Improving outcomes after total hip arthroplasty

The impact of patient factors, surgical approach & implant design

Loes W.A.H. van Beers

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TABLE OF CONTENTS

Chapter 1

General introduction

Total Hip Arthroplasty

A total hip arthroplasty (THA) is one of the most performed orthopaedic interventions. A THA is a highly successful treatment for patients with end-stage hip osteoarthritis (OA). (1-6) OA is the most common reason for total hip replacement.(7) In the Netherlands, 86% of all THAs is performed in patients with OA.(8) A THA reduces pain and disability and improves function in patients suffering from hip joint disorders. With the increasing life expectancy of the population, the number of patients who will undergo a THA is likely to increase.(9) Worldwide, the number of total hip replacements is increasing. This not only depends on the incidence and prevalence of osteoarthritis, but is also influenced by factors such as a higher life expectancy, a more active lifestyle in elderly people and improved outcomes of arthroplasties. In 2021 31.500 primary THAs were performed in the Netherlands(10), despite the restrictions following the COVID-19 pandemic. These restrictions resulted in fewer surgeries being performed as elective care was downscaled and operation room capacity was restricted.

Guidelines recommend that the indication for a THA should be based on factors such as pain, loss of function, radiographic changes and individual contra-indications. It is recommended to involve the patient in a shared decision making process. Since the number of THAs continues to rise, with the population getting older and more patients suffering from comorbidities, it is important to evaluate the influence of patient selection on treatment outcomes.
Although THA has been recognized as a reliable and successful intervention for patients with end-stage OA, studies have identified at least 7% of patients who remain dissatisfied.(5, 11-13) There are several potential factors influencing poor outcome after THA. A common factor is pain, which can be due to prosthesis-related factors, implant position, and patient-related factors. Other well-known reasons for poor outcome are limited function and complications such as dislocation, infections or implant loosening. To address poor outcomes after THA, additional research is necessary.

Which outcome measures are important?

Evaluating outcomes after THA is very important to assess its effectiveness. In this thesis we focus mostly on outcomes that are relevant for patients, such as physical functioning, satisfaction, pain and general health, measured with patient reported outcome measures (PROMs). In addition we focus

on outcomes which are also interesting for surgeons and clinical practice, including radiological outcomes, complications, implant survival and costs. Each of these outcomes has advantages and disadvantages, which are detailed below. It is recommended to follow patients up at several moments in time.

Patient reported outcomes

Patient Reported Outcome Measures (PROMs) are instruments that can be used to measure the symptoms of OA or outcomes after a treatment from the patients' perspective. This direct assessment of the patients'experience is an important advantage. PROMs are self-administered questionnaires, filled out by patients to score their pain, physical function or quality of life. PROMs can have several types of bias, such as: response bias (giving socially desirable answers); recall bias (difficulty recalling their experience or symptoms); interpretation bias (patients may interpret questions differently, leading to differences in responses). Other disadvantages of PROMs are limited clinimetric properties such as floor or ceiling effects. The advice from the Dutch guideline is to register PROMs prior to the THA and during follow-up at 3 and 12 months postoperatively. In general, PROMs assessing general health and joint specific outcomes should be measured. To measure general health, the EuroQol-5 Dimension (EQ-5D) and a numeric rating scale (NRS) for pain in rest and during weight bearing are suggested.(14) For joint specific outcomes, the Hip disability and Osteoarthritis Outcome Score - Physical function Shortform (HOOS-PS) is advised for use in daily practice, potentially combined with the Oxford Hip Score since this is an internationally widely used PROM.(15-17)

Radiological outcomes

Besides the use of PROMs, radiological outcomes still have an important role to assess the outcome of a THA. Radiological images are frequently used to assess the outcome of THAs, such as implant positioning, stability and wear. Roentgenograms are the most commonly used to assess these outcomes. They can provide detailed images of the implant components and facilitate in the early detection of complications such as fractures, dislocation or implant loosening. Disadvantages of using radiological outcomes in research is that it may not always correlate with clinical outcomes or patient reported outcomes.

Complications and implant survival

Complications after THA can have a serious impact on patients and are also affecting the healthcare providers. In general, a subdivision can be made into early and late complications. Early complications can consist of peri-prosthetic infection, dislocation, peri-prosthetic fracture, deep venous thrombosis or nerve injury. Typical late complications are aseptic loosening, low grade infections and implant wear, although also the above mentioned complications can occur in a later stage. Complications can lead to revision surgery, in which at least one of the implant components is revised. In the Netherlands, the most common reasons for revision surgery within 3 years after surgery are infection (39% of all revisions), dislocation (25% of all revisions), peri-prosthetic fractures (19% of all revisions) and loosening (15% of all revisions).(18) In research, it is challenging to collect all complications thoroughly and reliable. Outcomes about revision surgeries are generally expressed in implant survival. Implant survival refers to the time of implant to extraction of an implant. Implant survival is usually used as a quality criterion for implants.(19) Implant survival can be influenced by a multitude of factors, including patient characteristics as age, fixation type (cemented or uncemented), surgical technique (such as surgical approach) or implant design.

National implant registries are of significant importance in studying implant survival. These registries have been developed to aggregate valuable information about implants and their survival. Implant registries are of additional value compared to local hospital complication databases, since they contain information on all implant related revision surgeries. For instance, if a patient underwent revision surgery in a different hospital than where the initial prosthesis was implanted, this is registered in the arthroplasty registry and not necessarily in the complication database of the index surgery. Prospective registries are important for monitoring the safety and quality of implants. In addition, they also provide unique opportunities to complement clinical research databases with long term data at low costs and less burden for patients. There are also disadvantages with the collection of data on complications. It can be challenging to achieve a standardized and systematic registration of complications, due to variability in definitions and classifications. Furthermore, complications may not be consistently documented, potentially leading to reporting bias and compromising completeness of data.

Costs

With the growing number of THAs performed, both in the Netherlands and worldwide, the healthcare costs will also increase. It is more and more important to evaluate the costs that are associated with medical treatments and interventions. This plays an important role in value-based healthcare, which

aims to maximize the benefits of healthcare interventions while minimizing costs. It may be difficult to obtain cost data and it may not always be comparable across different healthcare settings. Average costs of a total hip arthroplasty depend on which factors are taken into account. Factors can be the number of days a patient is hospitalized, the amount of radiographs taken, the number of follow-up visits etcetera. These costs may vary between hospitals and include both direct and indirect costs. Direct costs contain for instance costs for the hospital, medical specialists and implants. Indirect costs consist of factors such as loss of income, a decreased quality of life, rehabilitation costs and informal care. In the United States, the reported average costs of a THA are $25.000,- and of a revision THA $50.000,-.(20) In the Netherlands, estimates vary between €6500 and €22.000.(21, 22) In conclusion, the costs of a THA are substantial. When innovations in primary THA focus on increasing patient satisfaction and lowering complication rates, this might result in a decrease in revision surgeries, which ultimately will reduce costs.

How to evaluate outcomes?

Innovations in total hip arthroplasty, such as changes in surgical approaches or improvements in implants are focusing on improving outcomes after THA. Before implementing these innovations in clinical practice, it is essential to conduct rigorous clinical trials to evaluate safety, (cost-)effectiveness and efficacy. For new implants, it is recommended, also by the Dutch Arthroplasty Registry, to perform a stepwise introduction into clinical practice, including pre-clinical testing, clinical radiostereometric analysis (RSA) trials, larger multicenter clinical trials and post-market surveillance in national registries.(23, 24)

To evaluate outcomes of innovations in THA, the quality of the conducted scientific research is very important. In evidence based medicine, randomized controlled trials (RCTs) are considered as the highest level of evidence in primary studies.(25-28) RCTs are given the highest level of evidence because they are designed to be unbiased and have less risk of systematic errors.(29) For example, by randomly allocating subjects to two or more treatment groups, these types of studies correct for known and unknown confounding factors that may otherwise bias results. Therefore, RCTs are the best method to evaluate surgical techniques, implant designs for improvements in outcomes of treatments. Although traditional RCTs have many advantages, there are also practical limitations. Conducting a RCT comes with significant costs. Personnel costs for the research staff are considerable, since most RCTs are highly time consuming. The inclusion of patients is a time consuming process,

since patients are not always willing to be randomized. This is an important factor in the delay of RCTs. A solution can be to randomize at hospital level instead of at an individual patient level. Another limitation of RCTs is that they usually are conducted in a highly controlled setting, which might limit generalizability. Furthermore, the follow-up length is limited, to prevent very high costs and a high burden for patients. New study designs such as registry nested randomized trials are a useful option to overcome these limitations.

Aims and outline of this thesis

This thesis consists of three parts, aiming to provide insight in different factors that influence outcomes in patients with a hip prosthesis:

- Part I: The influence of patient factors on outcomes after THA.
- Part II: The influence of surgical approach on outcomes after (hemi) arthroplasty of the hip.
- Part III: The influence of implant design on outcomes after THA.

Part I. The influence of *patient factors* on outcomes after THA.

This first part consists of two chapters, in which the influence of patient factors on outcomes after THA is investigated. Not all patients experience similar improvement of physical function after THA. The variance in outcome might be explained by patients' preoperative characteristics.

- **Chapter 2** is a systematic review into predictors of physical function after THA.
- **Chapter 3** describes a prediction model with data of our own hospital, to test the predictive variables that were found in chapter 2 and in other literature. This chapter aims to identify predictors for physical function 1 year after THA, with the ultimate goal to facilitate doctors and patients in making a shared decision and managing expectations with respect to THA surgery.

Part II. The influence of *surgical approach* on outcomes after (hemi) arthroplasty of the hip.

In this part, the influence of surgical approach on outcomes after hemiarthroplasty and THA is investigated. This part consists of two chapters, containing a systematic review and a registry study. Hemiarthroplasty is a commonly used procedure in the treatment of displaced proximal femur fractures. The posterolateral approach (PLA) and direct lateral approach (DLA) are the most commonly used approaches for inserting a hemiarthroplasty in the treatment of femoral neck fractures.

- **Chapter 4** is a systematic review to provide an updated overview and critical appraisal of the available evidence of these two surgical approaches in hemiarthroplasty. We focus on outcomes most relevant for patients, with the patients' independence in activities of daily living (ADL) as primary outcome.
- **Chapter 5** describes the effect of different surgical approaches for primary THA on patient reported outcome measures (PROMs). The anterior, anterolateral, straight lateral and posterolateral approaches are studied, using data from the Dutch arthroplasty registry (LROI).

Part III. The influence of *implant design* on outcomes after THA.

This third part consists of four chapters, investigating the influence of implant design on outcomes after THA.

- **Chapter 6** contains the detailed study protocol of the Curved versus Straight Stem Uncemented Total Hip Arthroplasty Osteoarthritis Multicenter (CUSTOM) trial. It is a maximally blinded randomized controlled trial (RCT), comparing two implants: a conventional straight stem and a short curved stem, and their influence on physical functioning after primary THA. The primary outcome of this RCT was the Hip disability and Osteoarthritis Outcome Score (HOOS) 3 months after primary THA in patients up to 70 years old. Naturally, mid-term and long-term results of prosthetic stems are valuable. For that reason, patients were followed up to 5 years after surgery.
- **Chapter 7** describes the long term outcomes of the CUSTOM trial. Data up to 5 years follow-up is analyzed. Additionally, a survival analysis is performed with data from the Dutch arthroplasty registry. Data up to 12 years postoperatively was available for our analysis. The studies mentioned in part 2 report that the posterolateral approach is a commonly used approach, showing good

results. A known disadvantage of this approach are hip dislocations. Hip dislocations are one of the main reasons for early revision surgery after THA. Besides the high impact on patients, dislocations also lead to high costs for healthcare and society. The next two chapters aim to investigate the influence of cup design on dislocation.

- **Chapter 8** is a systematic review to evaluate the evidence about dual mobility cups and unipolar cups and their influence on hip dislocation.
- **Chapter 9** extensively describes the study protocol of the REDEP trial: 'REduce Dislocations in Elderly Patients'. This is a RCT nested in the Dutch arthroplasty registry. The primary objective is to investigate whether there is a difference in the number of hip dislocations following primary THA, using the posterolateral approach, with a dual mobility cup compared to a standard unipolar cup in elderly patients one year after surgery. Alongside, the number of revision surgeries, patient-reported outcome measures (PROMs), and cost-effectiveness is studied.

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Part 1

The influence of *patient factors* on outcomes after total hip arthroplasty

Chapter 2

Predictors of physical functioning after total hip arthroplasty: a systematic review

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Abstract

Objective

The objective of this systematic review of the literature was to identify the predictors of functional outcome after total hip arthroplasty (THA).

Method

A systematic literature search in Web of Science, CINAHL, EMBASE and PubMed was conducted on 23 June 2015. The articles were selected based upon their quality, relevance and measurement of the predictive factor. The level of evidence of all studies was determined using the GRADE rating scheme.

Results

The initial search resulted in 1092 citations. After application of the inclusion and exclusion criteria, 33 articles met our eligibility criteria and were graded. Included studies were classified as level of evidence low (11), moderate (17) or high (5). Of the included studies, 18 evaluated body mass index (BMI), 17 evaluated pre-operative physical function, 15 evaluated age, 15 evaluated gender, and 13 evaluated comorbidity. There was strong evidence suggesting an association between BMI, age, comorbidity, preoperative physical functions, and mental health with functional outcome after THA. There was weak evidence suggesting an association between quadriceps strength and education with functional outcome after THA. The evidence was inconsistent for associations with gender and socio-economic status and functional outcome following THA. We found limited evidence suggesting that alcohol consumption, vitamin D insufficiency and allergies were predictors of functional outcome following THA.

Conclusion

We have identified multiple predictors of functional outcome after THA, which will enable general practitioners and orthopedic surgeons to better predict the improvement in physical functioning for their patients with THA. They can use this information to provide patient-specific advice regarding the referral for THA and the expected outcomes after THA. Further research with consistent measurement tools, outcomes and duration of follow-up across studies is needed to confirm the influence of these factors.

Introduction

Total hip arthroplasty (THA) is a surgical procedure performed to reduce pain and improve function in patients with osteoarthritis (OA) of the hip. According to the Agency for Healthcare Research and Quality, more than 305000 total hip replacements are performed each year in the USA[1]. Following THA, the majority of patients experience reductions in pain, improvements in function, and better health related quality of life[2]. However, not all patients achieve the same level of functional improvement after THA. Specifically, more than 30% of patients undergoing THA report moderate-to-severe activity limitations 2 years post-THA [3]. It is unclear which factors are associated with these limitations in function [4;5].

In the last decade, many studies have been published investigating the predictors of functional outcome after THA. Young et al. published a systematic review on this topic in 1998. Since then considerable research has been published on predictors of functional outcome which justifies a new systematic review[6]. Therefore, we conducted a systematic review of predictors of mid-term and long-term functional outcome after THA.

Methods

Registration

This systematic review is registered at Prospero (http://www.crd.york.ac.uk/PROSPERO/) with registry number CRD42015016929.

Selection criteria

Studies that met the following criteria were included in our review: (1) included patients undergoing a THA; (2) included physical functioning was an outcome measure; (3) had at least one variable that was considered as a predictor of physical functioning; and (4) was written in English. We did not select a time period.

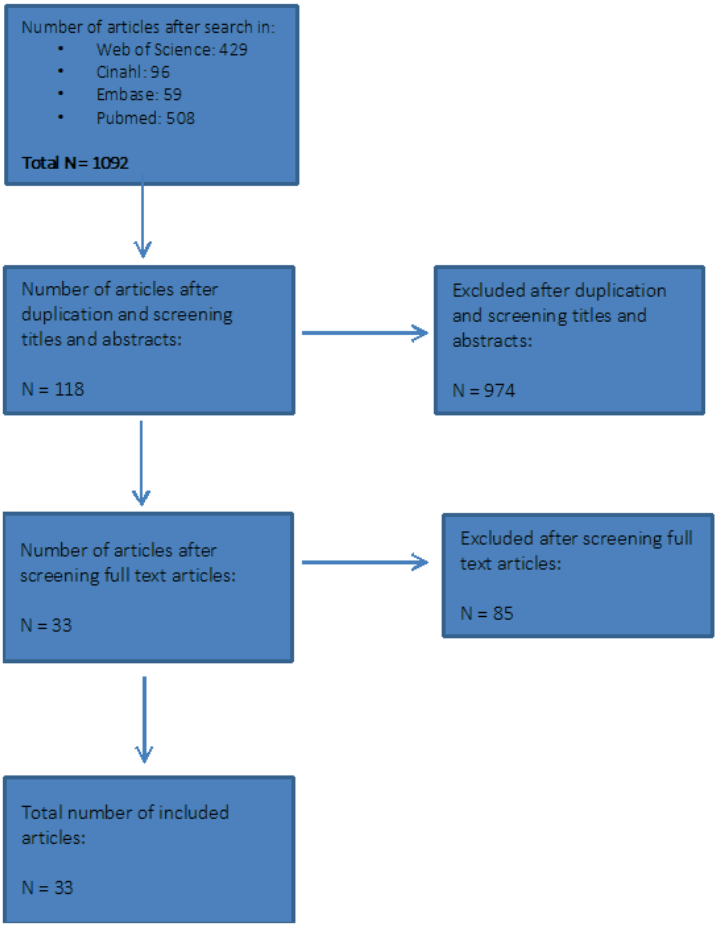
Search strategy

With the guidance of an independent medical librarian we conducted a literature search through four medical databases: Web of Science; CINAHL; EMBASE and PubMed. This literature search was performed on 23 June 2015. In Web of Science we used the following search terms: TOPIC: (total hip arthroplasty) *AND* TOPIC: (predictor*). In CINAHL we searched for: (MM "Arthroplasty, Replacement, Hip") AND predictor*. In Embase we searched for: exp hip arthroplasty/ exp prediction/ or exp predictor variable/ exp prognosis/ or exp functional assessment/ or exp treatment outcome/ or exp daily life activity/. In PubMed we searched for ("Arthroplasty, Replacement, Hip"[Majr] OR "Hip Prosthesis"[Majr]) AND (predictor* OR risk Factor* OR risk assessment OR predictive value of tests OR prognostic factor* OR Prognostic*) AND (HOOS OR "hip disability and osteoarthritis outcome score " OR WOMAC OR "Western Ontario and McMaster Universities Arthritis Index" OR "Harris hip score" OR HHS OR SF-12 OR short form 12 OR SF 36 OR "short form 36" OR Trendelenburg OR TUG OR "timed up and go" OR "Oxford hip score" OR "IOWA hip score" OR "Functional recovery score" OR FRS OR AFI OR "Hospital for special surgery" OR AAOS OR "Charnley hip score" OR HSS OR LEGS OR "Mayo clinical hip score"). The results of these four different searches were combined in Reference Manager and duplicates were discarded.

Study selection

Two of the authors (LWAHVB and TP) independently screened the titles and abstracts of all the articles using the above mentioned selection criteria. Both reviewers screened the full-text articles of the articles found eligible in the first round. A third author (LDB) compared these results and in case of different opinions, consensus was reached. The study selection procedure is schematically presented in Figure 1.

Figure 1: Flowchart of the study selection procedure



Data extraction

One of the authors (LDB) extracted the data, which was double checked by a second author (LWAHVB). From each article, the following information was extracted: (1) predictor variable; (2) author; (3) year of publication; (4) level of evidence; (5) number of patients; (6) measurement tools used; (7) follow-up period; (8) significance level; (9) association between predictor variable and outcome measure; (10) predictor level of measurement (Table 1). The results were categorized by predictor variable.

Methodological quality assessment

The level of evidence of all studies was determined by one of the authors (LDB) with the GRADE rating scheme (http://www.gradeworkinggroup.org).

Measurement tools

We aimed to include all predictors mentioned in previous studies, and did not limit ourselves to the most common predictors. Some of the widely used measurement tools to define functional outcome are the Harris Hip Score (HHS)[7], Oxford Hip Score (OHS)[8,9], Short Form-36 (SF-36)[10], Lower Extremity Functional Scale (LEFS)[11], Timed Up and Go test (TUG)[12;13] and the Western Ontario and McMaster Universities OA Index (WOMAC)[14]. We used all these measurement tools as outcome in this study.

Best evidence synthesis

A follow-up period up to 24 months was considered as 'short term' and a follow-up period of more than 24 months was considered as 'long term'. Results were divided into four categories of evidence: Strong evidence: at least 60% of the studies, with a minimum of three studies, describing the same significant (p-value <.05) association. Weak evidence: (1) only two studies describe the same significant association; (2) three studies describe the same association of which two are significant and one is not significant (p-value >.05). Limited evidence: (1) only one study available; (2) more studies available of which none found a significant association. Inconsistent evidence: all other scenarios[15]. No conclusions can be drawn in this literature review when no or inconsistent evidence is available.

This systematic review conforms to the PRISMA statement[16].

Results

Selection and methodological quality

The initial search resulted in 1092 citations (Figure 1) and 33 articles met our eligibility criteria. The articles included were designated as level of evidence low (11), moderate (17) or high (5) (Table 1).

Table 1 Methodological quality of included studies

Study	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GRADE
Kessler, 2007	observational study	not serious	not serious	not serious	not serious	strong association	moderate
Villalobos, 2012	observational study	not serious	not serious	not serious	not serious	none	low
Nankaku, 2013	observational study	not serious	not serious	not serious	not serious	strong association	moderate
Slaven, 2012	observational study	not serious	not serious	not serious	not serious	none	low
Moran, 2005	observational study	n.a.	not serious	not serious	not serious	strong association	moderate
Stevens, 2012	observational study	not serious	not serious	not serious	not serious	strong association	moderate
Wang, 2010	observational study	not serious	not serious	not serious	not serious	none	moderate
Dowsey, 2010	observational study	serious	not serious	not serious	not serious	strong association	low
Judge, 2014	observational study	not serious	not serious	not serious	not serious	very strong association	high
Bergschmidt, 2010	observational study	not serious	not serious	not serious	not serious	strong association	moderate
Jones, 2012	observational study	not serious	not serious	not serious	not serious	strong association	moderate
Smith, 2012	observational study	not serious	not serious	serious	not serious	strong association	moderate
Judge, 2013	observational study	not serious	not serious	not serious	not serious	very strong association	high
Bischoff, 2004	observational study	not serious	not serious	not serious	not serious	strong association	moderate
Gandhi, 2010	observational study	serious	not serious	not serious	not serious	none	low
Nilsdotter, 2003	observational study	not serious	serious	not serious	not serious	strong association	low
Davis, 2012	observational study	not serious	not serious	not serious	not serious	very strong association	high
Hamilton, 2012	observational study	not serious	not serious	not serious	not serious	none	low
Quintana, 2009	observational study	not serious	not serious	not serious	not serious	strong association	moderate
Nilsdotter, 2002	observational study	not serious	not serious	not serious	not serious	strong association	moderate
Dowsey, 2014	observational study	not serious	not serious	not serious	not serious	very strong association	high
Lavernia, 2010	observational study	serious	not serious	not serious	not serious	strong association	low

Study	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GRADE
Mahomed, 2002	observational study	not serious	not serious	not serious	not serious	strong association	moderate
Vogl, 2014	observational study	not serious	serious	not serious	not serious	n.a.	low
Clement, 2011	observational study	not serious	not serious	not serious	not serious	very strong association	high
Johansson, 2010	observational study	not serious	not serious	not serious	not serious	strong association	moderate
Fortin, 2002	observational study	not serious	not serious	not serious	serious	strong association	low
Badura-Brzoza, 2009	observational study	not serious	not serious	not serious	not serious	strong association	moderate
Holstege, 2011	observational study	not serious	not serious	not serious	not serious	strong association	moderate
Schafer, 2010	observational study	not serious	not serious	not serious	n.a.	strong association	low
Graves, 2014	observational study	not serious	not serious	not serious	not serious	strong association	moderate
Lavernia, 2012	observational study	not serious	not serious	not serious	n.a.	none	low
Lavernia, 2013	observational study	not serious	not serious	not serious	not serious	strong association	moderate

GRADE: Grading recommendations assessment development and evaluation
High: true effect lies close to the estimate of the effect
Moderate: true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low: true effect may be substantially different from the estimate of effect
Very low: true effect is likely to be substantially different from the estimate of effect

Measures of functional outcome

Multiple outcome measures were used across these studies including the HHS, OHS, SF-36 physical function (PF), LEFS, TUG and the WOMAC score. The follow-up period ranged from 3 to 72 months with an average of 18 (SD 17) months (Table 2).

Table 2: Characteristics of all included studies.

author, year, nr	age baseline	n of pts	female (n, %)	inclusion criteria	follow-up time	measurement tool
Badura-Brzoza, 2009, nr 42	61(54-75)	156	59, (58%)	prim THA, OA	6 months	SF-36 PF
Bergschmidt, 2010 nr 113	66(58- 74)	100	48 (50%)	prim THA, OA	6-12-24 months	HHS
						WOMAC
						SF-12
Bischoff, 2004, nr 51	73,1(65-93)	922	60%	OA, prim THA >65 y	3 years	WOMAC PF
Clement, 2011, nr 101	68,1(65-74)	1312	n.a	Prim OA, THR	12 months	OHS
						SF-12
Davis, 2011, nr 100	69(34-96)	1617	994	cemented THA	5 years	HHS
						SF-36 PF
Dowsey, 2010, nr 32	68,6/67/65,6	471	60,70%	prim THA OA	12 months	HHS
						SF-12 PF
Dowsey, 2014, nr 15	68,4	835	60,10%	prim THA	12 months	SF-12
Fortin, 2002, nr 145	65,7	222	59%	prim THA OA	2 years	WOMAC
						SF-36
Hamilton, 2012, nr 17	68,1	1410	57,20%	prim THA OA	6-12 months	OHS
						SF-12
Gandhi, 2010, nr 30	63,2(13.7)	636	53,50%	<18y, prim OA,	3.3 years	WOMAC
						SF-36 PF
Graves, 2014, 29	59,5	459	61,00%	THA OA	10,4 months	WOMAC
						SF-36
Holstege, 2011, nr 102	72,7(6,8)	55	41 (74,5)	THA OA	3 months	WOMAC PF
Johansson, 2010, nr 114	67(7)	75	36(48%)	THA OA	6-12-24 months	HHS
						WOMAC
						SF-36

author, year, nr	age baseline	n of pts	female (n, %)	inclusion criteria	follow-up time	measurement tool
Jones, 2012, nr 90	68,2(10,9)	231	138 (60%)	prim THA	6-36 months	WOMAC
Judge, 2013, nr 14	70	1431	887(62%)	OA	1-6 years	OHS
Kessler, 2007, nr 131	63,6	76	44,8 (59%)	THA OA	3 months	WOMAC
Lavernia, 2012, nr 73	70	60	48(80%)	prim THA	3-24 months	QWB-7
						SF-36 PF
						WOMAC
						HHS
Lavernia, 2013, nr 81	62	191	70	prim THA	12 months	WOMAC
						SF-36
Lavernia, 2010, nr 103	61(15)	532	59%	THA	6-7 years	SF-26
						HHS
						WOMAC
Mahomed, 2002, nr 149	66(9)	103	57(55%)	THA OA	6 months	WOMAC PF
						SF-36 pcs
Moran, 2005, nr 136	68	749	61%	prim THA	6, 18 months	HHS
Nankaku, 2013, nr 83	60,4	204	173	THA OA	6 months	ambulatory status
Nilsdotter, 2002, nr 147	71	148	83	THA OA	3-6-12 months	WOMAC
						SF-36
Nilsdotter, 2003, nr 52	71	211	106	prim THA	3,6 years	WOMAC PF
Quintana, 2009, nr 35	69,1	788	381(48%)	prim THA OA	6-24 months	SF-36 PF
						WOMAC
Schafer, 2010, nr 110	61	1007	55%	prim THA	6 months	WOMAC
Slaven, 2012, nr 15	68,2(8,2)	40	22 (55%)	prim THA	6 months.	LEFS
Smith, 2012, nr 92	68,5(9,9)	1683	n.a	prim THA	3 years	HHS

author, year, nr	age baseline	n of pts	female (n, %)	inclusion criteria	follow-up time	measurement tool
Stevens, 2012, nr 22	70,3(8,2)	653	74,20%	prim THA, OA	52,4 weeks	WOMAC
Villalobos, 2012, nr 80	62,39(13,6)	63	35(55,55%)	prim THA	3 months	HHS
						OHS
						WOMAC
						SF-12 PF
Vogle, 2014, nr 108	68	321	58%	prim THA	6 months	WOMAC
Wang, 2010, nr 107	61,65	97	62,40%	OA/osteonecrosis	3-12-24 months	WOMAC

SF-36 PF= Short Form 36 physical function; WOMAC= Western Ontario and Mcmaster universities Osteoarthritis Index; LEFS=lower extremity functional scale; OHS= Oxford Hip Score; THA= total hip arthroplasty; PF= physical function; HHS= Harris Hip Score; N of pts= number of patients;

Predictive factors of functional outcome

Body Mass Index

Eighteen studies evaluated body mass index (BMI) as a potential predictor of functional outcome after THA [17-34] (Table 3). A total of 14432 patients were included in all articles concerning the impact of BMI, with a mean follow-up time of 22 months. The applied levels of measurement of BMI were continuous, dichotomous or categorical.

The measurement tools used to determine the functional outcome were WOMAC score, HHS, OHS, LEFS, SF-12 PF and the ambulatory status. The classification of a high BMI ranged from >28 to >35 kg/m^2.

Of the 18 studies, 13 found a significant association[17-19;22;23;25;27-31;33;34]. Twelve studies evaluated the short-term functional outcome of which eight studies[17;20;22;25;28;30;33;34] found a significant negative association and one article a significant positive association[31]. Of the seven studies evaluating the long-term functional outcome, five articles found a significant negative association[18;19;23;27;29]. Studies were designated as level of evidence low (5), moderate (9) or high (4).

Since more than 60% of the studies report a significant negative association, there is strong evidence of a negative association between BMI and short-term and long-term functional outcome after THA. These results were consistent when we only considered the studies with high or moderate level of evidence according to GRADE.

TABLE 3: Studies reporting BMI as possible predictor of funtional outcome after THA.

Author & Year	GRADE	N of pts	Measurement tool	FU-period (months)	Significance level (p-value)	Association	*Predictor Level of Measurement*
Kessler, 2007	moderate	76	WOMAC	ST (3m)	0.49	no	*cont (BMI)*
Villalobos, 2012	low	63	SF-12 PCS WOMAC HHS OHS	ST (3m)	**0.004*** **0.041*** 0.793* 0.428*	pos pos no no	*dich* *(1: BMI >28 2: BMI ?28)*
Nankaku, 2013	moderate	204	ambulatory status	ST (6m)	0.06	no	*cont (BMI)*
Slaven, 2012	low	40	LEFS	ST (6m)	**n.a.**	neg	*dich* *(1: BMI >34 2: BMI ?34)*
Moran, 2005	moderate	749	HHS	ST (6m) ST (18m)	**0.02** **0.001**	neg neg	*cont (BMI)*
Stevens, 2012	moderate	653	WOMAC	ST (12m)	**0.001**	neg	*cont (BMI)*
Wang, 2010	moderate	97	WOMAC	ST (12m)	0.11	no	*cont (BMI)*
Dowsey, 2010	low	471	HHS SF-12 PCS	ST (12m)	**<0.01** **0.05**	neg neg	*cat (3)* *(1: BMI <30 2: BMI 30-39 3: BMI >=40*
Dowsey, 2014	high	835	HHS	ST (12m)	**<0.0001**	neg	*cont (BMI)*
Judge, 2014	high	4413	OHS	ST (12m)	**0.003**	neg	*cat (5)* *(1: BMI 18.5-25 2: BMI 25-30 3: BMI 30-35 4: BMI 35-40 5: BMI >40*
Bergschmidt, 2010	moderate	100	HHS	ST (24m)	**0.007**	neg	*cat (3)* *(1: BMI <26 2: BMI 26-29 3: BMI >29*
Jones, 2012	moderate	231	WOMAC	ST (6m) LT (36m)	**0.001** no	neg no	*dich* *(1: BMI >35 2: BMI ?35)*

Smith, 2012	moderate	1683	HHS	LT (36m)	**<0.01**	neg	*cont (BMI)*
Judge, 2013	high	1431	OHS	LT (36m)	**<0.001**	neg	*cont (BMI)*
Bischoff, 2004	moderate	922	WOMAC PF	LT (36m)	**n.a.**	neg	*cont (BMI)*
Gandhi, 2010	low	636	WOMAC	LT (39m)	0.06	no	*cont (BMI)*
Nilsdotter,2003	low	211	WOMAC PF	LT (42m)	**0.03**	neg	*cont (BMI)*
Davis,2011	high	1617	HHS	LT (60m)	**<0.001**	neg	*cont (BMI)*

*** All significant results are bold; studies that used change in function as outcome are marked with *; cont= continuous; dich=dichotomous; cat= categorical; SF-36 PF= Short Form 36 physical function; WOMAC= Western Ontario and Mcmaster universities Osteoarthritis Index; LoE: level of evidence; LEFS=lower extremity functional scale; OHS= Oxford Hip Score; THR= total hip replacement; ST=short-term; LT=long-term; BMI= Body Mass Index; HHS= Harris Hip Score; N of pts= number of patients; FU= follow-up; n.a.= not applicable; pos= positive; neg= negative**

Age

Fifteen studies evaluated age as a possible predictor of functional outcome after THA[17;18;21;23;24;26-30;32;34-37] (Table 4). A total of 9234 patients were included in all studies that identified age as a possible predictor, with a mean follow-up time of 19 months. The applied levels of measurement of age were continuous, dichotomous or categorical.

The measurements tools used to determine the functional outcome were WOMAC score, HHS, OHS, SF-36 PF, SF-12 PF and the ambulatory status. Different classifications of greater age were used, ranging from >60 to >75 years.

