the period 2007–2014. Based on the manufacturers of the components, 4 groups were discerned: non-mixed THAs with components from the same manufacturer (n = 142,964); mixed stem-head THAs with different manufacturers for the femoral stem and head (n = 3,663); mixed head-cup THAs with different head and cup manufacturers (n = 12,960), and mixed stem-head-cup THAs with different femoral stem, head, and cup manufacturers (n = 1,773). Mixed prostheses were defined as THAs (stem, head, and cup) composed of components made by different manufacturers.

Results: 11% of THAs had mixed components (n = 18,396). The 6-year revision rates were similar for mixed and non-mixed THAs: 3.4% (95% CI: 3.1–3.7) for mixed THAs and 3.5% (95% CI: 3.4–3.7) for non-mixed THAs. Revision of primary THAs due to loosening of the acetabulum was more common in mixed THAs (16% vs. 12%).

Conclusion: Over an 8-year period in the Netherlands, 11% of THAs had mixed components—with similar medium-term revision rates to those of non-mixed THAs.

INTRODUCTION

There is a discrepancy between what guidelines recommend and the practice of mixing implant components (stem, head, or cup) from different manufacturers in assembling a total hip replacement. National arthroplasty register data show that components from different manufacturers are often combined, contrary to the advice in the product guidelines for these components. Mixed prostheses are defined as total hip arthroplasties (THAs) (stem, head, and cup) composed of components made by different manufactures. Non-mixed prostheses are defined as prostheses made up from components produced by one and the same manufacturer. With very little published in the literature on the consequences of implanting mixed prostheses, there is a need for evaluation of large numbers of mixed and non-mixed prostheses. Such data can be obtained from national arthroplasty registers (Graves 2010).

Mixing and matching of THA component brands is common worldwide. Surgeons may use various combinations of cups, heads, and stems made by different manufacturers. Using the National Joint Registry of England and Wales (NJR), Tucker (2015) identified over 90,000 cases in which mixing of components was recorded between 2003 and 2013. However, the manufacturers emphasize that their implants were not designed, tested, or validated to be combined. In addition, there is a liability issue. Legally, the advice is not ever to implant a mixed arthroplasty unless you have familiarized yourself with the manufacturer's product compatibility information (Michel, 2009).

It has been hypothesized that mixing and matching of components from different manufacturers can lead to adverse effects (Ljung 1989, Barrack 1993, Morlock 2001, Andrew 2008, Higgs 2013, Kurtz 2013). However, recent research from the NJR of England and Wales revealed that combining a cemented stem with a polyethylene cup from a different manufacturer did not result in higher revision rates (Tucker 2015).

We determined the proportion of THAs used in the Netherlands that consist of mixed components and examined the revision rate for mixed THAs. We compared this with revision rates for non-mixed THAs. We hypothesized that mismatch between stem, head, and cup would result in higher revision rates for mixed THAs than for non-mixed THAs.

MATERIALS AND METHODS

Dutch Arthroplasty Register

The Dutch Arthroplasty Register (LROI) is a nationwide population-based registry that has information on joint arthroplasties in the Netherlands since 2007. The LROI was initiated by the Netherlands Orthopedic Association (NOV), and almost all Dutch orthopedic surgeons are members of this society. The LROI is well-supported by these members, resulting in an inter-institutional database with a completeness of more than 95% for primary THAs and 88% for hip revision arthroplasty (van Steenbergen 2015).

Data collection

The LROI contains information on patient characteristics such as age, sex, and general health (ASA score), hospital of surgery, type of surgery, date of surgery, fixation, and prosthesis characteristics. The acetabular cup, femoral stem, femoral head, and inlay component of the hip prostheses can be registered in the LROI. Stickers supplied by the manufacturer, containing information on the implanted component, are attached to the registration form. Prosthesis characteristics are derived from an implant library within the LROI, which contains several core characteristics of all the prostheses used in the Netherlands since 2007, including the name and type of the prosthesis, the manufacturer, the material, and the head size of the hip prosthesis. The characteristics are supplied by all the implant manufacturers or distributors in the Netherlands.

A primary THA is defined as the first implantation of a hip prosthesis, to replace a hip joint. Hip revision arthroplasty is defined as any exchange (placement, replacement, or removal) of one or more components of the hip prosthesis, including head exchange (van Steenbergen, 2015).

The vital status of all patients was obtained from Vektis (2015), the national insurance database on healthcare in the Netherlands. For the present study, we included all the patients who underwent a primary THA in a Dutch hospital, from the start of the registry in 2007 until 2014 (n = 171,255). Patients with unknown prosthesis components were excluded (n = 4,711; 2.8%), as were cases with missing components (n = 5,184; 3.0%). These excluded patients generally had similar patient and treatment characteristics, although a slightly higher proportion underwent THA for reasons other than osteoarthritis than in the study population. The median length of follow-up was 3.0 years, with a maximum of 8.0 years.

Implant information

The category of mixed THAs was based on the manufacturer of the femur, the femoral head, and the acetabular component. Prostheses consisting of components from the same manufacturer were defined as non-mixed THAs (manufacturer A

(femur) – manufacturer A (head) – manufacturer A (cup)). Mixed THAs were named after the manufacturer of the femoral component. Prostheses consisting of an acetabulum and a femoral head from the same manufacturer, but a femur from a different manufacturer were defined as mixed stem-head THAs (A-B-B). Similarly, mixed head-cup THAs were defined as a femur and a femoral head from the same manufacturer combined with an acetabulum from a different manufacturer (A-A-B). A fourth category, mixed stem-head-cup THAs, consisted of THAs with a different manufacturer for all components (femur, femoral head, and acetabulum) or THAs with the same manufacturer for femur and acetabulum, but a different manufacturer for the femoral head (A-B-C or A-B-A) (Fig. 1).

	Stem component	**Head component**	**Cup component**
Non-mixed THA	A	A	A
Mixed stem-head THA	A	B	B
Mixed head-cup THA	A	A	B
Mixed stem-head-cup THA	A	B	C
	A	B	A

FIGURE 1. Combinations of components used in assembling a non-mixed or mixed THA, where A, B, and C represent different manufacturers.

In addition to the retrieved prosthesis information, we collected demographic data on all patients who received a THA in the period 2007–2014 in the Netherlands (Table 1). There were 3 age categories: < 60, 60–74, and ≥75 years. Overall physical condition of the patient was scored using the ASA score (I–IV). Diagnosis was categorized as osteoarthritis or non-osteoarthritis (consisting of mainly acute fracture, osteonecrosis, dysplasia, and late posttraumatic conditions). Previous operation of the same hip mainly involved osteosynthesis and osteotomy. Fixation of the hip was categorized as cementless, hybrid (where the acetabular component is implanted uncemented and the femoral component is implanted cemented), cemented, reversed hybrid (where the acetabular component is implanted cemented and the femoral component is implanted uncemented), or unknown. Head size was categorized as 22–28 mm, 32 mm, 36 mm, or ≥38 mm. Hip arthroplasty articulation was differentiated based on the bearing surface of the head and the bearing surface of the inlay or monoblock cup, and categorized as ceramic-on-polyethylene (PE), metal-on-PE, metal-on-metal, ceramic-on-ceramic, or other. Period of surgery was divided into 2007–2009, 2010–2011, and 2012–2014. Reasons for revision were infection, periprosthetic fracture, symptomatic metal-on-metal bearing, dislocation, loosening of the femoral or acetabular component, wear of the liner/cup, periarticular ossification, or establishment of a Girdlestone situation.

TABLE 1. Demographic and clinical data of all patients who received a THA in 2007-2014 in the Netherlands (n = 161,360).

	Non-mixed THA (n = 142,964)		Mixed stem-head THA (n = 3,663)		Mixed head-cup THA (n = 12,960)		Mixed stem-head-cup THA (n = 1,773)		Total (n = 161,360)	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Age (years)										
<60	26,586	19	502	14	3,078	24	280	16	30,446	19*
60-74	75,156	53	1,743	48	6,436	50	875	50	84,210	52
≥75	40,891	29	1,412	39	3,421	26	611	35	46,335	29
Gender (%)										
Male	46,656	33	1,093	30	4,147	32	583	33	52,479	33*
Female	95,491	67	2,554	70	8,755	68	1180	67	107,980	67
ASA score (%)										
I	33,483	25	947	26	3,508	29	383	25	38,321	25*
II	85,068	63	1973	55	6,846	57	977	64	94,864	62
III-IV	16,745	12	686	19	1,772	15	161	11	19,364	13
Diagnosis (%)										
Osteoarthritis	124,464	87	3,191	87	10,568	82	1,545	87	139,768	87*
Non-osteoarthritis	18,500	13	472	13	2,392	19	228	13	21,592	13
Previous operation										
No	127,244	94	3,225	90	10,815	87	1,559	94	142,843	93*
Yes	6,599	4.9	277	8	1,087	8.8	88	5.3	8,051	5.3
Unknown	1,605	1.2	90	2.5	497	4.0	4	0.2	2,195	1.4

TABLE 1. Continued.

	Non-mixed THA (n = 142,964)		Mixed stem-head THA (n = 3,663)		Mixed head-cup THA (n = 12,960)		Mixed stem-head-cup THA (n = 1,773)		Total (n = 161,360)	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Fixation										
Cementless	92,150	65	747	20.5	4,135	33	1,464	91	98,496	62*
Hybrid	3,519	2.5	272	7.5	3,538	28	19	1.2	7,348	4.6
Cemented	41,878	30	2,515	69	2,390	19	75	4.7	46,858	29
Reversed hybrid	3,898	2.8	106	2.9	2,589	20	43	2.7	6,636	4.2
Unknown	125	0.1	2.0	2.0	37	0.3	0	0.0	164	0.1
Diameter head										
22-28 mm	53,543	38	2,806	77	7,523	58	509	29	64,381	40*
32 mm	59,911	42	293	8.0	4,011	31	1,193	67	65,408	41
36 mm	26,302	18	232	6.3	1,343	10	35	2.0	27,912	17
≥38 mm	3,207	2.2	323	8.8	83	0.6	36	2.0	3,649	2.3
Articulation										
Metal-on-metal	6,411	4.5	87	2.4	16	0.1	0	0.0	6,514	4.0*
Metal-on-PE	48,107	34	1,957	54	3,672	28	134	7.7	53,870	33
Ceramic-on-PE	66,704	47	1,245	34	7,417	57	1,551	89	76,917	48
Ceramic-on-ceramic	11,962	8.5	349	9.6	1,275	9.9	52	3.0	13,638	8.5
Other	7913	5.6	12	3.3	447	3.5	3	0.2	8,375	5.2
Period (%)										
2007-2009	35,241	24	939	26	4,256	33	923	52	41,359	26*
2010-2011	37,907	27	1,452	40	3,814	29	748	42	43,921	27
2012-2014	69,816	49	1,272	35	4,890	38	102	5.8	76,080	47

* p< 0.0001. NB. Numbers do not add up to total due to unknown or missing components.

Statistics

The 4 groups of non-mixed, mixed stem-head, mixed head-cup, and mixed stem-head-cup components were taken separately and compared using chi-square test to test differences in patient and prosthesis characteristics, including manufacturer. Survival time (with 95% confidence interval (CI)) was calculated as the time from primary THA to first revision arthroplasty for any reason (Nelissen, 1992), death of the patient, or January 1, 2015 (the end of follow-up). Standard survival analysis treats death simply as censored information, but this approach overestimates revision rates (Lacny 2015, Wongworawat 2015). Thus, crude cumulative incidence of revision was calculated using competing risk analysis, where death was considered to be a competing risk. Crude revision percentages within 1 year and 6 years were estimated according to the mixed-component group. Furthermore, revision rates within 6 years according to the reason for revision were estimated for non-mixed THAs and mixed THAs. The mixed-THA group contained all the mixed THAs, including mixed stem-head THAs, mixed head-cup THAs, and mixed stem-head-cup THAs. Differences in revision rates were compared using chi-square test. Crude and multivariable Cox proportional hazards regression analyses were performed. Adjustments were made for possible confounding variables, e.g. age at surgery, gender, ASA score, diagnosis (osteoarthritis vs. non-osteoarthritis), previous operation, fixation, head diameter, articulation, and period of surgery, to discriminate independent risk factors for revision. For all covariates added to the multivariate Cox proportional hazards regression analyses, the proportional hazards assumption was checked and met. Any p-values less than 0.05 were considered to be statistically significant. All analyses were performed using SPSS 22.0.

RESULTS

161,360 THAs were included in the analysis. 11% of those performed in the period 2007–2014 were composed of mixed components (n = 18,396). This included 2.3% with a mixed stem and head, 8.0% with a mixed head and cup, and 1.1% with a mixed stem, head, and cup (Table 1).

Mixed stem-head THA

Mixing of stem and head components from different manufacturers was found in 3,663 (2.3%) of the THAs. Almost 40% of the patients with a THA with a mixed stem and head were aged 75 years or older. A relatively large proportion of 22- to 28-mm diameter head components (77%), cemented THAs (69%), and metal-on-polyethylene articulations (54%) were used in THAs with a mixed stem and head (Table 1).

Mixed head-cup THA
The most frequent combination of mixed components used in THA was between the femoral head and the acetabular component (n = 12,960; 8.0%), with a relatively large proportion of patients aged under 60 years. The number of mixed head-cup THAs remained relatively constant over the periods 2007–2009, 2010–2011, and 2012–2014. Similar to the mixing of stem and head, a relatively large proportion of 22- to 28-mm diameter head components (58%) were used in head-acetabulum mixed THAs, while this group contained a relatively small number of cemented THAs (19%) (Table 1).

Mixed stem-head-cup THA
Mixing of femur, femoral head, and cup was found in 1,773 cases (1.1%). Most of these patients had a low ASA score (I or II in 89%) and no previous operations on the affected hip joint (94%). A relatively large proportion of 32-mm diameter head components (67%), ceramic-on-polyethylene articulations (89%), and cementless fixations (91%) were used in THAs with mixed femur, femoral head, and acetabulum. In the most recent time period (2012–2014), only 102 patients received a THA with a mixed stem, head, and cup (Table 1).

Manufacturers
The implanted THAs were manufactured by 21 different manufacturers. The femoral stem components were manufactured by 16 different manufacturers, femoral head components by 17, and the acetabular components by 19 companies. Manufacturers with more than 500 THAs (n = 8) are listed in Table 2. For these manufacturers, the percentages of non-mixed implants varied between 65% (Link) and 98% (Mathys Medical). A mixed stem and head component (n = 3,663) varied from 0% (Stryker) to 15% (Link) between different manufacturers. Mixed femoral head and acetabular components manufactured by Mathys Medical were rarely combined with acetabular components from other manufacturers (2%). Head-cup mixing was more common in THAs with femoral stem and head components from the manufacturers Link (20%) and Wright Medical (16%). Mixing of femoral stem, femoral head, and cup was detected in 1,773 THAs, ranging from 0% (Stryker and DePuy J&J) to 5% (Smith and Nephew) (Table 2). Many different combinations of manufacturers were seen in all the mixed-THA groups, with the most frequently used combinations of manufacturers being the same for mixed stem-head THAs and mixed head-cup THAs (Table 3).

TABLE 2. Manufacturers of total hip prosthesis represented in the groups with non-mixed or mixed components (n = 161,360).

Manufacturer	Non-mixed THA (n = 142,964)		Mixed stem-head THA (n = 3,663)		Mixed head-cup THA (n = 12,960)		Mixed stem-head-cup THA (n = 1,773)		Total [1] (n = 161,360)
	N	%	N	%	N	%	N	%	N
Zimmer	38,883	89	403	0.9	4,388	10	53	0.1	44,837
Stryker	22,572	94	10	0.0	1,456	6.1	6	0.0	24,121
Biomet	28,649	94	221	0.7	1,272	4.2	295	1.0	30,664
Smith & Nephew	19,225	88	147	0.7	1,200	5.5	1,171	5.4	21,874
DePuy J&J	13,672	96	33	0.2	528	3.7	3	0.0	14,329
Link	11,826	65	2,734	15	3,659	20	30	0.2	18,370
Mathys Medical	6,016	98	23	0.4	108	1.8	17	0.3	6,199
Wright Medical	831	79	53	5.0	167	16	2	0.2	1,053

[1] Total included prostheses with unknown or missing components.
NB. A prosthesis is categorized according to manufacturer of the most distal component of the mixed prosthesis. Manufacturers with <500 THAs were not shown.

TABLE 3. The 5 most frequently registered combinations of manufacturers of components of total hip arthroplasties according to mixed component group (n = 18,396).

	Mixed stem-head THA (n = 3,663)			Mixed head-cup THA (n = 12,960)			Mixed stem-head-cup THA (n = 1,773)			
	Stem	Head	N	Head	Cup	N	Stem	Head	Cup	N
1	a	b	2,623	a	b	2,377	f	d	f	945
2	c	d	207	c	d	2,147	b	a	b	92
3	b	e	117	c	e	867	f	h	g	63
4	f	e	66	g	b	753	g	a	i	32
5	c	b	63	c	f	631	c	f	c	23

The letters represent anonymized manufacturers of hip arthroplasty components.

Revision

The overall 1-year revision rates of non-mixed THAs and mixed THAs for all causes were similar (1.3% (CI: 1.3–1.4) for non-mixed THAs and 1.4% (CI: 1.2–1.5) for mixed THAs). The overall 6-year revision rate for all causes was not significantly different for non-mixed THAs and for mixed THAs (3.5% (CI: 3.4–3.7) for non-mixed THAs and 3.4% (CI: 3.1–3.7) for mixed THAs). No statistically significant differences were found between the mixed-component groups (Table 4).

TABLE 4. Cumulative incidence of revision in THAs performed in 2007-2014 in the Netherlands (n = 161,360).				
	Non-mixed THA (n = 142,964)		**Mixed THA[1] (n = 18,396)**	
	%	95% CI	%	95% CI
Revision for all reasons				
1 year	1.3	1.3 - 1.4	1.4	1.2-1.5
6 year	3.5	3.4 – 3.7	3.4	3.1-3.7

[1] This group includes the mixed stem-head THAs, mixed head-cup THAs and the mixed stem-head-cup THAs.

Cumulative incidence of revision in the mixed-component groups showed no statistically significant difference in revision rate, although the revision rate was somewhat lower in the first years in the group with mixed stem-head components (Fig. 2).

