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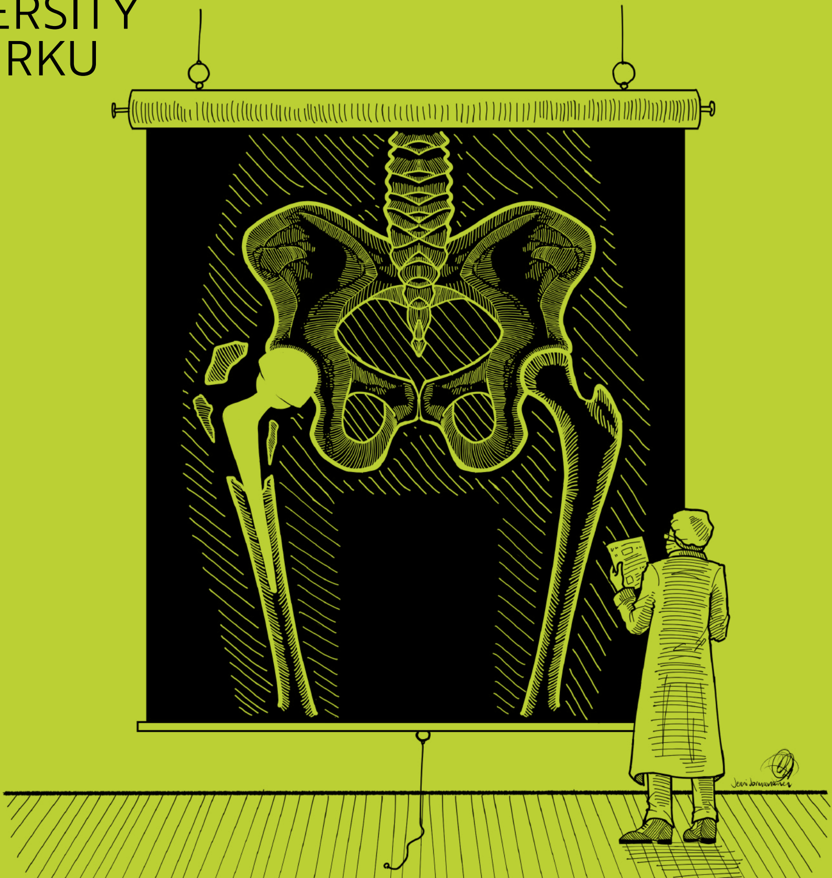

RISK FACTORS AND RISK PREDICTION MODELS FOR EARLY COMPLICATIONS FOLLOWING TOTAL HIP ARTHROPLASTY

Valtteri Panula

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To my family

UNIVERSITY OF TURKU
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ABSTRACT

Treatment of end-stage hip osteoarthritis was revolutionized in the 1960s with the newly invented low-friction total hip arthroplasty (THA). Since then, an increasing number of both primary and revision THAs have been performed annually, especially over the past two decades. To achieve better outcomes, orthopedic surgeons should carefully select optimal patients and appropriate methods and devices. Risk prediction models have been developed to inform the surgeon and patient more precisely about the expected outcomes of the surgery. The use of such a tool could engage patients more closely in the decision-making process and guide surgeons in avoiding unnecessary risk.

The aims of this doctoral thesis were: 1) to determine the risk factors for revision due to dislocation after primary THA; 2) to determine the risk factors for revision due to periprosthetic joint infection (PJI) after primary THA; 3) to develop risk prediction models for assessing the risk of the most common adverse outcomes after primary THA, based on versatile registry data from Finland; and 4) to develop risk prediction models for early revisions and death, and to evaluate the predictive potential of various machine learning algorithms for complications following primary THA, based on the Nordic Arthroplasty Register Association (NARA) dataset.

We found that posterior approach, fracture diagnosis, and American Society of Anesthesiologists class III–IV were associated with an increased risk of revision for dislocation after primary THA. The use of a 36 mm femoral head size decreased the risk of revision for dislocation. For PJI, we identified several modifiable variables increasing and decreasing the risk of revision. Especially patients with a high body mass index may be at even higher risk of developing infection than previously reported. We also successfully developed preoperative risk prediction models for PJI, dislocation, periprosthetic fracture, and death after primary THA. Based on the NARA dataset, we were able to demonstrate that complex risk prediction methods are not required to achieve maximum predictive potential. Hence, simpler models can improve usability. All the developed models can easily be used in clinical practice to serve individual risk estimations for adverse outcomes.

KEYWORDS: revision surgery, dislocation, infection, periprosthetic fracture, death, machine learning, risk assessment

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
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TIIVISTELMÄ

Pitkälle edenneen lonkan nivelrikon hoito mullistui, kun moderni lonkan tekonivelleikkaus yleistyi 60-luvulla. Lonkan tekonivelen ensi- ja uusintaleikkausten määrät ovat kasvaneet merkittävästi erityisesti kahden viimeisen vuosikymmenen aikana. Uusintaleikkausten välttämiseksi ortopedien tulisi huolellisesti valita ensileikkaukseen sopivat potilaat sekä parhaat mahdolliset leikkausmenetelmät ja komponentit. Viime aikoina onkin kehitetty riskilaskureita, jotta sekä kirurgien että potilaiden ymmärrys odotettavissa olevasta lopputuloksesta paranisi. Riskilaskureiden avulla potilaat voidaan ottaa paremmin mukaan yhteiseen päätöksentekoon.

Tässä väitöskirjatutkimuksessa selvitettiin riskitekijöitä lonkan tekonivelleikkauksen jälkeisille uusintaleikkauksille. Erityishuomion kohteena olivat tekonivelen sijoiltaanmenot sekä infektiot. Lisäksi kehitimme riskilaskurimalleja ennustamaan potilaskohtaista riskiä tyypillisimmille komplikaatioille ja kuolemalle lonkan ensitekonivelleikkauksen jälkeen. Tämä väitöskirja perustuu uudistetun Suomen Endoproteesirekisterin ja Pohjoismaisen tekonivelrekisterin tietoihin.

Tutkimuksessa havaittiin taka-avauksen, reisiluun kaulan murtumadiagnoosin ja anestesiariskiluokkien III–IV altistavan uusintaleikkaukselle tekonivelen sijoiltaanmenon vuoksi. Käytettäessä 36 mm:n halkaisijan omaavia nuppeja sijoiltaanmenoriski oli matala. Lisäksi tunnistimme useita muuttujia, jotka olivat yhteydessä tekonivelen infektoitumiseen. Erityisesti potilaat, joilla on korkea painoindeksi, saattavat olla alttiimpia tekonivelinfektiolle, kuin mitä aikaisemmin on raportoitu. Kehitimme myös onnistuneesti riskilaskurimallit ennustamaan riskiä tekonivelen uusintaleikkaukselle infektion, sijoiltaanmenon ja periproteettisen murtuman johdosta sekä kuolemalle lonkan ensitekonivelleikkauksen jälkeen. Tärkeä havainto riskilaskurimallien kehityksessä oli myös se, että yksinkertaisilla menetelmillä pystytään ennustamaan riskiä yhtä hyvin kuin monimutkaisilla menetelmillä. Kaikkia kehittämiämme malleja voi käyttää kliinisen päätöksenteon tukena arvioimaan potilaskohtaista riskiä leikkauksen jälkeiselle epäsuotuisalle päätetapahtumalle.

AVAINSANAT: uusintaleikkaus, lonkan sijoiltaanmeno, proteesi-infektiot, proteesinvierusmurtumat, kuolema, koneoppiminen, riskinarviointi

Table of Contents

Abbreviations

ACS	American College of Surgeons
AJRR	American Joint Replacement Registry
AOANJRR	Australian Orthopaedic Association National Joint Replacement Registry
ARMD	Adverse reaction to metal debris
ASA	American Society of Anesthesiologists
AUROC	Area under the receiver operating characteristic curve
BMI	Body mass index
CI	Confidence interval
CMN	Cephalomedullary nail
CoC	Ceramic on ceramic
CoP	Ceramic on polyethylene
CoX	Ceramic on crosslinked polyethylene
CRP	C-reactive protein
CT	Computerized tomography
DAA	Direct anterior approach
DAG	Directed acyclic graph
DAIR	Debridement, antibiotics and implant retention
EBJIS	European Bone and Joint Infection Society
FAR	Finnish Arthroplasty Register
GBM	Gradient boosting machine
HA	Hydroxyapatite
HR	Hazard ratio
HRA	Hip resurfacing arthroplasty
KM	Kaplan-Meier
Lasso	Least absolute shrinkage and selection operator
LIA	Local infiltrative anesthesia
LROI	Landelijke Registratie Orthopedische Interventies (Dutch Arthroplasty Register)
MIS	Minimally invasive surgery
MoM	Metal on metal

MoP	Metal on polyethylene
MoX	Metal on polyethylene crosslink
MRSA	Methicillin-resistant Staphylococcus aureus
MSIS	Musculoskeletal Infection Society
NARA	Nordic Arthroplasty Register Association
NJR	National Joint Registry
NRS	Numeric Rating Scale
NSQIP	National Surgical Quality Improvement Program
OA	Osteoarthritis
OR	Odds ratio
ORIF	Open reduction and internal fixation
PJI	Periprosthetic joint infection
PMN	Polymorphonuclear neutrophils
PPF	Periprosthetic fracture
PROM	Patient reported outcome measure
RCT	Randomized controlled trial
RF	Random forest
ROC	Receiver operating characteristic
RR	Relative risk
SD	Standard deviation
SHS	Sliding hip screw and side plate
SHAR	Swedish Hip Arthroplasty Register
SIVS	Stable iterative variable selection
THA	Total hip arthroplasty
TJA	Total joint arthroplasty
TKA	Total knee arthroplasty
UHXLPE	Ultra-highly crosslinked polyethylene
UK	United Kingdom

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Panula V, Ekman E, Venäläinen M, Laaksonen I, Klén R, Haapakoski J, Eskelinen A, Elo L, Mäkelä K. Posterior approach, fracture diagnosis and ASA class III–IV are associated with increased risk of revision for dislocation after total hip arthroplasty: An analysis of 33,337 operations from the Finnish Arthroplasty Register. Scand J Surg. 2021;110(3):351–358.

II Panula V, Alakylä K, Venäläinen M, Haapakoski J, Eskelinen A, Manninen M, Kettunen J, Puhto AP, Vasara A, Elo L, Mäkelä K. Risk factors for prosthetic joint infection following total hip arthroplasty based on 33,337 hips in the Finnish Arthroplasty Register from 2014 to 2018. Acta Orthopaedica. 2021;92(6):665–672.

