Draft guideline Total hip prosthesis

INITIATIVE
Dutch Orthopaedic Association (Nederlandse Orthopaedische Vereniging, NOV)

IN COLLABORATION WITH
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Nationale Vereniging ReumaZorg Nederland
Dutch Society of Medical Microbiology (Nederlandse Vereniging voor Medische Microbiologie, NVMM)
Dutch Geriatrics Society (Nederlandse Vereniging voor Klinische Geriatrie, NVKG)
Patients Federation Netherlands (Patiëntenfederatie Nederland)
Polyartrose Vereniging
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WITH THE HELP OF
Knowledge Institute of the Dutch Association of Medical Specialists (Kennisinstituut van de Federatie Medisch Specialisten)

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Colophon

DRAFT GUIDELINE TOTAL HIP PROSTHESIS

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Summary

This is a summary of the most important recommendations from the multidisciplinary evidence-based clinical guideline Total hip prosthesis. The aim of the guideline is to promote uniform operative treatment of patients with osteoarthritis of the hip.

This summary does not contain the description of the evidence and the considerations leading to the recommendations. For this information readers are referred to the text of the full guideline.

The recommendations should not be used without further consideration. In medical decision-making the context and preferences of the patient should be taken into account. Decisions about individual patients' treatments and procedures should be based on communication between patient, physician and other caregivers.

The summary will be added after the consultation period.

Introduction

Motivation for compiling these guidelines

Clinical practice guidelines are being used in many countries throughout the world to improve the quality of patient care. The Dutch Orthopaedic Association has a long tradition of guideline development, starting in the mid-1980s with “eminence-based consensus” and following in the mid-1990s the renewed calls for the establishment of international methodologies to promote the rigorous development of clinical guidelines and to assess their quality and their impact on practice.

In 2016 almost 29,000 patients underwent a total hip arthroplasty and this annual number is still increasing (LROI Annual Report, 2017). At the same time new materials, technologies and clinical pathways are continuously presented and/or promoted, which justifies this update of the last Guideline Total Hip Prosthesis 2010.

Aim of the guideline

The main purpose of the guideline is to provide the best possible care to patients with osteoarthritis of the hip, by informing optimal treatment decisions and reducing unwarranted variation in the delivery of care and long-term failure of the implants.

Defining the guideline

The guideline focuses on surgical treatment of adult patients with osteoarthritis of the hip. The most relevant outcome measures are pain and function, complications and survival of the prosthesis.

Envisaged users of the guideline

This guideline was developed for all Dutch healthcare providers of patients with osteoarthritis of the hip.

Literature

LROI Annual Report, 2017.

Methods

Reading guide

The draft guideline text below will be included in the Guideline Database (www.richtlijnendatabase.nl) upon completion of the commentary and authorisation phase. Together with the NOV, it was decided to draft the text in English, except for the sections “initial question” and “recommendation”. References to “tab sheets” can be found in the “appendices” at the end of the main text in the current version of the guideline text. Due to the modular layout of guidelines in the database, we refer to modules (instead of chapters) and related products (appendices).

Guideline working group

This guideline was developed and sponsored by the Dutch Orthopaedic Association (NOV), using government funding from the Stichting Kwaliteitsgelden Medisch Specialisten in the Netherlands (SKMS, Quality foundation of the Dutch Federation of Medical Specialists). The early preparative phase started in October 2016 and the guideline was officially authorised by the Dutch Orthopaedic Association ….(date). Decisions were made by consensus. At the start of guideline development, all working group members completed conflict of interest forms.

Declaration of interests

The members of the working group have declared in writing if, in the last five years, they have held a financially supported position with commercial businesses, organisations or institutions that may have a connection with the subject of the guidelines. Enquiries have also been made into personal financial interests, interests pertaining to personal relationships, interests pertaining to reputation management, interests pertaining to externally financed research, and interests pertaining to valorisation of knowledge. These Declarations of Interest can be requested from the secretariat of the Knowledge Institute of Medical Specialists. See below for an overview.

Werkgroeplid	Mogelijke conflicterende belangen met betrekking tot deelname werkgroep	Toelichting
Dr. B.W. Schreurs	Presentaties voor Stryker over de Exeter totale heupprothese (educational fee naar afdeling) Doet reviews voor DEKRA KEMA (betaald) Voorzitter European Hip Society (onbetaald) Voorzitter wetenschappelijke adviesraad LROI (onbetaald) Voorzitter adviesraad botbank Sanquin (onbetaald) Lid Commissie Orthopedisch Implantaten Classificatie NOV (onbetaald)	
Dr. P.C. Jutte	hoofdonderzoeker LEAK studie (ZonMW) Voorzitter werkgroep weke delen en bottumoren lid werkgroep orthopedische infecties NOV lid werkgroep bot tumoren NOV lid commissie beentumoren Nederland lid onderwijscommissie NOV lid medische adviesraad patientvereniging Sarcoma NL	
M.E. Lopuhaä	Geen belangen	
Dr. R.H.M. ten Broeke	Voorzitter werkgroep "Heup" (Dutch Hip Society) NOV sinds 2015. Daarvoor gedurende 3 jaar reeds bestuurslid van deze werkgroep.	

	Klinisch onderzoek gefinancierd door firma Stryker (RSA en PET-CT onderzoek bij vergelijking van 2 ongecementeerde cup designs)	
Dr. W.F.H. Peter	Geen belangen	
Dr. P.D. Croughs	Geen belangen	
Dr. S.B.W. Vehmeijer	Directeur Orthoparc (onbetaald) Bestuurslid Dutch Hip Society (onbetaald) National Representative European Hip Society (onbetaald) Consulent Zimmer Biomet (betaald)	
Dr. B.A. Swierstra	Voorzitter Stichting OrthoResearch (onbetaald) Advisory Board Arthroplasty Watch (onbetaald) Lid Wetenschappelijke Advies Raad Landelijke Registratie Orthopaedische Implantaten (onbetaald) Board of Directors International Society of Orthopaedic Centers (onbetaald) Coeditor Acta Orthopaedica (onkostenvergoeding)	
Dr. R.A. Faaij	Geen belangen	
Dr. A.M.J.S. Vervest	Lid-beroepsgenoot Regionaal Tuchtcollege voor de Gezondheidszorg Den Haag (betaald) Voorzitter Centrale Opleidings Commissie Tergooi (onbetaald)	
J. Vooijs	Geen belangen	
Drs. G. Willemsen – de Mey	Geen belangen	
Meelezers		
Drs. S. Nijssen	ISO 15189 auditor, betaald door RvA	
Dr. R.J. Rentenaar	Commissie bacteriologie Stichting Kwaliteitsbewaking Medische Laboratoria (SKML) (tegen onkostenvergoeding). Verschillende producenten stellen soms kleine hoeveelheden van producten ter beschikking kosteloos of tegen gereduceerd tarief t.b.v. verificatie doeleinden.	
Dr. A.T. Bernards	Geen belangen	

Methodology

The guideline was developed in agreement with the criteria set by the advisory committee on guideline development of the Federation of Medical Specialists in the Netherlands (Medisch Specialistische Richtlijnen 2.0; OMS 2011), which are based on the AGREE II instrument (Brouwers 2010; www.agreetrust.org). The guideline was developed using an evidence-based approach endorsing GRADE methodology, and meeting all criteria of AGREE-II. Grading of Recommendations Assessment, Development and Evaluation (GRADE) is a systematic approach for synthesising evidence and grading of recommendations offering transparency at each stage of the guideline development (Guyatt 2011; Schünemann 2013).

The guideline development process involves a number of phases: a preparatory phase, development phase, commentary phase, and authorisation phase. After authorisation, the guideline has to be disseminated and implemented and its uptake and use have to be evaluated. Finally, the guideline has to be kept up-to-date. Each phase involves a number of practical steps (see Schünemann 2014).

As a first step in the early preparatory phase, a broad forum discussion was held and all relevant stakeholders were consulted to define and prioritise the key issues the recommendations should address. Subsequently, the methodologist together with the chairman of the working group created a draft list of key issues, which was extensively discussed in the working group.

Despite aiming for an update of the guideline from 2010, due to financial constraints not all clinical questions from the former edition could be updated, so it was decided to perform a so-called modular update. Selecting modules with a higher priority for update formed part of this discussion and selection process. This resulted in the following approach.

Modules that were updated:

- Indications for primary total hip replacement
- Surgical techniques in primary total hip replacement
    - Type of bearing
    - Diameter of the head
    - Surgical approach
- Perioperative care in primary total hip replacement
    - Systemic antibiotics
    - Antibiotic-impregnated bone cement
    - Preoperative decontamination
- Routine follow-up
- Fast track treatment
- Organization of care for frail elderly

Modules considered still valid:

- Cemented versus uncemented hip prosthesis

Modules removed from the guideline:

- Resurfacing hip prosthesis
- Minimally invasive surgery

Modules that were replaced by a reference to related guidelines:

- Hematogenous infection
- Prevention of thrombo-embolic complications

Modules not updated because guidelines are expected soon:

- Physical therapy
- Anaesthesiological technique

Module that was added:

- Patient Reported Outcome Measures

The selected (high priority) issues were translated into carefully formulated clinical questions, defining patient/problem, intervention, and prioritising the outcomes relevant for decision-making.

The literature was systematically searched using the databases MEDLINE (Ovid), Embase and the Cochrane Database of Systematic Reviews. Selection of the relevant literature was based on predefined inclusion and exclusion criteria and was carried out by a member of the working group in collaboration with the methodologist. For each of the clinical questions, the evidence was summarised by the guideline methodologist using the GRADE approach: a systematic review was performed for each of the relevant outcomes and the quality of evidence was assessed in one of four grades (high, moderate, low, very low) by analysing limitations in study design or execution (risk of bias), inconsistency of results, indirectness of evidence, imprecision, and publication bias. The evidence synthesis was complemented by a working group member considering any additional arguments relevant to the clinical question. Evidence synthesis, complementary arguments, and draft recommendations were extensively discussed in the working group and final

recommendations were formulated. Final recommendations are based on the balance of desirable and undesirable outcomes, the quality of the body of evidence across all relevant outcomes, values and preferences, and (if relevant) resource use. The strength of a recommendation reflects the extent to which the guideline panel was confident that desirable effects of the intervention outweigh undesirable effects, or vice versa, across the range of patients for whom the recommendation is intended. The strength of a recommendation is determined by weighting all relevant arguments together, the weight of the body of evidence from the systematic literature analysis, as well as the weight of all complementary arguments. Guideline panels must use judgment in integrating these factors to make a strong or weak recommendation. Thus, a low quality of the body of evidence from the systematic literature analysis does not exclude a strong recommendation, and weak recommendations may follow from high quality evidence (Schünemann, 2013).

After reaching consensus in the working group, the draft guideline was subjected to peer review by all relevant stakeholders. Amendments were made and agreed upon by the working group, and the final text was presented to the Dutch Orthopaedic Association and …. for formal authorisation and to the …. for approval. The final guideline was approved by …. and officially authorised by the Dutch Orthopaedic Association and …. on … (date). The guideline was published and is freely accessible in the Dutch guideline database (Richtlijnendatabase, www.richtlijnendatabase.nl). The Dutch guideline database has a modular structure, with each clinical question as a separate entry, thus allowing for modular updates.

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Module 1 Indications for total hip replacement

Research question

What are the indications and contra-indications for total hip replacement in patients with osteoarthritis?

Uitgangsvraag

Wat zijn de indicaties en contra-indicaties voor een totale heupprotese bij patiënten met artrose?

Introduction

Pain and loss of function, in combination with radiographic changes due to end stage osteoarthritis of the hip, are the mean reasons for total hip replacement. Since the population is getting older and more patients suffer from comorbidities, the question is which patients will benefit most from total hip replacement and should comorbid conditions be seen as contra-indications?

Search and select

To answer the question a systematic literature analysis was performed for the following research questions:

PICO 1: What are the favourable and unfavourable effects of total hip replacement in patients with osteoarthritis using immunosuppressants, versus patients with osteoarthritis not using immunosuppressants?

P: patients with osteoarthritis of the hip who underwent total hip replacement;
I: taking immunosuppressive medication;
C: not taking immunosuppressive medication;
O: complications, survival, functional gain, pain relief.

PICO 2: What are the favourable and unfavourable effects of total hip replacement in patients with osteoarthritis and cancer, versus patients with osteoarthritis and no cancer?

P: patients with osteoarthritis of the hip who underwent total hip replacement;
I: patients with cancer;
C: patients without cancer;
O: complications, survival, functional gain, pain relief.

PICO 3: What are the favourable and unfavourable effects of total hip replacement in patients with osteoarthritis and diabetes, versus patients with osteoarthritis and no diabetes?

P: patients with osteoarthritis of the hip who underwent total hip replacement;
I: patients with diabetes;
C: patients without diabetes;
O: complications, survival, functional gain, pain relief;

PICO 4: What are the favourable and unfavourable effects of total hip replacement in obese patients with osteoarthritis, versus non-obese patients with osteoarthritis?

P: patients with osteoarthritis of the hip who underwent total hip replacement;
I: patients with obesity;
C: patients without obesity;
O: complications, survival, functional gain, pain relief.

PICO 5: What are the favourable and unfavourable effects of total hip replacement in smokers with osteoarthritis, versus non-smokers with osteoarthritis?

P: patients with osteoarthritis of the hip who underwent total hip replacement;
I: patients who smoke;
C: patients who do not smoke;
O: complications, survival, functional gain, pain relief.

Relevant outcome measures

The working group did not define outcomes a priori, but used definitions as provided in the studies.

Search and select (Method)

A literature search was performed in the Medline database (via OVID) with relevant search terms on 18 September 2017. The search strategy is provided in the tab "Methods". The literature search resulted in 476 hits. Studies reporting complications, survival, functional gain and pain relief after total hip replacement in patients with osteoarthritis and obesity, cancer, diabetes, patients using immunosuppressants or who smoke were selected. Initially, 16 studies were selected. After obtaining full text, 5 studies were included in the literature analysis.

The most important study characteristics are described in evidence-tables. The assessment of risk of bias is provided in risk of bias tables.

Literature summary

Description of studies

Five studies were included in the literature summary (Chee., 2010; Li, 2017; Fu, 2016; Jämsen, 2013, Davis, 2011).

The case-control study by Chee (2010) compared total hip replacements performed in morbidly obese patients with osteoarthritis (n=55) with a matched group of non-obese patients (n=53). Morbid obesity was defined as a BMI >40 kg/m^2 or as >35 kg/m^2 with at least one comorbidity. Participants were categorised as non-obese when their BMI was <30 kg/m^2. The participants were matched for age, gender, type of prosthesis, laterality and pre-operative Harris Hip Score (HHS). Reported outcome measures were post-operative HHS, SF-36 scores, complication rate (superficial wound infection, deep joint infection, deep-vein thrombosis, pulmonary embolism, peri-operative mortality and dislocations) and survival (with revision surgery as endpoint) (Chee, 2010).

The study by Li (2017) evaluated to which extent osteoarthritis patients (n=2040) with various levels of obesity benefited from total hip replacement. The study was based on a large, prospective national cohort of patients treated with total hip replacement.

Patients were grouped according to their pre-operative BMI as underweight or normal weight (≤24.99 kg/m^2), overweight (25.00 to 29.99 kg/m^2), obese (30.00 to 34.99 kg/m^2), severely obese (35.00 to 39.99 kg/m^2) or morbidly obese (≥40.00 kg/m^2). Adjustments were performed for baseline function and pain score, gender, age, ethnicity, household income, education, living alone, type of insurance, medical comorbidities, low back pain, number of other painful joints and surgical volume of the hospital. Reported outcome measures were physical function (Physical Component Summary (PCS) score) and pain (Hip disability and Osteoarthritis Outcome Score (HOOS score)) (Li, 2017).

The study by Fu (2016) investigated the independent morbidity risk of malnutrition relative to obesity in patients with osteoarthritis (n=20,210) who underwent a total hip replacement. Data from the National Surgical Quality Improvement Program (NSQIP) database were used in this study. Despite the quality and prospective nature of data collection for the NSQIP, pre-operative serum albumin data were not available for a significant percentage of cases. Demographic variables, modified CCI, and obesity classifications were compared between patients with and without pre-operative albumin measurements. Propensity scores were used as a control for potential selection bias in this analysis. Patients were classified as non-obese (BMI: 18.5-29.9), obese I (BMI: 30 to 34.9), obese II (BMI: 35 to 39.9), or obese III (BMI >40). Reported outcome measures were 30-day complications (any complications, any major complications, wound complications, respiratory complications, blood transfusions, return to operation room within 30 days, extended length of stay (LOSS)) (Fu, 2016).

The register-based study by Jämsen (2013) examined how comorbid diseases affect survival in patients with osteoarthritis (n=43,737) who underwent total hip replacement. The reported outcome measure was survival. Adjustments were performed for age, gender, year of operation, laterality of operation (unilateral, simultaneous bilateral), method of prosthesis fixation and type of operating hospital (university, central, regional or other type of hospital) (Jämsen, 2013).

The study by Davis (2011) examined the effect of body mass index (BMI) on the medium-term outcome after total hip replacement in patients with osteoarthritis (n=1617). The reported outcome measures were dislocation, revision, duration of surgery, deep and superficial infection, HHS and SF-36. In the multivariate analysis adjustments were performed for age, gender, operating consultant, pre-operative HHS and SF-36 scores and a diagnosis of cancer, atherosclerotic disease, cardiac disease, diabetes mellitus, osteoporosis or phlebitis.

Results

PICO 1: What are the favourable and unfavourable effects of total hip replacement in patients with osteoarthritis using immunosuppressants, versus patients with osteoarthritis not using immunosuppressants?

No studies were found describing the outcomes in patients using immunosuppressants compared to patients not using immunosuppressants.

PICO 2: What are the favourable and unfavourable effects of total hip replacement in patients with osteoarthritis and (a history of) cancer, versus patients with osteoarthritis and without (a history of) cancer?

No studies were found describing complications, functional gain and pain relief in patients with (a history of) cancer compared to patients without (a history of) cancer.

Survival

In the study by Jämsen (2013) a history of cancer was associated with impaired survival of the hip prostheses (revision surgery) during 10-years of follow-up in the univariate (HR: 1.28 (95%CI 1.06 to 1.55)) and multivariate (HR: 1.27 (95% CI 1.05 to 1.54)) adjusted model.

Grading of evidence

Grading the evidence started at a level of low evidence, because the data used was derived from an observational study. Downgrading by one level was necessary, because of imprecision (width of confidence interval).

Conclusion

Very low GRADE	Survival of the prosthesis after total hip replacement for osteoarthritis is impaired in patients with a history of cancer, compared to patients without a history of cancer. *Sources (Jämsen, 2013)*

PICO 3: What are the favourable and unfavourable effects of total hip replacement in patients with osteoarthritis and diabetes, versus patients with osteoarthritis and no diabetes?

No studies were found describing complications, functional gain and pain relief in patients with diabetes compared to patients without diabetes.

Survival

In the study by Jämsen (2013) diabetes did not affect survival of hip replacements up to 5 years of follow-up in the univariate (HR: 1.08 (95%CI 0.88 to 1.34)) and multivariate (HR: 1.03 (95%CI 0.83 to 1.27)) adjusted model. Diabetes also did not affect survival of hip replacements after 5 years of follow up in the univariate (HR: 0.77 (95%CI 0.29 to 2.06)) and multivariate (HR: 0.60 (95%CI 0.22 to 1.63)) adjusted model.

Grading of evidence

Grading the evidence started at a level of low evidence, because the data used was derived from an observational study. Downgrading by one level was necessary because there was imprecision (width of confidence interval).

Conclusion

Very low GRADE	There is no difference in survival of the prosthesis after total hip replacement for osteoarthritis in patients with diabetes compared to patients without diabetes. *Sources (Jämsen, 2013)*

PICO 4: What are the favourable and unfavourable effects of total hip replacement in obese patients with osteoarthritis, versus non-obese patients with osteoarthritis?

Complications

The study by Chee (2010) reported a significantly higher overall peri-operative complication rate in morbidly obese patients (12) compared to non-obese patients (3) (22% versus 5%, p = 0.012).

The study by Fu (2016) reported significant differences in any complication(s) overall, any major complication(s), wound complications, blood transfusions, return to the operating room and extended LOS between the different obesity classes (all P <0.004). All obesity classes were associated with having any complication (obese I OR 1.19, CI: 1.01 to 1.40 ; obese II OR 1.29, CI: 1.05 to 1.59; and obese III OR 1.54, CI: 1.21 to 1.98) and wound complications (obese I OR 1.80, CI: 1.30 to 2.50; obese II OR 2.18, CI: 1.47 to 3.25; and obese III OR 3.23, CI: 2.09 to 4.99). Obese II and obese III were also associated with return to operating room (obese II OR 1.59, CI: 1.16 to 2.18 and obese III OR 1.80, CI: 1.22 to 2.63). Obese III was the only obesity class that reached statistical significance as a predictor of extended LOS (OR 1.22, CI: 1.05 to 1.43).

The study by Davis (2011) reported a 6.8% risk of dislocation in patients with a BMI ≥35 kg/m^2 compared with a 3.2% risk of dislocation in patients with a BMI between 30 and 34.9, a 2.0% risk in patients with a BMI between 25 and 29.9 and a 1.5% risk in patients with a BMI lower than 25 kg/m^2. Multivariate adjustments showed a 113.9% increase in odds per 10 point BMI increase (CI: 11.5 to 308.1, p-value = 0.023). The risk of superficial infection was 14.2% in patients with a BMI of 35 kg/m^2 compared to 4.6% in patients with a BMI of 30 to 34.9, 3.7% in patients with a BMI between 25 and 29.9 and 4.4% in patients with a BMI lower than 25 kg/m^2. Multivariate analysis showed that there were no statistically significant differences between adjacent BMI groups, until the comparison between BMI ≥35 and 30 to 34.9, where patients in the heavier group had a 3.37 times (CI: 1.494 to 7.583) greater chance of superficial wound infection than those with a BMI between 30 and 34.9. Revision and deep infection were also not significantly different with a 10 point BMI increase.

Grading of evidence

Grading the evidence started at a level of low evidence, because the data used was derived from observational studies. Downgrading by one level was, however, necessary as there were risk of bias (small sample size) and imprecision (width confidence interval).

Survival

The study by Chee (2010) reported a five-year survival, using revision surgery as an endpoint, of 90.9% (CI: 82.9 to 98.9) for morbidly obese patients and 100% for non-obese patients.

Grading of evidence

Grading the evidence started at a level of low evidence, because the data used was derived from an observational study. Downgrading by one level was, however, necessary as there was imprecision (small sample size and width confidence interval).

Functional gain

The study by Li (2017) reported that greater levels of obesity were associated with lower (worse) Physical Component Summary (PCS) scores 6 months after THR (trend test, p <0.001). However, the mean preoperative-to-postoperative changes in PCS scores did not significantly differ by BMI status (P=0.07). Differences in pre-operative-to-postoperative changes in the PCS score became greater after covariate adjustment, with severely and morbidly obese patients having substantially less gain than other patients (p <0.001).

The study by Davis (2011) reported a 8.19% significant decrease in SF-36 score on physical function by 10 points BMI increase (CI: 4.74 to 11.63, p-value <0.001). This study also reported a 10.41 significant decrease in score for the category physical role limitation (CI: 4.64 to 16.18, p-value <0.001).

Grading of evidence

Grading the evidence started at a level of low evidence, because the data used was derived from an observational study. Downgrading by one level was necessary as there were limitations in study design (short follow-up time) and imprecision (overlap confidence intervals).

Pain relief

The study by Li (2017) reported that patients with greater levels of obesity had a greater improvement in the mean pre-operative-to-postoperative changes in Hip disability and Osteoarthritis Outcome Score (HOOS) (trend test, p <0.001). However, after covariate adjustment, pre-operative-to-postoperative pain relief did not significantly differ by BMI level.

The study by Davis (2011) reported a 3.98 significant decrease in SF-36 score on pain with every 10 points BMI increase (CI: 0.29 to 7.66, p-value <0.034).

Grading of evidence

Grading the evidence started at a level of low evidence, because the data used was derived from an observational study. Downgrading by one level was necessary as there were limitations in study design (short follow-up time) and imprecision (overlap confidence intervals).

Conclusions

Very low GRADE	Complication rates after total hip replacement for osteoarthritis are higher in obese patients compared to non-obese patients. *Sources (Chee, 2010; Fu, 2016; Davis, 2011)*

Very low GRADE	Survival of the prosthesis after total hip replacement for osteoarthritis is lower in obese patients compared to non-obese patients. *Sources (Chee, 2010)*

Very low GRADE	Functional gain after total hip replacement for osteoarthritis is lower in obese patients compared to non-obese patients. *Sources (Li, 2017; Davis, 2011)*

Very low GRADE	There is no difference in pain relief after total hip replacement for osteoarthritis in obese patients compared to non-obese patients. *Sources (Li, 2017; Davis, 2011)*

PICO 5: What are the favourable and unfavourable effects of total hip replacement in smokers with osteoarthritis, versus non-smokers with osteoarthritis?

No studies were found describing the outcomes in patients undergoing total hip arthroplasty who smoked compared to patients who did not smoke.

Considerations

Total hip replacement is an effective and successful surgical procedure for end stage osteoarthritis of the hip when conservative treatment has failed. In the early development of total hip replacement, only healthy patients with single end stage osteoarthritis underwent surgery. Nowadays patients with comorbidities are also eligible for surgery. It is questionable whether outcomes in these patients are comparable to patients without comorbidities.

In general, comorbidities are associated with higher anaesthetic risks and operative complications after total hip replacement. For comorbidities, a distinction should be made between diseases causing osteoarthritis and disorders coexisting with (primary or secondary) osteoarthritis.

In this literature analysis, comorbidities affecting the outcome of total hip arthroplasties were studied. The term “comorbidity” is used as a container concept to describe possible risk factors for impaired outcome (for example smoking is not a real comorbidity). In addition, one patient with a history of cancer might have an impaired physical condition and life expectancy, while another patient might have been cured years ago and have a (nearly) normal life expectancy. The study by Jämsen (2013) concluded that in general a history of cancer was associated with impaired survival of the hip prosthesis in patients with osteoarthritis.

Studies reporting adverse reactions, complications, survival, functional gain and pain relief after total hip replacement in patients with osteoarthritis and a history of cancer, diabetes, obesity, who are smokers or are using immunosuppressants were selected. These factors were selected because the prevalence of these comorbidities is increasing. Furthermore, these comorbidities influence anaesthesia and functional gain after total hip replacement.

Obese patients have higher surgical risks. A higher BMI is associated with an increased incidence of peri-operative complications and decreased functional gain after the total hip replacement (Chee, 2010; Fu, 2016; Li, 2017, Davis, 2011). Ideally, diabetes mellitus should be divided in type 1 and 2, because the duration of the disease is different in these patients. These differences have different effects on surgery. Proper control of the diabetes will diminish the peri-operative complication rate. Having diabetes was not associated with more joint infections. Moreover, the survival of the prosthesis was also not impaired (Jämsen, 2013). We found no studies investigating the influence of smoking habits and the use of immunosuppressants on the defined outcomes. Only five observational studies were found (Chee, 2010; Fu, 2016; Li, 2017; Jämsen, 2013, Davis, 2011). Because of the observational design of the included studies the evidence was graded low.

Generally, studies from Joint Replacement Registries showed worse outcomes after a total hip arthroplasty in patients suffering from avascular osteonecrosis or rheumatoid arthritis compared to patients with idiopatic osteoarthritis.

Surgeons must weigh the risks against the benefits for each patient with comorbidities individually. In the pre-operative phase, they must evaluate if there are any comorbidities that can increase the surgical risk. The life expectancy of the individual patient with a history of cancer should be evaluated, diabetes patients must have proper control and obese patients should be advised to lose weight. To decide upon surgery the surgeon should consult other medical professionals like an anaesthesiologist or oncologist. Finally, the surgeon will discuss the possibilities with the patient and make decisions together.

Recommendations

Offer total hip replacement to patients with osteoarthritis of the hip if they suffer from pain and/or loss of function, if radiographic changes indicate end-stage osteoarthritis and if conservative treatment fails.

(History of) cancer, diabetes or obesity should not be considered contra-indications.

Make the decision whether or not to operate together with the patient, who should be informed of the following:

- Patients with diabetes or obesity (BMI >30 kg/m²) have a higher complication rate and might benefit less from the total hip arthroplasty.
- Implant survival is diminished in patients with a history of cancer and in patients with diabetes or obesity.

Aanbevelingen

Bied patiënten een totale heupvervanging aan als er radiologische afwijkingen zijn die wijzen op een eindstadium van heupartrose, als er sprake is van pijn en/of functieverlies, en als conservatieve behandeling heeft gefaald.

Kanker (in de anamnese), diabetes en overgewicht zijn geen contra-indicaties.

Neem het besluit om al dan niet te opereren samen met de patiënt, nadat deze geïnformeerd is dat:

- Patiënten met diabetes of met overgewicht (BMI >30 kg/m²) een grotere kans hebben op complicaties en mogelijk minder baat hebben van de heupvervanging.
- De levensduur van het implantaat minder is bij patiënten met kanker in de anamnese en bij patiënten met diabetes of overgewicht.

Literature

Chee YH, Teoh KH, Sabnis BM, et al. Total hip replacement in morbidly obese patients with osteoarthritis: results of a prospectively matched study. J Bone Joint Surg Br. 2010;92(8):1066-71. doi: 10.1302/0301-620X.92B8.22764. PubMed PMID: 20675748.

Davis AM, Wood AM, Keenan ACM, et al. BallantyneDoes body mass index affect clinical outcome post-operatively and at five years after primary unilateral total hip replacement performed for osteoarthritis? J Bone Joint Surg Br. 2011;93(9):1178-82. doi: 10.1302/0301-620X.93B9.26873.

Fu MC, D'Ambrosia C, McLawhorn AS, et al. Malnutrition Increases With Obesity and Is a Stronger Independent Risk Factor for Postoperative Complications: A Propensity-Adjusted Analysis of Total Hip Arthroplasty Patients. J Arthroplasty. 2016;31(11):2415-2421. doi:10.1016/j.arth.2016.04.032. Epub 2016 May 6. PubMed PMID: 27237966.

Jämsen E, Peltola M, Eskelinen A, et al. Comorbid diseases as predictors of survival of primary total hip and knee replacements: a nationwide register-based study of 96 754 operations on patients with primary osteoarthritis. Ann Rheum Dis. 2013;72(12):1975-82. doi: 10.1136/annrheumdis-2012-202064. Epub 2012 Dec 19. PubMed PMID: 23253916; PubMed Central PMCID: PMC3841739.

Li W, Ayers DC, Lewis CG, et al. Functional Gain and Pain Relief After Total Joint Replacement According to Obesity Status. J Bone Joint Surg Am. 2017;99(14):1183-1189. doi: 10.2106/JBJS.16.00960. PubMed. PMID: 28719557; PubMed Central PMCID: PMC5508191.

Appendixes module 1

Validity and maintenance

Module	Party in control	Year of authorization	Next assessment of actuality	Frequency of assessment of actuality	Which party/parties monitors actuality?	Important factors that might lead to change in recommendations
Indications and contra-indications	NOV	2018	2023	5 years	NOV	Worse outcome for several comorbities

Knowledge gaps

What is the effect of specific immunosuppressants (DMARDs) on the risk of complications after total hip arthroplasty?

Indicators

Not applicable

Implementation plan

Recommendation	Time needed for implementation: <1 year, 1 to 3 years or >3 years	Expected effects on costs	Conditions for implementation	Possible barriers for implementation[1]	Actions for implementation[2]	Reponsibility for these actions[3]	Other remarks
All	<1 year	No	No	No	No	NOV	No

Evidence tables

Research question: What are the indications and contra-indications for total hip replacement in patients with osteoarthritis?

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Chee et al., 2010	Type of study: Prospectively matched study (The groups were matched for age, gender, type of prosthesis, laterality (right or left, unilateral or bilateral) and pre-operative HHS. It was not always possible to identify a non-obese patient with exactly the same pre-operative HHS as a morbidly obese patient. In this instance, the control with the next 'worst' score was identified. If no other control with a 'worse' score could be identified, the	Inclusion criteria: Morbidly obese patients (BMI > 40 or BMI > 35 with at least on serious comorbidity) with osteoarthritis who underwent total hip replacements between 1998 and 2013. Comorbidities included hypertension, cardiovascular disease, diabetes, cancer, previous deep-vein thrombosis or pulmonary embolus. Exclusion criteria: Unclear N total at baseline: N = 108 (53 morbidly obese patients and 53 non-obese patients) Important characteristics: Age and sex = not relevant (matched study) Groups comparable at baseline? = not relevant (matched study)	Total hip replacement in morbidly obese patients. Two types of cemented femoral component were used: the Charnley primary THR (De Puy International, Leeds, United Kingdom) and the Lubinus SPII (Waldemar-Link GmbH, Hamburg, Germany). Each harnley component had a 22.225 mm femoral head and each Lubinus one of 32 mm. All acetabular components were cemented Charnley allpolyethylene components. A standard anterolateral approach was used by all eight surgeons. Thromboprophylaxis with low molecular weight heparin was	The same intervention as described in the column 'Intervention only performed in patients without morbidly obesity.	Length of follow-up: Five years of follow-up Loss-to-follow-up: Nine patients (10 hips) were excluded because of incomplete follow-up, a further three were lost to follow-up and ten (11 hips) had died.	Complications Overall complication rate Morbidly Obese: 12 (22%) Non-obese: 3 (5%) (p-valule = 0.012) Superficial infections Morbidly obese: 7 Non-obese: 2 (p-valule = 0.014) Deep infections Morbidly obese: 2 Non-obese: 0 (p-valule = 0.015) Deep-vein thrombosis Morbidly obese: 0 Non-obese: 0 (p-valule = NR) Pulmonary embolism Morbidly obese: 1 Non-obese: 0 (p-valule = 0.31) Peri-operative mortality Morbidly obese: 0 Non-obese: 0 (p-valule = NR) Dislocations	Only patients with complete follow-up were include in the data-analysis.

	control with the next 'better' score was used.) <u>Setting:</u> Patients from 1 hospitals, total hip replacement operations between 1998 and 2003 <u>Country:</u> United Kingdom <u>Source of funding:</u> No		used in all patients. A routine post-operative rehabilitation programme, based on an integrated care pathway, was used. Independent prospective follow-up was undertaken by a dedicated audit team consisting of two specialist nurses. All patients were followed up at six, 18, 36 and 60 months.			Morbidly obese: 3 Non-obese: 1 (p-value = 0.30) <u>Survival</u> 5-year survival (using revision surgery as an endpoint) Morbidly obese: 90.9% (95% CI 82.9 to 98.9) Non-obese: 100%	
Li et al. (2017)	<u>Type of study:</u> Prospective national cohort of TJR patients <u>Setting:</u> FORCE-TJR is a large, prospective, national cohort of TJR patients enrolled from diverse high-volume centers and >100 community orthopaedic	<u>Inclusion criteria:</u> - The first 2040 patients who underwent primary unilateral THR between May 2011 and March 2013; - completed the 6-month postoperative questionnaire; - and had a primary diagnosis of osteoarthritis. <u>Exclusion criteria:</u> Patients were excluded if they had another diagnosis for total hip replacement (for example, osteonecrosis, inflammatory arthritis, an acute fracture or	Type of total hip replacement is not described in the study.	Type of total hip replacement is not described in the study.	<u>Length of follow-up:</u> 6 months of follow-up <u>Loss to follow-up:</u> Patients were only included in the data-analysis when they completed the 6-month postoperative questionnaire.	<u>Of the patients who underwent THR:</u> Underweight or normal weight = 26% Overweight = 37% Obese = 22% Severely obese = 10% Morbidly obese = 4% <u>PCS Score (Mean (95% CI)):</u> Baseline Under or normal weight = 32.4 (31.7, 33.2) Overweight = 32.7 (32.0, 33.2) Obese = 30.2 (29.4, 31.0) Severely obese = 28.3 (27.1, 29.4)	Type of intervention not described. Only patients with complete follow-up were include in the data-analysis.

	practices, distributed across 22 states in the U.S. <u>Country:</u> United States <u>Source of funding:</u> The FORCE-TJR cohort was funded by the Agency for Healthcare Research and Quality (AHRQ) to answer multiple research questions including: What is the relative role of body mass index (BMI) on postoperative functional status?	cancer.)) <u>N total at baseline:</u> N = 2040 (underwent total hip prothesis (N = 2964 underwent total knee replacement) <u>Important characteristics</u>: Age (Mean±SD) Under of Normal weight = 66.7 (11.2) Overweight = 66.2 (10.1) Obese = 63.8 (9.9) Severely Obese = 63.0 (9.3) Morbidly Obese = 60.0 (9.1) Sex (Male%) Under of Normal weight = 30.2 Overweight = 48.5 Obese = 45.5 Severely Obese = 38.2 Morbidly Obese = 33.3 Groups comparable at baseline? = No p-values were calculated. However, some percentages of prognostic risk factors were different at baseline (e.g. ≥1 medical comorbidities (%), moderate or severe low-back pain (%), ≥1 painful joint).				Morbidly obese = 26.6 (25.1, 28.1) All patients = 31.3 (31.0, 31.7) 6 Months Under or normal weight = 46.5 (45.6, 47.4) Overweight = 45.7 (45.0, 46.4) Obese = 44.8 (43.9, 45.7) Severely obese = 41.2 (39.8, 42.6) Morbidly obese= 39.6 (37.6, 41.6) All patients = 45.0 (44.6, 45.4) Adjusted Preop. – Postop. Change Under or normal weight = 14.0 (13.1, 14.8) Overweight = 13.2 (12.5, 13.9) Obese = 13.3 (12.4, 14.2) Severely obese = 10.8 (9.5, 12.0) Morbidly obese= 9.6 (7.7, 11.4) All patients = 13.0 (12.5, 13.6) <u>Pain Score (Mean (95% CI)):</u> Baseline Under or normal weight = 51.0 (49.2, 52.7) Overweight = 51.1 (49.8, 52.5) Obese = 47.3 (45.5,49.0) Severely obese = 45.5 (42.6, 48.4) Morbidly obese = 38.2 (34.0, 42.4) All patients = 49.1 (48.2, 50.0) 6 Months Under or normal weight = 91.8 (90.7, 92.9) Overweight = 90.6 (89.7, 91.6) Obese = 89.7 (88.4, 90.9)	

						Severely obese = 88.4 (86.4, 90.5) Morbidly obese = 88.4 (85.6, 91.1) All patients = 90.4 (89.8, 91.0) Adjusted Preop. – Postop. Change Under or normal weight = 42.4 (41.0, 43.7) Overweight = 41.0 (39.8, 42.2) Obese = 41.0 (39.6, 42.4) Severely obese = 40.01 (38.1, 42.1) Morbidly obese = 41.5 (38.6, 44.4) All patients = 41.3 (40.3, 42.4)	
Fu et al. (2016)	Type of study: Observational study Setting: The American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database was used for this cohort study. There are more than 370 participating hospitals and medical centres across the united states participating in	Inclusion criteria: The NSQIP database from 2005 to 2013 was queried using Current Procedural Terminology code 27130 for THA cases as the primary Current Procedural Terminology code for OA of the hip, as identified by International Classification of Diseases, Ninth Revision codes 715.15, 715.35, and 715.95. Exclusion cirteria: Cases with a history of previous infections, cases performed on an emergent basis, and cases with missing preoperative information such as age, gender, height, and weight were excluded. N total at baseline:	Type of total hip replacement is not described in the study.	Type of total hip replacement is not described in the study.	Length of follow-up: 30 days Loss to follow-up: not mentioned	Complications (%) 1. Any complication(s) Nonobese = 4.4 Obese I = 5.4 Obese II = 6.0 Obese III = 7.8 ($p < 0.001$) 2. Any major complication(s) Nonobese = 3.1 Obese I = 3.9 Obese II = 4.3 Obese III = 5.0 ($p < 0.001$) 3. Wound complications Nonobese = 0.8 Obese I = 1.5 Obese II = 1.9 Obese III = 3.2 ($p < 0.001$)	Odds ratios were calculated. Odds ratio may only be used in prospective cohort studies when the risk on the outcome <10% (this was not the case for the outcomes: blood transfusions and extended los. Given the multiple comparisons, a Bonferroni correction determined the appropriate level of significance to be P < .004.