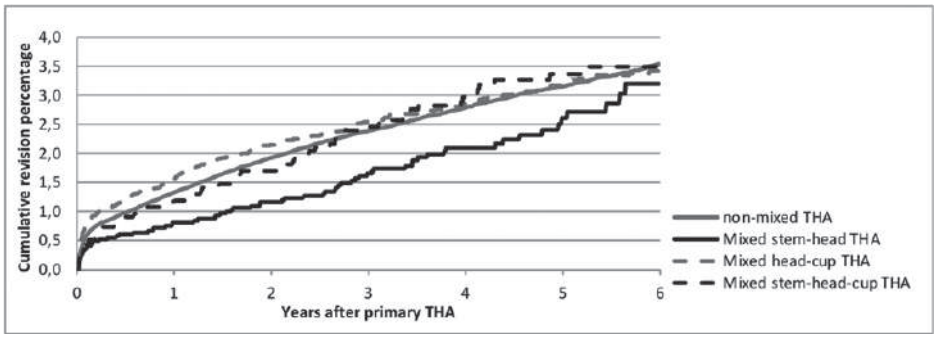

FIGURE 2. Cumulative incidence of revision according to mixing type of THA in the Netherlands in the period 2007-2014 (n = 161,360).

Revision of a primary THA due to loosening of the acetabulum was more common in mixed THAs (16% for mixed THAs and 12% for non-mixed THAs). Revision due to a symptomatic metal-on-metal bearing was less common in mixed THAs, although this was mainly due to the fact that the proportion of metal-on-metal THAs was much higher in the non-mixed-component group (1.7% vs. 6.6%) (Table 5).

TABLE 5. Reasons for revision or reoperation in revised THAs performed in 2007-2014 in the Netherlands (n = 3,879).

	Non-mixed THA (n = 3,403)		Mixed THA[1] (n = 476)		Total (n = 3,879)	
	N	**%**	**N**	**%**	**N**	**%**
Revision within 6 years for:						
Infection	379	11	57	12	436	11
Periprosthetic fracture	450	13	62	13	512	13
Symptomatic MoM bearing	223	6.6	8	1.7**	231	6.0
Dislocation	969	29	152	32	1,121	29
Loosening femur	712	21	84	18	796	21
Loosening acetabulum	421	12	77	16*	498	13
Cup/liner wear	119	3.5	16	3.4	135	3.5
Peri-articular ossification	71	2.1	14	2.9	85	2.2
Girdlestone	141	4.1	19	4.0	160	4.1
Other	549	16	78	16	627	16

[1] This group includes the mixed stem-head THAs, mixed head-cup THAs and the mixed stem-head-cup THAs. *p<0.05. ** p<0.0001

The crude survival analysis showed that patients with a mixed stem-head THA had a lower risk of revision than those with non-mixed THAs (hazard ratio (HR) = 0.78, 95% CI: 0.62–0.98) (Table 6). However, after adjustment for confounders there was no statistically significant difference in revision rate between the different mixed-component groups and non-mixed THAs. Younger patients (< 60 years), those with previous operation of the affected hip, patients with an ASA score of II–IV, those with a diagnosis other than osteoarthritis—and also those with a reversed hybrid THA, a small femoral head component (22–28 mm), a large femoral head component (≥ 38 mm), a metal-on-metal or metal-on-polyethylene articulation, or a THA implanted in the period 2012–2014 were more frequently revised. THAs with cemented fixation and ceramic-on-ceramic articulation resulted in a lower frequency of revision (Table 6).

TABLE 6. Multivariate survival analyses of patients with a THA in the period 2007-2014 in the Netherlands (n = 161,360).

	Crude hazard ratio for revision (95% CI)	Adjusted hazard ratio[1] (95% CI)
Mixing category		
Non-mixed THA	1.0	1.0
Mixed stem-head THA	0.78 (0.62-0.98)*	0.80 (0.63-1.03)
Mixed head-cup THA	1.03 (0.92-1.15)	1.11 (0.97-1.27)
Mixed stem-head-cup THA	1.01 (0.77-1.31)	1.02 (0.77-1.37)

TABLE 6. Continued.

	Crude hazard ratio for revision (95% CI)	Adjusted hazard ratio[1] (95% CI)
Age at surgery (years)		
<60	1.42 (1.32-1.54)*	1.20 (1.11-1.31)*
60-74	1.0	1.0
≥75	0.84 (0.78-0.91)*	0.93 (0.85-1.01)
Gender		
Male	1.20 (1.13-1.28)*	1.08 (1.01-1.16)*
Female	1.0	1.0
ASA score		
I	1.0	1.0
II	0.99 (0.92-1.06)	1.18 (1.09-1.27)*
III-IV	1.18 (1.06-1.31)*	1.46 (1.31-1.64)*
Diagnosis		
Osteoarthritis	1.0	1.0
Non-osteoarthritis	1.31 (1.20-1.42)*	1.18 (1.07-1.29)*
Previous operation		
No	1.0	1.0
Yes	1.36 (1.20-1.54)*	1.19 (1.08-1.32)*
Fixation		
Cementless	1.0	1.0
Hybrid	0.72 (0.61-0.85)*	0.78 (0.65-0.94)
Cemented	0.58 (0.53-0.63)*	0.63 (0.57-0.69)*
Reversed hybrid	1.19 (1.03-1.37)*	1.17 (0.99-1.37)
Unknown	1.21 (0.58-2.54)	1.18 (0.44-3.14)
Diameter head		
22-28 mm	1.07 (0.99-1.15)	1.12 (1.03-1.21)*
32 mm	1.0	1.0
36 mm	1.15 (1.04-1.27)	1.11 (0.99-1.23)
≥38 mm	4.23 (3.78-4.73)*	2.86 (2.44-3.35)*
Articulation		
Metal-on-metal	2.92 (2.65-3.22)*	1.71 (1.49-1.97)*
Metal-on-PE	1.01 (0.94-1.09)	1.16 (1.07-1.26)*
Ceramic-on-PE	1.0	1.0
Ceramic-on-ceramic	1.04 (0.92-1.18)	0.88 (0.77-1.01)
Other	0.82 (0.69-0.97)*	0.93 (0.78-1.11)
Period		
2007-2009	1.14 (1.05-1.23)*	1.06 (0.97-1.15)
2010-2011	1.0	1.0
2012-2014	1.16 (1.06-1.26)*	1.28 (1.17-1.40)*

[1] Adjusted for age at surgery, gender, ASA score, diagnosis, previous operation, fixation, diameter head, articulation and period. * p-value <0.0001

DISCUSSION

There is an ongoing debate about the use of components from different manufacturers in assembling a total hip arthroplasty. Based on a nationwide register, we found similar short-term survival of mixed and non-mixed THAs. These findings are supported by recent research from the NJR of England and Wales, in which even lower revision rates were found in patients with mixed cemented stems with polyethylene cups from another manufacturer (Tucker, 2015).
It has been hypothesized that mixing and matching of components from different manufacturers can lead to adverse effects due to unforeseen size mismatching of heads and tapers, and between heads and cups (Ljung 1989, Barrack 1993, Morlock 2001, Andrew 2008). Moreover, mixing and matching of components from different manufacturers may result in an alloy mismatch (Morlock, 2001). Recent awareness of taper corrosion has revealed that dissimilar alloy pairing is associated with increased taper damage at the modular interfaces (Higgs, 2013). Although ceramic femoral heads on metal tapers appear to reduce taper fretting corrosion compared to metal heads (Kurtz, 2013), there is very little literature on the long-term results. However, the recent research from the NJR of England and Wales revealed that mixing of a cemented stem with a polyethylene cup from a different manufacturer did not result in higher revision rates (Tucker, 2015).

Our registry study should be considered in the light of having certain limitations. First of all, the validity of the LROI has not been 100% since its introduction, but has been improving over the years. The validity of the registry increased from 88% completeness for THAs in 2009 to 98% in 2012 (van Steenbergen, 2015). Secondly, patient-reported outcome measures (PROMs) will be reported in the very near future, and the LROI does not yet report on surgeon experience. Retrieval analysis is the only method of confirming size mismatch, and may therefore be underrepresented in national joint registries that record the diagnosis for revision at the time of revision. Finally, our study had a limited follow-up time of 8 years. We acknowledge that possible complications of mixing components of different manufacturers, e.g. osteolysis, may have resulted in adverse events that would not be detected within the 8-year follow-up period.
Revision of primary THAs due to loosening of the acetabulum appeared to be more common in mixed THAs. Theoretically, loosening of components in the mixed-component group may be explained by increased trunnion wear due to a taper mismatch.

Manufacturers generally issue warnings and precautions regarding their products, cautioning against mixing of components from different manufacturers. However, surgeons prefer combinations that have the highest Orthopaedic Data Evaluation Panel (ODEP) rating, but will ask for combinations to fulfill certain criteria that may

not be within the reach of many manufacturers. For example, a cemented stem suitable for an anterior approach combined with an uncemented cup with a bearing type that is only possible by combining one manufacturer's highly ODEP-rated cup with a stem from a competitor. However, the question remains as to whether this is allowable by law. Orthopedic surgeons should comply with all the regulations that are set by manufacturers—such as instructions for product surveillance, vigilance, and maintenance to avoid restrictions based on civil law (Michel, 2009). Legally, a THA that has been tested for its configuration and has been approved by a declaration of conformity is modified when components from different manufacturers are mixed. With the replacement or substitution of an incompatible component, the declaration of conformity of the original manufacturer expires (Michel, 2009). The implications of these laws are not foreseeable yet, but surgeons should be cautioned to check whether mixing of the products is not restricted in the precaution sheets of the prostheses they use. With the recent merger of Biomet and Zimmer, and the manufacture of ceramic heads for several different companies by CeramTec, extra care should be applied to interpretation of the precaution sheets for newly released prosthesis combinations.

Mixed THAs are also described as off-label arthroplasties. "Offlabel use" refers to use of medical devices for purposes or subpopulations other than those approved by the United States Food and Drug Administration (Malcolm, 2015). Malcolm (2015) demonstrated that the prevalence of offlabel THAs and TKAs was 30% and 37%, respectively, in the USA. They predicted an increase in the prevalence of off-label arthroplasties in the future. Tucker (2015) described over 90,000 cases recorded between 2003 and 2013. In half of these cases, stems and heads from one manufacturer were mixed with a polyethylene cemented cup from another manufacturer. These numbers emphasize the differences between countries regarding the frequency of mixing of different components, as only 1% of the Dutch implants are used with this mixed combination.

The use of different taper sizes by the different manufacturers has made it difficult for surgeons to combine the right combination of stem and head junction, especially in revision hip arthroplasty. Manufacturers often have extensive overviews of which stems (male taper) can be combined with which heads (female taper), as these may differ in shape, roughness, inclination, and angle (Werner, 2015). Another issue is that manufacturers have changed tapers over the years in the same stem, e.g. Omnifit stems produced before the year 1991 had a Morse taper, but nowadays they have a C-taper (D'Lima, 1999). With very few literature overviews on taper dimensions of components, more research efforts towards unraveling the clinical significance of the potential mismatches are required.

In conclusion, 11% of THAs in the Netherlands were composed of mixed components, with similar medium-term revision rates to those of non-mixed THAs. Further studies on the use of mixed components in THA are needed, and they should be performed with a similar nationwide or international cohort with long-term follow-up.

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TO MIX OR NOT TO MIX? MEDICOLEGAL IMPLICATIONS OF MIXED COMPONENTS IN TOTAL HIP ARTHROPLASTY

RINNE M. PETERS
JANTINA T. HIEMSTRA
WIERD P. ZIJLSTRA
SJOERD K. BULSTRA
MARTIN STEVENS

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About 300 different hip prostheses promoted by a multitude of distributors are available on the European market. Most total hip arthroplasties (THAs) are assembled from components produced by the same manufacturer (non-mixed THAs), yet certain situations require a combination of components from different manufacturers within a single hip prosthesis (mixed THAs). Despite it being against manufacturers' guidelines (Smith & Nephew 2013, Link 2018), orthopedic surgeons who do this are encouraged by clinical results that are comparable to and sometimes even superior to those obtained without mixed components (Tucker 2015, Peters 2016, Taylor 2018). This mixing and matching is common clinical practice. The question does remain as to whether it is allowable by law. In this annotation paper we assess the legality of mixed THAs based on European law.

Mix and match: clinical perspective

Mixed prostheses are defined as THAs (stem, head, and cup) comprising components made by different manufactures. With a reported prevalence of 11%, 24%, and 15% in the Netherlands, New Zealand, and England and Wales, respectively, mixing and matching is common clinical practice (Tucker 2015, Peters 2016, Taylor 2018). Based on these national joint registry studies, it was demonstrated that mixed THAs yield at least comparable and for certain combinations even better outcomes than THAs with components from the same manufacturer (Tucker 2015, Peters 2016, Taylor 2018).

The concept of mixed THA refers to both fixed (trunnion/taper) and mobile (head/cup) combinations as well as hard-on-soft and hard-on-hard bearings. A distinction should additionally be made between primary and revision procedures. An argument for the use of mixed components in primary THA could be the need for a dual mobility cup in case of high risk of instability. Other arguments could be altered anatomy (e.g., developmental dysplasia of the hip), patient characteristics (e.g., frail elderly patients requiring cemented stems), and high-risk patients (e.g., prior lumbar spine fusion with irradiated pelvis). In revision arthroplasty, combining components from different manufacturers could be considered in order to prevent additional patient morbidity (e.g., leaving a well-fixed stem from another company in situ during a cup revision) (Mueller, 2018), or to optimize component placement performed by surgeons with extensive clinical experience. This is all in the best interest of the patient.

Hard-on-soft mixing and matching across the femoral head and acetabular component (mobile bearings) have demonstrated excellent results for several combinations. For example, data from the National Joint Registry of England and Wales (NJR) showed that cemented stems with mixed polyethylene cups were associated with a lower risk for revision compared with their manufacturer-matched equivalents (Tucker, 2015).

For fixed combinations, different taper sizes used by the various manufacturers have made it difficult for surgeons to combine the stem and head junction properly,

as the stems and head can vary in shape, metallurgy, roughness, inclination, and angle (Werner, 2015). Mixed components over the trunnion–taper junction in THAs with large head and hard-on-hard bearings may result in wear of the femoral head–neck interface (trunnionosis), which has been reported as an increasingly prevalent cause of failure (Mistry, 2016). In THAs with ceramic heads, a mismatch can result in a fractured femoral head component.

Legal implications

The use of mixed components gives rise to legal implications from public and private law. One aspect of public law is that orthopedic implants have to be approved and marked Conformité Européene by an appropriate body before being allowed on the European market. This approval is given if the product meets the requirements of the Medical Devices Directive or its successor, the Medical Device Regulation, e.g., that the implant does not entail a safety risk (Directive 93/42/EEC 1993, Regulation (EU) 2017/745 2017). If a product is altered or a new product is designed by using several components that are not tested together, this approval might no longer be valid.

Implications may derive from private law too. The unauthorized mixing of components can give rise to a risk of liability toward patients, as liability could be imposed for (1) producing a defective product or (2) medical negligence.

Product liability

Orthopedic surgeons who combine components from different manufacturers that are not designed, tested, or meant to be combined in compliance with the producers of the components bear a liability risk toward the patient. This risk derives from the European Product Liability Directive (85/374/EEC), which states that the producer of a product is liable for damages suffered by a patient if this product appears to be defective. This Directive is transposed into national law of all member states of the European Union and the European Free Trade Association. A healthcare provider who mixes components, such as a femoral head and stem from manufacturer A with a cup from manufacturer B, into a THA could qualify as a "manufacturer of a finished product" to whom the liability regime of the Directive applies (Gabrielczyk, 2017).

Defective product

In order for a producer (manufacturer or orthopedic surgeon) to be liable, the product has to be defective. This means that the product does not provide the safety that an individual is entitled to expect (article 6 of the Directive). Relevant in this respect is a recent English ruling that metal-on-metal (MoM) prostheses were not defective in terms of the entitled expectation of safety of such prostheses in 2002 (Colin Gee and others v. Depuy International Limited 2018). To determine whether a product provides the safety a person is entitled to expect, relevant circumstances are: the presentation of the product, the use to which the product could reasonably

be expected to be put, and the time when the product was put into circulation. With regard to the latter: the defectiveness will be determined based on the state of knowledge and safety standards at the time it was put into circulation. The fact that a better product was subsequently put into circulation will not lead to the conclusion that the product in question must be considered defective. For orthopedic surgeons, this means that the state of knowledge at the time of insertion of the prothesis is important. In this respect it is relevant, for instance, that it was demonstrated in 2015 that the use of heads and stems from different manufacturers in mixed THAs leads to increased revision rates (Tucker, 2015).

Under certain circumstances, the producer can avoid the liability described above. Article 7 from the Directive sums up several defenses. For example, the producer will not be liable if it was impossible to know the risk that led to the defect because of a lack of knowledge. This refers to the objective scientific and technical knowledge available and accessible at that time, "including the most advanced level of such knowledge" (Commission of the European Communities v. United Kingdom of Great Britain and Northern Ireland 1997). As regards THAs the defense will most likely be unsuccessful if, at the time the THA was used by the surgeon, there was published scientific research available pointing out the risks of mixing components and materials.

Medical negligence

Mixing of components could also result in liability of the healthcare provider if it qualifies as negligence. Liability for medical negligence is not regulated at the EU level, so regimes will vary per country. Generally, liability will require negligent behavior from the healthcare provider, meaning that he or she must have breached a standard of care (Cass 1936, HR 1990, BGH 1994, Bolam v. Friern HMC 2015). As opposed to the previous regime of strict liability of the producer, medical negligence generally requires that the healthcare provider commits a fault. Mixing of components might be considered negligent when it is unauthorized and discouraged by the manufacturer, untested by the orthopedic surgeon and unapproved according to public law—all the more in a primary situation, when reasonable alternatives are available and when medical publications have shown clinical risks. Whether or not the healthcare provider has acted negligently will be influenced by the communication of these risks to the patient and the receipt of the patient's consent. And yet this might not be decisive due to the differences in knowledge and expertise between healthcare providers and patients. So, when mixing is a reasonable option, it is important to inform the patient about the use of mixed components, the benefits and potential risks, and reasonable alternatives, in order to gain the patient's consent.

A search of case law in the United Kingdom (UK), Germany, and the Netherlands revealed that until now no orthopedic surgeon has ever been held responsible as

the manufacturer of a finished product of mixed components. In the past one trial in the UK has been started but this has not resulted in a ruling in which the orthopedic surgeon was held responsible as the manufacturer of a finished product of mixed components.

Conclusion

Mixing and matching in total hip arthroplasty is common practice worldwide. It is generally done in the interest of the patient, aiming to optimize the outcome of the treatment. We assessed the rules for mixed THAs based on European law, to create awareness of the legality. Despite evident medical benefits and similar or even superior revision rates compared with non-mixed THAs (Tucker 2015, Peters 2016, Taylor 2018), from a legal perspective it is advisable to avoid mixing when reasonable alternatives are available, especially in primary arthroplasty. The unauthorized mixing of components can create a liability risk based on European and national law. An orthopedic surgeon who mixes components from different manufactures could qualify as a "manufacturer of a finished product" and may be held liable without fault if the product appears to be defective. However, to date, no orthopedic surgeon has been held legally responsible or ended up in a lawsuit for the use of mixed components, based on case law review in the United Kingdom, Germany, and the Netherlands. Although no search was done of case laws in other European countries we presume that the situation in these countries can be considered representative of the situation in Europe as a whole.