III Venäläinen M, Panula V, Klén R, Haapakoski J, Eskelinen A, Manninen M, Kettunen J, Puhto AP, Vasara A, Mäkelä K, Elo L. Preoperative risk prediction models for short-term revision and death after total hip arthroplasty: Data from the Finnish Arthroplasty Register. JBJS Open Access 2021;25;6(1):e20.00091.

IV Venäläinen M, Panula V, Eskelinen A, Fenstad AM, Furnes O, Hallan G, Rolfson O, Kärrholm J, Hailer N, Pedersen A, Overgaard S, Mäkelä K, Elo L. Prediction of early adverse events after THA: A comparison of different machine learning strategies based on 251,438 observations from the Nordic Arthroplasty Register Association (NARA) dataset. Manuscript.

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1 Introduction

Total hip arthroplasty (THA) is the treatment of choice for end-stage hip osteoarthritis (OA), relieving pain, restoring physical activity, and improving patients' quality of life (Learmonth et al. 2007). THA is said to have been one of the most momentous surgical operations of the 20th century (Markatos et al. 2020). The past few decades have seen a steady rise in the number of both primary and revision THAs (Kurtz et al. 2005, Pabinger and Geissler 2014, Shichman et al. 2023). In 2020, the number of primary elective and revision THAs performed in Finland was 9,608 and 1,538, respectively (FAR 2021). Despite some successful technical improvements, orthopedic surgeons still face the same major complications as before, like infection and dislocation. To counteract the ongoing rise in revision THAs, preoperative risk prediction models are being developed to help reduce unnecessary revision surgery (Paxton et al. 2015, Kunutsor et al. 2017, Tan et al. 2018).

THA is usually a cost-effective and safe procedure. However, it can lead to major complications requiring revision surgery. Revision operations are often demanding and are associated with an increased risk of further complications and repeated surgery. (Jo et al. 2015, Shichman et al. 2022, Edmiston et al. 2023) Typical major complications following primary THA include dislocation, periprosthetic joint infection (PJI), aseptic loosening, and periprosthetic fracture (PPF) (Bozic et al. 2009, Badarudeen et al. 2017, Weber et al. 2018, AOANJRR 2020, FAR 2021). Risk factors for complications following THA can be divided into patient- and surgery-related factors (Cherian et al. 2015, Lenguerrand et al. 2018, Ramavath et al. 2020, Hermansen et al. 2021).

A surgeon's decision to treat a patient with THA is largely based on average rates of risk versus benefit for a diverse population of patients with THAs. It may not be ideal for estimating an individual's patient-specific risks. (Bozic et al. 2013) Therefore, preoperative risk prediction models have been developed for surgeons to obtain more accurate information on expected individual outcomes after primary THA (Trela-Larsen et al. 2020). These models also focus on shared decision-making of treatment choices appropriate to the circumstances of the individual patient.

The aim of this doctoral thesis was to determine risk factors for revision surgery for dislocation and PJI after primary THA, based on the revised database of the Finnish Arthroplasty Register (FAR). Further, we developed patient-specific preoperative risk prediction models for typical early adverse outcomes and death following primary THA, using data from the FAR and Nordic Arthroplasty Register Association (NARA) datasets.

2 Review of the Literature

2.1 Early complications of total hip arthroplasty (THA)

Significant technical improvement has occurred since the mid-20th century pioneers Smith-Petersen, Wiles, Charnley, and others introduced their major developments of THA. Despite successful improvements throughout the history of THA, today's orthopedic surgeons still face the same major complications as did their predecessors (Figure 1). Number of primary THAs performed annually is growing. This growing number is mainly the result of an aging population and increasing obesity rates (Ferguson et al. 2018, Hunter and Bierma-Zeinstra 2019). The main indications for THA in Finland are OA (87%) and femoral neck fracture (4%) (FAR 2021). The same is true in Australia and the United Kingdom (UK) (AOANJRR 2020, NJR 2020).

Although primary THA is considered a cost-effective and safe procedure, a significant number of THAs can still lead to devastating complications shortly after the primary operation (Shearer et al. 2015, Weber et al. 2018). Complications which occur during the first three postoperative months even to five postoperative years after the primary THA have been classified as early complications (Table 1). These early complications typically include dislocation, PJI, and PPF (Shearer et al. 2015, AOANJRR 2020, NJR 2020, FAR 2021). Detecting the risk factors for postoperative complications is hugely important for reducing the number of revision surgeries (Ferguson et al. 2018).

Table 1. Early complications after primary total hip arthroplasty.

Original study	Outcome	N	Time frame
(Bozic et al. 2014a)	E.g. dislocation, infection, PPF	56,030	1 year
(Bozic et al. 2016)	Dislocation, infection, periprosthetic fracture.	64,260	1 and 3 years
(Bülow et al. 2022)	PJI	88,830	90-days
(Calkins et al. 2022)	PPF	3,433	2.2 years
(Haynes et al. 2016)	Aseptic loosening, infection and instability	870	5 years
(Luger et al. 2021)	PPF	1,052	90-days
(Meyer et al. 2017)	E.g. infection, instability, PPF	5,543	1.1 ± 2.1 years and 3.0 ± 3.2 years
(Pakarinen et al. 2020)	Dislocation	1,381	1 year
(Pakarinen et al. 2022)	Dislocation	16,454	2 years
(Peters et al. 2020)	Infection, dislocation, periprosthetic fracture	218,214	1 year

N = number of included primary total hip arthroplasties

The reported overall complication rate following primary THA varies with time of follow-up and what kinds of complications are included in the analyses. For 1-, 3-, 5-, 6- and 9-year follow-up times, the overall complication rates have been reported to be 1.5%, 2.5–3.4%, 3.0%, 5.8% and 4.0%, respectively, including complications such as infection, dislocation, PPF, loosening of femoral or acetabular component, and nerve injuries (Huddleston et al. 2012, Wolf et al. 2012, Peters et al. 2020). To analyze and compare the reasons leading to complications is not straightforward, because there are no universally accepted definitions of complications. There are also many different methods for identifying postoperative complications (Healy et al. 2016, Millstone et al. 2017, Magneli et al. 2019).

Revision operations are often more demanding and expensive than the primary operations. Also the outcome after revision surgery is usually inferior compared to that after primary surgery. Further complications may lead to repeated surgery. (Evans et al. 2019) Risk factors for revision surgery can be divided into patient- and surgery-related factors (Bozic et al. 2014a, Millstone et al. 2017). In practice, the reason for a revision operation is often multifactorial and patient-specific (Bozic et al. 2014a, Kunutsor et al. 2019).

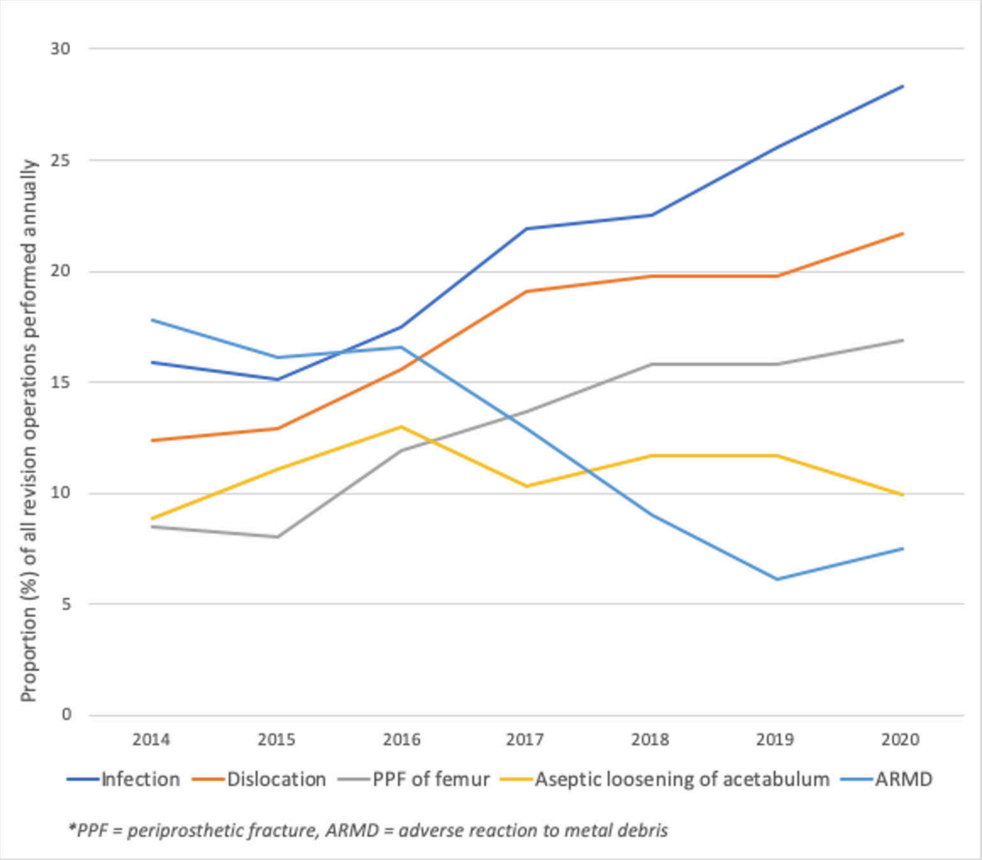


Figure 1. The five most common reasons for revision following primary THA in Finland between 2014 and 2020. Data adapted from Finnish Arthroplasty Register, Copyright: 2014–2023 National Institute for Health and Welfare, Finland.

2.2 Risk of revision for dislocation

Dislocation is still one of the most common postoperative complications leading to revision operation after primary THA. The total number of dislocation revisions is increasing because the annual number of THAs is also on the rise (Saiz et al. 2019), driven by an array of factors such as an aging population, technical improvement of implants, and surgical techniques (Wolf et al. 2012). Dislocations can be classified as early and late based on elapsed time since the primary operation. Early dislocations usually occur within 2 years after primary surgery and late dislocations beyond the second postoperative year (Malkani et al. 2010). Patients who suffer their first dislocation closer to the primary THA have a lower risk of further recurrent dislocations and revision operations (Norambuena et al. 2019).

The proportion of dislocation revisions is currently 17–21% of all revisions (AOANJRR 2017, FAR 2021). Dislocation revision risk varies from 0.1% to 10% during the first postoperative year (Brooks 2013, Dargel et al. 2014, Saiz et al. 2019). The risk of first-time dislocation varies as a function of time after primary THA and the risk of dislocation is highest during the first 3 postoperative months (Berry et al. 2004, Meek et al. 2008). Around two thirds of dislocations occur during the first postoperative year after primary elective THA (Meek et al. 2008, Hailer et al. 2012, Werner and Brown 2012).