	this database. Country: United States Source of funding: Unclear (One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work.)	N = 40653 Important characteristics: 1. Age (%) Non Obese 18-64 = 38.9 65-79 = 43.8 80+ = 17.3 Obese I 18-64 = 45.1 65-79 = 44.7 80+ = 10.2 Obese II 18-64 = 54.0 65-79 = 41.0 80+ = 4.9 Obese III 18-64 = 63.0 65-79 = 34.5 80+ = 2.5 2. Sex (% Male) Non Obese = 41.4 Obese I = 50.2 Obese II = 46.3 Obese III = 40.4				4. Septic complications Nonobese = 0.3 Obese I = 0.5 Obese II = 0.7 Obese III = 0.5 (p = 0.009) 5. Cardiac complications Nonobese = 0.3 Obese I = 0.4 Obese II = 0.2 Obese III = 0.3 (p = 0.802) 6. Respiratory complications Nonobese = 0.4 Obese I = 0.6 Obese II = 0.4 Obese III = 0.5 (p = 0.586) 7. Blood transfusions (intraoperative/postoperative) Nonobese = 18.9 Obese I = 13.5 Obese II = 12.4 Obese III = 14.4 (p < .001) 8. Urinary complications Nonobese = 1.1. Obese I = 1.3 Obese II = 1.4 Obese III = 1.9 (p =0.045)	

						9. Return to OR within 30 d Nonobese = 1.6 Obese I = 2.1 Obese II = 2.7 Obese III = 3.4 (p < 0.001) 10. Deep vein thrombosis or Pulmonary embolism Nonobese = 0.7 Obese I = 0.7 Obese II = 0.7 Obese III = 0.6 (p = 0.957) 11. Extended length of stay Nonobese = 19.2 Obese I = 18.9 Obese II = 20.4 Obese III = 22.8 (p = 0.002) 12. Death Nonobese = 0.1 Obese I = 0.2 Obese II = 0.2 Obese III = 0.0 (p = 0.354) Complications (OR(95%CI) Any complications Obese I = 1.19 (1.01, 1.40) P-value =0.036 Obese II = 1.29 (1.05,1.59) P-value =0.016 Obese III = 1.54 (1.21, 1.98) P-	

						value =0.001 <u>Any major complications</u> Obese I = 1.17 (0.97, 1.41) P-value =0.100 Obese II = 1.27 (0.99, 1.61) P-value =0.059 Obese III = 1.34 (1.00, 1.81) P-value=0.054 <u>Wound complications</u> Obese I = 1.80 (1.30, 2.50) P-value < 0.001 Obese II = 2.18 (1.47, 3.25) P-value < 0.001 Obese III = 3.23 (2.09, 4.99) P-value < 0.001 <u>Respiratory complications</u> Obese I = 1.23 (0.76, 2.00) P-value = 0.402 Obese II = 0.83 (0.41, 1.68) P-value = 0.596 Obese III = 0.91 (0.39, 2.15) P-value = 0.832 <u>Blood transfusions</u> Obese I = 0.71 (0.64, 0.79) P-value <0.001 Obese II = 0.64 (0.56, 0,74) P-value <0.001 Obese III = 0.77 (0.65, 0.92) P-value = 0.004 <u>Return to OR within 30 d</u> Obese I = 1.20 (0.93, 1.55) P-value = 0.158 Obese II = 1.59 (1.16, 2.18) P-value	

						=0.004 Obese III = 1.80 (1.22, 2.63) P-value =0.003 <u>Extended LOS</u> Obese I = 0.97 (0.89, 1.06) P-value=0.504 Obese II = 1.08 (0.96, 1.22) P-value=0.197) Obese III = 1.22 (1.05, 1.43) P-value =0.010	
Jämsen (2017)	<u>Type of study:</u> Register based study <u>Setting:</u> This study was based on the PERFECT (PERFormance Effectiveness and Cost of Treatment episodes database, maintend by the Finnish National Institute for Health and Welfare. The database was created for continuous monitoring of performance in hip and knee surgery in	<u>Inclusion criteria:</u> Patients underwent primary total hip and total knee replacements performed owing to primary osteoarthritis in 1998 through 2008. <u>Exclusion criteria:</u> - Operations were excluded in the register when the were entered in the Hospital Discharge Register but lacking corresponding record in the Finnish Artrhoplasty Register (n = 3997). - Operations in patients with a history of conditions suggesting that the aetiology underlying the need for joint replacement was other than primary osteoarthritis (n=8182). - Records with missing necessary data in the Finnish Arthroplasty Register (n=2403) - Operations performed on foreigners or citizen of the	Type of total hip replacement is not described in this study.	Type of total hip replacement is not described in this study.	<u>Length of follow-up:</u> Median 4.9 years (range 1-4382 days) <u>Loss to follow-up:</u> Death: 5018/43747 (11.5%)	<u>Survival (HR (95% C.I.):</u> One or more comorbid disease = 1.16 (1.08, 1.23) Diabetes Univariate 0-5 years follow-up (fu) = 1.08 (0.88, 1.34) > 5 years fu = 0.61 (0.34, 1.08) Age-and sex-adjusted 0-5 years fu = 1.10 (0.89, 1.35) > 5 years fu = 0.63 (0.36, 1.12) Multivariate 0-5 years fu = 1.03 (0.83, 1.27) > 5 years fu = 0.60 (0.34, 1.06) Cancer Univariate 1.28 (1.06, 1.55) Age- and sex-adjusted 1.30 (1.08, 1.57)	

	Finland by combining data from several nationwide health registers. Country: Finland Source of funding: Not mentioned	autonomous region of Åland Islands (n=566) - Simultaneous replacements of hip and knee on the same patient (n=56) N total at baseline: N = 43747 Important characteristics: 1. Age (median(range)) 68.5 (21 -97) 2. Male (N (%)) 18776 (42.9)				Multivariate 1.27 (1.05, 1.54)	
Davis (2011)	Type of study: Multivariate analysis of prospective data Setting: Hospital based (Hospital Kirkcaldy, Kirkcaldy) Country: United Kingdom Source of funding: Not mentioned	Inclusion criteria: Patients with osteoarthritis which underwent total hip replacement. Exclusion criteria: - Patients without a diagnosis of osteoarthritis or a recorded diagnosis (n=123) - Patients without one of the three main prostheses (n=56) - Patients without information on BMI (n=45) N total at baseline: N = 1617 Important characteristics: 1. Age (mean (range): 69 (34 – 96) 2. Male (N): 623	Most operations (96.8%) involved cemented stems using either a Charnley prosthesis (De Puy International, Leeds, United Kingdom), a Charnley Elite prosthesis (De Puy International), or a Lubinus SPII prosthesis (Waldemar-Link GmbH, Germany). Each Charnley component had a 22 mm femoral head and each Lubinus a 32 mm head. All acetabular	The same intervention as described in the column 'Intervention only performed in patients without morbidly obesity.	Length of follow-up: 5 years. A follow-up of around 70%.	Complications: Dislocation Overall odds of event: 0.026 % increase in odds per 10 points BMI increase: 113.9 95% confidence interval: 115 to 308.1 p-value: 0.023 Revision Overall odds of event: 0.0247 % increase in odds per 10 points BMI increase: 52.4 95% confidence interval: 27.0 decrease to 219.0 p-value: 0.262 Deep infection Overall odds of event: 0.0094 % increase in odds per 10 points BMI increase: 61.3	

			components were cemented Charnley all-polyethylene Ogee cups. A standard anterolateral surgical approach was used by all surgeons. Low molecular weight heparin was used for thromboprophylaxis in all patients. The post-operative rehabilitation programme was the same in every case, mobilising with a physiotherapist on the first post-operative day, with daily physiotherapy thereafter until discharge. Independent prospective follow-up was undertaken at five years by an audit team consisting of two specialist nurses who were not directly involved in this, or any other, study during data collection.			95% confidence interval: 52.1 decrease to 450.6 p-value: 0.440 Superficial infection Overall odds of event: 0.0541 % increase in odds per 10 points BMI increase: 89.5 95% confidence interval: 18.4 to 205.1 p-value: 0.008 <u>SF-36 per category:</u> Physical function % decrease in score per 10 point BMI increase: 8.19 95% confidence interval: 4.74 to 11.63 p-value: < 0.001 Role limitation: physical % decrease in score per 10 point BMI increase: 10.41 95% confidence interval: 4.64 to 16.18 p-value <0.001 Pain % decrease in score per 10 point BMI increase: 3.98 95% confidence interval: 0.29 to 7.66 p-value : 0.034	

Risk of bias table for intervention studies (observational: non-randomized clinical trials, cohort and case-control studies)

Research question: What are the indications and contra-indications for total hip replacement in patients with osteoarthritis?

Study reference (first author, year of publication)	Bias due to a non-representative or ill-defined sample of patients?[1] (unlikely/likely/unclear)	Bias due to insufficiently long, or incomplete follow-up, or differences in follow-up between treatment groups?[2] (unlikely/likely/unclear)	Bias due to ill-defined or inadequately measured outcome ?[3] (unlikely/likely/unclear)	Bias due to inadequate adjustment for all important prognostic factors?[4] (unlikely/likely/unclear)
Chee, 2010	Likely	Unclear	Unlikely	Unlikely
Li,. 2017	Unlikely	Likely	Unlikely	Unlikely
Fu,.2016	Unlikely	Likely	Unlikely	Unlikely
Jämsen, 2013	Unlikely	Unlikely	Unlikely	Unlikely
Davis, 2011	Unlikelly	Unclear	Unlikely	Unlikely

1. **Failure to develop and apply appropriate eligibility criteria: a) case-control study: under- or over-matching in case-control studies; b) cohort study: selection of exposed and unexposed from different populations.**
2. **2 Bias is likely if: the percentage of patients lost to follow-up is large; or differs between treatment groups; or the reasons for loss to follow-up differ between treatment groups; or length of follow-up differs between treatment groups or is too short. The risk of bias is unclear if: the number of patients lost to follow-up; or the reasons why, are not reported.**
3. **Flawed measurement, or differences in measurement of outcome in treatment and control group; bias may also result from a lack of blinding of those assessing outcomes (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is not necessary. If a study has "soft" (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary.**
4. **Failure to adequately measure all known prognostic factors and/or failure to adequately adjust for these factors in multivariate statistical analysis.**

Search strategy

Database	Search terms	Total
Medline (OVID) English 2005-sept. 2017	1 Arthroplasty, Replacement, Hip/ or Hip Prosthesis/ or (hip adj3 replacement*).ti,ab,kf. (40569) 2 arthroplasty/ or arthroplasty, replacement/ or joint prosthesis/ or metal-on-metal joint prostheses/ (20694) 3 Hip/ or exp Hip Joint/ or (hip? or femur* or femoral* or trochant* or pertrochant* or intertrochant* or subtrochant*).ti,ab,kf. (256045) 4 2 and 3 (5786) 5 1 or 4 (44547) 6 limit 5 to (english language and yr="2005 -Current") (20592) 7 "Factors That Affect Outcome Following Total Joint Arthroplasty: a Review of the Recent Literature.".m_titl. (1) 8 "adverse peri-operative outcomes following elective total hip replacement in diabetes mellitus: a systematic review and meta-analysis of cohort studies".m_titl. (1) 9 7 or 8 (2) 10 6 and 9 (2) 11 exp Diabetes Mellitus/ (390598) 12 exp Immunosuppressive Agents/ (300302) 13 Immunosuppression/ (30754) 14 exp Neoplasms/ (3107069) 15 exp Obesity/ (185383) 16 Smoking/ (142777) 17 (immunosuppres* or cancer* or carcinoma or neoplasm* or diabet* or obesit* or adipositas or smoking).ti,ab,kf. (2932314) 18 (contraindicat* or contra-indicat*).ti,ab,kf. (44561) 19 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 (4768430) 20 6 and 19 (1292) 21 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (345234) 22 20 and 21 (56) 23 (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or clinic$ trial$1.tw. or (clinic$ adj trial$1).tw. or ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo$.tw. or randomly allocated.tw. or (allocated adj2 random$).tw.) not (animals/ not humans/) (1412096) 24 20 and 23 (107) 25 19 and 22 (56) 26 22 or 24 (158) – 146 uniek 27 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ (Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies) (2984735) 28 comparative study.pt. (1863843) 29 (registry or registries).ti,ab. or registries/ (134276) 30 27 or 28 or 29 (4494520) 31 20 and 30 (705) 32 31 not 26 (621) 33 "Arthroplasty, Replacement, Hip"/ae, co or "Postoperative Complications"/ or (contraindicat* or contra-indicat*).ti,ab,kf. or treatment failure/ or Risk Assessment/ or (treatment adj3 failure*).ti,ab,kf. or (complication* or adverse or risk or predict*).ti. (1333085) 34 32 and 33 (367) – 330 uniek	476

Exclusion table

Table Exclusion after reading full text

Author and year	Reason for exclusion
Andrew (2008)	Not only patients with osteoarthritis included.
Haverkamp (2011)	Not only studies about patients with osteoarthritis included.
Haynes (2017)	Not only studies about patients with osteoarthritis included.
Ibrahim (2015)	Not only patients with osteoarthritis included.
Liu (2015)	Not only studies about patients with osteoarthritis included.
Ma (2016)	Not only studies about patients with osteoarthritis included.
Khan (2009)	Not only patients with osteoarthritis included.
Teng (2015)	Not only studies about patients with osteoarthritis included.
Tsang (2013)	Not only patients with osteoarthritis included.
Zhang (2015)	Outcomes were not separated for total hip and knee replacement.
Dy (2011)	Outcomes were not separated for total hip and knee replacement.
Gossec (2011)	(Contra-)indication not of interested

Table Exclusion after reading full text

Author (year)	Reason for exclusion
Santaguida (2008)	Not specific about patients with osteoarthritis
Flugsrud (2009)	Not specific about patients with osteoarthritis
Lübekke (2007)	Not specific about patients with osteoarthritis
Röder (2007)	Another intervention
Sadr Azodi (2008)	Only construction workers included
Bussato (2008)	Not specific about patients with osteoarthritis

5

Module 2 Patient Reported Outcome Measures in total hip arthroplasty

Research question
What Patient Reported Outcome Measures should be used to assess the effect of total hip arthroplasty?

Uitgangsvraag
Welke Patient Reported Outcome Measures zijn geschikt om het effect van een totale heupvervanging te evalueren?

Introduction
Patient Reported Outcome Measures (PROMs) are questionnaires which patients complete. PROMs are intended to quantify burden of disease and therefore may be helpful in the measurement of quality of care. PROMs have been used for a long time in scientific studies, but their use in the evaluation of regular care is relatively new. It is important to define an optimal set of PROMs that can be used in the assessment of the effect of a total hip arthroplasty from a patients' perspective.

Search and select
No systematic literature search was performed.

Literature summary
The recommendations are based on the advisory report of the Dutch Orthopaedic Association: Patient Reported Outcome Measures. Advies Nederlandse Orthopaedische Vereniging 2012a (https://www.orthopeden.org/downloads/32/advies-proms-orthopedie.pdf).

Considerations
In general there is an increased use of both disease-specific and general PROMs. PROMs might particularly be valuable for measuring the effect of specific (surgical) interventions or for evaluation of care. In the future, PROMs may possibly be useful for determining practice variation.

The Dutch Orthopaedic Assiciation (NOV) aims to identify a set of PROMs that can contribute to continuous improvement of orthopaedic care, through recording of the outcomes in quality registrations like the LROI.

The NOV recommends to use the EQ-5D as a general PROM. For pain (in rest and during physical activity) in patients undergoing total hip arthroplasty the NOV initially advised the VAS. However, the NRS seems at least equivalent and is more feasible in clinical practice. As a joint-specific PROM for THA patients the NOV recommends the HOOS PS, which might be combined with the OHS. The PROMs should be administered at the time of indication, and three months and one year after the operation.

Recommendation

Register PROMs prior to total hip arthroplasty and during follow-up: at least at the time of indication, and at three and twelve months after the operation.

Use for general PROMs the EQ-5D, and the NRS to evaluate pain in rest and during physical activity.

Use as a joint-specific PROM the HOOS-PS, eventually combined with the OHS (for scientific aims).

Aanbeveling

Registreer PROMs voorafgaand aan de plaatsing van een totale heupprothese en tijdens follow-up: in ieder geval bij indicatiestelling, en postoperatief na drie en twaalf maanden.

Gebruik als algemene PROMs de EQ-5D, en voor pijn in rust en bij activiteit de NRS.

Gebruik als gewrichtsspecifieke PROM de HOOS-PS, eventueel gecombineerd met de OHS (voor wetenschappelijk onderzoek).

Literature

Patient Reported Outcome Measures. Advies Nederlandse Orthopaedische Vereniging 2012a (https://www.orthopeden.org/downloads/32/advies-proms-orthopedie.pdf).

Module 3 Surgical techniques in primary total hip replacement

Research questions

3.1 Which type of bearing should be used in total hip arthroplasty?

3.2 What is the preferred diameter of the head in total hip arthroplasty?

3.3 Which approach for total hip arthroplasty is preferable: anterior, posterior or straight lateral?

Uitgangsvragen

3.1 Welk type lagering geniet de voorkeur bij totale heupprothese?

3.2 Wat is de optimale kopdiameter bij totale heupprothese?

3.3 Welke benadering geniet de voorkeur bij totale heupprothese: anterior, posterior of lateraal?

3.1 Bearing surface total hip replacement

Research question

Which type of bearing should be used in total hip arthroplasty?

Uitgangsvraag

Welk type lagering geniet de voorkeur bij totale heupprothese?

Introduction

Only a few materials are suitable as joint bearings for a total hip prosthesis. Traditionally the bearing materials consist of a metal femoral head and a polyethylene cup. Some disadvantages of these materials include wear, with osteolysis and implant loosening, and - dependent on head size - dislocation. To diminish these risks, alternative materials have been developed, creating less wear and at the same time providing the opportunity of using larger heads to decrease the risk of dislocation. Although the more wear-resistant properties of these materials have been illustrated in hip simulators and short-term to mid-term clinical follow-up, it is still unknown whether improved tribological properties will result in reduced wear and osteolysis and consequently in improved implant survival, in the mid to long term. Currently, a number of total hip bearing materials are available, which are used in the following combinations (see Table 3.1).

Table 3.1

Head	Cup
Metal	Conventional Polyethylene
Metal	Highly-cross-linked Polyethylene or vitamin E stabilised Polyethylene
Ceramic	Conventional Polyethylene
Ceramic	Highly cross-linked Polyethylene or vitamin E stabilised Polyethylene
Metal	Metal
Ceramic	Ceramic

The working group chose to focus this chapter on three relatively new bearing materials (compared to traditional materials):

1. Highly cross-linked polyethylene (compared to conventional polyethylene cup).

2. Ceramic head (compared to metal head).
3. Ceramic insert (compared to conventional or highly cross-linked polyethylene insert) in uncemented cup.

There is strong advice against the use of large-head metal on metal articulations in the Netherlands (NOV, 2015) and the disappointing outcomes of these large-head metal on metal articulations reported in the European and Australian registries confirm the problems associated with these articulations. There are many unexpected findings in the metal on metal articulations leading to toxic metal ion loads in patients causing general medical problems and local hip joint problems, such as pseudotumours and loosening. Therefore, studies using metal on metal articulations are not included in this analysis.

Search and select

To answer the question, a systematic literature analysis was performed for the following research questions:

P: primary total hip replacement for osteoarthritis or avascular necrosis;
I: (highly) cross-linked polyethylene or Vitamin E stabilised polyethylene cup;
C: conventional polyethylene cup;
O: periprosthetic fractures, dislocation, wear, revision, survival, osteolysis.

P: primary total hip replacement for osteoarthritis or avascular necrosis;
I: ceramic head;
C: metal head;
O: periprosthetic fractures, ceramic fractures, dislocation, wear, revision, survival, osteolysis.

P: primary total hip replacement for arthrosis or avascular necrosis;
I: ceramic insert (in uncemented cup);
C: (highly) cross-linked polyethylene insert (in uncemented cup);
O: periprosthetic fractures, ceramic fractures, dislocation, wear, revision, survival, osteolysis.

Relevant outcome measures

De working group decided that revision (for any reason) and survival were critical outcome measures for decision-making; and osteolysis and wear were important for decision-making.

The working group defined these outcomes in the following way:

- Revision was defined as the exchange of any component of the femoral implant (stem and/or head) or the acetabular implant (cemented cup or uncemented cup and/or insert), for aseptic loosening and/or any other reason.
- Survival was defined as the revision-free presence of the implant component(s) in the human body during clinical follow-up.
- Wear is the tribological phenomenon of volumetric loss of material due to friction of contacting surfaces in relative motion. Amongst others, this can be assessed with conventional radiography or radiostereometry. Dependent on the type of wear (abrasive, adhesive, fatigue, delamination or 3rd body), the type of material (metal,

ceramic, polyethylene, other materials) and the size and dose of the wear-particles, this can result in osteolysis and eventually loosening of the implant.

Search and select (Method)

A literature search was performed with relevant search terms on 17 november 2016 in the databases Medline (OVID) and Embase (via Embase.com). The search strategy is provided in the tab "Methods". The literature search resulted in 1558 hits. Studies were selected using the following selection criteria: systematic reviews of RCTs or RCTs, comparing the material combinations in the research questions identified, follow-up of preferably five to ten years or more. Also, observational studies, in particular national hip registry studies were included. After obtaining full text, relevant and high quality studies were included in the literature analysis. Based on title and abstract 43 studies were pre-selected. After reading full text, 31 studies were excluded (see exclusion table below) and 12 studies were selected.

The most important study characteristics are described in evidence tables. The assessment of risk of bias is provided in risk of bias tables.

Literature summary

Description of studies

Systematic reviews

A network meta-analysis was included that analysed the difference in the risk of revision or prosthesis survival using 40 RCTs involving 5321 total hip replacements with a postoperative follow-up of at least two years for different bearing material combinations (Yin, 2015). This study systematically reviewed and meta-analysed RCTs among commonly used THA bearing surfaces, including ceramic-on-ceramic, ceramic-on-conventional polyethylene, ceramic-on-highly-cross-linked polyethylene, metal-on-conventional polyethylene, metal-on-highly-cross-linked polyethylene and metal-on-metal articulations.

Furthermore, five systematic reviews were found that compared two combinations of bearing materials each time, partly these included the same RCTs as Yin (2015).

Dong (2015) compared ceramic-on-ceramic and ceramic-onpolyethylene (highly cross-linked polyethylene, polyethylene, uncrosslinked ultrahigh molecular weight polyethylene and ultrahigh molecular weight polyethylene liner) total hip prostheses including eight RCTs enrolling a total of 1,508 patients and 1,702 THA surgeries. Follow-up of the included studies varied from 2 to 12 years. Outcomes reported were clinical outcomes, complications such as fractures, dislocation, osteolysis and revision rates, and radiographic outcomes.

Hu (2015) compared ceramic-on-ceramic versus ceramic-on-polyethylene bearing surfaces for total hip replacement in 9 RCTs involving 1575 patients (1747 hips). Follow-up varied from 12 to 96 months postoperatively. Outcomes reported were ceramic fractures, dislocation, revision and osteolysis.

Shen (2014) compared highly-cross-linked polyethylene with conventional polyethylene bearing surfaces for total hip replacement in 8 RCTs involving 735 patients. Follow-up ranged from 5 to 10 years. Outcomes reported were wear-related revision and osteolysis.

Si (2015) compared ceramic-on-ceramic with ceramic-on-(highly-cross-linked) polyethylene bearing surfaces for total hip replacement in 13 RCTs involving 2488 total hip arthroplasties. Follow-up ranged from one to twelve years. Outcomes reported were revision and overall ceramic fractures.

RCTs

In addition, six RCTs were found that were not included in the network meta-analysis of Yin.

Beaupré (2016) compared ceramic-on-ceramic with ceramic-on-highly-cross-linked-polyethylene in an RCT in 92 subjects. Ten-year follow-up was completed in 35 of the 48 patients in the ceramic-on-ceramic group and in 33 of the 44 patients in the ceramic-on-highly-crosslinked-polyethylene group. Outcomes reported were PROMs, wear and revision (Beaupré, 2016).

Glyn-Jones (2016) performed an RCT that compared long-term steady wear of highly-cross-linked-polyethylene with ultra-high-molecular-weight-polyethylene. Outcomes reported were revision and wear.

Langlois (2015) conducted a prospective randomised study to assess the rates of penetration in 100 patients of two distinct types of polyethylene in otherwise identical cemented all-polyethylene acetabular components. After 8 years of follow-up 68 hips had complete follow-up data.

Registry studies

Several registry studies were found. Paxton (2014) compared risk of revision between metal-on-conventional-polyethylene and metal-on-highly-cross-linked-polyethylene in six national and regional registries: USA (Kaiser Permanente, HealthEast), Italy (Emilia-Romagna region), Spain (Catalan region), Norway and Australia. Inclusion criteria were osteoarthritis as the primary diagnosis, cementless implant fixation and a patient age of 45 to 64 years. These criteria resulted in a sample of 16,571 primary total hip arthroplasties.

Paxton (2015) describes 26,823 total hip arthroplasties from the Kaiser Permanente's Total Joint Replacement Registry performed between April 2001 and December 2011. Endpoints of interest were all-cause and aseptic revisions. Of the 26,823 THAs included in the study, 1815 (7%) were metal-on-conventional polyethylene and 25,008 (93%) were metal-on-highly-cross-linked-polyethylene.

Epinette (2016) analysed data from the National Joint Registry (England and Wales) of 45,877 hips. It compared cross-linked annealed polyethylene (n=21,470) with conventional polyethylene (n=8,225) and ceramic-on-ceramic (n=16,182) at 6 years follow-up and focused on revision risk (Epinette, 2016).

Furhermore, the 2016 Annual Report of the Australian Orthopedic Association National Joint Replacement Registry (AOANJRR) was used.

Results

A *Do highly cross-linked polyethylene or vitamin E stabilised polyethylene cups perform better than conventional polyethylene cups in patients having a primary total hip replacement for osteoarthritis or avascular necrosis, on the outcomes ceramic fractures, dislocation, wear, revision, survival, osteolysis?*

Revision

The network meta-analysis of 40 RCTs showed no significant difference in relative risk (RR) of revision for metal-on-highly-cross-linked-polyethylene versus metal-on-conventional-polyethylene (11 studies, RR for conventional polyethylene vs highly-cross-linked-polyethylene = 2.04 (0.89 to 5.09) (Yin, 2015).

The study by Paxton (2014) showed a five-year rate of revision surgery ranging from 1.9% to 3.2% among the different registries. There was no significant difference in revision rates between bearing surfaces, with a hazard ratio of 1.20 (95% CI 0.80 to 1.79) for metal-on conventional-polyethylene compared to metal-on-highly-crosslinked-polyethylene.

The large registry study by Paxton (2015) included 26,823 patients with a follow-up up to 10 years (median follow-up 5.1 years). The adjusted risks of all-cause revision (HR 1.75; 95%CI, 1.37 to 2.24; p<0.001) and aseptic revision (HR 1.91; 95% CI, 1.46 to 2.50; p<0.001) were higher in patients with metal-on-conventional polyethylene bearing surfaces compared with metal-on-highly-cross-linked-polyethylene. At 7 years follow-up, the cumulative incidence of revision was 5.4% (95% CI, 4.4% to 6.7%) for metal-on-conventional and 2.8% (95% CI, 2.6% to 3.2%) for metal-on-highly-cross-linked-polyethylene. When accounting for differences in femoral head size distribution, the results were not substantively different.

The National Joint Registry of England and Wales hip data set, including 45,877 hips, showed better survival (revision for any cause) of cross-linked annealed polyethylene (6 years survival rate 98.0%; 95%CI 0.976-0.983) versus conventional polyethylene (6 years survival rate 97.3%; 95%CI 0.969-0.977; p=0.072). When considering revision for bearing related failures, 6-year survival was significantly better for cross-linked annealed polyethylene (99.6%) than for conventional polyethylene (98.8%; P<0.001). Separate analyses were carried out for small metallic heads, small alumina heads and large heads. For metallic and alumina small heads (≤32mm), survival of cross-linked annealed polyethylene was significantly better than of conventional polyethylene. For large heads this comparison could not be made because there were no large heads used in combination with conventional polyethylene liners (Epinette, 2016).

According to the 2016 Annual Report of the Australian Orthopedic Association National Joint Replacement Registry (AOANJRR), which contains 363,561 primary total hip replacements, of which 44,710 hips were added in 2015, cross-linked-polyethylene has a lower rate of revision than conventional polyethylene regardless of the femoral head used (both independent of size and bearing material); the 15-year cumulative percent revision for cross-linked-polyethylene is 5.6% versus 10.5% for non-cross-linked-polyethylene. The cumulative incidence of loosening/lysis and prosthesis dislocation at 15 years is 1.1% and

1.2% for cross-linked-polyethylene, compared to 3.6% and 1.6% for non-cross-linked-polyethylene bearings respectively.

Revision varies depending on head size. In the Australian registry, this is most evident for non-cross-linked-polyethylene where the rate of revision increases with larger head size, mainly due to osteolysis and loosening. For cross-linked-polyethylene there is no difference between head sizes <32 mm and >32 mm, but revision risk is lowest for 32 mm heads.

Comparing all bearing combinations, the cumulative percent revision at 10 years for ceramic-on-cross-linked-polyethylene and metal-on-cross-linked-polyethylene is lower (resp. 4.4; 4.0 to 4.8 and 4.3; 4.1 to 4.5), compared to ceramic-on-non-cross-linked-polyethylene and metal-on-non-cross-linked-polyethylene (7.0; 6.3 to 7.8 and 6.3; 6.1 to 6.6). The percent revision of ceramic-on-ceramic lies in between the cross-linked-polyethylene and non-cross-linked-polyethylene values (5.0; 4.8 to 5.3).

Fractures

Highly-cross-linked-polyethylene versus conventional polyethylene

None of the studies reported fractures.

Dislocation

Highly-cross-linked-polyethylene versus conventional polyethylene

None of the studies reported dislocation.

Osteolysis

Highly-cross-linked-polyethylene versus conventional polyethylene

A meta-analysis of 8 RCTs that compared highly cross-linked with conventional polyethylene showed no difference in osteolysis (RD -0.12 95% CI (-0.26 to 0.03) P=0.12) after five to ten years follow-up (Shen, 2014).

Wear

Highly-cross-linked-polyethylene versus conventional polyethylene

A meta-analysis of 8 RCTs that compared highly cross-linked with conventional polyethylene showed significantly reduced radiological wear of cross-linked polyethylene at midterm follow-up periods, but no difference in wear-related revision (RD -0,02 95% CI (-0.05 to 0.01); P=0.20 after five to ten years follow-up (Shen, 2014). However, the study did not provide information on the bearing material at the femoral side.

Two small RCTs were published after this review. Langlois (2015) showed that at nine year follow-up the yearly linear wear can be significantly reduced by using a highly cross-linked PE (-0.0002 mm/year versus 0.132 mm/year for contemporary annealed polyethylene, p<0.001). Glyn-Jones (2015) reported linear wear (using radiostereometric analysis) for the highly cross-linked polyethylene being significantly less (0.003 mm/year) than for the conventional ultrahigh-molecular weight polyethylene (0.030 mm/year; p<0.001) at 10 years. The volumetric wear between 1 and 10 years was lower in the highly-cross-linked-polyethylene group (14 mm3) compared to the conventional ultrahigh-molecular weight polyethylene group (98 mm3, p = 0.01).

Grading of evidence

Revision

Level of evidence was graded as low as the conclusion was based on the network meta-analysis of Yin (2015), which had some methodological limitations (details regarding randomisation and blinding were not always clear), together with observational registry data, and because results were inconsistent.

Fractures

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Dislocation

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Osteolysis

The level of evidence was graded as high as the systematic literature search of Shen (2014) was of good quality.

Wear

The systematic review of Shen (2014) was of good quality. The level of evidence was graded as high.

Conclusions

Revision

Low GRADE	Highly-cross-linked-polyethylene results in a lower revision risk than conventional polyethylene. *Sources (Yin, 2015; Paxton, 2014; Paxton, 2015; Epinette, 2016; AOANJRR, 2016)*

Osteolysis

Moderate GRADE	No differences in osteolysis were found after 5 to 10 years follow-up for highly cross-linked compared to conventional polyethylene. *Sources (Shen, 2014)*

Wear

High GRADE	Wear is reduced for highly-cross-linked polyethylene as compared to conventional polyethylene. *Sources (Shen, 2014; Langlois, 2015; Glyn-Jones, 2015)*

B *Do ceramic heads perform better than metal heads with use of the same type of polyethylene on the cup side in patients having a primary total hip replacement for osteoarthritis or avascular necrosis, on the outcomes fractures, dislocation, wear, revision, survival, osteolysis?*

Revision

The network meta-analysis of 40 RCTs showed no significant difference in risk of revision for ceramic-on-conventional-polyethylene prosthesis versus metal-on-conventional-polyethylene (3 studies; RR 1.74 (0.58 to 5.24). There was also no difference in risk of revision for ceramic-on-highly-cross-linked-polyethylene versus metal-on-highly-cross-linked polyethylene (2 studies; RR 0.74; 95% CI 0.17; 3.01) (Yin, 2015).

Ceramic fractures

None of the studies reported ceramic fractures.

Dislocation

None of the studies reported dislocation.

Osteolysis

None of the studies reported osteolysis.

Wear

None of the studies reported wear.

Grading of evidence

Revision

The study by Yin had some methodological limitations, as details regarding randomisation and blinding were not always clear and results were heterogeneous. Level of evidence was graded as low.

Fractures

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Dislocation

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Wear

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Osteolysis

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Conclusion

Low GRADE	Ceramic-on-(highly-cross-linked) polyethylene showed no difference in risk of revision compared to metal-on-(highly-cross-linked) polyethylene. *Sources (Yin, 2015)*

C. *Do ceramic cups perform better than (highly) cross-linked polyethylene cups (both in uncemented shells) in patients having a primary total hip replacement for osteoarthritis or avascular necrosis, on the outcomes fractures, dislocation, wear revision, survival, osteolysis?*

Revision

A network meta-analysis of 40 RCTs showed that the relative risk of revision for ceramic-on-highly-cross-linked polyethylene versus ceramic-on-ceramic was 1.95 (4 studies; 95% CI 0.68-6.60) (Yin, 2015).

A meta-analysis of 8 RCTs that compared ceramic-on-ceramic versus ceramic-on-(highly cross-linked)-polyethylene showed no difference in revision rate (RR=0.99; 95% CI (0.54 to 1.83)) (Dong, 2015). Another meta-analysis of 9 RCTs that made the same comparison, did not show differences in revision rates for ceramic-on ceramic compared to ceramic-on-polyethylene (2.7% versus 2.8%) (Hu, 2015).

A third meta-analysis of 13 RCTs showed no differences with respect to revisions (RR 1.28 (0.60 to 2.75)) (Si, 2015).

The RCT by Beaupré (2016) reported three revisions in the ceramic-on-highly-crosslinked-polyethylene group and no revisions in the ceramic-on-ceramic group. The results might be caused by the differences in head sizes (mainly 28 mm ceramic-on-highly-crosslinked-polyethylene vs 32 mm in ceramic-on-ceramic).

Ceramic Fractures

A meta-analysis of 8 RCTs that compared ceramic-on-ceramic versus ceramic-on-(highly cross-linked)-polyethylene showed a higher rate of fractures for ceramic-on-ceramic fracture than (highly-cross-linked) polyethylene (RR = 4.46, 95% CI: 1.16 to 17.25; P = 0.03) (Dong, 2015). Another meta-analysis of 9 RCTs also showed a higher incidence of intra- and postoperative fractures for ceramic-on-ceramic than ceramic-on-polyethylene (Risk ratio 5.10 (1.32 to 19.71); P=0.02) (Hu, 2015).

A third meta-analysis of 13 RCTs also showed a higher rate of overall fractures for ceramic-on-ceramic than ceramic-on-polyethylene (RR 6.02 (95%CI (1.77 to 20.1)) (Si, 2015).

Dislocation

A meta-analysis of 8 RCTs that compared ceramic-on-ceramic versus ceramic-on-(highly-cross-linked) polyethylene showed no difference in dislocation rate (RR=0.73 (95%CI 0.44 to 1.19). There was no information on head sizes used in the studies (Dong, 2015). Another meta-analysis of 9 RCTs (Hu, 2015) made the same comparison and found no significant difference in dislocation rates between ceramic-on-ceramic versus ceramic-on-polyethylene (3.1% versus 4%, RR = 0.77 (0.47 to 1.25); P=0.29).

A third meta-analysis of 13 RCTs showed no differences with respect to dislocations (RR 0.72 (95%CI (0.43 to 1.19)) (Si, 2015).

The RCT by Beaupré (2016) reports four patients with recurrent dislocations in the ceramic-on-highly-crosslinked-polyethylene group (of which three underwent a surgical revision), and two in the ceramic-on-ceramic group.

Wear

Three studies in the meta-analysis by Dong (2015) that compared ceramic-on-ceramic versus ceramic-on-(highly-cross-linked) polyethylene reported wear rate. In the ceramic-on-ceramic group, the mean linear wear rate was 30.5 ± 7.0 µm/year and the mean volumetric wear rate was 21.5 ± 4.5 mm3/year. In the ceramic-on-polyethylene group, the mean linear wear rate was 218.2 ± 13.7 µm/year and the mean volumetric wear rate was 136.2 ± 8.5 mm3/year. The increase in mean linear and volumetric wear rates in the ceramic-on-polyethylene group was statistically significant (P < 0.001).

Osteolysis

Dong (2015) showed no significant difference in osteolysis rate in a meta-analysis (four studies reported osteolysis) between the ceramic-on-polyethylene and the ceramic-on-ceramic group (RR = 0.39 (in favour of COC), 95% CI: 0.10 to 1.56, P = 0.18).

A pooled analysis of 7 studies (1155 hips) revealed no significant difference in the incidence of osteolysis and radiolucent lines in the ceramic-on-ceramic and ceramic-on-polyethylene groups (0.3% versus 1.2%, respectively; RR=0.43; 95% CI, 0.11-1.68; P=.22; homogeneity, P=.80) (Hu, 2015).

Grading of evidence

Revision

Level of evidence was graded as low as the systematic literature search by Dong (2015) and Hu (2015a) was not completely clear and results were heterogeneous.

Fractures

The level of evidence was graded as moderate as the systematic literature search by Dong (2015) and Hu (2015a) was not completely clear and adjustment for potential confounders was unclear in Dong (2015) and Si (2015). Due to these methodological limitations it was graded as moderate.

Dislocation

The level of evidence was graded as moderate as the systematic literature search by Dong (2015) and Hu (2015a) was not completely clear and adjustment for potential confounders was unclear in Dong (2015) and Si (2015). Also it was downgraded as results were heterogeneous. Due to these limitations it was graded as low.

Wear

The level of evidence was graded as moderate as the systematic literature search by Dong (2015) was not completely clear.

Osteolysis

The level of evidence was graded as moderate as the systematic literature search by Dong (2015) was not completely clear.

Conclusions

Revision

Moderate GRADE	Ceramic-on-ceramic versus ceramic-on highly-cross-linked-polyethylene showed similar revision risks. *Sources (Yin, 2015; Dong, 2015; Hu, 2015; Si, 2015, Beaupré, 2016)*

Ceramic fractures

Moderate GRADE	Ceramic-on-ceramic showed a 4 to 6 times higher rate of ceramic fractures than ceramic-on-polyethylene. *Sources (Dong, 2015; Hu, 2015; Si, 2015)*

Dislocation

Low GRADE	The incidence of dislocation is comparable for ceramic-on-ceramic and ceramic-on-highly-cross-linked-polyethylene. *Sources (Dong, 2015; Hu, 2015; Si, 2015; Beaupré, 2016)*

Wear

Moderate GRADE	Wear is reduced for ceramic-on-ceramic as compared to ceramic-on-(highly-cross-linked)-polyethylene. *Sources (Dong, 2015)*

Osteolysis

Moderate GRADE	No differences in osteolysis were found for ceramic-on-ceramic as compared to ceramic-on-highly-cross-linked-polyethylene. *Sources (Dong, 2015; Hu 2015a)*

Considerations

Considering the ever younger patient group being treated with total hip arthroplasty, there is a growing need for more wear-resistant bearing materials that allows the use of larger femoral head components preventing dislocation, without increasing friction and allowing motion without component to component impingement.