Of the 15 studies, 10 found a significant association[21;23;24;26;27;29;30;34;36;37]. Ten studies evaluated the short-term functional outcome of which six studies found a significant negative association [24;26;30;34;36;37]. The other four studies did not find a significant association. Of the six studies evaluating the long-term functional outcome, five studies found a significant negative association [21;23;29;36;37]. Studies were designated as level of evidence low (4), moderate (9) or high (2).

Since more than 60% of the studies report a significant negative association, there is strong evidence of a negative association between high age and short-term and long-term functional outcome after THA. These results were consistent when we only considered the studies with high or moderate level of evidence according to GRADE.

TABLE 4: Studies reporting age as possible predictor of functional outcome after THA.

Author & Year	GRADE	N of pts	Measurement tool	FU-period (months)	Significance level (p-value)	Association	*Predictor Level of Measurement*
Kessler, 2007	moderate	76	WOMAC	ST (3m)	**0.03**	neg	*cont (age)*
Nankaku, 2013	moderate	204	ambulatory status	ST (6m)	yes	neg	*dich (1: age >67.5 2: age ?67.5)*
Slaven, 2012	low	40	LEFS	ST (6m)	no	no	*dich (1: age >68.5 2: age ?68.5)*
Hamilton, 2012	low	1410	OHS SF-12	ST (6m) ST (12m)	x x	no no	*cont (age)*
Quintana, 2009	moderate	788	WOMAC PF	ST (6m) ST (24m)	0.41 **0.001**	no neg	*dich (1: age >70 2: age ?70)*
Stevens, 2012	moderate	653	WOMAC	ST (12m)	**0.01**	neg	*cont (age)*
Wang, 2010	moderate	97	WOMAC	ST (12m)	no	no	*cont (age)*
Dowsey, 2014	high	835	HHS SF-12 PCS	ST (12m)	**<0.0001** **0.003**	neg neg	*cont (age)*
Nilsdotter, 2002	moderate	148	WOMAC PF SF-36	ST (12m)	**0.004** **0.002**	neg neg	*dich (1: age >72 2: age ?72)*
Bergschmidt, 2010	moderate	100	HHS WOMAC SF-12	ST (12m)	>0.097 >0.097 >0.097	no no no	*cat (3) (1: age <60 2: age 60-69 3: age >69*
Bischoff, 2004	moderate	922	WOMAC PF	LT (36m)	x	no	*dich (1: age >75 2: age ?75)*
Judge, 2013	high	1431	OHS	LT (36m)	**n.a.**	neg	*cat (3) (1: age <50 2: age 50-60 3: age >60*

Smith, 2012	moderate	1683	HHS	LT (36m)	**<0.001**	neg	*cont (age)*
Nilsdotter, 2003	low	211	WOMAC PF	LT (43m)	**0.002**	neg	*cont (age)*
Gandhi, 2010	low	636	WOMAC SF-36	LT (39m)	**<0.05** **<0.05**	neg	*cont (age)*

*** All significant results are bold; studies that used change in function as outcome are marked with *; cont= continuous; dich= dichotomous; cat= categorical; SF-36 PF= Short Form 36 physical function; WOMAC= Western Ontario and Mcmaster universities Osteoarthritis Index; LoE: level of evidence; LEFS=lower extremity functional scale; OHS= Oxford Hip Score; THR= total hip replacement; ST=short-term; LT=long-term; BMI= Body Mass Index; HHS= Harris Hip Score; N of pts= number of patients; FU= follow-up; n.a.= not applicable; pos= positive; neg= negative**

Gender

Fifteen studies evaluated gender as a possible predictor of functional outcome after THA [17;18;21;22;24;26-30;32;34;36-38](Table 5). A total of 7156 patients were included in all studies that evaluated gender as a possible predictor, with a mean follow-up time of 23.3 months. The measurement tools used to determine the functional outcome included the WOMAC score HHS, LEFS, SF-36 and the ambulatory status.

Of the 15 studies, 7 found a statistically significant association between preoperative physical function and functional outcome [21;28-30;32;37;38]. Nine studies evaluated the short-term functional outcome of which four studies found a significant association [28;30;32;37]. Six studies evaluated the long-term functional outcome of which three found a significant association [21;29;38]. All studies were designated as level of evidence low (5), moderate (9) or high (1).

In four of the seven studies with a significant outcome, being male predicted a better outcome [29;30;32;37] whereas three studies reported being female as a predictor of better functional outcome [21;28;38]. This demonstrates inconsistent evidence for an association between gender and functional outcome after THA.

TABLE 5: Studies reporting gender as possible predictor of functional outcome after THA.

Author & Year	GRADE	N of pts	Measurement tool	FU-period (months)	Significance level (p-value)	Association	*Predictor Level of Measurement*
Kessler, 2007	moderate	76	WOMAC	ST (3m)	n.a.	no	*dich (1: men 2: woman)*
Nilsdotter, 2002	moderate	148	WOMAC SF-36	ST (3m) ST (12m)	0.7	no	*dich (1: men 2: woman)*
Nankaku, 2013	moderate	204	ambulatory status	ST (6m)	0.10	no	*dich (1: men 2: woman)*
Slaven, 2012	low	40	LEFS	ST (6m)	**0.039**	pos, woman	*dich (1: men 2: woman)*
Quintana, 2009	moderate	788	SF-36 PF	ST (6m) ST (24m)	**n.a.** n.a.	pos, men no	*dich (1: men 2: woman)*
Bergschmidt, 2010	moderate	100	HHS	ST (12m)	n.a.	no	*dich (1: men 2: woman)*
Stevens, 2012	low	653	WOMAC	ST (12m)	**0.002**	pos, men	*dich (1: men 2: woman)*
Dowsey, 2014	high	835	HHS	ST (12m)	0.06	no	*dich (1: men 2: woman)*
Wang, 2010	moderate	97	WOMAC	ST (16.8m)	**0.0001**	pos, men	*dich (1: men 2: woman)*
Bischoff, 2004	moderate	922	WOMAC PF	LT (36m)	no	no	*dich (1: men 2: woman)*
Jones, 2012	moderate	231	WOMAC	LT (36m)	0.118	no	*dich (1: men 2: woman)*
Smith, 2012	moderate	1683	HHS	LT (36m)	**<0.001**	pos, men	*dich (1: men 2: woman)*

Gandhi, 2010	low	636	WOMAC SF-36 PF	LT (39m)	no **<0.05**	no pos, woman	*dich* *(1: men 2: woman)*
Lavernia, 2010	low	532	WOMAC PF	LT (42m)	**<0.001***	pos, woman	*dich* *(1: men 2: woman)*
Nilsdotter,2003	low	211	WOMAC PF	LT (66m)	0.37	no	*dich* *(1: men 2: woman)*

*** All significant results are bold; studies that used change in function as outcome are marked with *; dich= dichotomous;**
SF-36 PF= Short Form 36 physical function; WOMAC= Western Ontario and Mcmaster universities Osteoarthritis Index;
LoE: level of evidence; LEFS=lower extremity functional scale; OHS= Oxford Hip Score; THR= total hip replacement; ST=short-term;
LT=long-term; BMI= Body Mass Index; HHS= Harris Hip Score; N of pts= number of patients; FU= follow-up; n.a.= not applicable
pos= positive; neg= negative

Preoperative physical function

Seventeen studies evaluated preoperative physical function as a possible predictor of functional outcome after THA [17;23;25-29;32;34-37;39-43] (Table 6). A total of 9689 patients were included in all studies that evaluated preoperative physical function, with a mean follow-up time of 16 months. The applied levels of measurement of preoperative physical function were continuous, dichotomous or categorical.

The WOMAC score [14] was the measurement tool most used to determine the preoperative physical function [17;27;32;36;37;39-41;43]. Other measurement tools used were the HHS, TUG, OHS, SF-36, SF-12 and the ambulatory status.

Of the 17 studies, 16 found a statistically significant correlation between preoperative physical function and functional outcome. Fourteen studies evaluated the short-term outcome of which 13 reported a significant association. Three studies evaluated the long-term outcome; all three found a significant association. The only study that did not report a significant association, was a study with a small patient group that used the TUG to determine the preoperative physical function[28]. Studies were designated as level of evidence low (5), moderate (9) or high (3).

As more than 60% of the studies report a significant negative association, there is strong evidence of a short-term and long-term association between the preoperative physical function and the functional outcome after THA.

TABLE 6: Studies reporting pre-operative physical function as possible predictor of functional outcome after THA.

Author & Year	GRADE	N of pts	Measurement tool	FU-period (months)	Significance level (p-value)	Association	*Predictor Level of Measurement*
Quintana, 2009	moderate	788	WOMAC PF SF-36 PF	ST (6m)	**<0.001**	yes	*cont (WOMAC + SF-36*
Slaven, 2012	low	40	TUG	ST (6m)	n.a.	no	*dich (successful/unsuccessful)*
Mahomed, 2002	moderate	103	WOMAC PF+P SF36 PF	ST (6m)	**<0.05** **<0.05**	yes	*cont (WOMAC + SF-36)*
Hamilton, 2012	low	1410	OHS SF-12	ST (6m) ST (12m)	yes	yes	*cont (OHS)*
Nankaku, 2013	moderate	204	ambulatory status	ST (6m)	**n.a.**	yes	*dich (TUG score 10)*
Vogl, 2014	low	281	WOMAC	ST (6m)	**n.a.**	yes	*cont (WOMAC)*
Bergschmidt, 2010	moderate	100	WOMAC SF-36	ST (12m)	<0.022 0.003	yes	*cat (3)* *1: HHS ,<48 2: HHS 48-59 3: HHS >59*
Clement, 2010	high	1312	OHS SF-12	ST (12m)	**0.001***	yes	*cont (OHS)*
Johansson, 2010	moderate	75	HHS WOMAC SF-36	ST (12m)	**?0.006** **<0.001** **?0.005**	yes yes yes	*cat (3)* *1: HHS ,<45 2: HHS 45-55 3: HHS >55*
Nilsdotter, 2002	moderate	148	WOMAC SF-36	ST (12m)	**<0.0001**	yes	*dich* *low quartile vs high quartile WOMAC*
Dowsey, 2014	high	835	HHS	ST (12m)	**<0.0001**	yes	*cont (HHS)*
Wang, 2010	moderate	97	WOMAC	ST (16.8m)	**0.0001**	yes	*cont (WOMAC PF)*
Moran, 2005	moderate	749	HHS	ST (18m)	**n.a.**	yes	*cont*

Fortin, 2002	low	222	WOMAC SF-36	ST (24m)	**n.a.** **n.a.**	yes yes	*dig (1: high WOMAC 2. low WOMAC*
Smith, 2012	moderate	1683	HHS	LT (36m)	**<0.001**	yes	*cont (HHS)*
Nilsdotter,2003	low	211	WOMAC PF	LT (42m)	**0.007**	yes	*dich* *low quartile vs high quartile SF-36 PF*
Judge, 2013	high	1431	OHS	LT (60m)	**<0.001**	yes	*cont (OHS)*

*** All significant results are bold; studies that used change in function as outcome are marked with *; cont= continuous; dich= dichotomous; cat= categorical; SF-36 PF= Short Form 36 physical function; WOMAC= Western Ontario and Mcmaster universities Osteoarthritis Index; LoE: level of evidence; OHS= Oxford Hip Score; THR= total hip replacement; ST=short-term; LT=long-term; BMI= Body Mass Index; HHS= Harris Hip Score; N of pts= number of patients; FU= follow-up; n.a.= not applicable; pos= positive; neg= negative**

Comorbidity

Thirteen studies evaluated comorbidity as a possible predictor of functional outcome after THA (Table 7). A total of 9,363 patients were included in all studies that evaluated comorbidity as a possible predictor, with a mean follow-up time of 23.3 months. The applied levels of measurement of preoperative status were continuous, dichotomous or categorical.

The measurements tools used to determine the functional outcome were the WOMAC score, HHS, LEFS, SF-36 and the ambulatory status. Most studies used the number of comorbidities or American Society of Anesthesiologists (ASA) grade as predictor of functional outcome. Other studies used the presence of a specific comorbidity as a predictor like cardiac disease, coronary heart disease and thromboembolism.

Of the 13 studies, 11 found a significant negative association [18;21;22;25;27;29;30;32-34;37;39;42]. Seven studies evaluated the short-term outcome of which six reported a significant negative association[22;22;23;25;30;32;34;39;42]. Six studies evaluated the long-term outcome, of which five found a significant negative association[18;21-23;29]. All articles were designated as level of evidence low (2), moderate (8) or high (3).

Since more than 60% of the studies report a significant negative association, there was strong evidence of a negative association between comorbidities and short-term and long-term functional outcome after THA.

TABLE 7: Studies reporting comorbidity status as possible predictor of functional outcome after THA.

Author & Year	GRADE	N of pts	Measurement tool	FU-period (months)	Significance level (p-value)	Association	*Predictor Level of Measurement*
Quintana, 2009	moderate	788	WOMAC PF SF-36 PF	ST (6m)	n.a. n.a.	no	*cat(3)* *1: 0 comorb 2: 1-2 comorb 3: >2 comorb*
Mahomed, 2002	moderate	103	WOMAC PF+P	ST (6m)	**<0.05**	neg	*cont* *(number of comorbidities)*
Moran, 2005	moderate	749	HHS	ST (6m) ST (18m)	**n.a.**	neg	*dich* *(presence of coronary heart disease and previous thromo-embolism)*
Stevens, 2012	moderate	653	WOMAC	ST (12m)	**0.01**	neg	*cat(3)* *1: 0 comorb 2: 1-2 comorb 3: >2 comorb*
Clement, 2010	high	1312	OHS SF-12	ST (12m)	**0.01**	neg	*cont* *(number of comorbidities)*
Dowsey, 2014	high	835	HHS	ST (12m)	**0.0001**	neg	*cont* *(age adjusted CCI)*
Wang, 2010	moderate	97	WOMAC	ST (16.8m)	**0.0246**	neg	*dich* *(1: >0 comorbidities 2: 0 comorbidities)*
Jones, 2012	moderate	231	WOMAC	LT (36m)	**0.012**	neg	*dich* *(1; 0 cardiac diseases* *2: >0 cardiac diseases)*
Bischoff, 2004	moderate	922	WOMAC PF	LT (36m)	**n.a.**	neg	*dich* *(1; >2 chron diseases* *2. 0-1 chronic diseases)*
Smith, 2012	moderate	1683	HHS	LT (36m)	**<0.001**	neg	*cont* *(asa grade)*
Gandhi, 2010	low	636	WOMAC SF-36 PF	LT (39m)	**<0.05**	neg	*cont* *(number of comorbidities)*

Nilsdotter,2003	low	211	WOMAC PF	LT (42m)	0.08	no	*dich* *(1: >1 comorbidities 2: 0-1 comorbidities)*
Judge, 2013	high	1431	OHS	LT (60m)	**0.001**	neg	*cont* *(number of comorbidities)*

*** All significant results are bold; studies that used change in function as outcome are marked with *; cont= continuous; dich= dichotomous; cat= categorical; SF-36 PF= Short Form 36 physical function; WOMAC= Western Ontario and Mcmaster universities Osteoarthritis Index; LoE: level of evidence; LEFS=lower extremity functional scale; OHS= Oxford Hip Score; THR= total hip replacement; ST=short-term; LT=long-term; BMI= Body Mass Index; HHS= Harris Hip Score; N of pts= number of patients; FU= follow-up; n.a.= not applicable; pos= positive; neg= negative**

Other predictors

The predictors that were evaluated in five studies or less are displayed in Table 8. Five studies evaluated *mental health* as a possible predictor of functional outcome after THA, with a total of 3563 patients [18;23;34;37;44]. All four studies evaluating the short-term functional outcome found a significant positive association [23;34;37;44]. Both studies that evaluated the long-term outcome found a significant positive association. Since more than 60% of the studies report a significant positive association, there is strong evidence of an association between good mental health and better short-term physical function outcome after THA. Because only two studies evaluated the long-term outcome, this evidence is weak.

Two studies evaluated *alcohol consumption* as a predictor of functional outcome [18;45]. Neither of them found a significant result and therefore none show evidence of an association.

The two studies evaluating *quadriceps strength* as a possible predictor [26;46] looked at the short-term functional outcome and both found a significant association. Therefore the evidence for an association is weak.

All three studies that evaluated *educational level* as a possible predictor, found a significant association [18;39;47]. Two studies evaluated the short-term outcome and both found a significant association [39;47]. One study evaluated the long-term effect and found a significant association [18]. All three studies used the WOMAC score to measure the functional outcome. These results show weak evidence for a short-term association, and incomplete evidence for a long-term association.

One study reported *socio-economic status* (SES) as a predictor, using the SES score as measurement tool[34]. They did not find a significant result and therefore show limited evidence of an association.

The influence of having more than 3 *allergies* on the short-term functional outcome was reported in one study [48]. Patients with allergies had diminished improvements on SF-36 PCS and WOMAC scores 6.5 months after THA. There was limited evidence of an association between having more than 3 allergies and functional outcome.

Vitamin-D insufficiency as a predictor of functional outcome after THA was evaluated in one study [49]. A preoperative 25-hydroxyvitamin-D3 plasma level of under 30 ng/ml, predicted a worse HHS 11 months postoperative. Because no other studies evaluated vitamin-D insufficiency as a possible predictor, this result shows limited evidence of an association.

TABLE 8: All predictors that are evaluated in five studies or less

predictor	Author & Year	GRADE	N of pts	Measurement tool	FU-period (months)	Significance level (p-value)	Association	*Predictor Level of Measurement*
Mental health	Badura-Brzoza, 2009	moderate	102	SF-36 PCS	ST (6m)	**0.005**	neg	*cont (anxiety as a trait)*
	Quintana, 2009	moderate	788	SF-36 PF WOMAC P	ST (6m) ST (24m)	**<0.001** **0.002**	yes	*cont (SF-36 MH score)*
	Dowsey, 2014	high	835	HSS	ST (12m)	**<0.0001**	yes	*cont (SF-12 MH score)*
	Bischoff, 2004	moderate	922	WOMAC PF	LT (36m)	**n.a.**	yes	*dich (1: >60 pts on the SF-36 MH score 2: ?60pts on SF-36 MH score)*
	Judge, 2013	high	916	OHS	ST (12m) LT (60m)	**0.045**	yes	*cont (SF-36 MH score)*
Alcohol consumption	Bischoff, 2004	moderate	914	WOMAC PF	LT (36m)	**n.a.**	no	*dich (1: >1 alcoholic drinks per day 2: 0-1 alcoholic drinks per day)*
	Lavernia, 2012	low	191	WOMAC	LT (72m)	**n.a.**	no	*cat (3) (1: nondrinkers 2: occasional drinkers 3: moderate drinkers)*
Quadriceps strength	Holstege, 2011	moderate	55	WOMAC PF	ST (3m)	**0.004**	pos	*cont (knee extensor strength)*
	Nankaku, 2013	moderate	204	ambulatory status	ST (6m)	**n.a.**	pos	*dich (1: > 1.25 N m/kg 2: ?1.25 m/kg knee extensor strength)*
Education	Schafer, 2010	low	1007	WOMAC	ST (6m)	**n.a.**	pos	*dich (1; >12 years school 2: <9 years school)*
	Mahomed, 2002	moderate	103	WOMAC PF+P	ST (6m)	**0.007**	pos	*cont (level of education)*
	Bischoff, 2004	moderate	922	WOMAC PF	LT (36m)	**n.a.**	pos	*dich (1:college education 2:less than college education)*

Socio economic status	Dowsey, 2014	high	835	HHS	LT (12m)	0.63	no	*cont (SES score)*
Allergies	Graves, 2014	moderate	459	WOMAC PF SF-36 PCS	ST (6.5m)	**0.04** **0.0002**	neg	*dich (>3 allergies)*
Vitamin-D insufficiency	Lavernia, 2013	moderate	60	HHS WOMAC	ST (11m)	**0.002** 0.478	neg	*dich (25-hydroxyvitamin-D3) (1; >30 ng/ml 2: <30 ng/ml)*

*** All significant results are bold; cont= continuous; dich= dichotomous; cat= categorical; SF-36 PF= Short Form 36 physical function; WOMAC= Western Ontario and Mcmaster universities Osteoarthritis Index; LoE: level of evidence; LEFS=lower extremity functional scale; OHS= Oxford Hip Score; THR= total hip replacement; ST=short-term; LT=long-term; BMI= Body Mass Index; HHS= Harris Hip Score; N of pts= number of patients; FU= follow-up; n.a.= not applicable; pos= positive; neg= negative**

Discussion

In this systematic literature review, we sought to provide a clear overview of a range of patient-related predictors of functional outcome after THA.

Key findings

Our review found strong evidence of an association of BMI, age, comorbidity, preoperative physical function and mental health with functional outcome after THA. Weak evidence was found for the predictors like quadriceps strength and education. Inconsistent evidence was found for the predictors like gender and socio-economic status. Limited evidence was found for the predictors like alcohol consumption, vitamin-D insufficiency, and allergies.

In our review, thirteen studies found a significant negative association between BMI and functional outcome after THA. A prior review of Young et al [6] found the same significant negative association. Although the review of Young et al and our current review come to the same conclusion, the clinical impact of this outcome is still questionable. A large study by Judge et al., showed a small significant correlation between a high BMI and a worse functional outcome, but concluded that the total improvement in function outweighs the small lack of improvement caused by a high BMI[33].

Although our review shows strong evidence of an association between BMI and functional outcome, different classifications of high BMI were used. Owing to these different classifications, it is difficult to define a specific BMI that predicts who will do well after THA. We could not conduct a meta-analysis since different classifications of BMI were used and there was heterogeneity in outcome instruments. Therefore future research on the impact of BMI should use clearly defined outcomes that are consistent across studies.

In our review, eight of the 14 studies found an association between higher age and poorer functional outcome, therefore age is an important factor predicting functional outcome. Some articles used a linear regression analysis for age. When looking at age, it is not only interesting to see the effect of high age, but also of low age. Therefore linear regression analysis might not be the best statistical analysis with variables as age or BMI. There is no consensus among studies about what specific age limit is recommended for THA. This current review shows inconclusive evidence of an association between gender and functional outcome because six out of 14 studies found a statistically significant result.

Three studies reported being female led to a better functional outcome [21;28;38]. The other four significant articles found the opposite result where being male had a positive association with

functional outcome after THA [29;30;32;37]. The results are contradictory and the differences may be attributable to confounding factors.

Pre-operative physical function was found to be a strong predictor of long-term functional outcome. With the exception of one study reporting the TUG test as an outcome, better preoperative physical function was consistently associated with better long-term physical function [28]. This might be due to the use of TUG score as measurement tool[28]. The WOMAC score was the measurement tool most used to define the pre-operative status (nine times)[17;27;32;36;37;39-41;43]. Other preoperative measurement tools that were good predictors of functional outcome were the HHS, OHS, SF-12 PF, SF-36 PF, and ambulatory status.

Of the 13 studies that evaluated comorbidity as a possible predictor of functional outcome, 11 found a significant negative association [18;21-23;25;29;30;32;34;37;39;42]. Comorbidity can be measured in several ways, for example: the number of comorbidities, the presence of a specific comorbidity, the Charlson index [50] and the Elixhauser comorbidity measure [51]. Comorbidities can affect the true functional outcome after THA but can also affect the score on the measurement tool. For example: if a patient is unable to walk to the grocery store after a THA due to a lung disease, his functional outcome score will be lower despite a possible good functioning total hip. Except for one article, all studies found a significant negative effect. Therefore having comorbidities can be seen as a predictor of negative functional outcome.

All five studies that evaluated mental health as a predictor of functional outcome found a statistically significant positive association. Four of these studies used SF-36 MH [52] as the measurement tool to measure mental health[18;23;34;37]. These results show strong evidence of a positive association between mental health and short-term functional outcome after THA. The two studies reporting quadriceps strength as a predictor had both small sample sizes which can affect the external validity of the studies[26;46]. Therefore this evidence is weak and more research must be done on the effect of quadriceps strength.

Three studies evaluated education as predictor of functional outcome. Mahomed et al[39] and Bischoff et al[18] used the level of school education as a predictor, and Schafer et al[47] used years of education as a predictor. Because education is in part a surrogate of socioeconomic status, this might also indicate that low socioeconomic status is a factor associated with poor functional outcome. Dowsey et al however did not find a correlation between socioeconomic status and functional outcome[34]. Future research is needed on various components of socioeconomic status to specify the impact on

functional outcome. As only one study evaluated each of the allergies[48] and vitamin-D insufficiency[49] as possible predictors of functional outcome, no conclusions can be drawn.

Previous systematic reviews

The previous systematic review of Young et al. concluded that important research remained to be done to examine the magnitude and interaction of patient factors on the outcome of THA[6]. The review of Young et al. used only one database (MEDLINE) and is more than 15 years old. Young et al. also looked at implant survivorship. In our systematic review we used multiple databases (Web of Science, CINAHL; EMBASE and PubMed) and reported only patient related-predictors evaluated in the literature.

Strengths and Limitations

We included a range of patient related predictors and did not limit ourselves to the most common predictors. This led to a broad overview of predictors evaluated. The reason we could not apply a meta-analysis is because of the heterogeneity across studies regarding measurement tools, predictors and duration of follow-up. Not all studies used in this review adjusted their outcomes for potential confounders. Therefore some outcomes may be due to confounding factors. A limitation of our review is that we looked at functional outcome without including pain. Some patients will not see an improvement in their function after THA, but will lose the hip related pain. For this reason especially people with a high BMI and older age can benefit from THA, without improving the function of the hip. Some predictors such as quadriceps strength, education, socioeconomic status and alcohol consumption are reported only a few times and therefore conclusions cannot be reached. More research in large datasets is needed to draw definitive conclusions on these predictors.

Implications for practice

Our review provides a clear overview of the current literature on the predictors for physical functioning after THA. Orthopedic surgeons and general practitioners can use this information to predict the improvement in physical functioning for their patients and it enables them to provide patient-specific advice on THA.

Implications for future research

In the future, we suggest studies that evaluate possible predictors of functional outcome after THA to use similar measurement tools, outcomes and durations of follow-up. In that way a meta-analysis can be applied and the influence of these factors can be specified.

Conclusion

This review shows that several patient-related characteristics can predict the functional outcome after THA. It shows strong evidence of an association between BMI, age, comorbidity, preoperative physical function and mental health with functional outcome after THA. Weak evidence suggested that quadriceps strength and education were predictive of functional outcomes after THA. Inconsistent evidence was found for the predictors gender and socio-economic status. Alcohol consumption, vitamin-D insufficiency and allergies showed limited evidence predicting functional outcome after THA. Understanding predictors will help orthopedic surgeons and general practitioners predict the outcomes in physical functioning after THA; they can use this information to provide patient-specific advice and target care for patients with THA. Further well-conducted cohort studies are necessary to confirm these findings.

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Chapter 3

Functional outcome of uncemented total hip replacement: development of a multivariable prediction model

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Submitted

ABSTRACT

Background

Not all patients experience similar improvement of physical function after total hip arthroplasty (THA). The variance in outcome might be explained by patients' preoperative characteristics. The current study aims to identify predictors for physical function 1 year after uncemented THA. This may aid physicians in setting the indication for surgery and balance patients' expectations.

Methods

Data was used from a multicentre randomized clinical trial (CUSTOM trial), comparing two different stem types in patients undergoing uncemented THA. The outcome was physical function, measured with the Hip disability and Osteoarthritis Outcome Score Physical function Short form (HOOS-PS), 1 year after THA. Candidate predictors were selected based on literature. Multivariable logistic regression with a backward stepwise selection was used to develop the prediction model. Internal validation was performed to present an optimism corrected model.

Results

Patients had a higher chance to be responsive (ΔHOOS-PS ≥23) to THA when at baseline experiencing: (1) more pain of the contralateral hip (higher NRS score); (2) worse physical functioning (higher HOOS-PS score); (3) better mental wellbeing (higher SF-12 MCS score); and (4) less back pain (lower NRS score). Discrimination of the model showed an area under the curve of 0.85. The explained variance R^2 was 45% after correction for optimism.

Conclusion

This internally validated model is able to discriminate between responders and non-responders of uncemented THA. Before using it for personalized care, it should be externally validated, preferably with data from other hospitals or a registry.

INTRODUCTION

The majority of patients with osteoarthritis (OA) experience improvement in physical function, quality of life and reduction of pain following total hip arthroplasty (THA).(1) However, a small but relevant number of patients feel less satisfied or even experience no post-operative improvement of physical function at all.(1-4)

The main goal for OA patients to undergo hip surgery is the expectation of pain reduction, restoration of physical function and improvement of quality of life.(5) In recent years patient reported outcome measures (PROMs) are used more frequently in orthopedic clinics.(2, 6) The variance in patient reported physical function after THA might be explained by patients' preoperative characteristics. Preoperative identification of patients at risk for minor improvement after THA may aid physicians in setting the indication for surgery and balance patients' expectations for the outcome.(2)

Earlier systematic reviews aim to identify predictors of physical function after THA.(3, 7, 8) Preoperative physical function is the only consistently reported predictor. Worse preoperative function is associated with larger postoperative improvement, however these patients do not reach the same level as patients with better preoperative function.

Other strong and often reported predictors are Body Mass Index (BMI), comorbidities, and radiological OA severity. Less consistent reported predictors are: pain, age, mental health status, educational status and general health. (3, 7, 8)

Patient characteristics at baseline may more strongly affect patient outcome than surgical variables that are typically studied (e.g. prosthesis type or surgical approach). This is supported by the fact that over 80 percent of all randomized controlled trials (RCTs) in primary hip arthroplasty reported no statistically significant or clinically relevant differences between intervention groups.(9)

Therefore, the current study aims to identify predictive variables for physical function 1 year after uncemented THA.

METHODS

Patients

Data from a multicenter RCT on uncemented THA was used. Patients were recruited from 2 general hospitals in the Netherlands, with THA procedures performed between August 2009 and October 2012. Details on the original RCT 'curved versus straight stem uncemented total hip arthroplasty osteoarthritis multicentre trial' (CUSTOM), and the primary outcomes have been published.(10, 11) In brief, this trial compared functional outcome of 2 hip prosthesis stems used for uncemented THA; a conventional straight stem and a curved short stem. In total 150 patients were included who were diagnosed with hip osteoarthritis and on the waiting list for an uncemented THA, aged between 18 and 70 years, having a BMI of ≤40, no previous or planned contralateral THA .

No differences in functional outcome were observed between the 2 different stem types. Therefore, both treatment groups were treated as 1 population in the current study for developing a prediction model for physical function after THA.

Ethics

The CUSTOM trial was approved by the Medical research Ethics Committees United (MEC-U) under registration number NL21637.100.08. The study was conducted according to the Declaration of Helsinki and is registered in the Dutch trial register (http://www.trialregister.nl, file number NTR1560). Signed informed consent is obtained from all participants prior to participating in the trial.

Outcome

Outcome of interest was physical function 1 year after uncemented THA. To quantify physical function we used the Hip disability and Osteoarthritis Outcome Score Physical function Short form (HOOS-PS).(12) The HOOS-PS is a 5-item measure of physical function derived from the items of the 'function', 'daily living and function', 'sports and recreational activity' subscales of the HOOS. The measure is scored by summing the responses and converting this raw sum to the Rasch-based interval score (provided in the HOOS-PS user guide) that ranges from no difficulty (0) to extreme difficulty (100). The HOOS-PS is easy to administer and commonly used in the THA population. It is recommended by the International Consortium of Health Outcomes Measurement (ICHOM) and by the Osteoartrhitis Research Society International / Outcome Measures in Rheumatoid Arthritis Clinical Trials (OARSI/OMERACT) initiative(13, 14) and is therefore included in the mandatory PROMs

dataset of the Dutch Orthopaedic Association. For clinical applicability of the prediction model, the population was dichotomized into responders and non-responders to THA treatment.(15, 16) Responders had a change score between preoperative and 1 year postoperative of at least the minimal clinically important difference (MCID) of 23 points on the HOOS-PS scale and were used as the reference group in the analyses.(17) Patients with a missing baseline score, missing 1 year score, or both were excluded from the analyses.

Selection of candidate predictors

Candidate predictors were selected based on literature.(3, 7, 8) For an overview see table 1. Predictors were selected if they were classified as 'strong or 'conflicting' in at least 1 of the previous systematic reviews. Socioeconomic status (7) and educational level (8) were not selected because they were not available in the CUSTOM database. All other selected predictors were measured preoperatively in the CUSTOM RCT.

The following patient characteristics were included in the current prediction model: age (continuous); sex (female/male); body mass index (continuous); pulmonary- and/or cardiac comorbidity (yes/no); degree of osteoarthritis (OA) measured by the Kellgren & Lawrence (K&L) score (categorical: 0 = no OA, 1 = doubtful OA, 2 = minimal OA, 3 = moderate OA, 4 = severe OA)(18). In addition, several patient reported outcomes at baseline were included in the model. Pain (continuous) in the affected hip, contra-lateral hip, knee and back was measured on an 11-point numerical rating scale (NRS), ranging from 0 (no pain) to 10 (worse pain). Preoperative physical function was measured with the HOOS-PS, ranging from no (0) to extreme difficulty (100).(12) Mental wellbeing was measured with the short form health survey (SF-12) mental component summary (MCS), ranging from worse (0) to the best health status (100).(19)

Table 1. Overview of potential predictors.

Variable	Buirs et al. 2016	Hofstede et al. 2016	Lungu et al. 2015
Age	+	+/-	-
Sex	+/-	+/-	-
BMI	+	+/-	+
Comorbidity	+	+/-	+
Degree of OA	?	+	+
Pain	?	+/-	+
Preoperative physical function	+	+	+
Mental wellbeing	+	+/-	+/-

+ = strong evidence, - = no significant evidence, +/- = conflicting evidence, ? = not studied

Statistics

Descriptive analysis was used to describe patient characteristics. Continuous data were presented as mean with standard deviation (SD) and categorical as number (%). The CUSTOM dataset had missing values, which were imputed as follows: in case an item response concerning physical function was missing, the answer of a comparable question was used when available. Remaining missing values were imputed, following the instructions of the questionnaire. Patients with missing values on candidate predictors were excluded from the analyses.