The definition of recurrent dislocation is two or more episodes of dislocation. Anywhere from 10% to 60% of patients will have a recurrent dislocation after the first one (Kotwal et al. 2009, Brooks 2013, Rowan et al. 2018, Crompton et al. 2020). This wide variation in the reported prevalence is a reflection of differences in study designs and patient demographics (Kotwal et al. 2009). There remains approximately a 5% to 30% risk of recurrent dislocation after revision surgery due to dislocation (Brooks 2013, Saiz et al. 2019, Sutphen et al. 2020). The reason for dislocation after primary THA is multifactorial, with contributions by patient-, implant- and surgery-related factors (Rowan et al. 2018).

2.2.1 Risk factors

Dislocation is a devastating complication for both patient and surgeon and leads to substantial costs for healthcare (Zijlstra et al. 2017, Rowan et al. 2018). The causes and pathology behind instability were studied already in the late 20th century. Hip position, soft tissue imbalance, and component malpositioning are important causes of instability. (Dorr et al. 1983, Dorr and Wan 1998) Examination of the history, nature, direction of dislocation, and risk factors for dislocation are mandatory for treating the patient correctly and avoiding further dislocations (Meneghini 2018).

When a patient suffers a dislocation after primary THA, the first question that comes to mind is what kind of situation led to the event. Posterior dislocation is usually caused by a flexed and adducted hip position, which should be avoided for at least 3 months postoperatively (Peak et al. 2005, Meek et al. 2008, Meneghini 2018). Most dislocations are posterior (Lu et al. 2019). Dislocations typically occur when getting out of a chair, where the hip has been in deep flexion. Anterior dislocation may occur while standing and turning, with the hip extended and the leg rotating externally. It is important to consider the extent of trauma energy and whether the patient had pain before the dislocation. Also relevant is how much time has passed since the primary operation. Any neurological and/or lumbar spine disease and recent lumbar spine fusions are important to clarify. Neurological diseases may change the strength of the hip muscles and proprioception. Lumbar spine fusion and/or disease has been associated with changes in the lumbopelvic alignment, which may affect THA stability due to malpositioning of the acetabular component. Attention should also be paid to examining the strength and integrity of the hip abductor muscles. Primary THA can lead to leg shortening, which may cause inadequate abductor tension with resulting instability. (Meneghini 2018)

Potential risk factors for dislocation can be divided into patient-, implant- and surgery-related factors. Patient-related factors include older age, female sex, advanced American Society of Anesthesiologists (ASA) class, fracture as the indication for surgery, and neurological and cognitive disorders (Meek et al. 2008, Hailer et al. 2012). Implant- and surgery-related factors include posterior approach, small femoral head size, implant choice, suboptimal component positioning, and poor repair of the soft tissues, external rotators, and hip capsule (Rowan et al. 2018, Kunutsor et al. 2019). The impact on dislocation of these previously reported risk factors also varies with the time of dislocation.

In 1978, Lewinnek described a safe zone for the acetabular component position to decrease dislocation rates. The safe zone consists of an abduct inclination of 40±10 degrees and an anteversion of 15±10 degrees. Implants positioned outside the safe zone are at higher risk of dislocation. (Lewinnek et al. 1978, Saiz et al. 2019) Early first-time dislocation may be caused, for example, by a surgical approach combined with poor repair of soft tissues, inadequate soft-tissue tension, or patient noncompliance with precautionary instructions during the postoperative period. Even though the implants are well positioned within the Lewinnek safe zone, the hip may dislocate under these circumstances. On the other hand, late first-time dislocation may occur despite well-positioned implants because of eccentric liner wear. (Saiz et al. 2019, Laaksonen et al. 2020) Nowadays, the understanding of the spine-pelvis-hip motion has increased and this has led to a introduction of a new safe zone called functional safe zone in THA. The idea of functional safe zone is to understand the changes in pelvic tilt when patient stands and sits. (Figure 2) (Ike et al. 2018, Tezuka et al. 2019)

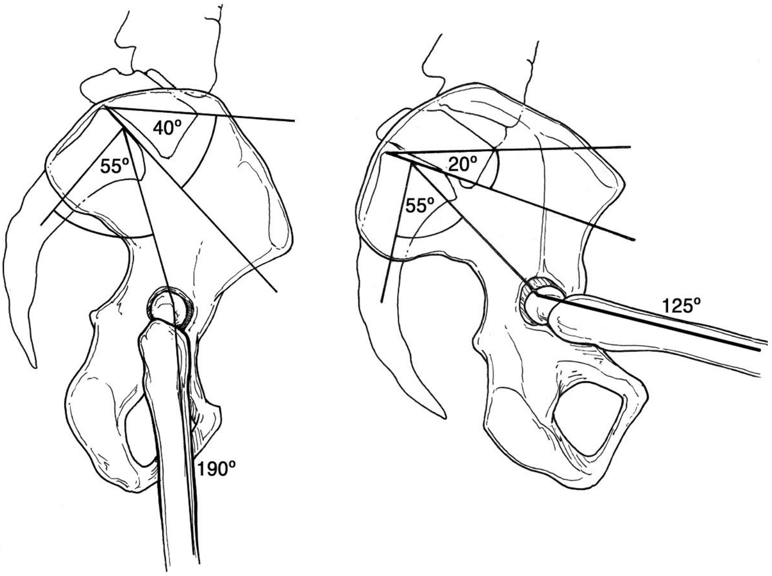


Figure 2. Anatomy of normal spine-pelvis-hip motion descripted in standing and sitting positions. Standing position on the left and sitting position on the right. In both positions the 55° angle is formed by the lines from the center of S1 vertebra to the center of femoral head. The angle formed by the endplate of the S1 vertebra and horizontal line descripts pelvic motion which differs in standing and sitting potions (40° and 20°, respectively). Femoral motion is measured from the angle formed by the line from the center of S1 vertebra through the center of the femoral head and to the femoral shaft (190° standing, and 125° sitting). Ideally, normal spine-pelvis-hip motion leads to an anterior tilt of the pelvis due to lordosis of the spine while standing. Whereas to a posterior tilt of the pelvis when the spine straightens while sitting. Further, in a sitting position anteversion of the acetabulum increases. (Tezuka et al. 2019) This illustration is reproduced with permission from Elsevier.

2.2.1.1 Femoral head size

The bearing surfaces of a THA articulation have two components, the femoral head and the acetabular liner or cup (Ferguson et al. 2018). Small femoral head sizes are associated with an increased risk of dislocation after primary THA (Werner and Brown 2012, Zijlstra et al. 2017). Already in the 1960s, when Charnley's low-friction arthroplasty was introduced, a 22 mm head size was found to be more prone to dislocation than 32 mm. However, the use of larger femoral heads in early metal-on-polyethylene (MoP) THA led to an increased rate of polyethylene wear. (Stinchfield and Eftekhar 2006) The early MoP bearings had high rates of wear due to the softness of polyethylene (Ferguson et al. 2018). Metal-on-metal (MoM) and ceramic-on-ceramic (CoC) bearings were introduced to solve the polyethylene wear problem. The toughness of MoM implants also allowed larger femoral head sizes. (Lombardi et al. 2001, Grammatopoulos et al. 2009) The theory behind the use of larger femoral head sizes was to increase jump distance. A bigger femoral head center must travel a longer lateral translation before it displaces out of the acetabular cup. (Werner and Brown 2012)

The second rise of MoM implants started over 20 years ago and peaked in 2008, after which an increased failure rate of MoM devices gradually became obvious. The mode of failure was called adverse local tissue reaction (ALTR) or adverse reaction to metal debris (ARMD) (Ferguson et al. 2018, Perino et al. 2021). Metal debris can trigger an adverse immunological reaction resulting in gluteal muscle necrosis, soft tissue masses, and fluid collection around the prosthesis (Ollivere et al. 2009, Perino et al. 2021). In Finland, over 20,000 MoM THA or hip resurfacing arthroplasties (HRAs) were performed between 2000 and 2015 (FAR 2021). Despite the high ARMD incidence, MoM THA and HRA also had a clinical advantage: they were both associated with very low dislocation rates, mostly due to stability achieved with the use of larger-diameter heads (Miettinen et al. 2019).

Nowadays, the bearing couple most commonly used in Finland is metal on ultra-highly crosslinked polyethylene (UHXLPE). The most common head size is currently 36 mm (FAR 2021). A large registry study of 166,231 primary THAs based on the Dutch Arthroplasty register (Landelijke Registratie Orthopedische Interventies, LROI) found that using 32 mm femoral heads carried a lower dislocation risk than using 22 to 28 mm heads in all surgical approaches (straight lateral, posterolateral, anterolateral, and anterior) (hazard ratios [HRs] 1.6 for 22 to 28 mm heads vs. 32 mm heads). In the same study, they only found a reduced dislocation risk for 36 mm heads versus 32 mm heads with the posterolateral approach (HR 0.6). (Zijlstra et al. 2017) Tsikandylakis et al. (2018) found no statistically significant difference in dislocation risk between 36 mm and 32 mm heads (HR 0.9), based on the NARA database from 2003 to 2014. However, 28 mm heads increased dislocation risk compared to 32 mm heads (HR 1.7). (Tsikandylakis et al. 2018) Later, Tsikandylakis et al. (2020) conducted another NARA database study from 2006 to 2016 and also found no statistically significant difference between 36 mm and 32 mm heads in relation to dislocation revision risk among patients with proximal femur fractures (Tsikandylakis et al. 2020). These findings do not support those of a previous randomized control trial (RCT), which showed a five-fold lower risk of dislocation among patients with 36 mm metal-on-UHXLPE bearings compared to 28 mm heads within the first year after primary THA. However, it should be emphasized that larger femoral heads may predispose to liner wear, osteolysis, acetabular liner fractures, and eventually late dislocations. (Howie et al. 2012) It has been recommended to use 32 mm or larger head sizes among patients with prior lumbar fusion undergoing primary THA (Mononen et al. 2020).