During the last decade the tribological characteristics of bearing couples in hip arthroplasty have been improved resulting in less particle wear, diminished osteolysis and improved survivorship. On the one side the innovation in hard on hard bearings has led to better ceramics, using hot isostatic pressing with different and smaller grain sizes as well as higher grain density resulting in lower fracture risk. Modern ceramics show better wettability and lubrication and almost no wear, while furthermore these products are inert and locally not bioactive and therefore do not cause osteolysis. Additionally, improvements of designs have almost excluded rim impingement and chipping.

Polyethylene quality has been dramatically improved by cross-linking of the polyethylene chains. This can be performed by gamma irradiation creating free radicals that in turn are

used for cross-linking. Free radicals however are also responsible for oxidative degradation of polyethylene. This can either be prevented through vitamin E stabilisation, or through heating of the polyethylene, in that way capturing remaining free radicals. Heating is performed by remelting or annealing (below melting temperature of the polyethylene), which have both advantages and disadvantages in terms of changing polyethylene crystallinity and wear properties.

Most information concerning the tribological properties of these materials has come from in-vitro preclinical testing using hip simulators. Furthermore, the clinical assessment of linear and volumetric wear has been improved by using radiostereometry. However long-term data on survivorship using different combinations of bearing materials have been lacking and only gradually become available.

Summarising the available evidence, it can be said that metal-on-conventional-polyethylene carries a higher risk of revision than all other couplings (metal–on-cross linked-polyethylene, ceramic-on-conventional-polyethylene, ceramic-on-cross-linked-polyethylene, ceramic-on-ceramic). Because ceramic-on-ceramic shows lowest volumetric wear, it allows the use of large femoral heads diminishing the risk of dislocation in the young and active age group. In some studies however, survivorship of this coupling seems to be compromised through ceramic fractures and chipping of the older designs. Because of the more wear-resistant properties of cross-linked polyethylene (compared to conventional polyethylene), thinner cross-linked polyethylene is possible, also allowing larger femoral head components. Consequently, the use of these improved polyethylenes has a similar advantage as ceramic liners in terms of reducing dislocation risk. In some cases of ceramic-on-ceramic couplings, patients may complain of squeaking. Although there is no evidence of any relation with wear or higher fracture risk, this may be a cause for revision because of the annoying sound. The combination of ceramic or metal on cross-linked polyethylene seems to be the most safe, durable and cost-effective, although there is no clear evidence of its superiority over ceramic-on-conventional polyethylene in long-term follow-up studies of good quality.

Recommendation

Preferably use a metal or ceramic head and a highly cross-linked polyethylene cup.

Aanbeveling

Gebruik bij voorkeur een metalen of keramische kop en een highly cross linked polyethyleen kom.

Literature

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Yin S, Zhang D, Du H, et al. Is there any difference in survivorship of total hip arthroplasty with different bearing surfaces? A systematic review and network meta-analysis. Int J Clin Exp Med. 2015;8(11):21871-85. PubMed PMID: 26885157.

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Validity and maintenance

In theory, assessment will take place after five years to determine whether this module is still up-to-date. Are there reasons to suspect a need for earlier revision? For example, large studies that still need to be published?

Module	Party in control	Year of authorization	Next assessment of actuality	Frequency of assessment actuality	Which party/parties monitors actuality	Important factors that might lead to change in recommendations
Bearing surface total hip replacement	NOV	2018	2023	Every 5 years	NOV	-

Indicators

See LROI database

Implementation plan

Recommendation	Time needed for implementation: <1 year, 1 to 3 years or >3 years	Expected effects on costs	Conditions for implementation	Possible barriers to implementation[1]	Actions for implementation[2]	Reponsibility for these actions[3]	Other remarks
All	1 to 3 years	Reduction	No	Surgeons might not be used to work with this type of bearing	Annual quality audit. Adjustment of NOV classification	NOV	

Evidence tables

Research question: Which type of hip prosthesis bearing is preferable?

Is there a significant benefit of (highly) cross-linked polyethyleen (PE) or Vitamine E-stabilised PE over a conventional PE after (moderate)long-term with outcome parameter PE-wear (linear or volumetric), osteolysis, prothesis survival, with use of same head material and size?

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Dong et al., 2015 PS., study characteristics and results are extracted from the SR (unless stated otherwise)	SR and meta-analysis of 8 RCTs *Literature search up to 2013* **A**: Kim, 2013 **B**: Lauren, 2013 **C**: Bal, 2005 **D**: Derek, 2011 **E**: Lombardi, 2010 **F**: Cai, 2012 **G**: Lewis, 2010 **H**: Hamilton, 2010 Country: China Source of funding: unknown	Inclusion criteria SR: RCT of Ceramic On Ceramic-Total Hip Arthroplasty and Ceramic On Polyethylene-Total Hip Arthroplasty and provided sufficient numerical information on at least one of the following prespecified endpoints: Revision for any cause, local and general complications, radiographic outcomes. >=2 yrs follow-up Exclusion criteria SR: quasi RCTs and non-RCTs	Describe intervention: **A**: alumina on alumina **B**: alumina on alumina **C**: alumina on alumina **D**: alumina on alumina **E**: alumina matrix composite **F**: Alumina **G**: Alumina **H**: Ceramic on ceramic	Describe control: **A**: alumina on highly cross-linked polyethylene **B**: alumina on highly cross-linked polyethylene **C**: alumina on polyethylene **D**: alumina on uncross-linked ultrahigh molecular weight polyethylene **E**: highly cross-linked polyethylene **F**: ultrahigh molecular weight polyethylene liner **G**: ultrahigh molecular weight polyethylene liner **H**: Delta ceramic on highly cross-linked polyethylene	End-point of follow-up: 2-12.4 y **A**: 12.4 y **B**: 5 y **C**: 2 y **D**: 5 y **E**: 6 y **F**: 3.2 y **G**: 8 y **H**: 2.6 y For how many participants were no complete outcome data available? (intervention/control) unclear	Outcome measure-1 fracture Effect measure: RR, RD, mean difference (95% CI): meta-analysis shows that the COC has a significant higher rate of fracture than the COP (RR = 4.46, 95% CI: 1.16–17.25; P = 0.03). Outcome measure-2 dislocation dislocation rates in COC group seemed a little lower but it didn't reach a statistical significant difference (RR = 0.73, 95% CI: 0.44–1.19; P = 0.21) Outcome measure-3 Revision Overall revision rate between the groups was similar (RR = 0.99, 95% CI: 0.54–1.83; P = 0.98)....	

		N=1508 patients and 1702 THA <u>N, mean age</u> **A**: XX patients, XX yrs **B**: **C**: **….** <u>*Sex:*</u> **A**: % Male **B**: **C**: **….** Groups comparable at baseline?				<u>Outcome measure-4 Osteolysis</u> Four studies reported osteolysis. The meta-analysis results demonstrated a little higher osteolysis rate in the COP group (RR = 0.39, 95% CI: 0.10–1.56), but didn't reach a significant statistical difference (P = 0.18).	
Hu, 2015 (a) PS., study characteristics and results are extracted from the SR (unless stated otherwise)	SR and meta-analysis of 9 RCTs *Literature search up to October, 2013* **A**: Ammanatulah et al.,5 **B**: Beaupre et al., 10 **C**: Cai et al., 6 **D**: Hamilton et al., 2 **E**: Kim et al., 9	Inclusion criteria SR: patients underwent primary THA; (2) study compared COC and COP bearing surfaces; (3) studies reported clinical or radiographic outcomes of THA (at least 1 desirable outcome); (4	Describe intervention: **A**: Alumina **B**: Alumina **C**: Alumina matrix **D**: Alumina matrix **E**: Alumina **F**: Alumina **G**: Alumina matrix **H**: Unkown **I**: Alumina	Describe control: **A**: HXLPE **B**: HXLPE **C**: UHMWPE **D**: HXLPE **E**: HXLPE **F**: UHMWPE **G**: HXLPE **H**: Unkown **I**: HXLPE	<u>Mean follow-up (months)</u>: **A**: >60 **B**: >60 **C**: 40 (36-45) **D**: 31 (21-49) **E**: 12.4 (11-13) **F**: 96 (60-120) **G**: 73 (26-108) **H**: 96 (85.2-110.4)>24 **I**: >24 <u>For how many participants were no</u>	<u>Outcome measure-1 fracture</u> The total incidence of intra- and postoperative implant fractures in the COC group was statistically significantly higher (P=.02) than that of the COP group (Figure 8), indicating that COC increased the total implant fracture rate. <u>Outcome measure-2 dislocation</u>	

	F: Lewis et al., 11 **G**: Lombardi et al., 12 **H**: Ochs et al., 13 **I**:Sony et al., 14 <u>Study design</u>: RCT (parallel / cross-over), cohort (prospective / retrospective), case-control <u>Setting and Country</u>: **A**: USA **B**: Canada **C**: China **D**: Canada **E**: South Korea **F**: Canada **G**: USA **H**: Germany **I**: USA <u>Source of funding:</u> (commercial / non-commercial / industrial co-authorship)	studies were prospective RCTs; and (5) fulltext was published in English. Exclusion criteria SR: not enough details <u>Important patient characteristics at baseline</u>: <u>N, mean age</u> **A**: I: 50.4 C:54.7 **B**: I:51.3 C:53.6 **C**: I:42.1 C:42.0 **D**: I: 56.4 C:57.3 **E**: 45.3 **F**: I: 41.5 C:42.8 **G**: I: 57 C:60 **H**: I: 56.0 C: 61.5 **I**: I: 55.0 C:61 Groups comparable at baseline?			<u>complete outcome data available?</u> (intervention/control) unclear	A forest plot of all 9 studies (1747 hips) indicated no significant difference in THA dislocation rates between the COC and COP groups (3.1% vs 4.0%, respectively; RR=0.77; 95% CI, 0.47-1.25; P=.29; homogeneity, P=.98) <u>Pooled fixed effects Outcome measure-3 revision</u> Effect measure: RR, RD, mean difference (95% CI): No significant difference was found in the THA revision rates of the COC and COP groups (2.7% vs 2.8%, respectively; RR=0.95; 95% CI, 0.54-1.68; P=.85; homogeneity, P=.56)	
Shen, 2014	SR and meta-analysis of 8 RCTs	Inclusion criteria SR: patients underwent THA,	Describe intervention: **A**: Highly cross-linked polyethylene	Describe control:	<u>End-point of follow-up</u>: **A**: 10 y ± 1.8 **B**: 10	<u>Wear-related revision</u> Meta-analysis of the wear-related revision incidence showed that	The current limited evidence suggests that cross-linked polyethylene significantly reduced the

PS., study characteristics and results are extracted from the SR (unless stated otherwise)	*Literature search up to July 2013* **A**: Engh et al;., 2012 **B**: Johanson et al., 2012 **C**: Garcia-Rey et al., 2012 **D**: Thomas et al., 2011 **E**: Mutimer et al., 2010 **F**: Mc Calden et al., 2009 **G**: Geerdink et al., 2009 **H**: Nikolao et al., 2012 <u>Setting and Country</u>: <u>Source of funding:</u> No funding received	28mm femoral head, reported wear-related revision, follow-up >= 5 years Exclusion criteria SR:- <u>Important patient characteristics at baseline</u>: *Number of patients; characteristics important to the research question and/or for statistical adjustment (confounding in cohort studies); for example, age, sex, bmi, ...* <u>N, mean age</u> **A**: XX patients, XX yrs **B**: **C**: **….** <u>*Sex:*</u> **A**: % Male **B**: **C**:	(Marathon, DePuy) N=116 **B**: Highly cross-linked polyethylene (Durasul, Zimmer) N=25 **C**: Highly cross-linked polyethylene (Durasul, Zimmer) N=42 **D**: Highly cross-linked polyethylene (Longevity, Zimmer) N=22 **E**: Highly cross-linked polyethylene (Marathon, DePuy) N=55 **F**: Highly cross-linked polyethylene (Longevity, Zimmer) N=50 **G**: Highly cross-linked polyethylene (Duration Stryker) N=22 **H**: Highly cross-linked polyethylene (Smith &Nephew) N=32	**A**: Conventional polyethylene (Enduron, Depuy) N=114 **B**: Conventional polyethylene (Sulene, Zimmer) N=27 **C**: Conventional polyethylene (Sulene, Zimmer) N=41 **D**: Conventional polyethylene (Zimmer) N=22 **E**: Conventional polyethylene (Enduron, De Puy) N=55 **F**: Conventional polyethylene (Trilogy, Zimmer) N=50 **G**: Conventional polyethylene N=26 **H**: Conventional polyethylene (Smith &Nephew) N=36	**C**: 10 to 12 **D**: 7 **E**: 5 **F**: 6.8 **G**: 8 **H**: 5 <u>Risk assessment for incomplete outcome data?</u> (intervention/control) **A:** low risk **B**: low risk **C**: low risk **D**: low risk **E**: high risk **F**: low risk **G**: low risk **H**: low risk	there was no difference between the wear-related revision rate between cross-linked and conventional polyethylene group (RD -0,02 95% CI (-0.05 to-0.01); P=0.20; fig 2 provides details) Osteolysis Meta-analysis of the incidence of osteolysis showed that there was no difference between the cross-linked and conventional polyethylene group (RD -0.12 95% CI (-0.26 to 0.03) P=0.12)	radiological wear compared with conventional polyethylene at midterm follow-up periods. However, there is no evidence that cross-linked polyethylene had an advantage over conventional polyethylene in terms of reducing osteolysis or wear-related revision. Nevertheless, future long-term RCTs on this topic are needed. Note: 7 of these 8 RCTs were included in network meta-analysis Yin,

		…. Groups comparable at baseline?					
Si, 2015 PS., study characteristics and results are extracted from the SR (unless stated otherwise)	SR and meta-analysis of (RCTs / cohort / case-control studies) *Literature search up to August 2014* **A**: Kim et al., 2013 **B**: Beaupre et al., 2013 **C**: Cai et al., 2012 **D**: Amanatullah et al., 2011 **E**: Lombardi et al., 2010 **F**: Lewis et al., 2010 **G**: Hamilton et al., 2010 **H**: Poggie et al., 2007 **I**: Kim et al., 2007 **J**: Bal et al., 2005 **K**: Nygaard et al., 2004	Inclusion criteria SR: 1) published RCTs (Level I evidence); 2) compared CoC with CoP THAs with regard to functional outcomes, radiographic outcomes and/or complications; 3) all patients received a primary THA; 4) written in English Exclusion criteria SR: review articles, case reports, meeting abstracts, technique articles or expert opinions *13 studies included*	Describe intervention: Ceramic on ceramic **A**: Alumina-Alumina Ceramic **B**: Alumina-Alumina ceramic **C**: Delta-Delta ceramic **D**: Alumina-Alumina ceramic **E**: Delta-Alumina ceramic **F**: Alumina-alumina ceramic **G**: Delta-delta ceramic **H**: Alumina-alumina ceramic **I**: Alumina-alumina ceramic **J**: Alumina-alumina ceramic **K**: Alumina-alumina ceramic **L** Alumina-alumina ceramic **M**: Alumina-alumina ceramic	Describe control: Ceramic on polyethylene **A**: Alumina Ceramic-HCL PE **B**: Alumina Ceramic-HCL PE **C**: Alumina Ceramic-UCL PE **D**: Alumina Ceramic-UCL PE **E**: Zirconia Ceramic-HCL PE **F**: Alumina Ceramic-UCL PE **G**: Delta Ceramic-MCL PE **H**: Alumina Ceramic-UCL PE **I**: Alumina Ceramic-UCL PE **J**: Alumina Ceramic- PE (UC) **K**: Zirconia Ceramic-UCL PE **L** Alumina Ceramic-UCL PE **M**: Alumina Ceramic-PE (UC)	<u>End-point of follow-up</u>: **A**: 12.4 year **B**: 5 year **C**: 3.3 year **D**: 5 year **E**: 6 year **F**: 8 year **G**: 2.6 year **H**: 2 year **I**: 4.8 year **J**: 2 year **K**: 1 year **L** 1.1 year **M**: 5 year <u>Risk assessment for incomplete outcome data?</u> (intervention/control) **A:** low risk **B**: high risk **C**: low risk **D**: low risk **E**: low risk **F**: low risk **G**: low risk **H**: low risk **I**: low risk **J**: unclear risk **K**: low risk **L**: low risk	<u>Outcome measure-1 revision</u> Defined as revisions with follow-up >= 5 years (5 studies) 26 events in 813 THA Effect measure: RR (95% CI): 1.28 (0.60-2.75) <u>Outcome measure-2</u> **Overall ceramic fracture** I: 24/1053 C: 0/761 Pooled effect (fixed effects model) RR: 6.02 (95% CI 1.77 to 20.51) favoring Ceramic on polyethylene. Heterogeneity (I^2): 0% <u>Outcome measure-3 Dislocation</u> <u>58 events in 1490 THA</u> Effect measure: RR (95% CI): 0.72 (0.43-1.19)	

	L: Pitto et al., 2003 **M**: Pitto et al., 2000 Setting: hospital Source of funding: China Health Ministry Program (201302007).	Important patient characteristics at baseline: Mean age varied from 42 to 68			**M**: low risk		
Yin, 2015 PS., study characteristics and results are extracted from the SR (unless stated otherwise)	SR and network meta-analysis of 40 RCTs, see PDF for all details of these studies *Literature search up to May 2015* Source of funding: unknown	Inclusion criteria SR: all RCTs comparing survivorship or revision rates between THA bearing surfaces for the treatment of degenerative hip diseases in English were identified through an electronic search and manual research by two clinical librarians (S Yin and D Zhang) independently, patients younger than 75	In network meta-analysis the following comparisons were used that were made in the studies: MoPc versus MoPxl versus CoPc versus CoPxl (8), one MoPc versus MoPxl versus CoC (9), one MoPc versus MoM versus CoPc (10), eleven MoPc versus MoPxl (11-21), five MoPc versus MoM (22-26), four CoC versus CoPc (27-30), four CoC versus CoPxl (31-34), three CoC versus MoPc (35-37), three MoPc versus CoPc (38-40), two MoPxl versus CoPxl (41, 42), two MoPxl versus MoM (43, 44), one CoC versus MoPxl (45), one CoC versus MoM (46), and one CoPc versus MoM (47). MoPc = metal-on-conventional polyethylene, MoPxl = metal-on-highly crosslinked polyethylene, CoPc = ceramic-on-conventional polyethylene, CoPxl = ceramic-on-highly crosslinked polyethylene, CoC = ceramic-on-ceramic, MoM = metal-on-metal		End-point of follow-up: at least two years Average 6.6 (2-12) years; Subgroup analysis presented for at least 10 year follow-up	Outcome measure-1 revision The pooled data of network meta-analysis showed no difference in terms of risk of revision among CoC, CoPc, CoPxl and MoPxl implants. However, MoM implants were associated with significant higher risks of revision when compared with CoC (RR 5.10; 95% CI=1.62 to 16.81), CoPc (RR 4.80; 95% CI=1.29 to 17.09), MoPxl (RR 3.85; 95% CI=1.16 to 14.29), and a non-significant trend towards a increased risk of revision when compared with CoPxl implants (RR 2.56; 95% CI=0.51 to 12.16).	Summary of author's conclusion: present evidence indicated the similar performance in survivorship among CoC, CoPc, CoPxl and MoPxl bearing implants, and that all likely have superiority compared with the MoM and MoPc bearing implants in THA procedures. Long-term RCT data are required to confirm these conclusions and better inform clinical decisions. Sensitivity analyses When the network meta-analysis was restricted to trials with at least 10 years follow-up time, the

		years of age at the time of surgery, (inclusion of arms treated with THA procedures with different bearing surfaces, such as CoC, CoPc, CoPxl, MoPc, MoPxl or MoM bearings, (5) included studies had to report valid data of survivorship or revision rates of bearing prostheses Exclusion criteria SR: lack of relevance <u>Important patient characteristics at baseline</u>: *N=5321 hips*			MoPc implants were demonstrated with a significant increased risk of revision compared with CoC RR 2.83; 95% CI=1.20 to 6.63), and non-significant trends of higher risk of revision when compared with CoPc (RR 2.64; 95% CI=0.89 to 7.04), CoPxl (RR 1.42; 95% CI=0.35 to 5.46) and MoPxl (RR 2.10; 95% CI=0.82 to 5.48) implants.	MoM implants were non-significantly associated with a 11-fold, 11-fold, 4-fold and 4-fold increased risks of revision when compared with CoPxl, CoC, MoPxl, and CoPc implants, respectively (Table 3). MoPc implants were non-significantly associated with a 5-fold, 5-fold, 2-fold and 2-fold increased risks of revision when compared with CoPxl, CoC, MoPxl, and CoPc implants, respectively.

Research question: Which type of hip prosthesis bearing is preferable?

Is there a significant advantage of ceramic for the cup over cross-linked PE, with use of a ceramic head of the same size after (medium)long-term with outcome parameter cup-wear (linear or volumetric), osteolysis, prothesis survival?

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Beaupré, 2016	Type of study: RCT Setting: hospital Country: Canada Source of funding: Trial was supported by grant from Stryker Canada Inc for the first five years of follow-up, no funding was received for the last five years	Inclusion criteria: subjects undergoing total hip arthroplasty and <61 years recruited from 1998 to 2003 in a Canadian health region. Standard surgical technique a Hardinge or posterolateral approach, all subjects had noncemented femoral and acetabular fiaxtion Exclusion criteria: Prognostic factors (completed 10 y follow-up\): *Age ± SD: 53.2 ± 6.4* *Sex: 54%* Groups comparable at baseline? yes	Describe intervention (treatment/procedure/test): CERAMIC group received an arc-deposited hydroxylapatite (HA)-coated shell (Secure fit arc-deposited HA surface ceramic) and an aluminia-bearing couple ceramic insert and ceramic C-taper head Femoral stem Omnifit HA More likely to receive 32 mm femoral head N=48	Describe control (treatment/procedure/test): POLYETHYLENE group received secure fit shell, a crossfire insert, and a ceramic C-taper head Femoral stem Omnifit HA More likely to receive 28mm femoral head N=44	Length of follow-up: 10 years Loss-to-follow-up: Intervention: 5 Control: 1 Reasons (describe): 7% deceased Incomplete outcome data: 68 (79%) completed the HRQL and/or radiographic follow-up at 10 years; 44 (51%) completed both clinical and radiographic follow-ups, 11 (13%) completed only the clinical follow-up, and 13 (15%) completed only the radiographic follow-up	Outcome measures and effect size (include 95%CI and p-value if available): Complications: I: 3 injurious falls C: 4 dislocations, with 2 head/cup/liner revisions, another revision in year 5-10 due to recurrent instability	

Epinette, 2016	Type of study: registry study Setting: hospital Country: England and Wales Source of funding: unknown	Inclusion criteria: trident acetabular system variations between april 2003 and March 2013; primary hip arthroplasty; complete data about material and diameterof head and material and diameter of implanted liner; metal or alumina head featuring a 22.2 diameter or over; fixed nonconstrained liner, excluding both mobile bearings and constrained liners; either X3, N2vac, or AL liners, other types of HXLPE liners which were not sequentially irradiated and annealed were excluded (namely Crossfire liners), osteoarthritis as the only indication, HA-coated Trident as metallic shell N total at baseline: 45877 Important prognostic factors[2]: *Age ± SD:*	Describe intervention (treatment/procedure/test): HA coated trident shell, in osteoarthritis, with fixed-nonconstrained liners, and inserts belonging to either X3HXLPE, N2 Vac UHMPE or Alumina types	Describe control (treatment/procedure/test): See intervention group	Length of follow-up: 6 years Loss-to-follow-up: - Incomplete outcome data: -	Outcome measures and effect size (include 95%CI and p-value if available): Survival: Global X3: 98.6% Global CoC: 97.6% AL-S and X3: 99.0% AL-S and CoC: 97.8% AL-L and X3: 98.3% AL-L and CoC: 97.4% Bearing-related failures: Global X3: 99.8% Global CoC: 99.4% AL-S and X3: 99.9% AL-S and CoC: 99.4% AL-L and X3: 99.7% AL-L and CoC: 99.3% A first study demonstrated better survivorship with X3-HXLPE liners vs conventional ultrahigh molecular weight polyethylene. On the second parallel study, the cumulative survival rates were better for X3 liners as compared to CoC bearings. Moreover, when ranking the yearly cumulative	

		Alumina: 60.13 ± 11.3 *N2Vac UHMPE: 68.8 ± 9.2* *X3 HXLPE: 69.9 ± 9.7* *Sex:* *Not significantly different between groups* Groups comparable at baseline? yes				percent revision rates, again the best results were obtained with X3 liners with small alumina heads (cumulative revision rate at 0.298).	
Glyn-Jones, et al., 2014	Type of study: RCT Setting: Country: Source of funding:	Inclusion criteria: patients with hip osteoarthritis from routine inpatient waiting list between 2001 and 2002 Exclusion criteria: N total at baseline: N=54, 39 with complete follow-up Important prognostic factors[2]: *Age ± SD:* *I: 68 (52-76)* *C: 67 (51-76)* *Sex:* *I: 55% M* *C: 47% M* Groups comparable at baseline? yes	Describe intervention (treatment/procedure/test): Highly cross-linked polyethylene cemented, collarless, polished, tapered femoral component (CPT; Zimmer, Warsaw, IN, USA) with a 28-mm bearing surface and an uncemented acetabular component (Trilogy; Zimmer) were used. At the time of surgery with HXLPE liner (Longevity; Zimmer) N=27	Describe control (treatment/procedure/test): Conventional polyethylene cemented, collarless, polished, tapered femoral component (CPT; Zimmer, Warsaw, IN, USA) with a 28-mm bearing surface and an uncemented acetabular component (Trilogy; Zimmer) were used. At the time of surgery with a conventional UHMWPE acetabular liner (Zimmer) (N = 27)	Length of follow-up: 10 years Loss-to-follow-up: Intervention: N (%) 3 Reasons (describe) 1 deceased and 2 ill health Control: N (%) 4 Reasons (describe) 2 deceased and 2 ill health Incomplete outcome data: 8 patients had radiographs that were inadequate	Outcome measures and effect size (include 95%CI and p-value if available): Revision: There were no revision operations during the period of study At 10 years there was significantly less wear of HXLPE (0.003 mm/year; 95% confidence interval (CI), ± 0.010; SD 0.023; range, -0.057 to 0.074) compared with UHMWPE (0.030 mm/year; 95% CI, ± 0.012; p\0.001; SD 0.0.27; range, -0.001 to	

						0.164). The volumetric penetration from 1 to 10 years for the UHMWPE group was 98 mm3 (95% CI, ± 46 mm3; SD 102 mm3; range, -4 to 430 mm3) compared with 14 mm3 (95% CI, ± 40 mm3; SD 91 mm3; range, -189 to 242 mm3) for the HXLPE group (p = 0.01).	
Langlois, 2015	Type of study: RCT Setting: hospital Country: France Source of funding: unknown	Inclusion criteria: between July 2000 and July 2002 100 patients (100 hips) with primary or secondary osteoarthritis who needed THA were enrolled Exclusion criteria: - Important prognostic factors[2]: *For example* *age ± SD: 66.4 ± 12.9* *Sex: 41% M* Groups comparable at baseline? yes	Describe intervention (treatment/procedure/test): Highly XL all-PE acetabular component (Durasul, Centrepulse OrthopaedicsLtD) N=50	Describe control (treatment/procedure/test): Annealed contemporary component (Duration, Stryker-Howmedica, Herouville, Saint-Clare, France) N=50	Length of follow-up: minimum eight years Loss-to-follow-up: Intervention: 4 (died), Control: 7 (died), 2 (complications requiring early revision), N (%) Reasons (describe) Incomplete outcome data: unclear	Outcome measures and effect size (include 95%CI and p-value if available): Revision: C: 2 patients required revision, 1 due to deep surgical site infection and 1 due to recurrent dislocation Ostelolysis: No loosening or osteolysis was seen in relation to either component in any patient Wear:	

						I: femoral head penetration 0.012 mm/year (SD 0.684) C: 1.090 mm/year (SD 0.904) Steady state wear rate I: -0.0002 mm/year (SD 0.108) C: 0.1382 mm/year (SD 0.129	
Paxton, 2015	Type of study: registry study Country: USA Setting: hospital Source of funding: Kaiser Permanente orthopaedic surgeons who contribute to the TJRR and the Surgical Outcomes and Analysis Department, which coordinates Registry operations	<u>Inclusion criteria</u>: elective nonbilateral primary THAs, in which patients were at least 18 years old at the time of their procedure and had metal-on-conventional polyethylene or metal-on-HXLPE bearing surfaces registered between April 1, 2001, and December 31, 2011, were included in the sample Exclusion criteria: Revision procedures, bilateral (same-day) primary procedures, and conversion procedures <u>N total at baseline</u>: N= 26823 total hip arthroplasties	Describe intervention (treatment/procedure/test): metal-on-highly cross-linked polyethylene (all head sizes)	Describe control (treatment/procedure/test): metal-on-conventional polyethylene (head size of <32 mm)	<u>Length of follow-up</u>: metal-on-HXLPE: 2.9 years Duraloc cohort: 8.2 years Reflection cohort: 5.1 years <u>Loss-to-follow-up</u>: unclear <u>Incomplete outcome data</u>: unclear	Outcome measures and effect size (include 95%CI and p-value if available): <u>Revision:</u> Metal on conventional: 5.4% (95%CI 4.4%-6.7%) Metal on XLPE: 2.8% (95% CI 2.6%- 3.2%) Reasons (metal-on conventional): instability (49%), aseptic loosening (20%), infection (15%), other (22%) Reasons (metal-on-HXLPE): instability (40%), infection (25%), periprosthetic fracture (13%) and other (14%) Duraloc cohort:	

		Mean age: 70 *± 10* *Sex:* *40 % M*				Metal on conventional polyethylene: 8.3% (95% CI 5.8%-11%) Metal on HXLPE polyethylene: 2.6% (95% CI 1.7%-4.2%) Reasons (metal-onconventional polyethylene): instability (43%), aseptic loosening (27%), infection (20%), and other (33% each). Reasons (metal-on-HXLPE): instability (68%), aseptic loosening (14%), pain (14%), infection (9%), and periprosthetic fracture (9%). Reflection cohort: Metal on conventional polyethylene: 4.6% (3.2%-6.6%) Metal on HXLPE: 2.2% (95% CI 1.7%-2.7%) Reasons (metal on conventional polyethylene): instability (65%), other (26%), infection (13%), periprosthetic fracture (10%), and	

						aseptic loosening (10%). Reasons (metal-on-HXLPE group): instability (40%), infection (26%), other (17%), and periprosthetic fracture (12%).	
AOANJRR							

Notes:

1. **Prognostic balance between treatment groups is usually guaranteed in randomized studies, but non-randomized (observational) studies require matching of patients between treatment groups (case-control studies) or multivariate adjustment for prognostic factors (confounders) (cohort studies); the evidence table should contain sufficient details on these procedures.**
2. **Provide data per treatment group on the most important prognostic factors ((potential) confounders).**
3. **For case-control studies, provide sufficient detail on the procedure used to match cases and controls.**
4. **For cohort studies, provide sufficient detail on the (multivariate) analyses used to adjust for (potential) confounders.**

Table of quality assessment for systematic reviews of RCTs and observational studies

Based on AMSTAR checklist (Shea, 2007; BMC Methodol 7: 10; doi:10.1186/1471-2288-7-10) and PRISMA checklist (Moher, 2009; PLoS Med 6: e1000097; doi:10.1371/journal.pmed1000097)

Study First author, year	Appropriate and clearly focused question?[1] Yes/no/unclear	Comprehensive and systematic literature search?[2] Yes/no/unclear	Description of included and excluded studies?[3] Yes/no/unclear	Description of relevant characteristics of included studies?[4] Yes/no/unclear	Appropriate adjustment for potential confounders in observational studies?[5] Yes/no/unclear/notapplicable	Assessment of scientific quality of included studies?[6] Yes/no/unclear	Enough similarities between studies to make combining them reasonable?[7] Yes/no/unclear	Potential risk of publication bias taken into account?[8] Yes/no/unclear	Potential conflicts of interest reported?[9] Yes/no/unclear
Dong, 2015	Yes	Yes, not completely clear	Yes	Yes	Unclear	Yes	Yes	Yes, but not assessed with funnel plots	Yes
Hu, 2015a	Yes	Yes, not completely clear	Yes	Yes	No			Yes, assessed with funnel plots	Yes
Shen, 2014	Yes	Yes	Yes	Yes	Unclear	No	Yes	No	Yes
Si, 2015	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	No	Yes
Yin, 2015	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	No	Yes

1. **Research question (PICO) and inclusion criteria should be appropriate and predefined.**
2. **Search period and strategy should be described; at least Medline searched; for pharmacological questions at least Medline + EMBASE searched.**
3. **Potentially relevant studies that are excluded at final selection (after reading the full text) should be referenced with reasons.**
4. **Characteristics of individual studies relevant to research question (PICO), including potential confounders, should be reported.**
5. **Results should be adequately controlled for potential confounders by multivariate analysis (not applicable for RCTs).**
6. **Quality of individual studies should be assessed using a quality scoring tool or checklist (Jadad score, Newcastle-Ottawa scale, risk of bias table et cetera).**
7. **Clinical and statistical heterogeneity should be assessed; clinical: enough similarities in patient characteristics, intervention and definition of outcome measure to allow pooling? For pooled data: assessment of statistical heterogeneity using appropriate statistical tests (for example. Chi-square, I^2)?**
8. **An assessment of publication bias should include a combination of graphical aids (for example funnel plot, other available tests) and/or statistical tests (for example Egger regression test, Hedges-Olken). Note: If no test values or funnel plot included, score "no". Score "yes" if mentions that publication bias could not be assessed because there were fewer than 10 included studies.**
9. **Sources of support (including commercial co-authorship) should be reported in both the systematic review and the included studies. Note: To get a "yes," source of funding or support must be indicated for the systematic review AND for each of the included studies.**

Search strategy

Database	Search terms	Total
Medline (OVID) 21-10-2009 t/m 17 11-2016 English, Dutch	1 Arthroplasty, Replacement, Hip/ (22181) 2 Hip Prosthesis/ (21771) 3 1 or 2 (35693) 4 arthroplasty/ or arthroplasty, replacement/ (14653) 5 joint prosthesis/ or metal-on-metal joint prostheses/ (10914) 6 "Prostheses and Implants"/ (43550) 7 (arthroplast* or replacement* or prosthes#s).ti,ab,kf. (331021) 8 4 or 5 or 6 or 7 (368730) 9 hip/ or hip joint/ or hip.ti,ab. (128192) 10 8 and 9 (41706) 11 3 or 10 (50628) 12 (THA or THAs or THP).ti,ab,kf. (19349) 13 11 or 12 (64207) 27 exp Metals/ or exp Polyethylenes/ or exp Ceramics/ or (polyethylene* or metal* or metallic or alumin* or titani* or ceramic or ceramics or bearing* or "bearing surface" or "bearing material").ti,ab. (1506671) 28 26 and 27 (10) 29 13 and 27 (12196) 30 limit 29 to (yr="2010 -Current" and (dutch or english)) (4412) 31 limit 29 to ed=20091021-20101231 (627) 32 30 or 31 (4677) 33 limit 32 to (dutch or english) (4633) 34 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (323782) 35 33 and 34 (149) 36 (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (1754954) 37 33 and 36 (450) 39 ((cohort adj (study or studies)) or Cohort analy$ or (Follow up adj (study or studies)) or (observational adj (study or studies)) or Longitudinal or Retrospective* or prospective*).tw. (1378400) 40 (registry or registries).ti,ab. or registries/ (128842) 41 (wear or revision or survival).ti,ab. or "Prosthesis Failure"/ or (reoperat* or ((failed or failure) adj3 (prosthes* or arthroplast*))).ti,ab. (917023) 42 exp cohort studies/ (1713821) 43 32 and 42 (1243) 44 39 or 40 or 42 (2313892) 45 33 and 44 (1589) 46 (wear or revision or survival or survivor* or year* or long-term).ti. or *"Prosthesis Failure"/ or (reoperat* or ((failed or failure) adj3 (prosthes* or arthroplast*))).ti,ab. (666069) 47 45 and 46 (858) 48 45 not 47 (731) 49 35 or 37 or 47 (1239) 50 remove duplicates from 49 (1083) 51 remove duplicates from 35 (125) - SR 52 remove duplicates from 37 (385) – RCTs – 340 uniek 53 33 and 40 (202) 54 51 or 52 (465) 55 53 not 54 (170) 56 remove duplicates from 55 (150) – 141 uniek 57 54 or 56 (615) 58 47 not 57 (644) 59 remove duplicates from 58 (577) – Obs – 541 uniek 60 from 50 keep 1-125 (125) 61 from 55 keep 1-150 (150) – Reg.	1558
Embase (Elsevier)	'hip prosthesis':ti,ab OR 'total hip':ti,ab OR 'hip replacement':ti,ab OR 'total hip prosthesis'/exp/mj OR 'femur head prosthesis'/exp/mj OR 'hip arthroplasty'/exp/mj OR tha:ti,ab OR thas:ti,ab OR thp:ti,ab AND ('polyethylene'/exp OR 'metal'/exp OR 'alumina'/exp OR 'titanium'/exp OR 'ceramic'/exp OR 'ceramics'/exp OR bearings:ti,ab OR metal*:ti,ab OR alumina:ti,ab OR titanium:ti,ab OR ceramic:ti,ab OR ceramics:ti,ab) AND ((dutch)/lim OR (english)/lim) AND (21-10-2009)/sd NOT (17-11-2016)/sd NOT 'conference abstract':it	

	AND 'meta analysis'/de OR cochrane:ab OR embase:ab OR psycinfo:ab OR cinahl:ab OR medline:ab OR (systematic NEAR/1 (review OR overview)):ab,ti OR (meta NEAR/1 analy*):ab,ti OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de NOT ('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp NOT 'human'/exp) (101) – 38 uniek AND 'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti NOT 'conference abstract':it) (538) > 309 uniek AND ('survival'/exp/mj OR 'prosthesis loosening'/exp/mj OR 'prosthesis failure'/exp/mj OR 'reoperation'/exp/mj OR ((failed OR failure) NEAR/3 (prosthes* OR arthroplast*)):ti OR reoperat*:ti OR revision*:ti OR wear:ti OR survival:ti OR revision:ti) AND ('implant registry'/exp OR registry:ti,ab OR registries:ti,ab) (80) > 7 uniek AND 'major clinical study'/de (168) > 64 uniek	

Exclusion table

Table Exclusion after reading full text

Author and year	Reason for exclusion
Ayers, 2014	Radiostereometric analysis
Bjorgul, 2013	Metal-on -metal verus metal-on-conventional polyethylene or ceramic on polyethylene
Borgwardt, 2017	Not the right comparison
Callary 2015	Radiostereometric analysis on in vivo wear of XLPE
Carli, 2015	Corosion on head-neck interface
Clarke 2015	Economic evaluation
D 'Antonio, 2014	Cementless hip implants with a titanium alloy stem and alumina ceramic bearings (Trident; Stryker Orthopaedics; Mahwah, NJ, USA
Dahl, 2013	aim of this study was to investigate a possible difference in wear patterns between 2 different head materials (cobaltchrome and alumina) of the same size (28 mm) articulating on liners made of identical PE in the same type of acetabular shell.: 2 types of metal head compared → not one of the research questions
Desmarchelier, 2011	Metal on metal compared to ceramic on ceramic→ not one of the research questions
Dion, 2015	Review but not systematic
Furnes, 2014	Metal on metal compared to metal on polyethylene → metal on metal is no longer used
Hu, 2015b	Not the right comparison
Jassim, 2015	Oxidized zirconium versus cobalt chrome (two metals compared, not PICO)
Jonsson, 2015	Not the right comparisons
Joyce, 2015	Commentary
Karidakis, 2015	Not all patients were randomized
Lee, 2016	Metal on metal compared with ceramic on ceramic: metal-on-metal is no longer used, therefore study excluded
Lubbeke, 2014	Metal on metal compared with ceramic on polyethylene: metal-on-metal is no longer used, therefore study excluded
Marques, 2016	Only protocol
Mihalko, 2014	Lack of details
Morison, 2013	80 patients, 4 options: CoCr, oxinium, UHMWPE, XLPE, small groups
Nebergall, 2015	47 patients: small numbers
Nieuwenhuijse, 2014	Five selected innovations among which ceramic on ceramic bearings, but no comparison with another material
Salemyr, 2015	Follow-up only two years
Scemama, 2014	Follow-up only three years
Shareghi, 2015	Follow-up only two years
Traina, 2013	Not conform PICO focuses on fracture of ceramic bearing
Walker, 2016	Only case series included in this review of patients aged 30 years or less
Wyles, 2014	Review of studies with only two years follow-up
Zaoui, 2015	4 small subgroups: 25 patients in each of the four bearing couple combinations
Zywiel, 2011	Not the right comparisons

5

3.2 Head diameter

Research question
What is the preferred diameter of the head in total hip arthroplasty?