Model development

Candidate variables were tested for multicollinearity using Pearsons R correlation coefficient. In case of a correlation higher than r=0.50, multicollinearity was assumed and the variable with the weakest univariable predictive value was excluded from the model development. Multivariable logistic regression with a backward stepwise selection was used to develop the prediction model. The p-value for selecting predictors for removal was conservatively set at p>0.20.

Internal validation

Internal validation was performed on the apparent prediction model by bootstrapping 250 times. (20) A shrinkage factor was obtained to correct for optimism and develop our final prediction model. The optimism-corrected coefficients were fitted to estimate a new intercept of the optimism-correct model.

Model performance

Model performance of both the uncorrected model (apparent model) and the optimism-corrected model was expressed in calibration and discrimination of the models. Calibration of the model was performed to explore the agreement between the predicted and observed values. Calibration was assessed with the calibration intercept, calibration slope and using the Hosmer-Lemeshow test.(16, 20) A good fit was defined by a calibration slope close to 1, a calibration intercept close to zero and a non-significant outcome of the Hosmer-Lemeshow test (with $p<0.05$ considered statistically significant).

Discrimination was assessed with the area under the receiver-operating-curve, resulting in a score between 0.5 and 1.0, with a score of 0.5 indicating no discriminative power and a score of 1.0 indicating perfect ability to discriminate between patients with and without at least 23 points (MCID) improvement on the HOOS-PS.

Nagelkerke's R^2 was estimated as a measure of overall model performance. Furthermore, we determined the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the final clinical prediction model.

IBM SPSS statistics version 22.0 (IBM Corp, 2012) was used for descriptive analysis and model development and R version 3.4.2 was used for the internal validation and estimation of model performance.

RESULTS

Population

A total of 150 patients were included in the CUSTOM trial. Out of these 150 patients, 139 (93%) patients completed both the HOOS-PS at baseline and at 1 year follow-up and were included in the present study. Patient characteristics at baseline are presented in table 2 for all candidate predictors. In total, 99 of these patients (71.2%) showed clinically important improvement in physical function 1 year after THA (Δ HOOS-PS ≥ 23 points) and were therefore called 'responders'. Mean improvement on the HOOS-PS was 41.6 points (SD 13.6; Range 23.9 - 90.8) for the 'responders' and 11.8 points (SD 10.7; Range -29 -22.7) for the 'non-responders'.

After selection of potential predictor variables, 128 complete cases (85%) remained and were included in the analyses for model development. Analysis of model performance and internal validation of the final model was performed for all patients with complete scores on the predictive variables included in the final model, with a total of 135 complete cases (90%).

Table 2. Patient characteristics at baseline for responders and non-responders to THA treatment (n=139)

	Responders ΔHOOS-PS ≥23 (n=99)		Non-responders ΔHOOS-PS <23 (n=40)	
Candidate predictors	Value	Missings (%)	Value	Missings (%)
Age (mean years ± SD)[a]	59.6 ± 7.7	0	61.9 ± 5.0	0
Male sex (n, %)	25 (25,3)	0	15 (37.5)	0
BMI (mean ± SD)	26.8 ± 4.2	1	26.8 ± 4.1	0
Cardiac comorbidities (n, %)	17 (17.7)	3	7 (17.5)	0
Pulmonary comorbidities (n, %)	5 (5,2)	3	5 (12.5)	0
Severity of osteoarthritis		1		5
K&L 1 (n, %)	1 (1,0)		1 (2.6)	
K&L 2 (n, %)	18 (18.4)		3 (7.9)	
K&L 3 (n, %)	42 (42.9)		20 (52.6)	
K&L 4 (n, %)	37 (37.8)		14 (36.8)	
Pain in operated hip (mean ± SD)[b]	6.6 ± 1.7	0	6.0 ± 2.2	0
Pain in contra-lateral hip (mean ± SD) [b]	1.3 ± 2.2	3	0.9 ± 1.6	2.5
Pain back (mean ± SD) [b]	3.2 ± 2.8	3	3.2 ± 2.8	2.5
Pain knees (mean ± SD) [b]	2.9 ± 2.7	3	3.2 ± 2.7	2.5
Physical function (mean ± SD) [c]	52.6 ± 15.3	0	36.2 ±15.2	0
Mental health (mean ± SD) [d]	49.2 ± 10.2	0	8. ± 11.2	0

SD = Standard Deviation; a = measured on a numerical rating scale; b = measured on the HOOS-PS; c = measured on the SF-12 mental health score; K&L = Kellgren and Lawrence score.

Model development

Pearson's R correlation coefficient showed multicollinearity of the baseline scores for HOOS and HOOS-PS (r = -0.897, p<0.001). The HOOS-PS had the best univariable predictive value and is used in clinical practice and recommended internationally by ICHOM(14, 21) for patients with hip osteoarthritis, therefore we included this variable in the model and excluded the HOOS.

A total of 12 candidate predictors were included (table 2). Stepwise backward logistic regression revealed 4 variables to be independent predictors of physical function of the operated hip 1 year after THA. Results of this first, apparent model are shown in table 3.

Patients had a higher chance to be responsive to THA treatment when at baseline they (1) experienced more pain of the contralateral hip, indicated by a higher score on the NRS; (2) experienced increased difficulty in daily activities, indicated by a higher score on the HOOS-PS; (3) scored better on mental wellbeing, indicated by a higher score on the SF-12 MCS; and (4) experienced less back pain, indicated by a lower score on the NRS for back pain.

Table 3. Presentation of apparent model and model corrected for optimism

Apparent model (=128)				
Predictor	Coefficient	Odds ratio	95%CI	p-value
Intercept	-7.584	n.a.	n.a.	<0.001
Pain in contra-lateral hip	0.241	1.27	(0.95-1.71)	0.109
Pain back	-0.135	0.87	(0.73-1.04)	0.134
Physical function at baseline	0.131	1.14	(1.08-1.20)	<0.001
Mental health	0.063	1.07	(1.01-1.12)	0.010
Model corrected for optimism [a] (n=135)				
Intercept	-6.554	n.a.	n.a.	n.a.
Pain in contra-lateral hip	0.210	1.23	(0.92-1.66)	
Pain back	-0.118	0.89	(0.75-1.06)	
Physical function at baseline	0.115	1.12	(1.07-1.18)	
Mental health	0.055	1.06	(1.01-1.10)	

[a] = A shrinkage factor of 0.873 was determined after internal validation and applied to correct the apparent model for optimism; n.a. = not applicable.

Internal validation

Internal validation of the apparent model generated a shrinkage factor of 0.873. The optimism-corrected coefficients are presented in table 3.

Model performance

Model performance for both the apparent model and the optimism-corrected model are presented in table 4. Overall, in the apparent model, the effect of predictive variables on physical function at 1 year after surgery are overestimated. In the model corrected for optimism, we found a calibration slope close to 1 (1.145) and a calibration intercept close to zero (-0.077) and can therefore be considered as a good fit (table 3). These results were confirmed as tested with the Hosmer and Lemeshow goodness-of-fit test (p=0.562). Discrimination of the model showed an area under the curve of 0.85.These results show that the model is able to discriminate between non-responders and responders (ΔHOOS-PS ≥23). In the optimism-corrected model, 91% (87 out of 96) of the patients would be correctly predicted as patients with a good recovery of hip function (sensitivity), while 54% (21 out of 39) would be correctly predicted as patients at risk for a minor recovery of hip function (specificity). The positive predictive value of the corrected model is 83%, meaning these patients are correctly predicted to be responsive to surgery. The negative predictive value is 70%, meaning these patients are correctly predicted to be non-responsive to surgery. The explained variance R^2 was 45% after correction for optimism.

Table 4. Model performance (n=135)

	Apparent model	Model corrected for optimism
Calibration		
Calibration intercept	0	-0.077
Calibration slope	1	1.145
Discrimination		
AUC*	0.852	0.852
R^2**	0.456	0.453

*AUC = Area Under the Curve; **Nagelkerke's R^2.

DISCUSSION

Interpretation

This study shows that patients with worse preoperative functional status, better mental health, more pain of the contralateral hip and less back pain are more likely to have a clinically relevant improvement in physical function 1 year after uncemented THA, measured with the HOOS-PS. These results support 3 in the literature reported predictors of physical function after THA: preoperative functional status (HOOS-PS), mental health (SF12-MCS), and pain.(3, 7, 8)

In contrast to the earlier reviews(3, 7, 8), BMI and age were not significant predictors in our study. This might be due to the inclusion criteria of the RCT: only patients with a BMI lower than 40 and younger than 70 years old were eligible for participation.

Previous studies showed that pain was an important predictor for functional outcome after THA. Because we collected several pain scores in our RCT, with no multicollinearity, these were all included as candidate predictors. Quite surprisingly, the pain scores in the contralateral hip and back were more predictive of functional outcome than pain in the affected hip. Specifically, more contralateral hip pain indicated a higher chance to be responsive to THA in our study population. This finding is in contrast with earlier studies, which reported contralateral hip or knee pain as a predictor of worse physical function after total hip or knee arthroplasty.(22, 23) 2 of the reviews also found that radiological status was a strong predictor for functional outcome.(3, 8) Our prediction model does not support this finding. The lack of predictive ability of K&L scores for functional outcome remained similar when exploring this categorical variable as dichotomized variable with mild (K&L scores 1 and 2) versus serious (K&L scores 3 and 4) OA. In clinical practice, the vast majority of patients undergoing THA has serious (end stage) OA.

With an area under the curve of 0.85, this internally validated model is well able to discriminate between responders and non-responders of uncemented THA.

Strengths and limitations

Although several studies have reported predictors of physical function after uncemented THA, little was known about their relative importance. This study provides further insight by combining these variables in 1 prediction model.

Our RCT resulted in a highly complete database and included many of prior reported predictors of physical function as baseline variables. However, the RCT and thus the model are based on data with only uncemented THA using the direct lateral surgical approach, in patients with a BMI below 40 and

between 18 and 70 years old. It is unknown whether the results of this prediction model are generalizable to cemented THA and to other surgical approaches. However, worldwide there is an increased preference for uncemented THA.(24-26) The direct lateral approach is known to have good exposure and a relatively low risk of dislocation, but also shows less improvement on physical function compared to other surgical approaches.(27-30) However, clinical differences are small and the direct lateral approach is still a commonly used approach.(27, 29) The sample size of the RCT limited the statistical power of this prediction model. This study developed a clinical prediction model and validated this internally, but did not further develop the model into a risk score. Before developing a risk score, it would be valuable to externally validate our findings in a larger sample, preferably from other hospitals or a registry. Inquiries among other hospitals in The Netherlands and the Dutch Arthroplasty Registry revealed that they had no suitable data on pain scores and mental health. Therefore, there was no possibility for external validation within the current study.

Ideally, existing joint arthroplasty registries would be expanded with detailed information on pain and mental health. Using registry data to develop prediction models has the advantage of containing data of a large amount of patients, with all types of prostheses and surgical approaches.

CONCLUSION

The results of this prediction model contribute to the debate on which patient characteristics are predictive for change in i functional outcome at one year postoperatively compared to baseline. This knowledge can help physicians, surgeons and patients in enhancing realistic expectations of outcome after uncemented total hip arthroplasties. Patients with a worse preoperative physical function, more contralateral hip pain, less back pain and a better mental health, are expected to have a higher chance to be a 'responder', indicated as having a change score of at least 23 points on the HOOS-PS. These factors can be discussed with the patient. In this way, patients and doctors can make a shared decision whether to undergo THA or prefer other treatment. The results may also inform future clinical trials aimed at comparing interventions in a uncemented THA population of patients with OA.

This study provides valuable insight in the importance of different patient characteristics at baseline for the prediction in change of functional outcome after THA, but it is recommended to validate these findings externally before using this model for personalized care.

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Part 2

The influence of *surgical approach* on outcomes after hip arthroplasty

Chapter 4

Posterolateral or direct lateral approach for hemiarthroplasty after femoral neck fractures: a systematic review

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Abstract

Background

The posterolateral approach (PLA) and direct lateral approach (DLA) are the most commonly used approaches for inserting a hemiarthroplasty in the treatment of femoral neck fractures. A recent review concludes that the routine use of PLA should be questioned, but this conclusion itself can be questioned. The aim of this study is to provide an updated overview and critical appraisal of the available evidence, focussing on outcomes most relevant for patients.

Methods

We conducted a comprehensive search of literature in the MEDLINE and EMBASE databases and Cochrane Library. Studies (till June 2018) to identify hip fracture clinical trials/comparative studies comparing alternative surgical approaches (PLA and DLA). We explored sources of heterogeneity and conducted pooled analyses when appropriate.

Results

264 potentially eligible studies were identified of which 1 RCT, 3 prospective, 3 registry data and 5 retrospective studies were included. The RCT consisted performance and attrition bias. The mean MINORS score of the prospective/register studies was 17.3 (SD 3.5) and 13.8 (SD 1.9) of the 5 retrospective studies. The GRADE score for all the outcomes were very low . Due to the high and various types of biases across the included studies, we did not pool the data. None of studies assessed the activities of daily living functionality. Six studies reported significantly more dislocations or reoperations due to dislocation in the PLA group, six other studies found no differences. DLA patients were more likely to develop abductor insufficiency leading to limping and more need for walking aids. The PLA patients tended to have better quality of life, less pain and more satisfaction compared to the DLA patients.

Conclusion

Based on low quality studies, PLA may be associated with more dislocations, but patients had less walking problems and a lower tendency to abductor insufficiency compared with DLA. Further clinical trials with methodology rigor are needed to determine which approach is more effective in terms of outcomes relevant to patients.

INTRODUCTION

Hemiarthroplasty is a commonly used procedure in the treatment of displaced proximal femur fractures. One of the first hemiarthroplasties was introduced in 1940 by Moore and a posterolateral approach (PLA) was initially recommended as surgical technique(1, 2). In the subsequent years various operative techniques were described in the literature including the direct lateral approach (DLA) of Hardinge(3). In the Netherlands, 83% of all hemiarthroplasties are inserted through a PLA or DLA(4).

A recent systematic review and meta-analysis concludes that the routine use of PLA for fracture related hemiarthroplasty should be questioned. This conclusion was based on an increased risk of dislocation compared with other approaches, with no evident advantages to counterbalance this disadvantage of the PLA (5). However, the methodological quality of the included studies was low, and combining data of studies with a high and differential risk of bias may result in misleading findings and compromise the conclusion(6). Moreover, potential advantages of the PLA may be less evident, but could still be present. Therefore, the firm conclusion that a PLA would be inferior to DLA should also be questioned.

When inserting a hemiarthroplasty through a DLA the fibers of the gluteus medius and vastus lateralis muscles are split in their own line and when closing the muscles are sutured(7). This approach may lead to abductor insufficiency, resulting in a positive Trendelenburg sign or limping after surgery(8, 9). However, in the DLA the posterior capsule is preserved, preventing dislocation. With a PLA, the surgeon performs a posterior capsulotomy, dividing the short external rotators(7). During a PLA the hip abductors are protected and preserved to prevent limping. However, due to inadequate posterior capsule support there may be an increased risk of dislocations(10-12).

Sustaining a hip fracture increases the risk of falling and often leads to subsequent fractures, which results in high morbidity and increased mortality in these patients(13). While highly relevant for patients, the effect of surgical approach on subsequent fall risk is unknown. It could be speculated that the PLA may lead to faster rehabilitation and better balance due to the scatheless gluteus musculature. Contrarily, the loss of abductor muscle strength as a result of the DLA could cause a loss of balance which may increase the risk of falling and subsequent trauma, further reducing patients' mobility.

In this systematic review we aim to provide an update and critical appraisal of the available evidence of the differences between the most frequently performed surgical approaches for inserting hemiarthroplasty after femoral neck fractures: PLA and DLA. We focus on outcomes most relevant for

patients, with the patients' independence in Activities of Daily Living (ADL) as primary outcome. Secondary outcomes include: postoperative complications, mobility, function, quality of life and falls.

METHODS

We conducted this systematic review using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (14). The protocol of this study is registered in the PROSPERO register (CRD42017055162).

Eligibility criteria

For the effects on patient outcome after acute hip fracture, we included all study designs in which the posterolateral approach was directly compared with the direct lateral approach in hemiarthroplasty after hip fractures. We excluded studies that enrolled patients with pathological fractures, fractures due to advanced rheumatoid- or osteoarthrosis, multi-trauma-patients (ISS> 16) or patients who had secondary surgery after failed internal fixation.

Information sources and Literature search

An independent clinical librarian conducted a literature search in the MEDLINE and EMBASE databases and Cochrane Library at the 13th of June 2018. There were no restrictions to publication year and languages. Search terms were: Femoral neck fracture*, Hip fracture*, Proximal femur fracture*, Hemiarthroplasty, Direct lateral, Posterolateral.(Appendix I)

Study selection

Two reviewers (*first and second author, initials blinded for peer review*) independently screened all titles and abstract for eligibility with the criteria mentioned above using Covindence(15). References resulting from the included studies were reviewed for additional relevant articles. When there was any discrepancy between the two reviewers consensus was reached through discussion.

Data collection process

One researcher (*first author, initials blinded for peer review*) extracted all data of the following predefined data items: (1) study information: authors and year of publication, study design, number of patients enrolled and follow-up; (2) baseline characteristics: surgical approach, age, gender,

cemented/uncemented prosthesis, cognitive impairment and ASA classification; (3) patient outcomes

Outcomes

In a focus group formed from members of the collaboration of orthopaedics, trauma surgeon and clinical geriatrics we determine the outcomes of this systematic review by their expert opinion. These outcomes were supported by the Dutch Federation of patients.

The primary outcome of this study is the patients' independence in ADL using the KATZ index(16). Secondary outcomes are postoperative complications, mobility, function, Health Related Quality of Life and falls.

Critical appraisal

To assess the level of evidence we used the Oxford Level of Evidence criteria (17). Two reviewers (*first and second author, initials blinded for peer review*) independently completed the critical appraisal. Consensus was reached after discussion. The quality assessment for Randomised controlled trials was conducted by the Cochrane tool for risk of bias using Review Manager(18). Studies are classified as "low risk", "moderate risk" or "high risk". We assessed the methodological quality for non-randomised controlled trials with the MINORS criteria(19). The MINORs criteria contains 12 items subsequently scored 0-2; 0 indicating that it was not reported, 1 indicating that it was reported but inadequate, and 2 indicating that it was reported and adequate. The maximal score for comparative studies is therefore 24 points.

The type of study design was considered to be of significant importance for the for the interpretation of the study results. Based on observational data causal inferences cannot be made. Causation is defined by a different risk in the study population under two potential exposure values, which only can be reached after randomisation. Therefore, in observational studies only associations could be made(20). Recently, Natural Experiments (NE) are growing interest as a alternative to RCT's(21). A NE is a study design, whereby the dividing of the population into exposed and unexposed to an intervention is not under control of the researcher(22). Natural factors, such as geographical location, leads to exposed and unexposed individuals, which creates as-if randomness. There are several methods to evaluate the selective exposure in NE's. These additional design features can strengthen the causal inference(21).

We also assessed the overall quality of evidence and strength of recommendation by the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach(23). This approach quantifies potential limitations for each outcome in five domains: risk of bias, inconsistency, imprecision, indirectness, and publication bias.

RESULTS

Search results

The search produced 264 records, of which 90 records were duplicates and were removed. A total of 174 records remained to be screened for title and abstract, after which 113 irrelevant records were eliminated. Sixty-one full-text articles were assessed for eligibility, of which 49 were excluded for the following reasons: different surgical approaches (n=24), different study methods (n=16), review (n=2), meeting abstract (n=7). There were no articles added after screening the references of the included studies. A total of 12 articles were included in this systematic review (Figure 1).

Of the 12 included articles one was a RCT (24), 3 were prospective studies(9, 25, 26), 3 were registry studies(10, 12, 27) and 5 were retrospective studies(11, 28-31).

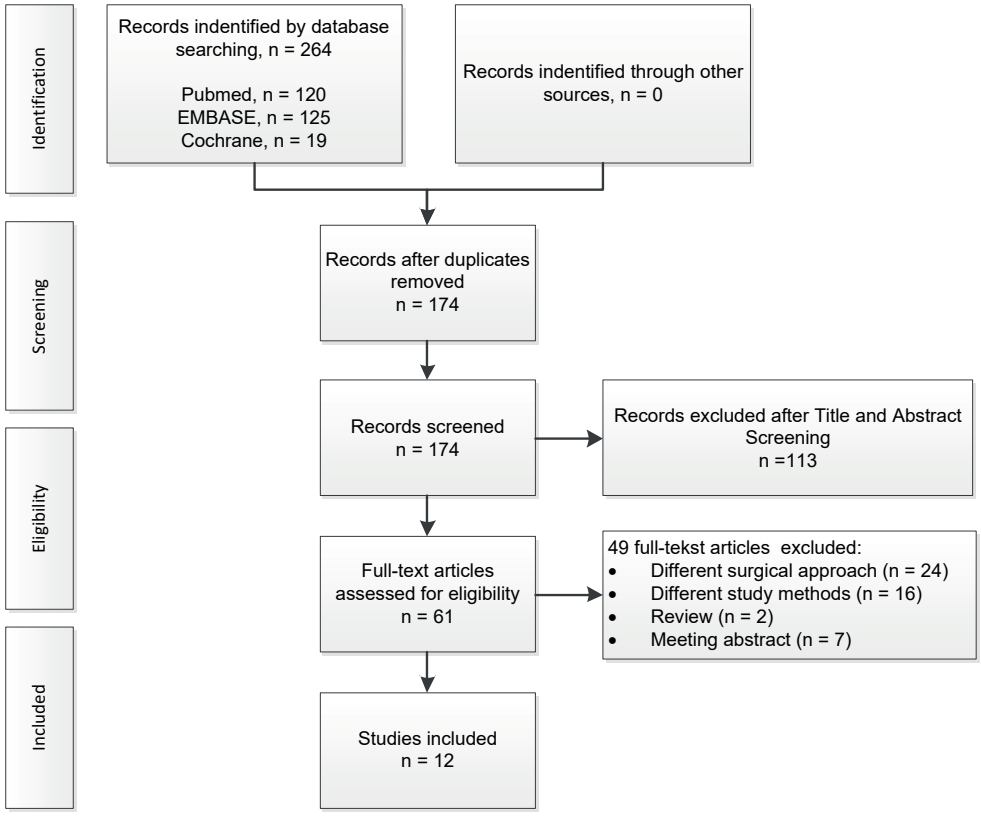
Study populations

The study populations ranged from 48 to 33205 patients. In total, more than 60.000 patients participated in the included studies. Baseline characteristics of the patient populations are presented in Table 1. The patient population of Sayed-Noor et al.(9) was a subset of the population that participated in Mukka et al.(25) (confirmed after contact with the corresponding author). Rogmark et al.(10) combined the Norwegian register database, which was also used by Leonardsson (27), with the Swedish registry, which was also used by Kristensen et al. (12).

There was heterogeneity in populations across the included studies (Table 1). Patients treated using the PLA in Kristensen et al.(27) had more cognitive impairment (29%) compared with DLA (25%)(27). They also reported more cemented prostheses in the DLA group (75% vs. PLA 43%)(27). These differences in the use of cemented prostheses were seen across several included studies: the percentage of cemented prostheses in the DLA group was >90% in four studies (9-12), 72% in one registry study (27), 21% in one retrospective study(29) and only 13% of the patients were treated with a cemented prosthesis in the study of Hongisto(31). The latter study reported significantly more

patients in the PLA group (20%) treated with a cemented hemiarthroplasty compared with DLA (8%) (31). Also, Hongisto et al.(31) reported a significant difference in surgeon's expertise. Patients in the DLA group were more frequently treated by a post-registrar (76%) compared to the PLA patients (64%)(31). In five studies the surgical approach was not equally divided in the study population(10, 11, 26, 27, 30). No other significant differences between the PLA and DLA groups were described in the included studies. Other co-morbidities were not reported in the included studies.

Figure 1, flowchart of literature search



Methodological quality

The RCT, all prospective and retrospective studies had level of evidence 2b (individual cohort studies or low quality RCT (<80% follow-up)). The RCT was prematurely ended when half of the sample size was included, because the PLA was found technically more difficult(24). This might have introduced performance bias in the included patients and attrition bias due to incomplete outcome data (Figure

2). The MINORS criteria of the non-randomised studies are listed in Table 2. The mean MINORS score of the prospective cohort and registry studies was 17.3 (SD 3.5) and of the 5 retrospective cohort studies the mean MINORS score was 13.8 (SD 1.9) out of 24 points. Figure 3 presents the overall MINORS score of the individual methodological items of all included studies. In 7 of the 12 items there were considerable differences in methodological quality. Hence, the majority of the included studies showed imperfections in the study design. By design, non-randomised studies lack random allocation of patients to study groups. This increases the risk for selection bias and confounding, especially when factors other than surgical approach also differ between groups (see above). Due to the diverse study designs and the high and differential risk of bias, pooling of the data may result in misleading findings and therefore should be avoided(6).

Figure 2, Risk of bias of randomised controlled trial

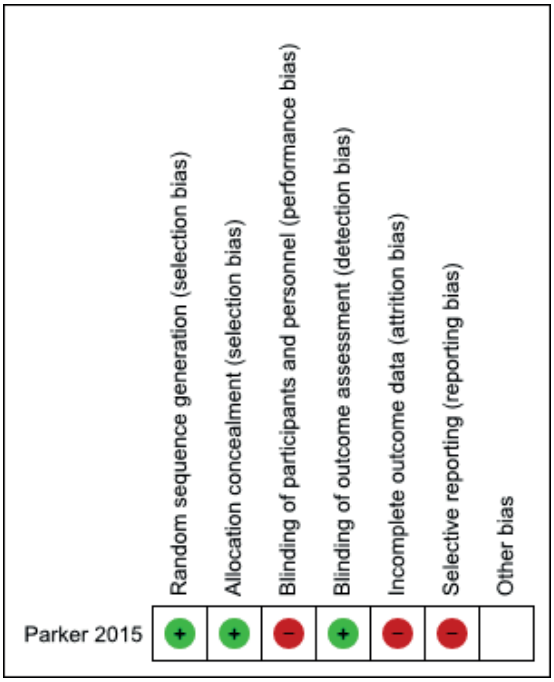
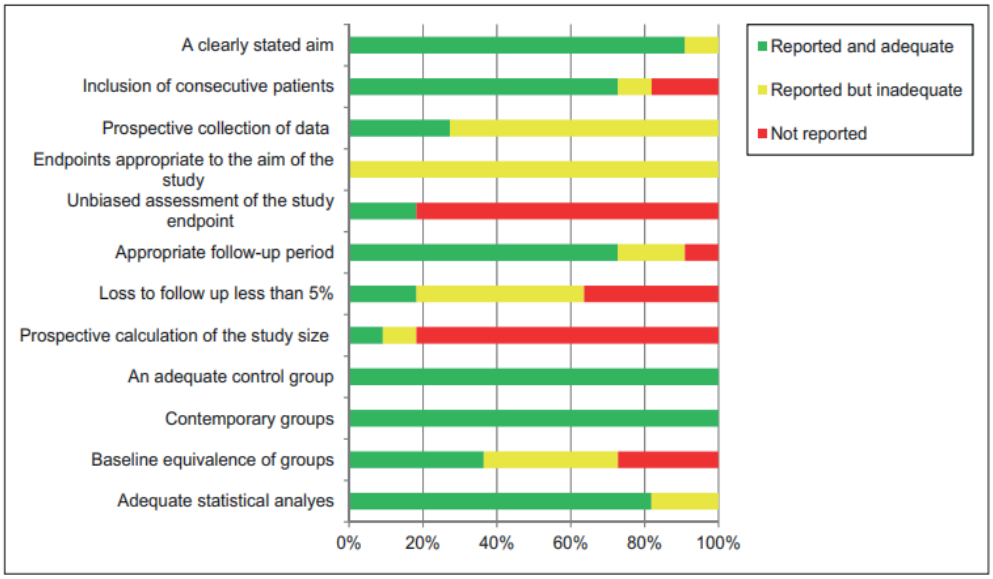


Figure 3, Quality assessment of randomised studies (Cochrane tool for risk of bias)



Grade approach

The GRADE approach was feasible for the following outcomes: postoperative complications, Health Related Quality of Life and function. The summary of findings for each of the included outcomes is listed in the GRADE evidence profile (Table 3). The GRADE quality of all outcomes was very low, in other words, any estimate of effect is very uncertain.

Primary Outcome

None of the included studies assessed the Independence in Activities of Daily Living using the KATZ score or anything similar.

Secondary outcomes

Postoperative complications

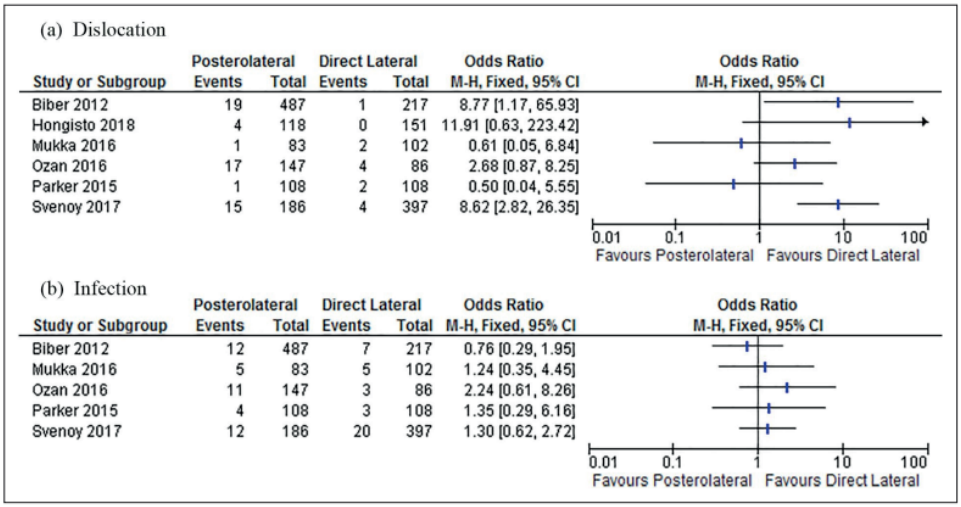
All postoperative complications are listed in Table 4.

Dislocations

Ten out of twelve included studies with in total 59111 included patients reported dislocation (Figure 4a)(10, 11, 24-31). Dislocation rates ranged from 1% to 12% in the PLA group and from 0% to

6% in the DLA group during a follow-up period of 3 to 48 months (11, 24-26, 28-31). The only included RCT found no differences in dislocation rate between the two approaches(24). A large registry study which combined the Norwegian and Swedish registry data, (n= 33205), showed that PLA was a significant risk factor for reoperation due to dislocation (10). The Swedish registry data alone supported this finding, with 2% of all PLA patients undergoing a reoperation due to dislocation versus 0.9% in the DLA group(12). However, the Norwegian registry study (n=20908) found similar risks of reoperation due to dislocation of both approaches in the first 8 year(27). After one year follow-up three retrospective studies described an increased risk of dislocation in patients treated using the PLA (11, 29, 31). Other observational studies with in total 589 patients did not report more dislocations in the PLA group(25, 28, 30)(Table 4).

Figure 4



Infections

One registry study (n=20908) reported DLA as a risk factor for reoperation due to infection compared to PLA. No other significant differences in occurrence of infection between PLA and DLA were described in previous studies (Figure 4b, Table 4)(11, 24-26, 30).

Length of stay

Only the RCT assessed the length of hospital stay, and found no significant differences between PLA (18.5 days) and DLA (20.3 days, p=0.4)(24).

Quality of life, pain and satisfaction

One RCT and three prospective studies with 23924 patients reported quality of life after hip fracture(9, 12, 24, 27). The patient reported quality of life, mobility and function are listed in Table 5. In the RCT (n=216) no differences in modified Charnley pain score(32) were found between PLA and DLA(24). Two studies that prospectively assessed the HRQoL using the EQ-5D reported significant differences after 1-year follow-up in favour of the PLA(12, 27). Specifically, Kristensen et al. (27) observed an adjusted mean difference of 0.03. (n=20908)(27). When assessing the patient's self-rated health on a vertical visual analogue scale (EQ-VAS), in which the endpoints were labelled 'The best health you can imagine' (100 points) and 'The worst health you can imagine' (0 points), PLA patients scored after adjustment 61 points vs. 59 points in DLA patients(27). In addition, when measuring the VAS pain ranged from zero (no pain) to 100 (unbearable pain) and the level of satisfaction ranged from zero (very satisfied) to 100 (dissatisfied), PLA patients had less pain and were more satisfied compared with DLA patients one year after surgery(27). Leonardsson et al.(12) also observed significant differences favouring PLA, however after adjusting for confounders, no significant difference in EQ-5D, pain and satisfaction between the approaches were seen(12).

Mobility, Function

Five studies, of which 1 RCT, 3 prospective and 1 retrospective studies, with a total of 21626 patients reported mobility or function after hip fracture surgery. The RCT (n=216) used a mobility score with a range from 0 to 9 points and found no clinically relevant differences between the groups(24). Patients in a prospective cohort, treated using the DLA had an 18 times higher risk of having a positive Trendelenburg sign and had a 16-fold higher risk of developing limping(9). Remarkably, no differences in abductor muscle strength, measured with an electronic dynamometer, were found in this same patient population(9). This may be due to the difficulty to follow the instructions when using the dynamometer is this elderly population(9). The Harris Hip Score (HHS) was assessed in one prospective study, and no difference was observed(25)(Table 5). The Norwegian registry data estimated a rate of 42% of the PLA group with no walking problems one year after surgery compared with the estimated rate of 30% in the DLA group ($p<0.01$)(27). A retrospective study reported a significant OR of 2.73 for being mobile without walking aid favouring the PLA(31). However in this retrospective study, both groups were equally fully mobile (with or without walking aids), since there were no differences in mobility level between the groups(31).