2.2.1.2 Surgical approach

Currently, the most frequently used surgical approaches are posterior, anterolateral (modified Hardinge), and anterior (Smith-Petersen) (Meermans et al. 2017). The use of one approach over another depends on the surgeon’s preference and the standards of the hospital (Peters et al. 2018). Each approach has unique advantages and disadvantages. Typical approach-related complications of THA are dislocation, abductor insufficiency, PPF, and nerve injury. (Petis et al. 2015, Aggarwal et al. 2019)

In the 1950s, Moore popularized the posterior approach. Currently, this is the most common approach in Finland and is used in 90% of all operations (FAR 2021) (Figure 3). This approach provides adequate, safe, and extensile exposure of the femoral head and acetabulum and helps to protect the sciatic nerve. In this approach, the fibers of the gluteus maximus muscle are split with dissection of the short external rotators. (Kwon et al. 2006, Petis et al. 2015, Markatos et al. 2020) The main benefit of the posterior approach is its intact preservation of the abductor mechanism. However, dissection during exposure or retractors lying over the external rotator muscles may cause injury to the sciatic nerve. The inferior gluteal artery may also sustain damage during the surgery. The posterior approach is generally associated with an increased risk of dislocation due to the inherent weakness of the posterior capsule, and this is the main disadvantage of this approach. (Petis et al. 2015, Meermans et al. 2017, Peters et al. 2018)

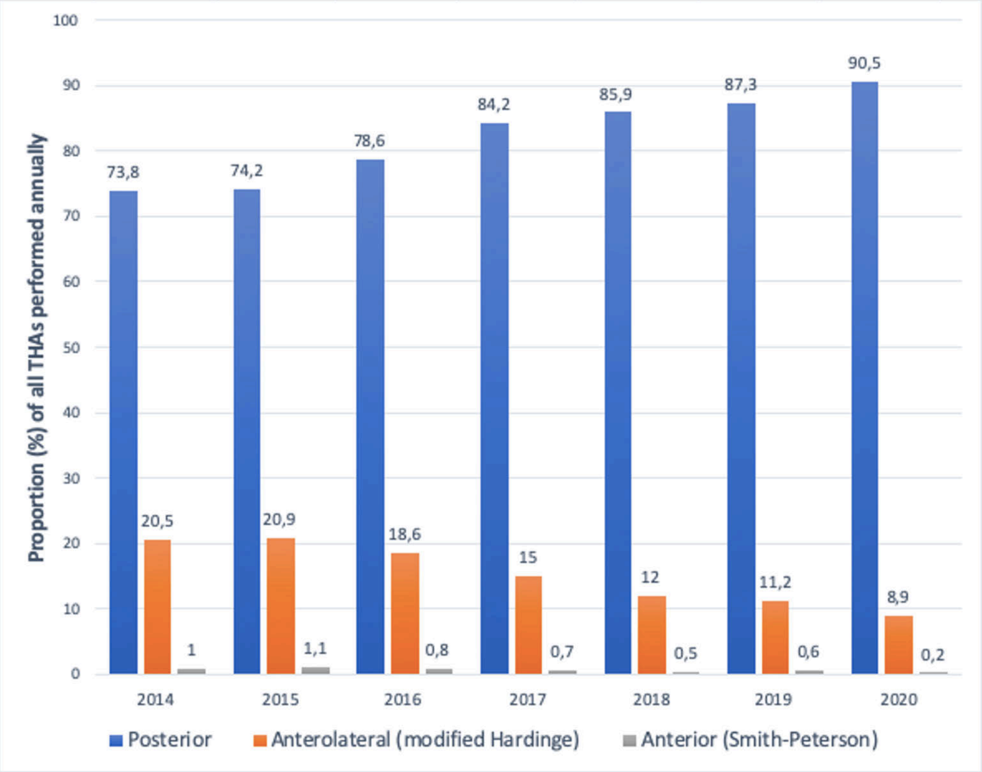


Figure 3. The three most commonly used THA surgical approaches in Finland from 2014 to 2020. Data adapted from the Finnish Arthroplasty Register, Copyright: 2014–2023 National Institute for Health and Welfare, Finland.

The anterolateral (modified Hardinge) approach was described by Hardinge in 1982 (Petis et al. 2015). This approach provides extensile visualization of the femur (Petis et al. 2015, Markatos et al. 2020). Achieving an adequate view of the anterior capsule of the hip joint requires releasing the abductor mechanism, which can be done by releasing the gluteus medius. There is a risk of damage to the superior gluteal nerve, which is associated with gait problems. (Meermans et al. 2017) Gait problems include limping due to abductor weakness and a positive Trendelenburg sign. Patients operated on with the anterolateral approach have reported having more postoperative pain during activity and at rest compared to those operated on with the posterior approach. (Amlie et al. 2014, Moyer et al. 2018, Peters et al. 2018) However, the anterolateral approach is associated with a decreased dislocation risk (Sheth et al. 2015, Mjaaland et al. 2017, Zijlstra et al. 2017).

Smith-Petersen was the first to describe the direct anterior approach, with wide exposure of the hip joint, in the 1940s (Smith-Petersen 1948). This approach was later modified by Heuter in the 1950s (Petis et al. 2015, Connolly and Kamath 2016). In this technique, exposure of the hip joint is done intra-muscularly and intra-nervously through the tensor fasciae latae and sartorius muscles (Connolly and Kamath 2016). The anterior approach has a steep learning curve, with an increased risk of nerve injuries, calcar and trochanter fractures, and difficulty using in obese patients (Meermans et al. 2017). The most common nerve injury is sciatic nerve palsy, but the lateral femoral cutaneous and femoral nerves are injured more frequently following a direct anterior approach (Vajapey et al. 2020). The direct anterior approach is related to diminished muscle trauma, which is associated with less postoperative pain, narcotic assumption and dislocations, shorter postoperative length of stay, and earlier return of function (Peters et al. 2018).

Dislocation rates differ between approaches. The benefit of using anterior and lateral approaches is low dislocation rates of 0.6% to 1.5% and 0.4% to 0.6%, respectively. The dislocation risk is highest when using the posterior approach and varies from 1% to 5%. (Petis et al. 2015) Kwon et al. (2006) performed a meta-analysis of dislocation rates following the posterior approach with and without soft-tissue repair and found an eight-fold risk of dislocation in the latter. Thus it is necessary to carefully repair the posterior capsule, short external rotators, and piriformis muscles to reduce the incidence of dislocation after use of the posterior approach. (Kwon et al. 2006) Hoskins et al. (2020) reported that the posterior approach was associated with an increased risk of revision for dislocation compared to anterior (HR 1.9) and lateral approaches (HR 1.3), based on Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR) data on 122,345 primary THAs in OA patients. Furthermore, during the first 6 postoperative months the lateral approach was associated with an increased dislocation revision risk compared to the anterior approach (HR 1.5). (Hoskins et al. 2020) Similar findings of the posterior approach increasing the risk of revision due to dislocation compared to the anterolateral approach was reported by Lindgren et al. (2012). In their large nationwide study based on data from the Swedish Hip Arthroplasty Register (SHAR), they compared the three most commonly used cemented THA designs in Sweden (relative risks [RRs] of 0.7 and 0.3 for Lubinus SPII and Spectron EF Primary prosthesis and use of the anterolateral approach, respectively, compared to posterior approach) (Lindgren et al. 2012). Contradictory data also exists. Jameson et al. (2014) found no difference between the posterior and lateral approaches in relation to dislocation during the first postoperative year based on the National Joint Registry (NJR) for England, Wales, Northern Ireland and the Isle of Man. They also reported better early patient-reported outcome measures (PROMs) for the posterior approach compared to the lateral approach. (Jameson et al. 2014) Charney et al. (2020) examined data from the Kaiser Permanente Total Joint Replacement Registry following a dramatic increase in the use of the direct anterior approach (DAA) from 4.5% in 2009 to 27.8% in 2017. One of their interests was to investigate the difference between dislocation risk and the use of DAA and posterior approaches. They found that the DAA had a lower risk of revision due to dislocation compared to the posterior approach (HR 0.4). (Charney et al. 2020)

The use of minimally invasive surgery (MIS) THA has also gained some popularity in the last decade. A minimally invasive anterior approach requiring less soft tissue disruption has been achieved by some surgeons (Wall and Mears 2008, Ferguson et al. 2018, Markatos et al. 2020). Also the posterolateral approach can be shortened to an MIS technique, as can the anterolateral and modified anterolateral Watson-Jones approach. Early reports of MIS approaches were promising, but enthusiasm has waned following reports of neurovascular injuries and component malpositioning associated with these approaches. (Shitama et al. 2009, Ferguson et al. 2018)

All approaches may be associated with nerve injuries, with varying reported incidences from 0.1% to 4% (Farrell et al. 2005, Macheras et al. 2016, Shetty et al. 2019, Vajapey et al. 2020). The incidence is even higher after revision THA, increasing up to 7.6% (Brown and Swanson 2008). The posterior approach is most commonly associated with sciatic nerve palsy, with an incidence of 0.1% to 0.6% (Yacoubian et al. 2010, Amlie et al. 2014, Vajapey et al. 2020). The direct anterior approach is associated with nerve injuries of the lateral femoral cutaneous and femoral nerves, with reported incidences from 3% to 81% and from 0.3% to 5%, respectively (Hasija et al. 2018, Vajapey et al. 2020). Anterolateral and lateral approaches increase the risk of superior gluteal nerve injury, and the risk has been reported to range from 43% to 77% (Picado et al. 2007, Amlie et al. 2014, Hasija et al. 2018). However, from a clinical point of view, limping is a very rare complication following the use of anterolateral and lateral approaches.

2.2.2 Treatment of unstable THA

Treatment options for a dislocated THA involve either non-operative or surgical management. First-time dislocations that occur within the first 3 postoperative months are generally treated by closed reduction, especially if the implants are properly positioned. (Lu et al. 2019) Closed reduction is usually performed in a hospital emergency room. Propofol sedation and analgesia are administered by an anesthesiologist to achieve proper muscular relaxation. Sedation may predispose the patient to aspiration, which should be carefully considered in older patients. If closed reduction is not achieved in the emergency room, it is performed by an orthopedic specialist in an operating room under regional or general anesthesia. If this fails, a revision operation is required. A first-time dislocation may be associated with immature scar tissue or patient noncompliance with postoperative precautions (Lu et al. 2019, Saiz et al. 2019). Two thirds of dislocated hips respond well to closed reduction and remain stable subsequently (Lu et al. 2019).