Uitgangsvraag
Wat is de optimale kopdiameter bij totale heupprothese?

Introduction
Since the last version of the Dutch guidance on primary total hip arthroplasty, more data have become available, especially from the registries, on the trends in head sizes used worldwide and there is more evidence about the most effective head size. However, head size cannot be seen independently from the coupling bearing used.

The most frequently used head sizes of hip prostheses are 28 and 32 mm. Larger and smaller head sizes are also used and especially in the last decade there is a trend towards the use of bigger heads. The hypothesis is that larger head sizes are associated with lower dislocation rates. We are especially interested in the effect of head size on the frequency of dislocation, on complications, on the risk of revision for instability and on the overall risk of revision.

There is strong advice against the use of large-head metal-on-metal articulations in the Netherlands (NOV, 2015) and the reported disappointing outcomes of these large-head metal-on-metal articulations in the European and Australian registries confirm the problems associated with these articulations. There are many unexpected findings in the metal-on-metal articulations leading to toxic metal ion loads in patients, causing general medical problems and local hip joint problems like pseudotumours and loosening. Therefore, studies using metal-on-metal prostheses are not included in this analysis.

To include the relatively new trend of using dual mobility cups in primary total hip arthroplasty to prevent dislocation, we have added a short comment on the growing use of these newer designs in the considerations section.

Search and select
To answer the question a systematic literature analysis was performed for the following research question:

P: patients planned for THA;
I: THA with head diameter of 22mm, 36mm or >36 mm;
C: THA with head diameter of 28 or 32 mm;
O: survival data after five and preferably ten years with regard to revisions for failure, reoperations and complications.

Relevant outcome measures

The working group decided that number of dislocations, head size related complications and number of revisions (both specifically for dislocation as well as for any reason) were critical outcome measures for decision-making.

The working group did not define outcomes a priori, but used definitions as provided in the studies.

Only studies with a minimum follow-up of five years after surgery - and preferably ten years or more - were included.

The working group tried to balance the data based on the number of patients available in the original papers and the statistical analysis provided in these documents.

The working group has taken into account that one of the most important outcome measurements, the rate of dislocation, is underreported. Most dislocations are treated conservatively and are not reported in registries. This is a severe methodological flaw and hence this limits the conclusions on this topic.

Search and select (Method)

A literature search was performed with relevant search terms on 17 november 2016 in the databases Medline (OVID) and Embase (via Embase.com). The search strategy is provided in the tab ”Methods”. The literature search resulted in 575 hits. Studies were selected using the following selection criteria: follow-up of at least 5 years, outcome reported as survival of the prosthesis, reoperations or complications. After obtaining full text, two studies were included in the literature analysis. In addition, data from registries were studied.

The most important study characteristics are described in evidence tables. The assessment of risk of bias is provided in risk of bias tables.

Literature summary

Description of studies

Two large studies based on registries were included in the literature analysis (Allepuz, 2014 and Sedrakyan, 2014). They both described data from the same six national and regional registries: Kaiser Permanente, HealthEast, the Emilia-Romagna region in Italy, the Catalan region in Spain, Norway, and Australia. However, the reviews focus on outcome of head size with different bearing types.

Allepuz (2014) studied the effect of femoral head size on the risk of revision when an HXLPE liner was used on a metal head. In this study, 14,372 total hip arthroplasties were included. Main outcome was risk of revision (for any reason). A possible bias of this study was that the included group of patients was limited in age (only patients between the age of 45 to 65 were included).

Sedrakyan (2014) compared femoral head sizes of >28mm and ≤28 mm for ceramic-on-ceramic articulations and compared ceramic-on-ceramic with metal-on-HXLPE articulations. A total of 34,985 patients were included. Main reported outcome was risk of revision (for any reason).

In addition, annual registry reports from Australia and the UK of 2016 were analysed and included, as both reports focussed on the influence of head size on the outcomes, with endpoints revision for dislocation or revision for any reason.

Results

Revision

In the study by Allepuz (2014), for highly-cross-linked-polyethylene liner on metal head implants, the risk of revision (for any reason) did not differ significantly between <32mm and 32-mm head sizes (HR (hazard ratio) = 0.91, 95% CI (confidence interval) = 0.69 to 1.19) or between >32-mm and 32-mm sizes (HR = 1.05, 95% CI = 0.70 to 1.55).

Sedrakyan found a lower risk of revision associated with use of ceramic-on-ceramic implants when a larger head size (>28mm) was used, compared to ≤28mm (HR (hazard ratio) = 0.73, 95% CI (confidence interval) = 0.60 to 0.88, p = 0.001). Use of ≤28mm head in ceramic-on-ceramic bearings was associated with a higher risk of failure compared with any head size metal-on- highly-cross-linked-polyethylene bearings (HR = 1.36, 95% CI = 1.09 to 1.68, p = 0.006). Use of >28mm head ceramic-on-ceramic bearings was associated with a small protective effect relative to any head size metal-on- highly-cross-linked-polyethylene bearings (not subdivided by head size) in years zero to two, but this difference dissipated over the longer term.

The Australian registry report 2016 (AOANJRR 2016) showed that risk of revision for any reason varied depending on head size. This was most evident for non-cross-linked-polyethylene (table HT29), where the rate of revision after 5 years was 8.7% (95% CI 5.6 to 13.2) for >32mm, compared to 3.7% (95% CI 3.2 to 3.6) for 32 mm, and 3.4% (95% CI 3.2 to 3.6) for <32mm. However, the number of patients in the >32mm group was small. After 10 years, the rate of revision was 5.9% (95% CI 5.0 to 6.9) for 32 mm and 6.5% (95% CI 6.2 to 6.8) for <32mm heads (no data for >32mm).

For highly cross-linked cross-linked-polyethylene, 32mm head size had the lowest rate of revision relative to both smaller and larger heads. There was no difference between head sizes smaller than 32mm and bigger than 32mm. The rate of revision after 5 years was 3.1% (95% CI 2.9 to 3.2) for >32mm, compared to 2.6% (95% CI 2.5 to 2.7) for 32 mm, and 2.9% (95% CI 2.8 to 3.1) for <32mm. After 10 years, the rate of revision was 4.4% (95% CI 4.0 to 4.8) for >32mm head, 3.8% (95% CI 3.6 to 4.1) for 32 mm and 4.4% (95% CI 4.1 to 4.6%) for <32mm heads.

For ceramic-on-ceramic articulations (AOANJRR 2016, table HT31), head size ≥32mm had a lower rate of revision compared to head sizes 28mm or less. There was no difference when head size 32 mm was compared to the 36-38mm head size group. Head sizes 40 mm or larger had a lower rate of revision compared to the other sizes, although marginally significant and depending on fixation type. After 5 years, the rate of revision for ≤28mm was 4.3% (95% CI 3.8 to 4.8), for 32mm 3.1% (95% CI 2.9 to 3.3), for 36-38mm 3.1% (95% CI 2.9 to 3.3), and for ≥40mm 2.4% (95% CI 2.0 to 3.0). After 10 years, the rate of revision for ≤28mm was 6.6% (95% CI 6.0 to 7.3), for 32mm 4.8% (95% CI 4.4 to 5.1) and for 36-38mm 5.0% (95% CI 4.5 to 5.5). There were no data for ≥40mm after 10 years.

The UK report 2016 of the National Joint Registry showed that for metal-on- polyethylene (unspecified) cemented monobloc cups, there was a statistically significant effect of head size (overall difference P<0.001 by logrank test) on revision rates. Up to five years, implants with a head diameter of 36mm had the worst failure rates compared to all smaller heads. At ten years, implants with a head diameter of 32mm were worse than those with head sizes of 22-25mm, 26mm and 28mm.

Revision rates for different head sizes for metal-on-polyethylene uncemented metal shell with polyethylene liners were also analysed. There was a statistically significant effect of head size (overall P<0.001), with head size 44mm showing worse failure rates, but there were small numbers after five years.

For ceramic-on-polyethylene cemented monobloc cups there was a statistically significant difference between the head sizes overall (P=0.002) and the largest head size 36mm showing worse failure rates.

For ceramic-on-polyethylene uncemented metal shells used with polyethylene liners, there was a statistically significant difference between the three head sizes (P=0.005), the best survival rate was in the intermediate size group (32mm) with 28mm and 36mm both showing similar worse outcomes.

For ceramic-on-ceramic uncemented metal shells used with ceramic liners head sizes 28mm, 32mm, and 36mm showed similar worse failure rates (P=0.01). Head size 40mm showed the best survival rate, though there were small numbers available.

Grading of evidence

Risk of revision

Risk of revision was reported in several registries, which are observational studies that are graded as low level of evidence. Results for highly cross-linked polyethylene were inconsistent.

Conclusions

Low GRADE	It is unclear whether head size has an effect on revision rate for hip prostheses consisting of a metal head on a HXLPE liner. Based on registry data in most cases a 32mm head on an HXLPE liner tends to be the safest option. *Sources (Allepuz, 2014; Australian registry, 2016; UK registry, 2016)*

Low GRADE	There was a lower risk of revision when a larger head was used using ceramic-on-ceramic. However the number of included patients with these implants is relatively limited. *Sources (Sedrakyan, 2014; Australian registry report, 2016; UK registry, 2016)*

Considerations

In the past, most total hip implants had a femoral head diameter of 22, 28 or 32mm. To overcome one of the major complications after a total hip prosthesis - dislocation - there has been a trend to larger heads of 36mm and more. However, this trend is not without disadvantages. Larger heads lead to more friction and more wear. In addition, especially in these larger head sizes the choice of the bearings seems to be more critical.

There is a strong trend in many registries to use 32mm heads. This trend is relatively safe, the dislocation tendency of a 32mm head is lower than a 22 or 28mm head and there is no evidence that it will result in higher overall revision rates. However, in some studies using heads larger than 32mm to prevent dislocation, less favourable results have been reported.

It is rather complicated to draw clear scientific conclusions as other factors also play a role, like patient selection, type of bearing and surgical approach. In addition, as already stated the rate of dislocations who have been treated conservatively are greatly underestimated in many studies due to the study design.

It is advisable to use 32mm heads in most patients. Smaller heads still may be indicated in cases with abnormal anatomy. If a larger head diameter than 32mm is indicated, it seems best to use a ceramic-on-ceramic prosthesis, although there is little scientific evidence to support that.

Dual mobility cups

In the last decade there is a new trend to use dual mobility cups in primary total hip arthroplasty to prevent dislocation, especially in patients with a higher risk of dislocation. These implants do not fit within the definitions used in this chapter to study the effect of head size on dislocation. However, since this type of implant is being used in the same patients, it is important to pay attention to these devices in this considerations paragraph.

In a literature analysis performed on 6 january 2018 four studies of interest were found. The largest study by Darrith (2018) was based on a literature review of 54 papers and the authors included 10,783 total hip arthroplasties who had a dual mobility cup, with a mean follow-up of 8.5 years (range 2 to 16.5). The mean rate of extra-articular dislocation was 0.46% (41 hips), which is lower than after routine single bearing THA. The overall rate of revision (any revision of the acetabular component or the dual mobility bearing) was 2.0% (178 hips). However, in the 2016 Report of the Australian Registry, dual mobility prostheses have a higher rate of revision compared to other acetabular prostheses at 5 years or more.

Dual mobility articulations are a viable alternative to traditional bearing surfaces in cases with a high risk for dislocation, however high-quality studies are needed to evaluate further the use of dual mobility components in THA.

Recommendation

Preferably use a 32mm head size by standard hip prothesis.

Aanbeveling

Gebruik bij voorkeur een 32 mm kop bij totale heupartroplastiek.

Literature

Allepuz A, Havelin L, Barber T, et al. Effect of Femoral Head Size on Metal-on-HXLPE Hip Arthroplasty Outcome in a Combined Analysis of Six National and Regional Registries. J Bone Joint Surg Am. 2014;96 Suppl 1(E):12-18. http://dx.doi.org/10.2106/JBJS.N.00461.

Australian Orthopaedic Association National Joint Replacement Registry. Annual Report. Adelaide: AOA; 2016.

Darrith B, Courtney PM, Della Valle CJ. Outcomes of dual mobility components in total hip arthroplasty: a systematic review of the literature. Bone Joint J. 2018;100-B(1):11-19. doi: 10.1302/0301-620X.100B1.BJJ-2017-0462.

National Joint Registry for England, Wales, Northern Ireland and the Isle of Man. 13th Annual Report. www.njrreports.org.uk. 2016.

Nederlandse Orthopaedische Vereniging. Advies Metaal-op-Metaal Heupprothesen per 1 augustus 2015.

Sedrakyan A, Graves S, Bordini B, et al. Comparative Effectiveness of Ceramic-on-Ceramic Implants in Stemmed Hip Replacement. A Multinational Study of Six National and Regional Registries. J Bone Joint Surg Am. 2014;96 Suppl1(E):34-41.http://dx.doi.org/10.2106/JBJS.N.00465

Validity and maintenance

5 In theory, assessment will take place after five years to determine whether this module is still up-to-date. Are there reasons to suspect a need for earlier revision? For example, large studies that still need to be published?

Module	Party in control	Year of authorization	Next assessment of actuality	Frequency of assessment actuality	Which party/parties monitors actuality	Important factors that might lead to change in recommendations
Head diameter	NOV	2018	2023	5 years	NOV	-

10

Knowledge gaps

What is the chance of dislocation by different head sizes after total hip replacement?

15 **Implementation plan**

Recommendation	Time needed for implementation: <1 year, 1 to 3 years or >3 years	Expected effects on costs	Conditions for implementation	Possible barriers to implementation[1]	Actions for implementation[2]	Reponsibility for these actions[3]	Other remarks
All	1 to 3 years	Reduction	No	Not used to work with this type of bearing	Annual quality audit	NOV	

Evidence tables

Evidence table for intervention studies (randomized controlled trials and non-randomized observational studies (cohort studies, case-control studies, case series))[1]

Research question: What is the preferred diameter of the head in total hip arthroplasty?

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Allepuz, 2014	Type of study: meta-analysis of six registries (cohort studies) Setting: distributed health data network ICOR (International consortium of Orthopaedic Registries), international collaborative of orthopaedic registries and US FDA Country: Italy, Spain, Norway and Australia Source of funding: unknown	Inclusion criteria: patients with osteoarthritis who underwent total hip arthroplasty without cement from 2001 to 2010 Exclusion criteria: age <45 or >64 N total at baseline: 14372	Describe intervention (treatment/procedure/test): Metal on HXLPE articulations involving various head sizes: <32, 32 and >32 mm	Describe control (treatment/procedure/test): Metal on HXLPE articulations with head size 32 mm	Length of follow-up: Maximum 8 years, results presented in one year intervals, main results presented after five years Loss-to-follow-up: Not described Incomplete outcome data: Not described	Outcome measures and effect size (include 95%CI and p-value if available): Five year rate of revision surgery varied from 1.9 to 3.2% A head size of <32 mm was not associated with an increased risk of revision compared with a size of 32 mm HR=0.91 95%CI (0.69 to 1.19) A head size of >32 mm was not associated with an increased risk of revision compared with 32 mm HR 1.05 95%CI (0.71 to 1.53)	

Sedrakyan, 2014	Type of study: registry Six national and regional registries (Kaiser Permanente and HealthEast in the U.S., Emilia-Romagna region in Italy, Catalan region in Spain, Norway, and Australia) Setting: hospital Source of funding: unknown	Inclusion criteria: total hip arthroplasty performed without cement from 2001 to 2010 in patients forty-five to sixty-four years of age with osteoarthritis. N total at baseline: Important prognostic factors[2]: *Age is described as percentage up to 54 and older for each region and per head size group* *Sex 48% male*	Describe intervention (treatment/procedure/test): >28 mm	Describe control (treatment/procedure/test): <=28	Length of follow-up: maximum ten years Loss-to-follow-up: average follow-up rate >90% Incomplete outcome data:	Outcome measures and effect size (include 95%CI and p-value if available): CC implants >28mm and <=28mm lower risk of C-C implant revision associated with use of larger compared with smaller head size (HR (hazard ratio) = 0.73, 95% CI (confidence interval) = 0.60 to 0.88, p = 0.001) <=28mm C-C implants and M-HXLPE any head size: Smaller C-C bearings were associated with a higher risk of failure compared with M-HXLPE bearings (HR = 1.36, 95% CI = 1.09 to 1.68, p = 0.006)	Loss to follow-up might occur if patients move to another region.

Notes:

1. **Prognostic balance between treatment groups is usually guaranteed in randomized studies, but non-randomized (observational) studies require matching of patients between treatment groups (case-control studies) or multivariate adjustment for prognostic factors (confounders) (cohort studies); the evidence table should contain sufficient details on these procedures.**
2. **Provide data per treatment group on the most important prognostic factors ((potential) confounders).**
3. **For case-control studies, provide sufficient detail on the procedure used to match cases and controls.**
4. **For cohort studies, provide sufficient detail on the (multivariate) analyses used to adjust for (potential) confounders.**

Search strategy

Database	Search terms	Total
Medline (OVID) 21-11-2009 t/m 17-11-2016 English, Dutch	1 Arthroplasty, Replacement, Hip/ (22160) 2 Hip Prosthesis/ (21757) 3 1 or 2 (35671) 4 arthroplasty/ or arthroplasty, replacement/ (14642) 5 joint prosthesis/ or metal-on-metal joint prostheses/ (10910) 6 "Prostheses and Implants"/ (43540) 7 (arthroplast* or replacement* or prosthes#s).ti,ab,kf. (326153) 8 4 or 5 or 6 or 7 (363848) 9 hip/ or hip joint/ or hip.ti,ab. (126327) 10 8 and 9 (41078) 11 3 or 10 (49999) 12 (THA or THAs or THP).ti,ab,kf. (18937) 13 11 or 12 (63353) 35 ((head* or ball* or femoral or femur) adj3 (diameter* or size* or large* or small*)).ti,ab. (13166) 36 (dual adj3 mobil*).ti,ab. (219) 37 35 or 36 (13348) 38 23 or 29 (12) 39 37 and 38 (12) 40 13 and 37 (1466) 41 35 and 40 (1353) 42 limit 40 to (english language and yr="2010 -Current") (814) 43 limit 40 to ed=20091021-20101231 (94) 44 42 or 43 (856) 45 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (314179) 46 44 and 45 (37) 47 (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (1727827) 48 42 and 47 (106) 49 case control studies/ or exp cohort studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or comparative studies.pt. (2412476) 50 ("research support, american recovery and reinvestment act" or research support, nih, extramural or research support, nih, intramural or research support, non us gov't or research support, us gov't, non phs or research support, us gov't, phs).pt. (9234423) 51 49 or 50 (10730879) 52 44 and 51 (483) 53 (registry or registries).ti,ab. or registries/ or review.pt. (2457424) 54 44 and 53 (138) 55 46 or 48 or 52 or 54 (591) 56 remove duplicates from 55 (516) 57 remove duplicates from 46 (25) - SRs 58 48 not 46 (93) 59 remove duplicates from 58 (80) - RCTs 60 46 or 58 (130) 61 52 or 54 (569) 62 61 not 60 (461) 63 remove duplicates from 62 (411) – Obs & Reg.	575
Embase (Elsevier)	'hip prosthesis':ti,ab OR 'total hip':ti,ab OR 'hip replacement':ti,ab OR 'total hip prosthesis'/exp/mj OR 'femur head prosthesis'/exp/mj OR 'hip arthroplasty'/exp/mj OR tha:ti,ab OR thas:ti,ab OR thp:ti,ab AND ('polyethylene'/exp OR 'metal'/exp OR 'alumina'/exp OR 'titanium'/exp OR 'ceramic'/exp OR 'ceramics'/exp OR bearings:ti,ab OR metal*:ti,ab OR alumina:ti,ab OR titanium:ti,ab OR ceramic:ti,ab OR ceramics:ti,ab) AND (21-10-2009)/sd NOT (17-11-2016)/sd NOT 'conference abstract':it AND (((head* OR ball* OR femoral OR femur) NEAR/3 (diameter* OR size* OR large* OR small*)):ti,ab OR (dual NEAR/3 mobil*):ti,ab) AND ((dutch)/lim OR (english)/lim) AND (embase)/lim AND ('meta analysis'/de OR cochrane:ab OR embase:ab OR psycinfo:ab OR cinahl:ab OR medline:ab OR (systematic NEAR/1 (review OR overview)):ab,ti OR (meta NEAR/1	

	analy*):ab,ti OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de) NOT ('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp NOT 'human'/exp) AND ('clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti) NOT 'conference abstract':it) AND 'major clinical study'/de) OR ((registry:ti,ab OR registries:ti,ab OR 'implant registry'/exp))	

Exclusion table

Table Exclusion after reading full text

Author and year	Reason
Cafri, 2016	Main outcome was revision after one year
Garbuz, 2012	Follow-up 2 years
Howie, 2012	Follow-up only one year
Jorgensen, 2014	Follow-up only 90 days
Lachiewitz, 2015	Retrospective study of only 23 patients included with follow-up of 10 years
Lee, 2014	Prospective cohort study of 120 patients
Lindalen, 2014	Follow-up only 2 years, 50 patients, wear main outcome
Mokka, 2013	Metal on metal
Nebergall, 2015	Only 12 patients with 13 year follow-up
Prokopetz, 2012	Review that described a few studies looking into head diameter, lacks detail about follow-up and outcomes assessed
Selvarajah, 2015	Prospective cohort study
Triantafyllopoulos, 2015	Outcome fretting and corosion
Tsertsvadze, 2014	Review that described one study looking into head diameter, lacks detail about follow-up and outcomes assessed
Zagra, 2013	Outcome gait pattern
Zijlstra, 2011	Follow-up 1 year, only 50 patients

5

3.3 Surgical approach

Research question
Which approach for total hip arthroplasty is preferable: anterior, posterior or straight lateral?

Uitgangsvraag
Welke benadering geniet de voorkeur bij totale heupprothese: anterieur, posterieur of lateraal?

Introduction
Traditionally total hip arthroplasties (THA's) are placed through the posterior, anterolateral (anterior) or the straight lateral approach. In the past decade the anterior approach has gained in popularity. In this chapter, the three most commonly used approaches in The Netherlands - the posterior, anterior and straight lateral approach - are compared in terms of complications, need for revision and functional recovery.

Search and select
To answer the question a systematic literature analysis was done for the following research question:

PICO 1
P: adult patient with total hip prosthesis;
I: posterior approach;
C: lateral approach;
O: complications, need for revision and functional recovery.

PICO 2
P: adult patient with total hip prosthesis;
I: anterior approach;
C: posterior or lateral approach;
O: complications, need for revision and functional recovery.

Relevant outcome measures
The working group decided that complications such as dislocation and need for revision were critical outcome measures for decision-making and postoperative functional recovery was important for decision-making.

Search and select (Method)
A literature search was performed with relevant search terms on 23 january 2017 in the databases Medline (OVID) and Embase. The search strategy is provided in the tab "Methods". The literature search resulted in 632 hits. Studies were selected using the following selection criteria: using an anterior, posterior or lateral approach for total hip arthroplasty, describing at least one of the selected outcome measures and including at least 50 patients. Based on title and abstract 33 studies were preselected. After obtaining full text, 25 studies were excluded (see exclusion table) and eight studies were included in the literature analysis.

The most important study characteristics are described in evidence tables. The assessment of risk of bias is provided in risk of bias tables.

Literature summary

Lateral versus posterior approach

Description of studies

Two studies were included: one meta-analysis including three RCTs and three prospective cohort studies (Berstock, 2015) and two cohort studies (Amlie, 2014; Mjaaland, 2017).

Berstock (2015) included three RCTs and three prospective cohort studies (517 patients) in a systematic review and meta-analysis that compared the posterior and lateral surgical approach. Primary outcome was dislocation; functional recovery was also reported by using functional assessment scores.

In a cohort study (Amlie, 2014) 1,273 patients filled out PROMs questionnaires one to three years after total hip arthroplasty surgery. These patients were identified through the Norwegian Arthroplasty Register. Patients reported complications (such as dislocation) and patient-reported outcome measures (PROMs) including the Hip disability Osteoarthritis Outcome Score (HOOS), the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), health-related quality of life (EQ-5D-3L) and visual analogue scales (VAS) addressing pain and satisfaction.

Mjaaland (2017) is a cohort study from the Norwegian arthroplasty register with 21,690 total hip arthroplasties. MIS anterior, MIS anterolateral, posterior and direct lateral approach were compared. Outcomes reported were implant survival, and revision for any cause and specifically for infection, dislocation, femoral fracture, aseptic loosening and other causes.

Results

Dislocation

The meta-analysis (Berstock, 2015) showed that there was no difference in dislocation (OR: 0.37 (95%CI (0.09 to 1.48)), p=0.16) between the posterior approach and the lateral approach.

In the cohort study by Amlie (2014), the patient self-reported dislocation rate was 3.7% for the lateral approach and 2.4% for posterolateral approach, which was not statistically significant.

Mjaaland (2017) reported a relative risk of revision due to dislocation using the posterior approach of 2.1 (95% CI = 1.5 to 3.1, p <0.001) compared to the direct lateral approach.

Functional outcome

Berstock (2015) does not report individual study results and there were not enough data to enable a meta-analysis for functional outcomes.

In the cohort study (Amlie, 2014) patients filled out PROMs questionnaires one to three years after surgery. Lateral approach had worse HOOS scores for pain (adjusted mean difference -3.6 (-6.3 to -0.9)), other symptoms (-3.2 (-6.1 to -0.4)), activities of daily living

(ADL) (-4.0 (-6.8 to -1.3)), sport/recreation (-4.6 (-8.6 to -0.6)) and quality of life (-3.7 (-7.2 to -0.3)). The lateral approach was associated with statistically significantly worse outcomes than the posterolateral approach on the VAS-scales for both patient satisfaction (adjusted mean difference -4.8 (-8.4;-1.2)) and pain in the operated hip (adjusted mean difference -4.8 (-7.8; -1.7)).

Grading of evidence

Dislocation

Results of the different studies were inconsistent and mainly based on cohort studies, therefore the level of evidence was graded as low.

Functional outcome

This was assessed in a cohort study and graded as very low.

Lateral versus posterior

Conclusions

Dislocation

Low GRADE	It is unclear whether a lateral or posterior approach results in a higher risk of dislocation. *Sources (Berstock, 2015; Amlie, 2014, Mjaaland, 2017)*

Functional outcomes

HOOS-scores

Very low GRADE	Functional outcome (as measured with HOOS) is better for posterior than for lateral approach. *Sources (Amlie, 2014)*

VAS pain

Very low GRADE	The lateral approach results in more pain than the posterior approach. *Sources (Amlie, 2014)*

VAS satisfaction

Very low GRADE	The lateral approach results in less satisfaction than the posterior approach. *Sources (Amlie, 2014)*

Anterior versus posterior

Description of studies

A systematic review of 17 comparative studies (Higgins, 2015) was selected, together with one RCT (Christensen, 2014) and one retrospective study (Maratt, 2016).

Higgins (2015) included 17 studies that compared the anterior with the posterior approach (two RCTs, five prospective comparative studies and ten retrospective

comparative studies). Reported outcomes were dislocation rate and validated patient-reported outcome measures (pain, functioning); secondary outcomes were intra-operative, post-operative and radiographic comparisons. Follow-up ranged from direct postoperative to 2 years.

Christensen (2015) conducted an RCT in 51 patients that compared functional recovery during the early postoperative period (6 weeks) after direct anterior and posterior approaches. Outcomes measured were length of hospital stay, pain score and functional recovery.

Maratt (2016) retrospectively compared the direct anterior approach for a total hip arthroplasty with a posterior approach. In total 2147 patients who underwent the direct anterior approach were propensity score matched with 2147 patients who underwent a posterior approach. Outcomes measured were dislocation rate and complications such as fractures and hematomas within 90 days.

Mjaaland (2017) is a cohort study from the Norwegian arthroplasty register with 21,690 total hip arthroplasties. MIS anterior, MIS anterolateral, posterior and direct lateral approach were compared. Outcomes reported were implant survival, revisions for any cause and specifically for infection, dislocation, femoral fracture, aseptic loosening and other causes.

Results

Dislocation rate

Maratt showed no difference in dislocation rate, which was 0.84% for the anterior approach versus 0.79% for the posterior approach (P=0.88).

Higgins (2015) estimated the Peto odds ratio and showed a pooled (fixed) effect of 0.29 (95% CI (0.09-0.95)) favouring the anterior approach. In this analysis 728 patients (2 dislocations) who underwent an anterior approach were compared with 745 patients (9 dislocations) who were operated using the posterior approach.

Mjaaland (2017) does not report a direct comparison between anterior versus posterior approach, but reports relative risks of MIS anterior/anterolateral and posterior approach compared to direct lateral. The relative risk of revision due to dislocation (154 patients) using the posterior approach was 2.1 (95% CI = 1.5 to 3.1, p<0.001) compared to the direct lateral approach. The RR for the MIS anterior and MIS anterolateral approaches compared with the direct lateral approach was 0.71 (95% CI = 0.40 to 1.3, p = 0.25) (Mjaaland, 2017).

Functional recovery

Higgins: one RCT included in the systematics review of Higgins reported patient-reported pain (VAS) and function (HHS and HOOS). Early functional results favoured the anterior approach, there was no difference on the longer term. There was no difference in pain between the two approaches. The other prospective and retrospective studies in Higgins' review showed little or no difference in functional outcome.

Christensen (RCT, 2015): Pain relief after surgery was greater in the anterior group (P=0.04), none of the other functional measures differed between the two groups. There

were no differences in Harris Hip Scores after six weeks.

LOS

Higgins: Length of hospital stay was shorter in the anterior group compared to the posterior approach (mean difference -0.53, 95%CI -1.01;-0.04).

The RCT of Christensen, 2014 showed that length of hospital stay was significantly shorter for the anterior approach than the posterior approach (1.4 versus 2.0 days, p=0.01).

Another retrospective study (Maratt, 2016) did not find a difference in length of hospital stay between the anterior and the posterior approach (2.37 versus 2.54 days, P=0.28).

Grading of evidence

Dislocation rate

Evidence of the systematic review was graded as low due to high risk of bias, for the outcome length of hospital stay it was graded as very low because of high heterogeneity. The RCT had a high risk of bias and was graded as low. The retrospective study was graded as very low. The level of evidence of the cohort study was graded as low.

Functional recovery

This was estimated based on one RCT and two cohort studies with a high risk of bias and a retrospective analysis and graded as very low, because of inconsistency.

Conclusions

Dislocation

Very low GRADE	There were more postoperative dislocations in patients operated using the posterior than the anterior approach. *Sources (Higgins, 2015; Mjaaland, 2017; Maratt, 2016)*

Functional recovery

Low GRADE	There was no difference in functional recovery measured by unlimited walking and Harris Hip Score between the anterior and posterior approach. *Sources (Higgins, 2015; Christensen, 2015)*

Length of hospital stay

Low GRADE	Length of hospital stay was shorter for anterior approach than for posterior approach *Sources (Higgins, 2015; Christensen, 2014, Maratt, 2016)*

Anterior versus lateral

Description of studies

Three studies compared the anterior with lateral approach (Amlie, 2014; De Anta Diaz, 2015, Mjaaland, 2017).

In a cohort study (Amlie, 2014) 1273 patients filled out PROMs questionnaires one to three years after total hip arthroplasty surgery. These patients were identified through the Norwegian Arthroplasty Register. Patients reported complications such as dislocation, and patient-reported outcome measures (PROMs) including the Hip disability Osteoarthritis Outcome Score (HOOS), the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), health-related quality of life (EQ-5D-3L), and visual analog scales (VAS) addressing pain and satisfaction.

De Anta Diaz (2015) was an RCT study of 49 patients who received a direct anterior total hip arthroplasty and 50 patients who received a lateral approach total hip arthroplasty. Outcomes reported were muscle damage and functional recovery.

Mjaaland (2017) is a cohort study from a registry with 21,690 total hip arthroplasties. MIS anterior, MIS anterolateral, posterior and direct lateral approach were compared. Outcomes reported were implant survival, revisions for any cause and femoral fractures.

Results

Dislocation

Self-reported dislocation was 3.7% for lateral approach and 3.1% for anterior approach; this difference was not statistically significant (Amlie, 2014). Mjaaland found no difference in dislocation, the RR of revision due to dislocation using the anterior/anterolateral approach compared to the direct lateral approach was 0.71 95% CI (0.40 to 1.30), p=0.25).

Functional recovery

The cohort study (Amlie, 2014) had the following results. Lateral approach scored worse on HOOS scores for pain (adjusted mean difference -3.6 (-6.1 to -1.1)), other symptoms (-3.8 (-6.5 to -1.1)), ADL (-4.8 (-7.3 to -2.2)), sport/recreation (-4.8 (-8.6 to -1.0)) and quality of life (-5.0 (-8.3 to -1.8)). The lateral approach was associated with statistically significantly worse outcomes than the anterior approach on the VAS scales for both patient satisfaction (adjusted mean difference -3.8 (-7.2; -0.4) and pain in the operated hip (adjusted mean difference -3.9 (-6.9; -1.1)).

One RCT compared the anterior with the lateral approach. It showed no difference in Harris Hip Scores (96.2 versus 94.5) (De Anta Diaz, 2015).

Grading of evidence

Dislocation

Evidence was graded as very low as there were two cohort studies used here that had heterogeneous results.

Functional recovery

Evidence was graded as very low as these results were mainly based on a cohort study.

Conclusions

Dislocation

Very low GRADE	There is no difference in risk of revision due to dislocation between a lateral approach and an anterior approach. *Sources (Amlie, 2014; Mjaaland, 2017)*

Functional recovery

Very low GRADE	Functional recovery showed inconsistent results comparing the lateral approach and the anterior approach. *Sources (Amlie, 2014; DeAntaDiaz, 2015)*

Considerations

The differences between the three most frequently used hip approaches in The Netherlands are small in current literature. Each of the approaches has their own set of complications and benefits.

Learning curves exist for all approaches and therefore proper surgical training is warranted.

If surgeons choose the posterior approach, they should reconstruct the posterior capsule and the external rotators. This has been shown to decrease the risk of dislocation.

Recommendation

The working group has no preference for one of the three surgical approaches.

Aanbeveling

De werkgroep kan geen voorkeur voor één van de drie chirurgische benaderingswijzen aangeven.

Literature

Amlie E, Havelin LI, Furnes O, et al. Worse patient-reported outcome after lateral approach than after anterior and posterolateral approach in primary hip arthroplasty. A cross-sectional questionnaire study of 1,476 patients 1 to 3 years after surgery. Acta Orthop. 2014;85(5):463-9. PubMed PMID: 24954494.

Berstock JR, Blom AW, Beswick AD. A systematic review and meta-analysis of complications following the posterior and lateral surgical approaches to total hip arthroplasty. Ann R Coll Surg Engl. 2015;97(1):11-6. PubMed PMID: 25519259.

Christensen CP, Jacobs CA. Comparison of Patient Function during the First Six Weeks after Direct Anterior or Posterior Total Hip Arthroplasty (THA): A Randomized Study. J Arthroplasty. 2015;30(9 Suppl):94-7.

De Anta Diaz B, Serralta-Gomis J, Lizaur-Utrilla A, et al. No differences between direct anterior and lateral approach for primary total hip arthroplasty related to muscle damage or functional outcome. International Orthopaedics. 2016;40:2025-2030.

Higgins BT, Barlow DR, Heagerty NE, et al. Anterior versus posterior approach for total hip arthroplasty, a systematic review and meta-analysis. J Arthroplasty. 2015;30(3):419-34. PubMed PMID: 25453632.

Maratt JD, Gagnier JJ, Butler PD, et al. No Difference in Dislocation Seen in Anterior versus Posterior Approach Total Hip Arthroplasty. J Arthroplasty. 2016;31(9 Suppl):127-30. PubMed PMID: 27067754.

Mjaaland KE, Svenningsen S, Fenstad AM, et al. Implant Survival After Minimally Invasive Anterior or Anterolateral Versus Conventional Posterior or Direct Lateral Approach: An Analysis of 21,860 Total Hip Arthroplasties from the Norwegian Arthroplasty Register (2008 to 2013). J Bone Joint Surg Am. 2017;99(10):840-847.

Validity and maintenance

In theory, assessment will take place after five years to determine whether this module is still up-to-date. Are there reasons to suspect a need for earlier revision? For example, large studies that still need to be published?

Module	Party in control	Year of authorization	Next assessment of actuality	Frequency of assessment actuality	Which party/parties monitors actuality	Important factors that might lead to change in recommendations
Surgical approach	NOV	2018	2023	5 years	NOV	-

Knowledge gaps

Which approach for total hip arthroplasty is preferable based on patient characteristics?
Which approach for total hip arthroplasty leads to the best functional outcomes?

Indicator

Not applicable

Implementation plan

Recommendation	Time needed for implementation: <1 year, 1 to 3 years or >3 years	Expected effects on costs	Conditions for implementation	Possible barriers to implementation[1]	Actions for implementation[2]	Reponsibility for these actions[3]	Other remarks
All	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.

Evidence tables

Research question: Which chirurgical approach is preferred?