Falls

Parker et al. observed the incidence of falling and found no difference between the approaches during the hospital stay(24). No study reported falls or fall incidents during follow up.

DISCUSSION

This review is an update of the available evidence of the differences between the two most common surgical approaches of hemiarthroplasty after femoral neck fractures. We focussed on outcome measures that are most relevant for patients.

Key findings

Since all outcomes were rated as very low quality according to the GRADE approach, any estimated effect could be considered as uncertain. There were major concerns about the quality of the included studies. Eleven out of twelve studies were non-randomised studies(9-12, 25-31), which might have introduced selection bias due to lack of randomisation that could have caused unbalanced confounding factors among patient groups. The MINORS tool identified various types of biases across the included studies. It is unclear which of these biases have had the greatest impact and how they have varied between clinical situations. The only RCT was prematurely ended and was therefore underpowered. Moreover, the RCT terminated because the PLA was felt technically more difficult by the surgeon. Therefore the quality of the study results can be questioned.

Large nationwide registry data could be seen as a NE, such as Kristensen et al.(27) However, in the other included registry studies it was not clearly described whether the surgical approach was chosen based on particular patient characteristics, or because the surgeon was only competent in one single approach. The latter case, as-if randomness could be reached when the surgical approach is merely determined by chance (which surgeon is on call when the patient is admitted to the hospital).

Previous literature

None of the included studies focussed on the independency in ADL and therefore we have no results on the primary outcome. From our point of view, in in this frail population where the life expectancy is not high, the ADL dependency and quality of life is paramount. Especially because hip fracture patients can become more vulnerable and more dependent after subsequent falls.

This current critical appraisal focussed on the outcomes relevant to the patient, which makes our study different compared to Van der Sijp et al. that described a variety of outcome measures(5). Moreover, we performed an additional assessment of the study quality (i.e. GRADE) which could have resulted in a different study interpretation. Furthermore, the study of Van der Sijp et al. mentioned that the Scandinavian registry studies excluded cognitively impaired patients and therefore they introduced sampling bias(5). However, in contrast to this statement, both studies have actually included all consecutive patients including those with cognitive impairment(12, 27). Lastly, Van der Sijp et al also stated that the high prevalence of a Trendelenburg sign and limping does not affect the clinical outcome(5). However, this conclusion was based on a sample of 48 patients, which is underpowered for this patient reported quality of life outcome.

In regards to the secondary outcome measure we found that the majority of the literature reported less dislocations in the DLA group 1 year after surgery(10-12, 31). The only RCT found similar dislocation rates, however this study was ended halfway(24). Contrary results were also found in the Scandinavian registry studies were the Swedish data showed that PLA was an increased risk for reoperation due to dislocation (12) but the Norwegian data observed no differences in reoperation 8 years after surgery between the approaches(27). Recurrent dislocation is a major complication which results in a loss of HRQoL and can lead to a reoperation, but a single dislocation seems to cause only a temporary deterioration of the quality of life (33). This is supported by the Swedish registry study, that reported more reoperation due to dislocation in PLA patients but also a slightly higher quality of life in this group one year postoperatively. The natural experiment by Kristensen et al also showed a better quality of life in PLA patients, which supports the findings of better outcomes regarding pain, satisfaction and quality of life after a total hip arthroplasty using the PLA(34, 35).

The mobility was assessed in the included RCT, which reported no difference. Patients were randomised and treated by one single surgeon. It might have introduced a performance bias due to the fact that the PLA was felt technically more difficult and with no differences of better functional outcomes, the study was terminated prematurely(24). On the contrary, more than 10% less walking problems in the PLA group were found in the natural experiment(27). Furthermore, more patients operated using the DLA needed a walking aid one year postoperatively compared with the PLA, which suggest a worse functional outcome after hemiarthroplasty using the DLA(31). However, when assessing the Harris Hip Score in a prospective study, this effect was not seen (25).One study with a low risk of bias according to the MINORS criteria, reported a strong association with abductor

insufficiency (a positive Trendelenburg sign) leading to limping in DLA patients(9). Whether limping after hemiarthroplasty is associated with a higher tendency to fall has never been investigated. However, it seems likely that the loss of muscle strength leads to a loss of function and to a higher level of frailty, which might intensify the risk of falling and possibly lead to more consecutive injuries and disability during daily activities(36). Only the RCT reported the incidence of falling. They observed no differences in the incidents of falling during a hospital stay(24). However, there is no literature on the tendency to fall after discharge and it remains unknown if the abductor insufficiency after DLA causes to more falls. Too little is currently known about the effect of abductor insufficiency on the patient's daily activities and the risk of falling after both approaches.

Strengths and limitation

There were limitations to our study. First, we were not able to pool the results in a meta-analysis due the heterogeneity of the included studies. Second, in this systematic review the adult population as a whole was described and it is unknown if certain subpopulations (i.e. patients with cognitive impairment) had different outcomes and might benefit from one of the two approaches. Finally, we excluded seven meeting abstracts because there was no data available, this might have introduced publication bias. The strengths of this study are the thorough critical appraisal including the GRADE approach and the comprehensive description of outcomes that matter to patients.

Conclusion

Compared with DLA, PLA might be associated with more dislocations, but patients had less walking problems and a lower tendency to abductor insufficiency. However, based on the current evidence causal inference can not be made. Moreover, little is known on the consequences of the major risks (dislocation vs. abductor insufficiency) in terms of fall risk and independent functioning in ADL.

Implications for future research

Randomised clinical trials with methodological rigor are needed, focusing on outcomes which are important for the patient.

Acknowledgements

We would like to thanks F. S. van Etten-Jamaludin (clinical librarian) for help with compiling the search strategy.

Table 1, Baseline characteristics of the patient populations

Study	Design	n	Mean Follow-up time, mo	Surgical approach, n (%)	Age, mean (SD)	Female, n (%)	Cemented prothesis, n (%)	ASA 3-5, n (%)	Cognitive impairement, n (%)	Primary outcomes	Main conclusion
Hongisto, 2018	ROS	269	12	PLA: 118 (44) DLA: 151(56)	82.8 (6.3)	PLA: 94 (80) DLA: 118 (78)	PLA: 24 (20) DLA: 12 (8)	PLA: 103 (87) DLA: 129 (85)	PLA: 25 (21) DLA: 40 (27)	Living arrangements, need for mobility aids, mobility level and pain	DLA needs more ambulatory aids 1 year after hip fracture
Svenoy, 2017	POS (NE)	583	12	PLA: 186 (32) DLA: 397 (68)	82.8 (7.8)	PLA: 143 (77) DLA: 291 (73)		PLA: 89 (48) DLA: 235 59)	PLA: 48 (26) DLA: 128 (32)	Early complications	PLA has an increased risk for (recurrent) dislocations
Sayed-Noor, 2016*	POS	48	12	PLA: 24 (50) DLA: 24 (50)		PLA: 19 (79) DLA: 20 (83)	PLA: 24 (100) DLA: 24 (100)	PLA: 9 (38) DLA: 14 (58)	NR	Sign of Trendelenburg	The incidence of Trendelenburg was higher in DLA
Mukka, 2016*	POS	185	12	PLA: 83 (45) DLA: 102 (55)		PLA: 61(74) DLA: 68 (67)	NR	PLA: 42 (51) DLA: 57 (56)	NR	Hip function, pain, complication and reoperation rate	No differences in function or complications
Leonardsson, 2016	RS	2118	12	PLA: 978 (46) DLA: 1140 (54)	85 (8)	PLA: 731 (75) DLA: 838 (74)	PLA: 954 (98) DLA: 1110 (97)	PLA: 349 (44) DLA: 579 (55)	PLA: 173 (22) DLA: 237 (23)	Patient-reported outcomes (PROMs)	After adjusting, no differences in PROMs

Study	Design	n	Mean Follow-up time, mo	Surgical approach, n (%)	Age, mean (SD)	Female, n (%)	Cemented prothesis, n (%)	ASA 3-5, n (%)	Cognitive impairement, n (%)	Primary outcomes	Main conclusion
Ozan, 2016	ROS	233	17	PLA: 147 (63) DLA: 86 (37)		PLA: 79 (54) DLA: 57 (66)	NR	PLA: 102 (69) DLA: 60 (69)	NR	Postoperatieve complications	No differences in postoperative complications
Kristensen, 2016	RS	20908	12	PLA: 1990 (10) DLA: 18918 (90)	83 (7)	PLA: 1424 (72) DLA: 137770 (73)	PLA: 851 (43) DLA: 14283 (75)	PLA: 1242 (63) DLA: 11970 (64)	PLA: 582 (29) DLA: 4809 (25)	PROMs and reoperation rate	PLA results in better PROMs. No differences in reoperation rate.
Parker, 2015	RCT	216	12	PLA: 108 (50) DLA: 108 (50)		PLA: 98 (91) DLA: 100 (93)	NR	PLA: 65 (60) DLA: 64 (59)	NR	Regain of walking ability	No differences in mobility between both approaches.
Rogmark, 2014	RS*	33205	32	PLA: 11999 (36) DLA: 21206 (64)	84 (6.7)	Overall 24059 (72)	Overall 29990 (90)	NR	NR	Reoperation rate	PLA: more reoperation due to dislocation and due to infection in DLA.

Study	Design	n	Mean Follow-up time, mo	Surgical approach, n (%)	Age, mean (SD)	Female, n (%)	Cemented prothesis, n (%)	ASA 3-5, n (%)	Cognitive impairement, n (%)	Primary outcomes	Main conclusion
Biber, 2012	ROS	704	NR	PLA: 487 (69) DLA: 217 (31)	80.4 (9.8)	Overall 492 (70)	Overall 673 (96)	NR	NR	Early surgical complications	PLA is predisposed to dislocation, DLA is predisposed to haematoma.
Unwin, 1994	ROS	2906	3	PLA: 1656 (57) DLA: 1250 (43)	NR	NR	Overall 628 (22)	NR	NR	Dislocation rate	Higher dislocation rate in PLA
Paton, 1989	ROS	171	6-48	PLA: 93 (54) DLA: 78 (46)	79.3	NR	NR	NR	NR	Dislocation rate	No differences in dislocation rate between approaches

Abbreviations: mo= months, RCT= randomised controlled trial, POS= prospective observational study, ROS= retrospective observational study , NE= Natural Experiment, RS= register study,
NR= not reported, SD= standard deviaton, ASA= American Association of Anesthesiologists, DLA=Direct lateral approach, PLA= posterolateral approach
*consist the same patient population

Table 2, Quality assessment of non-randomised studies (MINORS)

Quality evaluation criteria*	Hongisto 2018	Svenoy 2017	Kristensen 2017	Ozan 2016	Mukka 2016	Sayed-Noor, 2016	Leonardsson 2016	Rogmark 2014	Biber 2012	Unwin 1994	Paton 1989
Clearly stated aim	2	2	2	1	2	2	2	2	2	2	2
Inclusion of consecutive patients	2	0	2	1	2	2	2	2	2	0	2
Prospective collection of data	1	2	1	1	2	2	1	1	1	1	1
Endpoints appropriate to the study aim	1	1	1	1	1	1	1	1	1	1	1
Unbiased assessment of the study endpoint	0	0	0	0	2	2	0	0	0	0	0
Appropriate follow-up period	2	2	2	2	2	2	2	1	0	2	1
Loss to follow-up less than 5%	1	0	1	0	2	1	1	0	2	1	0
Prospective calculation of the study size	0	0	0	0	2	1	0	0	0	0	0
Adequete control group	2	2	2	2	2	2	2	2	2	2	2
Contemporary groups	2	2	2	2	2	2	2	2	2	2	2
Baseline equivalence	2	2	1	1	2	2	1	0	1	0	0
Adequate statistical analysis	2	2	2	2	2	2	2	2	2	1	1
Total	17	15	16	13	23	21	16	13	15	12	12

Table 3, GRADE evidence profile

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**PLA**	**DLA**	**Relative (95% CI)**	**Absolute (95% CI)**		
Dislocation (follow up: mean 12-17 months)												
6	observational studies	very serious [a]	not serious	not serious	serious [b]	none	57/1129 (5.0%)	13/1061 (1.2%)	not pooled	see comment	⨁◯◯◯ VERY LOW	
Infection (follow up: mean 12-17 months)												
6	observational studies	very serious [a]	not serious	not serious	very serious [c]	none	44/1011 (4.4%)	38/910 (4.2%)	not pooled	see comment	⨁◯◯◯ VERY LOW	
Quality of life (follow up: mean 1 years; assessed with: EQ-5D; Scale from: -0.11 to 1.0)												
3	observational studies	very serious [a]	not serious	not serious	serious [d]	none	2992	20082	not pooled	see comment	⨁◯◯◯ VERY LOW	
Pain (follow up: mean 1 years; assessed with: VAS (SD); Scale from: 0 to 100)												
2	observational studies	very serious [e]	not serious	not serious	not serious	none	2968	20.058	not pooled	see comment	⨁◯◯◯ VERY LOW	
Satisfaction (follow up: mean 1 years; assessed with: VAS (SD); Scale from: 0 to 100)												
2	observational studies	very serious [e]	not serious	not serious	not serious	none	2968	20058	not pooled	see comment	⨁◯◯◯ VERY LOW	
Limping (follow up: mean 1 years; assessed with: OR)												
1	observational studies	serious [f]	not serious	not serious	not serious	none	24	24	not pooled	see comment	⨁◯◯◯ VERY LOW	

CI: Confidence interval.
Explanations: a. No blinding, no randomisation, follow-up not reported properly in some studies; b. Of 6 of the 7 included studies the sample size is too small; c. Of 5 of the 6 included studies the sample size is too small; d. Of 1 of the 3 included studies the sample size is too small; e. No blinding, no randomisation; f. No randomisation.

Table 4, Postoperative complications

		Follow-up	PLA	DLA	p-value
Single dislocation, n (%)					
Hongisto, 2018		12 mo	4 (3.4)	0 (0)	0.04
Svenoy, 2017		12 mo	15 (8)	4 (1)	< 0.01
Mukka, 2016		12 mo	1 (1.2)	2 (2)	ns
Ozan, 2016		6-39 mo	17 (11.5)	4 (4.6)	ns
Parker, 2015		12 mo	1 (0.9)	2 (1.9)	ns
Biber, 2012		Unknown	19 (3.9)	1 (0,5)	0.01
Unwin, 1994		3 mo	149 (9)	41 (3.3)	< 0.01
Paton, 1989		6-48 mo	8 (8.6)	2 (2.6)	ns
Recurrent dislocation, n (%)					
Svenoy, 2017		12 mo	9 (5)	2 (0.5)	< 0.01
Mukka, 2016		12 mo	6 (7.2)	1 (1)	ns
Reoperation due to dislocation, n (%)					
Mukka, 2016		12 mo	5 (6)	1 (1.2)	ns
Leonardsson, 2016		7-22 mo	20 (2)	10 (0.9)	0.02
Rogmark, 2014	HR	32 mo	2.2 (CI 1.8-2.6)		< 0.01
Kristensen, 2016	RR	96 mo	1.2 (CI 0.92-1.4)		ns
Infection, n (%)					
Svenoy, 2017		12 mo	12 (6)	20 (5)	ns
Mukka, 2016		12 mo	5 (6)	5 (5)	ns
Ozan, 2016		6-39 mo	11 (7.4)	3 (3.4)	ns
Parker, 2015		12 mo	4 (3.7)	3 (2.8)	ns
Biber, 2012		Unknown	12 (2.5)	7 (3.2)	ns
Reoperation due to infection, n (%)					
Mukka, 2016		12 mo	5 (5)	4 (3)	ns
Leonardsson, 2016		7-22 mo	13 (1.3)	12 (1.1)	ns
Rogmark, 2014	HR	32 mo	0.8 (0.7-1.3)		0.05

Abbreviations: PLA = posterolateral approach, DLA = Direct lateral approach, mo = months, ns = non significant, HR = Hazard Ratio, RR = Risk Ratio

Table 5, Patient reported quality of life, mobility and function

	PLA	DLA	p-value	Adjusted difference	p-value
Quality of life					
EQ-5D (SD)					
Sayed-Noor, 2016*	0.71 (0.33)	0.81 (0.22)	ns		
Leonardsson, 2016	0.52 (0.37)	0.47 (0.37)	<0.01	- 0.01	ns
Kristensen, 2016	0.64	0.61	0.01	- 0.03	0.01
EQ-VAS					
Kristensen, 2016	64	62	0.05	- 2.1	0.05
Pain, VAS (SD)					
Leonardsson, 2016	17 (19)	19 (20)	0.02	1.4	ns
Kristensen, 2016	17	20	<0.01	3.1	< 0.01
Satisfaction (SD)					
Leonardsson, 2016	22 (23)	24 (24)	0.02	1.5	ns
Kristensen, 2016	21	25	<0.01	4.7	< 0.01
Mobility					
No walking problems (%)					
Kristensen, 2016	42	30	<0.01		
Mobile without walking aid (%)				OR	
Hongisto, 2018	22	11.9	0.02	2.73	0.02
Full mobility after surgery (%)					
Hongisto, 2018	46.2	54	ns		
Function					
Trendelenburg (OR)					
Sayed-Noor, 2017	1	17.5	0.02		
Limping (OR)					
Sayed-Noor, 2017	1	16	<0.01		
HHS (SD)					
Mukka, 2017	72 (17)	71 (18)	ns		
Mean mobility score					
Parker, 2015	5	5.2	ns		

* is a subset of the population of Mukka, 2017
Abbreviations: PLA: posterolateral approach, DLA: direct lateral approach, SD: standard deviation, OR: odds ratio, HHS: Harris hip score, ns: non significant.

Appendix I

("Femoral Neck Fractures"[Mesh] OR "Hip Fractures"[Mesh] OR proximal femur fracture*[tiab] OR femoral neck fracture*[tiab] OR femur neck fracture*[tiab] OR hip fracture*[tiab]) AND ("Hemiarthroplasty"[Mesh] OR hemiarthroplast*[tiab] OR hemi-arthroplast*[tiab]) AND (direct lateral*[tiab] OR lateral*[tiab] OR transgluteal[tiab] OR hardinge[tiab] OR posterolateral[tiab] OR anterior[tiab] OR smith-petersen[tiab] OR anterolateral[tiab] OR watson-jones[tiab] OR posterior[tiab])

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Chapter 5

Similar Superior Patient Reported Outcome Measures (PROMs) for anterior and posterolateral approach after total hip arthroplasty.

Postoperative patient reported outcome measure improvement after 3 months in 12,774 primary THAs using the anterior, anterolateral, straight lateral or posterolateral approach.

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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 with 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 [1]. 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 [2].

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 [3]. The direct lateral approach is associated with post-operative limping secondary to abductor weakness [4, 5]. The anterolateral approach, theoretically facilitates early patient recovery and low dislocation rates [6]. However, damage to the femoral shaft and malalignment of the femoral component have been reported [7]. 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 [5, 8], perhaps because of diminished muscle trauma [1, 9]. However, the anterior approach is a technically demanding procedure, associated with a steep learning curve [10], and seems to be associated with increased femoral loosening at medium term [3, 11].

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 [4, 12]. Amlie et al. demonstrated inferior PROM scores for the direct lateral approach compared to the anterior and posterolateral approach using the Norwegian Arthroplasty Registry [1]. 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.

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 [13]. 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 [14], in order to obtain information on the vital status and date of death of registered patients [13].

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. In order to measure health related quality of life (HRQoL), pain and functional outcomes, a set of PROMs as recommended by the Netherlands Orthopedic Association 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 [15-16]. 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 [17-18]. 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) [19]. 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 [20]. 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 [21-23]. 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) [24]. Furthermore, surgical outcome 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) [1, 25]. 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 Figure 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
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

	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)	
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	24	0.7	33	5.8	9	0.9	508	7.0	574	4.7
PE	67	2.0	9	1.6	45	4.3	106	1.5	227	1.9
Other										
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).

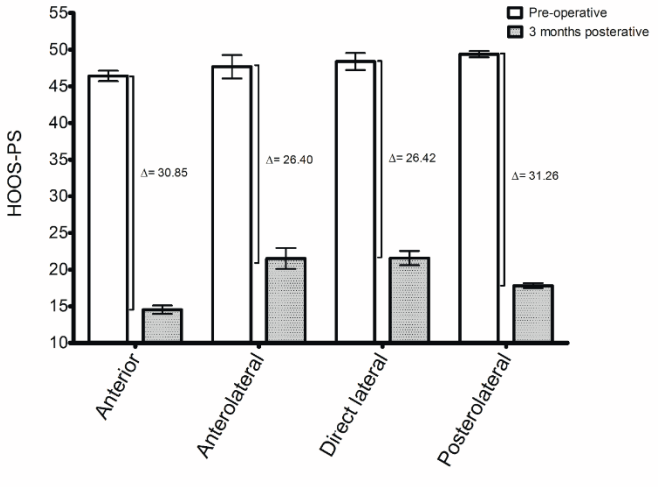

Fig. 1. Crude (non-casemix corrected) pre-operative and postoperative HOOS-PS scores for different approaches.

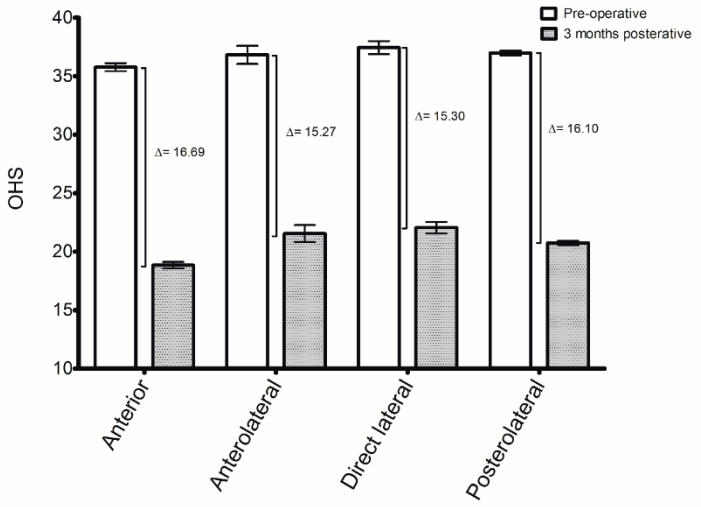

Fig. 2. Crude (non-casemix corrected) pre-operative and postoperative OHS scores for different approaches.

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: 0.21-0.24) (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, 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).

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
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

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
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
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	0.086	0.08

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). Furthermore, the anterior approach was associated with a larger improvement in NRS pain, in rest, compared to the anterolateral approach. 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 (Fig. 6). These differences measured an effect size lower than 0.2 (Table 3).

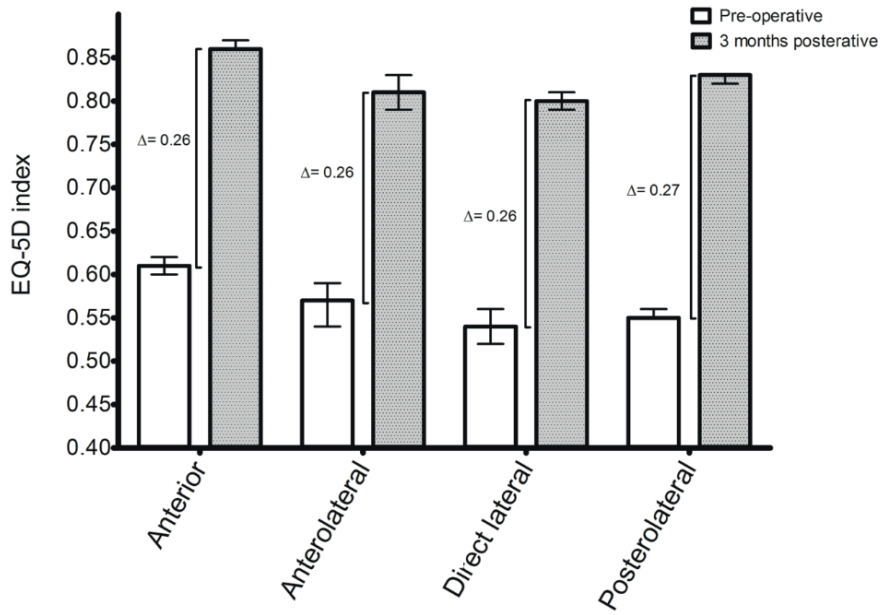

Fig. 3. Crude (non-casemix corrected) pre-operative and postoperative EQ-5D index scores for different approaches.

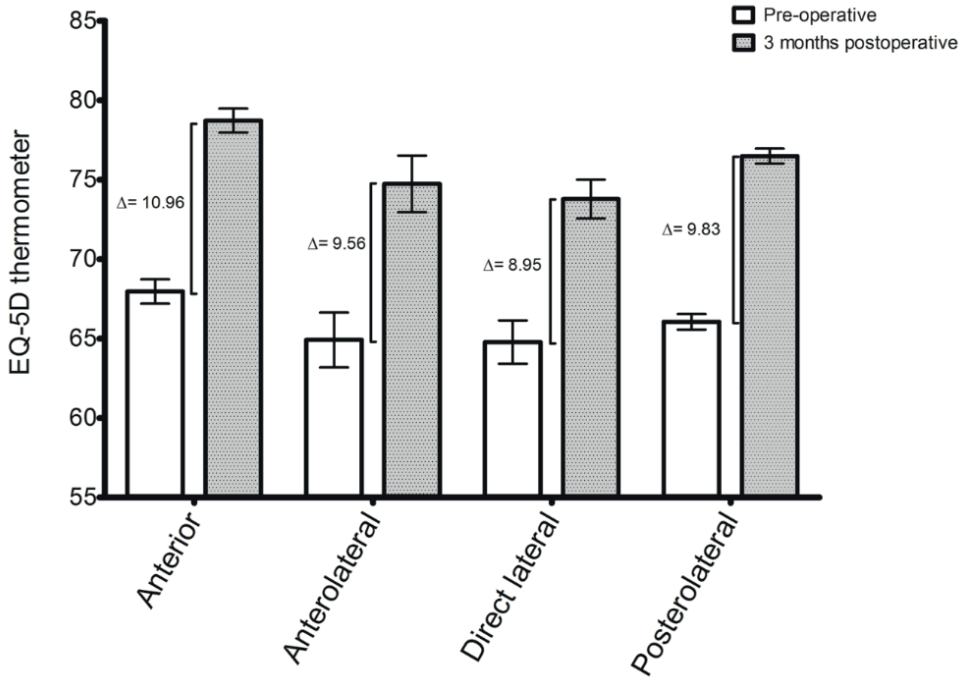

Fig. 4. Crude (non-casemix corrected) pre-operative and postoperative EQ-5D thermometer scores for different approaches.

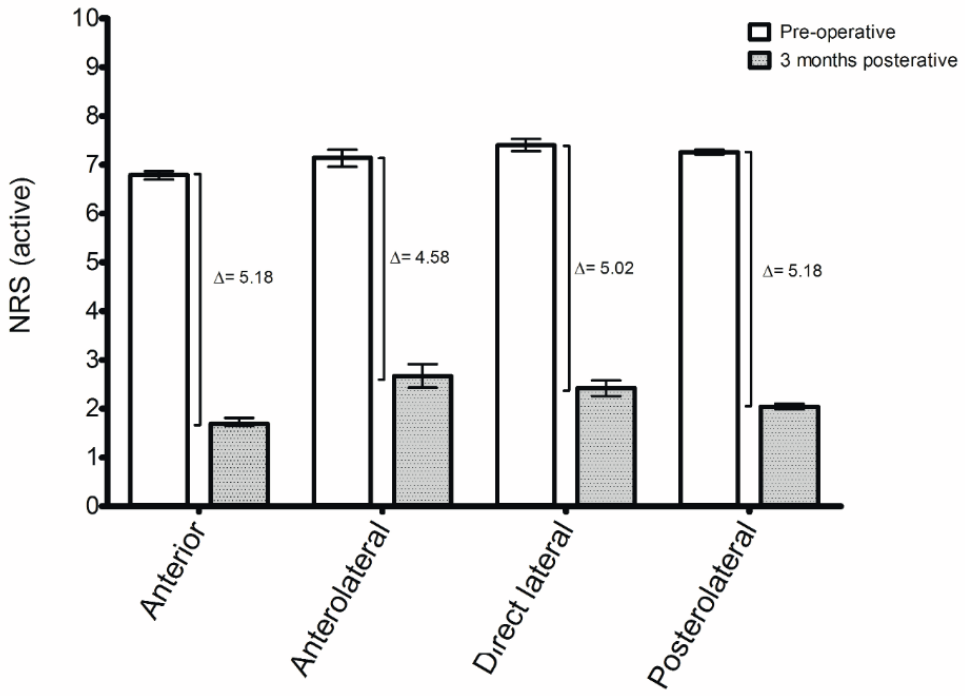

Fig. 5. Crude (non-casemix corrected) pre-operative and postoperative NRS (active) scores for different approaches.

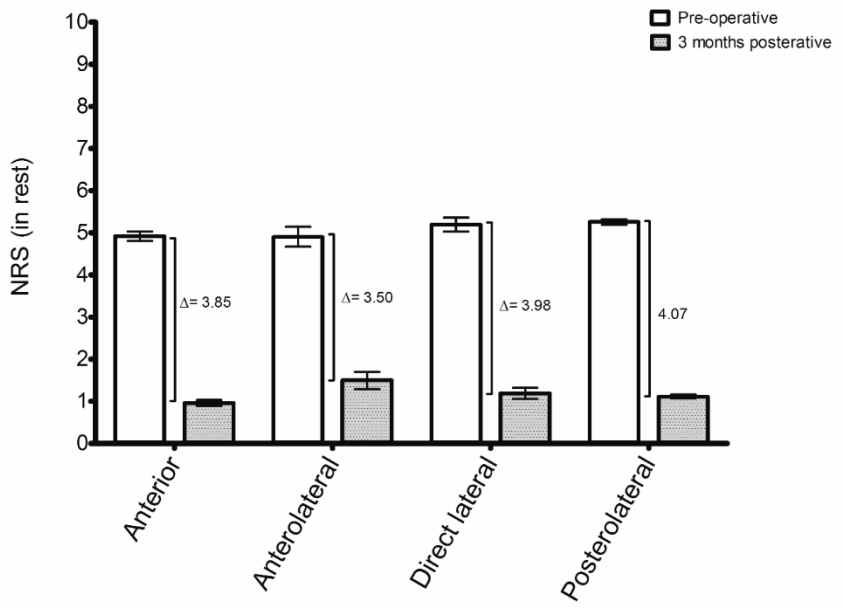

Fig. 6. Crude (non-casemix corrected) pre-operative and postoperative NRS (in rest) scores for different approaches.

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 [9]. 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 et al. found worse outcomes 1-3 years after primary THA performed with the direct lateral approach rather than the anterior and posterolateral approach [1]. 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 [1]. Lindgren et al.demonstrated that patients operated through a posterolateral approach perceived less residual pain and greater satisfaction after elective THAs compared to the direct lateral approach [12]. 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 [26]. 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 [4, 18, 27]. The MCID for the HOOS-PS is determined at 23 [28]. 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 [3, 10].

In addition to the MCID, an effect size (Cohens' d) can be calculated. This method was adopted previously by the Norwegian Arthroplasty Register [1]. 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 [25].

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 et al. found that differences found at 3 months postoperative were likely to persist over a 6-year period, indicating a long-term benefit [12]. 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 [4]. 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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Online version of the paper:

Part 3

The influence of *implant design* on outcomes after total hip arthroplasty

Chapter 6

Curved versus Straight Stem Uncemented Total Hip Arthroplasty Osteoarthritis Multicenter trial (CUSTOM): Design of a prospective blinded randomised controlled multicentre trial.

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ABSTRACT

Introduction

Answering the demands of an increasingly young and active patient population, recent developments in total hip arthroplasty (THA) have shifted towards minimising tissue damage. The Collum Femoris Preserving (CFP) stem was developed to preserve the trochanteric region of the femur, which potentially preserves the insertion of the gluteus musculature. This might accelerate early postoperative rehabilitation and improve functional outcome. Currently the functional results of the CFP stem have not been compared with conventional straight stems in a randomised controlled trial (RCT). The primary purpose of this trial is to compare the functional result of CFP stem THA with conventional uncemented straight stem THA, measured by the Dutch Hip disability and Osteoarthritis Outcome Score (HOOS) at three months follow-up.

Methods

A prospective blinded multicentre RCT will be performed. We aim to recruit 150 patients. The patients will be randomly allocated to a THA with a straight or a curved stem. All patients, research assistants, clinical assessors and investigators will be blinded for the type of prosthesis for 5 years. Clinical assessments and roentgenograms will be taken preoperative, at six weeks after surgery, at one, two, three, four and five years after surgery. Patient reported outcome measures (PROMs) will be obtained at the same follow-up moments. In addition, the PROMs will also be send to the patients at three and six months after surgery. The HOOS scores at three months follow-up will be our primary outcome.

Ethics and dissemination

This trial will be performed in accordance with the Declaration of Helsinki. A local ethics committee has approved this trial. Written informed consent will be obtained from all participating patients. All serious adverse events will be reported to the ethics committee. Results will be submitted for publication to an orthopaedics related journal.

Trial registration

Dutch Trial Registry (www.trialregister.nl) NTR1560.