Revision surgery is needed for patients suffering recurrent dislocations following closed reductions and for those with malpositioned implants. Several surgical managements for treating recurrent dislocations have been described in the literature, such as trochanteric advancement, elevated rim liners, jumbo femoral heads, constrained liners, bipolar and dual mobility prostheses, and ischiofemoral hip ligament and Achilles tendon allograft reconstructions. (Lu et al. 2019, Saiz et al. 2019)

Elevated rim polyethylene acetabular liners may increase hip stability by reducing the tendency for posterior dislocations. An elevated rim is usually positioned in the posterior-superior position, which provides more stability due to its asymmetric configuration in the regions of instability. Elevated liners are used in both primary and revision surgery. However, disadvantages include impingement of the liner and femoral neck. Impingement may also lead to polyethylene wear debris, which may even result in aseptic loosening with a higher rotatory moment arm. (Hemmilä et al. 2019, Lu et al. 2019)

Constrained acetabular liners are used for the same reasons as elevated rim liners. A more violent force is required to dislocate the larger outer head from the acetabulum compared with traditional implant designs. However, these devices should be used with caution as they cannot compensate for malpositioning of the components. (Saiz et al. 2019) It has been suggested that constrained acetabular liners should only be used in elderly and low-demand patients (Lu et al. 2019). The use of constrained devices also predisposes to impingement, leading to restriction of the range of motion and increased dislocation risk (Beaulé et al. 2002, Karvonen et al. 2020). Karvonen et al. (2020) used data from the FAR collected prospectively between 2006 and 2017 to investigate the 8-year survivorship of the constrained acetabular device in primary THAs, compared to conventional THAs with revision for any reason as the endpoint. In their study, overall revision risks were equal in both groups but very few dislocation revisions were done in the constrained group. (Karvonen et al. 2020) This is in line with some previous studies (Berend et al. 2006, Karvonen et al. 2017).

Malposition of either the acetabular and/or femoral component may cause dislocation. Acetabular component malposition is more common and predisposes to dislocation, especially if the components are outside the Lewinnek safe zone. However, the meaning of the safe zone has recently been better understood. The ideal position of an implant may be more multifactorial and patient-specific than previously thought. (Lewinnek et al. 1978, Meneghini 2018, Saiz et al. 2019) In practice, if the components are malpositioned and the hip is dislocating repeatedly, the malpositioned components should be changed.

Dual mobility acetabular components were introduced in France in 1974 by Bousquet and Rambert (Figure 4). They increase the range of movement and head-neck ratio thanks to their large-diameter outer head sizes. Reported disadvantages of this treatment option include increased wear debris, which can lead to osteolysis and aseptic loosening. Intraprosthetic dislocation between the outer and inner femoral heads is regarded as a new mode of failure. (De Martino et al. 2017, Lu et al. 2019) Jobory et al. (2019) conducted a registry study based on the NARA database and found that patients treated with dual-mobility acetabular cups in primary THA for hip fracture have a decreased risk of revision due to dislocation, and also in general, compared to conventional THA. The data covered a variety of dual mobility brands like the Saturne (Amplitude), Avantage (Zimmer Biomet), and Polarcup (Smith & Nephew). (Jobory et al. 2019) Another NARA study by Kreipke et al. (2019) analyzed data from 1995 to 2013 and concluded that dual-mobility acetabular cups decreased the dislocation revision risk in primary THA performed for OA (Kreipke et al. 2019).

Figure 4. Left hips' recurrent dislocation of THA with malposition of the cup treated with dual-mobility acetabular components. Radiographs from the Turku University Hospital radiograph archive.

2.3 Risk of revision for prosthetic joint infection (PJI)

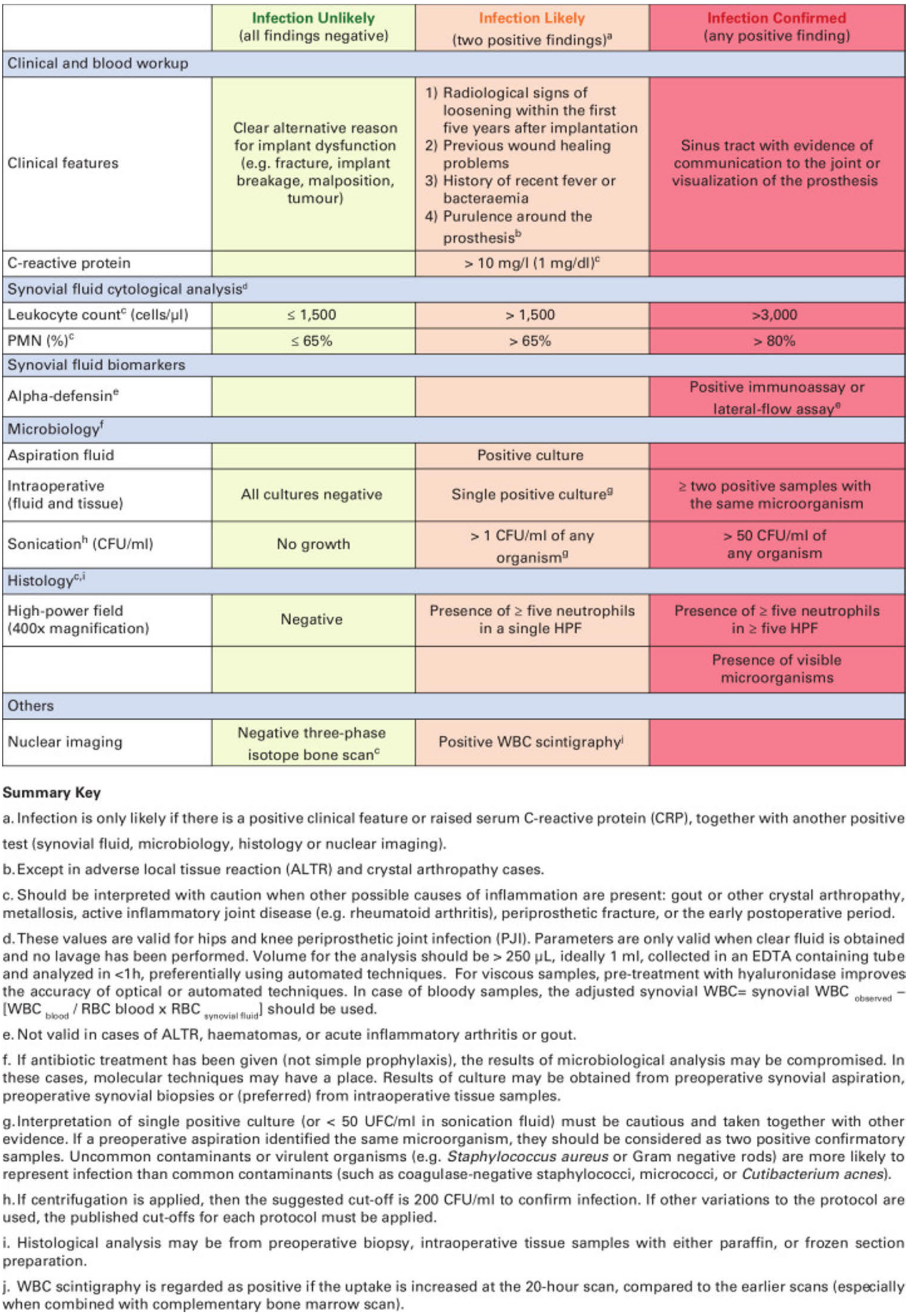
The PJI rate after THA is 0.8%–1.3% and varies depending on the definition (The McMaster Arthroplasty Collaborative 2020, Dale et al. 2021, Renner et al. 2021). Revision surgery for PJI is demanding, and first-time revisions are associated with a greater mortality risk and increased rate of repeated surgery (Gundtoft et al. 2017b, Kheir et al. 2017, Steinicke et al. 2023). In Finland, the cumulative incidence of PJI after primary THA was 0.92% between 1998 and 2009. The annual incidence of PJI decreases over time and the risk is highest during the first 2 postoperative years. (Huotari et al. 2015) Liukkonen et al. reported that the incidence of revision operations due to PJI was increased by 12-fold in primary THAs from 2008 to 2021 (from 0.11 per 100 primary THAs to 1.34 per 100 primary THAs, respectively), especially in early infections (≤90 after the primary THA) (Liukkonen et al. 2023).

The most common microorganisms causing PJI are Staphylococcus aureus and coagulase-negative staphylococci (Gundtoft et al. 2017a, Li et al. 2018). Gundtoft et al. (2017) reported that Staphylococcus aureus caused 36% and coagulase-negative staphylococci 33% of the PJIs after primary THA. Other identified bacteria were Enterobacteriaceae, enterococci, and streptococci. (Gundtoft et al. 2017a) Senthi et al. (2011) reviewed the literature from 2005 to 2011 and found that 42% of PJIs are infected by Staphylococcus aureus and 8% by methicillin-resistant Staphylococcus aureus (MRSA) (Senthi et al. 2011). Honkanen et al. (2019) analyzed data from Coxa Hospital for Joint Replacement, Finland, and found that Staphylococcus aureus, beta-hemolytic streptococci, and viridans group streptococci were the most common bacteria causing PJI (20%, 21% and 16%, respectively) (Honkanen et al. 2019). There are three ways in which a prosthesis can become infected. The first is early contagion during the surgery itself. The second is hematogenous infection, which can occur at any time after implantation of the prosthesis. The third pathway is through direct contact with infected adjacent tissues. PJI infections are classified as acute (<4–8 weeks after surgery) or chronic (≥4–8 weeks after surgery). (Li et al. 2018)

Diagnosis of PJI can be difficult due to the variety of symptoms. Fulminant joint sepsis has clear signs of infection like pain, dysfunction of the hip, fever, erythema, swelling, warmth of palpation, and wound leakage. (Springer 2015, McNally et al. 2021) Specific signs of chronic PJI are a sinus tract from the joint to the surface of the skin and an exposed prosthesis (McNally et al. 2021). During revision, the surgeon takes a perioperative microbe culture from the synovial fluid and soft tissues. Conclusive microbiological results are usually available in 2 to 7 days postoperatively. Debridement, antibiotics and implant retention (DAIR) are performed for treatment of an acute PJI. Prosthesis removal is usually needed in chronic PJI (Figure 5). The surgeon completes the register notification form in the operating theatre based on the clinical assessment.

Figure 5. Chronic PJI of the left hip after primary THA. Photograph by Jari Mokka.