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Berstock, 2015 PS., study characteristics and results are extracted from the SR (unless stated otherwise)	SR and meta-analysis of 3 RCTs and 3 non-randomised prospective cohort studies *Literature search up to January 2014* **A**: Weale, 1996 **B**: Baker, 1989 **C**: Downing, 2001 **D**: Witzleb, 2009 **E**: Teratani, 2010 **F**: Ji, 2012 <u>Setting and Country</u>: <u>Source of funding:</u> (commercial / non-commercial / industrial co-authorship)	Inclusion criteria SR: adult participants (>19 years old) undergoing primary total hip arthroplasty, largely for the treatment of osteoarthritis, who were either operated on via the direct lateral or the posterior approach Exclusion criteria SR: minimally invasive surgery, the anterolateral (Watson-Jones) approach or an approach utilising a trochanteric osteotomy, surgical approach in the setting of hip fracture, infection, revision surgery or resurfacing arthroplasty, retrospective studies and cohorts *XX studies included*	Posterior approach:	Lateral approach: direct lateral approach was defined as an approach requiring a release of approximately one-third of the gluteus medius from the trochanter but not the use of an osteotomy.	<u>End-point of follow-up</u>: Unclear <u>For how many participants were no complete outcome data available?</u> Evaluated in quality assessment, in one of five studies not OK	<u>Dislocation</u>: I: 2 (1%) C: 6 (3%) OR: 0.37, 95% CI: 0.09–1.48, p=0.16 <u>Heterotopic ossification:</u> I: 4 C: 9 Peto OR: 0.41, 95% CI: 0.13–1.31, p=0.13 <u>Stem malposition</u> Two studies observed fewer stem malpositions with the posterior approach (Peto OR: 0.24, 95% CI: 0.08–0.78, p=0.02). <u>Functional assessment scores:</u> not enough studies	

		<u>Important patient characteristics at baseline</u>: *Number of patients; characteristics important to the research question and/or for statistical adjustment (confounding in cohort studies); for example, age, sex, bmi, ...* <u>N, mean age</u> **A**: XX patients, XX yrs **B**: **C**: **….** <u>*Sex:*</u> **A**: % Male **B**: **C**: **….** Groups comparable at baseline?					
Higgins, 2015 (individual study characteristics	SR and meta-analysis of 17 comparative studies	Inclusion criteria SR: patients underwent primary THA, one group received anterior THA and the other posterior THA, at least one	Describe intervention: single incision anterior THA	Describe control: Single incision posterior THA	<u>End-point of follow-up</u>: unclear <u>For how many participants were no</u>	<u>Rapportage op basis van prioritering uitkomstmaten</u> <u>blood loss, intraoperative fractures, length of</u>	<u>Facultative</u>: Brief description of author's conclusion Personal remarks on study quality,

deduced from (1st author, year of publication)) PS., study characteristics and results are extracted from the SR (unless stated otherwise)	*Literature search up to February 2014* For details of these studies see publication Country: USA Source of funding: No external funds were received	quantifiable pre-specified outcome was reported Exclusion criteria SR: - *17 studies included* Important patient characteristics at baseline: *Number of patients; characteristics important to the research question and/or for statistical adjustment (confounding in cohort studies); for example, age, sex, bmi, ...* N, mean age **A**: XX patients, XX yrs **B**: **C**: **….** *Sex:* **A**: % Male **B**: **C**: **….**			complete outcome data available? (intervention/control) **A:** **B**: **C**: **D**: **E**: **F**: **G**: **H**: **I**: ….	hospital stay, postoperative dislocation Estimated blood loss Effect measure: mean difference (95% CI): **A**: N=378 **B**: N=381 Pooled effect (random effects model): 76.02 (95% CI -38.12 to 190.16) favoring posterior Heterogeneity (I^2): 91% Intraoperative fractures Effect measure: Peto odds ratio (95% CI): **A**: N=9/675 **B**: N=8/686 Pooled effect (random effects model): 1.14 (95% CI 0.44 to 2.96) favoring none Heterogeneity (I^2): 0% Length of hospital stay Effect measure: Mean difference (95% CI): **A**: N=369 **B**: N=375 Pooled effect (random effects model): -0.53 (95% CI -1.01 to 0.04) favoring anterior Heterogeneity (I^2): 84%	conclusions, and other issues (potentially) relevant to the research question Level of evidence: GRADE (per comparison and outcome measure) including reasons for down/upgrading Sensitivity analyses (excluding small studies; excluding studies with short follow-up; excluding low quality studies; relevant subgroup-analyses); mention only analyses which are of potential importance to the research question Heterogeneity: clinical and statistical heterogeneity; explained versus unexplained (subgroupanalysis)

		Groups comparable at baseline?				<u>Postoperative dislocation</u> Effect measure: Peto odds ratio (95% CI): **A**: N=2/728 **B**: N=9/745 Pooled effect (fixed effects model): 0.29 (95% CI 0.09 to 0.95) favoring anterior Heterogeneity (I^2): 0%	

Table of quality assessment for systematic reviews of RCTs and observational studies

Based on AMSTAR checklist (Shea, 2007; BMC Methodol 7: 10; doi:10.1186/1471-2288-7-10) and PRISMA checklist (Moher, 2009; PLoS Med 6: e1000097; doi:10.1371/journal.pmed1000097)

Study First author, year	Appropriate and clearly focused question?[1] Yes/no/unclear	Comprehensive and systematic literature search?[2] Yes/no/unclear	Description of included and excluded studies?[3] Yes/no/unclear	Description of relevant characteristics of included studies?[4] Yes/no/unclear	Appropriate adjustment for potential confounders in observational studies?[5] Yes/no/unclear/notapplicable	Assessment of scientific quality of included studies?[6] Yes/no/unclear	Enough similarities between studies to make combining them reasonable?[7] Yes/no/unclear	Potential risk of publication bias taken into account?[8] Yes/no/unclear	Potential conflicts of interest reported?[9] Yes/no/unclear
Berstock et al., 2015	Yes	Yes	Yes	Unclear	Unclear	Yes	Unclear	Yes	Yes
Higgins, 2015	Yes	Yes	Yes	Yes	Unclear	Yes	Unclear	No	

1. **Research question (PICO) and inclusion criteria should be appropriate and predefined.**
2. **Search period and strategy should be described; at least Medline searched; for pharmacological questions at least Medline + EMBASE searched.**
3. **Potentially relevant studies that are excluded at final selection (after reading the full text) should be referenced with reasons.**
4. **Characteristics of individual studies relevant to research question (PICO), including potential confounders, should be reported.**
5. **Results should be adequately controlled for potential confounders by multivariate analysis (not applicable for RCTs).**
6. **Quality of individual studies should be assessed using a quality scoring tool or checklist (Jadad score, Newcastle-Ottawa scale, risk of bias table et cetera).**
7. **Clinical and statistical heterogeneity should be assessed; clinical: enough similarities in patient characteristics, intervention and definition of outcome measure to allow pooling? For pooled data: assessment of statistical heterogeneity using appropriate statistical tests (for example Chi-square, I^2)?**
8. **An assessment of publication bias should include a combination of graphical aids (for example funnel plot, other available tests) and/or statistical tests (for example Egger regression test, Hedges-Olken). Note: If no test values or funnel plot included, score "no". Score "yes" if mentions that publication bias could not be assessed because there were fewer than 10 included studies.**
9. **Sources of support (including commercial co-authorship) should be reported in both the systematic review and the included studies. Note: To get a "yes," source of funding or support must be indicated for the systematic review AND for each of the included studies.**

Evidence table for intervention studies

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Amlie, 2014	Type of study: cohort from a registry Setting: hospital Country: Norway Source of funding: unknown	Inclusion criteria: Patients registered in the NAR (population-based clinical database for arthroplasty operations) as having undergone THA for primary osteoarthritis between Jan 2008 and Jan 2010, femoral head size 28-32mm, 50-80y Exclusion criteria: registered before 2011 with bilateral THA or trochanteric osteotomy N total at baseline: A: 421 L: 431 P: 421 Important prognostic factors[2]: *age ± SD:* *A: 67 ± 7.1* *L: 66 ± 7.3* *P: 66 ± 7.1* *Sex:* *A: 31 % M* *L: 36 % M* *P: 36 % M* Groups comparable at baseline? In P group the average femoral head diameter	Describe intervention (treatment/procedure/test): Anterior approach (A) Posterolateral approach (P)	Describe control (treatment/procedure/test): Lateral Approach (L)	Length of follow-up: 24-33 months (1-3 years) Response rate to follow-up questionnaire 86% Incomplete outcome data: 170 patients did not answer after a reminder and 25 did not want to or were unable to participate, 6 patients were not reached and 2 had died Of those who underwent THA with a lateral approach, the non-responders were generally older (mean 69 years, SD 7.1) than the study participants (mean 66 years, SD 7.3; p = 0.001).	Outcome measures and effect size (include 95%CI and p-value if available): HOOS (adjusted mean difference): L vs A: Pain: -3.6 (-6.1 to -1.1) Other symptoms: -3.8 (-6.5 to –1.1) ADL: -4.8 (-7.3 to -2.2) Sport/recreation: -4.8 (-8.6 to -1.0) Quality of life: -5.0 (-8.3 to -1.8) L vs P: Pain: -3.6 (-6.3 to -0.9) Other symptoms: -3.2 (-6.1 to -0.4) ADL: -4.0 (-6.8 to -1.3) Sport/recreation: -4.6 (-8.6 to -0.6) Quality of life: -3.7 (-7.2 to -0.3) VAS Absence of Pain Score: L: 84 A: 89 P: 90	Average femoral head diameter was greater in patients who underwent THA with the posterolateral approach than in those who underwent THA with anterior and lateral approaches. In posterolateral patients, the proportion of those with 32-mm head size increased from 45% to 72% during the study period. The groups also differed regarding follow-up time, with the anterior

		was greater than in the other groups				L vs A (adjusted mean difference): -3.9 (-6.9; -1.1) L vs P (adjusted mean difference): -4.8 (-7.8; -1.7) <u>Dislocation</u> L: 16 (3.7%) A: 13 (3.1) P: 10 (2.4%)	approach having a shorter mean followup time than the other 2 approaches.
Christensen, 2014	Type of study: RCT Setting: hospital Country: USA Source of funding: unknown	<u>Inclusion criteria</u>: <u>Exclusion criteria</u>: <18 or >85 y, diagnosed with inflammatory or rheumatoid arthritis, BMI>40, or previously undergone ipsilateral hip surgery including arthroscopy, if patients had characteristics that led the surgeon to believe that the patient would clearly benefit from one particular technique over the other <u>N total at baseline</u>: Intervention: 28 Control: 23 <u>Important prognostic factors[2]</u>: *For example* *age ± SD:* *I: 64.3 ± 9.1* *C: 65.2 ± 9.1* *Sex:* *I: 52% M, C: 48% M*	Describe intervention (treatment/procedure/test): Direct anterior (A) N=28	Describe control (treatment/procedure/test): Posterior (P) N=23	<u>Length of follow-up</u>: 6 weeks <u>Loss-to-follow-up</u>: Intervention: 3 patients did not receive allocated intervention because of medical reasons Control: 1 patient chose not to participate in the study prior to having surgery.	Outcome measures and effect size (include 95%CI and p-value if available): <u>Length of hospital stay:</u> A: 1.4 ± 0.6 days P: 2.0 ± 1.1 days <u>Unlimited walking:</u> A: 4 (14%) P: 5 (22%) <u>Pain (increase in score)</u> A: 27.8 ± 16.6 P: 20.7 (+/- 14.8) <u>Harris hip score</u> A: 42: P: 32	Follow-up is only 6 weeks!

De Anta Diaz, 2015	Type of study: RCT Setting: hospital Country: Spain Source of funding: unknown	Inclusion criteria: >=55 y, diagnosis of primary osteoarthritis, asymptomatic opposite hip Exclusion criteria: prior hip surgery, arthroplasty to treat a fracture, inflammatory arthroplasties, autoimmune disease, immunosuppressive treatment, cancer N total at baseline: Intervention: 49 Control: 50 Important prognostic factors[2]: I: 63.5 ± 12.5 C: 64.8 ± 10.1 Sex: I: 53 % M C: 52 % M Groups comparable at baseline? Yes	Describe intervention (treatment/procedure/test): Direct anterior approach (A)	Describe control (treatment/procedure/test): Lateral approach (L)	Length of follow-up: 12 months Loss-to-follow-up: Intervention: 2 Intraoperative wound infection Control: 1 intra-operative trochanteric fracture Incomplete outcome data: Intervention: N (%) Reasons (describe) Control: N (%) Reasons (describe)	Outcome measures and effect size (include 95%CI and p-value if available): Harris Hip Score: A: 96.2 L: 94.5	
Maratt, 2016	Type of study: retrospective analysis in a registry Setting: hospital Country: USA	Inclusion criteria: included in MARCQI registry, undergoing unilateral primary THA utilizing a DAA or PA between Feb 2012 and Sept 2014, Exclusion criteria: cases were matched based on propensity scores, they were excluded if there was no match in 9 cases	Describe intervention (treatment/procedure/test): Direct Anterior Approach (A)	Describe control (treatment/procedure/test): Posterior approach (P)	Length of follow-up: unclear Loss-to-follow-up: unclear Incomplete outcome data: unclear	Outcome measures and effect size (include 95%CI and p-value if available): Dislocation rate: A: N=18 (0.84%) P: N=17 (0.79%) No significant difference	Retrospective, patients not randomly assigned to treatment

	Source of funding: Blue cross blue shield and the Blue Care Network as part of the BCBSM Value Partnership Program	N total at baseline: Intervention: 2147 Control: 2147 Important prognostic factors[2]: I: 64.8 Sex: 47% M Groups comparable at baseline?				Blood transfusion A: 173 (8.06%) P: 208 (9.69%) Fracture postoperative A: 31 (1.44%) P: 24 (1.12%) Fracture intraoperative A: 21 (0.98%) P: 26 (1.21%) Hematoma A: 43 (2.0%) P: 27 (1.26%)	
Mjaaland, 2017	Type of study: cohort study from a registry Setting: hospital Country: Norway Source of funding: No financial support or grant was received for the study.	Inclusion criteria: primary THAs done with an uncemented stem performed between 2008 and 2013, Exclusion criteria: - N total at baseline: MIS anterior: 2017 MIS anterolateral: 2087 Conventional posterior:5961 Conventional direct lateral: 11795 Important prognostic factors[2]: Age: MIS anterior: 67 ± 11 MIS anterolateral: 67 ± 11 Conventional posterior: 65 ± 12 Conventional direct lateral: 64 ± 12	Describe intervention (treatment/procedure/test): MIS anterior MIS anterolateral	Describe control (treatment/procedure/test): Conventional posterior Conventional direct lateral	Length of follow-up: Five years Loss-to-follow-up: unknown Incomplete outcome data: unknown	Outcome measures and effect size (include 95%CI and p-value if available): Implant survival MIS anterior: 96.8 (96.0-97.6) MIS anterolateral: 96.5 (95.5-97.5) Posterior 96.4 (95.8-97.0) Direct lateral 96.0 (95.6-96.4) Revision (any cause): Direct lateral: comparison MIS anterior: 0.90 (0.68-1.2)	

		Sex: MIS anterior: 33.5 %M MIS anterolateral: 36.5 %M Conventional posterior:35.3 %M Conventional direct lateral:38.7 %M Groups comparable at baseline? Differences in age distribution, head size, ,type of articulation, use of cemented cups and primary diagnosis				MIS anterolateral 0.95 (0.71-1.3) Posterior 0.90 (0.75-1.1) <u>Dislocation</u> Direct lateral: comparison: 0.71 (95% CI = 0.40 to 1.3, p = 0.25) MIS anterior/ anterolateral: Posterior: 2.1, 95% CI = 1.5 to 3.1, p < 0.001) Revision due to fracture Direct lateral: MIS anterior/anterolateral: 0.85 (0.40-1.8) Posterior:0.87 (0.43-1.7)	

Notes:

1. **Prognostic balance between treatment groups is usually guaranteed in randomized studies, but non-randomized (observational) studies require matching of patients between treatment groups (case-control studies) or multivariate adjustment for prognostic factors (confounders) (cohort studies); the evidence table should contain sufficient details on these procedures.**
2. **Provide data per treatment group on the most important prognostic factors ((potential) confounders).**
3. **For case-control studies, provide sufficient detail on the procedure used to match cases and controls.**
   For cohort studies, provide sufficient detail on the (multivariate) analyses used to adjust for (potential) confounders.

Risk of bias table for intervention studies (randomized controlled trials)

Study reference (first author, publication year)	Describe method of randomisation[1]	Bias due to inadequate concealment of allocation?[2] (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation?[3] (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation?[3] (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation?[3] (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results?[4] (unlikely/likely/unclear)	Bias due to loss to follow-up?[5] (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis?[6] (unlikely/likely/unclear)
Christensen, 2014	No details provided	Likely	Likely	Likely	unclear	unlikely	unlikely	unlikely
De Anta Diaz, 2015	No details provided	Likely	Likely	Likely	unclear	unlikely	unlikely	unlikely

1. **Randomisation: generation of allocation sequences have to be unpredictable, for example computer generated random-numbers or drawing lots or envelopes. Examples of inadequate procedures are generation of allocation sequences by alternation, according to case record number, date of birth or date of admission.**
2. **Allocation concealment: refers to the protection (blinding) of the randomisation process. Concealment of allocation sequences is adequate if patients and enrolling investigators cannot foresee assignment, for example central randomisation (performed at a site remote from trial location) or sequentially numbered, sealed, opaque envelopes. Inadequate procedures are all procedures based on inadequate randomisation procedures or open allocation schedules.**
3. **Blinding: neither the patient nor the care provider (attending physician) knows which patient is getting the special treatment. Blinding is sometimes impossible, for example when comparing surgical with non-surgical treatments. The outcome assessor records the study results. Blinding of those assessing outcomes prevents that the knowledge of patient assignement influences the proces of outcome assessment (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is not necessary. If a study has "soft" (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary.**
4. **Results of all predefined outcome measures should be reported; if the protocol is available, then outcomes in the protocol and published report can be compared; if not, then outcomes listed in the methods section of an article can be compared with those whose results are reported.**
5. **If the percentage of patients lost to follow-up is large, or differs between treatment groups, or the reasons for loss to follow-up differ between treatment groups, bias is likely. If the number of patients lost to follow-up, or the reasons why, are not reported, the risk of bias is unclear.**
6. **Participants included in the analysis are exactly those who were randomized into the trial. If the numbers randomized into each intervention group are not clearly reported, the risk of bias is unclear; an ITT analysis implies that (a) participants are kept in the intervention groups to which they were randomized, regardless of the intervention they actually received, (b) outcome data are measured on all participants, and (c) all randomized participants are included in the analysis.**

Risk of bias table for intervention studies (observational: non-randomized clinical trials, cohort and case-control studies)

Study reference (first author, year of publication)	**Bias due to a non-representative or ill-defined sample of patients?**[1] (unlikely/likely/unclear)	**Bias due to insufficiently long, or incomplete follow-up, or differences in follow-up between treatment groups?**[2] (unlikely/likely/unclear)	**Bias due to ill-defined or inadequately measured outcome ?**[3] (unlikely/likely/unclear)	**Bias due to inadequate adjustment for all important prognostic factors?**[4] (unlikely/likely/unclear)
Amlie, 2014	unlikely	Likely	unlikely	unlikely
Lin, 2016	unclear	Likely	unlikely	unlikely
Maratt, 2016	unlikely	Unlikely	unlikely	unlikely
Mjaaland, 2017	unlikely	Unlikely	unlikely	unlikely

1. **Failure to develop and apply appropriate eligibility criteria: a) case-control study: under- or over-matching in case-control studies; b) cohort study: selection of exposed and unexposed from different populations.**
2. **2 Bias is likely if: the percentage of patients lost to follow-up is large; or differs between treatment groups; or the reasons for loss to follow-up differ between treatment groups; or length of follow-up differs between treatment groups or is too short. The risk of bias is unclear if: the number of patients lost to follow-up; or the reasons why, are not reported.**
3. **Flawed measurement, or differences in measurement of outcome in treatment and control group; bias may also result from a lack of blinding of those assessing outcomes (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is not necessary. If a study has "soft" (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary.**
4. **Failure to adequately measure all known prognostic factors and/or failure to adequately adjust for these factors in multivariate statistical analysis.**

Search strategy

Database	Search terms	Total
Medline 26-08-2009 – jan. 2017 English Dutch	1 Arthroplasty, Replacement, Hip/ (23476) 2 Hip Prosthesis/ (23541) 3 1 or 2 (38279) 4 arthroplasty/ or arthroplasty, replacement/ (15706) 5 joint prosthesis/ or metal-on-metal joint prostheses/ (11930) 6 "Prostheses and Implants"/ (45473) 7 (arthroplast* or replacement* or prosthes#s).ti,ab,kf. (342447) 8 4 or 5 or 6 or 7 (382080) 9 hip/ or hip joint/ or hip.ti,ab. (137145) 10 8 and 9 (44214) 11 3 or 10 (53644) 12 (THA or THAs or THP).ti,ab,kf. (20169) 13 11 or 12 (67685) 16 Minimally Invasive Surgical Procedures/ (22110) 17 Video-Assisted Surgery/ (2008) 18 ("minimal invasive" or robotics or keyhole or key hole or "minimal incision*").ti,ab,kf. (13325) 19 (((posterior or posterolateral or anterior or lateral or anterolateral or surgical) adj2 approach*) or (AMIS or ASI) or (mini* adj2 approach*)).ti,ab,kf. (57424) 20 16 or 17 or 18 or 19 (89242) 21 13 and 20 (2159) 22 limit 21 to yr="2009 -Current" (1207) 23 limit 21 to ed=20090826-20091231 (35) 24 22 or 23 (1208) 25 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (332912) 26 24 and 25 (65) 27 (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (1836462) 28 24 and 27 (249) 29 ((cohort adj (study or studies)) or Cohort analy$ or (Follow up adj (study or studies)) or (observational adj (study or studies)) or Longitudinal or Retrospective* or prospective*).tw. or (registry or registries).ti,ab. or registries/ (1526037) 30 24 and 29 (442) 38 remove duplicates from 26 (58) – EN > 48 39 remove duplicates from 28 (212) – EN > 158 40 39 not 26 (184) 41 30 not (26 or 28) (299) 42 remove duplicates from 41 (261) – EN > 251	632
Embase	'total hip prosthesis'/exp OR 'hip arthroplasty'/exp OR 'hip prosthesis':ab,ti OR 'total hip':ab,ti OR 'hip replacement':ab,ti AND ((dutch)/lim OR (english)/lim) AND (26-8-2009)/sd NOT (6-2-2017)/sd AND ('endoscopic surgery'/exp/mj OR 'minimally invasive surgery'/exp/mj OR 'minimal invasive':ti,ab OR robotics:ti,ab OR keyhole:ti,ab OR 'key hole':ti,ab OR 'minimal incision*':ti,ab OR ((posterior OR posterolateral OR anterior OR lateral OR anterolateral OR surgical) NEAR/2 approach*):ti,ab OR amis:ti,ab OR asi:ti,ab OR (mini* NEAR/2 approach*):ti,ab) NOT 'conference abstract':it AND (embase)/lim AND ('meta analysis'/de OR cochrane:ab OR embase:ab OR psycinfo:ab OR cinahl:ab OR medline:ab OR (systematic NEAR/1 (review OR overview)):ab,ti OR (meta NEAR/1 analy*):ab,ti OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de) NOT ('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp NOT 'human'/exp) (39) – 30 uniek AND ('clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti)) (156) 40 uniek AND ('major clinical study'/de OR 'implant registry'/exp OR registry:ti,ab OR registries:ti,ab) (247) – 122 uniek	

Exclusion table

Table Exclusion after reading full text

Author and year	Reason for exclusion
Barrett, 2013	Included in review Higgins
Berstock, 2014	About mini-incision
Dienstknecht, 2014	Minimally invasive surgery
D'Arrigo	Other outcome measures
Ha, 2013	Letter to the editor
Khan, 2011	Letter 99to the editor
Khan, 2012	Minimal invasive surgery
Khan, 2012	Piriformis sparing approach
Khanuja, 2012	Letter to the editor
Lee, 2015	Review of studies without control group
Li, 2012	Minimaly invasive surgery
Lin, 2016	Radiographic parameters
Martin, 2011	Minimally invasive surgery
Mayr, 2009	Minimally invasive surgery
Moskal, 2013	Limited incision versus standard incision
Petis, 2010	Comprehensive review
Reininga, 2010	Minimal invasive surgery
Rathod,	This study included only 22 patients
Restreppo,2009	Modified Smith Peterson approach compared with direct lateral approach
Sibia	HOOS and Harris Hip Score were only filled out by a small percentage of patients
Smith, 2011	Minimal invasive surgery
Winther, 2016	Wrong outcome measures
Xu, 2013	Mini-incision versus standard incision
Yang, 2012	Minimally invasive surgery
Zhand,2014	Posterior approach with soft tissue repair compared with posterior approach without soft tissue repair

3.4 Prevention of thrombo-embolic complications

See guideline ‘Antitrombotisch beleid’:
https://richtlijnendatabase.nl/richtlijn/antitrombotisch_beleid/preventie_vte/keuze_en_duur_profylaxe_grote_ingrepen.html

Module 4 Perioperative care in primary total hip replacement

Research question

4.1 What is the policy regarding systemic antibiotics for the prevention of postoperative wound infection?

4.2 What is the role of antibiotic-impregnated bone cement?

4.3 What is the policy regarding the use of a combination of mupirocin and chlorhexidine for patients undergoing a total hip arthroplasty?

Uitgangsvragen

4.1 Wat is het beleid met betrekking tot systemische antibiotica ter preventie van postoperatieve wondinfectie?

4.2 Wat is de plaats van antibioticumhoudend botcement?

4.3 Wat is het beleid met met betrekking tot het gebruik van een combinatie van mupirocin and chloorhexidine in patiënten die een totale heupprothese ondergaan?

3.1 Systemic antibiotic prophylaxis

Research question

What is the policy regarding systemic antibiotics for the prevention of postoperative wound infection?

Uitgangsvraag

Wat is het beleid met betrekking tot systemische antibiotica ter preventie van postoperatieve wondinfectie?

Introduction

The percentage of deep surgical wound infection after total hip replacement in the Netherlands in the period 2012 to 2016 was 1.2% (1,162/100,254) (RIVM, 2017). Although total hip replacement is regarded as “clean surgery”, due to the severe consequences of these infections administration of systematic antibiotic prophylaxis is indicated. The antibiotic used for prophylaxis should be effective against the main bacterial causes and optimising the timing and dosage are essential to achieve the optimal concentration during the procedure, to prevent infection of the prosthesis.

Search and select

To answer the question a systematic literature analysis was performed for the following research question:

P: patients selected for total hip arthroplasty;
I: systemic antibiotics;
C: no antibiotics;
O: surgical site infection.

Relevant outcome measures
The working group decided that surgical site infections and deep infections were critical outcome measures for decision making.

The working group defined any decrease of deep infections as clinically relevant.

Search and select (Method)
A literature search was performed with relevant search terms on 23 november 2016 in the databases Medline (via OVID) and Embase (via Embase.com). The search strategy is provided in the tab "Methods". The literature search resulted in 209 hits. Studies were selected using the following selection criteria: original article, systematic review or meta-analysis; relevant to the question. Based on title and abstract 14 studies were preselected. After obtaining full text, thirteen studies were excluded (see exclusion table) and one study was included in literature analysis. Another study, included in the previous guideline, also fulfilled the PICO and was added to the literature summary.

The most important study characteristics are described in evidence tables. The assessment of risk of bias is provided in risk of bias tables.

Literature summary
Results
Two studies were included in this literature summary, see also evidence table. One study on pre-operative systemic antibiotics and antiseptics included a meta-analysis of 3 RCTs on pre-operative systemic antibiotics (N=1176) compared to placebo (N=1172) for hip replacement (Voigt, 2015). This study showed that systemic antibiotics decreased the risk of infection after total hip prosthesis (RR 0.23 (95%CI (0.12; 0.43), though quality of this evidence was low as there was not enough information provided in the RCTs to evaluate their quality regarding randomisation procedure, allocation concealment and outcome assessors were not blinded to group assessment. Main outcome reported was infection at 6 months.

Another study, also included in the previous guideline, included seven RCTs (3065 patients) the administration of antibiotics reduced the relative risk (RR) of wound infection by 81% (RR 0.19; 95% CI 0.12 to 0.31; chi-squared test, p< 0.00001). Because such events are rare, this translates to an absolute risk reduction of 8%, meaning that one wound infection would be prevented for every 13 people treated compared with no administration of antibiotics (risk difference -0.08; 95% CI -0.03 to -0.12) (AlBuhairan, 2008).

Grading of evidence
<u>Infection risk</u>
Very low, owing to risk of bias as many details related to study quality such as randomisation procedures are not described clearly in older studies also there is imprecision as there are broad confidence intervals.

Conclusions

Very low GRADE	Systemic antibiotics decrease the risk of infection after total hip prosthesis. *Sources (AlBuhairan, 2008; Voigt, 2015)*

Considerations

Given the enormous consequences of prosthetic joint infections, a low threshold for antibiotic prophylaxis is required. The prophylaxis should cover the main causes of infections after total hip implantation.

Stichting Werkgroep Antibiotica Beleid (SWAB) is a Dutch organisation involved in optimising the use of antibiotics, amongst others by developing guidelines. The guideline "peri-operatieve profylaxe", is a generally accepted guideline, on which recommendations regarding choice, dosage and duration in this guideline are based.

Cefazolin (2 g IV)(BMI > 40, or >130 kg: 3 g), 15 to 60 minutes before incision is administered.

According to the SWAB guideline, a single dose of antibiotics is sufficient. In orthopaedic implant surgery it is recommended by the working party for orthopaedic infections to provide prophylaxis for 24 hours. Limited evidence exists regarding a difference in outcome between a single dose and 24 hours in favour of the latter (Engesaeter, 2003). Administration for longer than 24 hours has no additive value.

In case the patient has a history of a rash in response to a penicillin (amoxicillin et cetera), the chance of an adverse reaction to a cephalosporin is very small and cefazolin can be given.

In case the patient has a history of an IgE-mediated reaction (or a direct reaction) to a penicillin - like pruritus, urticaria, angiooedema, laryngeal oedema - cephalosporins are contra-indicated and alternatives are: clindamycin 600 mg (>180 kg: 900 mg), 30 to 60 minutes before incision, or vancomycin 1 g IV (>100 kg: 10 mg/kg), start infusion 60 to 120 minutes before incision.

Recommendations

Treat all patients undergoing total hip arthroplasty with systemic antibiotics, preferably cefazoline (kefzol) i.v. 2 grams (body weight >130 kg and/or BMI >40: 3 grams), 15 to 60 minutes before incision.

Give an additional dose (1 gram cefazoline i.v.) if the operation lasts more than 4 hours or in case of blood loss >1500 ml.

In case 24 hours profylaxis is preferred, treat with 1 g cefazoline after 8 hours and after 16 hours postoperatively (NB maximum dose 6 g/24 h).

Profylaxis should not be given for more than 24 hours.

Be aware of impaired renal function: if clearance 10-34, give 500 mg cefazoline 12 hours postoperatively; if clearance <10 no postoperative dose).

In case of cefalosporine allergy: clindamycine 600 mg (>180 kg: 900 mg), 30 to 60 minutes before incision. Give an additional dose (600 mg clindamycine i.v.) if the operation lasts more than 6 hours or in case of blood loss >1500 ml.

In case 24 hours profylaxis is preferred: treat with 600 mg 8 and 16 hours postoperatively (clindamycine dose irrespective of renal funtion).

Or treat with vancomycine 1 g i.v. (>100 kg: 10 mg/kg), start 60-120 minutes before incision. Give an additional dose (1 g vancomycine i.v.) if the operation lasts more than 8 hours or in case of blood loss >1500 ml. In case 24 hours profylaxis is preferred: repeat 1 g i.v. after 12 hours*** (if clearance < 50: no second dose).

***(assuming a daily dose of 2000 mg)

Aanbevelingen

Geef bij implantatie van een totale heupprothese altijd systemisch antibiotica, en kies dan voor cefazoline (kefzol) i.v. 2 g (gewicht >130 kg en/of BMI >40: 3 gram), 15 to 60 minuten voor incisie.

Geef een hernieuwde dosering (1 g cefazoline iv) bij operatieduur van 4 uur of meer en bij bloedverlies van >1500 ml.

Als gekozen wordt voor 24 uur profylaxe, geef dan postoperatief 1 g cefazoline na 8 en na 16 uur (NB maximale dosering 6 g/24 uur).

Geef de profylaxe niet langer dan 24 uur.

Let op bij nierfunctiestoornis: geef bij een klaring 10 to 34 postoperatief 500 mg cefazoline na 12 uur; bij een klaring <10 geen postoperatieve gift).

Geef bij allergie voor cefalosporines: clindamycine 600 mg (>180 kg: 900 mg), 30 to 60 minuten voor incisie. Geef een hernieuwde dosering (600 mg clindamycine iv) bij een operatieduur van 6 uur of meer en bij bloedverlies van >1500 ml.

Als gekozen wordt voor 24 uursprofylaxe: geef dan postoperatief 600 mg na 8 en na 16 uur (clindamycine dosering onafhankelijk van nierfunctie).

Of geef vancomycine 1 g i.v. (>100 kg 10 mg/kg), start 60-120 min. voor incisie. Geef een hernieuwde dosering (1 g vancomycine iv) bij een operatieduur van ≥8 uur en bij bloedverlies van >1500 ml. Als gekozen wordt voor 24 uursprofylaxe: herhaal 1 g iv na 12 uur*** (bij klaring < 50: geen tweede gift).

***(uitgaande van dagdosering 2000 mg)

Literature

AlBuhairan B, Hind D, Hutchinson A. Antibiotic prophylaxis for wound infections in total joint arthroplasty: a systematic review. J Bone Joint Surg Br. 2008;90(7):915-9. PMID:18591602.

Engesaeter LB, Lie SA, Espehaug B, et al. Antibiotic prophylaxis in total hip arthroplasty: effects of antibiotic prophylaxis systemically and in bone cement on the revision rate of 22,170 primary hip replacements followed 0-14 years in the Norwegian Arthroplasty Register. Acta Orthop Scand. 2003;74(6):644-51.

PREZIES. Referentiecijfers 2012 tot 2016: Postoperatieve Wondinfecties PREZIES – versie: september 2017, Rijksinstituut voor Volksgezondheid en Milieu, RIVM.

SWAB-Richtlijn: peri-operatieve profylaxe. 2017.

Voigt J, Mosier M, Darouiche R. Systematic review and meta-analysis of randomized controlled trials of antibiotics and antiseptics for preventing infection in people receiving primary total hip and knee prostheses. Antimicrob Agents Chemother. 2015;59(11):6696-707. PMID: 26259793.

Validity and maintenance

Module	Party in control	Year of authorization	Next assessment of actuality	Frequency of assessment actuality	Which party/parties monitors actuality	Important factors that might lead to change in recommendations
Systemic antibiotic prophylaxis	**NOV en NVMM**	**2018**	**2023**	**Eens in de vijf jaar**	**NOV en NVMM**	**?**

Knowledge gaps

Which type of systemic prophylaxis (single dose or 24-hours) is preferred to decrease the risk of infection after total hip arthroplasty?

Indicators

Not applicable

Implementation plan

Recommendation	Time needed for implementation: <1 year, 1 to 3 years or >3 years	Expected effects on costs	Conditions for implementation	Possible barriers to implementation[1]	Actions for implementation[2]	Reponsibility for these actions[3]	Other remarks
All	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.

Evidence tables

Evidence table for systematic review of RCTs

Research question: Wat is het beleid met betrekking tot systemische antibiotica ter preventie van postoperatieve wondinfectie?

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control ©	Follow-up	Outcome measures and effect size	Comments
Voigt et al., 2015	SR and meta-analysis of 10 RCTs for preoperative systemic antibiotics in hip and knee: 4 RCTs studied preoperative systemic antibiotics compared to placebo Literature search up to April 2015 A: Ericson, 1973, Sweden B: Gunst, 1984, France C: Hill, 1981, France D; Schulitz, 1980	Inclusion criteria: RCTs that investigated the effect of perioperative antibiotic prophylaxis, with or without antiseptics, on outcomes related to surgical site infections (SSIs) during primary THA (a first-time replacement of the femoral head of the femoral bone and the acetabulum (socket) of the pelvic bone) Exclusion criteria: -	Describe intervention: Postoperative antibiotic prophylaxis with no restrictions applied to agent, dose or duration **A**: cloxacillin (a type of penicillin) 1 g IM 1 h prior to operation and thereafter 3 times at 6 h intervals followed by oral administration of 2 x 0.5 g cloxacillin tablets every 6 h until day 14 plus 2 x 0.5 g probenecid tablets (which make antibiotics more effective by preventing body from passing them in urine) orally twice a day for 14 days (n = 60) **B**: IV cefamandole 1,5 g before incision followed by 1,5 g every h up to 24 h	Describe control: Placebo or no treatment **A**: placebo administered in the same manner along with probenecid (n = 58) **B**: no antibiotic **C**: placebo given at induction of anaesthesia and every 6 h post-surgery for 5 days **D**: no antibiotic therapy was administered at any time	End-point of follow-up: **A**: 1-2,5 years and up to 5-6,5 years **B**: 6 days, 3 months and 1 year **C**: 2 years and 3-5 years in publication Doyton 1987 **D**: 2 years For how many participants were no complete outcome data available? A: 59 participants were eliminated/excluded from the trial 31 (19 from cloxacilin; 12 from placebo) because of side effects) B: all participants in report after one year C: study conducted at 10 sites, but 1 did not send follow-up forms and was excluded from the analysis. Consequently the data for evaluation	Outcome measure-1 Surgical site infection at 6 months (**A**, **B** and **C**): I: 11/1176 C: 50/1172 Pooled effect (random effects model) RR 0.23 (0.12-0.43) I^2=0% Outcome measure-1 Surgical site infection at 2,5 years (**A** and **D**) I: 3/165 C: 20/147 Pooled effect (random effects model) RR 0.15 (0.05-0.47) I^2=26% Outcome measure-1 Surgical site infection at >5 years (**A** and **C**) I: 12/1130 C: 63/1125	Risk of bias tables showed that much information needed for quality evaluation was not reported Study A conducted from November 1970-may 1972

			C: cefazolin at induction of anesthesia, and every 6 h post-surgery for 5 days **D**: 600 mg lincomycin (for participants allergic to penicillin or where bacteria have developed resistance to penicillin) IV 1 h and 6 h post-surgery and 2 further 600 mg lincomycin IV injections on 2nd day post-surgery. From day 3 to day 10, 1 g lincomycin given 3 times daily		came from 9 study sites. It was not clear how many participants were excluded as a result of this D 65/259 participants were excluded due to: 18 deaths; 12 from Group 2 who received antibiotics post-surgery; 16 received another antibiotic during the 2 year follow-up; 7 because additional surgery was required for reasons other than infection; and 10 had a bilateral implant within < 6 months of the first surgery. In total, 40 were excluded from Group 2 and 25 from Group 1	Pooled effect (random effects model) RR 0.19 (0.10-0.35) I^2=0%	
Albuhairan, 2008	SR and meta-analysis of 7 RCTs *Literature search up to July 2007* **A**: Heydemann et al., 1986; United States **B**: Kanellakopoulou et al., 2009, Greece	Inclusion criteria: 1) types of participant, patients undergoing a primary or revision THR or TKR, irrespective of the type of prosthesis; 2) types of antibiotic administered at any time pre-operatively,	Describe intervention: Postoperative antibiotic prophylaxis with no restrictions applied to agent, dose or duration	Describe control: Placebo or no treatment	Follow-up ranged from ten days to ten years	In a pooled analysis of seven studies32–34,36,38,41,43 (n = 3065) the administration of antibiotics reduced the relative risk (RR) of wound infection by 81% (RR 0.19; 95% CI 0.12 to 0.31; chi-squared test, p < 0.00001). There was no statistical heterogeneity (I2 = 0%).	Because such events are rare, this translates to an absolute risk reduction of 8%, meaning that one wound infection would be prevented for every 13 people treated compared with no administration of antibiotics (risk difference −0.08; 95% CI −0.03 to −0.12). Methodological quality was variable

	C: Ritter et al., 1989 **D**: Wymenga et al., 1991 <u>Setting and Country</u>: USA <u>Source of funding:</u>	irrespective of dose and route of administration and including β-lactams, glycopeptides, aminoglycosides and any others; 3) outcome, wound infection being defined as visible purulent exudate at the surgical site (deep or superficial) reported at the maximum follow-up time; and 4) types of study (randomised controlled trial (RCT) Exclusion criteria: wound infection was not an outcome or if they only compared different doses of the same drug					

Table of quality assessment for systematic reviews of RCTs and observational studies

Based on AMSTAR checklist (Shea, 2007; BMC Methodol 7: 10; doi:10.1186/1471-2288-7-10) and PRISMA checklist (Moher, 2009; PLoS Med 6: e1000097; doi:10.1371/journal.pmed1000097)

1. Research question (PICO) and inclusion criteria should be appropriate and predefined.

2. Search period and strategy should be described; at least Medline searched; for pharmacological questions at least Medline + EMBASE searched.

Study First author, year	Appropriate and clearly focused question?[1] Yes/no/unclear	Comprehensive and systematic literature search?[2] Yes/no/unclear	Description of included and excluded studies?[3] Yes/no/unclear	Description of relevant characteristics of included studies?[4] Yes/no/unclear	Appropriate adjustment for potential confounders in observational studies?[5] Yes/no/unclear/notapplicable	Assessment of scientific quality of included studies?[6] Yes/no/unclear	Enough similarities between studies to make combining them reasonable?[7] Yes/no/unclear	Potential risk of publication bias taken into account?[8] Yes/no/unclear	Potential conflicts of interest reported?[9] Yes/no/unclear
Voigt, 2015	yes	yes	Yes	yes	unclear	Yes	yes	yes	yes
ALbuhairan, 2008	Yes, though joints are hip and knee	yes	Yes	no	unclear	No, only description: quality variable	unclear	no	no

3. Potentially relevant studies that are excluded at final selection (after reading the full text) should be referenced with reasons.