If a situation does require the use of mixed components, surgeons are best advised to (1) avoid mixing across the fixed articulation (i.e., use a head from the same manufacturer as the stem), (2) appropriately match sizes across the mobile articulation in hard-on-soft THAs (Tucker 2015, Taylor 2018), and (3) avoid mixing in hard-on-hard bearings. Surgeons are likewise advised to gain knowledge on the results of specific component combinations (e.g., based on arthroplasty registry results) and to explain the choices to the patient in order to receive his/her consent.

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GENERAL DISCUSSION

In this thesis a number of current issues affecting outcome for patients undergoing total hip arthroplasty (THA) is discussed. The general aim was to assess factors associated with survival and patient-reported outcome measures (PROMs) after primary THA in the Netherlands based on national arthroplasty registry data. This thesis is divided into three parts, according to three major determinants of treatment success: the patient, the orthopaedic surgeon and the prosthesis. In this chapter, we will first discuss our main findings based on these determinants as well as the value of arthroplasty registry data and the use of PROMs in arthroplasty registry studies. Lastly, we will reflect on the clinical implications of our findings, and suggest some potential directions for future research.

THA is consistently identified as one of the most successful procedures in orthopaedics, with excellent long-term results in terms of implant survival and improved quality of life (Habermann 1986, Learmonth 2007). National arthroplasty registers have importantly contributed to the development and quality improvement of care for patients undergoing hip replacement surgery. Arthroplasty registers by themselves have also been subject to change and development over time. Initially, national joint registers were primarily used as a safety instrument with a post-market surveillance function ensuring long-term device follow-up (Robertsson, 2014). At the time of conception, registers began with a minimal dataset, ensuring a high degree of completeness (Robertsson 2014, De Steiger 2019). Registration was performed with paper-based forms, which were completed at the operation theatre and subsequently entered into a central database (van Steenbergen 2015, De Steiger 2019). Limited patient and procedure information (age, operation date, diagnosis, type of prosthesis, method of fixation) was collected. These data could be used to provide nationwide information on the use of different types of prostheses in both primary and revision arthroplasty and to evaluate the effectiveness of different implant types and fixation methods (de Steiger, 2019). As data collection expanded, the function and aim of arthroplasty registers gradually changed over time. The majority of arthroplasty registries currently include more advanced patients details (ASA score, BMI, smoking status, surgical history of the affected joint, Charnley score) and procedure-related information (surgical approach, bearing type, femoral head size) (van Steenbergen, 2015). Hereby, the function of these registers evolved from merely device registration, follow-up and safety monitoring to quality registers with an important scientific function – linking outcome of arthroplasty to not only the prosthesis but also to patient (case-mix) and surgically related factors. In addition, since registers have been expanded by the registration of PROMs, outcomes of joint arthroplasty can be evaluated in terms of functional results and health-related quality of life (Rolfson, 2016).

This thesis contains a number of studies that demonstrate the various possibilities of the Dutch Arthroplasty Register (LROI). We posit that the outcome following

primary THA is influenced by a number of factors, such as (1) the patient, (2) the orthopedic surgeon, and (3) the prosthesis (Fig. 1). These determinants will be discussed separately.

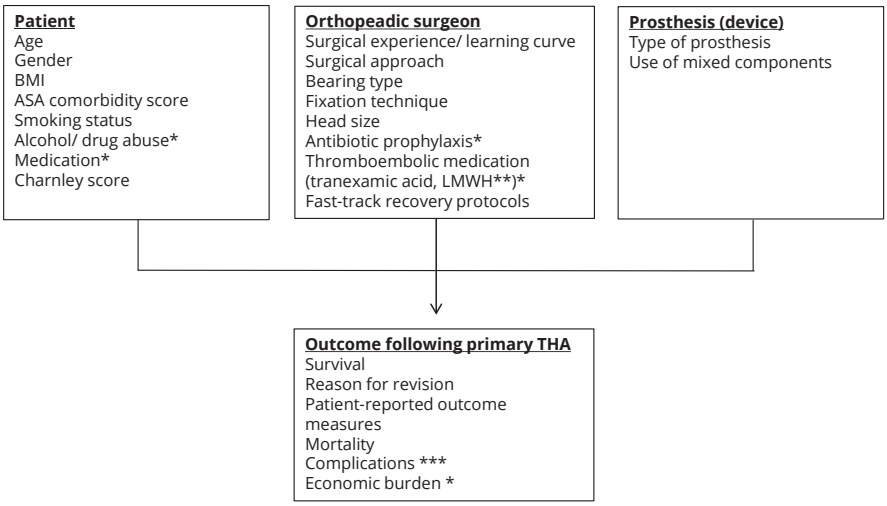

FIGURE 1. Determinants of outcome following primary THA.
* Not registered in LROI. ** Low molecular weight heparin. *** Complications not leading to revision are not registered in LROI (e.g. first dislocation, prolonged wound leakage for which surgical debridement without femoral head/liner exchange is performed)

PART I. PATIENT CHARACTERISTICS AND THE IMPACT ON THA.

It is anticipated that the global burden of disease for osteoarthritis (OA) will become larger, and consequently the incidence of THA is expected to grow in the coming decades (Cross, 2013). A shift in the proportion of elderly patients (e.g. aged 80 year or older) is apparent from an increasing life expectancy globally. This demographic group is accelerating faster than any other age group thanks to advancements in medical care, nutrition, socio-economic status and technology (Naughton, 2016), resulting in a larger number of 'aged' patients with OA. A longer length of life, however, may be accompanied by potentially declining health and therefore a large variation in physical fitness of this group of patients (Naughton, 2016). On the other hand, the increase in obesity can result in the development of OA at a younger age, in patients who are still participating in the labour market (Onggo, 2019). This will boost the number of young OA patients (younger than 60). Both trends will, among others, lead to a more heterogeneous population of patients undergoing THA. A relevant concept in this respect is case-mix. Case-mix is the

term used in orthopaedics to describe this variation in the population, relating to factors such as diagnosis, patient age, gender and health condition (e.g. ASA physical status, smoking, BMI) (LROI annual report, 2019). These case-mix factors or patient characteristics are known to influence outcome after THA (Ferguson, 2019). It is important to know preoperatively which patients are at a higher risk for adverse events. In the first part of this thesis we aimed to determine the effect of case-mix on revision rates (Chapter 2) and PROMs (Chapter 3) after primary THA using data of the Dutch Arthroplasty Register (LROI).

In chapter 2, 218,214 patients with OA of the hip joint who underwent a primary THA between 2007-2018 in a Dutch hospital were selected. We found an increased risk for revision after 1 year in patients with morbid obesity (BMI >40) and with a high ASA score (III-IV), patients aged 75 or older, and male patients. After 3 years a high BMI, previous operation to the affected hip, Charnley score C, male gender and a high ASA score were independently associated with increased risk for revision. A high ASA score and obesity (especially BMI >40) were the strongest predictors for revision. In addition, the reason for revision differed according to length of follow-up and between patients with differences in case-mix. Main reasons for revision were dislocation, infection and periprosthetic fracture. The risk for revision due to a periprosthetic infection was high in patients with obesity (BMI ≥30) and a higher ASA score (III-IV). Revisions for a periprosthetic fracture were more common in patients with a high ASA score (III-IV) or Charnley score C, and in elderly patients (75 or older). Dislocation revisions were equally distributed over the various case-mix groups. Stratified analysis revealed an increased risk for revision due to dislocation in patients with an acute femoral neck fracture and late posttraumatic changes.

These findings are in concordance with previous arthroplasty registry studies demonstrating an association between BMI and revision and overall complication rate (Jeschke, 2018, Sayed-Noor, 2019). An increasing risk of revision with each overweight and obesity class (according to the World Health Organization) was found, with a more-than-doubled risk for morbidly obese patients (Sayed-Noor, 2019).

Revision due to periprosthetic infection

The higher risk for revision due to prosthetic joint infection (PJI) in obese and morbidly obese patients could be explained by the fact that the procedure is more technically demanding. Altered localisation of anatomical reference points, extensive subcutaneous soft tissue and weakened fatty-infiltrated periarticular structures may contribute to a prolonged procedure plus an increased risk for wound leakage and infection (Elson 2013, Hanly 2016 , Sayed-Noor 2019). A patient-tailored approach with preoperative optimisation and prophylactic measures (e.g. weight-adjusted

antibiotic prophylaxis and meticulous wound closure and/or incisional vacuum-assisted closure) should be considered in obese patients to minimise the increased risk for infection. Morbidly obese patients could be sent to an obesity care physician aiming to decrease body weight prior to placement of the prosthesis (Jeschke 2018, Sayed-Noor 2019). In addition, we found an almost-doubled risk for revision due to PJI in patients with a higher comorbidity score (ASA III-IV). This is relevant since comorbid conditions are on the rise globally, as patients tend to have a longer life expectancy (Podmore, 2018). Risk factors due to lifestyle (physical inactivity, smoking) may likewise contribute to the increased number of people living with multiple comorbidities. Chronic illnesses such as rheumatoid arthritis, diabetes mellitus and congestive heart failure make patients more susceptible to PJI due to immunopathy and/or the use of immunomodulating agents such as corticosteroids (both systemically and intra-articular), hyperglycaemia and microvascular damage, respectively (Schrama 2015, Kunutsor 2015, Lenguerrand 2018). Chronic pulmonary disease and liver disease have also been reported as factors leading to an increased revision risk (Lenguerrand, 2018).

Revision due to dislocation

In our dataset with OA patients, case-mix was not associated with the risk for revision due to dislocation. In contrast, multiple studies suggest an association between patient characteristics and the risk for dislocation revision. Jones (2019) found an increased revision risk for dislocation in patients of advanced age (>75 years), male gender, history of alcohol abuse, neurodegenerative diseases and a BMI >30. A high ASA score (>3) and poor rehabilitation skills were also identified as risk factors for postoperative dislocation of the hip (Jolles, 2002). A study using the Kaiser Permanente Total Joint Registry database for THA procedures identified over 3,000 THA patients with a minimum 1-year follow-up. A higher dislocation risk with ASA III-IV was found compared to a lower ASA score. It was suggested that patients with a higher comorbidity index might have an impaired ability to adhere to hip precautions after THA, possibly due to impaired cognitive or physical skills (Khatod, 2006). In order to reduce the risk for dislocation in high-risk patients (high ASA score, acute femoral neck fracture), the use of a larger (e.g. 36 versus 32mm) femoral head component or a change in surgical approach could be considered, to reduce the risk for revision due to recurrent dislocation (Zijlstra, 2017). Dual-mobility bearings can be chosen to further reduce the dislocation revision risk (Bloemheuvel, 2019). These strategies aimed to prevent dislocation (e.g. using a larger femoral head component or a dual-mobility bearing) might have resulted in the absence of an association between case-mix and dislocation in our data.

Revision due to periprosthetic fracture

Periprosthetic femoral fractures (PFF) after THA are devastating complications, associated with functional deficits and increased overall mortality (Carli, 2017). In

our data, revision arthroplasty due to a periprosthetic fracture was more frequently encountered in patients with a high ASA score (III-IV) and Charnley score C, and in elderly patients (>75 years). This is in accordance with previous literature. Revision for a periprosthetic fracture accounted for 14.3% of all revisions in the Netherlands. Thien (2014) used the Nordic Arthroplasty Register Association (NARA) database to evaluate the risk of revision arthroplasty due to a periprosthetic fracture within two years from operation of a primary THA. It was demonstrated that a periprosthetic femoral fracture is more common in uncemented stems (relative risk 8.72), in polished cemented stems and during the early postoperative months, and increases with age, especially in older women (Thien, 2014). PFF in patients with uncemented stems generally occurred intraoperatively or in the early postoperative period (within 6 months), while fractures in patients with cemented implants generally occurred later. It is also known that preoperative diagnosis is a risk factor for PFF. A previous hip fracture and osteonecrosis of the femoral head are risk factors for subsequent periprosthetic fracture (Thien, 2014). This might be related to reduced bone-mineral density due to other comorbidities, systemic abnormalities, corticosteroid use, alcohol consumption or disuse (Thien 2014, Singh 2013, Chang 1993). Hence for patients with ASA III-IV, advanced age and other comorbidities one might consider a cemented prosthesis in order to reduce the risk of periprosthetic fracture.

Case-mix and the influence on patient-reported outcome measures

In addition to surgical outcome variables (e.g. survival, re-operations, 90-day mortality rate, complications), disease-specific and health-related quality of life (HRQoL) as measured in PROMs can be used to evaluate outcome of THA (Lindgren, 2014). Measuring patient-centred outcomes has yielded important information about outcomes that matter to patients (Rolfson, 2016). **The association between patient characteristics and improvement of PROMs after primary THA in the Netherlands is assessed in chapter 3. We found that patients benefiting most in terms of postoperative improvement of self-reported physical functioning, pain relief and quality of life after primary THA were young, female, had high ASA or BMI scores, and had no previous hip operations. However, clinical differences were small.**

Patients with a high ASA score (III-IV) and patients with a high BMI (>30) demonstrated larger improvement of physical function 3 and 12 months after primary THA. In addition, patients with a high BMI showed more postoperative improvement on HRQoL. Patients with high ASA or BMI scores had lower preoperative scores on the Hip disability and Osteoarthritis Outcome Score (HOOS-PS), which might be an effect of more advanced disease. It is known that obesity and severe obesity are associated with early onset and accelerated progression of OA of the hip (Onggo, 2019). Severe obesity is widely associated with reduced cardiopulmonary capacity,

metabolic abnormalities and decreased haemostasis, which may predispose to postoperative morbidity and mortality (Onggo, 2019). These factors might lead to a higher threshold for orthopaedic surgeons to progress with surgery. In addition, our data demonstrated that obesity in combination with OA of the hip joint was associated with more preoperative pain, both during activity and at rest. More pain might result in lower preoperative physical functioning as measured by the HOOS-PS.

Severe comorbidity, as reflected by a high ASA score, in combination with more advanced OA might lead to a lower preoperative level of physical performance, reflected in low preoperative PROM scores. Simply put: in ASA III+ and obese patients the risks are high and so are the gains.

Young age at the time of the procedure was associated with higher postoperative improvement in physical functioning and health perception. Osteoarthritis of the hip is not limited to advanced age, as it also affects younger patients still participating in the labour market. Such patients might be unable to fulfil their work responsibilities, especially in physically demanding jobs. Among patients younger than 65 years, 15-45% are working at the time of the procedure (Tilbury, 2014). In a younger and more active patient population, a postoperative return to daily activities includes return to sports (RTS) and return to work (RTW), both of major importance to the patient (Hoorntje, 2018). Consequently, RTW after the procedure might result in greater improvement of patients' quality of life.

PART II. THE SURGICAL PROCEDURE: THE ROLE OF THE ORTHOPAEDIC SURGEON.

Multiple techniques have been described to perform a total hip replacement and there is large variance in practice. In the second part of this thesis we focussed on factors predominantly determined by the orthopaedic surgeon. Various surgically and non-surgically modifiable factors could be identified, such as antibiotic prophylaxis, surgical approach, bearing surface, type of fixation, thrombosis prophylaxis and fast-track surgery protocols (Fig. 1). In this section we will elaborate further on two of these factors: surgical approach used to insert the hip prosthesis and THA bearing type. We considered discussing the latter in part III (prosthesis), but given that the decision for a bearing type is made by the involved orthopaedic surgeon the topic will be covered here.

Bearing surface

Hip arthroplasty articulation can be differentiated based on the bearing surface of the femoral head and the acetabular insert or cup (Annual Report AOANJRR 2019).

Chapter 4 examines the effect of bearing type on survival after primary THA in the Netherlands. In short, we concluded that there is a significant benefit in mid-term revision rates for ceramic-on-highly-crosslinked-polyethylene (CoHXLPE), oxidized-zirconium-on-(highly crosslinked)-polyethylene (Ox(HXL)PE) and ceramic-on-ceramic (CoC) bearings, compared to traditional metal-on-polyethylene (MoP) bearings.

Conventional THAs with a cobalt-chromium (metal) femoral head articulating with a polyethylene (PE) acetabular bearing have the longest track record with a reliable safety profile and the most widespread use (Lachiewicz, 2018). Although the demand for hip replacement surgery is largely driven by an aging population, indications are concomitantly expanding in younger patients with a more active lifestyle (Wiles, 2015). An increased life expectancy combined with higher physical demands place young patients at risk for mechanical failure of the prosthesis (Wiles, 2015). Aseptic loosening of components is the most frequent cause for revision surgery in the Netherlands (Annual report LROI, 2019). Over time, wear of the polyethylene liner in a traditional MoP THA can generate the formation of PE particles. These particles can result in an adverse local host response, leading to localised areas of periprosthetic bone resorption (osteolysis) and subsequent loosening of components and pain (Hu 2015, Varnum 2015). Therefore, alternative bearing surfaces such as ceramics, oxidized zirconium and HXLPE were introduced to decrease wear of conventional polyethylene, aiming to increase prosthetic longevity (Wiles, 2015).

Ceramic is harder and offers more scratch resistance than cobalt-chrome, which improves lubrication through a low friction coefficient, resulting in excellent wear resistance and low osteolysis rates (Wang 2013, Hu 2015). Our results demonstrate a 13% lower risk for revision in CoHXLPE compared to MoP. This is in concordance with a meta-analysis of randomised controlled trails (RCTs) showing lower revision rates, osteolysis, component loosening, and dislocation for CoC THAs compared to MoP, despite more squeaking (Hu, 2015). A well-described drawback of CoC components includes higher cost and adverse events, such as intraoperative or postoperative ceramic fractures and audible squeaking (Hu 2015, Wiles 2015).

Oxidized zirconium or ceramicized metal (Oxinium, Smith & Nephew, Memphis, TN, USA) femoral head components comprise a 5µm-thick ceramic layer on the metal alloy core, which makes it more resistant to fractures than alumina ceramic heads (Jassim, 2015). We found significantly lower risk for revision in patients with an Ox(HXL)PE bearing surface (hazard ratio 0.81) compared to MoP. This finding is consistent with previous reports. Davis (2020) examined the risk for revision in 420,339 primary THAs with uncemented acetabular components with different bearings, using the National Joint Register for England, Wales, Northern Ireland and the Isle of Man (NJR). The lowest risk for revision was found in THAs with an

OxXLPE bearing. The Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR) reported that ceramicized metal-on-XLPE has the lowest rate of revision at 10 years with a 3.7% cumulative percentage of revision compared to 6.4% for traditional MoPE. The register does urge caution when interpreting these results. Ceramicized metal is a single-company product, used with a small number of femoral stem and acetabular component combinations, which may have a confounding effect on the outcome (Annual Report AOANJRR, 2019).