INTRODUCTION

For years developments in total hip arthroplasty have focussed mainly on improving implant survival, resulting in long term survival rates of more than 90% for uncemented as well as cemented stems.(1) Answering the demands of an increasingly young and active patient population, recent developments have shifted towards minimising tissue damage, thereby retaining normal physiology without compromising implant stability. This resulted in the modification of surgical techniques and the development of innovative bone and soft tissue preserving implants. The aim of these developments was to accelerate early postoperative rehabilitation, improve long lasting functional outcome and preserve bone stock for future revisions.(2) Short stem total hip arthroplasty aims to combine well-established anchoring principles with bone preservation. Short stems can be classified into the following categories (2-4): (1) "collum"; conical or cylindrical ultra-short stems, with complete anchorage in the femoral neck; (2) "partial collum"; partial femoral neck-sparing curved designs; and (3) "trochanter-sparing": trochanter-sparing but not neck-sparing, and shortened tapered stem. A large number of observational studies on "partial collum" and "trochanter-sparing" stems are available, demonstrating adequate survival rates at medium-term follow-up. Clinical evidence from "collum stem" studies is limited to a small number of studies with a medium-term follow-up period. These studies did not show a satisfactory overall survival rate, as shown in a recent systematic review.(2) The use of conventional straight stems, such as the Zweymuller stem, has shown a 10 year survival rate of 90-100%.(5-8) Weissinger et al. have shown a re-operation rate of 6.8% after 20 years.(9) However, their diaphyseal fixation may result in proximal stress shielding resulting in potential proximal osteolysis which may cause aseptic loosening.(10-12) The Zweymuller hip stem is a widely used uncemented straight stem, designed and introduced by prof. dr. K. Zweymuller. Both the Stepless design as well as the initial Hochgezogen type, have shown excellent survival rates [refs].(12-15) Furthermore, stability of the implant was not affected by any proximal osteolysis (12;16) although osteolysis may complicate future revisions. The improved proximal anchorage of this stem requires the use of a box chisel cutting a slot in the trochanteric fossa near the insertion of both the gluteus medius and the piriformis tendon to obtain entry in neutral alignment. A previous cadaver study by Van Oldenrijk et al. demonstrated a median gluteus medius midsubstance surface area damage of 22% (min 6- max 40%) after Zweymuller stem placement using a lateral transgluteus approach.(17) Moreover, the external rotators were found to be unintentionally transected in one out of five hips using this approach. Damage to the insertion of the gluteus musculature is an important cause of postoperative pain at the greater trochanter and reduced abductor strength,

resulting in limping and a positive Trendelenburg gait.(18-20) Magnetic Resonance Imaging (MRI) of postoperative asymptomatic as well as symptomatic patients showed damage to the gluteus medius and minimus muscles and tendons to be significantly more common in symptomatic patients.(19) Tendon diameter changes as well as fatty atrophy of the gluteus medius muscle and the posterior aspect of the gluteus minimus muscle were significantly more common in patients with trochanteric pain, limping and / or abduction weakness. Pipino et al. introduced the Biodynamic stem with the aim to retain physiological load on the bone, thereby reducing stress shielding and potential proximal bone loss. The main innovation was the preservation of the collum femoris, thereby preserving proximal bone stock for any future revisions. Furthermore, preservation of the trochanteric region of the femur potentially preserves the insertion of the gluteus musculature. The initial biodynamic stem showed good medium and long term survival rates.(21;22) The Biodynamic was later modified into the Collum Femoris Preserving (CFP) stem (Waldemar Link, Germany). The CFP was specifically designed to: 1) achieve rotational stability by triplanar fixation through the lateral cortical cylinder of the neck and resistance to varus-valgus stress; 2) preserve proximal bone stock; 3) achieve stable fixation on the cortex and impacted metaphyseal bone; 4) increase cortical contact and oppose torsion forces by longitudinal ribs; 5) create a physiological load transfer; 6) preserve femoral circumflex arteries; 7) increase osseointegration with a microporous hydroxyapatite coating; 8) preserve gluteal insertions on the greater trochanter.(22;23) Previous case series with a mean follow-up of 5.1 years demonstrated a revisions / 100 component years rate of 0,21 thereby indicating excellent integration and survivorship.(23-33) Clinical follow-up showed good functional recovery and DEXA analysis of ten patients showed minimal periprosthetic bone loss.(21;24) Two year follow-up migration assessment using radiostereometry showed low migration, suggesting a favourable long-term outcome.(23;34) The CFP stem is only suitable for selected patients. The integrity of the collum needs to be sufficient, since it uses the collum and proximal femur for anchorage. Therefore, patients with large collum deformities, such as in extreme coxa vara, after a collum fracture and in extreme hip dysplasia, may be less suitable for CFP total hip arthroplasty. The quality of currently available evidence is low, so only a weak recommendation can be provided for clinical usage of these short stem designs.(35) Stronger evidence is necessary, including prospective multicentre randomized trials, before widespread use can be recommended.(35) Currently the functional results of the CFP stem have not been compared with conventional straight stems in a randomised controlled trial (RCT), therefore additional benefits remain to be determined. We aim to compare the early and medium term functional result of a CFP stem THA to conventional straight stem THA. The purpose of this trial is to compare the functional result of CFP stem THA with

conventional uncemented straight stem THA, measured by the Dutch version of the Hip disability and Osteoarthritis Outcome Score (HOOS) (36) at three months follow-up. The secondary objective will be an evaluation of secondary outcomes discussed in detail below. Since the CFP stem may require less dissection of the gluteus muscle off the greater trochanter we expect to find a better short term functional result after CFP stem THA compared to conventional straight stem THA as reflected in higher HOOS scores.

METHODS

Trial design

A prospective blinded randomized controlled multicentre trial will be performed at Onze Lieve Vrouwe Gasthuis (OLVG) in Amsterdam and at Ikazia hospital in Rotterdam, both in the Netherlands. 100 Patients from OLVG and 50 patients from Ikazia will be recruited. Three orthopaedic surgeons from OLVG and two orthopaedic surgeons from Ikazia participate in this trial. This trial is registered at the Dutch Trial Registry (Nederlands Trial Register, www.trialregister.nl), file number NTR1560.

Participants

We will include patients between 18 and 70 years old with osteoarthritis of the hip, who meet the clinical criteria to undergo a cementless total hip arthroplasty. Consecutive patients from the waiting list for a total hip replacement will be approached for participating in this trial if they meet the inclusion criteria. Patients will be excluded when they: are not able to fill out the Dutch questionnaires; have morbid obesity with a BMI of more than 40; have an altered anatomy resulting in impossibility for one of the procedures; have had a lower extremity amputation; have a known alcohol or drugs abuse; have an active malignant disease or current cytostatic treatment; have had a previous hip arthroplasty (ipsi- or contralateral) or when they have avascular head necrosis due to sickelcel anemia.

The attending orthopaedic surgeon will inform the eligible patient about the trial. A research assistant will contact the patient by phone to resolve any questions. When the patient agrees to participate in this trial, informed consent has to be signed by both the orthopaedic surgeon or research assistant and the patient. After enrolment in this trial, patients will be assigned to a study identification number. Only the study identification number will be used on data forms and in the

databases. The encryption between the study identification number and the personal information will only be accessible for the research coordinator of this trial.

Randomization and blinding

After signing informed consent, the patient will be randomly allocated to a total hip arthroplasty with a straight stem or a curved stem. Stratified block randomization will be used as allocation method. Blocks consist of 10 consecutive surgical procedures. At the end of each block an equal distribution of patients between the two groups will have been reached. Patient allocation will be stratified to surgeon, resulting in an equal distribution of surgical expertise and technique variation in each group. Randomisation will not be performed until the moment of surgery. The surgeon will therefor perform pre-operative templating for both stems, and both stems and their instrumentation trays will be available in the surgery room. Since a digital randomization system proved to be unsuccessful in our hospital due to technical difficulties, randomization will be performed using envelopes. We will use randomization envelopes that are sealed, sequentially numbered, opaque and blinded. An independent investigator will make these randomization envelopes available to the surgeon in the operating room, after the patient is under anaesthesia and just before incision. Both types of implants are ready to use in the operating room. All patients, research assistants, clinical assessors and investigators will be blinded for the type of prosthesis for the total duration of the follow-up: 5 years. A pop-up message will be attached to the patient records in the electronically hospital information system. This pop-up message is a reminder that the patient and clinical assessors are blinded, and therefore the roentgenograms should not be shown. Only the orthopaedic surgeon will verify the roentgenograms, so in case there are any problems there can be intervened. Data will be processed and analysed by blinded investigators. After finalising data analyses the blinding will be broken for publication purposes.

The number of deblinded patients will be recorded and presented in final reports.

Interventions

All participating surgeons should have gained experience with both implants. At least five procedures for both implants should have been performed prior to participating in the trial. The learning curve for the CFP stem is assessed in an earlier study (33;37), and an acceptable level of proficiency is assumed after performing five procedures.

A lateral transgluteal approach in lateral decubitus position is used in all patients.

The same rehabilitation protocol will be used for both groups. Postoperatively, patients are allowed to fully weight bear with the use of crutches from the first postoperative day, continuing crutches if necessary during the first six weeks.

Straight Stemmed Total Hip Arthroplasty

Patients randomized into the straight stem group will undergo surgery for a total hip arthroplasty wherein a straight, cementless, Alloclassic stem (Zimmer, Warsaw, USA) will be used. This stem is inserted parallel to the longitudinal axis of the femur.

Curved Stemmed Total Hip Arthroplasty

Patients randomized into the curved stem group will undergo surgery for a total hip arthroplasty wherein a curved, cementless, Collum Femoris Preserving (CFP) stem (Waldemar Link, Hamburg, Germany) will be used. This stem follows the curvature of the remaining femoral neck. Two curvatures are available: A for coxa valga and norma and B for coxa vara. The curvature will be assessed pre-operatively by templating the hip.

Cup

A Trabeculae Oriented Pattern (TOP) cementless hemispheric cup (Waldemar Link, Hamburg, Germany) with a polyethylene liner will be used in both groups. The TOP cup has a biequatorial dissociation with a medial-caudal recess to allow a wider range of motion and an elevated cranial rim to reduce the risk of dislocation.(22) A Follow-up study of 301 TOP cups showed no detachment, migration, or osteolysis after 7 years.(24) All implants are positioned without the use of navigation.

Head

In both groups a 32 or 28 mm. ceramic head is used.

Outcome measures

Primary Outcome

The Dutch version of the Hip disability and Osteoarthritis Outcome Score (HOOS) (36) will be our primary outcome. The HOOS is a patient reported outcome measure (PROM) that consists of five subscales; pain, other symptoms, function in daily living, function in sport and recreation and hip related quality of life. The week preceding the day of observation is taken into consideration when answering the questions. Standardized answering options are given for each question (five Likert

boxes) ranging from 0 to 4. A normalized score (100 indicating no symptoms and 0 indicating extreme symptoms) is calculated for each subscale.

Secondary Outcomes

Secondary outcomes will be the amount of re-operations due to implant related complications. For example: bleeding or vascular damage; neurogenic damage; fractures; dislocation; infection; loosening; deep venous thrombosis. Other secondary outcomes are pain in the ipsi- and contralateral hip, knees and back, measured by a numeric rating scale (NRS), abductor strength measured by the Trendelenburg test (38), walking ability measured by the Timed Up and Go (TUG) test (39;40), physical functioning measured by the Harris Hip Score (HHS) (41), general health measured by the Short-Form 12 item (SF-12) questionnaire (42), quality of life by the EuroQol 5 Dimension (EQ-5D) questionnaire (43) and position of the prosthesis. The position of the prosthesis will be measured on weight bearing anterior posterior pelvis with the patient's feet facing forward and hip faux profile roentgenograms. Pre-operatively an X-ray will be taken which includes a ball of known diameter to enable calibration. Post-operatively X-rays are taken at day one, 6 weeks, and annually up to 5 years after surgery. An assessor who is not involved with the surgical procedures will perform all measurements. The clinical assessments, containing the range of motion of the hip, the Trendelenburg test, the Timed up and Go test and measuring leg length discrepancy will be performed at baseline (within one week prior to surgery), at six weeks after surgery, at one, two, three, four and five years after surgery. A trained research assistant will perform all clinical tests. Roentgenograms will be taken at the same time points. The PROMs, containing the HOOS, NRS, HHS, SF-12 and EQ-5D, can be filled out using either pen and paper or web based forms. The PROMs will be sent to the patient's home address (including pre-stamped return envelopes) or e-mail address. Patients are asked to fill out the PROMs at the same follow up moments as the clinical assessments. In addition, the PROMs will also be send to the patients three and six months after surgery. Every patient will receive a reminding card containing the date of surgery and the subsequent months / years of clinical follow-up. For every follow-up visit, patients will be contacted by phone to make an appointment. Patients who have not responded to the PROMs, are contacted by phone as a reminder.

Sample size

Sample size calculation is based on the HOOS pain subscale. De Groot et al. found a mean HOOS pain score of 65.4 points with a standard deviation of 14.3 in patients 9.5 months after total hip arthroplasty.(36) We consider a 10% difference in outcome clinically relevant, resulting in a 7 point

difference.(44) Based on these assumptions setting **α** at 0.05 and the power level at 80% a sample size of 67 in each group is required to detect a statistically significant difference. We expect a maximum drop-out rate of 10%, resulting in a total of 150 patients (75 patients in the curved stem group and 75 patients in the straight stem group). We expect to recruit the 150 patients within a period of 2 years.

Statistical analyses

To investigate the effect of both implants, we will use generalized estimating equations (GEE) for longitudinal analysis in SPSS. All patients who withdraw from the trial after surgery and patients that undergo a revision surgery, will be included in an intention-to-treat analysis. Both intention-to-treat analysis and per-protocol analysis will be performed. This method takes into account the dependency of observations within a patient, and the fact that not all patients may be assessed at each time point (missing data).

Primary Analyses

In the primary GEE model, the outcome variable studied (e.g. physical function on the HOOS) will be analyzed as a dependent variable, using implant allocation (1, CFP; 0, Zweymuller) and time as key independent variables. The main interest of the study is on the effect at 3 months, but all time moments will be analyzed in the same GEE model.

Secondary Analyses

In the secondary GEE model, the outcome variables studied (e.g. physical function on the HHS, general health on the SF12, quality of life on the EQ5D, walking ability on the TUG, pain on the NRS, hip range of motion, abductor strength on the Trendelenburg test, position of the prosthesis and leg length discrepancy on the roentgenograms, satisfaction) will be analyzed in a similar way. To evaluate whether the two implant groups differed in change over time the interaction term of group and time (group x time) will be assessed. Time will be included as a dummy variable (reference = baseline T0), and seven interaction terms will be analyzed (T1 6weeks x group, T2 3months x group; T3 6months x group; T4 1year x group, T5 2years x group, T6 3years x group, T7 4years x group, T8 5years x group). All models will be corrected for center of inclusion and surgeon. In additional analysis, we will investigate the possible confounding effect (defined as more than 10% change in the parameter estimate for group x time) of several variables (body mass index, gender, ASA-classification, co-morbidity, mental health, other joint pain). At the following time points following the surgery (T4,

T5, T6, T7 and T8) we will describe the incidence of re-operations (both implant groups) using descriptives. For all analysis, a two-tailed value of $p < 0.05$ is considered to be significant.

Data storage

Data will be entered into a digital database (SPSS) and after the data entry, paper data collection forms will be stored in an archive. Both paper forms and digital databases will only be accessible by the research coordinator.

Ethics and dissemination

This trial will be performed in accordance with the Declaration of Helsinki. The ethics committee (Verenigde Commissies Mensgebonden Onderzoek, Nieuwegein, the Netherlands) has approved this trial on 16-09-2008, file number NL21637.100.08. Written informed consent will be obtained from all participating patients. All serious adverse events will be reported to the ethics committee. Results will be submitted for publication to an orthopaedics related journal.

Protecting Against Sources of Bias

Selection bias

In this trial, the risk of selection bias is reduced by approaching all consecutive eligible patients.

Furthermore, randomisation will not be performed until the moment of surgery. This will prevent selecting patients for a specific type of prosthesis.

Performance bias (Blinding)

Unblinded patients allocated to an intervention which they do not prefer, may feel resentful. This may lead to performance bias.(45;46) In this trial all patients will be blinded for the type of prosthesis, reducing the risk of performance bias.

Performance bias (Surgeon Expertise)

Requiring a minimum number of procedures prior to initiating the trial reduces the risk of performance bias.

Detection bias

The clinical assessors that will perform the clinical tests will be blinded, to reduce the risk of detection bias.

Attrition bias

To reduce attrition bias, a blinded research assistant is the direct contact person for all trial patients. Efforts are undertaken to minimize the amount of patient drop-out or lost-to-follow up. Moreover, all PROMs and clinical assessment data is verified to prevent incomplete data.

Publication bias

By publishing this protocol, we would like to prevent publication bias. Results of this trial will be submitted for publication in a peer-reviewed journal.

Minimizing Co-Interventions and Contamination

Cross-over between intervention groups can occur. For instance when a revision surgery will be performed and another type of stem will be implanted. All patients will be analyzed in the group to which they were allocated, following the intention-to-treat analysis. Additionally, we can perform per-protocol analysis.

DISCUSSION

Authors of surgical RCTs often fail to report measures to prevent bias.(47-51) Several reviews of RCTs in orthopaedic surgery have studied the reporting of bias prevention. They found that this is often not well reported. Blinding of outcome assessors, concealment of allocation and intention-to-treat analysis are types of bias prevention that are often not reported.(45;46;52) In this trial, extensive measures will be taken to reduce the risk of bias. It will be a challenge to keep all involved persons, patients as well as research staff, blinded for 5 years. These strenuous measures to reduce the risk of bias may serve as a model for future implant related orthopaedic RCTs. This trial will be the first RCT that compares the early and medium term functional results of the CFP stem THA with conventional straight stem (Zweymuller) THA. Herewith this trial can contribute to the clinical evidence around short stem THA.

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Online version of the paper:

Chapter 7

Short versus conventional straight stem in uncemented total hip arthroplasty: functional outcomes up to 5 years and survival up to 12 years: secondary results of a randomized controlled trial.

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ABSTRACT

Background and purpose

To date, the mid- and long-term outcomes of the Collum Femoris Preserving (CFP) stem compared with conventional straight stems are unknown. We aimed to compare physical function at 5-year follow-up and implant survival at an average of 10-year follow-up in an RCT.

Patients and methods

This is a secondary report of a double-blinded RCT in 2 hospitals. Patients aged 18–70 years with hip osteoarthritis undergoing an uncemented primary THA were randomized to a CFP or a Zweymüller stem. Patient-reported outcomes, clinical tests, and radiographs were collected at baseline, 2, 3, 4, and 5 years postoperatively. Primary outcome was the Hip disability and Osteoarthritis Outcome Score (HOOS) function in activities of daily living (ADL) subscale. Secondary outcomes were other patient-reported outcomes, clinical tests, adverse events, and implant survival. Kaplan–Meier and competing risk survival analyses were performed with data from the Dutch Arthroplasty Registry.

Results

We included 150 patients. Mean difference between groups on the HOOS ADL subscale at 5 years was –0.07 (95% confidence interval –5.1 to 4.9). Overall survival was 92% for the CFP and 96% for the Zweymüller stem. No significant difference was found.

Conclusion

No significant differences were found in physical function at 5-year and implant survival at 10-year follow-up between the CFP and Zweymüller stems. When taking cup revisions into account, the CFP group showed clinically inferior survival.

INTRODUCTION

A growing number of total hip arthroplasties (THAs), especially in young and more active patients, causes an increase in the number of revision surgeries [1]. In general, cementless fixation is preferred for younger patients and cemented fixation for older patients [2,3]. To improve the prognosis of first revisions, development in primary THA has aimed to preserve bone stock. This has resulted in short-stem implants, such as the Collum Femoris Preserving stem (CFP, Waldemar Link GmbH, Hamburg, Germany).

The CFP is meant to preserve bone stock because of less femoral neck resection and less femoral reaming. It is supposed to be easier to insert and extract, which might be beneficial for future revisions [4,5]. Possible sparing of soft tissue may accelerate early postoperative rehabilitation and also improve long-lasting functional outcomes [6-8].

In 2009 we initiated the CUSTOM trial; the first randomized clinical trial (RCT) to compare the CFP with a conventional uncemented straight Zweymüller Alloclassic stem (Zimmer Biomet, Warsaw, IN, USA) [7]. The primary aim was to compare the functional results of these stems at 3 months and 2 years postoperatively. We previously reported that functional outcomes of the CFP were not superior to the conventional uncemented Zweymüller stem up to 2 years after surgery [9]. Other studies investigating the CFP were mostly cohort studies [10-14]. Available RCTs have small sample sizes and a relatively short follow-up [15,16]. To date, high-quality evidence on mid- and long-term outcomes of CFP stems compared with conventional straight stems is lacking. Therefore, we aimed to compare physical function measured with the Hip disability and Osteoarthritis Outcome Score (HOOS) function in Activities of Daily Living (ADL) subscale, at 5 years postoperatively, between patients with a CFP and a conventional uncemented Zweymüller stem. Secondary aims were to compare other patient-reported outcome measures (PROMs), clinical tests, and adverse events up to 5 years' and implant survival at 10 years' follow-up.

METHODS

Design

We performed a double-blinded randomized controlled trial (RCT) in 2 general hospitals in the Netherlands. The protocol and the 2-year results have been published [7,9].

Participants

Patients aged 18–70 years with hip osteoarthritis and meeting the criteria for an uncemented primary THA were eligible for participation. Exclusion criteria were body mass index (BMI) > 40, anatomy not suited for 1 of the procedures, life expectancy < 5 years, inability to fill out the PROMs, and previous or planned contralateral THA. Patients were not financially compensated for participation.

Randomization and blinding

Patients were allocated to a CFP or conventional uncemented Zweymüller stem, on a 1:1 ratio, using block randomization resulting in even group numbers per surgeon. Patients were blinded to the type of prosthesis up to 5-year follow-up, to prevent performance bias. Clinical assessment and data analysis were performed by blinded researchers.

Intervention

Short stem

Patients received a THA with a curved, uncemented CFP stem. 2 curvatures are available: (A) for coxa valga and norma, and (B) for coxa vara. The curvature was assessed preoperatively by templating the hip.

Straight stem

Patients received a THA with a straight, uncemented Zweymüller stem.

Both groups

All patients received a THA using the direct lateral transgluteal surgical approach, with less gluteal dissection for the exposure of the femoral neck in the short stem group. A Trabeculae Oriented Pattern (TOP) uncemented hemispheric cup (Waldemar Link GmbH, Hamburg, Germany) with a polyethylene liner was used in both groups. All implants were positioned without the use of navigation. The same postoperative rehabilitation protocol was used for both groups.

Data collection

PROMs were sent at baseline and at 6 weeks, 3 months, 6 months, 1, 2, 3, 4, and 5 years postoperatively. Patients had the option to complete the PROMs online or paper based. In the online tool all questions were mandatory, preventing missing items. Multiple efforts were made to ensure compliance with the study procedures: digital reminders were sent, and patients were contacted by telephone in case of a missed follow-up or any missing items on the PROMs. Clinical tests were performed and radiographs were taken at the outpatient clinics at baseline and at 6 weeks, 1, 2, 3, 4, and 5 years postoperatively. This study focuses on the results from 2 years after surgery.

Primary outcome

Primary outcome was physical functioning measured with the HOOS ADL subscale (17), which is 1 of 5 subscales in HOOS. A score of 100 indicates no symptoms and 0 indicates extreme symptoms.

Secondary outcomes

PROMs

For secondary outcome, we used the other 4 subscales of the HOOS, which are "Symptoms," "Pain," "Function in Sport and Recreation" (Sport/Rec), and "Hip Related Quality of Life" (QoL) [17]. For each subscale, a score of 100 indicates no symptoms and 0 indicates extreme symptoms. Physical functioning was also measured with the modified Harris Hip Score (mHHS) [18,19]. Pain was also assessed on an 11-point Numeric Rating Scale (NRS). Physical health was measured with the Short Form-12 Physical Component Scale (SF-12 PCS) [20] and quality of life was assessed with the EQ-5D-3L score [21].

Clinical tests

We measured range of motion as a part of the mHHS, walking ability with the Timed Up and Go test (TUG) [22], abductor strength through the Trendelenburg test [23], and the presence of a leg length discrepancy.

Adverse events and revision surgery

Adverse events, defined as reoperations and implant-related complications, were reported at every follow-up moment. Radiology reports were screened for abnormalities, and the Dutch Arthroplasty Registry was consulted for revisions and mortality that occurred after the 5-year follow-up.

Sample size calculation

The sample size was calculated prior to conducting this trial, based on the HOOS Pain subscale. The

sample size was based on a standard deviation of 14.3, based on a study by de Groot et al. [17], an α of 0.05, and a power of 80%. A 10% difference in outcome was considered clinically relevant by the study team. This resulted in a sample size of 67 patients in each group. We anticipated a 10% loss to follow-up, resulting in 75 patients per group.

Statistics

Primary analyses were based on the intention-to-treat principle, according to the randomization results. An additional as-treated analysis was considered depending on any crossovers between the groups. A linear mixed model analysis with a random intercept for repeated measures within subjects was used for all continuous outcomes: the HOOS subscales; mHHS; TUG; pain in the operated hip/contralateral hip/back/knee; SF12 PCS; and EQ5D utility scores. An unadjusted model was built, with the baseline score for the outcome, time, and intervention group as independent variables. Time (follow-up moment) was used as categorical factor and an interaction term between time and intervention group was added to assess differences between the interventions for each follow-up moment. To test for robustness of the primary outcome results, a sensitivity analysis was performed in which only the completely blinded patients at 5 years' follow-up were analyzed. To improve precision of the group effect estimates, an adjusted model was built including ASA classification, age, BMI, sex, comorbidities (pulmonary and cardiac), and hospital as potential confounders. The minimal clinically important improvement (MCII) and patient acceptable symptom state (PASS) are reported for the HOOS Pain and QoL subscales [24].

Dichotomous outcomes—adverse events, revisions, Trendelenburg test, and leg length discrepancy—were analysed using chi-square tests.

A Kaplan–Meier survival analysis was carried out, complemented with a competing risk analysis, which takes the deceased patients into account. This analysis was based on the as-treated data. Observations were censored at time of revision, death, lost to follow-up, or end of study. SPSS version 22 (IBM Corp, Armonk, NY, USA) and R (version 4.2.2, survival package; R Foundation for Statistical Computing, Vienna, Austria) were used for all analyses.

Ethics, registration, funding, data sharing, and disclosures

Ethical approval was obtained by the Medical Research Ethics Committees United (MEC-U), the Netherlands (NL21637.100.08 _16 September 2008). This trial is registered on the International Clinical Trials Registry Platform, with ID number NTR1560 and is carried out according to the Declaration of Helsinki. All participants signed written informed consent. Link Nederland funded this trial based on

a predefined budget, including salary costs for research personnel and study-related procedures. All authors have no conflict of interest to report.

RESULTS

Patients

150 patients were included between August 2009 and October 2012 (Figure 1). Table 1 gives the baseline characteristics per group. There was only 1 crossover between the groups; this patient was randomized to a CFP stem but received a Zweymüller stem. Therefore, the intention-to-treat analyses and the as-treated analyses yielded highly similar results and only the intention-to-treat results are presented in this article.

130 patients (87%) completed the 5-year follow-up. 5 patients did not visit the hospital for clinical tests and radiographs but did fill out PROMs (3 CFP and 2 Zweymüller). One reason (CFP) was that the patient was living abroad, other reasons are unknown. 7 patients did not fill out PROMs but did visit the hospital for follow-up (5 CFP and 2 Zweymüller), reasons are unknown. 7 patients were lost to follow-up (3 CFP and 4 Zweymüller) (see Figure 1).

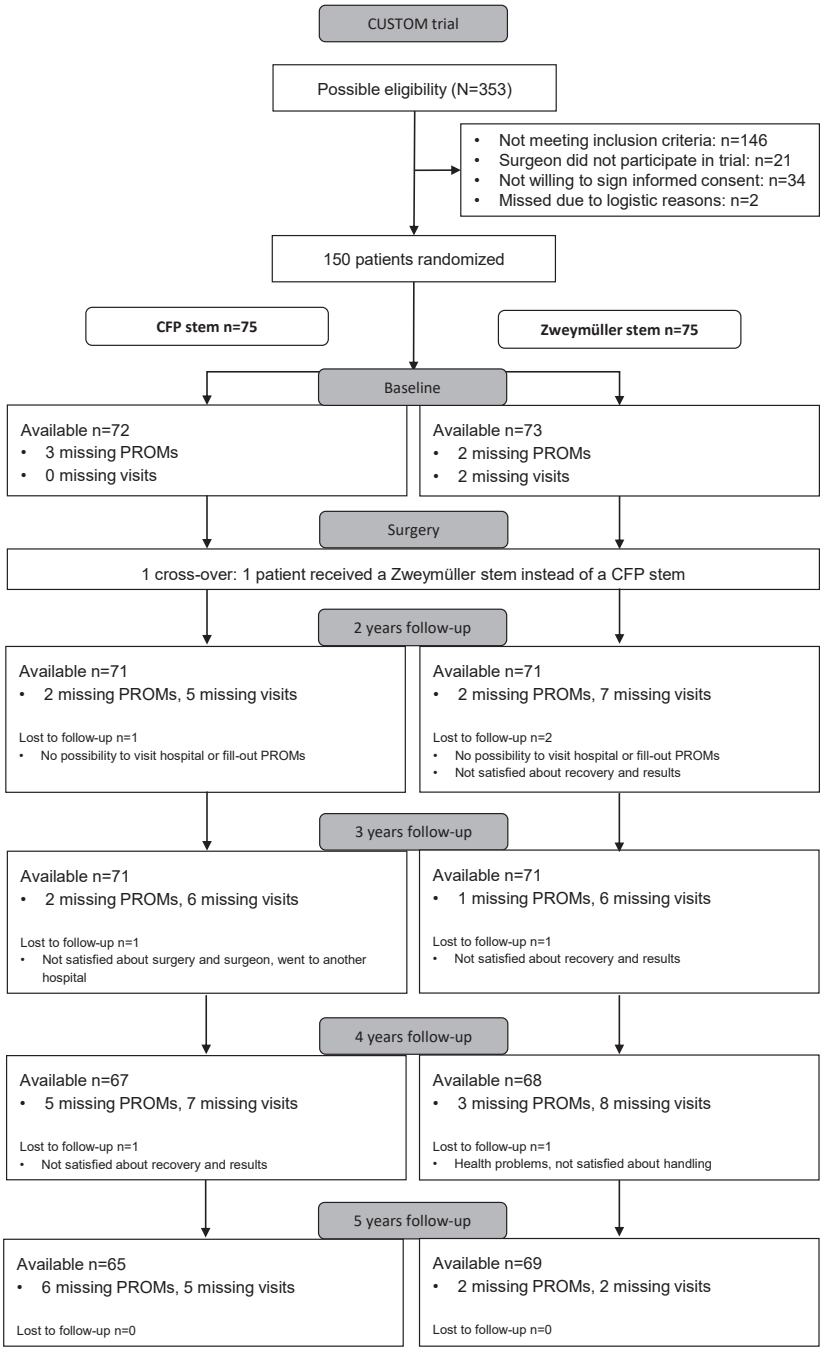
Blinding

At the 5-year follow-up, 105 (75%) out of 140 patients were still blinded to the type of stem. Data on 10 patients (6 CFP, 4 Zweymüller) was missing. In the CFP group, 24 out of 69 patients (35%) were deblinded. Reasons were: seen the radiographs (n = 9), heard during follow-up visit (n = 9), and unknown (n = 6). In the Zweymüller group, 11 out of 71 patients (15%) were deblinded. Reasons were: seen the radiographs (n = 4), heard during follow-up visit (n = 5), and unknown (n = 2).

Primary outcome measure: physical function measured with the HOOS

The mean difference (CFP vs. Zweymüller) at 5 years' follow-up was –0.07 (95% confidence interval [CI] –5.1 to 4.9, P = 1.0) (Table 2). We found no difference in HOOS or between-group differences in the unadjusted mixed-model analyses (Figure 2 and Table 2). The results of the sensitivity analyses and the the adjusted mixed-model analyses for all HOOS subscales showed no significant differences between groups (Appendices 2, 3 and 4).

Figure 1. Patient flow chart, following consolidated standards of reporting trials (CONSORT). Available = primary outcome is available.



Secondary outcomes

The largest between-group difference (CFP vs. Zweymüller) was observed in the Sports/Rec subscale at 3-year follow-up, with a mean difference of –6.0 (CI –14 to 1.8, P = 0.1), although this was not statistically significant. At 4- and 5-year follow-up, this difference is not apparent anymore (Table 2). Table 2, Figure 2, and Appendix 1 present the mean scores for both groups on all additional HOOS subscales and other secondary outcomes. The results of the unadjusted mixed-model analyses for all secondary outcomes at 5-year follow up showed small between-group differences in general (Tables 2 and 3). Only for the TUG were statistically significant differences in favor of the conventional uncemented stem seen at 3-year follow-up (unadjusted model) and at 3- and 4-year follow-up (adjusted model). Significant interaction effects between group and follow-up were seen for the TUG and pain in the contralateral hip; this can be seen in the supplementary figures (Appendix 1) in which the lines for both groups cross each other. The MCII of 23 points for the HOOS Pain subscale was reached by 79% patients in the CFP group (7 missing) and 84% patients in the conventional uncemented stem group (6 missing). The MCII of 17 points for the HOOS QoL subscale was reached by 81% patients in the CFP group (7 missing) and 85% patients in the conventional uncemented stem group (6 missing). The PASS of 91 points on the HOOS Pain subscale was reached in 69% of the CFP group and 76% of the conventional uncemented stem group. The PASS of 83 points on the HOOS QoL subscale was reached in 35% of the CFP group and 59% of the conventional uncemented stem group.

A list of all reported serious adverse events can be found in Appendix 5, which showed no significant differences. The Trendelenburg test showed no positive cases at 5-year follow-up. Radiographs were evaluated at 5-year follow-up and if not available, the former one (4- or 3-year follow-up) was used. The following stem-related findings were reported in 4 patients: radiolucent lines (1 Zweymüller, 1 CFP), partial loosening (1 Zweymüller), and osteolysis (1 CFP).

Table 1. Baseline characteristics of the included patients.