In 2011 the Musculoskeletal Infection Society (MSIS) made a revised suggestion for the definition of PJI. It was later modified by several international expert groups. Despite the development of definitions, no single definition has gained worldwide acceptance for clinical practice. Based on the most recent European Bone and Joint Infection Society (EBJIS) data, the definition of PJI has evolved into a three-level approach (infection unlikely, infection likely, infection confirmed) consisting of clinical signs, blood biomarkers, synovial fluid cytology and biomarkers, microbiology, histology, and nuclear imaging. C-reactive protein (CRP), white cell count, percentage of polymorphonuclear neutrophils (PMN), and erythrocyte sedimentation rate are analyzed from the blood. The amount of white blood cells and alpha-defensin and the microbiology are assessed from preoperative aspiration of synovial fluid. The microbiology and histology of inflammatory cells are also screened from intraoperative tissue samples taken pre- or intraoperatively. (Figure 6) (McNally et al. 2021)



	Infection Unlikely (all findings negative)	**Infection Likely** (two positive findings)[a]	**Infection Confirmed** (any positive finding)
Clinical and blood workup			
Clinical features	Clear alternative reason for implant dysfunction (e.g. fracture, implant breakage, malposition, tumour)	1) Radiological signs of loosening within the first five years after implantation 2) Previous wound healing problems 3) History of recent fever or bacteraemia 4) Purulence around the prosthesis[b]	Sinus tract with evidence of communication to the joint or visualization of the prosthesis
C-reactive protein		> 10 mg/l (1 mg/dl)[c]	
Synovial fluid cytological analysis[d]			
Leukocyte count[c] (cells/µl)	≤ 1,500	> 1,500	>3,000
PMN (%)[c]	≤ 65%	> 65%	> 80%
Synovial fluid biomarkers			
Alpha-defensin[e]			Positive immunoassay or lateral-flow assay[e]
Microbiology[f]			
Aspiration fluid		Positive culture	
Intraoperative (fluid and tissue)	All cultures negative	Single positive culture[g]	≥ two positive samples with the same microorganism
Sonication[h] (CFU/ml)	No growth	> 1 CFU/ml of any organism[g]	> 50 CFU/ml of any organism
Histology[c,i]			
High-power field (400x magnification)	Negative	Presence of ≥ five neutrophils in a single HPF	Presence of ≥ five neutrophils in ≥ five HPF
			Presence of visible microorganisms
Others			
Nuclear imaging	Negative three-phase isotope bone scan[c]	Positive WBC scintigraphy[j]	

Summary Key

a. Infection is only likely if there is a positive clinical feature or raised serum C-reactive protein (CRP), together with another positive test (synovial fluid, microbiology, histology or nuclear imaging).

b. Except in adverse local tissue reaction (ALTR) and crystal arthropathy cases.

c. Should be interpreted with caution when other possible causes of inflammation are present: gout or other crystal arthropathy, metallosis, active inflammatory joint disease (e.g. rheumatoid arthritis), periprosthetic fracture, or the early postoperative period.

d. These values are valid for hips and knee periprosthetic joint infection (PJI). Parameters are only valid when clear fluid is obtained and no lavage has been performed. Volume for the analysis should be > 250 µL, ideally 1 ml, collected in an EDTA containing tube and analyzed in <1h, preferentially using automated techniques. For viscous samples, pre-treatment with hyaluronidase improves the accuracy of optical or automated techniques. In case of bloody samples, the adjusted synovial WBC= synovial WBC $_{\text{observed}}$ − [WBC $_{\text{blood}}$ / RBC blood x RBC $_{\text{synovial fluid}}$] should be used.

e. Not valid in cases of ALTR, haematomas, or acute inflammatory arthritis or gout.

f. If antibiotic treatment has been given (not simple prophylaxis), the results of microbiological analysis may be compromised. In these cases, molecular techniques may have a place. Results of culture may be obtained from preoperative synovial aspiration, preoperative synovial biopsies or (preferred) from intraoperative tissue samples.

g. Interpretation of single positive culture (or < 50 UFC/ml in sonication fluid) must be cautious and taken together with other evidence. If a preoperative aspiration identified the same microorganism, they should be considered as two positive confirmatory samples. Uncommon contaminants or virulent organisms (e.g. *Staphylococcus aureus* or Gram negative rods) are more likely to represent infection than common contaminants (such as coagulase-negative staphylococci, micrococci, or *Cutibacterium acnes*).

h. If centrifugation is applied, then the suggested cut-off is 200 CFU/ml to confirm infection. If other variations to the protocol are used, the published cut-offs for each protocol must be applied.

i. Histological analysis may be from preoperative biopsy, intraoperative tissue samples with either paraffin, or frozen section preparation.

j. WBC scintigraphy is regarded as positive if the uptake is increased at the 20-hour scan, compared to the earlier scans (especially when combined with complementary bone marrow scan).

Figure 6. EBJIS definition of PJI (McNally et al. 2021). Illustration reproduced by the terms of Creative Commons Attribution Non-Commercial No Derivatives License (https://creativecommons.org/licenses/by-nc-nd/4.0/).

2.3.1 Risk factors

In order to reduce the incidence of PJI, it is important to identify the predisposing risk factors (Bozic et al. 2014b, The McMaster Arthroplasty Collaborative 2020). Risk factors for PJI can be divided into patient- and surgery-related factors. Patient-related risk factors include male sex, lower socioeconomic status, pre-existing comorbidities such as diabetes and dementia, high body mass index (BMI), advanced ASA classification, and rheumatoid arthritis. Long duration of the operation, wound drain, superficial infections, and lateral surgical approaches are generally accepted surgery-related factors. (Pedersen et al. 2010, Bozic et al. 2012, 2014b, Kunutsor et al. 2016, Lenguerrand et al. 2018, Smith et al. 2018, The McMaster Arthroplasty Collaborative 2020)

Bozic et al. (2012) analyzed Medicare patient data and found that obesity increased the risk of PJI after THA when compared to other comorbid conditions (HR 1.7). The risk diminished over time; 1 year postoperatively the risk of PJI due to obesity was 19% lower (Bozic et al. 2012). Similar findings with an almost two-fold PJI risk for a BMI of ≥ 30 kg/m^2 compared to a BMI of <25 kg/m^2 was found in a large cohort study by Lenguerrand et al. when they analyzed 623,253 primary THAs performed from 2003 to 2013 in England and Wales (Lenguerrand et al. 2018). These findings are consistent with prior studies (Kunutsor et al. 2016, Kurtz et al. 2018, Smith et al. 2018). Jämsen et al. (2012) analyzed data from single-center series of 7,181 primary hip and knee replacements and found that diabetes more than doubled the risk of PJI independently of obesity when compared to patients without diagnosis of diabetes (OR of 2.3). Further, only patients with BMI of ≥ 40 kg/m^2 were associated with an increased PJI risk when compared to patients with BMI of <25 kg/m^2 (OR of 6.4). (Jämsen et al. 2012) Diabetes was also associated to PJI in a large meta-analysis by Kong et al. (Kong et al. 2017). High ASA classification has been found to increase the risk of revision due to PJI in several prior studies (Kong et al. 2017, Lenguerrand et al. 2018, Smith et al. 2018). Smith et al. (2018) concluded a six-fold risk for PJI revision during the 6 postoperative months for patients with ASA class IV compared to ASA class I when they analyzed 91,585 primary THAs from 2000 to 2014 based on New Zealand Joint Registry data (Smith et al. 2018). Another important patient-related risk factor is male sex, which has been reported to have an increased risk of revision due to PJI (1.6–1.9-fold). There may be some confounding factors, such as smoking and alcohol consumption, that explain the sex difference. (Dale et al. 2012, Bozic et al. 2014b, Lenguerrand et al. 2018, Smith et al. 2018) The Charlson comorbidity index can be used to assess the presence of pre-existent comorbidities of the patient. Ong et al. (2009) analyzed Medicare patient data and found that patients with a Charlson index score of 5+ were associated with an increased PJI risk compared to patients with a score of 0 (OR of 2.6). (Ong et al.

2009) This means that comorbid conditions are paramount risk factors associated to PJI risk and special attention should be paid on those.

Mjaaland et al. (2017) extracted data from the Norwegian Arthroplasty Register with 21,860 THAs from 2008 to 2013 and reported a lower risk of revision due to PJI after the use of MIS anterior and anterolateral approaches and also the posterior approach compared to the direct lateral approach (RRs of 0.5, 0.5, and 0.6, respectively) (Mjaaland et al. 2017). Similar findings were also reported by Smith et al. when they analyzed the New Zealand Joint Registry data and compared the lateral approach to the posterior approach at 6 and 12 postoperative months (ORs of 1.6 and 1.6, respectively) (Smith et al. 2018).

Another suggested surgery-related factor associated with decreased PJI risk is the use of CoC bearings (Pitto and Sedel 2016, Kurtz et al. 2017, Lenguerrand et al. 2018, Madanat et al. 2018). Renner et al. (2021) found a decreased risk of revision for PJI when using a CoC bearing couple compared to ceramic-on-polyethylene (CoP) bearings. The authors had tried to minimize the influence of confounding covariates including age, sex, obesity, and complicated diabetes mellitus. (Renner et al. 2021) Pitto and Sedel (2016) analyzed 84,894 THAs over a 15-year time period and found that CoC bearings had a lower risk of revision due to PJI compared to CoP, MoP, and MoM bearings over this period (HRs of 1.3, 1.8, and 2.1, respectively) (Pitto and Sedel 2016). Based on data from the AOANJRR from 1999 to 2013, Madanat et al. (2018) reported a similar range of findings, with a lower risk of infection for CoC bearings in patients younger than 70 years with uncemented femoral components (Madanat et al. 2018). However, contradictory findings also exist (Hu et al. 2015). Si et al. (2015) did not find any correlation between PJI and ceramic bearings in a meta-analysis setting (Si et al. 2015). Ceramic bearings are often used in younger and healthier patients, which may cause confounding bias. Further, CoC bearing couples are usually used by experienced surgeons. However, CoC bearings have been found to diminish the risk of revision due to PJI even after adjustment for age and health status. (Lenguerrand et al. 2018). MoM implants are generally associated with an increased risk of infection mostly due to metal wear debris-related immunologic soft-tissue reactions (Bordini et al. 2019).

Leong et al. (2020) analyzed 418,857 THAs (397,896 THAs with antibiotic-loaded bone cement and 20,961 with plain cement) from NJR for England, Wales, Northern Ireland and the Isle of Man from 2005 to 2017 and found a decreased risk of revision due to PJI for the use of antibiotic-loaded bone cement compared to plain cement (HR 0.8) even after adjustment for operative year, age at the time of surgery, ASA-class, femoral head size, and BMI (Leong et al. 2020). Similar findings were also reported in a meta-analysis conducted by Farhan-Alanie et al. (RR of 0.7 for the antibiotic-loaded bone cement compared to plain cement) (Farhan-Alanie et al. 2021).

The use of a wound drain potentially predisposes to excessive blood loss and therefore to increased PJI risk (Kwong et al. 2012, Lychagin et al. 2021). Blood transfusions are associated with PJI after THA (OR of 1.7) (Kim et al. 2017).