HXLPE is defined as ultra-high-molecular-weight polyethylene that has been irradiated by high-dose (>50kGy) gamma or electron beam radiation (Annual Report AOANJRR, 2019). HXLPE was developed to reduce wear of traditional PE and subsequently late osteolysis and component loosening. In our data, adjusted overall hazard ratios at medium term were similar between HXLPE and traditional acetabular component THAs. However, revision due to loosening of acetabular components or liner wear were less frequently observed in HXLPE THAs compared with traditional PE. In the Netherlands, use of standard PE dropped from 34.8% in 2010 to 2.4% in 2018, while the use of HXLPE increased from 44.7% to 90.2% in primary THAs (LROI annual report, 2019). Australian data equally demonstrated a lower percentage of conventional PE components (proportion of HXPLE is 97.1% in 2018). HXLPE is associated with lower revision rates than PE, with an increasing difference in time favouring HXLPE (7.2% vs 13.7% at 18 years). HXLPE has also been associated with an increased use of larger head sizes compared to non-XLPE. This subsequently results in fewer revisions for dislocation (Annual Report AOANJRR, 2019).

In young patients (e.g. younger than 60) the implant choice is essential, given their generally more active lifestyle and higher physical demands. Sub-analysis for patients younger than 60 revealed that THAs with a CoHXLPE, CoC and Ox(HXL)PE bearing surface were revised less frequently than MoP. However, after adjustment for case-mix and confounders in a multivariable survival analysis, revision rates were not statistically different. This trend favouring the use of ceramics, HXLPE and ceramicized metal was consistent with results in patients younger than 55 in the AOANJRR and NJR (Annual Report AOANJRR 2019, Davis 2020).

Bearing surface – revision scenario

As described, ceramic-on-ceramic bearings in THA were introduced as alternative bearing type in young, active patients thanks to low rates of wear, osteolysis and component loosening (Hu, 2015). An adverse event is fracture of the ceramic component, for which revision surgery is indicated. The choice of a bearing combination in case of fractured ceramic component is important. **In appendix 1, we aim to highlight the potential for systemic cobalt toxicity in patients with a non-MoM THA. This report illustrates a case in which a fractured CoC THA was**

revised into a MoP bearing. At 1 year, postoperative imaging demonstrated flattening of the femoral head with a pattern of periarticular metal wear debris and pseudotumor formation. It was hypothesised that ceramic particles may become embedded in the polyethylene liner, causing a third body wear reaction with the relatively softer metal femoral head component. Before revision could take place, the patient was admitted with a clinical picture of systemic cobalt toxicity. Based on this case report we recommend that a fractured ceramic-on-ceramic articulations should be revised to ceramic-on-ceramic or ceramic-on-polyethylene THA, as replacement by a metal-on-polyethylene bearing can result in systemic cobalt toxicity with potentially severe consequences (appendix 1).

Surgical approach

Various surgical approaches are used for total hip replacement. The decision for a surgical approach is predominantly determined by the surgeon's preference and local hospital standards (Amlie, 2014). **Chapter 5 investigates the effect of surgical approach on PROMs after primary THA. We found a larger improvement in self-reported physical functioning 3 months after primary THA in 12,774 patients operated through the anterior (A) and posterolateral (PL) approaches compared with the anterolateral (AL) and direct lateral (DL) approaches. More pain reduction was observed in patients operated through posterolateral (pain during activity and in rest) and anterior (only during activity) approaches compared with the anterolateral approach. No relevant differences were found between the anterior and posterolateral approaches.**

The surgical approach chosen to insert a total hip prosthesis is a topic that continues to stir debate among orthopaedic surgeons, with specific pros and cons for each technique. The posterolateral approach is the most frequently used (55.1% in 2018) for primary THA in the Netherlands. Between 2010 and 2018 use of the PL approach remained relatively constant, whereas use of the DL and AL approaches diminished and the anterior approach gained popularity (from 4.7 to 32%) (Annual report LROI, 2019). The anterior approach was first described by Smith-Peterson and modified by Heuter (Somford, 2020). Potential benefits of this muscle-sparing and internervous approach include early mobilisation, reduced early postoperative narcotic consumption and low dislocation rates. This technique is associated with a lower risk for revision due to dislocation (Petis 2015, Higgins 2015). However, the approach is technically demanding with a long learning curve, and can result in neuropraxia of the lateral femoral cutaneous nerve (Petis 2015, De Steiger 2015) and increased risk of femoral stem revision (Zijlstra, 2017). The DL approach offers adequate exposure of both acetabulum and femur, with the benefit of providing extensile exposure to the proximal femur (Petis, 2015). This approach is associated with low dislocation rates, peri-trochanteric pain and postoperative limping secondary to abductor

weakness (Jameson 2014, Petis 2015). The AL approach theoretically facilitates early mobilisation and a low incidence of postoperative dislocation (Watson-Jones, 1936), but fractures of the femoral shaft and stem malalignment have nonetheless been described (Bernasek, 2010).

Our results were consistent with findings of Amlie and colleagues using PROMs data from the Norwegian Arthroplasty Register. It was found that the posterolateral and anterior approach provided higher PROM scores 1 and 3 years after primary THA compared to the direct lateral approach in terms of pain, HRQoL and limping (Amlie, 2014). Lindgren reported that both the PL and DL approaches resulted in significant improvement in HRQoL following primary THA, with less residual pain and greater satisfaction for the PL, using prospectively collected SHAR data (2014).

Lastly, we wish to emphasise that all examined approaches resulted in a significant improvement of PROMs scores 3 months after primary THA in the Netherlands and that absolute differences between approaches were small. All approaches have their specific pros and cons in terms of technical challenges, complications, reasons for revision and postoperative patient perception. Advancements in surgical techniques and approaches (e.g. improved closure techniques, minimally invasive approaches) and postoperative rehabilitation techniques will continue to stir debate aiming to further reduce adverse events after primary THA. Patient characteristics (case-mix) continue to be an important determinant of outcome in terms of both survival and PROMs, and the influence of case-mix may in fact be much larger than the effect of surgical approach.

Part II of this thesis has described the influence of bearing surface and surgical approach on risk for revision and PROMs after primary THA, respectively. Other surgically modifiable factors such as fixation technique, antiseptic measures and thromboembolic prophylaxis (Fig. 1) can be determined by the treating orthopaedic surgeon (Learmonth, 2007) in order to optimise the outcome for patients undergoing THA. However, these factors have not been investigated in this thesis and therefore remain undiscussed.

PART III. THE PROSTHESIS: IMPACT OF MIX AND MATCH.

The third part focuses on the prosthesis. National arthroplasty registers evidence the use of dozens of different THA implants worldwide, produced by a multitude of manufacturers. Hip prostheses can vary in design, bearing surface, head size, fixation technique, surface geometry and modularity. Registry studies demonstrate that these characteristics may impact outcome after primary THA. Most THAs are assembled of components produced by the same manufacturer (non-mixed THA),

yet certain medical situations require surgeons to combine a femoral component with an acetabular component from a different manufacturer (mixed THA).

In chapter 6 we assessed the incidence and risk for revision for THAs assembled of components produced by different manufacturers (mixed THA). Using nationwide registry data, we found that 11% of THAs performed between 2007 and 2014 in the Netherlands were assembled of mixed components. Mixed THAs yielded medium-term survival rates similar to non-mixed THAs.
It has been advocated that mixing components from different manufacturers within a single THA could result in adverse effects due to size mismatch at the stem-head taper and head-cup interface (Ljung, 1989). Use of mixed components may additionally lead to alloy mismatch (Morlock, 2001). Manufactures emphasise in their guidelines that components from different companies should not be combined since they are not designed, tested or validated together. This notwithstanding, mixing and matching of THA components brands is common practice worldwide.

Using the National Joint Register of England and Wales (NJR), Tucker (2015) identified over 90,000 mixed THAs inserted between 2003 and 2013. In 2013, 14.7% out of 78,479 performed THAs were assembled of components from different manufacturers. Mixed THAs were not associated with a higher risk for revision, except for those with mixed heads and stems (fixed bearings). For patients with mixed cemented stems with polyethylene cups from another manufacturer even lower revision rates were found. Taylor (2018) determined the proportion of THAs assembled of components from different manufactures using the New Zealand Joint Register (NZJR) and compared revision rates for mixed and non-mixed THAs. It was found that 24.6% of THAs in New Zealand contained mixed components. No significant differences in revision rates between matched and unmatched components were found after a 17-year follow-up.

The term mixed THAs can refer to both primary and revision total hip replacements. An argument for the use of mixed components in revision surgery could be prevention of additional patient morbidity (Mueller, 2018), e.g. in case of a cup revision to a cemented acetabular component (company A) when leaving the well-fixated uncemented stem in situ (company B). Removing the well-fixed stem in order to create a non-mixed THA would require a more extensive dissection and prolonged operation time, plus it places the patient at risk for adverse events (fractures of the proximal femur and bone loss). This is why mixing is mostly done in the best interest of the patients. Mixed components are additionally used in cases of altered anatomy (e.g. developmental dysplasia of the hip (DDH), pelvic fractures), in fragile patients (requiring cemented fixation of the stem) and in patients at risk for complications (e.g. lumbar spine fusion, pelvic radiation).

In conclusion, based on various arthroplasty registry studies, the use of mixed components is common practice worldwide and mixed THAs yield results that are at least comparable to non-mixed combinations (Tucker 2015, Peters 2016, Taylor 2018). In addition, mixed components can provide important medical benefits for specific patient categories, e.g. in case of altered anatomy or revision surgery. The question remains as to whether this is allowable by law.

In chapter 7 we aimed to assess the rules for mixed THAs based on European law, to create awareness among orthopaedic surgeons of the legality of this practice. Based on European and Dutch law, it was found that mixing of components can create a liability risk.
From a legal perspective it is advised to avoid the use of mixed components when reasonable alternatives are available that have been tested and approved, especially in primary THA. Following the European Product Liability Directive, an orthopaedic surgeon who uses mixed components within a THA (finished product) could qualify as a 'manufacturer of a finished product' and may be held liable if the product appears to be defective. However, based on case law reviews for the United Kingdom, Germany and the Netherlands, to date no orthopaedic surgeon has been held legally responsible or ended up in a lawsuit for using mixed components. Although no search was done of case law of other European countries, we presume that our reviewed countries can be considered representative for the situation in Europe as a whole.

Lastly, if a situation does require the use of mixed components, surgeons are best advised to 1) avoid mixing across the fixed articulation (i.e. use a head from the same manufacturer as the stem), 2) appropriately match sizes across the mobile articulation in hard-on-soft THAs (Tucker 2015, Taylor 2018), and 3) avoid mixing in hard-on-hard bearings. Surgeons are likewise advised to inform themselves on the results of specific component combinations (e.g. based on arthroplasty registry results) and to explain the choices to the patient in order to receive their consent.

THE VALUE OF ARTHROPLASTY REGISTRY STUDIES.

The majority of studies discussed above have been conducted using data from LROI. National arthroplasty registers have demonstrated to improve the outcome following total joint replacement and have developed into important generators of orthopaedic knowledge (Gliklich 2014, Lübbeke 2019). Registers provide nationwide prospective observational data that can be used to longitudinally monitor devices and improve outcome for the individual patient (Rolfson, 2011). Arthroplasty registers are known to generate relevant information and actionable knowledge which can be used to influence daily practice positively (Lübbeke, 2019). However,

the value of arthroplasty registry data with regard to randomised clinical trials continues to stimulate debate.

Ideally, decisions regarding treatment for individual patients should be based on the best available scientific evidence. To aid the interpretation and evaluation of research findings, hierarchies of evidence have been used that rank scientific research according to its internal validity, indicating the extent to which findings might be biased (Evans, 2003). The value of clinical studies has been derived from the place within the hierarchical level of evidence. The underlying basis for this hierarchy is the ability of data to establish causality with respect to outcome (Graves, 2010). Consequently, a randomised controlled study design is commonly recognised as providing the highest level of evidence and yield the lowest change of bias (Evans, 2003). For example, the Cochrane Collaboration ranks the validity of clinical studies on a scale from A to C, with the highest rank for studies with 'Grade A recommendations supported by Level I evidence' (Cook 1992, Evans 2003). Based on this hierarchical level-of-evidence structure, data derived from arthroplasty registers is qualified as observational data, so studies using these data would be considered as having a lower value than an RCT or meta-analysis. This statement might be true when it comes to the ability of arthroplasty registry studies to establish causality, but it could be asked whether this is the most fitting approach to compare the value of clinical trials and arthroplasty registry studies (Graves, 2010).

RCTs are designed to generate evidence to support or reject a hypothesis. Strengths of prospective clinical trials include the use of a predefined study protocol describing strict inclusion and exclusion criteria, a well-defined intervention and predefined endpoints (Faraoni, 2016). The number of confounding factors that could impact the outcome should be limited, which helps interpretation of the findings. A study protocol describes the surgeons involved, period of inclusion and follow-up, and the clinical site(s) where the study takes place. A study should be adequately powered to enable comparison of statistical differences found between treatment groups (Graves, 2010). An important advantage of clinical trials over observational studies is the ability to control for bias attributable to unmeasured differences between patients (Siderowf, 2004). Furthermore, with randomisation and the blinding of patients (and involved physicians), RCTs are able to limit selection, information and confounding-by-indication bias.

Clinical trials also have evident drawbacks. In order to answer a specific research question (and establish causality), the protocol should ensure high internal validity. A strict selection may imply failure to include a representative cross-sectional selection of patients (Graves, 2010), and the highly structured treatment regimen of a prospective clinical trial may be difficult to replicate in daily practice settings.

These limitations tend to reduce the generalisability of results from clinical trials and limit wider application (Siderowf 2004, Graves, 2010). Lastly, challenges of performing a large-scale multicentre RCT could be that these studies are labour-demanding and costly, which may limit their use, especially when examining rare outcomes (Varnum, 2017).

By contrast, registry-based studies do not aim to prove causality, so findings derived from them are considered to have a lower hierarchical level of evidence. However, arthroplasty registers are increasingly recognised as a valuable tool to improve orthopaedic care (Ferguson, 2019). Methods of data collection and purpose of analysis differ from clinical trials. Data collection is done at a regional or national level, aiming to include all arthroplasty procedures performed. Since a register monitors data longitudinally (no predefined inclusion period), registry studies are able to monitor changes in clinical practice and provide insight into the impact on results (Ferguson, 2019). Strengths of arthroplasty registry studies include their nationwide, prospective design and large numbers of patients, resulting in a high statistical power, and they make the results more applicable to the average orthopaedic clinic (Lindgren 2014, Paulsen 2014, Kristensen 2017). The large sample size also results in the ability to avoid performance bias, which can occur if patients are selected from single surgeons or centres (Rolson 2011, Malchau 2018). Registry studies can be used to perform adequate analyses of uncommon complications, especially in registers that collaborate (Malchau 2018, Varnum 2019).

A drawback of the use of nationwide arthroplasty registry data is that, as selection bias cannot be controlled for, some selected groups of patients may be given a specific treatment more often than others (Robertsson, 2014). Some authors advocate that registry data are more suitable for detecting problems than explaining them or establishing a causal relationship since the outcome is mostly crude (e.g. revision as a measure of failure). Since other unknown (or unregistered) confounders cannot be ruled out to influence the outcome, these studies could be used as hypothesis generators (Robertsson 2014, Lindgren 2014).

As discussed above, arthroplasty registry studies do not attempt to assign causality, but provide important supplementary knowledge that enables orthopaedic surgeons to use registry data to guide their clinical decisions. Arthroplasty registry data can be used to identify patient-, procedure- and prosthesis-related factors associated with favourable outcomes. An important point is made by Prof. Stephan Graves, director of AOANJRR: ‘to optimize community outcomes of joint replacement surgery, it is not necessary to know why there is a difference. Incremental improvement can be achieved by surgeons choosing treatment options that have been identified as having better outcomes or alternatively avoiding those that have not. Those that attempt to rank the value of registry data with respect to the capacity to

identify causality have entirely missed the point of the purpose of a register and the approach it uses to achieve this' (2010).

If the relative value of clinical trials and registers is compared and ranked, criteria should be used which apply to both of them. Registry-based studies represent a greater ability to obtain new information, more applicable to the 'average' orthopaedic population, with a possibly larger impact on daily practice. In addition, learning curve and surgical skill could be easily assessed using registy data (Graves, 2010).

We advocate that it is essential to understand the strengths and limitations of RCTs as well as observational arthroplasty registry studies when interpreting the results obtained by both. RCTs and arthroplasty registers use completely different approaches to collect and analyse data, subsequently generating different information. In our opinion, one is not superior to the other. Both methods are complementary, and each can contribute importantly to improve arthroplasty surgery (Graves 2010, Faraoni 2016).

PATIENT-REPORTED OUTCOME MEASURES IN ARTHROPLASTY REGISTRY STUDIES.

Traditionally, outcome measures in orthopaedic surgery consist of surgical endpoints such as revision rate, re-admission, reoperation and other adverse events (e.g. infection or thromboembolic events). The most frequently used outcome variable in arthroplasty registry studies is implant survival, yet the main aim of THA is to decrease pain, restore function and improve health-related quality of life. It would therefore be reasonable to assess those variables that matter to patients when analysing results of THA (Rolfson, 2011, Wilson 2019). PROMs were introduced to evaluate the outcome of joint replacement surgery in terms of functional results and health-related quality of life. A patient-reported outcome is defined as any report of a patient's perception of health status directly without interpretation from a medical professional (Rolfson, 2016 part 1). Two types of PROMs are distinguished. Generic or general health PROMs are used to measure a patient's physical or mental health status, regardless of presence or absence of disease, disability or specific symptoms. These generic PROMs represent global health status, which is comparable across different conditions (Rolfson, 2016 part 1). Disease-specific PROMs focus on specific symptoms, diseases and anatomical regions (e.g. joint-specific), and can be used to evaluate the effect of a specific intervention such as a THA (Rolfson 2016 part 1, Wilson 2019).

The use of PROMs in arthroplasty literature in leading orthopaedic journals has increased significantly since 2004. This trend is expected to continue since patient satisfaction is found to be increasingly important as a quality indicator for medical interventions (Huis in 't Veld, 2020). Routine administration of PROMs has been stimulated by the introduction of the concept of value-based healthcare, in which decisions about the optimal treatment and reimbursement should be based on determinants that add value for the patient (Porter 2010, Rolfson 2016 part 1, Siljander 2018).

In the Netherlands, hip-specific and general health-related PROMs have been registered in LROI since 2014 for patients with osteoarthritis undergoing THA (Peters, 2018). The set of PROMs consists of the Oxford Hip Score (OHS), the short version of the Hip disability and Osteoarthritis Outcome Score (HOOS-PS) (disease-specific: physical functioning and disability), the EuroQoL 5-Dimensions (EQ-5D-3L) questionnaire (generic: health perception and HRQoL), and a numeric rating scale (NRS) measuring pain during activity and rest (generic) (Peters, 2020).