Characteristics		Measure	Group	
			CFP	Zweymüller
Hospital	**A**	n	50	50
	B	n	25	25
Demographic				
Age (years)		mean ± SD	60.3 ±6.8	60.5 ± 7.1
Sex	**Men**	n (%)	21 (28%)	22 (29.3%)
	Women	n (%)	54 (72%)	53 (70.7%)
BMI		Mean ± SD	27.2 ± 4.2	26.4 ± 4.3
ASA level		n (I:II:III)	37:37:1	26:45:4
Cormorbidity	**Cardiac**	n (yes:no)	8:67	17:55 (3 missing)
	pulmonary	n (yes:no)	4:71	6:66 (3 missing)
Operated side		n (left:right)	31:44	20:55
Preoperative measures				
HOOS ADL		mean ± SD	46.14 ± 18.78	47.20 ± 15.37
HOOS symptoms		mean ± SD	41.88 ± 18.05	43.49 ± 18.68
HOOS pain		mean ± SD	46.01 ± 17.73	44.93 ± 15.57
HOOS sports/rec		mean ± SD	30.02 ± 21.41	29.17 ± 18.71
HOOS QoL		mean ± SD	25.17 ± 15.34	26.37 ± 15.98
mHHS		mean ± SD	56.94 ± 15.48	56.53 ± 15.51
TUG		mean ± SD	10.83 ± 3.46	10.37 ± 2.93
Pain operated hip		mean ± SD	6.40 ± 1.73	6.41 ± 1.98
Pain contralateral hip		mean ± SD	0.93 ± 1.76	1.45 ± 2.33
Pain back		mean ± SD	2.93 ± 2.56	3.33 ± 2.97
Pain Knees		mean ± SD	3.17 ± 2.64	2.99 ± 2.76
SF12 PCS		mean ± SD	33.42 ± 7.24	33.95 ± 7.87
EQ5D		mean ± SD	0.62 ± 0.23	0.59 ± 0.26
Radiologic scores				
Kellgren-Lawrence score	**0 (no OA)**	n (%)	-	-
	1 (doubtful)		-	2 (2.7%)
	2 (minimal OA)		12 (16%)	11 (14.7%)
	3 (moderate OA)		34 (45.3%)	33 (44%)
	4 (severe OA)		28 (37.3%)	27 (36%)
	Missing		1 (1.3%)	2 (2.7%)

SD = standard deviation; n = number; BMI = Body Mass Index; ASA = American Society of Anaesthesiologists; M = male; F = female; HOOS = Hip disability and Osteoarthritis Outcome Score; ADL = function in activities of daily living; sports/rec = function in sport and recreation; QoL = hip related quality of life; PCS = physical component scale; OA = osteoarthritis.

Table 2. Between group differences of all HOOS subscales, for the unadjusted model, at all follow-up moments.

		Mean (SD)		Unadjusted model			
Outcome	**Follow-up**	**CFP**	**Zweymüller**	**Between group difference**	**95% CI**		**p-value**
HOOS ADL	**2 yr**	86.8 (15.0)	89.4 (15.4)	-1.90	0.44	-6.70	2.90
	3 yr	87.1 (14.7)	89.6 (14.3)	-1.83	0.45	-6.64	2.98
	4 yr	88.7 (16.0)	90.4 (12.7)	-0.65	0.79	-5.52	4.23
	5 yr	90.3 (11.1)	89.6 (15.2)	-0.07	0.98	-5.08	4.94
HOOS symptoms	**2 yr**	81.8 (17.5)	85.1 (18.7)	-2.15	-7.52	3.22	0.43
	3 yr	83.0 (18.5)	86.4 (16.0)	-2.13	-7.51	3.26	0.44
	4 yr	87.4 (13.8)	88.4 (15.1)	-0.03	-5.47	5.41	0.99
	5 yr	83.3 (17.3)	88.8 (15.1)	-3.97	-9.36	1.43	0.15
HOOS Pain	**2 yr**	87.7 (15.0)	88.8 (15.4)	-1.12	-5.69	3.45	0.63
	3 yr	86.9 (14.5)	90.6 (13.8)	-3.35	-7.93	1.23	0.15
	4 yr	89.0 (13.0)	90.1 (11.9)	-0.45	-5.11	4.20	0.85
	5 yr	90.0 (10.8)	91.4 (13.3)	-2.30	-7.10	2.51	0.35
HOOS sports/rec	**2 yr**	70.4 (24.3)	74.4 (24.0)	-2.85	-10.60	4.90	0.47
	3 yr	69.1 (23.1)	75.9 (23.6)	-5.96	-13.73	1.80	0.13
	4 yr	74.8 (22.6)	76.8 (21.7)	-2.12	-10.00	5.76	0.60
	5 yr	74.1 (21.8)	75.5 (25.1)	-3.09	-11.20	5.02	0.45
HOOS QoL	**2 yr**	72.4 (20.6)	75.7 (22.5)	-2.15	-8.76	4.47	0.52
	3 yr	73.5 (20.6)	78.3 (22.1)	-3.50	-10.13	3.14	0.30
	4 yr	76.9 (18.4)	81.7 (16.7)	-2.84	-9.53	3.85	0.40
	5 yr	74.1 (20.1)	81.3 (20.8)	-5.08	-11.72	1.57	0.13

SD = standard deviation; yr = years; 95% CI = 95% confidence interval; CFP = collum femoris preserving; HOOS = Hip disability and Osteoarthritis Outcome Score; ADL = function in activities of daily living; sports/rec = function in sport and recreation; QoL = hip related quality of life.

Figure 2. HOOS scores per subscale and for all follow-up moments.

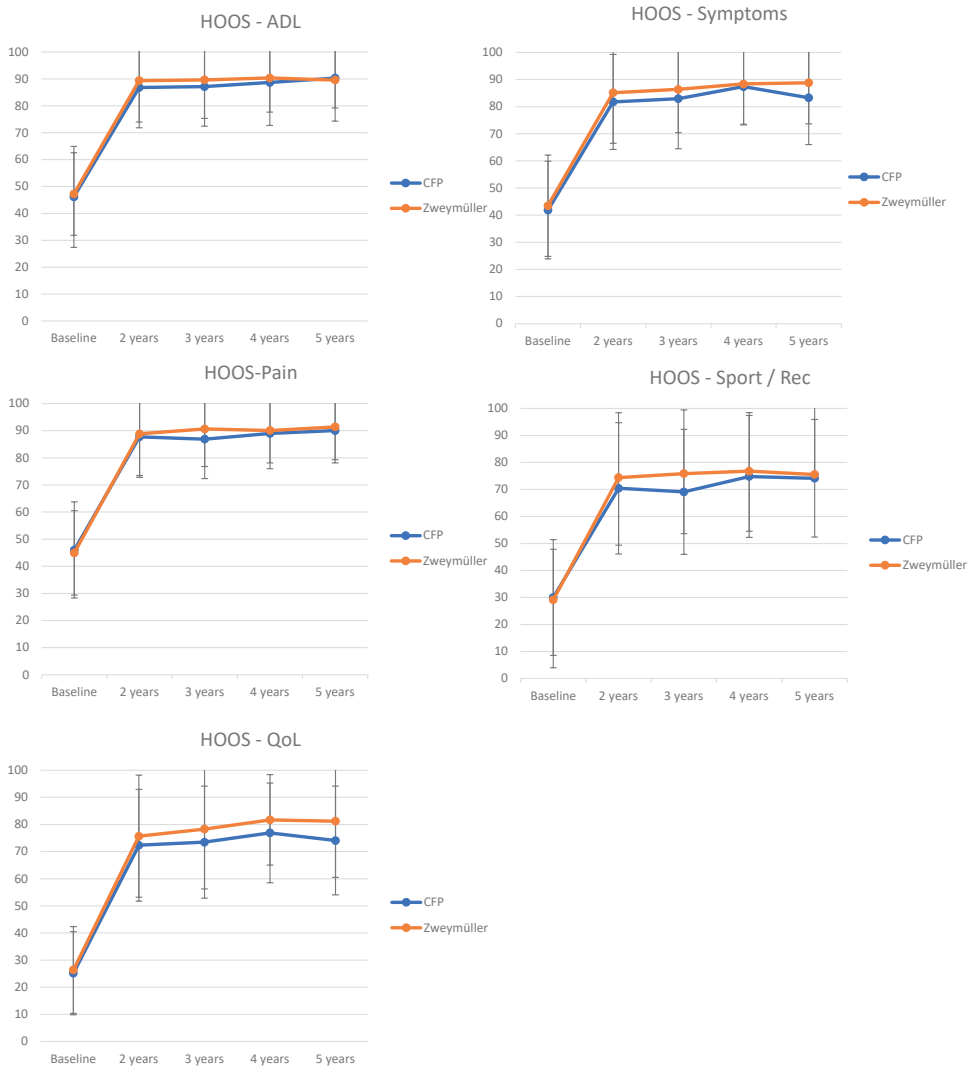


Table 3. Between group differences for secondary outcomes, for the unadjusted model, at 5 year follow-up.

	Mean score ± SD		Unadjusted model			
Outcome	**CFP**	**Zweymüller**	**Between group difference**	**95% CI**		**P-value**
mHHS	91.4 ± 12.0	91.3 ± 15.5	0.13	-4.31	4.57	0.95
TUG	8.7 ± 1.5	9.0 ± 1.5	-0.39	-0.90	0.12	0.13
Pain operated hip	1.0 ± 1.3	0.9 ± 1.8	0.07	-0.50	0.63	0.82
Pain contralateral hip	1.0 ± 2.0	0.7 ± 1.5	0.36	-0.23	0.95	0.23
Pain back	1.6 ± 2.0	1.7 ± 2.4	0.04	-0.64	0.73	0.90
Pain knee	0.9 ± 1.6	1.2 ± 1.9	-0.29	-0.87	0.30	0.33
SF12 PCS	48.4 ± 8.4	47.3 ± 11.1	0.44	-2.85	3.72	0.80
EQ5D	0.9 ± 0.1	0.9 ± 0.2	-0.03	-0.03	0.09	0.29

SD = standard deviation; yr = years; 95% CI = 95% confidence interval; CFP = collum femoris preserving; mHHS = modified Harris Hip Score; TUG = Timed Up and Go test; SF12 PCS = short form 12 physical component scale.

Survival analysis

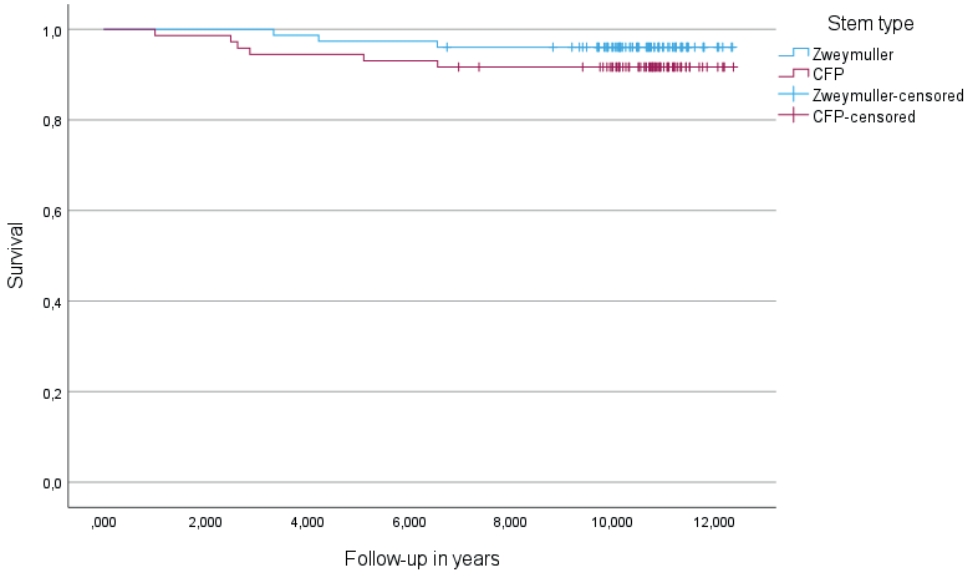
In the CFP group, 6 revisions were reported, of which 2 were solitary cup revisions. In the conventional uncemented stem group, 3 revisions were reported. Average follow-up time since the THA surgery was 10.8 years (range 9.2–12.4 years). Results from the Kaplan–Meier and the competing risk analyses yielded the same results and showed a survival of 92% for the CFP group compared with 96% for the conventional uncemented stem group. Revisions and mortality are specified in Table 4 and a survival plot is depicted in Figure 3. Censors indicate the current follow-up moment, or the death (n = 7) of study participants. No significant difference was found between the groups.

Table 4. Overview of all types of revision surgeries and deceased patients.

	No revision	Total revision	Stem revision	Cup revision	Deceased	Total
Zweymüller	N=69	N=2 2.3 years 5.5 years	N=1 3.2 years	N=0	N=4 5.7 years 7.8 years 8.3 years 8.5 years	N=76
CFP	N=63	N=2 1.6 years 2.9 years	N=2 2.5 years 4.1 years	N=2 5.6 years 0.008 years	N=3 6.0 years 6.4 years 9.1 years	N=72
Total	132	4	3	2	7	148 (2 missing)

CFP = collum femoris preserving; n = number

Figure 3. Survival plot of the Zweymüller and CFP stem.



DISCUSSION

We aimed to compare physical function at 5-year follow-up and implant survival at an average of 10 years' follow-up. No significant differences were observed between the groups at 5 years after THA, for either the primary or secondary outcomes. This is similar to our 2-year results [9] and to the vast majority of randomized trials in the primary THA population [25]. We used a rather conservative threshold for clinical relevance for the primary outcome: a difference of 10% [7,26]. At 5-year follow-up, the difference for HOOS ADL was 2.9%. For the other HOOS subscales, we observed differences of 4.5% for HOOS Symptoms, 1.4% for HOOS Pain, 0% for HOOS Sports/Rec, and 6.8% for HOOS QoL. The study was sufficiently powered for the primary outcome, and the lack of statistical significance should not be attributed to the study sample size. Overall revision rates of 8.3% for the CFP and 4.0% for the Zweymüller groups were found. The influence of chance is high because of the limited sample size. Earlier studies reported revision rates between 10% and 27% for the CFP stem [11,13] and 2% and 8% for the Zweymüller stem [27-30]. However, 2 of the revisions in our study were solitary cup revisions. It is unknown to what extent these cup revisions can be related to the stem. If the stem and total revisions only are considered, we observed no differences between the groups. Significant interaction effects between group and time were seen for the TUG and pain in the contralateral hip, indicating some dissimilarities in the between-group differences at the follow-up moments. These fluctuations over time between the groups might be caused by incidental missing data. For instance, if a patient with extreme scores at 1 follow-up moment has a missing score on the former or latter follow-up, this affects the mean scores.

The MCII scores reported by Paulsen et al. [24] are largely achieved by the patients in our trial. The same research group also reported the PASS, which was achieved only for the HOOS Pain subscale by the patients in our trial. Heiberg and Figved reported slightly higher scores (fewer problems) at 5 years for all HOOS subscales [31]. Their patients were older (mean 70) than in our trial but underwent their surgery by the posterior approach, which might influence their physical functioning. In the study of Bergvinsson et al. the HOOS scores seem similar to our results [32]. Lyman et al. reported comparable results: slightly higher scores at Symptoms and QoL subscales, lower score on the ADL subscale and equal for Pain [33]. Patients in that trial were on average older than in our trial. Summarizing, we can conclude that the HOOS scores at 5-year follow-up in our trial are comparable to those in previous literature and that our patients do not deviate from average patients in THA trials. The HOOS is a disease-specific PROM for patients undergoing THA but is not extensively used in the literature. Another commonly used PROM is the HHS, for which similar results were founded in our

trial [12-15]. The MCII and PASS for the EQ5D are both achieved by patients in our trial [24].

Strengths and limitations

All patients underwent THA with the straight lateral approach. In recent years, there has been a shift in surgical approach from straight lateral to the posterolateral and anterior approaches [34]. It is questionable whether our results are generalizable to other approaches. Although much effort has been undertaken to prevent missing data, this could not be avoided. Paper-based PROMs have the limitation that patients might leave out answers. Possibly these missing items are not at random but specifically occur for items with which the patient experiences difficulties. A frequently occurring missing item in the HOOS is the question about running, which might influence the mean score of the Sports/Rec subscale. When looking at implant survival, the strength of using the Dutch Arthroplasty Registry is that all revisions (performed in the Netherlands) are registered in this database. This is regardless of the hospital in which the patient had the initial surgery. Therefore, missing a revision is highly unlikely. No strong conclusions can be drawn on implant survival because this trial was not statistically powered for survival analysis. When looking at observational studies, we also see higher revision rates for the CFP than for the Zweymüller stem [11-13,27-30]. Although not statistically significant, our RCT supports these findings. Due to the design, our trial is of high methodological quality. Strong efforts were made to protect against different types of bias [7]. This RCT is maximally blinded, which was new in surgical trials at the time this trial was conducted. After a follow-up of 5 years, 75% of the patients were still blinded to the type of prosthesis. This indicates that, with effort, it is possible to conduct a blinded surgical trial. We expected a maximum dropout rate of 10%, but at 5-year follow-up only 5% were lost-to-follow-up.

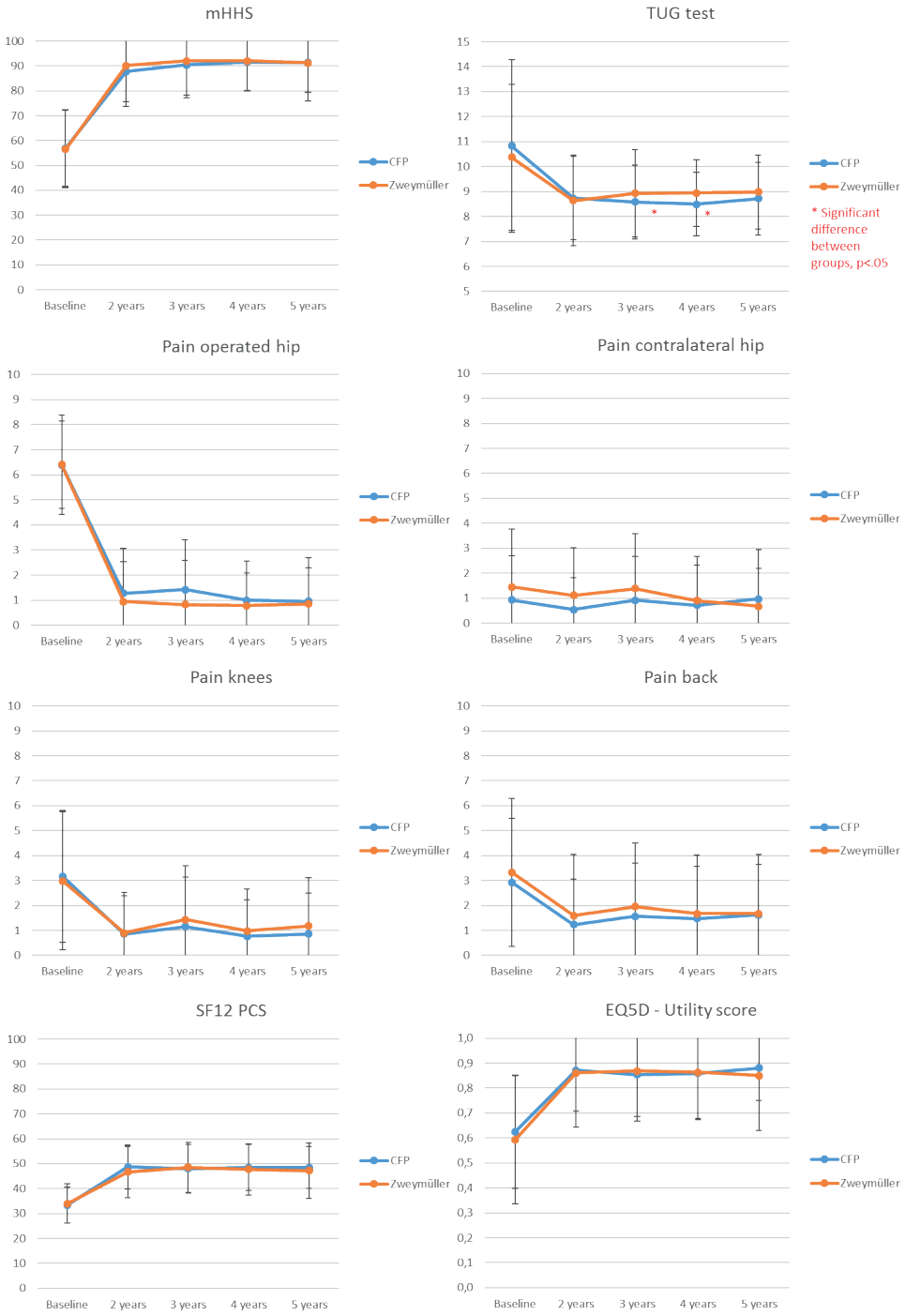
Conclusion

No significant differences were found in physical functioning at 5 years' and implant survival at 10 years' follow-up between the CFP and Zweymüller stems. When taking all revisions into account, the CFP group shows clinically inferior survival. To draw strong conclusions on implant survival, further research with larger numbers of patients is required.

Author contributions

LvB, JvO, CG, and RP contributed to the design. LvB, CG, BN, and RP contributed to the execution of this trial. LvB, ES, and NW performed the data analyses. LvB, NW, and RP contributed to the writing process. All authors revised and approved this manuscript.

Appendix 1: Mean scores (SD) of the mHHS, TUG, SF12-PCS and EQ-5D at all follow-up moments.



Appendix 2: HOOS ADL between group differences, for the sensitivity analyses.

		Mean (SD)		Sensitivity analyses			
Outcome	**Follow-up**	**CFP**	**Zweymüller**	**Between group difference**	**95% CI**		**p-value**
HOOS ADL	**5 yr**	91.3 (9.9)	89.2 (16.2)	1,077	-4,235	6,390	0,689
HOOS symptoms	**5 yr**	84.0 (16.6)	88.2 (15.8)	-3,008	-8,797	2,780	0.307
HOOS Pain	**5 yr**	91.4 (7.8)	90.4 (13.9)	0,073	-4,524	4,671	0,975
HOOS sports/rec	**5 yr**	73.5 (22.0)	75.1 (25.9)	-1,798	-11.026	7,430	0,701
HOOS QoL	**5 yr**	75.0 (19.3)	80.8 (20.3)	-4,978	-12,232	2,276	0,177

SD = standard deviation; yr = years; 95% CI = 95% confidence interval; CFP = collum femoris preserving; HOOS = Hip disability and Osteoarthritis Outcome Score; ADL = function in activities of daily living; sports/rec = function in sport and recreation; QoL = hip related quality of life.

Appendix 3: HOOS between group differences, for the adjusted model, at all follow-up moments.

		Mean (SD)		Adjusted model			
Outcome	**Follow-up**	**CFP**	**Zweymüller**	**Between group difference**	**95% CI**		**p-value**
HOOS ADL	**2 yr**	86.8 (15.0)	89.4 (15.4)	-1.94	-6.66	2.77	0.42
	3 yr	87.1 (14.7)	89.6 (14.3)	-1.70	-6.43	3.03	0.48
	4 yr	88.7 (16.0)	90.4 (12.7)	-1.50	-6.29	3.30	0.54
	5 yr	90.3 (11.1)	89.6 (15.2)	-0.45	-5.38	4.48	0.86
HOOS Symptoms	**2 yr**	81.8 (17.5)	85.1 (18.7)	-2.24	-7.67	3.18	0.42
	3 yr	83.0 (18.5)	86.4 (16.0)	-2.00	-7.45	3.44	0.47
	4 yr	87.4 (13.8)	88.4 (15.1)	-0.55	-6.05	4.95	0.85
	5 yr	83.3 (17.3)	88.8 (15.1)	-4.75	-10.20	0.71	0.09
HOOS Pain	**2 yr**	87.7 (15.0)	88.8 (15.4)	-1.41	-6.00	3.18	0.55
	3 yr	86.9 (14.5)	90.6 (13.8)	-3.55	-8.15	1.06	0.13
	4 yr	89.0 (13.0)	90.1 (11.9)	-1.41	-6.09	3.28	0.56
	5 yr	90.0 (10.8)	91.4 (13.3)	-2.54	-7.37	2.30	0.30
HOOS Sports/rec	**2 yr**	70.4 (24.3)	74.4 (24.0)	-2.94	-10.66	4.79	0.46
	3 yr	69.1 (23.1)	75.9 (23.6)	-5.58	-13.32	2.17	0.16
	4 yr	74.8 (22.6)	76.8 (21.7)	-2.85	-10.71	5.02	0.48
	5 yr	74.1 (21.8)	75.5 (25.1)	-3.60	-11.69	4.50	0.38

		Mean (SD)		Adjusted model			
HOOS QoL	**2 yr**	72.4 (20.6)	75.7 (22.5)	-1.81	-8.60	4.99	0.60
	3 yr	73.5 (20.6)	78.3 (22.1)	-2.90	-9.71	3.92	0.40
	4 yr	76.9 (18.4)	81.7 (16.7)	-2.51	-9.38	4.37	0.47
	5 yr	74.1 (20.1)	81.3 (20.8)	-4.75	-11.58	2.07	0.17

SD = standard deviation; yr = years; 95% CI = 95% confidence interval; CFP = collum femoris preserving; HOOS = Hip disability and Osteoarthritis Outcome Score; ADL = function in activities of daily living; sports/rec = function in sport and recreation; QoL = hip related quality of life.

Appendix 4: Between group differences for secondary outcomes at all follow-up moments, for the unadjusted and the adjusted analyses.

		Mean (SD)		Unadjusted model				Adjusted model			
Outcome	**Follow-up**	**CFP**	**Zweymüller**	**Between group difference**	**95% CI**		**p-value**	**Between group difference**	**95% CI**		**p-value**
mHHS	**2 yr**	87.8 (13.9)	90.1 (14.6)	-1.95	-6.37	2.48	0.39	-1.91	-6.33	2.51	0.40
	3 yr	90.5 (12.1)	92.1 (14.8)	-1.53	-5.96	2.90	0.50	-1.37	-5.79	3.06	0.54
	4 yr	91.6 (11.6)	92.1 (12.0)	0.01	-4.45	4.46	1.00	-0.21	-4.66	4.24	0.93
	5 yr	91.4 (12.0)	91.3 (15.5)	0.13	-4.31	4.57	0.95	0.23	-4.21	4.66	0.92
TUG	**2 yr**	8.7 (1.7)	8.6 (1.8)	-0.04	-0.55	0.47	0.88	-0.02	-0.52	0.48	0.93
	3 yr	8.6 (1.5)	8.9 (1.7)	-0.57	-1.08	-0.05	0.03	-0.59	-1.09	-0.08	0.02
	4 yr	8.5 (1.3)	8.9 (1.3)	-0.49	-1.01	0.02	0.06	-0.51	-1.02	0.00	0.05
	5 yr	8.7 (1.5)	9.0 (1.5)	-0.39	-0.90	0.12	0.13	-0.42	-0.92	0.08	0.10
Pain operated hip	**2 yr**	1.3 (1.8)	0.9 (1.6)	0.28	-0.28	0.84	0.33	0.28	-0.29	0.85	0.33
	3 yr	1.4 (2.0)	0.8 (1.7)	0.55	-0.02	1.11	0.06	0.56	-0.02	1.14	0.06
	4 yr	1.0 (1.6)	0.8 (1.3)	0.11	-0.46	0.68	0.71	0.14	-0.44	0.73	0.63
	5 yr	1.0 (1.3)	0.9 (1.8)	0.07	-0.50	0.63	0.82	0.07	-0.51	0.65	0.82
Pain contralateral hip	**2 yr**	0.5 (1.3)	1.1 (1.9)	-0.51	-1.10	0.07	0.08	-0.53	-1.13	0.06	0.08
	3 yr	0.9 (1.8)	1.4 (2.2)	-0.43	-1.02	0.16	0.16	-0.47	-1.07	0.13	0.13
	4 yr	0.7 (1.6)	0.9 (1.8)	-0.22	-0.81	0.38	0.48	-0.25	-0.86	0.36	0.42
	5 yr	1.0 (2.0)	0.7 (1.5)	0.36	-0.23	0.95	0.23	0.34	-0.26	0.94	0.26

		Mean (SD)		Unadjusted model				Adjusted model			
Pain back	**2 yr**	1.2 (1.8)	1.6 (2.4)	-0.29	-0.97	0.39	0.40	-0.21	-0.86	0.45	0.54
	3 yr	1.6 (2.1))	2.0 (2.5)	-0.30	-0.98	0.39	0.39	-0.23	-0.89	0.42	0.48
	4 yr	1.5 (2.1)	1.7 (2.3)	-0.20	-0.89	0.48	0.56	-0.14	-0.80	0.52	0.67
	5 yr	1.6 (2.0)	1.7 (2.4)	0.04	-0.64	0.73	0.90	0.05	-0.61	0.71	0.88
Pain knee	**2 yr**	0.9 (1.7)	0.9 (1.5)	-0.12	-0.70	0.46	0.69	-0.07	-0.65	0.51	0.82
	3 yr	1.2 (2.0)	1.4 (2.2)	-0.25	-0.84	0.33	0.39	-0.26	-0.84	0.33	0.39
	4 yr	0.8 (1.5)	1.0 (1.7)	-0.25	-0.84	0.34	0.40	-0.18	-0.77	0.41	0.56
	5 yr	0.9 (1.6)	1.2 (1.9)	-0.29	-0.87	0.30	0.33	-0.27	-0.86	0.32	0.37
SF12 PCS	**2 yr**	48.7 (8.9)	46.7 (10.2)	2.80	-0.30	5.90	0.08	2.47	-0.58	5.52	0.11
	3 yr	48.1 (9.8)	48.5 (10.0)	-0.13	-3.24	2.98	0.94	-0.52	-3.58	2.54	0.74
	4 yr	48.5 (9.2)	47.7 (10.2)	0.97	-2.19	4.14	0.55	0.50	-2.62	3.62	0.75
	5 yr	48.4 (8.4)	47.3 (11.1)	0.44	-2.85	3.72	0.80	-0.23	-3.48	3.01	0.89
EQ5D	**2 yr**	0.9 (0.2)	0.9 (0.2)	0.01	-0.05	0.07	0.77	0.01	-0.05	0.07	0.66
	3 yr	0.9 (0.2)	0.9 (0.2)	-0.02	-0.08	0.04	0.60	-0.01	-0.07	0.05	0.72
	4 yr	0.9 (0.2)	0.9 (0.2)	0.00	-0.06	0.06	0.99	0.00	-0.06	0.06	0.93
	5 yr	0.9 (0.1)	0.9 (0.2)	0.03	-0.03	0.09	0.29	0.04	-0.02	0.10	0.24

SD = standard deviation; yr = years; 95% CI = 95% confidence interval; CFP = collum femoris preserving; mHHS = modified Harris Hip Score; TUG = timed up and go test; SF-12 PCS = SF-12 Physical Component Scale.

Appendix 5: Overview serious adverse events at 5 years follow-up.

Type of event	Follow-up moment	CFP stem	Zweymüller stem	Action
Periprosthetic fracture	Surgery	2	0	• Plate fixation • Cerclage
Dislocation	2 days postoperative	1	0	Cuprevision
Infection	5 weeks postoperative	0	1	Intraoperative wound irrigation + antibiotics
Late infection	2 years postoperative	1	0	Two-stage revision
Loosening due to infection	2.5 years postoperative	0	1	Total revision
Fracture after fall	3 years postoperative	0	1	Stem revision
Loosening stem	2.5 years postoperative	1	0	Stem revision
Loosening stem	3 years postoperative	1	0	Stem revision
Urinary tract infection	1st week postoperative	1	0	Antibiotics
Infection	1st week postoperative	1	0	Intraoperative wound irrigation + antibiotics
TOTAL		**9**	**3**	

CFP = collum femoris preserving.

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Chapter 8

Can dual mobility cups prevent dislocation in primary total hip arthroplasty? A systematic review.

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ABSTRACT

Background

Dislocation is one of the leading causes for early revision surgery after total hip arthroplasty (THA). To address this problem, the dual mobility (DM) cup was developed in the 1970's by the French. Despite the increased and, in some countries, broad use of DM cups, high quality evidence of their effectiveness compared to traditional unipolar (UP) cups is lacking. There are a few well conducted literature reviews, but the level of evidence of the included studies is moderate to low. Therefore, we did a systematic review to investigate whether there is a difference in the rate of dislocations and revisions after primary total hip arthroplasty THA with a DM cup or a UP cup.

Methods

We conducted a systematic literature search in PubMed, Embase and Cochrane databases in July 2019. The articles were selected based upon their quality, relevance and measurement of the predictive factor. We used the MINORS criteria to determine the methodological quality of all studies.

Results

The initial search resulted in 702 citations. After application of the inclusion and exclusion criteria, eight articles met our eligibility criteria and were graded. Included studies were of medium to low methodological quality with a mean score of 14 (11-16) points following the MINORS criteria. In the case-control studies, a total of 549 DM cups and 649 UP cups were included. In the registry studies, a total of 5935 DM cups and 217.362 UP cups were included. In the case-control studies, 1 (0.2%) dislocation was reported for the DM cups and 46 (7.1%) for the UP cup (p=0.009, IQR=0.00-7.00). Nine (1.6%) revisions, of which 0 due to dislocation, were reported for the DM cup and 39 (6.0%), of which 30 due to dislocation, for the UP cup (p=0.046, CI=-16.93-5.73). In the registry studies 161 (2.7%) revisions were reported for the DM cup, of which 14 (8.7%) due to dislocation. For the UP cup 3332 (1.5%) revisions were reported (p=0.275, IQR=41.00-866.25), of which 1093 (32.8%) due to dislocation (p=0.050, IQR=3.50-293.25).