Pedersen et al. (2010) reported an increased risk of revision due to PJI with a long duration of surgery (RR of 2.0 for a surgery exceeding 2 hours compared to an operation time of under 1 hour) (Pedersen et al. 2010). Similar findings have also been found in other studies (Ong et al. 2009, Kong et al. 2017). There may be some confounding factors behind a long operative time and infection risk, such as surgeon's experience, complications during surgery, an otherwise difficult operation, anesthetic challenges, or high BMI of the patient (Pedersen et al. 2010, Bradley et al. 2014).

2.3.2 Treatment of PJI

The gold standard treatment for acute PJI is DAIR (Figure 7). If present, the modular femoral head and acetabular liner are changed (Bedair et al. 2011). It has been claimed that 90% of acute PJI can be successfully cured using DAIR with targeted antimicrobial therapy (Li et al. 2018).

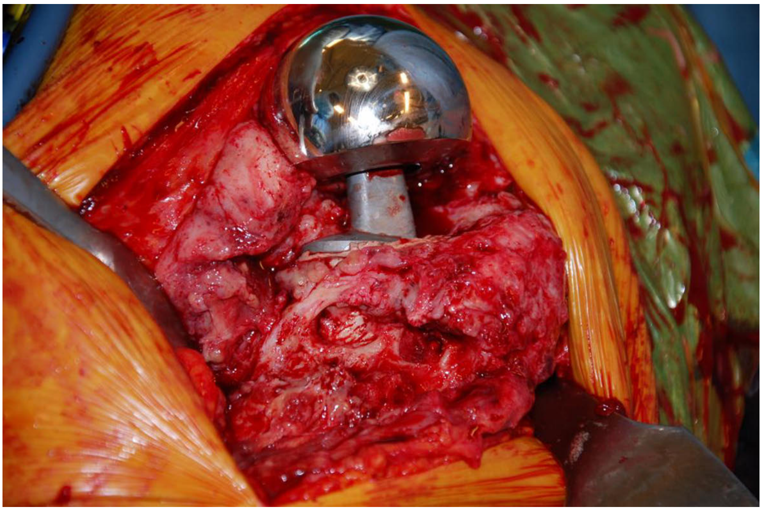


Figure 7. Acute PJI of hemiarthroplasty of the hip treated with DAIR. Photograph by Jari Mokka.

The gold standard for the treatment of chronic PJI is two-stage revision (Figure 8). Infected implant components are removed, and reimplantation of the components is delayed from at least 6 weeks until there is no evidence of infection left. During the period between removal and reimplantation there is no prosthesis in situ, although usually an antibiotic-loaded cement spacer is used. Two-stage revisions are associated with bone and muscle deficiency, overall morbidity, and even mortality. The period without a hip implant is often poorly tolerated and may lead to significant functional deficits. (Bedair et al. 2011, Leonard et al. 2014, Kunutsor et al. 2018) Another suggested method to treat chronic PJI is a one-stage revision where the infected implants are removed and replaced during the same operation (Kunutsor et al. 2018, Li et al. 2018). Kunutsor et al (2018) compared the outcome of one- and two-stage revision operations and concluded that a one-stage revision may be as effective as a two-stage revision (Kunutsor et al. 2018). Usually, however, two-stage revision cases are more complex. Surgical revision is always combined with appropriate antimicrobial treatment. The duration of antibiotic treatment is usually 12 weeks depending on the infection. (Li et al. 2018) The reported success varies widely, from 14% to 91% for DAIR, 60% to 83% for one-stage revision, and 70% to 93% for two-stage revision (Bedair et al. 2011, Sendi et al. 2017, Ford et al. 2018).

Figure 8. Anteroposterior pelvic radiograph of bilateral chronic PJI treated with prosthesis removal. Radiograph by Jari Mokka.

2.4 Risk of revision for periprosthetic fracture (PPF)

Nowadays THA can be performed on older and fragile patients (Wolf et al. 2012), which is also a reflection of technical improvement of implants, and surgical techniques (Huo et al. 2008). These patients may be more prone to falling, predisposing them to PPF. PPFs are relatively common at an early stage during the first postoperative days, weeks, and months, especially if uncemented stems are used (Abdel et al. 2015, 2016, Zhu et al. 2015, Pavone et al. 2019). Some patients may have symptoms caused by prosthetic loosening, such as thigh or groin pain. Polyethylene wear and osteolysis predispose to late PPF. Most PPFs occur after a low-energy trauma. Traumatic events both in younger and especially in older patients expose them to PPF. (Patsiogiannis et al. 2021) PPFs are associated with an increased mortality. Especially during the first postoperative year, PPF patients may have functional deterioration, limited mobility, and a high risk of postoperative complications leading to hospitalization. (Young et al. 2008, Islam et al. 2022)

The incidence of PPF varies from 0.1% to 4% but has been reported to be as high as 18% (Zhu et al. 2015, Pavone et al. 2019). The incidence is higher after revision than after primary surgery (Pavone et al. 2019). A large review of PPF revealed incidence rates of 1% after primary THA and 4% after revision surgery (Della Rocca et al. 2011). The number of PPFs is likely to rise at a similar rate to that of both primary and revision THAs, which are expected to increase by 174% and 137%, respectively, by 2030 (Abdel et al. 2015).

PPFs are classified as femoral or acetabular fractures. They can occur either intraoperatively due to impaction forces or immediately postoperatively during the first postoperative days, weeks, or months (Masri et al. 2004). Femoral PPFs are strongly associated with the use of uncemented fixation (Davidson et al. 2008, Jämsen et al. 2014) leading to higher share of cemented fixation in the oldest age groups (Figure 9).

It has been reported that 10% of THA-related PPFs are acetabular fractures and that 70–80% of these fractures occur intraoperatively. Intraoperative acetabular PPFs are also associated with uncemented fixation and revision operations (Patsiogiannis et al. 2021). The prevalence of intraoperative femoral PPFs has been reported to vary from 2.7% to 5.4% for uncemented fixation (Masri et al. 2004, Miettinen et al. 2016, Zhao et al. 2017) and from 0.3% to 1.2% for cemented fixation (Masri et al. 2004, Brüggemann et al. 2022). Thien et al. (2014) reported 0.5% and 0.07% incidences of revision due to PPF of the femur at 2 years for uncemented and cemented stems, respectively, based on the NARA database (Thien et al. 2014). Many PPFs occur beyond the 6th postoperative year, as patients are then older and may be more prone to falls (Zhu et al. 2015, Pavone et al. 2019). PPFs are also associated with increased morbidity, difficult complications, poor clinical outcome, and mortality (Zhu et al.

2015, Palan et al. 2016). Abdel et al. (2016) analyzed single-unit institutional data from 1969 to 2011 and reported a 1.7% incidence of intraoperative femoral fractures and a 3.5% cumulative incidence for postoperative fractures at 20 years. They also found a 14-fold higher risk of intraoperative fractures for uncemented compared to cemented implants. (Abdel et al. 2016)

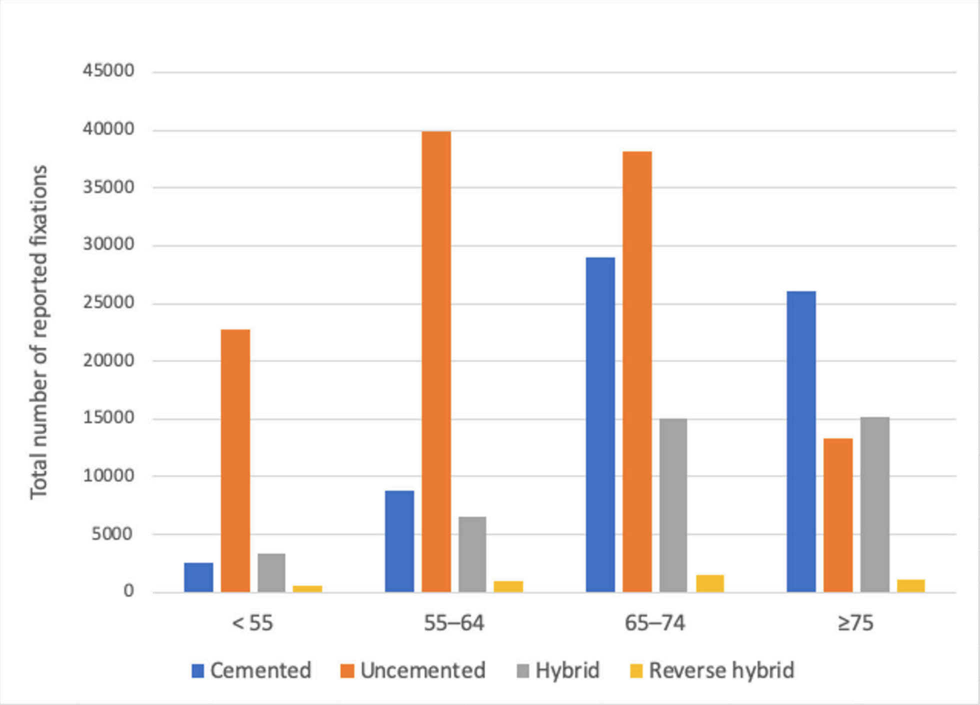


Figure 9. Number of used fixation methods among different age groups including both females and males in Finland. Data adapted from the Finnish Arthroplasty Register, Copyright: 2014–2023 National Institute for Health and Welfare, Finland.

The Vancouver classification is commonly used to guide the management of postoperative femoral PPFs (Figure 10). Femoral PPFs are classified into three major types, A, B, and C, and further subdivided based on implant stability and femoral bone quality. (Abdel et al. 2015) Acetabular PPFs are often classified according to the system by Pascarella et al. (Pascarella et al. 2018, Patsiogiannis et al. 2021).