In this thesis we used short-term postoperative improvement in physical function, pain and HRQoL following primary THA as outcome variable in two studies. In both studies a clear association with the intervention was found postoperatively. Chapter 5 demonstrated that all surgical approaches resulted in significant improvements of PROMs three months after primary THA. Chapter 3 showed that, regardless of variance in case-mix categories, the implantation of a total hip prosthesis led to significant improvement in physical function, reduction in pain and improved HrQoL after 3 and 12 months. Based on these studies, it can be concluded that PROMs measuring physical functioning, pain and health-related quality of life can be used as valuable tools to assess improvement in outcome of THA patients. These patient-based measures are helpful in determining treatment success and in convincing the stakeholders involved, e.g. patients, medical providers (orthopaedic surgeons, hospitals), financial partners (health insurers, government), public health and regulatory agencies, and the industry.

On the other hand, absolute differences between the groups examined in chapter 3 and 5 in this thesis were small, therefore PROMs might be of lesser clinical value than initially aimed and hoped for. Ideally, PROMs (as any measure) are able to detect even small differences in patient outcome, for example as a result of a technical or procedural change or case-mix variation (Marx, 2005). The ability of a PROM tool to detect differences in the patient's clinical condition is called responsiveness and includes recognition of the concept of minimal clinically important difference (MCID) (Wilson, 2019). MCID is defined as a change in PROM outcome that would be perceived as beneficial by the patient (or clinician), assuming the absence of serious adverse events or exorbitant costs. It could be used as threshold value for such a

change. When these studies were designed not all MCID values as calculated for commonly used PROMs were known, so to interpret our results we used effect size (Cohen's d), similarly to previous national arthroplasty registry studies.

As stated, our studies demonstrated limited clinical differences between the surgical approaches (chapter 5) and case-mix groups (chapter 3). In order to get an impression of these differences, effect sizes were calculated. The use of effect sizes was previously adopted by the Norwegian Arthroplasty Register (NAR) (Amlie, 2014). Based on the effect size calculated from our data, we concluded that differences in case-mix (e.g. BMI or ASA score) (chapter 3) or in technical variation (e.g. the surgical approach chosen) (chapter 5) had limited effect on PROMs. This raises the question of the extent to which the panel of selected PROMs is able to demonstrate clinically relevant differences in postoperative outcome between groups.

Another point that merits consideration is the fact that a large variety of PROMs have been collected in orthopaedic literature from across the world. For example, Siljander (2018) described a total of 42 unique PROMs used in studies reporting on unicompartmental knee and total hip and knee arthroplasty in four major orthopaedic journals between 2004 and 2017. It was recommended that orthopaedic registers and providers should aim to develop a gold standard for measuring patient-reported outcomes after total knee and hip arthroplasty, facilitating future cross-study comparisons (Siljander, 2018). Limiting the number of different PROMs used internationally could foster uniformity. For example, both the Dutch Arthroplasty Register and the National PROMs programme in England (as recorded by the NJR) record the EuroQol 5D (EQ-5D) index score, visual analogue score (VAS) and Oxford Hip Score, which theoretically facilitates cross-country comparisons.

Implementation of a PROM programme is a challenge, as it is costly and labour-intensive (Wilson 2019). Systematic collection of PROMs in a register requires efforts from orthopaedic surgeons, dedicated research staff, patients and supportive employees (including ICT) to fulfil data delivery, administer and complete questionnaires, and subsequently upload the data into a central database in order to ensure a sufficient response rate. For example, in the Netherlands the preoperative response rate of nearly 60% dropped to 40 and 32% at 3 and 12 months, respectively, following THA in 2017 (LROI annual report, 2019). A solution to increase response rates might be the application of computer-adaptive testing (CAT). CAT technology enables the administration of individually tailored PROM questionnaires with fewer items, by filtering out those items that do not apply to the respondent based on previous items. This might make people more inclined to complete the questionnaires.

According to the most recent NOV statement regarding PROMs, registration contributes to the process of shared decision-making and evaluation of treatment (NOV, 2019). PROMs can be used in daily orthopaedic practice to better inform individual patients and reflect on personal treatment outcomes. Preoperatively, information obtained via PROM questionnaires could be used to inform patients better before treatment, e.g. about the expected effect of treatment based on previous patient experience. After surgery, PROMs could lead to a better evaluation of outcome for individual patients. Graphs or other visual representations of improvement could be used to provide insight into current level of physical functioning, pain and HrQoL compared to the patient's previous outcomes. It was stated that the registration of PROMs could slightly shift the attention from purely medical treatment to preparation and support of patients, aiming at participation (in work, family, sports and leisure). Concrete changes according to the 'PROM NOV advice 2.0' include the fact that the OHS will become mandatory, the HOOS-PS will no longer be obligatory, and the EQ-5D 3l will be replaced by the EQ-5D 5l.

In conclusion, PROMs as used in national arthroplasty registers are a valuable tool to determine postoperative improvements in outcome measures that are relevant to patients with disabling osteoarthritis of the hip joint. Despite the evident benefits that registration of PROMs can bring, some remarks remain present. In this thesis we demonstrated that differences in postoperative improvement in PROMs between the various treatment groups were lower than initially hoped for. The clinical relevance of these small (but statistically significant) differences could be debated. In addition, the number of different PROMs registered in literature limits possibilities to make cross-study comparisons. A variety of PROMs also creates a considerable administrative task for individual doctors, patients or involved research staff. We should therefore aim for a limited selection of PROMs (preferably globally unified) to continue to prove the value of our operation, but tempering the enthusiasm for PROMs as suitable and discriminating instruments to measure effects of technical variation (e.g. surgical approach) or case-mix.

MAIN FINDINGS OF THESIS

- Independent risk factors for revision after THA are: comorbidity (ASA score), obesity (BMI), advanced age and gender (Chapter 2).
- Higher postoperative improvement on PROMs after primary THA is associated with: young age, female gender, high ASA score, high BMI score and no surgical history to the hip (Chapter 3).
- Improved survival rates after primary THA were found for ceramic-on-highly-crosslinked-polyethylene (CoHXLPE), ceramic-on-ceramic (CoC) and oxidized-

zirconium-on-(highly-crosslinked)-polyethylene (Ox(HXL)PE, compared to traditional metal-on-polyethylene (MoPE) (Chapter 4).

- The anterior (A) and posterolateral (PL) approach result in a larger improvement in PROMs after primary THA than the anterolateral and direct lateral approach. In general, differences between approaches were small. There was no clinically relevant difference between the A and PL approach in PROM improvements (Chapter 5).
- 11% of primary THAs in the Netherlands were assembled of components from different manufacturers within a single hip replacement (mixed THAs). Revision rates for mixed and non-mixed THAs were similar (Chapter 6).
- From a legal perspective it is advisable to avoid mixing when reasonable alternatives are available, especially in primary arthroplasty (Chapter 7). Based on case law review for the UK, Germany and the Netherlands, to date no orthopaedic surgeon has been held legally responsible or ended up in a lawsuit for the use of mixed components,.
- If a situation requires the use of mixed components, surgeons are best advised to 1) avoid mixing across the fixed articulation (i.e. use a head from the same manufacturer as the stem), 2) appropriately match sizes across the mobile articulation in hard-on-soft THAs, 3) avoid mixing in hard-on-hard bearings, 4) inform themselves on the results of specific component combinations (e.g. based on arthroplasty registry results), and 5) explain the choices to the patient in order to receive informed consent (Chapter 7).

FUTURE PERSPECTIVES AND CLINICAL IMPLICATIONS.

National arthroplasty registry data will continue to improve outcomes for patients undergoing THA. Post-market surveillance remains an important function of arthroplasty registers, warranting long-term monitoring of safety and identifying implant outliers. Given the success of THA (low revision rates, significant improvement in physical functioning and HRQoL), it has been suggested that future research should perhaps shift towards a more patient-tailored intervention for these procedures in order to further optimise outcomes and use of health resources (Wagner 2016, Peters 2020). Future registry research should therefore focus not only on the implant but increasingly on the patient (Varnum 2019).

Patient-tailored intervention

By identifying which modifiable patient-, procedure- and prosthesis-related factors influence arthroplasty outcome, efforts can be undertaken to positively influence these factors and obtain better outcomes (both risk for revision and functional results). An intriguing thought would be a situation in which we can optimise the outcome for the individual patient based on risk estimation during

the preoperative outpatient visit. A future goal can be to develop a register-based, validated digital prediction tool based on available patient data (age, gender, ASA score, surgical history to the affected hip, diagnosis, smoking status, Charnley score, BMI) to estimate risk for revision and satisfactory improvement in patient-reported outcome. Such a prediction tool could aid in patient selection for total joint arthroplasty and be used to discuss the benefits and risks of the operation with the patient at the preoperative consultation. In addition, if the decision to proceed with a THA is made, such a tool could be used to give the patient tailored advice on the intervention (surgical approach, cementation technique, bearing type, head size, antibiotic prophylaxis).

Based on the results of this thesis, patient characteristics can be used to help orthopaedic surgeons counsel patients and give patient-tailored advice, in order to decrease the risk for short-term revision after THA. For example:

TABLE 2. Treatment choices based on patient characteristics.

Patient characteristics*		**Treatment choice**
Age	Young (< 60 years)	Consider advanced bearing such CoHXPE, CoC or Ox(HXL)PE (Chapter 4).
BMI	High (>30)	Considerer strategies to minimize the risk for infection, e.g. adjust the dose of perioperative cefazolin (3g instead of 2g) if BMI >40 (Chapter 2).
ASA	High (III-IV)	Consider a cemented prosthesis to reduce the risk of periprosthetic fracture. Considerer strategies to minimize the risk for infection, e.g. adjust the dose of perioperative cefazolin (3g instead of 2g) (Chapter 2).
Charnley score	High (Charnley C)	Consider strategies to minimize the risk for a periprosthetic fracture, e.g. cemented fixation.
Diagnosis	- Acute femoral neck fracture - Late posttraumatic changes	Consider use of a large femoral head (e.g. 36 mm vs 32 or 28 mm), change of surgical approach, or use of a dual-mobility bearing to reduce risk for revision due to dislocation (Chapter 2).

* These results are based on observational data retrieved from the Dutch Arthroplasty Register, therefore causality cannot be inferred.

An important remark is that although these future register-based intelligent decision tools (Table 2) might be of assistance in allowing surgeons to think about risk-reduction strategies, clinical experience remains a key factor in the outcome of

THA – in the end, surgical decisions should always be made by the individual surgeon together with the patient (shared decision-making).

Future efforts could be directed towards further collaboration between arthroplasty registers and other healthcare databases, such as merging or linking with databases holding additional information on bacterial cultures, radiology reports, medication prescription and more detailed patient information. Such mergers could improve interpretation of arthroplasty registry data. The concept of nesting detailed clinical outcomes of studies in arthroplasty registries is a way to harness the benefits of both clinical data and registry models (Malchau 2018). In addition, the growing use of artificial intelligence through extraction from large data sources followed by machine learning by identifying risk factors for adverse events can play a role in future care for patients with disabling hip pathology (Varnum, 2019).

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APPENDICES

FATAL COBALT TOXICITY AFTER A NON-METAL-ON-METAL TOTAL HIP ARTHROPLASTY – A CASE REPORT

RINNE M. PETERS
PAX WILLEMSE
PAUL C. RIJK
MELS HOOGENDOORN
WIERD P. ZIJLSTRA

CASE REPORTS IN ORTHOPEDICS. 2017; 2017: 9123684.

ABSTRACT

This case illustrates the potential for systemic cobalt toxicity in non-metal-on-metal bearings, and its potentially devastating consequences. We present a 71 year old male with grinding sensations in his right hip following ceramic-on-ceramic total hip arthroplasty (THA). After diagnosing a fractured ceramic liner, the hip prosthesis was revised into a metal-on-polyethylene bearing. At one year postoperatively, X-rays and MARS-MRI showed a fixed reversed hybrid THA, with peri-articular densities, flattening of the femoral head component and a pattern of peri-articular metal wear debris and pseudo-tumor formation. Before revision could take place, the patient was admitted with the clinical picture of systemic cobalt toxicity, supported by excessively high serum cobalt and chromium levels, and ultimately died. At autopsy dilated cardiomyopathy as cause of death was hypothesized. A third body wear reaction between ceramic remnants and the metal femoral head very likely led to excessive metal wear, which contributed systemic cobalt toxicity leading to neurotoxicity and heart failure. This case emphasizes that fractured ceramic-on-ceramic bearings should be revised to ceramic-on-ceramic or ceramic-on-polyethylene bearings, but not to metal-on-polyethylene bearings. We aim to increase awareness among orthopedic surgeons for clinical clues for systemic cobalt intoxication, even when there is not a metal-on-metal bearing surface.

INTRODUCTION

The development of systemic cobalt toxicity after total hip arthroplasty (THA) appears to be very rare (Zywiel 2013, Cheung 2016). Case reports have highlighted systemic cobalt toxicity after failed metal-on-metal (MoM) articulations (Zijlstra 2009, Zijlstra 2010, Cheung 2016). Therefore, most practicing orthopedic surgeons probably associate systemic cobalt toxicity only with MoM bearings. However, revision of a broken ceramic liner to a MoP articulation can also cause mechanical wear and subsequent release of cobalt ions, due to contact between the new cobalt-chromium (CoCr) femoral head and remaining ceramic particles, which may become embedded in the PE inlay (Matziolis 2003, Hasegawa 2006 Oldenburg 2009, Zywiel 2013, Cheung 2016, Zywiel 2016, Kim 2016). Local consequences of this third body wear process include metallosis and hip complaints, and in more severe cases, migration into peri-articular soft tissues and subsequent systemic repercussions such as cobalt toxicity (hypothyroidism, polycythemia, cardiomyopathy, cognitive dysfunction, neuropathy, and fatigue). We present a rare case of suspected systemic cobalt toxicity following revision of a failed CoC THA with fatal outcome.

CASE REPORT

A 71-year old male with a history of diabetes and multiple myeloma visited the orthopedic outpatient clinic of a level 2 trauma hospital in 2004, with clinical and radiological signs of end-stage osteoarthritis of the right hip. The decision to proceed with total hip arthroplasty (THA) was made. A cementless ABG type II (Anatomique Benoist Gerard; Stryker Howmedica Osteonics, Newbury, UK) with a ceramic-on-ceramic (CoC) articulation was implanted. The postoperative course was uncomplicated.

In 2014, the patient perceived a squeaking sound and experienced increasing pain on the lateral side of the right hip after physical exercise. The patient denied prior trauma to the hip. The pain was present during flexion of the hip and he was not able of weight-bearing on his right leg. Clinical examination revealed pain on the lateral side of the hip upon flexion and inguinal pain during rotation. Alternative axial loading and traction to the hip joint was painful (positive push-pull test). Plain radiographs demonstrated a normal configuration of the acetabular component, albeit with an eccentric positioning of the head within the socket; there was no evidence for osteolytic lesions, subsidence of the stem, or loosening of the components (fig. 1).

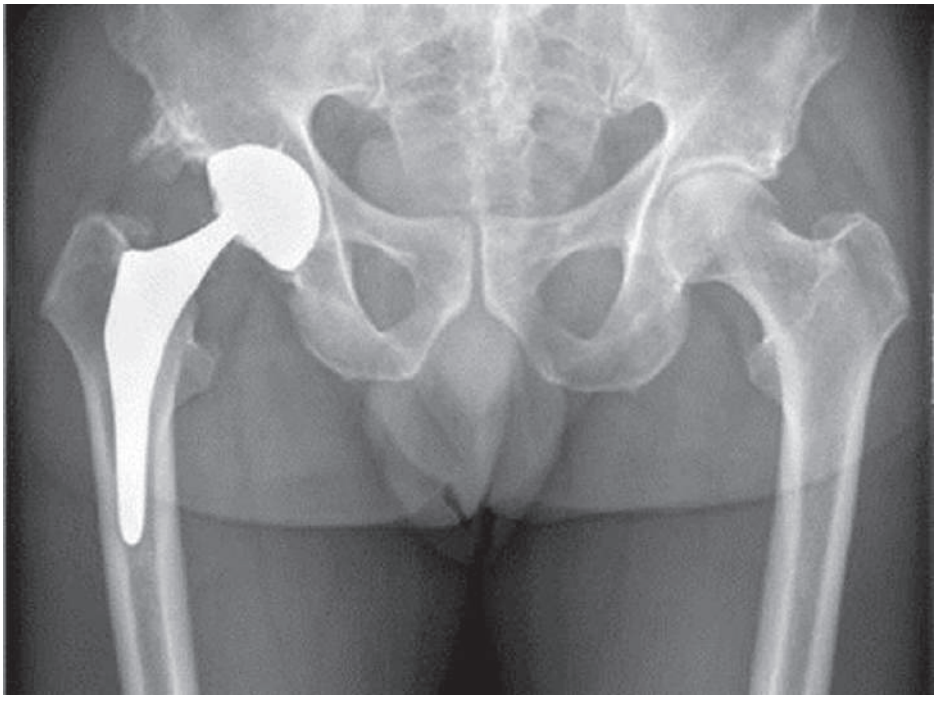

FIGURE 1. AP radiograph demonstrating eccentric positioning of the femoral head component of the right total hip arthroplasty without evidence for subsidence of the stem, and loosening of the components.

A skeletal scintigraphy excluded aseptic loosening of the prosthesis and no increased intensity around the femoral and acetabular components was observed. No signs of infection were present in whole blood samples. Considering the typical complaints and findings on clinical examination a fracture of the ceramic liner was suspected, and a revision procedure was performed.
Intraoperatively, more than 20 ceramic pieces of the broken liner were detected and thoroughly removed and the surgical wound was repeatedly flushed. Macroscopically, all ceramic particles were removed. The joint capsule demonstrated hypertrophic changes for which synovectomy and debridement were performed. The femoral stem and acetabular shell did not show any signs of loosening. The acetabular shell was removed and replaced by a polyethylene (PE) SHP cup (Scientific Hip Prosthesis; Biomet, Warsaw, Indiana, USA) combined with a 28 mm cobalt-chromium (CoCr) alloy femoral head, with a matching taper (fig. 2).