Conclusion

This review suggests lower rates of dislocation and revision for dislocation in favor of the DM cups. DM cups might be an effective solution to reduce dislocation in primary THA. To evaluate the efficacy of DM cups compared to UP cups, an economic evaluation alongside a randomized controlled trial is needed focusing on patient important endpoints.

INTRODUCTION

Total hip arthroplasty (THA) for end-stage osteoarthritis of the hip is one of the most successful orthopedic surgical procedures. It treats pain, improves function and thereby increases quality-of-life [1]. However, dislocation is the leading cause for early revision surgery after THA [2]. Most dislocations occur during the first year after surgery, of which approximately half within the first three months after surgery [3–5]. Hip dislocation is a major problem that results in reduced functioning and a deterioration in quality-of-life [6]. After a first dislocation, there is an increased chance that the THA will re-dislocate again, with reported rates up to 60% [7–9]. In addition to the negative consequences of dislocation for a patient, dislocations also increase healthcare costs. For an uncomplicated single dislocation these costs were estimated at 19% of total hospital costs, when revision surgery was required these costs increased up to 148% [10,11].

To address the problem of dislocation, Bousquet developed the dual-mobility (DM) cup in France in the 1970's [12]. This design is a combination of the low friction arthroplasty by Charnley [13] and a large diameter head [14]. The DM cup consists of two articulations between three different components; a metallic acetabular shell, a mobile polyethylene (PE) liner and a femoral head. The mobile liner articulates both with the acetabular shell and the femoral head. This should provide more stability and biomechanically reduce the risk of dislocation [15–17]. Dislocation rates reported for the DM cup range from 0 to 3.6% [16–21] which seems slightly lower than the 0.5 to 6% reported for the standard, unipolar (UP) cups [22–26]. Also, the use of DM cups for revision surgery in patients with recurrent dislocation has shown promising results [3,27,28]. Internationally, DM cups are used widely for revision surgery [29–31] and as primary THA in patients at high risk for dislocation [32,33]. In France DM cups are used in an estimated 30% of all primary THAs [34]. In the Netherlands, DM cups are mostly used in case of specific patient characteristics, such as cognitive impairment, neuromuscular diseases or as a standard procedure for revision surgeries due to recurrent dislocations [35]. These characteristics might negatively affect the risk for dislocation and revision surgery compared to the general THA population. Potential disadvantages of DM cups are known to include; increased liner wear [36], loosening [37,38] and intra prosthetic dislocation (IPD) [37,39]. These disadvantages may result in revision surgery at longer follow-up. However, when used for revision surgery, there seems to be a significantly lower re-revision rate for the DM cup at 5 years of follow-up [40]. Higher implant costs in several countries compared with many conventional UP cup implants [41] are of topic, but a systematic review of Rudy et al. [42] states that DM cups are cost-effective.

Despite the increased and, in some countries, widely use of DM cups, high quality evidence of their effectiveness is lacking [19]. There are a few well conducted literature reviews, but the level of evidence of the included studies is moderate to low. These studies do not make a distinction between case-control and registry studies, which is important because dislocations resolved by closed reduction will be missed in registry studies with revision as endpoint. Some of these reviews report on outcomes of the DM cup in revision surgery [43,44], or included patients with femoral neck fractures [45]. There are also reviews that do not make a direct comparison between the DM cup and UP cup [12,19,43–49]. Therefore, the aim of this study is to perform a systematic review of the literature to investigate whether there is a difference in the rate of dislocations and revisions after primary THA for degenerative diagnoses, between a DM cup or a UP cup.

METHODS

Search strategy and selection criteria

We performed a systematic review of literature in order to identify articles reporting on both dislocation rates in DM cups and UP cups for patients undergoing primary THA. We conducted a literature search of the PubMed, Embase and Cochrane databases in July 2019. To improve the search quality, a medical librarian assisted in the literature search. The search terms in PubMed for [Title/Abstract] were (((dual OR double) AND mobility) OR mobile bearing OR tripolar) AND hip. In Embase the search included: 1: dual mobility OR double mobility OR tripolar OR mobile bearing / 2: dislocat* / 3: hip / 4: 1+2+3. In Cochrane we searched for: (((dual OR double) AND mobility) OR tripolar OR mobile bearing) AND dislocat* AND hip (in title, abstract & keywords).

Inclusion criteria for our review were: (1) Patients receiving a primary THA, due to a degenerative diagnosis (e.g. osteoarthritis, necrosis, rheumatoid arthritis, dysplasia); (2) DM cup used as an intervention; (3) UP cup used as a control; and (4) dislocation or revision described as outcome. There was no selection in time period. Studies published in English or French were eligible for inclusion in this review. To gain reliable results on dislocation rates we set a minimum follow-up period of 6 months. Exclusion criteria included the use of the DM cup in revision or trauma surgery primarily and reports of the same patient cohorts in different journals.

Two authors (RJ and LvB) performed all data screening and data extraction, using the mentioned selection criteria. Both reviewers screened the full-text articles of the papers found eligible in the first

round. In case of different opinions, consensus was reached by discussion between both reviewers. Included articles were divided into two groups; case-control studies and registry studies.

Methodological quality assessment

We used Methodological Index for Non-randomized Studies (MINORS) to asses methodological quality [50]. This validation index was developed to determine the quality of observational and non-randomized studies. Two investigators (RJ and LvB) independently assessed the quality of each study, scoring the 12 item scale. In case of discussion, a third investigator (NW) was consulted. An item was scored as '0' when not reported, '1' when it was inadequately reported, and '2' when it was adequately reported, with a maximum and ideal score of 24 for comparative studies. This systematic review conforms with the PRISMA guidelines [51] and was registered at Prospero (registry number CRD42018091921).

Statistics

For descriptive statistics, we used totals, means and medians. Statistical analyses were performed using SPSS version 21. A test for normality was performed. With normally distributed data, an independent t-test was performed and the 95% confidence interval (CI) was given. In case of no normality, A Mann-Whitney-U test was used and the interquartile range (IQR) was given. A p value <0.05 was considered significant.

RESULTS

Study selection

The initial search identified 702 articles, of which, after screening for title, abstract and full-text, a total of eight articles met our inclusion criteria and were eligible for inclusion in this systematic review [15,18,35,52–56] (Figure 1).

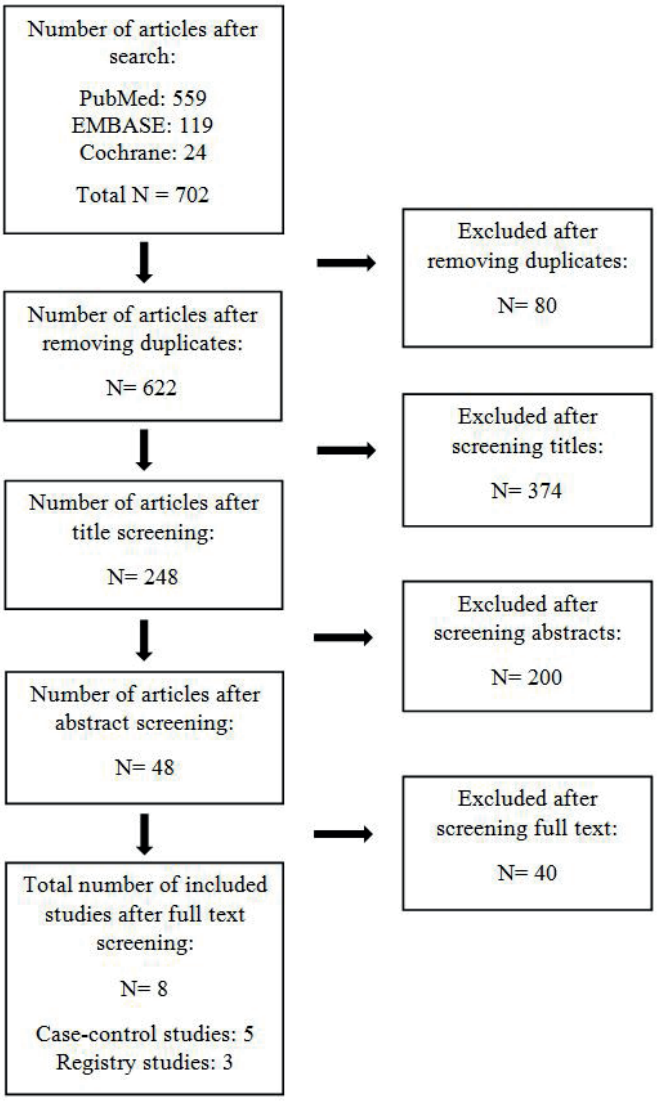

Figure 1. Flowchart of study selection procedure.

Study characteristics and methodological quality assessment

The eight articles that we included were published between 2011 and 2019, with a reported surgery period from 1995 to 2016. Five of the included articles were case-control studies of which three were single surgeon reports published by French authors [15,18,52]. The two other case-control studies were single center studies from Japan [53] and the United States of America [54]. We included three registry studies reporting on dislocation of the DM cup [35,55,56]. Head size differed from 22.2 mm to ≥38 mm for the UP cup and was 22.2 mm, 28 mm or not specified for the DM cup (Table 1). Implants used for the DM cup were; Novea by Serf, Quattro by Lepine, Avantage by Biomet, ADM and MDM by Stryker, Stafit by Zimmer, Saturne by Amplitude, Polarcup by Smith & Nephew, Selexys DS by Mathys and Gyros-cup by Depuy. The mean MINORS score for the assessment of methodological quality was 14 points (58% of ideal score), ranging from 11 to 16 (Table 2). No meta-analysis was performed, because there was too much dissimilarity in the methodology of the studies, resulting in clinical and methodological heterogeneity.

Case-control studies: dislocation and revision rates

A total of 1.198 hips were included, of which 549 were DM cups and 649 were UP cups (Table 3). Mean age at surgery was 68.2 years for the DM cups and 65.9 years for the UP cups. Follow-up differed from a minimum of 6 months up to 10 years. Only one dislocation was reported for the DM cup group (0.2%), in contrast to 46 reported dislocations for the UP cup group (7.1%), significant (p=0.009, IQR=0.00-7.00). The overall revision rate was 9 (1.6%) in the DM group and 39 (6.0%) in the UP group (p=0.046, CI=-16.93-5.73). All cause revisions reported in the DM group were for aseptic loosening (cup; n=1, stem; n=3, total; n=4), periprosthetic fracture (n=4) and groin pain (n=1). All cause revisions for the UP group were for instability (n=30), aseptic loosening (cup; n=2, stem; n=3, both; n=1, total; n=6), infection (n=2) and periprosthetic fracture (n=1). Overall cup revision rate (aseptic cup loosening, dislocation and groin pain) for the DM cup was two (0.4%) and 33 (5.1%) for the UP cup (p=0.081, IQR=0.00-3.25).

Registry studies: revision for dislocation and overall revision rates

A total of 223.297 hips were included, of which 5.935 were DM cups and 217.362 were UP cups (Table 4). Mean age at surgery was 71.4 years for the DM cups and 69.1 years for the UP cups. The median follow-up time differed from 2.5 to 3.2 years. The overall revision rate was 161 (2.7%) in the DM group and 3.332 (1.5%) in the UP group (p=0.275, IQR=41.00-866.25). There were 14 revisions for

dislocation reported in the DM cup group (8.7%) and 1.093 reported in the UP cup group (32.8%) (p=0.050, IQR=3.50-293.25).

DISCUSSION

Dislocation remains one of the most common complications of THA. Risk factors for dislocation can be patient-related, procedure-related or implant-related. Because patient related factors cannot be changed, investigation on procedure-related or implant-related factors has been a topic of research. This systematic review presents an overview of literature comparing the results of dislocation and revision rates between two principally different types of acetabular components for primary THA; the DM cup and the UP cup. Key findings of this systematic review are a lower rate of dislocations and lower rate of revision surgery for dislocation in DM cups, when used in primary THA, based on level 3 quality of evidence.

The case-control studies of this systematic review, reported only one [18] dislocation (0.2%) for the DM cup and 46 dislocations (7.1%) for the UP cup. Although research has shown that the use of a larger internal femoral head may provide more stability and thereby reduce the risk of dislocation [14,57–59], three out of five case-control studies used heads of 28 mm or smaller for the UP cup [15,18,52]. Caton et al. [18] in particular reported a high rate of dislocation (12.1%) with the use of small size 22.2 mm heads in this group, operated with a posterolateral approach. In contrast, Homma et al. [53], reported only on one dislocation in their UP group, using 32 mm (n=46) and 36 mm (n=14) heads using a direct anterior approach. Despite their great benefits on stability and range-of-motion, a potential disadvantage of a larger femoral head in combination with a thinner polyethylene liner may be the increased risk of liner fracture [60] and wear [61]. However, specifically in newer, highly cross-linked polyethylene DM liners, no implications of high failure rates due to wear have been reported [62–64].

Another factor that could have contributed to the low rate of dislocation reported by Homma et al. [53], may be the direct anterior surgical approach. Although, various studies have shown benefits of the direct anterior approach on dislocation rate [65,66], a systematic review of Higgens et al. [67] did not confirm any clear superiority on dislocation compared to the well known posterior approach.

Rates of revision surgery in the case-control studies also seem to be considerably lower in the DM cup group; 1.6% versus 6.0% in the UP cup group. In the UP cup, 30 out of 39 (76.9%) revisions were performed for recurrent instability. Despite the fact that this large share may probably be due to a selection bias for articles reporting on dislocation rates, other studies confirm that instability in UP cups is one of the most common reasons for revision surgery [2,3].

In contrast to the case-control studies, the registry studies showed higher rates of revision surgery for the DM cup. Whereas dislocation (32.8%) is the leading reason for revision of UP cups, infection (29.8%) seems to be a common reason for revision of DM cups. Literature on the relation between DM cups and revision for infection is not consistent and based on observational data [68,69]. Because DM cups are regularly used in frail patients at risk for dislocation, this risk of infection and overall increased rate of revision surgery in DM cups is probably due to confounding for patient characteristics and co-morbidities. Patient characteristics reported by Bloemheuvel et al. [35] confirm this suspicion, with an ASA-score of 3 and 4 in 31% in the DM group, compared to only 13% in the UP group.

The DM cup is becoming increasingly utilized worldwide. It is regularly selected in revision surgery to treat instability [29–31] and at present often used as primary THA in patients at high risk for dislocation [32,33]. Since the DM cup was already developed in the 1970's, many long term results of case series for the DM cup in primary THA have been published [16,17,20,21,38,70]. To our knowledge, there are only a few other systematic reviews reporting on the DM cup [12,19,42–49]. A network meta-analysis of four different bearings was performed by Pituckanotai et al. [46] in which all preoperative diagnoses were included for both primary THA and revision surgery. Batailler et al. [12], Martino et al. [48], Darrith et al. [19] Rudy et al. [42] Reina et al. [47] and Levin et al. [43] reported on outcomes of the DM cup in primary THA and revision surgery. However, no direct comparison between the primary DM cup and UP cup was made. Faldini et al. [44] only reported on revisions. Romagnoli et al. [45] included patients with femoral neck fractures and revision surgery. De Martino et al. [48] excluded French language articles. De Martino et al. [49] only reported on patients with early IPD.

There are some limitations applying to this study. Only eight articles met our inclusion criteria for comparing results of the DM cup to the UP cup. Although, the DM cup was already developed in France in the 1970's, we did not find any French comparative studies before 2011. Looking at the results of the MINORS-criteria, ranging from 11 to 16 points, the methodological quality of the

included articles may be rated as medium to low depending on the cut-off points [71,72]. Furthermore, we need to make two substantive remarks on the included studies. First, we must note that 24 stem revisions in the study of Rowan et al. [54] were excluded (table 3), because of a specific stem-type complication. This specific stem was only used in the DM group and because of the potential risk of fretting and corrosion at the modular neck junction, voluntarily recalled by its own manufacturer [73,74]. Secondary, we must note that there may be a selection bias by differences in population selection of the registry studies. Bloemheuvel et al. [35] reported on their entire study population, whereas Tarasevicius et al. [55] chose an implant selected control population and Kreipke et al. [56] a sex, age, component fixation and year of surgery matched control group. Results of this systematic review suggests lower rates of dislocation and revision for dislocation in favor of the DM cups. However, because included studies were of medium to low methodological quality, no clear conclusion on the use of DM cups for primary THA can be drawn. Therefore, level 1 studies (randomized controlled trials) should be conducted to confirm the results of the current literature.

CONCLUSION

This systematic review assed dislocation and revision rates of DM cups compared to UP cups in primary THA for degenerative diagnosis in five case-control studies and three registry studies. The case-control studies reported overall lower rates of dislocations and revisions for DM cups. However, this finding is not confirmed in the registry studies, which may be due to biased patient specific indication for using DM cups. Though, rates of revision for dislocation in DM cups seem considerably lower in the registry studies. Further research is necessary to evaluate the possible advantages using a DM cup in patients with hip osteoarthritis.

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Table 1. Study characteristics of included studies.

Author	Year	Country	Type of study	Surgery period	Pre-operative diagnoses	Approach	Implant head size
Bouchet et al. [15]	2011	France	Retrospective case-control, single center, One surgeon.	DM:2005-2007 UP:2003-2005	DM: osteoarthritis (n=95), trauma (n=4), osteonecrosis (n=3), other (n=3) UP: osteoarthritis (n=100), osteonecrosis (n=8)	Posterolateral	DM: not specified UP: 28 mm
Caton et al. [18]	2014	France	Retrospective case-control, one surgeon.	04/2000-09/2002	DM: osteoarthritis (n=95), osteonecrosis (n=6), fracture (n=4) UP: osteoarthritis (n=209), osteonecrosis (n=2), rheumatoid arthritis (n=4)	Posterolateral	DM: 22.2 mm UP: 22.2 mm
Epinette et al. [52]	2015	France	Prospective comparative cohort study. One surgeon.	02/2007-12/2011	DM: osteoarthritis (n=134), osteonecrosis (n=7), other (n=2) UP: osteoarthritis (n=111), osteonecrosis (n=12), other (n=7)	Posterolateral	DM: 28 mm UP: 28 mm
Homma et al. [53]	2016	Japan	Retrospect case-control, single centre. Age matched control group.	DM: ?/2013-01/2015 UP: 10/2011-?/2013	DM: osteoarthritis (n=41), osteonecrosis (n=3), fracture (n=14), other (n=2) UP: osteoarthritis (n=55), osteonecrosis (n=2), fracture (n=3)	Direct anterior	DM: not specified UP:32 mm (n=46) and 36 mm (n=14)
Rowan et al. [54]	2017	United States of America	Retrospective matched case-control, single center.	DM: 12/2011-12/2013 UP: 02/2007-06/2014	DM: osteoarthritis (n=106), dysplasia (n=11), osteonecrosis (n=10), inflammatory arthritis (n=3), trauma (n=3), other (n=3) UP: osteoarthritis (n=111), dysplasia (n=11), osteonecrosis (n=9), inflammatory arthritis (n=4), trauma (n=1)	Posterolateral	DM: 22.2 mm (n=9) and 28 mm (n=127) UP:28 mm (n=13), 32 mm (n=90) and 36 mm (n=33)

Author	Year	Country	Type of study	Surgery period	Pre-operative diagnoses	Approach	Implant head size
Tarasevicius et al. [55]	2017	Lithuania	Retrospective registry study of the Lithuanian Arthroplasty Register (LAR). DM systems compared to the Exeter cemented system.	01/2011- 12/2014	DM: osteoarthritis (n=371), fracture (n=138), rheumatoid arthritis (n=4), hip dysplasia (n=16), post-traumatic osteoarthritis (n=22), osteonecrosis (n=40), other (n=29) UP: osteoarthritis (n=1.614), fracture (n=365), rheumatoid arthritis (n=6), hip dysplasia (n=38), post-traumatic osteoarthritis (n=50), osteonecrosis (n=88), other (n=9)	DM: posterolateral (n=573) and anterolateral (n=47) UP: posterolateral (n=2.074) and anterolateral (n=96)	DM: not specified UP:28 mm
Kreipke et al. [56]	2019	Denmark	Retrospective registry study of the Nordic Arthroplasty Register Association (NARA). Matched cohort.	1995-2013	DM: all osteoarthritis UP: all osteoarthritis	DM: posterolateral (n=2.162) and anterolateral or other (n=115) UP: posterolateral (n=1.905) and anterolateral or other (n=372)	DM: not specified UP: 28 mm, 32 mm or 36 mm (not specified)

Author	Year	Country	Type of study	Surgery period	Pre-operative diagnoses	Approach	Implant head size
Bloemheuvel et al. [35]	2019	Netherlands	Retrospective registry study of the Dutch Arthroplasty Register (LROI).	2007-2016	DM: osteoarthritis (n=1.688), fracture (n=424), late posttraumatic (n=406), other (n=476) UP: osteoarthritis (n=185.062), fracture (n=7.065), late posttraumatic (n=4.415), 0ther (n=14.163)	DM: posterolateral (n=2.607), anterior (n=96), anterolateral (n=41), direct lateral (n=254), other (n=9) UP: posterolateral (n=128.275), anterior (n=21.102), anterolateral (n=15.801), direct lateral (n=44.249), other (n=706)	DM: 22-28 mm (not specified) (n=2.784) UP: 22-28 mm (n=66.703), 32 mm (n=93.619), 36 mm (n=4.002), ≥38 mm (n=1.452)

DM = dual mobility, UP = unipolar.

Table 2. Quality assessment of non-randomised studies , using MINORS [50] criteria.

Quality evaluation criteria*	**Bouchet 2011**	**Caton 2014**	**Epinette 2015**	**Homma 2016**	**Rowan 2017**	**Tarasevicius 2017**	**Kreipke 2019**	**Bloemheuvel 2019**
Clearly stated aim	2	2	1	2	2	2	2	2
Inclusion of consecutive patients	2	2	0	1	1	2	2	2
Prospective collection of data	0	0	1	0	0	1	0	0
Endpoints appropriate to the study aim	2	2	1	2	2	2	2	2
Unbiased assessment of the study endpoint	0	0	0	0	0	0	0	0
Appropriate follow-up period	2	2	2	1	2	1	2	2
Loss to follow-up less than 5%	0	1	2	0	0	0	0	0
Prospective calculation of the study size	0	0	0	0	0	0	0	0
Adequate control group	2	2	2	2	2	2	2	2
Contemporary groups	1	2	2	1	1	2	2	2
Baseline equivalence	1	1	1	1	1	1	1	1
Adequate statistical analysis	2	2	1	1	2	2	2	2
Total	**14**	**16**	**13**	**11**	**13**	**15**	**15**	**15**

NOTE: The items are scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). The global ideal score being 16 for non-comparative studies and 24 for comparative studies.

Table 3. Results of included case-control studies.

Author	Total operated hips (n)	DM cup (n)	UP cup (n)	Mean age DM cup (years)	Mean age UP cup (years)	Gender DM cup (M/F)	Gender UP cup (M/F)	Follow-up DM cup	Follow-up UP cup	Dislocation DM cup (n)	Dislocation UP cup (n)	Revision DM cup (n)	Revision UP cup (n)	Cup revision DM cup (n)	Cup revision UP cup (n)
Bouchet et al. [15]	213	105	108	76.6	74.2	45/60	52/56	mean 28 months	mean 52 months	0	5	0	1	0	1
Caton et al. [18]	320	105	215	78	70.8	42/63	91/124	minimum 10 years	minimum 10 years	1	26	2	26	1	23
Epinette et al. [52]	273	143	130	70.6	65.5	49/87	53/72	maximum 4.45 years	maximum 6.71 years	0	7	4	9	1	7
Homma et al. [53]	120	60	60	75.6	74	12/46	7/50	minimum 6 months	minimum 6 months	0	1	0	1	0	0
Rowan et al. [54]	272	136	136	48.5	48.4	43/74	48/79	median 3.2 years	median 3.4 years	0	7	3*	2	0	2

* 24 recalled modular femoral stems were excluded because of a specific stem-type complication.

DM = dual mobility, UP = unipolar, M = male, F = female.

Table 4. Results of included registry studies.

Author	Total operated hips (n)	DM cup (n)	UP cup (n)	Mean age DM cup (years)	Mean age UP cup (years)	Gender DM cup (M/F)	Gender UP cup (M/F)	Mean follow-up DM cup	Mean follow-up UP cup	Revision for dislocation DM cup (n)	Revision for dislocation UP cup (n)	Total revision DM cup (n)	Total revision UP cup (n)
Tarasevicius et al. [55]	2.790	620	2.170	63,2	68	237/383	787/1.383	median 2,5 years	median 2,5 years	4	52	14	86
Kreipke et al. [56]	4.554	2.277	2.277	75,5	75,5	896/1.381	914/1.363	median 2.99 years	median 3.2 years	2	24	97	72
Bloemheuvel et al. [35]	215.953	3.038	212.915	70	69	1.104/1.934	70.144/142.771	median 3 years	median 3 years	8	1.017	50	3.174

DM = dual mobility, UP = unipolar, M = male, F = female.

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Chapter 9

Effectiveness of dual-mobility cups for preventing dislocation after primary total hip arthroplasty compared to unipolar cups in elderly patients: design of a randomized controlled trial nested in the Dutch Arthroplasty Registry.

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Abstract

Background

Dislocation is the leading reason for early revision surgery after total hip arthroplasty (THA). The dual-mobility (DM) cup was developed to provide more stability and mechanically reduce the risk of dislocation. Despite the increased use of DM cups, high quality evidence of their (cost-) effectiveness is lacking. The primary objective of this randomized controlled trial (RCT) is to investigate whether there is a difference in the number of hip dislocations following primary THA, using the posterolateral approach, with a DM cup compared to a unipolar (UP) cup in elderly patients 1 year after surgery. Secondary outcomes include the number of revision surgeries, patient reported outcome measures (PROMs) and cost-effectiveness.

Methods and analysis

This is a prospective multi-center nationwide, single blinded RCT nested in the Dutch Arthroplasty Registry. Patients ≥70 years old, undergoing elective primary THA using the posterolateral approach will be eligible. After written informed consent, 1,100 participants will be randomly allocated to the intervention or control group. The intervention group receives a THA with a DM cup and the control group a THA with a UP cup. PROMs are collected pre-operative, and 3 months, 1 and 2 years postoperatively. Primary outcome is the difference in number of dislocations between the UP and DM cup within 1 year, reported in the registry (revisions), or by the patients (closed or open reduction). Data will be analysed using multilevel models as appropriate for each outcome (linear/logistic/survival). An economic evaluation will be performed from the health care and societal perspective, for dislocation and Quality Adjusted Life Years (QALYs).

Trial registration

This RCT is registered at www.clinicaltrials.gov with identification number NCT04031820.

INTRODUCTION

Dislocation after total hip arthroplasty (THA) is the leading reason for early revision surgery (1, 2). Most dislocations occur during the first year after surgery, of which approximately half within the first 3 months (3-6). Especially in patients with recurrent dislocation and the need for revision surgery, this leads to reduced physical functioning and quality of life (7). Dislocations also increase healthcare costs (8, 9). A single dislocation adds 19% to the hospital costs of an uncomplicated THA, and a revision surgery up to 148% (9).

Despite the increased and, in some countries, broad use of DM cups, high quality evidence of their effectiveness is lacking (10). Recent reviews did not identify any randomized controlled trials (RCT) comparing DM cups with UP cups (10-13) and the existing studies are of low methodological quality and high risk of bias due to the lack of experimental design. So far only one –non randomized- cost-effectiveness study has been performed, suggesting that the DM cup may result in cost savings compared with a UP cup (14). Although promising, the results of this cost-effectiveness database study are not transferrable outside France.

Therefore we initiated an RCT to establish the effectiveness of DM cups for primary THA. The primary objective is to investigate whether there is a difference in the number of hip dislocations following primary total hip arthroplasty (THA), using the posterolateral approach, with a DM cup compared to a UP cup in elderly patients within 1 year after surgery. Several secondary outcomes will be specified in the methods section. The registry-nested design will facilitate long term follow-up for all study participants.

METHODS

Study design

This is a prospective registry-nested multi-center single blinded RCT, which will be conducted in 10 general and academic hospitals in the Netherlands. This RCT compares the number of hip dislocations following primary THA with a DM cup compared to a UP cup and is nested in the Dutch Arthroplasty Registry (LROI).

All patients will be followed-up until 2 years after surgery. The recruitment phase started in April 2019 and was anticipated to last 2.5 years. After the first year of recruitment, we experience a slight delay. After final study follow up, participants remain traceable in the LROI for evaluation of long-term survival and mortality.

Participants

All patients at the orthopedic outpatient clinics of participating centers that meet the criteria to undergo an elective primary THA will be screened for the in- and exclusion criteria.
Patients can be included when they are 70 years or older; have adequate comprehension of written and spoken Dutch; and are eligible for elective primary THA with a cup large enough for a 32 or 36 millimeter head diameter, by a surgeon who is comfortable using the posterolateral approach. A previous contralateral THA is not a reason for exclusion. But patients who undergo bilateral hip arthroplasty can only participate in the trial with 1 of the hips. Patients will be excluded when they: are not able to complete PROMs; are not eligible for either a UP or DM cup; have epilepsy, spasticity, dementia, mental retardation or alcoholism. If dementia or mental retardation is not already mentioned in the medical chart, this can be determined by doctor's opinion.

Characteristics that will be collected are: age; sex; BMI; smoking; diagnosis; ASA classification; Charnley score; education level according to the Statistics Netherlands classification; surgical details (e.g. side, any complications); implant details (e.g. brand, size) ; type of fixation (cemented or uncemented); type of stem.

Interventions

All patients participating in the RCT will be treated with a THA using the posterolateral approach. Patients are randomly allocated to a DM cup or to a UP cup with a 1:1 allocation ratio. It is a

requirement for participating surgeons to feel confident with both procedures. The Dutch guidelines recommend reconstruction of the capsule and external rotators when using the posterolateral approach. There are no restrictions to a specific brand of implant, participating hospitals can use the implants of the companies they usually work with. This study does not investigate any specific implant, but rather pragmatically the concept of DM cups. The Avantage (Zimmer Biomet) and POLAR (Smith & Nephew) cups are examples of commonly used DM cups. The IP (Link), FAL (Link), Exeter (Stryker) and Pinnacle (Johnson & Johnson) cups are commonly used UP cups. Cemented DM and UP cups have 5 year survival rates of ≥96%, with cumulative revision rates ranging from 1.9-4.0% when revision was defined as any change (insertion, replacement, and/or removal) of one or more components of the prosthesis, for any reason (15). Lubinus SP2 (Link), Exeter (Stryker) and Corail (Johnson & Johnson) are the commonly used stems.

All patients receive the same standard pre- and postoperative care for both DM and UP cups according to their hospital's standard.

Sample size calculation

Exact dislocation rates in the Netherlands are unknown, as only those dislocations that result in revision surgery are registered. Based on previous studies and reviews, we assume that the current dislocation rate for UP cups is 4% whereas DM cups result in 1% dislocation (11, 16-21). Power analysis indicates that a total sample of 976 (488 in each group) is needed to detect a difference in dislocations between 4% in the UP cup group and 1% in the DM cup group, using the chi-square test with 80% power and α=0.05. To account for loss to follow-up, 550 patients will be included in each group.

Outcomes

Primary outcome

The primary outcome is the number of hip dislocations, regardless of type of treatment (i.e. closed or open reduction). This information is collected both from the LROI and the patient. Since the LROI only registers revisions, open and closed reductions would be missed. Therefore, patients are asked with a questionnaire at 3 months, 1- and 2 year follow-up whether they have had a hip dislocation.

Secondary outcomes

Secondary outcomes are any unplanned hip procedures, including revision surgery of any component, for any reason; cost-effectiveness and PROMs.

The following PROMs are collected pre-operatively, and 3 months, 1 and 2 years postoperatively: Physical functioning of the hip measured with the Hip disability and Osteoarthritis Outcome Score Physical Short form (HOOS-PS)(22); Quality of life measured with the EuroQol 5 Dimensions (EQ-5D) (23); pain measured with a numeric rating scale (NRS) ranging from 0-10 for pain in rest and during weight bearing; change in physical functioning measured with an anchor question; fear of hip dislocation measured on a five-point Likert scale. At all postoperative moments, the awareness of type of cup that was placed is asked.

At 3 months and 1 year postoperatively healthcare and societal costs related to hip dislocation or surgery are measured with a retrospective 4-week cost evaluation questionnaire which is filled out by the patient. We will obtain information on health care utilization, (pain) medication used, patient costs, use of domiciliary care, use of informal care, and sickness absenteeism from paid or unpaid work. Health care utilization consists of general practitioner care, allied health care, medical specialist care, imaging tests, admission to a hospital, rehabilitation center, nursing home or care home, and mobility aids. Participants' costs concern the patient contribution towards costs for mobility aids and travel. Domiciliary care consists of home nursing care and home help. Health care utilization, domiciliary care, informal care and sickness absenteeism will be valued with Dutch standard costs (24). If these are not available, prices reported by professional associations will used. The costs of prescribed medications will be calculated using prices charged by the Royal Dutch Society for Pharmacy.

Study procedures

Informed consent

During the pre-operative visit at the outpatient clinic, patients who are potential candidates for this study will be screened to determine if they meet the in- and exclusion criteria. If the patient is eligible, the investigator (or his designated representative) will propose participation in the study to the patient, according to GCP guidelines. Patients must sign an informed consent form approved by the ethical committee, prior to participating in any study specific related activities.

Randomization

1,100 patients will be randomized into 1 of the 2 study groups. After signing informed consent, the patients will be randomized to treatment group A (DM cup) or treatment group B (UP cup). Each group will consist of 550 patients. The investigator (or his designated representative) will perform the

randomization using the program CASTOR Electronic Data Capture. Variable randomization blocks of 2, 4 and 6 patients will be used, and we will stratify for center. Patients will be blinded for treatment allocation. The participating surgeons may divert from the randomization scheme based on intra-operative findings. Any deviation from the assigned treatment group will be reported as a deviation from the protocol.

Follow-up

Patients are evaluated at 3 months, 1 year and 2 years after surgery.