4. Characteristics of individual studies relevant to research question (PICO), including potential confounders, should be reported.

5. Results should be adequately controlled for potential confounders by multivariate analysis (not applicable for RCTs).

6. Quality of individual studies should be assessed using a quality scoring tool or checklist (Jadad score, Newcastle-Ottawa scale, risk of bias table et cetera).

7. Clinical and statistical heterogeneity should be assessed; clinical: enough similarities in patient characteristics, intervention and definition of outcome measure to allow pooling? For pooled data: assessment of statistical heterogeneity using appropriate statistical tests (for example Chi-square, I^2)?

8. An assessment of publication bias should include a combination of graphical aids (for example funnel plot, other available tests) and/or statistical tests (for example Egger regression test, Hedges-Olken). Note: If no test values or funnel plot included, score "no". Score "yes" if mentions that publication bias could not be assessed because there were fewer than 10 included studies.

9. Sources of support (including commercial co-authorship) should be reported in both the systematic review and the included studies. Note: To get a "yes," source of funding or support must be indicated for the systematic review AND for each of the included studies.

Search strategy

Database	searchterms	Total
Medline (OVID) English, Dutch 23-11-2009-dec. 2016	1 Arthroplasty, Replacement, Hip/ (22188) 2 Hip Prosthesis/ (21774) 3 1 or 2 (35700) 4 arthroplasty/ or arthroplasty, replacement/ (14655) 5 joint prosthesis/ or metal-on-metal joint prostheses/ (10917) 6 "Prostheses and Implants"/ (43549) 7 (arthroplast* or replacement* or prosthes#s).ti,ab,kf. (332205) 8 4 or 5 or 6 or 7 (369915) 9 hip/ or hip joint/ or hip.ti,ab. (128670) 10 8 and 9 (41847) 11 3 or 10 (50771) 12 (THA or THAs or THP).ti,ab,kf. (19460) 13 11 or 12 (64417) 19 Antibiotic Prophylaxis/ (12214) 20 (((antibiotic* or antimicrobial*) adj3 prophylaxi*) or (systemic adj3 (antibio* or antimicro*))).ti,ab,kf. (15470) 21 19 or 20 (23684) 22 13 and 21 (491) 23 limit 22 to (dutch or english) (403) 24 limit 23 to yr="2010 -Current" (153) 25 limit 23 to ed=20092311-20161214 (146) 26 24 or 25 (165) 27 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (326454) 28 26 and 27 (16) 29 (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (1761235) 30 26 and 29 (27) 35 28 or 30 (35) 39 26 not 35 (130) 40 remove duplicates from 35 (33) – 31 uniek 41 remove duplicates from 39 (116) – 114 uniek	209
Embase (Elsevier)	'total hip prosthesis'/exp OR 'hip arthroplasty'/exp OR 'hip prosthesis':ab,ti OR 'total hip':ab,ti OR 'hip replacement':ab,ti AND ('antibiotic prophylaxis'/exp OR ((antibiotic* OR antimicrobial* OR systemic*) NEAR/3 prophylaxi*):ti,ab OR (systemic NEAR/3 (antibio* OR antimicro*)):ti,ab) AND ((dutch)/lim OR (english)/lim) AND (23-11-2009)/sd NOT (14-12-2106)/sd AND ('meta analysis'/exp OR cochrane:ab OR embase:ab OR psychlit:ab OR cinahl:ab OR (systematic AND review:ab,ti) OR 'data extraction':ab AND ('total hip prosthesis'/exp OR 'hip arthroplasty'/exp OR 'hip prosthesis':ab,ti OR 'total hip':ab,ti OR 'hip replacement':ab,ti) AND ('antibiotic prophylaxis'/exp OR ((antibiotic* OR antimicrobial* OR systemic*) NEAR/3 prophylaxi*):ti,ab OR (systemic NEAR/3 (antibio* OR antimicro*)):ti,ab) OR 'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti (60) – 31 uniek AND 'major clinical study'/de (52) – 33 uniek	

Exclusion table

Table Exclusion after reading full text

Author and year	Reason for exclusion
Graves, 2016	Cost-effectiveness modelling of interventions (antibiotic prophylaxis, antibiotic-impregnated cement and ventilation systems)
Thornley, 2015	Only postoperative antibiotics
Chandrananth, 2015	Does not answer the question
Mak, 2014	Hip and knee replacement, more interventions studied than only antibiotics.
Yuasa, 2015	Other question: two doses of unasyne compared
Sprowson, 2013	Other primary outcome measure (diarrhoea)
Sewick, 2012	Other question: dual versus single
Bull, 2012	Also cardiac bypass and knee arthroplasty
Pedersen, 2010	Does not answer the question
Jamsen, 2010	No original data, does not answer the question
Hsu, 2009	Does not answer the question
Dale, 2009	Does not answer the question
Thornley 2015	Focuses on postoperative antibiotics

4.2 Antibiotic-impregnated bone cement

Research question
What is the role of antibiotic-impregnated bone cement?

Uitgangsvraag
Wat is de plaats van antibioticumhoudend botcement?

Introduction
Total hip replacement is regarded as 'clean surgery'. The absolute risk of superficial or deep wound infection is 1 to 2%. However, due to the severe consequences of these infections, several recommendations have been made in present guidelines considering the use of antibiotic prophylaxis. If bone cement is used in total joint replacement, in the Netherlands the advice is to use antibiotic-loaded cement as standard of care. This facilitates the local release of antibiotics, leading to a higher local concentration (Wang, 2012), with the aim to reduce the rate of deep infection.

The type of antibiotic used in bone cement should be effective against the main bacterial causes of deep infection.

Search and select
To answer the question a systematic literature analysis was performed for the following research question:

P: primary THP for arthrosis or avascular necrosis;
I: antibiotic containing bone cement;
C: bone cement without antibiotics;
O: superficial and deep wound infection, revision risk.

Relevant outcome measures
The working group decided that deep infection rates were critical outcome measures for decision-making, and superficial infection and revision risk as important outcome measures. Any significant difference in infection risk is considered clinically relevant.

Search and select (Method)
A literature search was performed with relevant search terms on 15 december 2016 in the databases Medline (via OVID) and Embase (via Embase.com). The search strategy is provided in the tab "Methods". The literature search resulted in 221 hits. Studies were selected using the following selection criteria: addressing the research question, methodological quality, randomised controlled trial, systematic review, meta-analysis, or registry study. Based on title and abstract 16 studies were preselected. After obtaining full text, thirteen studies were excluded (see exclusion table) and three studies were included in literature analysis. Also a registry study included in the 2010 guideline was added to the literature summary (Engesaeter, 2003).

The most important study characteristics are described in evidence tables. The assessment of risk of bias is provided in risk of bias tables.

Literature summary

Three studies were included to answer this question, two meta-analyses and a cohort study (Parvizi, 2008; Wang, 2012; Colas, 2015).

The meta-analysis by Parvizi included six RCTs (Lynch, 1987, Josefsson, 1990, Josefsson and Kolmert, 1993; Havelin, 1995; Espehaug, 1997), comprising 24,661 total hip replacements (primary and revision hip arthroplasty) comparing antibiotic impregnated cement (gentamicin) with non-antibiotic impregnated cement (Parvizi, 2008). Data with regard to the use of systemic antibiotics was limited. Outcomes required for inclusion in the meta-analysis were the incidence of deep infection and the overall survival rate at the specified interval after surgery.

The meta-analysis by Wang included eight RCTs that included patients undergoing a primary total hip arthroplasty (Pfarr, 1979; Wannske, 1979; Josefsson, 1981; Bohm, 2012) or total knee arthroplasty (Chiu, 2000; Hinarejos, 2013; Hip and knee: McQueen, 1987 and 1990); included an antibiotic-impregnated bone cement trial group and a control group that involved the use of plain bone cement or systemic antibiotics (Wang, 2012). Outcomes reported were superficial and deep wound infection.

The cohort study of Colas (2015) included 107,382 patients that had a total hip replacement for rheumatoid arthritis. It compared antibiotic-impregnated bone cement with non-impregnated cement after a median follow-up of 33 months. Fixation was uncemented in 74.8% of cases, with antibiotic-free cement in 3.8% and antibiotic-impregnated cement in 21.4%. The outcome reported was revision risk.

The registry study of Engesaeter (included in the 2010 guideline) included 22,170 total hip arthroplasties. Patients had received systemic antibiotic prophylaxis with cephalosporin or penicillin combined with antibiotic impregnated bone cement in 71% of the cases. These patients were compared with those who had received only systemic antibiotics (27%). Main outcome reported was revision risk.

Results

Risk of superficial infection

Wang (2013) found a Risk Ratio of 1.42 (95% CI (0.81; 2.50)) for antibiotic cement for superficial infection compared to plain bone cement in both hip and knee surgery. A risk ratio of 1.48 (95% CI (1.10 to 2.00)) was found for antibiotic cement for superficial infection compared to systemic antibiotics in both hip and knee surgery.

Risk of deep infection

Parvizi (2008) found a weighted mean effect of 0.506 (95% CI (0.341 to 0.751)), p=0.001 of antibiotic cement in reducing the risk of infection in primary total hip arthroplasty.

Meta-analysis of the cumulative data from all of the studies confirmed the efficacy of antibiotic cement in reducing the rate of deep infection in primary total hip replacement—

from 2.3% when no antibiotic was present in the cement to 1.2% with the use of antibiotic cement (Parvizi, 2008).

Wang (2013) found a Risk Ratio of 0.34 (95%CI (0.07; 1.58)) for antibiotic cement for deep infection compared to plain bone cement in both hip and knee surgery. A risk ratio of 0.37 (95% CI (0.14 to 0.98)) was found for antibiotic cement for deep infection compared to systemic antibiotics in both hip and knee surgery. In the subgroup of patients undergoing hip arthroplasty, the risk ratio for a deep infection was 0.21 (95%CI (0.08; 0.5)) for antibiotic cement compared to plain cement.

Revision risk

Colas (2015) showed that antibiotic-impregnated cemented total hip replacements had a better prognosis than uncemented total hip replacements: cumulative revision rates were 2.4% and 3.3%, respectively (P< .001) and the multivariate adjusted hazard ratio was 0.74 (95%CI, 0.67 to 0.84; P<0.001).

The registry study by Engesaeter, 2004 found that revision risk was 1.4 times higher for those who received antibiotics only systemically, as compared to a combined strategy of systemic antibiotics and impregnated bone cement (P<0.001).

Grading of evidence

Risk of superficial infection

For this analysis a meta-analysis of 5 RCTs was used, the level of evidence was considered high.

Risk of deep infection

For infection results are based on two meta-analysis of RCTs. Results pointed in the same direction, the level of evidence was not decreased and considered high.

Revision risk

Revision risk was studied in a cohort study and a registry, the level of evidence was considered low.

Conclusions

Risk of superficial infection

High GRADE	Antibiotic-impregnated bone cement did not reveal an advantage in decreasing the rate of **superficial** infection compared to plain bone cement in patients undergoing hip or knee replacement. *Sources (Wang, 2012)*

Risk of deep infection

High GRADE	Antibiotic-impregnated bone cement leads to fewer **deep wound** infections than non-antibiotic-impregnated bone cement in patients undergoing hip or knee replacement. *Sources (Parvizi, 2008; Wang, 2012)*

Revision risk

Low GRADE	Revision risk was lower for antibiotic-impregnated bone cement compared to non-antibiotic-impregnated bone cement in patients undergoing total hip arthroplasty. *Sources (Engesaeter, 2003; Colas, 2015)*

Considerations

The most commonly used antibiotic in cement is gentamicin, which is commercially available and has broad-spectrum activity and is effective against the main bacterial causes of deep infection. Since revision risk is lowest if antibiotic-impregnated cement is combined with systemic antibiotic prophylaxis, as shown by Engeseater (2003), the working group recommends always using systemic antibiotic prophylaxis too.

Recommendation

When inserting a primary cemented hip prosthesis, always use an antibiotic-impregnated cement (in combination with systemic antibiotic prophylaxis).

Aanbeveling

Gebruik bij een primaire gecementeerde totale heupprothese, altijd een antibioticumhoudend cement (in combinatie met systematische antibioticum profylaxe).

Literature

Colas S, Collin C, Piriou P, et al. Association Between Total Hip Replacement Characteristics and 3-Year Prosthetic Survivorship: A Population-Based Study. JAMA Surg. 2015;150(10):979-88.

Engesæter L, Lie SA, Espehaug B, et al. Antibiotic prophylaxis in total hip arthroplasty: Effects of antibiotic prophylaxis systemically and in bone cement on the revision rate of 22,170 primary hip replacements followed 0 to 14 years in the Norwegian Arthroplasty Register , Acta Orthopaedica Scandinavica, 2003;74:6, 644-651.

Parvizi J, Saleh KJ, Ragland PS, et al. Efficacy of antibiotic-impregnated cement in total hip replacement. A meta-analysis. Acta Orthopaedica, 2008;79(3):335-341.

Wang J, Zhu C, Cheng T, et al. A systematic review and meta-analysis of antibiotic-impregnated bone cement use in primary total hip or knee arthroplasty. PLoS ONE. 2013;8(12):e82745.

Validity and maintenance

Module	Party in control	Year of authorization	Next assessment of actuality	Frequency of assessment actuality	Which party/parties monitors actuality	Important factors that might lead to change in recommendations
Antibiotic-impregnated bone cement	NOV	2018	2023	Eens in de vijf jaar	NOV	-

Knowledge gaps

Which type of antibiotic-impregnated bone cement (gentamicine, vancomycine or tobramycine) for total hip arthroplasty is preferred?

Indicators

Please consult www.lroi.nl

Implementation plan

Recommendation	Time needed for implementation: <1 year, 1 to 3 years or >3 years	Expected effects on costs	Conditions for implementation	Possible barriers to implementation[1]	Actions for implementation[2]	Reponsibility for these actions[3]	Other remarks
All	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.

Evidence tables

Evidence table for systematic review of RCTs

Research question: Does antibiotic bone cement reduce deep infection compared to non-antibiotic containing bone cement?

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Parvizi, 2008	SR and meta-analysis of 6 RCTs *Literature search up to December 2004* **A**: Espehaug, 1997; Norway; supported by grants from the Norwegian Research Council and the Norwegian Medical Association's Fund for Quality Improvement **B**: Josefsson, 1990; Sweden, unknown **C**: Josefsson and Kolmert, 1993; Sweden, unknown	Inclusion criteria SR: primary and revision hip arthroplasty, comparative trials of antibiotic loaded versus non-antibiotic cement, if they included data on 100 or more primary hip replacements or 20 or more revision hip replacements, and if they included outcome data at specified follow-up times. Outcome data required for inclusion were the incidence of deep infection and the overall	Describe intervention: Antibiotic impregnated cement (gentamicin) **A**: 1) patients receiving antibiotic prophylaxis both systemically and locally in the bone cement (combined regime); 3) those receiving antibiotics in the cement only (cement only regime) **B**: gentamicin bone cement (GBC) **C**: gentamicin bone cement (GBC) **D**: antibiotic cement **E**: gentamicin-containing acrylic cement **F**: cefuroxime in bone cement	Describe control: Non-antibiotic impregnated cement **A**: Espehaug, 1997 2) those receiving antibiotics systemically only (systemic only regime); 4) those receiving no antibiotic prophylaxis (no antibiotic regime). **B**: systemic antibiotics **C**: systemic antibiotics **D**: cement without antibiotics **E**: plain bone cement (CMW) **F**: systemic cefuroxime	<u>End-point of follow-up (minimum follow-up of two years)</u>: **A**: five years **B**: five years **C**: ten years **D**: 3,2 years (range 0-6,4) **E**: 8,1 for CMW series and 3,6 for Palacos with gentamicin **F**: McQueen, 1987 **G**: **H**: **I**: …. <u>For how many participants were no complete outcome data available?</u> 1,081 hips (4.4%) were lost to follow-up or the patients died and were excluded	<u>Outcome measure-1 Deep wound infection</u> Pooled effect (random effects model): RR 0,51 (95%BI 0,34-0,75) favoring antibiotic cement <u>Outcome measure-2 overall survival of the hip prothesis</u> RR 0,72 (95%BI 0,63-0,83) favoring antibiotic cement	

	D: Havelin et al., 1995, Norway, unknown **E**: Lynch, 1987, England, unknown **F**: McQueen, 1987 <u>Setting and Country</u>: USA <u>Source of funding:</u> unknown	survival rate at the specified interval after surgery. Exclusion criteria SR: Studies that related to mechanical properties of cement, in vitro studies, and studies of joints other than the hip were excluded; non-clinical studies and non-outcome clinical studies, historical reports and studies without a control group; hips that had been inserted with low-viscosity "Boneloc" cements in the study by Havelin et al. (1995) were excluded; hips in the study by Espehaug et al.					

		(1997) that had been performed using Simplex cement containing erythromycin and colistin were also excluded <u>N=24.661 hip-replacements</u> <u>N=21.445 analysed</u>					
Wang, 2012	SR and meta-analysis of RCTs *Literature search up to june 2013* **B**: Chiu, 2002 Knee **C**: Hinarejos, 2013 Knee **D**: Josefsson, 1981 **E**: McQueen, 1987 Hip and knee **F**: McQueen, 1990 Hip and knee **G**: Pfarr, 1979 **H**:Wannske, 1979	Inclusion criteria SR: patients undergoing a primary THA or TKA; include an AIBC trial group and a control group that involved the use of plain bone cement (PBC) or systemic antibiotic (SA), irrespective of the dose and route of administration; and be a published RCT	Describe intervention: **B**: 2g cefuroxiume **C**: 0,5 g ERY and colistin **D**: 0,5 g gentamicin **E**: 1,5 g cefuroxime **F**: 1,5 g cefuroxime **G**: gentamicin **H**: gentamicin	Describe control: **B**: Simplex P **C**: Simplex P **D**: Palacos **E**: CMV **F**: CMV **G**: Palacos **H**: Palacos	<u>End-point of follow-up</u>: **B**: 49 months **C**: 12 months **D**: 24 months **E**: 3 months **F**: 24 months **G**: 24 months **H**: 29 months <u>For how many participants were no complete outcome data available?</u> (intervention/control) **A:** 5 due to missed examinations and further dropout **B**: N **C**: yes 52 **D**: yes 52	<u>Outcome measure-1 infection</u> Defined as..... We included the seven RCTs which involved the postoperative infection rate of patient as the data of the metaanalysis in Table S3 in File S1. In the aspect of superficial infection rate, because no significant heterogeneity was observed among the subgroups (P= 0.79; I2= 0%), a fixedeffect model was employed. The overall pooled results of 5 RCTs revealed a significant difference between AIBC and control	<u>Facultative</u>: Brief description of author's study included both hips and knees. Hip studies were performed in 1979 and 1981 Study A removed, studied no infection H: Wannske 1979, not included in reference list

	Study design: All RCTs Setting and Country: **B**: Taiwan, hospital **C**: Spain, hospital **D**: Sweden, hospital **E**: Scotland, hospital **F**: Scotland, hospital **G**: Germany, hospital **H**:	Exclusion criteria SR: (1) the outcomes were not reported for antibiotic cement use in primary total hip or knee replacement; (2) it was impossible to extrapolate or calculate the necessary data from the published results; (3) primary study patients had a poor physical condition, such as diabetes, malign nt tumor; and (4) studies were animal experiments, in vitro trials or revision arthroplasty, and the operated joint was not the hip or knee			**E**: yes **F**: yes 4 **G**: no **H**: no	group (RRs, 1.47; 95% CIs, 1.13 to 1.91; P= 0.004) (Figure 2). Furthermore, we found different results based on the respective analysis of two subgroups. In the subgroup of AIBC versus SA, SA had a lower superficial infection rate than AIBC (P= 0.01). However, in the subgroup of AIBC versus PBC, the pooled results showed that there was no statistically significant difference (P= 0.22). For deep infection, heterogeneity between the two subgroups was statistically different (P= 0.06; I2=53%), so we used a random-effect model to evaluate the deep infection rate. The total pooled results exhibited a significant statistical difference between AIBC and control treatments (RRs, 0.41; 95% CIs, 0.17 to 0.97; P= 0.04)	

		8 studies included <u>Important patient characteristics at baseline</u>: <u>N, mean age</u> **A**: N= 23 (25 hips, 73 yrs **B**: N=340, 69 yrs **C**: N=2948, 75 yrs D: N=1633, 69 yrs E: 295, 68 yrs F: N=401, 67 yrs G: N=200, 65 yrs H: N=476, 64 yrs					

Evidence table for intervention studies (randomized controlled trials and non-randomized observational studies (cohort studies, case-control studies, case series))[1]

Research question: What is the place of antibiotic impregnated bone cement?

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Colas, 2015	Type of study: cohort Setting: total hip replacement (THR) in hospital, data collected by national health insurance database Country: France Source of funding: unclear	Inclusion criteria: + 40 y, THR for osteoarthritis between 04/2010 and 12/2011 Exclusion criteria: THR for trauma or bone cancer, bilateral THR, rosthetic revision before inclusion period, no medical reimbursement after index THR, missing THR characteristics	Describe intervention (treatment/procedure/test): Antibiotic impregnated cemented THR CoC, ceramic-on-ceramic; CoP, ceramic-on-polyethylene; MoM, metal-on-metal; MoP,metal-on-polyethylene;	Describe control (treatment/procedure/test): Antibiotic free cemented THR CoC, ceramic-on-ceramic; CoP, ceramic-on-polyethylene; MoM, metal-on-metal; MoP,metal-on-polyethylene;	Length of follow-up: median 33 months Loss-to-follow-up: Not described Incomplete outcome data: Not described	Outcome measures and effect size (include 95%CI and p-value if available): THR revision (including any surgical reintervention in which implant or any of its components was changed or removed. Antibiotic-impregnated cemented THRs had a better prognosis than uncemented THRs: cumulative revision rates were 2.4% and 3.3%, respectively (P < .001), and the multivariate adjusted hazard ratio was 0.74 (95%CI, 0.67-0.84; P < .001). Revision risk for antibiotic-free cemented THRs was not different compared with uncemented THRs (HR, 0.95; 95% CI, 0.79-1.14)	21% used antibiotic loaded bonecement

Engesaeter, 2003	Type of study: registry Setting: hospital Country: Norway Source of funding: unknown	Inclusion criteria: solely prostheses and cements with documented good long-term results in the Register. Only primary prostheses in patients with idiopathic osteoarthritis of the hip were included. We selected prostheses with high-viscosity cement of the brands Palacos with or without gentamicin or Simplex with or without colistin/ erythromycin. Lastly, only those who had received systemic antibiotic prophylaxis with cephalosporin (the first-generation cephalotin or the second-generation cefuroxime) or penicillin (cloxacillin or dicloxacillin, both semisynthetic penicillinase-resistant) were included. Important patient characteristics at baseline: N=22170 THA Mean age: 72 (17-97) 29% males	Describe intervention (treatment/procedure/test): A combined antibiotic prophylaxis, both systemically and in cement, was used in 71% of the operations, in 1.1% antibiotic solely in the cement and in 1.3% no antibiotic prophylaxis was used at all. During the study, the prophylaxis regime was switched almost entirely to the combined regime after 1998.	Describe control (treatment/procedure/test): Only systemic antibiotics	Length of follow-up: median Loss-to-follow-up: who died or emigrated during the follow-up were identified from files provided by Statistics Norway and the follow-up time for the prostheses in these patients were censored on the date of death or emigration Incomplete outcome data: Not described	Revision: Systemic and cement: Systemic only: 50/15676 (0.4% 10-year revision) Systemic only: 46/5960 (0.7% 10-year revision) The revision risk for those who received only antibiotic systemically, as compared to a combined, revision was 1.4 times higher with all reasons for revision as endpoint ($p < 0.001$), 1.3 times higher with aseptic loosening ($p = 0.02$) and 1.8 times higher with infection ($p = 0.01$)	

Risk of bias table for intervention studies (observational: non-randomized clinical trials, cohort and case-control studies)

Study reference (first author, year of publication)	Bias due to a non-representative or ill-defined sample of patients?[1] (unlikely/likely/unclear)	Bias due to insufficiently long, or incomplete follow-up, or differences in follow-up between treatment groups?[2] (unlikely/likely/unclear)	Bias due to ill-defined or inadequately measured outcome ?[3] (unlikely/likely/unclear)	Bias due to inadequate adjustment for all important prognostic factors?[4] (unlikely/likely/unclear)
Colas, 2015	unlikely	Unlikely	unlikely	unlikely
Engesaeter, 2003	unlikely	Unlikely	unlikely	likely

1. **Failure to develop and apply appropriate eligibility criteria: a) case-control study: under- or over-matching in case-control studies; b) cohort study: selection of exposed and unexposed from different populations.**
2. **2 Bias is likely if: the percentage of patients lost to follow-up is large; or differs between treatment groups; or the reasons for loss to follow-up differ between treatment groups; or length of follow-up differs between treatment groups or is too short. The risk of bias is unclear if: the number of patients lost to follow-up; or the reasons why, are not reported.**
3. **Flawed measurement, or differences in measurement of outcome in treatment and control group; bias may also result from a lack of blinding of those assessing outcomes (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is not necessary. If a study has "soft" (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary.**
4. **Failure to adequately measure all known prognostic factors and/or failure to adequately adjust for these factors in multivariate statistical analysis.**

Table of quality assessment for systematic reviews of RCTs and observational studies

Based on AMSTAR checklist (Shea, 2007; BMC Methodol 7: 10; doi:10.1186/1471-2288-7-10) and PRISMA checklist (Moher, 2009; PLoS Med 6: e1000097; doi:10.1371/journal.pmed1000097)

Study First author, year	Appropriate and clearly focused question?[1] Yes/no/unclear	Comprehensive and systematic literature search?[2] Yes/no/unclear	Description of included and excluded studies?[3] Yes/no/unclear	Description of relevant characteristics of included studies?[4] Yes/no/unclear	Appropriate adjustment for potential confounders in observational studies?[5] Yes/no/unclear/notapplicable	Assessment of scientific quality of included studies?[6] Yes/no/unclear	Enough similarities between studies to make combining them reasonable?[7] Yes/no/unclear	Potential risk of publication bias taken into account?[8] Yes/no/unclear	Potential conflicts of interest reported?[9] Yes/no/unclear
Parvizi, 2008	yes	yes	Unclear	no	unclear	Described, but not provided	yes	yes	No
Wang,	yes	yes	Yes	yes	unclear	no	yes	yes	no

1. **Research question (PICO) and inclusion criteria should be appropriate and predefined.**
2. **Search period and strategy should be described; at least Medline searched; for pharmacological questions at least Medline + EMBASE searched.**
3. **Potentially relevant studies that are excluded at final selection (after reading the full text) should be referenced with reasons.**
4. **Characteristics of individual studies relevant to research question (PICO), including potential confounders, should be reported.**
5. **Results should be adequately controlled for potential confounders by multivariate analysis (not applicable for RCTs).**
6. **Quality of individual studies should be assessed using a quality scoring tool or checklist (Jadad score, Newcastle-Ottawa scale, risk of bias table et cetera).**
7. **Clinical and statistical heterogeneity should be assessed; clinical: enough similarities in patient characteristics, intervention and definition of outcome measure to allow pooling? For pooled data: assessment of statistical heterogeneity using appropriate statistical tests (for example Chi-square, I^2)?**
8. **An assessment of publication bias should include a combination of graphical aids (for example funnel plot, other available tests) and/or statistical tests (for example Egger regression test, Hedges-Olken). Note: If no test values or funnel plot included, score "no". Score "yes" if mentions that publication bias could not be assessed because there were fewer than 10 included studies.**
9. **Sources of support (including commercial co-authorship) should be reported in both the systematic review and the included studies. Note: To get a "yes," source of funding or support must be indicated for the systematic review AND for each of the included studies.**

Search strategy

Database	Search terms	Total
Medline (OVID) 23-11-2009 – dec. 2016 English, Dutch	1 Arthroplasty, Replacement, Hip/ (22188) 2 Hip Prosthesis/ (21774) 3 1 or 2 (35700) 4 arthroplasty/ or arthroplasty, replacement/ (14655) 5 joint prosthesis/ or metal-on-metal joint prostheses/ (10917) 6 "Prostheses and Implants"/ (43549) 7 (arthroplast* or replacement* or prosthes#s).ti,ab,kf. (327449) 8 4 or 5 or 6 or 7 (365159) 9 hip/ or hip joint/ or hip.ti,ab. (126855) 10 8 and 9 (41238) 11 3 or 10 (50162) 12 (THA or THAs or THP).ti,ab,kf. (19044) 13 11 or 12 (63588) 14 exp Anti-Bacterial Agents/ad (Administration & Dosage) (87708) 15 exp Bone Cements/ (20827) 16 14 and 15 (729) 17 ("antibiotic loaded cement*" or "antibiotic loaded bone cement*").ti,ab. (268) 18 16 or 17 (904) 19 (antibiotic* adj3 cement*).ti,ab,kf. (869) 20 18 or 19 (1278) 21 13 and 20 (405) 22 limit 21 to (yr="2010 -Current" and (dutch or english)) (131) 23 limit 21 to ed=20092311-20161214 (146) 24 22 or 23 (151) 25 remove duplicates from 24 (143) 27 limit 25 to (dutch or english) (135) > 132 uniek	221
Embase	'total hip prosthesis'/exp OR 'hip arthroplasty'/exp OR 'hip prosthesis':ab,ti OR 'total hip':ab,ti OR 'hip replacement':ab,ti AND (antibiotic* NEAR/3 cement* OR 'antibiotic loaded cement' OR 'antibiotic loaded bone cement') OR ('bone cement'/exp/mj AND ('antibiotic agent'/exp/dd_do,dd_ad OR 'antibiotic agent'/exp/dd_os)) AND ((dutch)/lim OR (english)/lim) AND (embase)/lim AND (23-11-2009)/sd NOT (15-12-2016)/sd 171 – 89 uniek	

Exclusion table

Table Exclusion after reading full text

Author and year	Reason for exclusion
Colas, 2015	Poster
Zheng, 2014	Broader than only bone cement, also includes other interventions
Gutowski, 2014	Cost effectiveness
Bordini, 2014	Knee arthroplasty
Sprowson, 2013	Protocol
Vonberg, 2012	This answers another question: nasal s aureus screening/decolonization
Tabutin, 2012	Not available
Perry, 2012	No original data
Namba, 2012	About risk factors surgical site infection
Dale, 2012	Does not answer the question
Bowden, 2011	Letter to the editor
Gorenoi, 2010	Review, dated
Cummins, 2009	Cost-effectiveness

4.3 Procedure for pre-operative decontamination

Research question
What is the policy regarding the use of a combination of mupirocin and chlorhexidine for patients undergoing a total hip arthroplasty?

Uitgangsvraag
Wat is het beleid met met betrekking tot het gebruik van een combinatie van mupirocine en chloorhexidine in patiënten die een totale heupprothese ondergaan?

Introduction
Staphylococcus aureus is an important cause of post-surgical wound infections and the use of intranasal mupirocin in carriers may decrease the rate of S. aureus infections in surgical patients.

Guidelines such as the "Clinical practice guidelines for antimicrobial prophylaxis in surgery" by the IDSA recommend application of mupirocin intranasally for all patients known to be colonised with S. aureus and undergoing joint replacement (Bratzler et al., 2013). Also, the SWAB guideline on surgical prophylaxis recommends screening patients undergoing orthopaedic implantation surgery and in the case of a positive result for S. aureus, to apply both mupirocin and chlorhexidine pre-operatively, but with an exception for centres with very low infection rates.

Nowadays in Dutch hospitals, there are different approaches, some hospitals do not have a mupirocin protocol in orthopaedic implantation surgery, there are hospitals that only apply mupirocin to S. aureus carriers and in other hospitals all patients receive mupirocin before implantation. This lack of uniformity is undesirable, as it could result in suboptimal prevention measures, or lead to unnecessary use of mupirocin, which may cause induction of resistance and unnecessary costs.

A literature study was performed to assess the influence on infection rates of prophylactic mupirocin and chlorhexidine body wash, applied to all patients undergoing joint replacement, to S. aureus carriers only, or to no patients at all.

Searching and selecting
There was no study available in which the effects of the application of mupirocin and chlorhexidine either to all patients, or to S. aureus carriers only were compared to no application. Therefore a new question was formulated to investigate the effect of screening and in case positive, application of mupirocin and chlorhexidine, compared to no screening protocol.

PICO-1: What are the effects of (S. aureus) screening and application of mupirocin and chlorhexidine, compared to no screening, in patients who underwent total joint arthroplasty?

P: (patients)	patients who underwent total joint arthroplasty;
I: (intervention)	screening and (in case positive for S. aureus) application of mupirocin and chlorhexidine;
C: (comparison)	no screening;
O: (outcome)	surgical Site Infection (SSI), revision.

The working group did not define outcomes a priori, but used definitions as provided in the studies.

Search and selection (Methods)
A literature search with relevant search terms was performed in the databases Medline (via OVID) and Embase (via Embase.com) on 14 june 2017. The search strategy is provided in the tab "Verantwoording". The literature search resulted in 138 hits. Studies about the (un)favourable effects of entering a screening protocol and pre-operative decontamination according to a decolonisation protocol, compared to no screening protocol, in patients who undergo total joint arthroplasty were selected. The studies that were found investigated the (un)favourable effects of mupirocin and chlorhexidine within a protocol, in which antibiotic prophylaxis was also given to the patients. Therefore, it is not clear if the results are solely related to mupirocin and chlorhexidine. The studies show the effects of entering a screening protocol on different outcomes. Based on title and abstract 17 studies were pre-selected. After obtaining full text, twelve studies were excluded and five studies were included in literature analysis (see exclusion table).

Summary of literature
Description of studies
Five studies were included, which compared the differences in SSIs between a group of patients who were screened and treated according to a decolonisation protocol, compared to a control group (Baratz, 2015; Rao, 2011; Schweizer, 2015; Sporer, 2016; Stambough, 2016). One study was included, which investigated whether there is a difference in amount of revisions between a group of patients who were screened and treated according to a decolonisation protocol, compared to a control group (Malcolm, 2016).

Because of heterogeneity in screening and decolonisation protocols used, the studies, their results and conclusions are described in three categories:

- *Category 1* included studies that investigated the number of SSIs after screening and application of mupirocin and chlorhexidine on indication compared to a (historical) control group with unknown history regarding application of mupirocin and/or chlorhexidine.

- *Category 2* included studies that investigated the number of SSIs after screening and application of mupirocin and chlorhexidine body wash on indication, compared to application of mupirocin and chlorhexidine body wash to all patients undergoing total joint arthroplasty.

- *Category 3* included studies that investigated the number of revisions due to SSIs after screening and application of mupirocin and chlorhexidine on indication,

compared to application of chlorhexidine to all, in patients undergoing total joint arthroplasty.

Characteristics of included studies:

Category 1

In four studies regarding patients undergoing total joint arthroplasty the differences in number of SSIs after screening and application of mupirocin and chlorhexidine on indication were compared to a (historical) control group with unknown history regarding mupirocin and/or chlorhexidine (Baratz, 2015; Rao, 2011 ; Schweizer, 2015; Sporer, 2016). Some studies included patients in the intervention group who were not screened before surgery. These patients were all treated with mupirocin and chlorhexidine until screening results were known.

The retrospective clinical study by Baratz (2015) compared the infection risks of a group of patients who were screened and treated according to a decolonisation protocol (intervention group) to a historical control cohort (control group) after elective total joint arthroplasty (Baratz, 2015).

All patients were screened for nasal carriage of MSSA or MRSA during their pre-operative visit to the hospital. Carriers were treated with mupirocin intranasally (Bactroban; GlaxoSmithKline, Middlesex, UK) and chlorhexidine soap for five days, including the day of surgery. A first-generation cephalosporin (cefazolin) was given as systemic prophylaxis and patients with a β-lactam allergy received vancomycin. In addition to cefazolin, carriers of MRSA received vancomycin. A patient group from a 2-year period (January 2009 to December 2010) before the implementation of the screening and decolonisation protocol was included as a control.

The intervention group consisted of patients who underwent primary (n = 2903) or aseptic revision (n = 531) total hip or knee arthroplasty (THA or TKA). In the intervention group, 158 patients (5%) tested positive for MRSA and 508 patients (15%) were positive for MSSA. The control group consisted of 3080 patients (primary cases, n = 2515; revision cases, n = 567). SSIs were defined according to the National Healthcare Safety Network guidelines of the Center for Disease Control and Prevention. No baseline values were given.

The prospective cohort study by Rao (2011) investigated the number of SSIs in patients who underwent elective total joint arthroplasty. The intervention group (n = 1440) was compared with two control groups. One concurrent control group with surgical patients who did not participate in the screening and decolonisation protocol (n = 2284) and a pre-intervention control group (n = 741) in which patients were included who underwent TJA one year before the implementation of a decolonisation protocol. No details were given regarding inclusion criteria for the pre-intervention group, concurrent control and intervention group. Also no information is available regarding systemic prophylaxis or the use of chlorhexidine in the control group.

Patients in the intervention group were screened two to four weeks before surgery. Carriers of S. aureus used mupirocin nasal ointment two times per day for five days and had chlorhexidine baths daily for five days. This protocol started five days before surgery. All patients received peri-operative antibiotic prophylaxis with cefazolin, or in case of

MRSA carriers or a history of MRSA or type I allergy to penicillin, vancomycin was given. In the intervention group, 321 participants were carriers of S. aureus (MSSA = 278; MRSA = 43). The reported outcome measure was SSI, with a follow-up of two years after total joint arthroplasty. No baseline values were given.

The quasi-experimental pragmatic study by Schweizer (2015) compared the risk of SSIs in patients undergoing primary hip or knee arthroplasty (and cardiac operations) between a group of patients who were screened and treated according to a decolonisation protocol (intervention group) and a control group. In total 31,701 operations, performed in 20 hospitals (8 hospitals implemented the bundle for joint arthroplasties, 4 for cardiac operations, and 8 for both categories), were included (n pre-intervention = 20,642; n intervention = 11,059). Hospitals that implemented parts of the intervention during the pre-intervention period were allowed to participate.

Patients in the intervention group were screened for S. aureus 10 to 14 days before surgery (no more than 30 days). Carriers of MRSA or MSSA received mupirocin intranasally twice daily for five days and bathed with chlorhexidine once daily for five days immediately before surgery. Patients with negative screening for MRSA or MSSA bathed with chlorhexidine the night and morning before operation. Patients received cefazolin or cefuroxime as peri-operative prophylaxis and in case of MRSA carriership, vancomycin was added. In case of β-lactam allergy, a combination of vancomycin and gentamicin or aztreonam was given. Patients with history of MRSA, but negative screening were treated as carriers. Patients who were not screened or whose screening results were not known received vancomycin and cefazolin or cefuroxime and decolonisation was started immediately before their operation. Mupirocin was discontinued if test results were negative. There were some differences in baseline values. The intervention group was younger, had lower CCI scores, and were less likely to have a history of MRSA carriership compared to the control group. The primary outcome measure was the amount of complex MSSA or MRSA SSIs.

The observational study by Sporer (2016) investigated the effect of a screening and decolonisation protocol on the risk of SSIs in participants who underwent total hip or knee arthroplasty. The treatment protocol came into effect on 1 January 2009. Patients who underwent total joint arthroplasty between 2008 and 2009 were included in the control group (n=1440). The intervention group consisted of 9825 participants. In the intervention group, 98.6% of the patients underwent screening, 2.9% had a positive screening for MRSA and 25.1% for MSSA.

All patients in the intervention group were screened at least 14 days before surgery. Carriers of MSSA or MRSA were treated with 2% mupirocin ointment (Bactroban; GlaxoSmithKline, Middlesex, United Kingdom) and 2% chlorhexidine gluconate showers for five days before admission to the hospital. Cefazolin was given as antibiotic prophylaxis. MRSA patients received vancomycin, all other S. aureus–positive patients received cefazolin. Patients identified with MSSA or MRSA less than five days before admission were instructed to take showers with chlorhexidine until admission and also mupirocin until completion of 10 doses. Patients with unknown colonisation status were screened on day of admission and received mupirocin immediately before surgery and until the screening results were negative for MSSA or MRSA, or the patient had completed 10 doses. All patients, regardless of nasal colonisation, were instructed to shower the

night before the operation and apply chlorhexidine, this was repeated on the morning of surgery. Peri-operative infection rates were compared from 1 year before implementation to 5 years after implementation of the screening protocol. The study mentioned that surgical skin preparation, administration of prophylactic antibiotics and environmental conditions in the operating room were not different between the control and intervention group. SSIs were monitored by the hospital within 30 days after index surgery. The criteria of the Centers for Disease Control and Prevention were used to identify SSI.