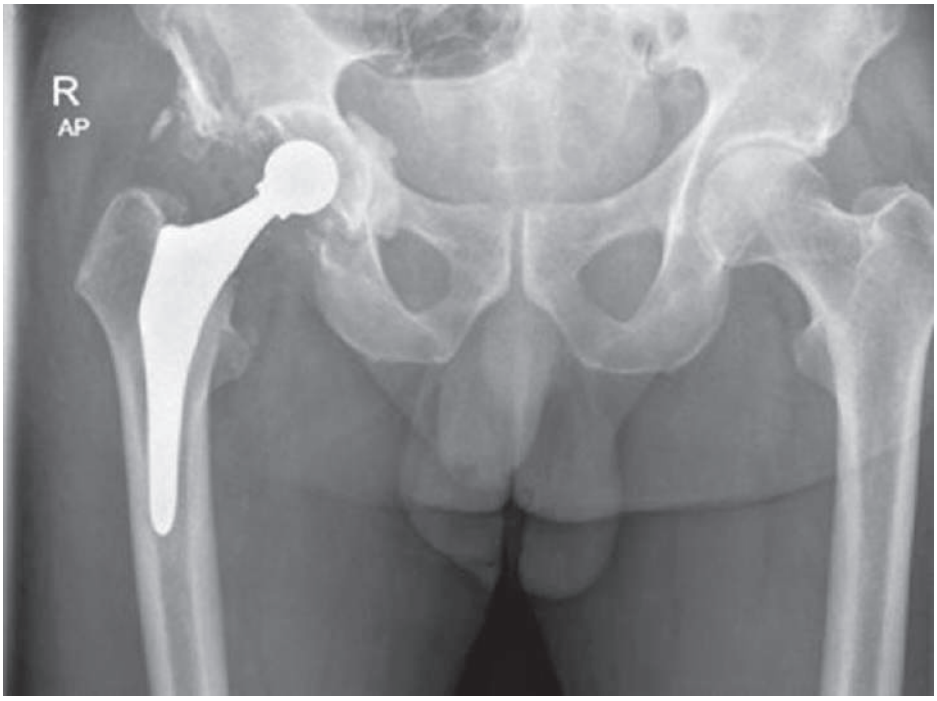

FIGURE 2. AP radiograph, 6 weeks following revision arthroplasty, demonstrating a polyethylene cup combined with a cobalt-chromium (CoCr) femoral head.

Postoperatively, he recovered well. At 6 weeks follow up the patient perceived an excellent function of the hip and there were no of signs radiological abnormalities. Six months after the revision procedure, the patient developed more pain in the right hip. To exclude progression of his multiple myeloma a fluorine-18-fluorodeoxyglucose-positron emission tomography with computer tomography was performed, which showed no active osteolytic lesions but revealed metabolic activity in the right hip and gluteus muscle. Additional plain radiographs showed a well fixed reversed hybrid total hip prosthesis and impressive peri-articular densities around the components combined with flattening of the femoral head component with loss of its sphericity (fig 3). Therefore, a magnetic resonance image (MRI) with metal artefact reduction sequence (MARS) was obtained which demonstrated metal wear debris with comprehensive pseudotumor formation surrounding the components of the total hip prosthesis (fig. 4). A second revision procedure was proposed to the patient but had to be postponed due to a ischemic cerebrovascular accident, for which both acetylsalicylic acid and dipyridamole were initiated. Hypothyroidism was diagnosed for which thyroxine supplementation was prescribed.

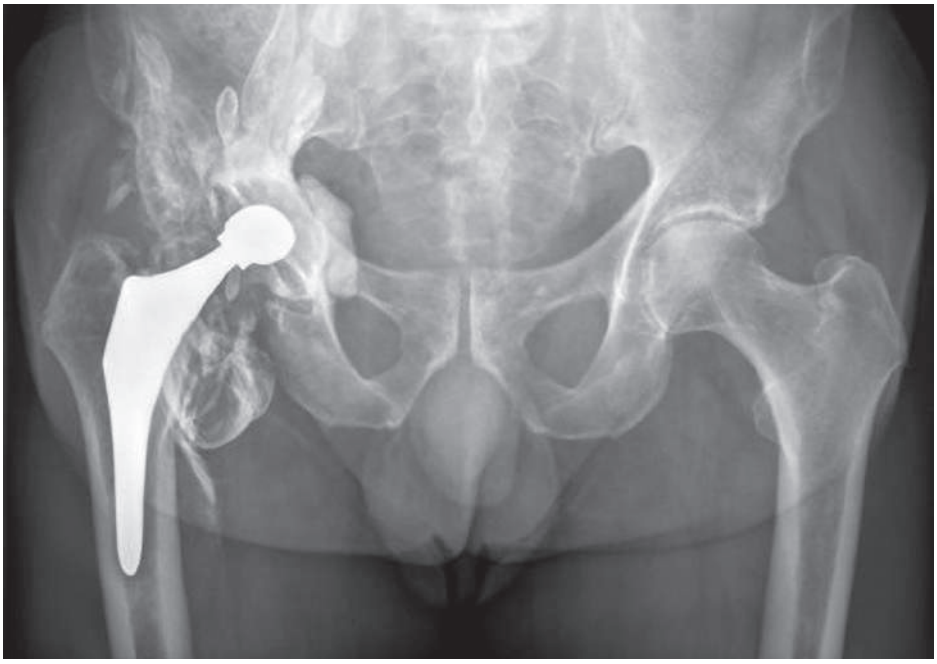

FIGURE 3. AP radiograph, one year postoperative. Peri-articular densities around all components with flattening of the femoral head.

Two weeks later, the patient was admitted in our hospital due to overall degradation of health with abdominal pain, vomiting and diarrhea for which he received broad-spectrum antibiotics, hydrocortisone, and bicarbonate. Furthermore, the patient reported asymmetrical hearing loss, visual impairment, complaints of vertigo, and unintentional weight loss. Within 2 days the patient deteriorated and subsequently died. At autopsy a hypertrofic heart with a weight of 615 gram (n: 350-400g) without any coronary artery disease was observed. No signs of stenosis, thrombi, or dissection of the coronary arteries were found. Serum metal ion analysis, obtained 13 days before death but only available a view days before death, showed excessively high cobalt (596,5 µg/l; normal range: 0 – 2,4 µg/l) and chromium levels (48,8 µg/l; normal range 0 – 2,1 µg/l) (Nederlandse Orthopaedische Vereniging, 2015). It was hypothesized that due to third body wear reaction between ceramic remnants and the metal femoral head severe and ultimately fatal cobalt toxicity occurred with dilated cardiomyopathy and neurotoxicity (hearing loss and visual impairment). The authors have obtained written informed consent from all subjects involved in this case for print and electronic publication of the case report.

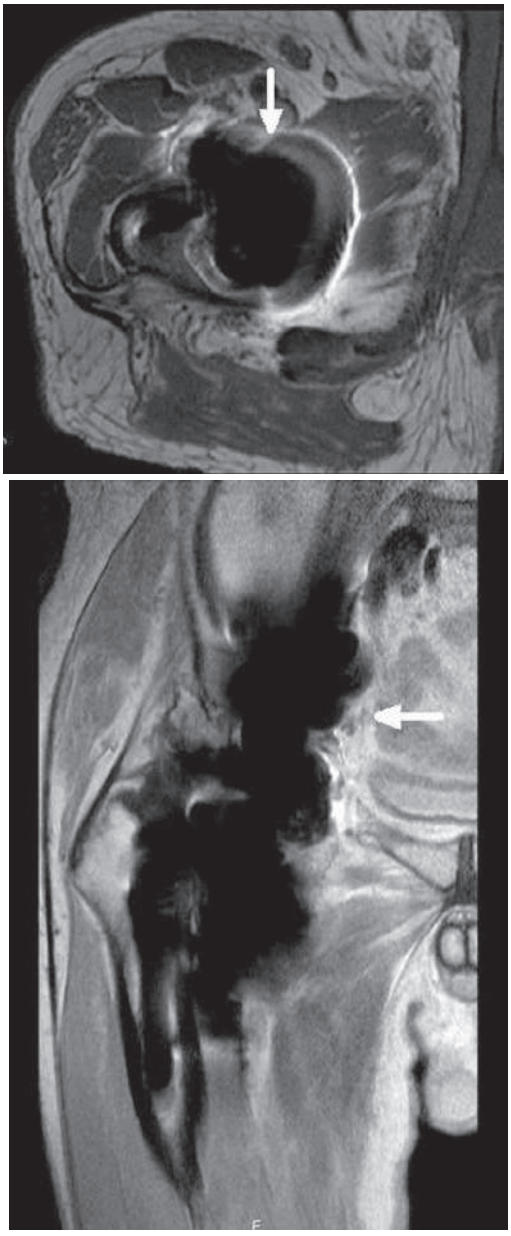

FIGURE 4. MARS-MRI of the right hip with metal wear debris with comprehensive pseudotumor formation (arrow).

DISCUSSION

We demonstrate a very rare case of systemic cobalt toxicity following revision of a failed CoC THA with fatal outcome. The aim of this case report is to emphasize the potential for systemic cobalt toxicity after revision of a broken ceramic liner into a metal-on-polyethylene (MoP) bearing, and its potentially devastating consequences. Our report provides comprehensive imaging including extensive metallosis, peri-articular metal artefacts, flattening of the femoral head, and pseudotumor formation. To the best of our knowledge this is the second reported case of suspected fatal cobalt toxicity secondary to catastrophic wear of a metal-on-polyethylene bearing following revision of a fractured ceramic component. In addition, MRI of the affected hip joint of in these patients has not been published before.

Local and systemic repercussions of cobalt toxicity have been described after THA from various bearing types. Systemic cobalt toxicity after failed metal-on-metal (MoM) articulations (Zijlstra 2009, Zijlstra 2010, Cheung 2016) as well as following failed CoC THA and subsequent revision to a MoP or MoM articular pairing was observed by several authors (Matziolis 2003, Hasegawa 2006, Oldenburg 2009, Zywiel 2013, Cheung 2016, Zywiel 2016, Kim 2016). CoC bearings in THA were introduced as alternative bearing type in young, active patients because of low rates of wear and minimal reactivity to wear debris (Boutin 1972, Zijlstra 2008). Since the introduction in the 1970s, ceramic articulations have undergone several changes aiming to improve fixation, wear characteristics and resistance to component fractures (Matziolis 2003, Zywiel 2013, Varnum 2015, Trebše 2016). The incidence of fractured ceramic components is unknown. Manufacturer retrieval data demonstrate a decreased incidence of femoral head fractures as the production quality improved from 13,4% for components manufactured before 1990 to 0.004% for ceramic Biolox ® femoral heads produced after 1994 (Willmann, 2000). However, clinical studies demonstrate fracture rates varying from 0,5% (40 out of 8,022 CoC THAs) (Traina, 2011) to 1.1% (Hamilton, 2010). Contributing factors responsible for fractures are inappropriate geometry of the head/ neck design, iatrogenic damage during surgery, and in case of acetabular component fractures, by wrong socket positioning – implantation at inappropriate angles (Trebše, 2016).

Revision

Treatment of a failed CoC THA in patients with well-fixed components is challenging and information on the long-term treatment results is scarce (Zywiel 2013, Trebše 2016). After a fracture of a ceramic component both surgeon and patients may be reluctant to implant another CoC articulation given concerns about a re-fracture. In order to eliminate the risk of a re-fracture after revision, surgeons and patients may opt for revision to a MoP articulation. Good longterm results of such revision have been described (Sharma, 2010).

Ideally, all fractured ceramic particles should be removed during revision surgery. Based on the size of the ceramic particles (5 µm in diameter), intraoperative localization and elimination of all particles seems to be not feasible. To remove all fragments of a fractured ceramic implant, the principles of tumor surgery should probably be followed, aiming for macroscopically clear margins with gross synovectomy. Nonetheless, even then microscopic particles may still be present locally. Since it is impractical to enforce this requirement in revision surgery, surgeons have to perform thorough lavage of the soft tissue and extensive synovectomy to remove as much of the ceramic particles as possible. However, it must be expected that ceramic particles will remain in adjacent tissue and may become embedded in a PE inlay, causing abrasive wear of the relatively softer CoCr femoral head (Matziolis 2003, Hasegawa 2006). Subsequently, nanoparticles (third body wear process) from the metal head are released, which undergo corrosion, resulting in the release of cobalt and chromion ions. This could potentially lead to metallosis, subsequent migration of metal degradation products into pericapsular soft tissues, and, in more severe cases, systemic repercussions such as cobalt toxicity (Matziolis 2003, Hasegawa 2006, Oldenburg 2009, Zywiel 2013, Zywiel 2016, Kim 2016). On radiographs loss of the spherical profile of the femoral head component and peri-articular densities might be encountered (Hasegawa 2006, Oldenburg 2009).

Cobalt toxity

Historically, cobalt toxicity became a recognized clinical problem after recreational consumption of beer with a foam-stabilizing agent containing cobalt sulphate or cobalt chloride. The addition of cobalt to beer was considered to play a key role in the development of the low-output 'beer-drinkers' cardiomyopathy, first described in Quebec, Canada, in the nineteen sixties (Morin 1967, Cheung 2016). The clinical presentation during that epidemic was quite similar to the case presented here, with rapidly progressive dysfunction of several vital organs in otherwise fairly healthy persons. Cobalt toxicity also has been described after industrial exposure to cobalt, as well as iatrogenic toxicity following treatment of anaemia with cobalt –chloride tablets (Zywiel 2013, Cheung 2016). In more recent years several cases of cobalt toxicity have been related to cobalt containing implants used in joint arthroplasty, especially in those with overt prosthetic failure or resurfacing of the MoM THA (Cheung, 2016). However, a narrative review on systemic cobalt toxicity after THA revealed that 8 of the 18 reported cases of cobalt toxicity were encountered in patients with non-metal-on-metal articulations (Zywiel, 2016).

Cobalt is a trace metal element which is essential for normal cellular metabolism, but at high levels may lead to reduced human osteoblast activity, changes in osteoprotegerin (OPG) / receptor activator of nuclear factor kappa B ligand (RANKL) ratio leading to oxidative DNA damage, cellular apoptosis , necrosis and oxidative DNA damage (Zijlstra 2012, Cheung 2016). Subsequently, elevated cobalt levels can elicit a multitude of symptoms including cardiomyopathy, hypothyroidism,

polycythemia, cognitive dysfunction, neuropathy, and fatigue (Devlin 2013, Cheung 2016).

This case report should be considered in the light of having certain limitations. First of all, no histological samples of the hip were obtained at autopsy. In addition, no samples of the myocardium were tested for elevated cobalt levels or mitochondrial damage. Mitochondrial injury by cobalt or other trace elements leading to low-output cardiomyopathy has been reported in literature (Cheung, 2016). Lastly, cobalt toxicity as cause of death in this case cannot absolutely confirmed, because significant pre-existing comorbidities such as multiple myeloma and diabetes might have contributed to his death. However, several features support fatal cobalt toxicity. These include very high levels of serum cobalt, measured short before dying, in association with observed cardiomyopathy without significant coronary artery disease at autopsy, the rapid deterioration of several neurologic functions, the recently diagnosed hypothyroidism and the visual symptoms. All above cardiac and non-cardiac organ involvement has been described in association with systemic cobalt toxicity (Cheung, 2016). Furthermore, the patient had no other sources of hard metal contamination apart from the THA, and the excessively elevated serum cobalt levels were measured simultaneously with the radiological appearance of metal artefacts on plain radiographs of the right hip.

Conclusion

We aim to highlight the potential for systemic symptoms of cobalt toxicity in patients without a MoM THA. Revision surgeons should recognize the clinical clues for a systemic cobalt intoxication such as hypothyroidism, polycythemia, cardiomyopathy, cognitive dysfunction, neuropathy, and fatigue, even when there is not a MoM bearing surface. We recommend that a failed CoC articulation should be revised to CoC or ceramic-on-polyethylene (CoP) bearings. Since ceramic particles may become embedded into the articular surface after revision, causing third body wear, relatively softer MoP or MoM bearings should be avoided (Zijwiel 2013, Devlin 2013, Fernández-Valencia 2016). Additionally, the surgeon must assure that contributing factors that increase the risk of a new ceramic fracture should be addressed during revision surgery. In case of revision of a failed CoC THA to a THA with a metal femoral head component, serial cobalt ion monitoring and radiographic screening is strongly advised.

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CORRESPONDENCE: NATIONWIDE REVIEW OF MIXED AND NON-MIXED COMPONENTS FROM DIFFERENT MANUFACTURERS IN TOTAL HIP ARTHROPLASTY

RINNE M. PETERS
LIZA N. VAN STEENBERGEN
RUDOLF W. POOLMAN

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Sir, — I read with great interest the recent paper by Peters et al. (2016) "Nationwide review of mixed and non-mixed components from different manufacturers in total hip arthroplasty: a Dutch Arthroplasty Register study." In this study the authors used the data of a nationwide database to compare the revision rate of primary total hip arthroplasty (THA) with components of the same or different manufacturers. Overall, they found similar medium-term revision rates for both groups. Currently, surgeons implanting not approved mixed combinations do so under their own liability (Michel, 2009). However, some mixed combinations used in high numbers have a similar revision rate compared with matched combinations. In cemented THA, the overall implant survivorship is even better in the mixed group than in the matched group (Tucker, 2015). The hip implant in the National Joint Registry for England, Wales and Northern Ireland that has the best performance is the Exeter stem (Stryker) in combination the Elite Plus Cemented Cup (DePuy Synthes) (National Joint Registry - Annual Report 2014). Interestingly, Peters et al. (2016) found a lower risk of revision in patients that had a mixed stem-head THA before adjustment of confounders (hazard ratio = 0.78, 95% CI: 0.62–0.98). These findings are in contrast to those of Tucker et al. (2015). In the latter study, using a mixed stem-head THA resulted in a higher failure rate. There are different hypotheses for this higher failure rate. Firstly, it could be due to variation regarding the exact dimensions of the trunnion, e.g. differences in taper length, taper angle, manufacturing tolerances, and surface finish (Rajpura and Board 2015). Secondly, in mixed alloy couples more fretting and corrosion at the head-neck junction can be found (Goldberg, 2002). Do the authors have any explanation for the conflicting findings regarding the revision rate in THA with a mixed stem and head in their study compared with Tucker et al.? Another point merits consideration. The authors state that there is a difference in the frequency of mixing different components. The study by Malcolm et al. (2015) refers to off-label use of THA in patients with contraindicated comorbidities (obesity, neurological or mental disease and derangement of metabolism or bony integrity) and does not refer to the mixing of components of different manufacturers. The overall prevalence of mixing THA components seems to be similar in The Netherlands and the UK (11% versus 15%). Some mixed combinations used in high numbers have similar revision rates and some even outperform matched combinations. Regulatory bodies should allow these specific combinations in future guidelines to make sure that we can offer the best available combination to our patients even if this means mixing and matching implants from different manufacturers.

Geert Meermans
Department of Orthopaedic Surgery
Bravis Hospital, Bergen op Zoom, The Netherlands

Sir,— We thank Mr. Meermans for his enriching comments on our study (Peters, 2016). Our unadjusted survival analysis demonstrated that patients with a femoral stem and femoral head component from different manufacturers (mixed stem-head THA) had a slightly lower risk of revision compared to those with non-mixed THAs. However, after adjustment for confounding variables, revision rates were similar. As pointed out rightly, these fi ndings are in contrast to the study of Tucker et al. (2015). Using the National Joint Registry for England, Wales and Northern Ireland, a higher failure rate was found in mixed stem-head THAs compared to non-mixed THAs. We agree that this might be caused by variations in the trunnion. Both studies compare mixed stem-head THA with non-mixed THA. However, these mixed stem-head subgroups contain different combinations of stem and head in the 2 countries. Both publications report findings from observational data and not from experimental designs controlling for known and unknown factors; thus any conclusion should be made with caution.