Data analysis plan

Interim analysis

Interim analysis for the primary study outcome will be performed when 200 patients have reached the 3 months postoperative PROM evaluation point. In the interim analysis the number of dislocations in each group will be compared. A chi-square test will be used and in case the assumptions of this test are not met, Fischer exact test will be applied. To guard against a type 1 error, we will use the O'Brien-Fleming approach. As only 1 interim analysis will be performed, the alpha for this analysis is set at 0.005. Testing will be done 2-sided. Furthermore, we will consider the number of revisions and SAE's in each group , but not formally test for differences in these. Results of the interim analysis will be discussed with the study team, Van Rens Foundation (funder of this study) and the ethical committee. In case of a statically significant and relevant higher number of dislocations in the DM group, or more revisions or SAE's, appropriate actions will be taken (such as an early termination of the study).

Primary outcome analysis

The primary outcome, the difference in number of dislocations in both groups, will be analysed using chi square analysis. Additional exploratory multivariable logistic regression analyses will adjust for clustering of data (e.g. at the hospital level), and possible confounding or effect modification of patient and surgical characteristics (e.g. age; sex; BMI; smoking; diagnosis; ASA classification; Charnley score; education level according to the Statistics Netherlands classification; surgical details; implant details ; type of fixation; type of stem). A multilevel survival model will be used to analyse the survival of the implant, corrected for covariates.

Analyses will be performed using both intention-to-treat as well as per-protocol analysis.

Missing values

Efforts will be made to prevent missing data by sending reminders and making phone calls when appropriate. A reasonable amount of drop-outs is anticipated for, and mixed model analyses will account for missing data using maximum likelihood estimation. In the event of unforeseen numbers of missing values, a state of the art solution will be sought in consultation with a statistician (e.g. imputation, depending on the nature of the missing data).

Secondary outcomes analyses

Secondary study outcomes are any surgical intervention on the affected hip including revision surgery, healthcare costs, societal costs, patient reported physical functioning, quality of life, pain, satisfaction, fear of hip dislocation and device-related complications and reoperations. The secondary outcomes will be analysed using similar multilevel models as appropriate for each outcome (linear/ logistic/survival).

An economic evaluation will be performed from the societal perspective, for dislocation and Quality Adjusted Life Years (QALYs). Prevailing guidelines of Zorginstituut Nederland will be observed. All costs and consequences relevant to THA, hip dislocation and hip revision will be accounted for.

To compare costs between groups, confidence intervals around the mean differences in costs at one year after THA will be estimated using the bias-corrected and accelerated bootstrap method. To account for possible clustering of data and to adjust for possible confounders, multi-level analyses will be performed. To graphically present the incremental cost-effectiveness ratios and uncertainty around them, bootstrapped cost-effect pairs will be plotted on cost-effectiveness planes. Cost-effectiveness acceptability curves will present the probability that the DM cup is more cost-effective than the UP cup for a range of willingness-to-pay thresholds. To study the robustness of these results, sensitivity analyses will be performed.

DISCUSSION

To the authors' knowledge, this is the first RCT comparing UP and DM cups for primary THA. In contrast to the observational nature of all (registry) studies to date, this study will be able to draw causal inferences. Previous literature is mostly from France, where DM cups are already used in approximately 30% of all primary THAs (14). Dislocation rates seem lower for dual mobility (DM) cups (range 0 to 3.6%) than for unipolar cups (range 0.5 to 6%) (25-30). Good results are also shown when DM cups are used in revision surgery for patients with recurrent dislocation (3, 31, 32). The Dutch Arthroplasty Registry shows that 3.9% of all cemented cups in 2015 were DM cups (33). The proportion of DM cups in all primary THA increased from 0.8% in 2010 to 2.6% in 2016 (34). In the Netherlands and other countries, DM cups are typically used for primary THA in patients with specific characteristics, such as cognitive impairment (not able to follow restrictions after surgery), neuromuscular diseases (spasms) or alcohol abuse, or as a standard procedure for revision surgeries due to recurrent dislocations (11, 34). These patient characteristics might negatively influence the risk for dislocation and revision surgery, so data of these specific patient groups cannot be generalized to the regular primary THA population.

Our registry-nested randomized design is an efficient way to obtain an unbiased comparison between DM and UP cups, both in the short term and long term. Currently, dislocations are only reported in the registry if they result in implant revision. Therefore, the primary – relevant to patients - outcome of this study is a composite measure of revisions due to dislocation reported in the registry and patient-reported dislocations that were treated with closed or open reduction. Not many studies used such a composite outcome, which complicated our sample size calculation. The current group sizes are based on informed assumptions, and considered large enough to detect substantial differences between groups. However, regarding this limitation we believe it is fair to compare groups in terms of incidence rates with corresponding confidence intervals rather than strictly focussing on p-values (35). Also, the registry nested design does allow for comparison with large groups of patients who underwent similar hip replacement surgery outside the study. Another limitation is that we do not collect radiographic outcomes for each participant.

Literature shows good survival rates up to 10 years for DM cups, ranging from 90.4% to 100% (36-44). Nevertheless, our population only includes patients aged 70 and older to minimize risk of revision for

other indications such as loosening and wear. The study results may therefore promote additional research with a younger study population that is generally more active.

Important strengths of this study are that we will keep track of complications (serious adverse events) other than dislocations as well. In the long term, we will be able to study survival of the implants as well as mortality in both study groups, as these remain available in the LROI. Finally, this trial not only evaluates effectiveness, but also the costs associated with both interventions. Such a trial-based economic evaluation is important to determine whether DM cups, which are typically more expensive, are worthwhile in a population undergoing primary THP.

ETHICS AND DISSEMINATION

This study (NL64819.100.18) is approved by the Medical research Ethics Committees United, the Netherlands, and will be conducted according to the principles of the Declaration of Helsinki (2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and Good Clinical Practice guidelines.
The protocol of this trial is registered at clinicaltrials.gov (NCT04031820) and will be published. The main and secondary results of this study will be reported in international peer-reviewed journals.

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Chapter 10

General discussion

What this thesis adds to the existing knowledge

- In chapter 2, the systematic review showed strong evidence for associations between BMI, age, comorbidity, preoperative physical function and mental health with functional outcome after total hip arthroplasty (THA).
- In chapter 3, the prediction model showed that patients had a higher chance to be responsive to THA when at baseline experiencing (1) more pain of the contralateral hip; (2) worse physical functioning; (3) better mental wellbeing; and (4) less back pain.
- In chapter 4, our systematic review on surgical approaches for hemiarthroplasty in patients with a hip fracture, with the patients' independence in activities of daily living as primary outcome, showed weak evidence that the posterolateral approach is associated with more dislocations, while the direct lateral approach is associated with more abductor insufficiency and walking problems.
- In chapter 5, the analysis of Dutch Arthroplasty Registry data showed that all four surgical approaches resulted in improvement of patient reported outcome measures (PROMs) after THA, although the anterior and posterolateral approaches showed slightly more improvement in physical functioning (HOOS-PS) and pain.
- In chapter 6, the CUSTOM study protocol describes a high-quality randomized controlled trial (RCT) comparing a conventional straight stem (Zweymüller) and a short curved stem (CFP) and their influence on physical functioning after primary THA. This protocol resulted in a multicenter maximally blinded RCT, in which 150 patients were included. Strong efforts were made to reduce bias.
- In chapter 7, our 5 year outcomes of the CUSTOM trial, supplemented with data from the Dutch Arthroplasty Registry for long-term survival analysis, showed no significant differences in physical functioning at 5-years and implant survival at 10-years follow-up between the CFP and Zweymüller stems.
- In chapter 8, the systematic review comparing dual mobility cups and unipolar cups in primary total hip arthroplasty showed weak evidence for lower rates of dislocation and revision due to dislocation with dual mobility cups. However, the risk for selection bias is large, because no RCTs are conducted.
- In chapter 9, our REDEP trial protocol describes the first registry-nested RCT comparing dual mobility cups with unipolar cups in elderly patients, resulting in an international multicenter RCT. This trial is still ongoing, and results are expected in 2025.

Current state of the literature

The sections below summarize our main findings in relation to recent literature. I specifically focused on studies that were published during my PhD project. In the general introduction of this thesis, as well as in the introduction sections of the individual chapters, earlier research is described.

The influence of *patient factors* on outcome after THA.

In this thesis, we aimed to identify factors that can predict the functional outcome after a THA. In our systematic review (Chapter 2), we found a strong association between functional outcome after THA and BMI, age, comorbidity, preoperative physical functioning and mental health. The prediction model based on data from the CUSTOM trial (Chapter 3) confirmed worse preoperative physical function and a better mental health to be predictive for good improvement in physical function after THA. Additionally, more contralateral hip pain and less back pain were found as a predictive factors. The results of this prediction model contribute to the discussion on which patient characteristics are predictive for improvement in functional outcome after THA. This knowledge can help physicians, surgeons and patients in managing their expectations of outcome after uncemented THA. The findings of our systematic review and prediction model are generally consistent with other literature on this topic. For example, a recent study developed and validated a machine learning model for the prediction of numerous patient-reported outcome measures after THA.(1) This model found a significant association between preoperative PROM scores, Charlson Comorbidity Index, American Society of Anaesthesiology score, insurance status, age, length of hospital stay, body mass index and ethnicity and postoperative PROM scores. A systematic review by O'Connor et al.(2) studied preoperative psychological factors and their influence on outcomes after THA. Their main finding was that preoperative depression, anxiety and somatization may negatively impact patient reported postoperative pain, functionality and complications following THA. Another study looked more in detail at different age groups and their influence on outcome after THA. They did not find any clinical significant difference between the age groups.(3) A multivariable prediction model by Aggarwal et al, based on registry data, found better pre-operative radiographic scores to be associated with worse outcomes.(4) Other factors they found associated with poor outcome were lower back pain and lower expectation (predicting poor improvement); lower education and higher ASA (predicting lower satisfaction); younger age, female sex, non-English speakers, lower preoperative EQ-VAS, lower education, back pain and anxiety/depression (predicting better Oxford Hip Scores). Overall, the findings of our systematic review and prediction model are consistent with other literature on

predictors of functional outcomes after THA, and highlight the importance of preoperative physical function, mental health and pain as predictors of postoperative function.

The influence of *surgical approach* on outcome after hip arthroplasty.

In hemiarthroplasty, a variety of surgical approaches is used. Which approach is used is mostly depending on the preferences of the surgeon and the standards of the hospital.(5) We conducted a systematic review comparing the direct lateral approach (DLA) with the posterolateral approach (PLA) in patients with a femoral neck fracture undergoing a hemiarthroplasty (Chapter 4). Results showed that PLA might be associated with more dislocations, but patients had less walking problems and a lower tendency to abductor insufficiency, however, this was based on studies of low methodological quality. Regarding independent functioning, it is important to gain a deeper understanding of the impact of dislocation and abductor insufficiency. Analyzing subgroups of patients can be an interesting addition to standard primary analyses detecting overall group effects. For some groups of patients, such as patients suffering from dementia, preventing dislocation might be more important than preventing limping or maintaining independent functioning. Other literature, for instance Leonardsson et al. show similar results for hemiarthroplasty.(6) They report that the PLA seems to result in a better health related quality of life, less pain and greater satisfaction one year after surgery, however these results did not remain after adjusting for relevant confounders. In contrast, a meta-analysis by van der Sijp et al. suggest that the PLA is not the preferred approach for a hemiarthroplasty, due to the higher risk for dislocations.(7) However, it is important to consider the impact of limping caused by DLA on the quality of life and independent functioning, as it can substantially affect these aspects. Therefore our group and colleagues initiated an RCT comparing these two approaches, focusing on outcomes that are most important for patients.(8)

The same variety in surgical approaches is seen in total hip arthroplasty (THA). A meta-analysis studying the complication rate among surgical approaches in THA concluded that the posterior approach has a higher risk of dislocation, compared to the anterior, lateral and anterolateral approach, but a lower risk of loosening compared to the lateral and anterolateral approach.(9) However, this was based on low-quality evidence. In contrast to our registry study (Chapter 5), this meta-analysis did not study patient reported outcomes. Another meta-analysis with higher quality studies, although still mostly non-RCTs, reported that the direct anterior approach (DAA) was superior to the PLA in early functional recovery, activity ability, pain relief and hospitalization duration after THA.(10)

However, the DAA is not a suitable approach for every patient. In our registry study no significant or clinical relevant differences on PROMs scores were observed between the DAA and PLA.

The influence of *implant design* on outcome after THA.

In total hip arthroplasty, different implant designs are being used. Short stems have gained interest over the last decade, due to their potential advantages compared to conventional straight stems. The most reported benefits are the preservation of femoral bone and soft tissue, which might be an advantage for future revision surgeries and might accelerate early rehabilitation and improve functional outcome.(11-14) In this thesis we focused on the Collum Femoris Preserving (CFP) stem, which we compared to a conventional straight stem (Zweymüller) in a multicenter RCT (Chapter 6, the CUSTOM trial). This trial showed good functional results for the CFP stem up to five years after cementless primary THA, although not superior to the Zweymüller stem. In accordance, several studies on short stem implants report positive clinical outcomes and good survival.(15-18) However, most of these studies are non-randomized studies with a higher risk of bias, for instance because short stems might be placed in younger patients anticipating the chance for a future revision. Two other RCTs show similar results but also report greater loss of bone mineral density and a greater rate of varus malalignment for the short stem group, which may influence implant survival.(18, 19) In the CUSTOM trial, we did not measure BMD or alignment of the prosthesis. The reports from radiographs that were taken at 5 years follow-up did not reveal differences in radiological complications between groups in our study population.

Also in acetabular cups, we see innovative developments to improve outcomes after THA. In this thesis, we focus on innovations to reduce the risk of hip dislocation. In primary THA using the posterolateral approach, the risk for dislocation is relative high. However, this approach has potential advantages over other approaches, such as a lower risk for limping and slightly more improvement in physical function.(20, 21) In our registry-nested RCT (REDEP trial, Chapter 9), we compare unipolar cups with dual mobility cups, to investigate whether there is a difference in the number of dislocations.(22) Promising results for reducing dislocations are also shown with the use of large femoral heads.(23, 24) Because femoral head size seems to be of influence on dislocation rates, we have eliminated this factor by using only femoral heads with a maximum size of 36mm in the REDEP trail. This allows us to solely investigate the influence of DM cups on dislocation in primary THA. It is important to point out that with increasing femoral head sizes, the probability for liner wear also increases, which may result in earlier revision surgery. However, there is no consistent evidence to

support this and long term evidence is lacking.(25-27) To date, most studies comparing dual mobility and unipolar cups have important limitations, as they were conducted in a non-randomized setting, only reported short term outcomes, or included a very specific population such as revision THA or patients at risk for a dislocation. For our REDEP trial, we chose a randomized design in a population with primary THA, nested in a registry to facilitate long term follow up. We aimed for a pragmatic design, but we did include an age restriction (minimum of 70 years), to minimize long term risk for revision for reasons other than dislocation, such as loosening and wear. An RCT using radiostereometric analysis (RSA) following patients for 6 years after a primary THA with a DM cup, found that PE wear rates for both cemented and cementless DM implants were below the treshold of 0.1mm/year, with no correlation to physical activity and implant position.(28) Since both this study and the REDEP trial include patients above 70 years old, no information is provided on potential polyethylene wear in younger patients. This remains a question that requires further research.

Strengths and limitations

This thesis is not without limitations. The least strong part of this thesis is chapter 3, where we tried to validate the findings of the systematic review in chapter 2, by developing a prediction model with the CUSTOM study database. Due to important methodological and clinical limitations, this study failed to provide new insights. Despite the shortcomings, it was a highly educational process and therefor this chapter is still included in this thesis. Another limitation is that the quality of a systematic review depends on the included articles. In our systematic reviews, there was a high level of heterogeneity among the included studies and therefore no meta-analyses could be performed. In the systematic review in chapter 8, no randomized studies were included and therefore no GRADE approach for the critical appraisal could be performed but instead the MINORS criteria were employed. A limitation of the study in chapter 5, and in general for studies only using registry data, is the inability to draw causal relationships.

This thesis has some strengths to notify. It contains a diverse range of research studies, including systematic reviews, study protocols, a prediction model and an RCT with long term follow-up. This thesis describes two RCTs in detail, of which one (CUSTOM trial, chapter 6 and 7) was maximally blinded, thereby enhancing the methodological quality of this trial. During the time of conducting this trial, (double)blinded surgical trials were uncommon and considered as challengingand the methodological quality of (non-pharmacological) trials in the treatment of hip osteoarthritis was often relatively low.(29-31) The more recently conducted trial (REDEP, chapter 9) has an even stronger

methodological design, by nesting the RCT in an implant registry. Valuable insights from previous trials, such as CUSTOM, were the reduction of outcome measures and performing no additional clinical tests, to enhance the trial's feasibility, minimize patient visits and reduce research costs. The study on surgical approaches used data from the national implant registry, resulting in a large sample size with prospectively collected data from multiple hospitals, thereby ensuring high generalizability.

Furthermore, the inclusion of two systematic reviews in this thesis underscores our thorough preparation and scientific foundation prior to initiating a clinical trial.

Implications for clinical practice

This thesis has implications for clinical practice:

- For femoral neck fractures, clinicians might consider both the posterolateral and direct lateral approaches when performing hemiarthroplasty after femoral neck fractures, knowing that there is no strong evidence in favor of one of these approaches and both approaches have their potential disadvantages such as dislocation (PLA) and abductor insufficiency (DLA).
- For primary THA, clinicians can consider different surgical approaches since all four studied approaches (anterior, anterolateral, direct lateral and posterolateral) result in significant improvement of PROMs and clinical differences were only small. The slightly better improvement in physical functioning (HOOS-PS) with the anterior and posterolateral approach and the lower pain score of the posterolateral approach compared to the anterolateral approach can be taken into account.
- According to the results of the CUSTOM trial, the CFP and Zweymüller stems show similar improvements in physical function up to 5-year follow-up. Therefore, both types of stems can be suitable options for primary uncemented THA.
- The outcomes of the REDEP trial are expected to give a recommendation for clinical practice, about whether or not to use the DM cup to prevent dislocation in primary THA in patients ≥70 years. This depends on whether it is cost-efficient or not.

Implications for future research

In addition to providing insights in the influence of patient, surgical and implant characteristics on the outcome after THA, this thesis also provides suggestions for the design of future clinical studies. Randomized controlled trials (RCTs) are considered the gold standard for evaluating the effectiveness and outcomes after THA. However, RCTs have limitations such as large time investments, challenges

with patient recruitment, high costs and the potential for selection bias (i.e. not all patients and physicians want to participate). Therefore, there is a need for more efficient and sustainable methodologies that can still enable the identification of causal relationships. Also, to increase the generalizability of findings, and to ensure that a study can be included in a systematic review or meta-analysis, a number of factors can be taken into account. Primarily, studies should standardize the outcome measures and follow-up moments to enable comparison of results across studies. Additionally, follow-up might be standardized and long enough. This is important to assess implant survival, identify complications such as loosening and late infections, patient satisfaction and cost-effectiveness. Also, for manufacturers long-term outcomes are important for obtaining a ODEP rating. Since classic RCTs aim to control for various variables, this leads to a highly homogenous patient population. To increase generalizability of RCT results in the future, alternative study designs should be considered. One of such alternatives is using data from implant registries to include clinical practice variation in the trial results, such as surgical approach; different brands of implants and fixation type. Using data from implant registries can provide important insights into the long-term outcomes of THA and can identify risk factors for complications or poor outcomes. Using registry data can be useful when developing a prediction model, as it typically includes larger numbers of patients in contrast to most databases, such as the database used in Chapter 3. Advantages of using larger databases include the ability to evaluate more variables in the model and increasing statistical power.

Registry nested RCTs might be considered for future orthopaedic trials. Incorporating registries can be a manner to design RCTs differently and more sustainable, resulting in the saving of substantial research funds and efforts from both patients and researchers. Another way to accomplish this can be to no longer conduct purely study-related clinical follow-ups. In addition, the use of wearable sensors such as smart watches can be helpful to collect objective data in an inexpensive way which is easy to conduct for patients. Furthermore, researchers should be critical at which PROMs are administered, by mainly focusing on those routinely collected PROMs within the implant registries. Registry data can also be used to amplify the results of RCTs in hip arthroplasty. This can be helpful to overcome limitations of RCTs such as limited sample sizes and short follow-up periods. Furthermore, implant registry data can also be used to identify patient characteristics that may influence treatment outcomes, such as age, gender, and BMI. This information can be used to develop personalized treatment plans that optimize outcomes and minimize risks for individual patients. The response to treatments or interventions can be very different for individual patients. This variability may be related to differences in patient characteristics. Therefore, subgroup analysis

can be interesting to add to the primary analyses. However, it is important to use these results for generating hypotheses for future research instead of drawing strong conclusions.

Using implant registries in clinical trials is highly recommendable, however it is important to consider its limitations. Registries can be prone to selection bias, because some implants are only used in specific patient groups, and therefore the generalizability of the results can be limited. Also, not all complications and adverse events are captured in implant registries.

Currently, there are many developments in the field of artificial intelligence (AI). The use of AI in big databases such as implant registries is suggested to provide new opportunities. It can provide a rapid access to information from different large databases, is capable to analyze complex associations between different databases and might provide a very efficient and probably cost-effective way to conduct analyses. However, at this moment it is still important to be aware of the limitations using AI, such as quality and completeness of data. Because AI relies on the input of data, any biases or faults in the collected data can affect the reliability and validity of the results. Therefore, it cannot replace experimental research such as well-designed RCTs. AI could be useful for continuous monitoring of patient outcomes. This might facilitate studies with other designs, such as natural experiments that use practice variation as a way of pseudo randomization.

The overview below summarizes the lessons learned from this thesis and suggestions for future clinical studies. Overall, incorporating implant registry data into RCTs, while being aware of its limitations, can provide a more complete and nuanced understanding of THA outcomes, while optimizing the use of scarce research resources.

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Chapter 11

Summary of this thesis

Dutch summary (Nederlandse samenvatting)

Summary of this thesis

This thesis contributes to the evidence-base of the influence of patient factors, surgical approach and implant design on outcomes after hip arthroplasty.

The influence of ***patient factors*** on outcome after total hip arthroplasty (THA). Several patient factors can predict functional outcome after THA. We conducted a systematic review to study these factors. Strong evidence is shown of an association between BMI, age, comorbidity, preoperative physical function and mental health with functional outcome after THA. Weak evidence suggested that quadriceps strength and education were predictive of functional outcomes after THA. Inconsistent evidence was found for the predictors like gender and socioeconomic status. Alcohol consumption, vitamin D insufficiency and allergies showed limited evidence predicting functional outcome after THA (**chapter 2**). Preoperative physical function, mental health and pain are factors reported in literature that were also supported by the prediction model that we built with data from the CUSTOM trial (chapter 6 and 7). This prediction model showed that patients had a higher chance to obtain the minimal clinically important improvement on the HOOS-PS, when at baseline experiencing (1) more pain of the contralateral hip (higher NRS score); (2) worse physical functioning (higher HOOS-PS score); (3) better mental wellbeing (higher SF-12 MCS score); and (4) less back pain (lower NRS score). Before using it for personalized care, this model should be externally validated, preferably with data from other hospitals or a registry (**chapter 3**).

The influence of ***surgical approach*** on outcome after hip arthroplasty. To treat femoral neck fractures, the posterolateral approach (PLA) and direct lateral approach (DLA) are the most commonly used approaches for inserting a hemiarthroplasty. We conducted a systematic review to provide an updated and critical evaluation of the available evidence, focusing on outcomes relevant for patients. Our findings suggest that PLA might lead to more dislocations compared to DLA, but patients had less walking problems and a lower tendency to abductor insufficiency. However, based on the current evidence a causal relationship cannot be made and the impact of the major risks (dislocation vs. abductor insufficiency) on fall risk and independent functioning in ADL is not well understood. Randomized controlled trials are necessary, focusing on outcomes relevant for patients- (**chapter 4**). We studied the effect of four surgical approaches on patient reported outcome measures (PROMs) after primary THA, using data from the Dutch Arthroplasty Registry. All four approaches resulted in a significant increase of PROMs after primary THA. Although, the anterior and posterolateral surgical

approaches showed more improvement in self-reported physical functioning (HOOS-PS) and pain. However, clinical differences were small (**chapter 5**).

The influence of ***implant design*** on outcome after THA. In **Chapter 6**, we describe the detailed protocol of the CUSTOM trial. This protocol was the basis for a multicenter RCT, in which 150 patients were included. In this maximally blinded RCT, strong efforts were made to reduce bias. The trial was successfully completed at 5 years follow-up and with the use of the Dutch Arthroplasty Registry, we were able to collect long-term survival data up to 12 years (**Chapter 7**). No significant differences were found in physical functioning at 5-years and implant survival at 10-years follow-up between the Collum Femoris Preserving and Zweymüller stems. When taking cup revisions into account, the CFP group shows a clinically inferior survival. To draw strong conclusions on implant survival, further research with larger numbers of patients is required. We conducted a systematic review to study the difference in the number of dislocations, between dual mobility cups and unipolar cups in primary THA (**Chapter 8**). The results suggest lower rates of dislocation and revision due to dislocation, in favor of the dual mobility cup. However, these results should be interpreted with caution, because the chance for selection bias is present due to differences in the selection of the populations in the registry studies, and the included studies were of medium to low methodological quality. Therefore, we designed the first registry based RCT comparing dual mobility cups with unipolar cups in elderly patients (**Chapter 9**). This protocol resulted in an international multicenter RCT. This trial is still ongoing, and to this date, more than 75% of the anticipated patients is included. Results of this trial will be expected in 2025. In addition to providing insights in the influence of patient, surgical and implant characteristics on the outcome after hip arthroplasty, this thesis also provides suggestions such as the use of implant registries, for the design of future clinical studies.

Nederlandse samenvatting

Dit proefschrift draagt bij aan de kennis over de invloed van patiëntfactoren, chirurgische benadering en implantaat kenmerken op de uitkomsten na een heupvervanging (heup arthroplastiek).

De invloed van ***patiëntfactoren*** op de uitkomst na een totale heup vervanging (THA).
Verschillende patiëntfactoren kunnen de functionele uitkomst na THA voorspellen. We hebben een systematische review uitgevoerd om deze factoren te bestuderen. Sterk bewijs toont aan dat er een verband is tussen BMI, leeftijd, comorbiditeit, preoperatief fysiek functioneren en mentale gezondheid en functionele uitkomsten na een THA. Zwak bewijs suggereerde dat quadricepskracht en opleiding voorspellend waren voor functionele uitkomsten na een THA. Inconsistent bewijs werd gevonden voor voorspellers zoals geslacht en sociaaleconomische status. Voor alcoholgebruik, vitamine D-tekort en allergieën werd beperkt bewijs gevonden voor het voorspellen van functionele uitkomsten na THA (**hoofdstuk 2**). Preoperatief fysiek functioneren, mentale gezondheid en pijn zijn factoren die genoemd worden in de literatuur en die ook worden ondersteund door het voorspellingsmodel dat we hebben gebouwd met gegevens uit de CUSTOM-studie (**hoofdstuk 6 en 7**). Dit voorspellingsmodel toonde aan dat patiënten een grotere kans hadden om de minimale klinisch belangrijke verbetering op de HOOS-PS te behalen, wanneer ze bij aanvang (1) meer pijn aan de contralaterale heup hadden (hogere NRS pijn score); (2) een slechtere fysieke functie hadden (hogere HOOS-PS score); (3) een beter mentaal welzijn hadden (hogere SF-12 MCS score); en (4) minder rugpijn hadden (lagere NRS pijn score). Voordat het wordt gebruikt voor individuele zorg, moet dit model eerst extern worden gevalideerd, bij voorkeur met gegevens van andere ziekenhuizen of een implantaat register (**hoofdstuk 3**).

De invloed van de ***chirurgische benadering*** op de uitkomst na een (totale) heup vervanging.
Voor het behandelen van heupfracturen (femorale hals fracturen), zijn de posterolaterale benadering (PLA) en de direct laterale benadering (DLA) de meest gebruikte chirurgische benaderingen voor het plaatsen van een kophalsprothese. We hebben een systematische review uitgevoerd om een bijgewerkte en kritische evaluatie van het beschikbare bewijs te presenteren, met de focus op uitkomsten die relevant zijn voor patiënten. Onze bevindingen suggereren dat de PLA mogelijk tot tot meer luxaties leidt in vergelijking met de DLA, maar dat patiënten minder loopproblemen en een lagere neiging tot abductor-insufficiëntie hadden. Op basis van het huidige bewijs kan echter geen

oorzakelijk verband worden aangetoond. Ook is het effect van de belangrijkste risico's (luxatie versus abductor-insufficiëntie) op het valrisico en zelfstandig functioneren in ADL nog niet voldoende duidelijk. Gerandomiseerde gecontroleerde onderzoeken (RCTs) die zich richten op uitkomsten die relevant zijn voor patienten, zijn noodzakelijk (**hoofdstuk 4**). We hebben het effect van vier verschillende chirurgische benaderingen onderzocht, op patiënt gerapporteerde uitkomst maten (PROM's) na een primaire THA, met behulp van gegevens uit het Landelijk Register Orthopedische Implantaten (LROI). Alle vier de chirurgische benaderingen resulteerden in een significante verbetering van PROM's na een primaire THA, maar de anterieure en posterolaterale chirurgische benaderingen vertoonden meer verbetering in fysiek functioneren (HOOS-PS) en pijn. De klinische verschillen waren echter klein (**hoofdstuk 5**).

De invloed van het ***implantaat kernmerken*** op de uitkomst na een THA.

In **hoofdstuk 6** beschrijven we het gedetailleerde protocol van de CUSTOM-studie. Dit protocol vormde de basis voor een multicenter RCT, waarbij 150 patiënten werden opgenomen. Deze maximaal geblindeerde RCT werden zodanig ontworpen om fouten (***bias***) zoveel mogelijk tegen te gaan. De trial werd na 5 jaar follow-up met succes afgerond en met behulp van het Nederlandse implantatenregister (LROI) konden we gegevens verzamelen tot 12 jaar na operatie (**hoofdstuk 7**). Er werden geen significante verschillen gevonden tussen de Collum Femoris Preserving (CFP) en Zweymüller stelen, in zowel het fysiek functioneren 5 jaar na operatie als in de overleving van het implantaat 10 jaar na operatie. Wanneer ook rekening wordt gehouden met cup-revisies, vertoont de CFP-groep een klinisch inferieure overleving. Om conclusies te trekken over de overleving de implantaten is verder onderzoek met grotere aantallen patiënten nodig.

We hebben een systematische review uitgevoerd om het verschil in het aantal luxaties te bestuderen tussen dual mobility cups en unipolaire cups bij primaire THA (**hoofdstuk 8**). De resultaten suggereren lagere luxatiecijfers en minder revisies als gevolg van luxatie in het voordeel van de dual mobility cup. Deze resultaten moeten echter voorzichtig worden geïnterpreteerd, omdat er kans is op selectiebias vanwege verschillen in de selectie van de populaties in de registratiestudies. Daarnaast waren de geïncludeerde studies van matig tot slechte methodologische kwaliteit. Daarom hebben we een RCT ontworpen waarin dual mobility cups worden vergeleken met unipolaire cups bij oudere patiënten (**hoofdstuk 9**). Dit protocol resulteerde in een internationale multicenter RCT, die aan het implantaat register is gekoppeld. Deze studie is nog gaande, momenteel is ruim 80% van de patiënten geïncludeerd. De resultaten van deze studie worden verwacht in 2025.

Naast het bieden van inzichten in de invloed van patiënt-, chirurgische en implantaatkenmerken op de uitkomst na een (totale)heupprothese, biedt dit proefschrift ook suggesties, zoals het gebruik van implantaatregisters, voor het ontwerp van toekomstige klinische onderzoeken.

Chapter 12

List of publications

Acknowledgement (Dankwoord)

Curriculum Vitae

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Curriculum Vitae

Loes Wilhelmina Antonia Helena van Beers was born on September 30th 1986 in Oostelbeers, where she grew up with her parents and two brothers. After graduating from high school (Heerbeeck College in Best) in 2003, she started studying Physiotherapy at Fontys Hogescholen in Eindhoven. In Eindhoven Loes had a fantastic student life, and she obtained a Bachelor's degree in 2007. Following this, she moved to Utrecht and she engaged in a Pre-Master's program in Human Movement Sciences at VU University, Amsterdam (2007-2008). In 2009 Loes obtained a Master's degree in Human Movement Sciences with a specialization in Rehabilitation and Physiotherapy from VU University.

Loes started her professional career as a researcher at the orthopaedic department of OLVG in Amsterdam. Her involvement in numerous (international) orthopaedic studies over the years, ultimately motivated her to pursue a PhD under supervision of prof. dr. R.W. Poolman, LUMC. She wrote two >€200K grant applications, both of which were awarded. With these grants, she initiated and coordinated two RCTs: the REDEP trial (Chapter 9) and the BeMobile study (comparing different brands and cementation techniques for dual mobility cups by means of röntgenstereomatric analysis (RSA)). Both studies are still ongoing, with 75 participants in the BeMobile study and over 900 participants in the international REDEP trial. Loes is a member of the Dutch Orthopaedic Association (NOV) and the Werkgroep Orthopedie en Wetenschap since 2015.

Simultaneously, Loes worked as a physiotherapist in various roles, first at private practices (Gezondheidscentrum Galgenwaard, MTC Zeist) and later with great pleasure at OLVG from 2015 to 2021. From 2013 to 2015 she worked as a research coordinator at Sint Lucas Andreas Hospital in Amsterdam. In May 2023, Loes started a new position as research coordinator at the department of orthopaedic surgery at St. Antonius Hospital in Utrecht. She is looking forward to continuing her contributions to orthopaedic research and initiating new studies from this position. In 2017 she married Ruben and they live in Utrecht with their two daughters Isa (2018) and Julie (2020).