Category 2

In one study, the differences in number of SSIs in patients undergoing total hip arthroplasty were compared between the application of mupirocin and chlorhexidine to all, or after entering a screening programme and application on indication (Stambough, 2016).

The study by Stambough, (2016) investigated the amount of SSIs of a decolonisation protocol in which mupirocin and chlorhexidine were applied to all, compared to the application to S. aureus carriers only. All patients who underwent elective primary hip or knee arthroplasty between 1 March 2011 and 31 March 2013 (n = 1864) were included in the control group and in case of surgery between 1 July 2013 and 31 July 2015 (n = 2049) in the intervention group. Patients in the control group were screened and mupirocin and chlorhexidine were given to S. aureus carriers only. In the intervention group, mupirocin and chlorhexidine were applied to all patients. Both instances were given for five days, including day of surgery. Patients were followed for 90 days to detect deep SSI and PJI, which were classified according to the National Healthcare Safety Network guidelines. In most patients, IV cefazolin was given as antibiotic prophylaxis and in case of allergy to penicillin, IV vancomycin and IV aztreonam were given. Patients who resided in a nursing facility, were on dialysis, had been hospitalised within the past year, or had a documented history of MRSA infection, were administered IV vancomycin in addition to cefazolin.

Category 3

In one study, the differences in number of revisions due to SSIs in patients who had undergone a total joint arthroplasty was compared between a group that had been screened and had received mupirocin and chlorhexidine on indication, to a group in which all patients had received chlorhexidine (Malcolm, 2016).

The retrospective clinical cohort study by Malcolm (2016) compared the risk of revision after total joint arthroplasty between a group of patients who had been screened and treated according to a decolonisation protocol (intervention group) and a group of patients who had not been screened and had received chlorhexidine (control group). No reason was given as to why these patients had not been screened. The reported outcome measure was revision arthroplasty after total hip arthroplasty (THA) or total knee arthroplasty (TKA). Revision was only assessed in patients with at least one year of follow-up. The criteria for revision surgery were not given.

In the intervention group, carriers of S. aureus had received topical mupirocin for three days two doses daily. All patients (both intervention and control groups) had used chlorhexidine body wipes pre-operatively and had received intravenous cefazolin as peri-operative antibiotic prophylaxis, or in case of MRSA carriage vancomycin. In total, 5678 patients were included in the study, of which 4042 (screened = 2291; not-screened =

1751) had at least one year of follow-up and were included in the analysis to report the number of revisions. The patients who had been screened (n = 2291; THA = 939; TKA = 1352), were compared to ones who had not been screened (n = 1751; THA = 700; TKA = 1051). The 1636 patients excluded from the analysis, were included in the study less than one year before the end of the study. Of the screened patients, twenty percent were colonised with MSSA and five percent were colonised with MRSA. At baseline, the intervention and control group were only different in Charlson Comorbidity index (CCI) score (p-value < 0.01).

Results

Surgical site infections (SSIs)

Category 1 *(number of SSIs after screening and application of mupirocin and chlorhexidine on indication compared to a (historical) control group with unknown history regarding mupirocin and/or chlorhexidine)*

In the study by Baratz (2015), no statistically significant difference was found in SSIs between the intervention and historical control cohort (Relative Risk: 0.74, CI: 0.44 to 1.22, p-value = 0.28). This remains with stratification of patients based on primary (Relative Risk: 0.77, CI: 0.40 to 1.49, p-value = 0.51) and revision cases (Relative Risk:0.76, CI: 0.34 to 1.7, p-value = 0.65). All SSIs required surgical intervention. There were no statistically significant differences between the intervention and control group in the organisms causing the infections: MSSA (Relative Risk : 0.75, 0.23 to 2.45, p-value = 0.66), MRSA (RR: 0.48, CI: 0.20 to 1.13, p-value = 0.10) and total S. aureus (Relative Risk :0.56, CI: 0.28 to 1.11, p-value = 0.11). All identified infections required surgical intervention (intervention group, n = 27; control group, n = 33).

In the study of Rao (2010) the infection rate in all patients, decreased from 2.7% in the pre-intervention control group to 1.2% in the intervention group (P = 0.009; OR 2.32 (95% CI 1.21 to 4.46). Eleven superficial (MRSA = 3; MSSA = 3; others = 5) and nine deep infections (MRSA = 5; others = 4) were found in the pre-intervention control group. Nine superficial (MSSA = 3; others = 6) and eight deep infections (MRSA = 2; others = 6) were found in the intervention group.

In the study of Schweizer (2015) the rate of complex SSIs was lower in the intervention group compared to the control group (Rate Ratio = 0.48; 95% CI 0.29 to 0.80; p-value = 0.005). After stratification for type of surgery the mean rate was significantly lower in the intervention group compared to the control group in patients who underwent elective surgery (Rate Ratio = 0.51; 95%CI: 0.30 to 0.85; p-value = 0.009), but not in patients who underwent urgent surgery (Rate Ratio: 0.44; 95%CI: 0.07 to 2.72; p-value = 0.38).

In the study by Sporer (2016), the SSI rates were lower in the intervention group compared (2009: 0.20%; 2010: 0.59%; 2011: 0.32%; 2012: 0.53%; 2013: 0.23%; 2014: 0.12%) to the historical control group (1.11%) in patients who underwent THA or TKA. In patients who underwent primary THA, the SSI rates were lower in the intervention group (2009: 0.36%; 2010: 1.02%; 2011: 0.37%; 2012: 0.48%; 2013: 0.30%, 2014: 0.16%) compared to the control group (1.54%). The proportion of S. aureus SSIs was 66.7% in the control group and 33.3% in the intervention group (p-value > 0.05).

Grading the evidence

The evidence was initially graded at a level of low evidence, because the data used was derived from three observational studies and one quasi-experimental study. Downgrading by at least one level was necessary as there were limitations in the study designs: eligibility criteria, (loss to) follow-up and outcome assessment were not always clearly specified. Moreover, most studies did not adjust for confounders. Besides, the indication for screening was not always given in the study protocol, resulting in possible selection bias. Screening also led to a more appropriate antibiotic prophylaxis in the intervention group. In addition, there was inconsistency (probably due to heterogeneity in the protocols), indirectness (some outcomes assessed for patients who underwent total joint arthroplasty instead of total hip arthroplasty) and imprecision (fewer outcomes noticed)

Conclusion

Very low GRADE	Screening for S. aureus carriership and subsequent application of mupirocin and chlorhexidine pre-operatively, combined with adapted systemic prophylaxis if MRSA was detected, was associated with a lower amount of SSI. *Sources (Baratz, 2015; Rao, 2010; Sporer, 2016; Schweizer, 2015)*

Category 2 *(number of SSIs after screening and application of mupirocin and chlorhexidine to all, compared to application on indication)*

In the study by Stambough (2016), the amount of SSI was significantly higher in the group of patients who received mupirocin and chlorhexidine on indication (control group) (n =15; 0.8%) compared to the group in which all patients received mupirocin and chlorhexidine (intervention group) (n = 5; 0.2%) in patients who underwent total joint arthroplasty (p-value = 0.013). This difference was also significant in patients who underwent total hip arthroplasty (control n = 9 (0.8%); intervention n = 2 (0.2%); p-value = 0.03).

Grading the evidence

The evidence was initially graded at a level of low evidence, because the data used was derived from one observational study. Downgrading by at least one level was necessary as there were limitations in the study designs (no adjustments for confounders).

Conclusion

Very low GRADE	Screening and application of mupirocin and chlorhexidine on indication, compared to application of mupirocin and chlorhexidine to all patients, seems to be associated with a higher amount of SSI in patients who underwent total hip arthroplasty. *Sources (Stambough, 2016)*

Category 3 *(number of revisions due to SSIs after screening and application of mupirocin and chlorhexidine on indication, compared to application of chlorhexidine to all)*

The study by Malcolm (2016) indicated no differences in rates of revision arthroplasty between patients who received mupirocin on indication (intervention group) (n = 22 (1%)) and patients who received no mupirocin (control group) (n = 25 (1.4%)) (p-value = 0.17). There was a significant difference in the reason for revision. The incidence of revision due to prosthetic joint infection was significantly lower in the intervention group (n = 9 (0.4%)) compared to the control group (n = 16 (0.9%)) (p-value = 0.04). Of the nine patients who underwent revision because of prosthetic joint infections, one person was a carrier of MSSA and eight were non-carriers.

Grading the evidence

The evidence was initially graded at a level of low evidence, because the data used was derived from one observational study. Downgrading by at least one level was necessary as there were limitations in the study designs: eligibility criteria, (loss to) follow-up and outcome assessment were not clearly specified. There was also some indirectness, because the outcome was assessed for patients who underwent total joint arthroplasty instead of total hip arthroplasty.

Very low GRADE	Screening and pre-operative decontamination of S. aureus with mupirocin, compared to no application of mupirocin seems to be associated with a lower amount of revision due to infections in patients who underwent total joint prosthesis. *Sources (Malcolm, 2016)*

Considerations

There is a minimal reduction of SSI by prophylactic use of mupirocin/chlorhexidine in all patients compared to selective use; selective use shows minimally reduced SSI compared to no use. The level of evidence for this reduction in SSI is very low grade because it is based on only a few cohort studies without any randomised controlled trials. The overall infection percentages of any regimen reports are well below 2%, so potential benefits are marginal at best.

It is questionable whether the study results mentioned can be extrapolated to the Netherlands since they are performed in countries with a much higher MRSA prevalence and the results may differ from our situation.

Furthermore, the studies performed are of heterogeneous nature regarding inclusion criteria and outcome reporting. In the studies it is not clearly stated what the procedures were for screening carriership and what the exact regimens of decolonisation were.

Another weakness is that it is unclear what the adherence to treatment was of all patients. Also in many studies, as a consequence of the screening for MRSA/MSSA, patients in the intervention group received a more adequate antibiotic prophylaxis (vancomycin in case of MRSA carriage), whilst in the control group, this carriage was unknown. In joint replacement surgery other micro-organisms, like Coagulase Negative Staphylococci are also known to be important causes of implant infections.

It is impossible with the limited current data to calculate exactly the cost effectiveness of any treatment. The costs of logistics, mupirocin, chlorhexidine, screening by PCR, costs of infection treatment and loss of labour participation are all involved, as well as the burden to the patients of infection treatment. Standard application to all patients undergoing total hip arthroplasty may result in increased mupirocin resistance and unnecessary costs; screening patients may be beneficial in reducing resistance, but has its costs and logistical burden too.

Due to the lack of solid data, we cannot support any recommendation on the prophylactic use of mupirocin/chlorhexidine. It seems wise to restrict the regimen of treating all patients to clinics with SSI levels above 2% in joint arthroplasty patients. Clinics with SSI percentages below 2% may choose to apply mupirocin/chlorhexidine selectively after screening or not at all.

Recommendation

Restrict the regimen of treating all patients with mupirocin and chlorhexidine to clinics with SSI levels in joint arthroplasty patients above 2%. Clinics with SSI percentages below 2% may choose to apply mupirocin and chlorhexidine selectively after screening or not at all.

Aanbeveling

Voor ziekenhuizen met een percentage postoperatieve wondinfecties na gewrichtsarthroplastieken boven de 2%: behandel alle patiënten met mupirocine en chloorhexidine. Voor ziekenhuizen met een percentage postoperatieve wondinfecties na gewrichtsarthroplastieken onder de 2%: behandel met mupriconine en chloorhexidine op indicatie.

Literature

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Sporer SM, Rogers T, Abella L. Methicillin-Resistant and Methicillin-Sensitive Staphylococcus aureus Screening and Decolonization to Reduce Surgical Site Infection in Elective Total Joint Arthroplasty. J Arthroplasty. 2016:31(9 Suppl):144-7. doi: 10.1016/j.arth.2016.05.019. Epub 2016 May 18. PubMed PMID: 27387479.

Stambough JB, Nam D, Warren DK, et al. Decreased Hospital Costs and Surgical Site Infection Incidence With a Universal Decolonization Protocol in Primary Total Joint Arthroplasty. J Arthroplasty. 2017;32(3):728-734.e1. doi: 10.1016/j.arth.2016.09.041. Epub 2016 Oct 8. PubMed PMID: 27823845.

Validity and maintenance

Module	Party in control	Year of authorization	Next assessment of actuality	Frequency of assessment actuality	Which party/parties monitors actuality	Important factors that might lead to change in recommendations
Pre-operative decontami-nation	**NOV, NVMM**	**2018**	**2021**	**Every three years**	**NOV, NVMM**	**New literature available**

Knowledge gaps

What is the effect of a combination of muprocin and chlorhexidine on SSI in patients who undergo a total hip arthroplasty?

Indicator

Not applicable

Implementation plan

Recommend ation	Time needed for implementa tion: <1 year, 1 to 3 years or >3 years	Expect ed effects on costs	Conditions for implementa tion	Possible barriers to implementa tion[1]	Actions for implementa tion[2]	Reponsibi lity for these actions[3]	Other remar ks
All	<1 year	Increa se	n.a.	Availabillty of mupirocin and chlorhexidin e	Quality audit	NOV	n.a.

Evidence tables

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Baratz et al. (2015)	Type of study: Retrospective clinical study Setting: Hospital-based Country: United States of America (USA) Source of funding: Not mentioned (only mentioned that the authors or a member of his or her immediate family, has no funding or commercial associations	Inclusion criteria for intervention group: In this study all patients undergoing primary or revision THA or TKA over a 2-year period at a single institution were included. Exclusion criteria for intervention group: Patients were excluded if they had a history of infection at the operative site Inclusion/exclusion criteria for control group: Not given N total at baseline:	Describe intervention (treatment/procedure/test): Two weeks before the intended surgical date, all patients were screened for nasal colonization with MSSA and MRSA. Microbiologic samples were obtained by trained nurses in the preoperative area using a nasal swab on the inside of the nares for 5 seconds in each naris. Samples were sent for rapid polymerase chain reaction (PCR) using GeneXpert1 XVI (Cepheid, Sunnyvale, CA, USA) for the detection of MRSA. Standard culture was used for the detection of MSSA. Patients determined to be carriers of either MSSA or MRSA were provided treatment with intranasal 2% mupirocin	Describe control (treatment/procedure/test): A patient group from a 2-year period before the implementation of the screening and decolonization protocol (January 2009 to December 2010). It is not written what the treatment was of patients in the control group.	Length of follow-up: Not given (SSI was defined as a hospital-acquired infection related to a surgical procedure as any infection diagnosed within 1 year of the procedure) Loss-to-follow-up: Not given Incomplete outcome data: Unclear	Outcome measures and effect size (include 95%CI and p-value if available): 2009-2010 Primary cases: 2513 Primary infections: 19 (1%) Revision cases: 567 Revision infections: 14 (3%) All cases: 3080 All infections: 33 (1%) 2012-2013 Primary cases: 2903 Primary infections: 17 (1%) Revision cases: 531 Revision infections: 10 (2%) All cases: 3434 All infections: 27 (1%) Relative risk (95% CI) Primary cases: 0.77 (0.40 – 1.49) p-value = 0.51 Revision cases: 0.76 (0.34 – 1.7)	No baseline values were given. It is not written if patients in the historical control group were treated with antibiotic prophylaxis. Incomplete outcome data is possible, because how outcome data was measured is not given.

	that might pose a conflict of interest in connection with the submitted article)	Intervention: 3080 Control: 3434 <u>Important prognostic factors[2]</u>: No baseline values were given <u>Groups comparable at baseline?</u> Not possible to assess	ointment (Bactroban; GlaxoSmithKline, Middlesex, UK) twice daily for 5 days and daily skin cleansing with 4% chlorhexidine soap (Dyna-Hex 4; Xttrium Laboratories, Chicago, IL, USA) for 5 days, including the day of surgery. Patients who were colonized received a phone call from a preoperative nurse and were provided with instructions on the treatment protocol and literature supporting the use of both products. Patients colonized with MRSA at the initial preoperative visit were rescreened on the day of surgery using the identical screening protocol for MRSA. The results of the day-of-surgery rapid PCR were made available before the start of the procedure. Standard perioperative antibiotic prophylaxis was consisted of an intraoperative dose of a first generation cephalosporin (cefazolin) followed by two			p-value = 0.65 All cases: 0.74 (0.44 - 1.22) p-value = 0.28	

			additional doses postoperatively at 8-hour intervals. Patients with a ß-lactam allergy, patients were treated with an intraoperative dose of vancomycin and one additional dose 12 hours postoperatively. Patients colonized with MRSA at either the 2-week preoperative screening visit or on the day-of-surgery screening received a single intraoperative dose of vancomycin in addition to the standard protocol of cefazolin. Patients who remained colonized with MRSA on the day of surgery were placed on isolation precautions during their hospitalization. Patients were monitored prospectively for SSI by a hospital-employed nurse responsible for quality control and infection prevention.				
Sporer et al. (2016)	Type of study: Observational study Setting:	Inclusion criteria intervention group: All patients who underwent primary total hip	Describe intervention (treatment/procedure/test): The hospital was started with screening for nasal colonization of MSSA and	Describe control (treatment/procedure/test): The surgical skin preparation, administration of	Length of follow-up: Not given (SSIs were determined if a patient's wound met the criteria of the CDC within 30 days of	Outcome measures and effect size (include 95%CI and p-value if available): Primary THA Infection Rate; %	

	Hospital-based Country: United States of America (USA) Source of funding: Not mentioned (only mentioned that one or more of the authors of this paper have disclosed potential or pertinent conflict of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which	arthroplasty (THA) or total knee arthroplasty (TKA) between 2009 and 2014 were included in this study. Exclusion criteria intervention group: Not mentioned Inclusion / exclusion criteria control group: Patients undergoing similar elective joint arthroplasty between January 1, 2008 and December 31, 2008 served as a control population. N total at baseline: Intervention: 9825 Control: 1443 Important prognostic factors[2]: Age (N(%)): 2008	MRSA before elective surgical procedure in 2009. All surgical patients were instructed to obtain a nasal swab a minimum of 14 days before the planned surgical date. Standard microbiologic culture methods were used to identify MSSA and MRSA strains. Patients who tested positive for Staphylococcus aureus were notified of their results and were instructed to begin 2% mupirocin ointment (Bactroban; GlaxoSMithKline, Middlesex, United Kingdom) applied intranasally along with 2% chlorhexidine gluconate (CHG) showers (HiBiClens is 4%, CHG cloths are 2%; HiBiClens; Monlnlycke Health Care, Norcross, Georgia) 5 days before admission to the hospital. Patients were instructed to apply a pea-sized amount of ointment into each nostril twice daily, morning and evening, along with compressing the nares several times to	prophylactic antibiotics, and environmental conditions in the operating room were the same in the intervention and control group.	the index surgical procedure. Loss-to-follow-up: Not given Incomplete outcome data: Unclear	Change from Previous Year 2008 1.54% 2009 0.36%; -76.91 2010 1.02%; 185.79 2011 0.37%; -63.92 2012 0.48%; 30.0 2013 0.30%; -37.41 2014 0.16%; -45.97	

	may be perceived to have potential conflict of interest with this work)	< 50 = 119 (8.3) 50 -59 = 376 (26.1) 60-69 = 452 (31.4) 70-79 = 360 (25.0) ≥ 80 = 133 (9.2) 2009 < 50 = 114 (7.5) 50 -59 = 370 (24.3) 60-69 = 521 (34.2) 70-79 = 354 (23.3) ≥ 80 = 163 (10.7) 2010 < 50 = 118 (7.1) 50 -59 = 446 (26.7) 60-69 = 568 (34.1) 70-79 = 405 (24.3) ≥ 80 = 130 (7.8) 2011 < 50 = 94 (6.1) 50 -59 = 374 (24.4) 60-69 = 546 (35.6) 70-79 = 371 (24.4) ≥ 80 = 145 (9.5) 2012 < 50 = 104 (6.1) 50 -59 = 397 (23.3) 60-69 = 622 (36.6) 70-79 = 416 (24.4)	distribute the ointment. Patients who tested positive for MRSA were treated with vancomycin within 2 hours before surgery. All other Staphylococcus aureus – positive patients were treated with cefazolin within an hour of surgery. Antibiotic prophylaxis was then discontinued with 24 hours after the surgical procedure. In addition, patients who tested positive for MRSA colonization were placed on contact precautions that included the use of barrier gowns and gloves during patient contact. Patients identified as positive for either MSSA or MRSA less than 5 days before admission began CHG showers as soon as possible and continued them until admission. Intranasal decolonization of these patients identified less than 5 days before surgery continued mupirocin until completion of 10 doses. Patients of unknown colonization status were screened on the day of				

		≥ 80 = 163 (9.6) 2013 < 50 = 86 (5.0) 50 -59 = 405 (23.6) 60-69 = 662 (38.6) 70-79 = 419 (24.4) ≥ 80 = 145 (8.4) 2014 < 50 = 101 (6.1) 50 -59 = 369 (22.3) 60-69 = 642 (38.8) 70-79 = 431 (26.1) ≥ 80 = 110 (6.7) Sex (male (N(%)) 2008 = 593 (41.2) 2009 = 616 (40.5) 2010 = 673 (40.4) 2011 = 606 (39.6) 2012 = 702 (41.3) 2013 = 691 (40.2) 2014 = 684 (41.4) Length of stay (days) (N (%)) 2008 <3 days = 393 (27.3) 3-4 days = 930 (64.6) > 5 days = 117 (8.1)	admission. Mupirocin was administered immediately before surgery in this cohort of patients and was continued postoperatively until the screening results were negative either MSSA or MRSA or the patient completed the 10-dose decolonization regime. All patients regardless of nasal colonization, were instructed to shower the night before surgery and apply a 6-cloth CHG regimen to all skin, except the face and genitals, a minimum of 1 hour after showering. The topical skin preparation with the chlorhexidine cloths was repeated on the morning of surgery in the holding area immediately before surgery.				

		2009 < 3 days = 395 (26.0) 3-4 days = 1024 (67.3) > 5 days =103 (6.8) 2010 < 3 days = 50.8 (30.5) 3-4 days = 1076 (64.5) >5 days = 83 (5.0) 2011 < 3 days = 386 (25.2) 3-4 days = 1072 (70.1) > 5 days = 72 (4.7) 2012 < 3 days = 477 (28.0) 3-4 days = 1150 (67.6) > 5 days = 75 (4.4) 2013 < 3 days = 526 (30.6) 3-4 days = 1123 (65.4) > 5 days = 68 (4.0) 2014					

		< 3 days = 583 (35.3) 3-4 days = 994 (60.1) > 5 days = 76 (4.6) Total < 3 days = 3268 (29.1) 3-4 days = 7369 (65.6) > 5 days = 594 (5.3) <u>Groups comparable at baseline?</u> Not comparable in age and length of stay					
Malcolm et al (2016)	<u>Type of study:</u> Retrospective observational study <u>Setting:</u> Hospital-based (Cleveland Clinic Foundation main campus. Hillcrest	<u>Inclusion criteria</u>: All patients who underwent primary total hip arthroplasty (THA) or total knee arthroplasty (TKA) between October 2011 and March 2014 were included in this study. <u>Exclusion criteria</u>: Patients were excluded if they	<u>Describe intervention (treatment/procedure/test):</u> Patients were screened by sampling the nasal flora with a nasal swab and subsequent analysis with either PCR testing or bacterial cultures up to four weeks before surgery. Approximately one week prior to surgery, patients who carried *S.*	<u>Describe control (treatment/procedure/test):</u> All patients in the study used chlorhexidine body wipes preoperatively and received appropriate perioperative antibiotic prophylaxis. Patients not carrying MRSA received weight-based intravenous cefazolin 30 to 60 minutes preoperatively followed by repeated	<u>Length of follow-up</u>: Not given (at least one year) <u>Loss-to-follow-up</u>: Not given <u>Incomplete outcome data</u>: Unclear	<u>Outcome measures and effect size (include 95%CI and p-value if available):</u> Total revision: Intervention group: 22 (1.0%) Control group: 25 (1.4%) p-value = 0.17 Reason for revision: Prosthetic joint infection: Intervention group: 9 (0.4%) Control group: 16 (0.9%) p-value = 0.04	Patients were included in the control group if they did not underwent screening. The reason why they did not underwent screening is not given in the studies.

	Hospital, Lutheran Hospital, Euclid Hospital) Country: United States of America (USA) Source of funding: Not mentioned	underwent revision TJA. <u>Inclusion/exclusion criteria control group:</u> Patients were included in the control group if they did not undergo nasal culture for Staphylococcus aureus at least four days prior to TJA. Patients were excluded if they were found to be undergoing revision TJA. <u>N total at baseline</u>: Intervention: 2291 (56.7%) Control: 1751 (43.4%) <u>Important prognostic factors[2]</u>: Mean age (SD) Intervention: 63.8 (11.2) Control: 64.2	*aureus* were treated with topical mupirocin twice daily for three days. All patients in the study used chlorhexidine body wipes preoperatively and received appropriate perioperative antibiotic prophylaxis. Patients not carrying MRSA received weight-based intravenous cefazolin 30 to 60 minutes preoperatively followed by repeated postoperative doses every eight hours for 24 hours. Patients who carried MRSA were administered weight-based vancomycin preoperatively followed by repeated postoperative doses every twelve hours for 24 hours. Those allergic to cephalosporin were administered either clindamycin or vancomycin in a similar manner.	postoperative doses every eight hours for 24 hours. Patients who carried MRSA were administered weight-based vancomycin preoperatively followed by repeated postoperative doses every twelve hours for 24 hours. Those allergic to cephalosporin were administered either clindamycin or vancomycin in a similar manner.		Mechanical failure: Intervention group: 13 (0.6%) Control group: 9 (0.5%) p-value = 1.0	

		(12.0) p-value = 0.24 Gender, n (%) Intervention: Female: 1352 (59%) Male: 1051 (60%) Control: Female: 1051 (60%) Male: 700 (40%) Groups comparable at baseline? Not comparable in Charlson Comoribity Index (p-value < 0.01					
Rao et al (2011)	Type of study: Prospective observational study Setting: Hospital-based Country: United States of America (USA)	Inclusion criteria: Not given (Its only written that patients in the intervention and preintervention control group were treated by the same surgeons. All patients who were treated by the other surgeons were included in the concurrent	Describe intervention (treatment/procedure/test): Patients were screened for S aureus nasal carriage two to four weeks before surgery. Patients were educated about the rationale for nasal cultures, and informed consent was obtained. Samples were collected from both nares on a single swab (BBL Culture Swab Plus; BD	Describe control (treatment/procedure/test): It is not written what the treatment was of patients in the control group.	Length of follow-up: Two years Loss-to-follow-up: The study mentioned no lost to follow-up, but 155 patients in the intervention group missed screening. Incomplete outcome data: Unclear	Outcome measures and effect size (include 95%CI and p-value if available): No. of SSIs in patients with positive nasal cultures confirmed (intervention group) and in the concurrent control group Intervention = 0 Concurrent control = 19 Surgical Site Infections among patients who underwent TJA by the	It is written that all patients were prospectively monitored for development of SSIs.

	Source of funding: Not funded	control group. In addition, all 741 patients whose surgery was performed by the 3 participating surgeons between October 2004 and October 2005 served as a preintervention control group) Exclusion criteria: Not given N total at baseline: Intervention group: 1440 Concurrent control group: 2284 Preintervention control group: 741 Important prognostic factors[2]: No baseline values given Groups comparable at baseline?	Diagnostics, Sparks, MD). The inside circumference of each anterior nares was rubbed for 3 to 5 seconds to obtain adequate sampling. Specimens were inoculated onto BBL CHROMagar MRSA and CHROMagar SA plates (BD Microbiology Systems, Sparks, MD), which were incubated for 20 to 28 hours at 35°C to 37°C. After 24 hours, we interpreted mauve colonies present on both plates as MRSA and on only the CHROMagar SA plate as MSSA. Negative plates were incubated for an additional 24 hours. Mauve colonies present on either medium at 48 hours were verified as S aureus by Gram stain and coagulase testing (Staphaurex; Remel, Lenexa, KS). Mauve colonies growing on both media were reported			same group of orthopaedic surgeons during the preintervention period and intervention period: MSSA = 3 MRSA = 2 Others = 6 Preintervention period: MSSA = 3 MRSA = 8 Others = 9 Type of infection (type intervention / n preintervention period or intervention period): Preintervention period: Risk of superficial infections 11/741 (1.5%) Risk of deep infections: 9/741 (1.2%) Total: 20/741 (2.7%) Intervention period: Risk of superficial infections: 9/1440 (0.6%) Risk of deep infections: 8/1440 (0.6%) Total: 20/741 (2.7%)	

		Not possible to assess	as MRSA, whereas colonies growing only on CHROMagar SA were reported as MSSA. Approximately 1 week before surgery, patients with nasal cultures positive for S aureus were educated about the rationale for the decolonization protocol, which was performed in the outpatient setting. Patients were instructed to apply mupirocin nasal ointment twice daily to both nares and to bathe with chlorhexidine daily for 5 days immediately before the scheduled surgery. During surgery, all patients received perioperative antibiotic prophylaxis. The standard regimen was cefazolin 2 g administered 30 to 60 minutes before surgery followed by 1 g every 8 hours for 24 hours. The alternative regimen for patients with a history of MRSA infection or type I allergy to penicillin and for MRSA carriers in the				

			intervention group was vancomycin 1 g 60 minutes before surgery followed by 1 g every 12 hours for 24 hours.				
Schweizer et al. (2016)	Type of study: A quasi-experimental study Setting: Hospital-based Country: United States of America (USA) Source of funding: This project was funded by the Agency for Healthcare Research and Quality (AHRQ; HHSA290200 6100021I and grant HS022467-02), US Department of Health and	Inclusion criteria intervention group: Eligible patients were 18 years or older and underwent scheduled, urgent, or emergent primary hip or knee arthroplasty (ie, replacement or resurfacing). Exclusion criteria intervention group: Arthroplasty revisions, cardiac transplants, transapical valve implantation, and operations performed using percutaneous or thoracotomy approaches were not eligible for this study. We	Describe intervention (treatment/procedure/test): Hospital staff swabbed patients' nares during scheduled preoperative clinic visits (usually 10-14 days, but no more than 30 days before the operations). Each laboratory used their standard tests (eg, polymerase chain reaction, culture on chromogenic agar, standard bacterial culture) to determine MRSA and MSSA carrier status. The most common tests were chromogenic agar for MRSA and standard culture for MSSA. Patients with positive screening tests for either MRSA or MSSA applied mupirocin intranasally twice daily and bathed with CHG once daily for up to 5 days immediately before	Describe control (treatment/procedure/test): The preintervention period extended from March 1, 2009, to the date on which a hospital began the intervention.	Length of follow-up: Patients were followed up for 90 days after their operations by infection preventionists at participating hospitals. Loss-to-follow-up: Not given Incomplete outcome data: Unclear	Outcome measures and effect size (include 95%CI and p-value if available): Complex Staphylococcus aureus Surgical Site Infections per 10000 operations Rate ratio for Bundled Intervention (95% CI) (intervention period vs preintervention period) Hip or knee arthroplasties RR 0.48 (95%CI 0.29 – 0.80) p-value = 0.005 Urgent/emergent RR 0l.44 (0.07 – 2.72) p-value = 0.38 Scheduled RR 0.51 (0.30 – 0.85) p-value = 0.009	Hospitals that using some, but not all bundle elements during the preintervention period could participate. Its not mentioned in the study how patients were followed up by infection preventionists.

	Human Services. It also received support from the VA Health Services Research and Development (CDA 11-211; Dr Schweizer).	excluded operations among patients with pre-existing infections at the surgical site. Inclusion/exclusion criteria control group: Only mentioned that hospitals using some, but not all, bundle elements during the preintervention period could participate. N total at baseline: Intervention group: 20642 operations Control group: 11059 operations Important prognostic factors[2]: Sex: Preintervention group: Female: 12661 (61.4) Intervention	their operations. Patients that received fewer than 10 doses of mupirocin before their operations received the remaining doses during the postoperative period. The CHG bathing was not continued after the operation. Patients with negative MRSA and MSSA nasal screens bathed with CHG the night before and the morning of their operations. Perioperative prophylaxis was administered using weight based dosing and redosing according to the 2013 American Society of Health-System Pharmacists (ASHP) guidelines. The antimicrobial agents used for perioperative prophylaxis varied by the patients' *S aureus* carrier status; noncarriers and MSSA carriers received either cefazolin or cefuroxime for perioperative prophylaxis, whereas MRSA carriers received both cefazolin or				

		group: Female: 6734 (60.9) p-value = 0.41 Age, median (range) Preintervention group: 68 (21-107) Intervention group: 68 (18 – 101) p-value < 0.001 <u>Groups comparable at baseline?</u> Not comparable in age, CCI and MRSA history	cefuroxime and vancomycin. If a patient had a confirmed β-lactam allergy, surgeons were encouraged to provide perioperative prophylaxis with vancomycin rather than cefazolin or cefuroxime and to add either gentamicin or aztreonam for gram-negative coverage. Patients with negative screening tests but with documented histories of MRSA carriage or infection were treated as carriers. Patients who were either not screened because they had emergent operations or whose screening results were not known at the time of their operations received vancomycin and cefazolin or cefuroxime for perioperative prophylaxis. In these situations, nasal swabs were obtained for MSSA and MRSA screening and patients began the decolonization regimen immediately before their operations. Mupirocin				

			was continued until screening test results were known; mupirocin was discontinued if test results were negative.				
Stambough et al. (2016)	Type of study: Retrospective review of prospective data Setting: Hospital-based Country: United States of America (USA) Source of funding: Its mentioned in the article that one or more of the authors of this paper have disclosed potential or pertinent conflicts of	Inclusion criteria: Cohort of patients from the academic medical center's infection surveillance program who underwent elective primary hip or knee arthroplasty between March 1, 2011 and July 31, 2015. Patients were divided in 2 cohorts based on the 25 months before (control group) and the 25 months after establishment of the universal decolonization protocol (intervention group). Exclusion criteria: Patients were excluded when	Describe intervention (treatment/procedure/test): Patients in the intervention group were screened within 30 days of their surgery. Swabs of both nares were obtained and sent to the laboratory. All patients were treated with 2% nasal ointment and a single preoperative chlorhexidine shower. At the day of surgery, all nasal screening results were available. Carriers of MRSA were perioperative treated with Vancomycin 1 gram every 12 hours starting at least 30 minutes before incision and lasting for 24 hours. The surgical technique, implants and postoperative care were similar in both groups. In addition to preoperative mupirocin nasal ointment and chlorhexidine scrub,	Describe control (treatment/procedure/test): Patients in the control group were all screened for S aureus colonization and selectively treated preoperatively with 5 days mupirocin. Patients were treated with a CHG wipes at the day of surgery.	Length to follow-up: 90 days Loss-to-follow-up: Not given Incomplete outcome data: Unclear	Outcome measures and effect size (include 95%CI and p-value if available): Total number of SSI infections (THA+TKA): Control group: 15 (0,8%) Intervention group: 5 (0,2%) (P-value = 0.013) Infection caused by MRSA or MSSA (THA+TKA): Control group: 10 (0.5%) Intervention group: 2 (0.09%) (P-value = 0.01) Infection caused by MRSA (THA+TKA): Control group: 6 (0.3%) Intervention group: 1 (0.04%) (P-value = 0.05) Total number of SSI infections (THA): Control group: 9 Intervention group: 2 (P-value = 0.03)	

	interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interests with this work.	they were admitted via the emergency department. Patients with prior instrumentation who were undergoing revision or conversion arthroplasty were also excluded. Patients treated in the 3 months surrounding the protocol change were removed to control for potential treatment bias during the transition period. <u>N total at baseline (n= 4186 replacements)</u>: Intervention group (2205 TJA in 2049 patients): TKA: 1003 THA: 1202 Control group (1981 TJA in 1846 patients): TKA: 836	all patients were administered IV antibiotics within 1 our before surgical incision. Antibiotic selection was based on a risk stratification protocol and was continued for 24 hours postoperatively. The majority of patients received a weight-based dose of IV cefazolin – 2g for those with a weight <120 kg and 3 g if >120 kg. Those with a true penicillin allergy were given 1 g of vancomycin and 1 g of IV aztreonam to cover both gram-positive and gram-negative microbes. Additionally, patients who resided in a nursing facility, were on dialysis, had been hospitalized within the past year, or had a documented history of MRSA infection from an unrelated previous admission were administered IV vancomycin in addition to weight-based cefazolin.			Infection caused by MRSA or MSSA (THA): Control group: 7 Intervention group: 0 (P-value = 0.003) Infection caused by MRSA (THA): Control group: 4 Intervention group: 0 (P-value = 0.05)	

		THA: 1145 <u>Important prognostic factors[2]</u>: Age (y mean±SD): Control group: 57.2±14.1 Intervention group: 58.2±13.5 (χ^2 = 0.08) Gender (n male): Control group: 548 Intervention group: 558 (χ^2 = 0.025) <u>Groups comparable at baseline?</u> Yes (only not in ASA)					

Notes:

1. **Prognostic balance between treatment groups is usually guaranteed in randomized studies, but non-randomized (observational) studies require matching of patients between treatment groups (case-control studies) or multivariate adjustment for prognostic factors (confounders) (cohort studies); the evidence table should contain sufficient details on these procedures.**
2. **Provide data per treatment group on the most important prognostic factors ((potential) confounders).**
3. **For case-control studies, provide sufficient detail on the procedure used to match cases and controls.**
4. **For cohort studies, provide sufficient detail on the (multivariate) analyses used to adjust for (potential) confounders.**

Risk of bias table for intervention studies (observational: non-randomized clinical trials, cohort and case-control studies)

Study reference (first author, year of publication)	Bias due to a non-representative or ill-defined sample of patients?[1] (unlikely/likely/unclear)	Bias due to insufficiently long, or incomplete follow-up, or differences in follow-up between treatment groups?[2] (unlikely/likely/unclear)	Bias due to ill-defined or inadequately measured outcome ?[3] (unlikely/likely/unclear)	Bias due to inadequate adjustment for all important prognostic factors?[4] (unlikely/likely/unclear)
Baratz et al. (2015)	Unclear	Unclear	Unclear	Likely
Sporer et al. (2016)	Unclear	Unclear	Unclear	Likely
Malcolm et al. (2016)	Unclear	Unclear	Unclear	Likely
Rao et al. (2011)	Unclear	Likely	Unclear	Likely
Schweizer et al. (2016)	Unclear	Unclear	Unclear	Unlikely
Stambough et al. (2016)	Unlikely	Unclear	Unclear	Likely

1. **Failure to develop and apply appropriate eligibility criteria: a) case-control study: under- or over-matching in case-control studies; b) cohort study: selection of exposed and unexposed from different populations.**
2. **2 Bias is likely if: the percentage of patients lost to follow-up is large; or differs between treatment groups; or the reasons for loss to follow-up differ between treatment groups; or length of follow-up differs between treatment groups or is too short. The risk of bias is unclear if: the number of patients lost to follow-up; or the reasons why, are not reported.**
3. **Flawed measurement, or differences in measurement of outcome in treatment and control group; bias may also result from a lack of blinding of those assessing outcomes (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is not necessary. If a study has "soft" (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary.**
4. **Failure to adequately measure all known prognostic factors and/or failure to adequately adjust for these factors in multivariate statistical analysis.**

Search strategy

Database	Search terms	Total
Medline (OVID)	1 arthroplasty/ or exp arthroplasty, replacement/ or exp Joint Prosthesis/ (74112) 2 *"Surgical Wound Infection"/pc or "Staphylococcal Infections"/pc or ("surgical site infection*" or SSI* or decolonali?ation or decontamination).ti,ab,kf. (29741) 3 Orthopedic Procedures/ or (hip or hips or knee or knees or Orthop?edic* or replacement* or implant*).ti,ab,kf. (802414) 4 2 and 3 (3005) 5 1 or 4 (76500) 6 Mupirocin/ or (Mupirocin* or bactroban*).ti,ab,kf. (1791) 7 5 and 6 (67) 8 limit 7 to english language (62) 9 remove duplicates from 8 (61)	138
Embase (Elsevier)	'replacement arthroplasty'/exp/mj OR 'joint prosthesis'/exp/mj OR 'arthroplasty'/exp/mj OR ('surgical infection'/exp/mj/dm_pc OR 'staphylococcus infection'/exp/mj/dm_pc OR 'surgical site infection*':ti,ab OR ssi*:ti,ab OR decolonalization:ti,ab OR decolonalisation:ti,ab OR decontamination:ti,ab AND ('orthopedic surgery'/exp/mj OR 'general surgery'/de OR hip OR hips OR knee OR knees OR orthopedic* OR orthopaedic* OR replacement* OR implant*:ti,ab)) AND ('pseudomonic acid'/exp OR mupirocin*:ti,ab OR bactroban*:ti,ab OR 'pseudomonic acid*':ti,ab) NOT 'conference abstract':it AND (english)/lim AND (embase)/lim (115), 77 uniek	

Exclusion table

Table Exclusion after reading full text

Author and year	Reasons of exclusion
Bode, (2010)	Not specific about patients which underwent total joint arthroplasty (no subgroup analyses).
Bode, (2016)	Not specific about patients which underwent total joint arthroplasty (no subgroup analyses).
George, (2016)	A systematic review in which studies about multiple comparisons were included.
Hacek,. (2008)	Intervention is mupirocin not in combination with chlorhexidine.
Hadley, (2010)	Screening was used to define type of antibiotic prophylaxis
Kalmeijer, (2002)	Intervention is mupirocin not in combination with chlorhexidine.
Lepelletier, (2014)	Guideline without systematic search
Levy, (2013)	Intervention is mupirocin not in combination with chlorhexidine.
Slover, (2011)	Cost effectiveness analysis
Van Rijen, (2012)	Cost analysis
Kim,. (2010)	Not specific about patients which underwent total joint arthroplasty

Module 5 Postoperative care

Research question

5.1 What is the optimal interval of routine follow-up after a total hip replacement and what role does imaging play in this?