The second issue raised by Mr. Meermans is the statement concerning variation in the prevalence of off-label arthroplasty worldwide. We want to emphasize that there is no unified definition of off-label arthroplasty. Malcolm et al. (2010) referred to off-label arthroplasty as use of medical devices outside the scope of indications or population subgroups specifically approved by the United States (US) Food and Drug Administration (FDA). The contraindicated total joint arthroplasty criteria used in their study were conditions inherently predisposed to falling, infection, implant loosening, noncompliance, and inadequate fixation such as obesity, neurological disorder and metabolic diseases (Malcolm 2010). The United States does not have an Arthroplasty Register with nationwide coverage. We used a definition for off-label use similar to Tucker et al. (2015) but differing to Malcolm et al (2010); THAs composed of components made by different manufacturers, despite manufactures recommendation that implants were not designed, tested, or validated to be combined (Michel, 2009). We agree that this definition does not refer to patients with contraindicated comorbidities for THA as referred by Malcolm et al. Subsequently, the prevalence's in these 2 studies should not be compared.

Lastly, we completely agree that some mixed combinations might have similar revision rates and some even outperform matched combinations. When nationwide register studies demonstrate superior results for some specific mixed combinations of components used in THA, future guidelines should allow these combinations in order to offer the best available combination for our patients. However, our study compared mixed and non-mixed THA as groups and does not include statements about specific combinations of component. To find definitive answers observational data may be insufficient. Randomized controlled trials nested within registries may overcome the shortcomings of observational data.

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SUMMARY

Total hip arthroplasty (THA) is consistently being identified as one of the most successful procedures in orthopedics with excellent long-term results in terms of implant survival and improvement in quality of life. National arthroplasty registries have made an important contribution to the development and quality improvement of care for patients undergoing hip replacement surgery. Initially, the Dutch arthroplasty registry and other national joint registries were primarily used as a safety instrument with a post-market surveillance function ensuring long-term device follow up. As data collection expanded, the function and aim of arthroplasty registries gradually evolved from merely device registration and monitoring safety, to quality registries, with an important scientific function, linking outcome of arthroplasty to not only the prosthesis, but also to patient (case-mix) and surgically related factors. Furthermore, since registries have been expanded by the registration of Patient Reported Outcome Measures (PROMs), outcome of joint arthroplasty can be evaluated in terms of functional results and health-related quality of life.

In this thesis a number of contemporary issues affecting outcome for patients undergoing primary THA are discussed. The general aim is to assess factors associated with survival of the prostheses and PROMs after primary THA in the Netherlands based on national arthroplasty register data.

Chapter 1 contains a general introduction. The history of THA is described, followed by a brief overview regarding the introduction and development of (inter)national arthroplasty registries. Hereafter, the main objectives are described. This thesis is divided into three parts according to three major determinants of outcome following THA: (1) the *patient*, (2) the *orthopedic surgeon* and (3) the *prosthesis*. In the first part of this thesis (chapter 2 and 3) we aim to determine the effect of patient characteristics or case-mix on the outcome of primary THA. The second part (chapter 4 and 5) focuses on factors predominantly determined by the orthopaedic surgeon (surgically modifiable factors). The third part (chapter 6 and 7) focuses on the prosthesis.

THE PATIENT

In chapter 2, a nationwide arthroplasty study was conducted to assess the association between patient characteristics (or case-mix) on the revision risk after primary THA in the Netherlands. All patients registered in the LROI with osteoarthritis of the hip joint, who received a primary THA between 2007-2018 in a Dutch hospital, were included. We found an increased risk for revision after 1 year in patients with morbid obesity (BMI >40), high ASA scores (III-IV), patients aged 75 or older, and male patients. After 3 years, a high BMI (>40), a previous

operation to the affected hip, Charnley score C, male gender, and a high ASA-score (III-IV) were independently associated with an increased risk for revision. A high ASA score and obesity (especially BMI > 40) were the strongest predictors for revision. This knowledge can help surgeons to identify patients at risk for revision surgery pre-operatively, and counsel them, so that appropriate preventive measures can be taken.

In chapter 3, the association between patient characteristics and improvement of PROMS after primary THA in the Netherlands was assessed. Similar to revision rates, PROMs can be affected by patient characteristics or case-mix factors. We concluded that patients benefiting most in terms of postoperative improvement of self-reported physical functioning, pain relief and quality of life were young, female, with high ASA (III-IV) and BMI score (>30), and without previous operations to the hip.

THE ORTHOPAEDIC SURGEON

The second part of this thesis focuses on factors predominantly determined by the orthopaedic surgeon (surgically modifiable factors). One of these factors is the choice of bearing surface. Hip arthroplasty articulation is differentiated based on the bearing surface of the femoral head and the acetabular component. Increased activity of patients and a younger age at the time of the procedure have sparked the development of alternative bearing surfaces in THA, such as ceramics, oxidized-zirconium, metal-on-metal and highly-crosslinked-polyethylene (HXLPE), in order to further increase implant survival. In chapter 4, we assessed whether these modern bearing surfaces were associated with improved survival compared to traditional metal-on-polyethylene (MoP) THAs. We concluded that there is a significant benefit in mid-term revision rates for ceramic-on-highly-crosslinked-polyethylene (CoHXLPE), oxidized-zirconium-on-(highly crosslinked)-polyethylene (Ox(HXL)PE) and ceramic-on-ceramic (CoC) bearings, compared to MoP bearings. A similar trend was seen in young patients (<60 years). THAs with a CoHXLPE, CoC, and Ox(HXL)PE bearing surface, were less frequently revised compared to traditional MoPE THAs. However, after adjustment for confounding variables, revision rates for all bearing types were not statistically different in young patients, perhaps due to low numbers or short follow-up. Our findings were in line with findings from other registries.
The decision for a surgical approach is predominantly determined by the surgeon's training and preference. In chapter 5, the difference in post-operative improvement in self-reported physical functioning, pain and quality of life, between THAs implanted using the posterolateral, direct lateral, anterolateral, and anterior approach was investigated. We found a larger improvement in self-reported physical functioning 3 months after primary THA in patients operated through the anterior and posterolateral approaches compared with the anterolateral and

direct lateral approaches. Higher pain reduction was observed in patients operated through posterolateral (pain during activity and in rest) and anterior (only during activity) approaches compared with the anterolateral approach. Furthermore, no clinically relevant differences were found between the anterior and posterolateral approaches.

THE PROSTHESIS

The third part of this thesis focuses on the prosthesis. Hip prostheses can differ in design, bearing surface, head size, fixation technique, surface geometry, and modularity. Most THAs are assembled from components produced by the same manufacturer (non-mixed THA). However, certain situations can require orthopedic surgeons to combine a femoral component with an acetabular component from different manufacturers (mixed THA). In chapter 6, we determined the proportion of THAs in the Netherlands that consist of components from different manufacturers. In addition, we investigated the risk for revision for mixed THAs. Using register data, we found that 11% of THAs performed between 2007 and 2014 in the Netherlands were composed of mixed components. Mixed THAs yielded similar medium-term survival rates compared to non-mixed THA. These findings are in line with results from national arthroplasty registries from England, New Zealand and Australia.
In chapter 7, we assessed the rules for mixed THAs based on Dutch and European law. As demonstrated in chapter 6, the use of mixed components is common practice and yield at least comparable results compared to non-mixed combinations. In addition, mixed components can provide important medical benefits for specific patient categories, e.g. in case of altered anatomy or revision surgery. However, the question remains as to whether this is allowable by law. Based on European and Dutch law, it was found that mixing of components can create a liability risk. From a legal perspective it is advised to avoid the use of mixed components when reasonable alternatives are available which have been tested and approved, especially in primary THA. An orthopaedic surgeon who mixes components from different manufacturers could qualify as a "manufacturer of a finished product" and may be held liable without fault if the product appears to be defective. However, to date, no orthopedic surgeon has been held legally responsible or ended up in a lawsuit for the use of mixed components, based on case law review in the United Kingdom, Germany and the Netherlands.

Lastly, if a situation does require the use of mixed components, surgeons are best advised to 1) avoid mixing across the fixed articulation (i.e. use a head from the same manufacturer as the stem), 2) appropriately match sizes across the mobile articulation in hard-on-soft THAs, and 3) avoid mixing in hard-on-hard bearings. Surgeons are likewise advised to gain knowledge on the results of specific

component combinations (e.g. based on arthroplasty registry results) and to explain the choices to the patient in order to receive his/her consent.

Finally, in chapter 8, a general discussion of the aforementioned studies is provided, including our main findings, the value of arthroplasty registry research, the use of PROMs in arthroplasty registry studies and propositions for future research.

MAIN FINDINGS OF THESIS

- Independent risk factors for revision after THA are: comorbidity (ASA score), obesity (BMI), advanced age (≥75 years), and male gender (Chapter 2).
- Higher postoperative improvement on PROMs after primary THA is associated with: a young age (<60 years), female gender, a high ASA-score (III-IV), a high BMI score (BMI ≥30), and no surgical history to the hip (Chapter 3).
- Improved survival rates after primary THA were found for ceramic-on-highly-crosslinked-polyethylene, ceramic-on-ceramic, and oxidized-zirconium-on-(highly-crosslinked)-polyethylene, compared to traditional metal-on-polyethylene (Chapter 4).
- The anterior and posterolateral approach result in a larger improvement in PROMs after primary THA than the anterolateral and direct lateral approach. Differences between approaches were small. There were no clinically relevant differences between the anterior and posterolateral approach in PROM improvements. (Chapter 5).
- Eleven percent of primary THAs in the Netherlands were composed of components from different manufacturers (mixed THAs). Revision rates for mixed- and non-mixed THAs were similar (Chapter 6).
- From a legal perspective it is advisable to avoid mixed THAs when alternatives are available (Chapter 7). To date, no orthopedic surgeon has been held legally responsible or ended up in a lawsuit for the use of mixed components.
- Surgeons are best advised to 1) avoid mixing across the fixed articulation (i.e. use a head from the same manufacturer as the stem), 2) appropriately match sizes across the mobile articulation in hard-on-soft THAs, 3) avoid mixing in hard-on-hard bearings, 4) gain knowledge on the results of specific component combinations and 5) explain the choices to the patient (Chapter 7).

DUTCH SUMMARY | SAMENVATTING

De totale heup prothese (THP) is een van de meest succesvolle behandelingen binnen de orthopedie. De procedure leidt in veel gevallen tot een reductie van pijn en een verbetering van kwaliteit van leven bij patiënten met invaliderende artrose van het heupgewricht. Nationale implantaat registers hebben in belangrijke mate bijgedragen aan de ontwikkeling en kwaliteitsverbetering van de zorg voor deze patiëntengroep. Initieel werden nationale prothese registers zoals het Landelijk Register Orthopedisch Implantaten (LROI) gebruikt als veiligheidsinstrument met een *post-market surveillance* functie voor langdurige monitoring van geplaatste implantaten. Naarmate de hoeveelheid verzamelde gegevens werd uitgebreid, veranderde de functie en het doel van de registers geleidelijk. Tegenwoordig hebben deze registers, naast veiligheid, ook een belangrijke wetenschappelijke functie. Het resultaat van de procedure kan niet alleen worden gekoppeld aan eigenschappen van de geplaatste prothese, maar ook aan patiënt kenmerken (*case-mix*) en chirurgische factoren. Door registratie van door de patiënt ervaren uitkomsten (*Patient Reported Outcome Measures*, PROMs) is het mogelijk om de uitkomsten van de THP te beschrijven met als uitkomstmaat fysiek functioneren en kwaliteit van leven.

In dit proefschrift worden determinanten onderzocht die van invloed zijn op de uitkomst bij patiënten met een primaire THP. De hoofddoelstelling is het identificeren van factoren die geassocieerd zijn met een verbeterde lange termijn overleving en PROMs na het plaatsen van een primaire THP in Nederland op basis van data uit de LROI.

Hoofdstuk 1 bevat een algemene introductie. Hierin wordt de geschiedenis van de THP beschreven, gevolgd door een overzicht van de opkomst en ontwikkeling van nationale implantaat registers binnen de orthopedie. Hierna worden de doelstellingen van de verschillende hoofdstukken separaat beschreven. Het proefschrift is opgedeeld in 3 delen: de invloed van (1) de patiënt (*case-mix*), (2) de orthopedisch chirurg en (3) de prothese, op de uitkomst na het plaatsen van een primaire THP.
In het eerste deel (hoofdstuk 2 en 3) van dit proefschrift wordt het effect van patiëntkenmerken of *case-mix* op de klinische uitkomst na een primaire THP onderzocht. De term *case-mix* verwijst hierbij naar de variatie in de populatie, gerelateerd aan factoren zoals diagnose, leeftijd, geslacht en gezondheidstoestand. Het tweede deel (hoofdstuk 4 en 5) van dit proefschrift richt zich op factoren die overwegend worden bepaald door de orthopedisch chirurg (chirurgisch modificeerbare factoren zoals de lagering (*bearing surface*) en de chirurgische benadering). Het derde deel (hoofdstuk 6 en 7) richt zich op de prothese.

DE PATIËNT

In hoofdstuk 2 werd een nationale, observationele studie beschreven naar de associatie tussen patiëntkenmerken (*case-mix*) en het risico op revisie na een primaire THP in Nederland met behulp van LROI data. Alle geregistreerde patiënten met coxartrose die tussen 2007-2018 een primaire totale heup prothese ontvingen in een Nederlands ziekenhuis werden geïncludeerd. We vonden een verhoogd risico op revisie na 1 jaar bij patiënten met morbide obesitas (BMI> 40), hoge ASA-scores (III-IV), bij patiënten van 75 jaar of ouder en bij mannelijke patiënten. Na 3 jaar waren een hoge BMI (> 40), een eerdere operatie aan de aangedane heup, Charnley-score C, mannelijk geslacht en een hoge ASA-score (III-IV) geassocieerd met een verhoogd risico op revisie. Hierbij waren een hoge ASA-score en obesitas (met name BMI hoger dan 40) de sterkste voorspellers voor revisie. Deze uitkomsten kunnen door orthopedisch chirurgen gebruikt worden om patiënten te identificeren met een verhoogde kans op een her-operatie (revisie), hen te adviseren, en zo mogelijk preventieve maatregelen te nemen.

Net als het risico op revisie (hoofdstuk 2) kunnen PROMs worden beïnvloed door patiëntkenmerken (*case-mix*). In hoofdstuk 3 werd de associatie tussen patiëntkenmerken en de verbetering in fysiek functioneren, kwaliteit van leven en reductie van pijnklachten na het plaatsen van een primaire THP in Nederlands onderzocht. Het verschil tussen de pre- en postoperatieve score werd berekend als delta-PROM en gebruikt als primaire uitkomstmaat. Wij vonden de grootste verbetering (delta-PROM) in fysiek functioneren, kwaliteit van leven en pijnreductie bij patiënten met een hoge ASA-score (III-IV), BMI-score (>30) en bij patiënten zonder voorafgaande operatie van het aangedane heupgewricht.

DE ORTHOPEDISCH CHIRURG

Het tweede deel van dit proefschrift richt zich op factoren die voornamelijk worden bepaald door de orthopedisch chirurg (chirurgisch modificeerbare factoren). Een van deze factoren is de keuze van het type *bearing surface*, ook wel articulatie van een heupprothese. Er wordt onderscheid gemaakt tussen verschillende articulaties op basis van het materiaal van de kop (*femoral head*) en de acetabulum component (*cup*).
Een actievere levensstijl van patiënten met een heupprothese en een jongere leeftijd ten tijde van de procedure hebben geleid tot de ontwikkeling van slijtvastere articulaties om de overleving van totale heup prothesen te verbeteren door het verminderen van slijtage partikels, osteolyse en aseptische loslating. Voorbeelden zijn componenten van keramiek, geoxideerd zirkonium (Ox), metaal-op-metaal (MoM) en *highly crosslinked* polyethyleen (HXLPE). In hoofdstuk 4 hebben we

onderzocht of deze alternatieve articulaties geassocieerd waren met een verbeterde overleving in vergelijking met de traditionele metaal-op-polyethyleen (MoP) lagering. Wij vonden een significant voordeel in het risico op revisie op middellange termijn voor heupprothesen met een keramiek-op-HXLPE (CoHXLPE), keramiek-op-keramiek (CoC) en geoxideerd zirconium met (HXL) PE (OxHXLPE) articulatie in vergelijking met MoP totale heup protheses. De bevindingen zijn in overeenstemming met uitkomsten uit andere registers. Een subanalyse bij patiënten jonger dan 60 jaar liet een vergelijkbare trend zien waarbij CoHXLPE, CoC en OxHXLPE articulaties minder vaak leiden tot een revisie operatie. Echter, na correctie voor *confounders* was dit verschil niet meer statistisch significant, mogelijk als gevolg van lagere aantallen of een relatief korte follow up.

De beslissing voor een chirurgische benadering bij het plaatsen van een THP wordt voornamelijk bepaald door de voorkeur en opleiding van de orthopedisch chirurg. In hoofdstuk 5 hebben we de associatie tussen chirurgische benadering en postoperatieve verbetering in fysiek functioneren, kwaliteit van leven en pijnreductie onderzocht voor patiënten met een primaire THP. We hebben hierbij onderscheid gemaakt tussen THPs geïmplanteerd via de posterolaterale, directe laterale, anterolaterale en anterieure benadering. We vonden een grotere verbetering in fysiek functioneren 3 maanden na een primaire THP bij patiënten geopereerd via de anterieure en posterolaterale benadering in vergelijking met de anterolaterale en directe laterale benadering. Een grotere pijnreductie werd gezien bij patiënten geopereerd via een posterolaterale (pijn tijdens activiteit en in rust) en anterieure (alleen tijdens activiteit) benadering in vergelijking met de anterolaterale benadering. Er werden geen klinisch relevante verschillen gevonden tussen de anterieure en posterolaterale benadering.

DE PROTHESE

Het derde deel van dit proefschrift richt zich op de prothese. Totale heup prothesen kunnen variëren wat betreft type prothese, articulatie, oppervlaktegeometrie, fixatie techniek, modulariteit en kopgrootte. Over het algemeen worden THPs samengesteld uit componenten geproduceerd door één fabrikant (niet-gemixte THP). In bepaalde situaties kan het echter nodig zijn dat de orthopedisch chirurg een steel van fabrikant A combineert met een acetabulum component van fabrikant B (gemixte THP). In hoofdstuk 6 hebben we het aantal en het aandeel THPs in Nederland bepaald, dat bestaat uit componenten van verschillende fabrikanten. Daarnaast onderzochten we het risico op revisie voor beide groepen (gemixte versus niet-gemixte THPs). We hebben een nationale, observationele studie verricht op basis van LROI data (2007-2014) en vonden dat 11% van alle in Nederland geregistreerde THPs bestond uit gemixte componenten. Er was geen verschil in

revisie percentage tussen gemixte en niet-gemixte totale heup protheses. Deze bevindingen zijn in overeenstemming met resultaten afkomstig uit het Verenigd Koninkrijk, Nieuw-Zeeland en Australië.

In hoofdstuk 7 hebben we gekeken naar de regelgeving voor het gebruik van gemixte componenten binnen één THP op basis van het Nederlands en Europees recht. In hoofdstuk 6 is aangetoond dat het gebruik van componenten van verschillende fabrikanten binnen een THP gangbaar is en vergelijkbare resultaten oplevert in vergelijking met niet-gemixte combinaties. Bovendien kunnen gemixte combinaties belangrijke medische voordelen opleveren voor specifieke patiënten, bijvoorbeeld in geval van afwijkende anatomie of tijdens een revisie ingreep. Het is echter de vraag of dit wettelijk is toegestaan. Op basis van de Europese en Nederlandse wetgeving is vastgesteld dat het mengen van componenten een aansprakelijkheidsrisico kan opleveren. Vanuit juridisch perspectief wordt geadviseerd het gebruik van gemixte componenten te vermijden als er een redelijk alternatief beschikbaar is dat is getest en goedgekeurd (*Conformité Européene*; CE) door een daarvoor bevoegde instantie, vooral in geval van een primaire THP. Een operateur die componenten van verschillende fabrikanten combineert kan worden aangemerkt als 'fabrikant van een eindproduct' en kan hierdoor aansprakelijk worden gesteld indien het uiteindelijke product (de THP) gebreken vertoond. Op basis van jurisprudentie uit het Verenigd Koninkrijk, Duitsland en Nederland stellen wij echter vast dat er tot op heden geen orthopedisch chirurg aansprakelijk is gesteld voor het gebruik van gemixte componenten.

Indien een situatie het gebruik van gemixte componenten vereist, adviseren wij op basis van bovenstaande studies en literatuur het volgende: 1) voorkom mixen over steel-kop overgang (dat wil zeggen gebruik een kop en steel van dezelfde fabrikant), 2) combineer de juiste maatvoering in THPs met een kop en kom van verschillende fabrikanten (*mixed head-cup*) in geval van een *hard-on-soft* articulatie, en 3) voorkom het gebruik van gemixte componenten in THPs met een *hard-on-hard* articulatie. Tevens wordt geadviseerd om kennis te vergaren over de resultaten van specifieke componentcombinaties (bijv. op basis van nationale implantaat registers) en om de keuze voor een gemixt implantaat te bespreken met de patiënt om zijn of haar toestemming (*informed consent*) te verkrijgen.

Tenslotte wordt in hoofdstuk 8 een algemene beschouwing over de genoemde studies gegeven, gevolgd door een overzicht van onze belangrijkste bevindingen, de waarde van registeronderzoek, het gebruik van patiënt gerapporteerde uitkomsten in register studies en suggesties voor vervolgonderzoek.

CONCLUSIES

- Onafhankelijke risicofactoren voor revisie na een primaire THP zijn: comorbiditeit (ASA-score), obesitas (BMI), gevorderde leeftijd (≥75 jaar) en mannelijk geslacht (Hoofdstuk 2).
- Een grotere verbetering (delta-PROM) in fysiek functioneren, kwaliteit van leven en pijnreductie na een primaire THP is geassocieerd met een jonge leeftijd (<60 jaar), vrouwelijk geslacht, een hoge ASA-score (III-IV), een hoge BMI-score (BMI ≥30) en patiënten zonder voorafgaande operatie van het aangedane heupgewricht (hoofdstuk 3).
- Het risico op revisie op middellange termijn is significant lager voor heupprothesen met een articulatie bestaande uit keramiek-op-*highly-crosslinked*-polyethyleen, keramiek-op-keramiek en geoxideerd-zirkonium-op-*highly-crosslinked*-polyethyleen, vergeleken met traditioneel metaal-op-polyethyleen (Hoofdstuk 4).
- De anterieure en posterolaterale benadering resulteren in een grotere verbetering van patiënt gerapporteerde uitkomsten na een primaire THP vergeleken met de anterolaterale en directe laterale benadering. De verschillen tussen de benaderingen waren klein. Er zijn geen klinisch relevante verschillen gevonden tussen de anterieure en posterolaterale benadering (Hoofdstuk 5).
- Elf procent van de primaire THPs in Nederland bestaat uit componenten van verschillende fabrikanten (gemixte THP). Revisiepercentages voor gemixte en niet-gemixte THPs waren vergelijkbaar (Hoofdstuk 6).
- Vanuit juridisch perspectief is het raadzaam om het gebruik van gemixte componenten te voorkomen als er redelijke alternatieven beschikbaar zijn. Tot op heden is er geen orthopedisch chirurg aansprakelijk gesteld voor het gebruik van gemixte componenten (Hoofdstuk 7).
- Indien een situatie het gebruik van gemixte componenten vereist adviseren wij: 1) voorkom mixen over steel-kop overgang (dus kop en steel van dezelfde fabrikant), 2) combineer de juiste maatvoering in gemixte protheses met een kop en kom van verschillende fabrikanten in geval van een '*hard-on-soft* articulatie, en 3) voorkom het mixen van componenten in THPs met een '*hard-on-hard*' articulatie, 4) vergaar kennis over de resultaten van specifieke componentcombinaties en 5) bespreek de keuze voor een gemixt implantaat vooraf met de patiënt (*informed consent*).

AUTHORS AND AFFILIATIONS

Adelgunde V.C.M. Zeegers, MD PhD, orthopaedic surgeon, department of orthopedic surgery, Medisch Spectrum Twente, Enschede, The Netherlands

Anton H. Hosman, MD PhD, medical advisor, Forum consult, Amsterdam, The Netherlands

Bas L.E.F. ten Have, MD, orthopaedic surgeon, department of orthopedic surgery, Martini Hospital, Groningen, The Netherlands

Harmen B. Ettema, MD PhD, orthopaedic surgeon, department of orthopedic surgery, Isala hospital, Zwolle, The Netherlands

Julius Wolkenfelt, MD, orthopedic surgeon, Bergman Clinics B.V, The Netherlands

Jantina T. Hiemstra, PhD, lawyer, Hausfeld Advocaten, Amsterdam, The Netherlands

Liza N. van Steenbergen, PhD, epidemiologist, Dutch Arthroplasty Register (Landelijke Registratie Orthopedische Implantaten), 's Hertogenbosch, The Netherlands

Loes W.A.H. van Beers, MSc, physiotherapist, orthopedic researcher, department of orthopedic surgery, OLVG, Amsterdam, The Netherlands

Martin Stevens, PhD, human movement scientist, department of orthopedic surgery, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Mels Hoogendoorn, MD PhD, internist-hematologist, department of internal medicine, Medical Center Leeuwarden, The Netherlands

Paul C. Rijk, MD PhD, orthopaedic surgeon, department of orthopedic surgery, Medical Center Leeuwarden, Leeuwarden, The Netherlands

Pax Willemse, MD, orthopaedic surgeon, department of orthopedic surgery, Medical Center Leeuwarden, Leeuwarden, The Netherlands

Roy E. Stewart, PhD, statistician, methodologist, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Rudolf W Poolman, MD PhD, orthopaedic surgeon, department of orthopedic surgery, OLVG, The Netherlands

Sjoerd K. Bulstra, MD PhD, orthopaedic surgeon, chairman Dutch Orthopedic Society, University Medical Center Groningen, University of Groningen, Groningen

Wierd P. Zijlstra, MD PhD, orthopaedic surgeon, human movement scientist, department of orthopedic surgery, Medical Center Leeuwarden, Leeuwarden, The Netherlands

PEER-REVIEWED PUBLICATIONS

L. de Blouw, R.M. Peters, JJW Ploegmakers. Risk of dislocation during childbirth with total hip arthroplasty: a systematic literature review. *Submitted jan 2021*.

Peters RM, Hiemstra J, Bulstra SK, Zijlstra WP, Stevens M. To mix or not to mix? Medical legal implications of mixed components in Total Hip Arthroplasty. *Acta Orthopaedica **2020**;91(6):624–626*.

Peters RM., van Steenbergen LN, Stewart RE, Stevens M, Rijk PC, Bulstra SK, Zijlstra WP. Which patients improve most after total hip arthroplasty? Influence of patient characteristics on patient-reported outcome measures of 22,357 THAs in the Dutch Arthroplasty Register. *Hip Int. **2020**;online ahead of print.*

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(prof CP van der Schans, prof M Hagedoorn, dr MP Mobach)

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Trajectories of health status in older people
(prof SEJA de Rooij, prof BC van Munster, dr N Smidt)

Roossien C
Sensors@work; towards monitoring physical workload for sustainable employability
(prof MF Reneman, prof GJ Verkerke)

Klerk R de
Development of a wheelchair propulsion laboratory
(prof LHV van der Woude, dr HEJ Veeger, dr RJK Vegter)

Zhou Y
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Tuvdenjorj A
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Kouwijzer I
HandbikeBattle A challenging handcycling event
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Nanninga CS
Home & place making after stroke; exploring the gap between rehabilitation and living environment
(prof K Postema, prof LB Meijering, dr AT Lettinga, dr MC Schönherr)

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PHD PORTFOLIO

Name PhD student: Rinne M. Peters
Ph.D. period: 2017 (jan) – 2021 (jan) (1 year fulltime)
Promotor: Prof. dr. S.K. Bulstra and dr. M. Stevens
Co-promotor: Dr. W.P. Zijlstra

1 - PhD TRAINING

General scientific courses:

2020 (02)	Teaching on the run, UMCG
2017 (07)	Scientific integrity, UMCG
2017 (06)	Basic medical statistics, UMCG
2017 (05)	Managing your PhD, UMCG
2017 (05)	Basic course Rules and Organization for Clinical Researchers (BROK®), UMCG
2015	Biostatistics for clinical research, Massachusetts General Hospital, Boston, USA

Orthopedic / surgical courses:

2021 (05)	Hybrid Oxford Partial Knee Instructional Course
2021 (03)	Total Knee Arthroplasty course, AUMC, Amsterdam
2021 (02)	Perioperative care for elderly - webinar, Infuse
2020 (10)	Exeter hip course – webinar series, Exeter hip unit, Princess Elizabeth Orthopaedic Centre, Exeter, England.
2020 (10)	Communication course, Wenckebach institute, UMCG, Groningen
2020 (1)	Radiation hygiene for medical specialists, LUMC, Sassenheim
2020 (1)	Total Hip Arthroplasty course, Radboud, Nijmegen
2019 (12)	Groninger Dissection course: upper extremity, UMCG, Groningen
2019 (05)	CASH 3: hand-wrist surgery course, UMCG, Groningen
2019 (04)	Advanced Life Support (ALS), Emmen
2018 (12)	Groninger Dissection course: lower extremity, UMCG, Groningen
2018 (06)	AO – Basic Principles of Fracture Treatment, Leeds, United Kingdom
2018 (03)	Basic course laparoscopy and laparoscopic cholecystectomy
2018 (02)	Systematic approach Medical Emergency Situations (SBMS), UMCG
2018 (01)	Advanced Life Support (ALS), Emmen
2018 (01)	CASH 1.1 Basic course general surgery, Nunspeet
2017 (11)	Advanced Trauma Life Support (ATLS), Tilburg

2 – (Inter)national conferences related to orthopedic surgery

Podium presentations:

2020 (11)	9th Congress of International Society of Arthroplasty Registries (ISAR), Adelaide, Australia (digital, 2 presentations)

2020 (08) Scientific symposium, Medical Center Leeuwarden (digital)
2019 (07) 20th EFORT congress, Lisbon, Portugal (2 presentations)
2018 (09) European Hip Society, The Hague (2 presentations)
2018 (03) Scientific symposium, Medical Center Leeuwarden
2018 (01) Dutch Orthopaedic Society, annual congress, Den Bosch (2 presentations)
2017 (02) Dutch Orthopaedic Society, annual congress, Den Bosch
2016 (01) Dutch Orthopaedic Society, annual congress, Den Bosch
2015 (11) Traumadagen, Amsterdam
2015 (09) European Society Shoulder and Elbow Surgery, annual congress, Milan, Italy
2015 (12) New England Hand Society, annual meeting, Sturbridge, MA, United States

Poster presentations:
2015 (11) Traumadagen, Amsterdam
2015 (09) Annual congress European Society for Shoulder and Elbow Surgery, Milan, Italy.

3 - OTHER

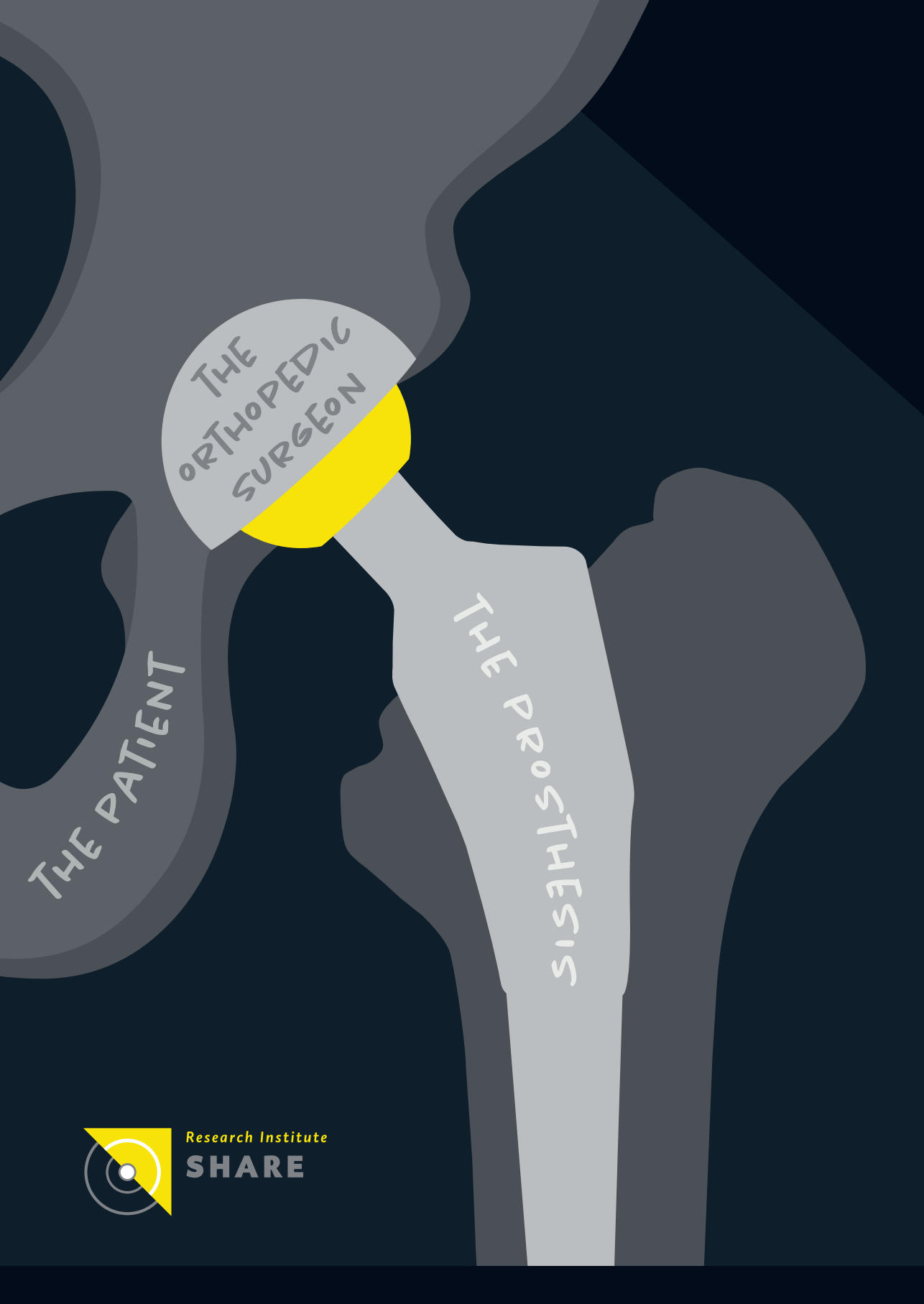
Grants and awards
2021 LROI grant, Dutch Orthopaedic Society
2020 Travel grant Dutch Arthroplasty Registry, Adelaide, Australia (cancelled)
2018 Nominee resident of the year (intern election), Treant Zorggroep, Emmen, Stadskanaal, Hoogeveen
2016 Nominee resident of the year (intern election), Medical Center Leeuwarden
2016 AGIKO research grant, UMCG
2016 Van Rens Fonds, Dutch Orthopaedic Society
2015 Jan Kornelis de Cock Stichting
2014 Marco Polo Grant

Teaching
Master student in Medicine from University Medical Centre Groningen
2020 Lisanne de Blouw. Risk of dislocation during childbirth after THA: a systematic literature review

Memberships
2016 – Dutch Orthopedic Association (NOV)
* Member workgroup AI
2019 – Association of Orthopedic Residents (VOCA)

CURRICULUM VITAE

Rinne Marijn Peters was born on 27 November 1988 in Emmen, the Netherlands. He attended the VWO (Atheneum) at the Carmel college in Emmen (2001-2007). After completing high school he started studying Human Movement Sciences at the University of Groningen. In 2008 he successfully re-applied to study Medicine in Groningen. In 2010 he travelled through Australia and Asia for 4 months together with his girlfriend Sanne. During the course of his master in medicine (2012-2015) he became increasingly interested in orthopaedics. In 2014 he moved to Boston, United States, for a 6-month research rotation at the orthopeadic surgery department of the Massachusetts General Hospital (prof. dr. D. Ring). After his return to the Netherlands, he started working on this thesis evaluating the outcome of primary total hip arthroplasty in the Netherlands using national arthroplasty registry data. After graduating medical school (2015) he commenced his clinical career as a registrar orthopaedic surgery in the Medical Center Leeuwarden (dr. P.C. Rijk). That year he received a grant from the Van Rens Foundation, initiated by the Dutch Orthopaedic Association, in order to pursue his research (dr. W.P. Zijlstra). In 2016 he was admitted to a combined residency and PhD program at University Medical Center Groningen (prof. dr. S.K. Bulstra). Basic surgical training was performed at Treant Zorggroep in Emmen, Hoogeveen and Stadskanaal (dr. M. van den Berg) (2018-2019). He continued his training in orthopaedic surgery at University Medical Center Groningen (prof. dr. S.K. Bulstra and prof. dr. P.C. Jutte) (2019-2021). In 2021 he will continue his residency training at the Medical Center Leeuwarden (dr. P.C. Rijk). Rinne lives together with Sanne *op* Erica. They recently became parents of their beautiful daughter Fenne.



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