5.2 Is antibiotic prophylaxis indicated before dental procedures in patients having a hip prosthesis?

Uitgangsvragen

5.1 Wat is het optimale interval van routinematige follow-up na een totale heupvervanging en welke rol speelt beeldvorming hierbij?

5.2 Is antibioticaprofylaxe geïndiceerd bij patiënten met een gewrichtsprothese die een tandheelkundige ingreep ondergaan

5.1 Routine follow-up

Research question

What is the optimal interval of routine follow-up after a total hip replacement and what role does imaging play in this?

Uitgangsvraag

Wat is het optimale interval van routinematige follow-up na een totale heupvervanging en welke rol speelt beeldvorming hierbij?

Introduction

After a successful total hip replacement the question is whether routine clinical and radiological examinations are indicated. At the moment routine clinical and radiological examinations are advised after the first and after the fifth year.

Search and select

To answer the question a systematic literature analysis was performed for the following research question: What are the (un)favourable effects of routine follow-up (including radiological follow-up), compared to no follow-up, in patients that underwent a total hip arthroplasty?

P: patients that had undergone a total hip arthroplasty;
I: follow-up with or without imaging for complications, radiological findings;
C: no follow-up;
O: missed diagnoses.

The working group did not define outcomes a priori, but used definitions as provided in the studies.

Search and select (Method)

A literature search was performed with relevant search terms on 18 May 2017 in the database (Medline (via OVID). The search strategy is provided in the tab "Methods". The literature search resulted in 197 hits. Studies were selected using the following selection criteria: use of radiological and another follow-up method. After obtaining full text, two studies were included in literature analysis. One study of the 2010 guideline also fulfilled the PICO and was included in the literature summary.

The most important study characteristics are described in evidence tables.

Literature summary

Description of studies and results

One study was included (Christensen, 2013). Also, two studies are described that were also included in the 2010 guideline and that fulfilled the PICO criteria (King, 2004 and Röder, 2003).

Christensen used a retrospective chart review of 249 patients after uncomplicated cementless primary THA, to study consequences of radiographic follow-up after three months and after twelve months. The radiographic examination had direct consequences in five cases (1.2%) out of 417 outpatient visits. However, in only two cases did the radiographs result in consequences other than increased follow-up (Christensen, 2013).

Röder, (2003) analysed the follow-up of 18,486 patients with a total hip arthroplasty between 1967 and 2001 (18,486 THAs). Sensitivity, specificity, negative and positive predictive values with respect to acetabular and femoral loosening were evaluated for ten clinical variables: five different locations of pain (hip, buttock, groin, thigh, knee), four elements of pain on testing (over trochanter, on axial compression, internal rotation and external rotation) and range of flexion. Sensitivities were all low (between 0.0 and 0.6), specificity values were all between 0.89 and 1.0. Positive predictive values increased from 0.00 to 0.66 in the ten years after surgery, negative predictive values decreased from 1.00 to 0.86. The authors concluded that routine follow-up of asymptomatic patients with THA was not necessary during the first five or six years.

King, (2004) found no difference in clinical outcome between 30 patients who had not shown up for follow-up between 6 months and 5 years following surgery, compared to 131 patients that had routine postoperative controls.

Grading of evidence

The quality of evidence started as low as only non-comparative studies were included and was downgraded one level to very low because of heterogeneity of the studies.

Conclusion

Very low GRADE	There is no benefit of routine follow-up in asymptomatic patients within 5 years after total hip arthroplasty. *Sources (Christensen 2013; King 2004; Röder, 2003)*

Considerations

Monitoring of patients shortly after the operation concentrates on healing of the wound and on recovery of function. Broadly speaking, this stage is complete 1 year after surgery, including the fixation of an uncemented prosthesis. After the first year, routine follow-up is aimed at detection of complications such as polyethylene wear or osteolysis and at deterioration of function.

Lovelock and Broughton (2018) (expert opinion) discussed the need for routine follow-up after arthroplasty of the hip and knee. They stated that the early failure of the total hip arthroplasty (within five years) is decreased because of the diminishing incidence of dislocation due to the increased use of the 32 mm head size and the use of components rated as Orthopaedic Data Evaluation Panel (ODEP) 10A. Nevertheless, they recommend to offer routine follow-up depending on age of the patient and type of prosthesis.

Polythylene particles could lead to osteolysis and subsequent loosening. When detecting this loosening on X-rays, an operative intervention should be advised. Loosening of components usually leads to complaints, although a few patients remain asymptomatic. Sandgren (2014) studied a cohort of 206 asymptomatic patients with several uncemented cup prostheses with a median follow-up of 10 years after surgery (range 7 to 14 years). They analysed peri-acetabular osteolysis using CT examinations. They found that 57 patients (27.7%) had peri-acetabular osteolysis of more than 10 mm. Wear was associated with osteolysis. Sandgren et al advised follow-up on a regular basis with CT scan. However, mostly these adverse reactions do not occur within the first 5 to 10 years after surgery. Therefore, it is questionable whether routine follow-up of many patients for a long time, with high radiation levels of the CT scan, to detect only a few patients with asymptomatic osteolysis or loosening is justified.

Absence of any routine follow-up might lead to undetected silent osteolysis or loss of function, which may increase risk of falling with possibly devastating consequences.

If routine follow-up is considered, the following aspects might play a role in determining the optimal frequency:

- Risk of complications. Risk is low in the first 5-10 years after surgery.
- Age of the patient at surgery. With a 10-year survival of 95% for a prosthesis, it is not necessary to routinely follow-up patients aged 70 years or older. These patients should be advised to return when they have complaints.
- Type of prosthesis.
- Not all patients will spontaneously contact their doctor. They should be reminded. By being followed up every 1, 2, or 3 years, patients get used to regular follow-up at a later stage, especially younger patients.
- Quality control. It is important for an orthopaedic surgeon to know the results of his/her own work (quality control). This is only possible by regular clinical and radiological monitoring of his or her own patients.

The working group recommends performing routine follow-up on patients one year after total hip arthroplasty. After that, asymptomatic patients do not need routine follow-up within the first five years after surgery. If wear is detected on X-ray during follow-up, a CT-scan may be considered.

Recommendations

The working group is of the opinion that routine follow-up of patients after a total hip arthroplasty should be performed at least during the first year and after a minimum of five years, or sooner if the surgeon deems it necessary.

A recommendation about the optimal frequency of routine follow-up after the first 5 years cannot be given based on the current literature.

Aanbeveling

Routinematige follow-up moet plaatsvinden in ieder geval gedurende het eerste jaar, en na het vijfde jaar, of eerder als de operateur daar aanleiding toe ziet.

Op basis van de recente literatuur is het niet mogelijk om een optimale frequentie van follow-up aan te geven na het vijfde jaar.

Literature

Christensen M, Folkmar K. No clinical value of post-operative routine X-ray following uncomplicated cementless primary total hip arthroplasty. Dan Med J. 2013;60(4):A4613. PubMed PMID: 23651720.2e.

Kingsbury SR, Dube B, Thomas CM, et al. Is a questionnaire and radiograph-based follow-up model for patients with primary hip and knee arthroplasty a viable alternative to traditional regular outpatient follow-up clinic? Bone Joint J. 2016;98-B(2):201-8. doi: 10.1302/0301-620X.98B2.36424. PubMed PMID: 26850425.3e.

King PJ, Malin, AS, Scott, RD, et al. The fate of patients not returning for follow-up five years after total knee arthroplasty. J Bone Joint Surg Am. 2004;86-A- 897.

Lovelock TM, Broughton NS. Follow-up after arthroplasty of the hip and knee; are we over-servicing or under-caring? Bone Joint J. 2018;100-B:6-10.

Röder C, Eggli S, Aebi M, et al. (2003). The validity of clinical examination in the diagnosis of loosening of components in total hip arthroplasty. J Bone Joint Surg Br. 2003;85:37-44.

Sandgren B, Crafoord J, Olivecrona H, et al. Risk factors for periacetabular osteolysis and wear in asymptomatic patients with uncemented total hip arthroplasties. ScientificWorldJournal. 2014;2014:905818. doi: 10.1155/2014/905818. Epub 2014 Nov 16.

Validity and maintenance

Module	Party in control	Year of authorization	Next assessment of actuality	Frequency of assessment actuality	Which party/parties monitors actuality	Important factors that might lead to change in recommendations
Routine follow-up	NOV	2018	2023	Every five years	NOV	-

Knowledge gaps

Is there an indication to perform radiographic and clinical follow-up in asymptomatic patients 5 years after total hip arthroplasty?

Is it possible to detect a need for revision in asymptomatic patients after total hip arthroplasty using PROMS and radiographs, without consulting the orthopaedic surgeon?

Indicator

Not applicable

Implementation plan

Recommendation	Time needed for implementation: <1 year, 1 to 3 years or >3 years	Expected effects on costs	Conditions for implementation	Possible barriers to implementation[1]	Actions for implementation[2]	Reponsibility for these actions[3]	Other remarks
All	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.

Evidence tables

Research question: What are the (un)favourable effects of routine follow-up (including radiological follow-up), compared to no follow-up, in patients that underwent a total hip arthroplasty?

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Christensen, 2013	Type of study: retrospective chart review Setting: hospital Country: Denmark Source of funding: unknown	Inclusion criteria: patients undergoing cementless primary THA from August to November 2009 at Hørsholm Hospital, Orthopaedic Hip Clinic Exclusion criteria: major per- or post-operative complications such as fracture, deep infection, or dislocation and cases requiring bone transplantation were excluded. Patients having complaints that led to early referral and additional outpatient follow-up outside of the planned three- and 12-month follow-up visits were also excluded. N total at baseline:	Describe intervention (treatment/procedure/test): Radiographic follow-up	Describe control (treatment/procedure/test): -	Length of follow-up: 3 and 12 months Loss-to-follow-up: A total of 11 patients were excluded before the three month follow-up visit; seven patients had fractures, four of which occurred during surgery. The remaining four patients had major post-operative complications requiring revision; two had loosening of the cup and two had deep infection. One patient had fallen between the two outpatient visits and had suffered a trochanteric	Outcome measures and effect size (include 95%CI and p-value if available): Among 417 outpatient visits, the radiographic examination had direct consequence in five cases (1.2%;95% confidence interval (CI): 0.4-2.8%); however, in only two cases (0.48%; 95% CI: 0.06-1.72) did the radiographs result in consequences other than increased follow-up.	

		N=249 Important prognostic factors[2]: *Age ± SD: 68 (26-93)* *Sex:* *36 % M* Main indication was osteoarthritis (OA) (n = 215; 91%). Other indications were dysplasia (n = 10; 4%), sequelae from fracture (n = 6; 2.5%), rheumatoid arthritis (n = 4; 1.7%) and caput necrosis (n = 1; 0.4%).			fracture and was thus excluded at the 12-month follow-up.		
Kingsbury, 2016	Type of study: audit Setting: hospital and outpatient clinic Country: UK Source of funding: partly by national institute for health research and partially by WELMEC a centre of excellence in	Inclusion criteria: Patients attending a standard care ACP-led THA/TKA follow-up outpatient clinic from Oct 2011 to Sept 2013 included in the audit Exclusion criteria: patients attending for follow-up or revision surgery or a procedure other than primary THA/TKA N total at baseline: Intervention:	Describe intervention (treatment/procedure/test): Arthroplasty Care practitioner-led follow-up in outpatient clinic consisting of: a pelvic/knee radiograph, a pain/function questionnaire and review by the Arthroplasty Care Practitioner	Describe control (treatment/procedure/test): An experienced orthopaedic surgeon reviewed the same radiographs and questionnaires without patient contact or knowledge of the ACP's decision.	Length of follow-up: unclear Loss-to-follow-up: Intervention: N (%) Reasons (describe) Control: N (%) Reasons (describe) Incomplete outcome data: Intervention: N (%)	Outcome measures and effect size (include 95%CI and p-value if available): Agreement between ACP and surgeon scored as kappa: 0.69 (95 % CI 0.62-0.76) Positive agreement was very high for discharge and routine follow-up; however, the ACP	Hip and knee

	medical engineering funded by welcome trust and EPSRC	Control: <u>Important prognostic factors[2]</u>: *For example* *age ± SD:* *I:* *C:* *Sex:* *I: % M* *C: % M* Groups comparable at baseline?			Reasons (describe) Control: N (%) Reasons (describe)	was more likely to select routine follow-up and the surgeon urgent review.	

Notes:

1. **Prognostic balance between treatment groups is usually guaranteed in randomized studies, but non-randomized (observational) studies require matching of patients between treatment groups (case-control studies) or multivariate adjustment for prognostic factors (confounders) (cohort studies); the evidence table should contain sufficient details on these procedures.**
2. **Provide data per treatment group on the most important prognostic factors ((potential) confounders).**
3. **For case-control studies, provide sufficient detail on the procedure used to match cases and controls.**
4. **For cohort studies, provide sufficient detail on the (multivariate) analyses used to adjust for (potential) confounders.**

Search strategy

Database	Search terms	Total
Medline (OVID) 2010-mei 2017 Engels	1 Arthroplasty, Replacement, Hip/ or Hip Prosthesis/ (35016) 2 arthroplasty/ or arthroplasty, replacement/ or joint prosthesis/ or metal-on-metal joint prostheses/ or "Prostheses and Implants"/ or (arthroplast* or replacement* or prosthes#s).ti,ab,kf. (359486) 3 hip/ or hip joint/ or hip.ti,ab. (125243) 4 2 and 3 (41024) 5 1 or 4 (49819) 6 (THA or THAs or THP).ti,ab,kf. (19081) 7 5 or 6 (62679) examination in the diagnosis of loosening of components in total hip arthroplasty.m_titl. (1) 11 ("clinical follow-up" or "pre-planned follow-up" or "clinical examination" or ((clinical or radiological) adj (surveillance or monitoring)) or "Routine follow-up" or "office visits after total" or "follow-up care" or (follow-up adj3 after adj3 total) or ("follow-up model*" or "outpatient follow-up" or "care pathway*")).ti,ab,kf. (64024) 12 exp *diagnostic imaging/ or dg.fs. or (imaging or radiolog* or mri or CT or tomograph*).ti,kf. or follow-up.ti. or complications.fs. or (loosening or revision or wear or outcome or follow-up).ti,ab,kf. or ((failed or failure) and (prosthes* or arthroplast*)).ti,ab,kf. or exp Prosthesis Failure/ (4442381) 13 7 and 11 and 12 (471) 14 limit 13 to yr="2010 -Current" (218) 15 "26850425".ui. (1) 16 14 and 15 (1) 17 8 and 13 (5) 18 8 not 17 (2) 19 remove duplicates from 14 (212) 20 limit 19 to (dutch or english or german) (197)	197

Exclusion table

Table Exclusion after reading full text

Author and year	Reason for exclusion
Bitsaki, 2017	About costs of mobile based healthcare combined with follow-up
Bolz, 2008	About costs and use of a PA
Marsh, 2014	Compares web-based follow-up with in-person follow-up
Meding, 2013	About knees
Kesterke, 2014	About PROMS and time investment of filling out a paper and digital questionnaire
Rolfson, 2011	Compares questionnaire on internet with paper version
Van Eck, 2014	Comment on Marsh, 2014

5.2 Hematogenous infection

See guideline Antibioticaprofylaxe bij gewrichtsprothese: https://richtlijnendatabase.nl/richtlijn/antibioticaprofylaxe_bij_gewrichtsprothese/antibioticaprofylaxe_bij_gewrichtsprothese.html

Module 6 Place and organization of fast track treatment

Research question

When is fast track surgery indicated and what measures in the organisation of fast track are required for a safe and satisfying result?

Uitgangsvraag

Wanneer is er een indicatie voor fast-track-behandeling en aan welke voorwaarden moet de organisatie voldoen?

Introduction

In the past decades, fast track programmes have successfully been introduced in orthopaedics. A combination of organisational and medical improvements in peri-operative protocols has led to an enhanced recovery of patients after total hip arthroplasty, lowering morbidity and mortality.

Search and select

To answer the question, a systematic literature search was performed for the following research question: what are desirable and undesirable effects of fast track surgery compared to traditional care?

P: adults undergoing total hip arthroplasty;
I: fast track or outpatient surgery;
C: traditional pathway;
O: complications, survival, revision, PROMS, outcomes, mortality, morbidity, postoperative functional recovery.

Search and select (Method)

No systematic reviews were found and only one randomised trial. Therefore, additionally several large cohort studies were included.

Five studies were included: one RCT (Goyal, 2017), one prospective cohort study (Gromov et al. 2017) and three retrospective observational studies (Jørgensen, 2017; Jørgensen, 2016; Khan, 2014).

Two recently published key articles (narrative reviews) were consulted and described in the considerations section (Hansen, 2017; Galbraith, 2018). Based on those studies conditions for the application of fast track surgery are described.

Literature summary

Description of studies

Outpatient surgery

The high-volume centre RCT by Goyal, (2017) evaluated 220 patients who had THA surgery between July 2014 and September 2015. Patients were randomised between outpatient

surgery (discharge planned on the same day as surgery) and inpatient surgery (discharge planned after an overnight stay). Primary endpoints were postoperative pain, peri-operative complications and healthcare provider visits (re-admission A&E or physician's office) and relative work effort for the surgeon's office staff. There was no significant difference in pain on the day of surgery and after 4 weeks, but on the first day after surgery outpatients reported more pain than inpatients. After 4 weeks, Harris Hip Scores showed no difference between the two groups. Of the 112 patients randomised to outpatient surgery, 85 (76%) were discharged as planned. Of the remaining 27 patients, 26 were discharged after one night in the hospital and one was discharged after two nights. Of the 108 patients randomised to inpatient surgery, 81 (75%) were discharged as planned. There was no difference in the number of re-operations, hospital re-admissions without re-operation, A&E visits without hospital re-admission, or acute office visits. Goyal concludes that outpatient THA can be implemented in a defined patient population. Because 24% (27 of 112) of patients planning to have outpatient surgery could not be discharged on the same day, facilities to accommodate an overnight stay should be available.

The prospective two-centre cohort study (Gromov, 2017) reports on the feasibility of outpatient THA (and TKA) in unselected patients. Of the 557 patients, 304 were THA and 253 were TKA. Of the 304 THA patients who were referred to the participating surgeons during the study period, 55% were potentially eligible for outpatient surgery. 34 patients were excluded for the reason of living alone. Of the remaining 133 patients, 47 (35%) were discharged on the actual day of surgery.

Fast track

Jørgensen (2017) describe the results of a prospective observational study in 13,775 consecutive THA (N=6553) and TKA (N=7222) patients with similar fast-track protocols and a median length of stay of 2 days. Of a total of 44 deaths (30 THA/ 14 TKA) (0.3%), 28 (20 THA/ 8 TKA) (0.2%) were found to have a certain or probable relation with surgery and were considered as surgery-related. Surgery-related deaths were more common after THA than TKA (0.3% versus 0.1% P = 0.044), occurred after median 14 days and 19 of 28 were between day 0 to 30. The most common initial organ dysfunction for surgery-related deaths was pulmonary (6/28) and gastro-intestinal (6/28), while the most commonly reported causes of death were pulmonary (9/28) and cardiac events (6/28).

Thrombo-embolic events (TEE) are serious complications after total hip (THA) and knee arthroplasty (TKA), with reported in-hospital incidences of about 0.5 to 1% for venous thrombo-embolic events (VTE) and 0.2% for myocardial infarctions (MI) and stroke with a traditional protocol. Jørgensen (2016) describe the results of a prospective observational study in 13,775 consecutive THA/TKAs with similar fast-track protocols and a median length of stay of 2 days. "Early" TEEs (within one week of surgery) consisted of 9 (0.07%) MI, 10 (0.08%) strokes, 13 (0.09%) pulmonary embolisms and 11 (0.08%) deep venous thromboses. Jørgensen conclude that the incidence of "early" thrombo-embolic events after fast-track THA and TKA is low. Improving peri-operative treatment of anaemia may further reduce the number of MIs.

Khan (2014) compare two consecutive unselected cohorts of 1,369 THA patients and 1,631 TKA patients with a traditional protocol (2004 to 2008) with 1,256 THAs and 1,744 TKAs with an enhanced recovery protocol (2008 to 2011). The median LOS in the

enhanced recovery group was reduced (3 days versus 6 days; p = 0.01). Blood transfusion rate was also reduced (7.6% versus 23%; p <0.001), as was return to theatre rate (p = 0.05). Myocardial infarction at 30 days (0.4 versus 0.9%, p=0.03) and mortality at 30 days (0.2 versus 0.5%, p=0.03) was lower in the enhanced recovery group, mortality at 90 days was not significantly different (0.5 versus 0.8%, p=0.1). Other outcomes showed no significant difference. Khan (2014) conclude that the enhanced recovery programme has achieved a statistically significant reduction in LOS and in cardiac ischaemic events for patients, with a near-significant decrease in return to theatre and in mortality rates.

Level of evidence
Since fast track or outpatient programmes differ considerably between different countries and health care systems, and outcomes are different, no meta-analyses were performed. All conclusions from observational studies are graded very low, because of the risk of bias. The conclusion based on the RCT by Goyal was graded low, because of risk of bias and small numbers of events.

Conclusions

Fast track THA

Very low GRADE	After fast track total hip arthroplasty, mortality is 0.3%, of which 2/3 is related to surgery. *Sources (Jørgensen, 2017)*

Very low GRADE	After fast track THA or TKA, early thrombo-embolic events (within one week of surgery) are seen in 0.32% of patients (MI 0.07%; stroke 0.08%; pulmonary embolisms 0.09%; deep venous thromboses 0.08%). *Sources (Jørgensen, 2016)*

Very low GRADE	An enhanced recovery programme for THA and TKA seems to result in lower LOS, need for blood transfusion and 30-day mortality compared to traditional care, but no significant difference in reoperation, other complications and 90-day mortality. *Sources (Khan, 2014))*

Outpatient THA

Low GRADE	There is no significant difference in functional recovery, number of re-operations, hospital re-admissions without re-operation, A&E visits without hospital re-admission, or acute office visits between outpatient surgery (discharge planned on the same day) and inpatient surgery (discharge planned day after surgery). Postoperative pain on the day after surgery was worse in the outpatient group. *Sources (Goyal, 2017)*

Very low GRADE	Outpatient surgery is feasible in about 55% of unselected patients, 15% of unselected patients may be discharged on the day of surgery.

	Sources (Gromov, 2017)

Considerations

The narrative review by Hansen (2017) summarises literature and provides insights into fast track surgery in THA. Fast track surgery in THA resulted in a reduction in postoperative length of stay, shorter convalescence and rapid functional recovery without increased morbidity and mortality. According to Hansen, fast-track THA surgery now works extremely well in the standard THA patient. However, all patients are different and fine-tuning of the multiple areas in fast-track pathways to get patients with special needs or high co-morbidity burden through a safe and effective fast-track THA pathway is important. Hansen provides an overview of possible pre-operative and peri-operative optimisations. These include patient information and teaching, an opioid-sparing pain and anaesthetic protocol and mobilisation on the day of surgery.

Another narrative review by Galbraith (2018) concluded that pre-operative education programmes, outpatient consultation, pre-anaesthetic assessment, pre-procedural physiotherapy, day-of-surgery admission, pre-operative medications, type of anaesthesia, blood loss reduction protocols, multimodal analgesia delivery, day-of-surgery mobilisation, thrombo-embolic prophylaxis and ongoing rehabilitation are essential in enhanced recovery. Galbraith also concluded that that the impact of individual variables requires further research.

Until recently, the reports of outpatient THA have been anecdotal, single surgeon or single institution based or with selected patient populations. However, two more recent papers by Goyal et al. and Gromov et al. report respectively on a multi-centre randomised trial and a multi-centre study with unselected patients (Goyal, 2017; Gromov, 2017). Both studies confirmed the feasibility of outpatient THA, although many challenges need to be overcome before it can be defined as an established treatment option and more widespread use recommended.

The published studies on outpatient THA from Europe have all been from institutions that have a well-established fast-track protocol. As a result of their programmes, these hospitals have seen their length of stay gradually decrease to a point where outpatient THA is feasible. For most hospitals, outpatient THA surgery should not be a goal in itself, but should rather be the result of a successful, already implemented fast-track programme based on the concept “first better – then faster.”

Recommendations

Fast track programmes should include patient information and teaching, opioid-sparing pain and anaesthetic protocol, blood loss reduction protocols and thrombo-embolic prophylaxis, mobilisation on the day of surgery and ongoing rehabilitation.

Fine-tuning fast track programmes for patients with special needs or high co-morbidity burden is important for a safe and effective fast-track THA pathway.

Aanbeveling

Een fast-track programma kan worden toegepast bij standaard THP's, onder voorwaarde dat er een protocol is waarin is opgenomen goede voorlichting, juiste pijn medicatie, maatregelen om bloedverlies te beperken, tromboseprofylaxe, mobilisering op de dag van de operatie en een revalidatietraject.

Een fast-track programma voor bij patiënten met multimorbiditeit moet aangepast zijn aan de individuele situatie.

Literature

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Validity and maintenance

Module	Party in control	Year of authorization	Next assessment of actuality	Frequency of assessment actuality	Which party/parties monitors actuality	Important factors that might lead to change in recommendations
Fast track	NOV	2018	2023	Every five years	NOV	

Knowledge gaps

How shoud a fast track programme be adjusted for patients with multimorbidity?

Indicator

Not applicable

Implementation plan

Recommendation	Time needed for implementation: <1 year, 1 to 3 years or >3 years	Expected effects on costs	Conditions for implementation	Possible barriers to implementation[1]	Actions for implementation[2]	Reponsibility for these actions[3]	Other remarks
All	<1 year	Reduction	Local motivation and collaboration	See conditions		Orthopedic surgeons and hospital management	Not applicable

Table of quality assessment for systematic reviews of RCTs and observational studies

Based on AMSTAR checklist (Shea, 2007; BMC Methodol 7: 10; doi:10.1186/1471-2288-7-10) and PRISMA checklist (Moher, 2009; PLoS Med 6: e1000097; doi:10.1371/journal.pmed1000097)

Study First author, year	Appropriate and clearly focused question?[1] Yes/no/unclear	Comprehensive and systematic literature search?[2] Yes/no/unclear	Description of included and excluded studies?[3] Yes/no/unclear	Description of relevant characteristics of included studies?[4] Yes/no/unclear	Appropriate adjustment for potential confounders in observational studies?[5] Yes/no/unclear/notapplicable	Assessment of scientific quality of included studies?[6] Yes/no/unclear	Enough similarities between studies to make combining them reasonable?[7] Yes/no/unclear	Potential risk of publication bias taken into account?[8] Yes/no/unclear	Potential conflicts of interest reported?[9] Yes/no/unclear

1. Research question (PICO) and inclusion criteria should be appropriate and predefined.
2. Search period and strategy should be described; at least Medline searched; for pharmacological questions at least Medline + EMBASE searched.
3. Potentially relevant studies that are excluded at final selection (after reading the full text) should be referenced with reasons.
4. Characteristics of individual studies relevant to research question (PICO), including potential confounders, should be reported.
5. Results should be adequately controlled for potential confounders by multivariate analysis (not applicable for RCTs).
6. Quality of individual studies should be assessed using a quality scoring tool or checklist (Jadad score, Newcastle-Ottawa scale, risk of bias table et cetera).
7. Clinical and statistical heterogeneity should be assessed; clinical: enough similarities in patient characteristics, intervention and definition of outcome measure to allow pooling? For pooled data: assessment of statistical heterogeneity using appropriate statistical tests (for example Chi-square, I^2)?
8. An assessment of publication bias should include a combination of graphical aids (for example funnel plot, other available tests) and/or statistical tests (for example Egger regression test, Hedges-Olken). Note: If no test values or funnel plot included, score “no”. Score “yes” if mentions that publication bias could not be assessed because there were fewer than 10 included studies.
9. Sources of support (including commercial co-authorship) should be reported in both the systematic review and the included studies. Note: To get a “yes,” source of funding or support must be indicated for the systematic review AND for each of the included studies.

Evidence table

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments

Notes:

1. **Prognostic balance between treatment groups is usually guaranteed in randomized studies, but non-randomized (observational) studies require matching of patients between treatment groups (case-control studies) or multivariate adjustment for prognostic factors (confounders) (cohort studies); the evidence table should contain sufficient details on these procedures.**
2. **Provide data per treatment group on the most important prognostic factors ((potential) confounders).**
3. **For case-control studies, provide sufficient detail on the procedure used to match cases and controls.**

For cohort studies, provide sufficient detail on the (multivariate) analyses used to adjust for (potential) confounders.

Risk of bias table for intervention studies (observational: non-randomized clinical trials, cohort and case-control studies)

Study reference (first author, year of publication)	Bias due to a non-representative or ill-defined sample of patients?[1] (unlikely/likely/unclear)	Bias due to insufficiently long, or incomplete follow-up, or differences in follow-up between treatment groups?[2] (unlikely/likely/unclear)	Bias due to ill-defined or inadequately measured outcome ?[3] (unlikely/likely/unclear)	Bias due to inadequate adjustment for all important prognostic factors?[4] (unlikely/likely/unclear)

1. **Failure to develop and apply appropriate eligibility criteria: a) case-control study: under- or over-matching in case-control studies; b) cohort study: selection of exposed and unexposed from different populations.**
2. **2 Bias is likely if: the percentage of patients lost to follow-up is large; or differs between treatment groups; or the reasons for loss to follow-up differ between treatment groups; or length of follow-up differs between treatment groups or is too short. The risk of bias is unclear if: the number of patients lost to follow-up; or the reasons why, are not reported.**
3. **Flawed measurement, or differences in measurement of outcome in treatment and control group; bias may also result from a lack of blinding of those assessing outcomes (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is not necessary. If a study has "soft" (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary.**
4. **Failure to adequately measure all known prognostic factors and/or failure to adequately adjust for these factors in multivariate statistical analysis.**

Search strategy

Database	Search terms	Total

Exclusion table

Table Exclusion after reading full text

Author and year	Reason for exclusion

Module 7 Organisation of the care surrounding frail elderly people who are eligible for a total hip arthroplasty

Research question
How to organise the care for frail elderly people who are eligible for a total hip prostheses?

Uitgangsvraag
Hoe moet de zorg georganiseerd worden voor kwetsbare ouderen die een totale heupprothese ondergaan?

Introduction
In the next decades, the total number of elderly people in society will increase, as well as the life-expectancy, leading to more and more of the "oldest old". Elderly people are more active than they used to be in the past and will probably ask for hip replacement at more advanced ages. A substantial part of the patients above the age of 70 years will be "frail" (due to co-morbidity, polypharmacy and cognitive disturbances) so specific considerations have to be taken into account on the one hand to avoid the need for joint replacement surgery and on the other hand, when this is indicated to minimise the length of stay in the hospital, to reduce the risk of complications and minimise the functional decline and the duration of rehabilitation.

In addition to the joint problems, elderly people often have additional diseases, id est diabetes and cardiac or vascular diseases. Nearly 70% of the Dutch elderly aged from 65 to 79 years have serious, life-shortening co-morbidities when they attend the out-patient clinic. Above the age of 80 years this figure rises to almost 80% (Piccirillo, 2008). Co-morbidity influences the chance of success of an operation, the length of stay in the hospital and the duration of the period of rehabilitation. Patients with cognitive disturbances and/or sensory deprivation have a greater chance of serious delirious episodes postoperatively. The presence and extent of co-morbidity can thus influence the choice of treatment and therefore personalised care adjusted to the frail elderly is needed.

Frailty increases with age: in the age group of 65 to 69 years about 4% can be considered frail; 7% from 70 to 74 years of age; 9% from 75 to 79 years of age; 16% from 80 to 84 years of age; and 26% above the age of 85 years (Clegg, 2013). In the year 2010, it was estimated that there were around 690,000 frail persons in the age range of 65 years and older in the Netherlands and - based on a demographic estimation - the number of frail elderly will increase by another 470,000 people to a total of 1,160,000 persons in the year 2030 (van Campen, 2011; Kwetsbare ouderen, Rapport van het Sociaal en Cultureel Planbureau).

Search and select
No systematic literature review was performed for this question.

Literature summary

No systematic literature review was performed for this question.

Results

No systematic literature review was performed for this question.

Conclusions

No systematic literature review was performed for this question.

Considerations

In addition to the choice of treatment, there are other important aspects that play a part in the performance of treatment of vulnerable elderly people. This concerns the concept of frailty. This is a condition associated with an increased risk of loss of function and which is distinguished from aging, constraints and multi-morbidity (NVKG, 2010; Richtlijn ”Comprehensive geriatric assessment”).

The geriatric patient distinguishes himself from other patients through (NVKG 2010; Richtlijn ”Comprehensive geriatric assessment”):

- a (greater risk of) frailty or ”the uncertain physical, psychological and social equilibrium”;
- usually a higher age;
- Illnesses and / or handicaps associated with high age;
- the inter-acting multi-morbidity;
- the bigger (inter-)individual variability;
- they often prefer improvement of self-reliance, mobility and quality of life instead of extension of life.

So, in the category of patients with osteoarthritis of the hip there must be specific attention for:

- functioning in general and self-reliance;
- complications or diseases, which present themselves through geriatric syndromes (delirium, falling);
- a decreased amount of social support;
- a decreased awareness of problems by the patient due to cognitive impairment or visual impairment during the treatment;
- polypharmacy.

In summary, it is important – in addition to the orthopaedic problem - to judge the extent of vulnerability of the person in question. The complexity of co-morbidity, polypharmacy and cognitive disturbances emphasises the importance of co-operation between the orthopaedic surgeons and geriatricians when setting the operation indication (or rejecting it). This can be done by selecting specific patient categories for more intensive peri-operative guidance by a geriatric team or a generalistic medical specialist with experience in elderly care.

The Comprehensive Geriatric Assessment (CGA) should be used to judge the frailty of a patient. Tools for screening might possibly give an indication of vulnerability, but are

unable to screen adequately and give a competent advice. The CGA is an extensive clinical geriatric examination, defined as a "multidisciplinary research that identifies and explains the multiple problems of an elderly as much as possible, examines a patient's abilities and needs, in order to achieve a coordinated and comprehensive care plan for the individual". A CGA has an added value with regard to vulnerable older people, especially in the areas of survival, quality of life, self-reliance and institutionalisation.

Screening lists are available for the various domains within the CGA. Some of these lists screen for vulnerability or risk of functional decline (i.e. the ISAR-HP), others focus more on geriatric syndromes, such as a delirium risk assessment or the Patient Safety Management System ("Veiligheidsmanagementsysteem") criteria (VMS-criteria screening bundle). The latter looks at four domains: delirium, risk of falling, malnutrition and functionality.

A CGA is not required for every elderly patient. It is advised to initially perform a screening for vulnerability in the patients over 70 years. Almost all hospitals in the Netherlands have implemented the screening according to the VMS criteria screening bundle. This screening is preferably done when the indication for hip replacement therapy is set and can be performed during pre-operative screening (POS) in an outpatient clinic setting (NVKG, 2013; Partridge, 2014).

It is of great importance that screening for frailty takes places systematically. Additionally, on indication, judgement by a geriatrician should be performed. In case of positive screening, it is useful to refer the patient pre-operatively to the outpatient clinic for further assessment by a CGA. Based on the outcome of the CGA, a programme can be drawn up. Pre-operative and peri-operative recommendations (id est prevention of delirium) can be given and advice about the care after the hospital admission. In the case of frail elderly people with a high risk of (geriatric) complications, structural co-treatment between the orthopaedic surgeon and the geriatrician should be considered. Then, the geriatrician is jointly responsible for ensuring that good protocols are in place to use geriatric expertise.

In short, the orthopaedic surgeon sets the indication for the treatment, the anaesthesiologist assesses the operation risk and the clinical geriatrician maps the vulnerability and co-morbidity. In the majority of patients, the attention of the orthopaedic surgeon and the anaesthesiologist before an operation is sufficient. All persons above 70 years of age should be screened. In case of positive screening (id est: increased vulnerability, possibly frailty) there is an indication for additional screening according to a comprehensive geriatric assessment to map frailty, co-morbidity and possible contra-indications and give advice leading to a better outcome.

Recommendation

Screen all patients above the age of 70 years on frailty using a validated tool (in the Netherlands possibly the VMS-criteria screening bundle).

In case of positive screening, pre-operative judgement is recommended by means of a comprehensive geriatric assessment by a specialist with competency in geriatric medicine.

Aanbeveling

Screen alle patiënten ouder dan 70 jaar op kwetsbaarheid met behulp van een gevalideerd instrument (bijvoorbeeld de VMS-screeningsbundel).

Laat patiënten die positief screenen op kwetsbaarheid preoperatief beoordelen door middel van een comprehensive geriatric assessment door een specialist met expertise op het gebied van geriatrie.

Literature

Campen C van. Kwetsbare ouderen. Rapport van het Sociaal en Cultureel Planbureau, Den Haag 2011. Link: http://www.scp.nl/Publicaties/Alle_publicaties/Publicaties_2011/Kwetsbare_ouderen 2011.

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Piccirillo JF, Vlahiotis A, Barrett LB, et al. The changing prevalence of comorbidity across the age spectrum. Crit Rev Oncol Hematol 2008;67:124-132. PubMed PMID: 18375141.

Rapport 'Ouderdom komt met gebreken'. Gezondheidsraad. 2008.

Validity and maintenance

Module	Party in control	Year of authorization	Next assessment of actuality	Frequency of assessment actuality	Which party/parties monitors actuality	Important factors that might lead to change in recommendations
Organisation of the care surrounding frail elderly people who are eligible for a total hip arthroplasty	NVKG	2018	2023	Eens in de vijf jaar	NVKG	-

Knowledge gaps

What are the outcomes of hip replacement in patients with cognitive impairment?

Implementation plan

Recommendation	Time needed for implementation: <1 year, 1-3 years or >3 years	Expected effects on costs	Conditions for implementation	Possible barriers to implementation[1]	Actions for implementation[2]	Reponsibility for these actions[3]	Other remarks
All	<1 year	Unknown	n.a.	n.a.	n.a	n.a.	Is already implemented in most hospitals