Vancouver type A fractures occur in the trochanteric region involving either the greater (AG) or lesser trochanter (AL). These fractures can also be subdivided based on the stability of the stem implant. A1 indicates that the stem is well-fixed and A2 that the stem is loose. (Abdel et al. 2015)

Vancouver type B fractures are divided into three subtypes that occur in the region of the stem and are based on the stability of the stem. B1 consists of fractures surrounding a stable stem. B2 consists of fractures that surround an unstable stem but have adequate bone quality. B3 consists of fractures that occur around an unstable stem with inadequate remaining bone stock. Vancouver type C fractures occur substantially below the stem implant, which is usually well fixed. (Abdel et al. 2015)

Full-length X-rays of the femur and pelvis should be taken. Computerized tomography (CT) provides additional information. (Patsiogiannis et al. 2021)

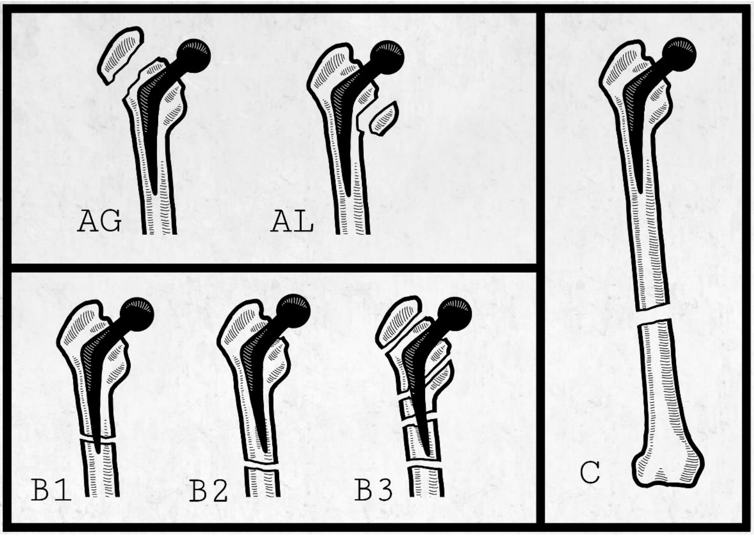


Figure 10. The Vancouver classification of femoral PPFs (Types A-C). Type A: greater (AG) or lesser (AL) trochanter fractures. Type B: fracture around the stem or just below the tip of the stem. B1: fracture around a stable stem. B2: fracture around an unstable stem with adequate bone quality. B3: fractures around an unstable stem with inadequate remaining bone stock. Type C: fracture below the stem. Illustration by Jenni Jormanainen.

PPF of the acetabulum is relatively rare, with a reported incidence of 0.8% (Pascarella et al. 2018). Acetabular PPFs can occur either intra- or postoperatively. Intraoperative fractures are associated with uncemented fixation with press-fit implantation of components. Also trauma and severe bone loss can cause acetabular PPF. (Masri et al. 2004, Patsiogiannis et al. 2021)

Pascarella et al. classify acetabular PPFs according to timing (intraoperative and postoperative/traumatic), stability of the prosthesis (stable or unstable), and the state of arthroplasty before the diagnosed injury. This classification can be used directly to guide surgical planning. CT should be used to get detailed analysis of the fracture patterns and cup mobilization in postoperative fractures. (Pascarella et al. 2018)

2.4.1 Risk factors

PPF risk factors can be divided into patient- and surgery-related factors. Patient-related risk factors include female sex, older age, osteoporosis, rheumatoid arthritis, Paget's disease, and hip dysplasia. Increased time from the primary arthroplasty operation, stem malposition, uncemented fixation, revision surgery, osteolysis, and aseptic loosening are surgery-related factors. (Zhu et al. 2015, Pavone et al. 2019, Patsiogiannis et al. 2021) The most important risk factors are older age, female sex, and uncemented implants (Thien et al. 2014).

Thien et al. (2014) conducted a NARA study of 325,770 cemented femoral stems and 111,899 uncemented femoral stems inserted from 1995 to 2009 and reported that uncemented fixation was associated with almost a nine-fold risk of revision due to PPF of the femur. Furthermore, there were more revision operations among the uncemented group with increasing age, and most of the PPFs occurred during the first 6 postoperative months. They also found that females in the age groups <50, 50–59, 60–69, 70–79, and >80 years with uncemented fixation had an increased risk of revision due to PPF compared to cemented fixation (RRs of 4.3, 6.8, 12.7, 16.8, and 15.2, respectively). (Thien et al. 2014) Jämsen et. al (2014) analyzed 4,777 primary THAs performed in Finland between 1998 and 2009 and found that PPF was the most common reasons for a revision operation of uncemented THA during the first postoperative year (50% of all revisions). After that only a slight difference was found in 10-year survival rate when uncemented fixation was compared to cemented and hybrid fixations (94%, 97%, and 98%, respectively). (Jämsen et al. 2014)

Based on the NJR's 18th Annual Report for England, Wales, Northern Ireland and the Isle of Man, the use of cemented fixation has almost halved over the past 14 years, whereas the use of hybrid fixation has more than doubled over the same time period and has overtaken the use of uncemented fixation in the past 2 years (NJR 2021). Mäkelä et al. suggested the use of cemented implants for patients aged 65 years or older, because cemented implants had a higher 10-year survival than uncemented, hybrid, and reverse hybrid implants based on the NARA database. Also, for the first 6 postoperative months, cemented implants had the lowest risk of overall revision, PPF included. (Mäkelä et al. 2014a)

2.4.2 Treatment of PPF of the femur and acetabulum

Vancouver type AG and AL fractures may be suitable for non-operative treatment with protected weight bearing and restricted active hip abduction for 6 to 12 weeks. Most of these fractures are associated with wear debris of the polyethylene, which has led to osteolysis. Therefore, the surgical treatment focuses on treating this wear debris problem as well as the fractures. Wear debris is treated with a polyethylene exchange and osteolysis with bone grafting procedures. Operative treatment is indicated if the greater trochanter fracture is displaced. Trochanteric osteosynthesis is performed using either tension band wiring or with specialized plates. Isolated AL fractures are usually treated conservatively. Vancouver A1 and A2 fractures can occur also intraoperatively and should be treated accordingly. (Abdel et al. 2015, Patsiogiannis et al. 2021)

Most of the femoral PPFs are Vancouver type Bs (86% to 87% of all femoral PPFs) (Lindahl et al. 2005, Toci et al. 2023). Identifying whether the stem is stable or loose and determining the remaining bone quality may be challenging. Most B1 fractures are treated with open reduction and internal fixation (ORIF) with the use of cables and plates, compression plates, cortical struts, locking plates, or a combination of the above. The use of bridging locking plates has gained popularity especially in patients with osteopenia or osteoporotic bone. (Abdel et al. 2015, Leino et al. 2015, Patsiogiannis et al. 2021)

In Vancouver type B2 fractures the stem is unstable but the bone quality is adequate. Stem revision is required with the aim of restoring stem stability and allowing the fracture to heal. Extensively porous-coated or modular fluted tapered stems can be utilized. Long revision stems can be used alone or in combination with plates or structural bone grafts. The use of a cemented stem is also an option for treating B2 fractures. (Abdel et al. 2015, Patsiogiannis et al. 2021)

The difference between Vancouver B3 and B2 fractures is that in the B3 fracture the bone quality is inadequate. Therefore, the treatment of B3 fractures is in practice similar to that for B2 fractures described above. Proximal femoral replacement or even proximal femoral allografts are used. In both B2 and B3 fractures, adequate stem stability needs to be achieved distally in the diaphysis. (Abdel et al. 2015, Patsiogiannis et al. 2021)

The standard treatment of a Vancouver C fracture is ORIF using bridge plating. Retrograde nailing is sometimes possible. (Patsiogiannis et al. 2021)

A standard rehabilitation protocol may be possible in cases of stable intraoperative acetabular fractures detected intra-operatively. Multiple screw fixation is still suggested. If the implant is unstable or the fracture displacement is over 2 cm, the treatment should be ORIF of the fracture, and acetabular ring fixation with screws should be considered. (Pascarella et al. 2018, Patsiogiannis et al. 2021)

The treatment of stable postoperative acetabular fractures may be either conservative or ORIF of the fracture. In the cases where the prosthesis has been unstable since the traumatic event, the treatment is implant revision, acetabular ring fixation, or ORIF of the fracture. Bone loss restoration with bone grafting is performed when needed. (Pascarella et al. 2018, Patsiogiannis et al. 2021)

2.5 Mortality following THA

Death is a rare complication following THA. Over the past few decades, indications for receiving THA have been expanded to include more fragile older patients with multiple comorbidities. (Aynardi et al. 2013) The risk of death is higher after revision THA compared to primary THA and general population (Gundtoft et al. 2017c, Yao et al. 2018).

Hunt et al. (2013) conducted a large registry study based on the National Registry for England and Wales with 409,096 primary THAs from 2003 to 2011 and found a decreasing incidence of death from 0.6% in 2003 to 0.3% in 2011 within 90 postoperative days (Hunt et al. 2013). Previously, the incidence of 30-day postoperative mortality was reported to vary from 0.2% to 0.7% (Jämsen et al. 2013, Belmont et al. 2014, Berstock et al. 2014). The 90-day mortality varies from 0.3% to 0.7% (Aynardi et al. 2013, Jämsen et al. 2013, Berstock et al. 2014). Badarudeen et al. (2017) analyzed Medicare data from 1998 to 2011 and found 1.4% and 2.1% incidences of death within the first 3 postoperative months and the first postoperative year after revision THA, respectively (Badarudeen et al. 2017). Aynardi et al. analyzed both primary and revision THAs with uncemented fixation from 2000 to 2006 and reported 0.4% and 1.2% 90-day mortality for primary and revision THAs, respectively (Aynardi et al. 2009).

Advanced age is a well-known risk factor for death following both primary and revision THAs (Fehring et al. 2010, Berstock et al. 2014, Mysore et al. 2023). A prior study of 6,502 primary and 2,138 revision THAs by Johnson et al. (2019) analyzed complications following THAs among frail patients, who were more commonly females, older (70 vs. 66 years old, frail and non-frail, respectively), and had an ASA classification of 3 or more. They reported an almost six-fold risk of death for frail compared to non-frail patients at 90 days and the first year after THA. The risk of mortality was increased at 90 days and 1 year after both primary (HRs of 4.6 and 5.2, respectively) and revision (HRs of 9.7 and 6.2, respectively) THAs among frail patients. (Johnson et al. 2019) Over 17,000 primary unilateral THAs were analyzed to identify risk factors for 30-day postoperative mortality. In that study, advanced age (70–79 and ≥80 years), ASA classification ≥3, male sex, renal failure, and cardiac disease increased mortality after THA (ORs of 7.9, 19.8, 2.9, 1.9, 5.8, and 3.8, respectively). (Belmont et al. 2014) Similar findings concerning male sex, older age, and comorbidities were reported by Berstock et al. (2014) in their meta-analysis (Berstock et al. 2014). Prior registry-based studies are in line with these findings (Lie et al. 2002, Memtsoudis et al. 2012, Singh and Lewallen 2012).

The risk of death depends on the indication for revision operation after primary THA. Khan et al. (2020) reported an increased overall mortality for first revision THA due to PPF of the femur compared to other reasons for revision (infection, dislocation, and aseptic loosening) based on data from the UK NJR on 675,078 primary and 74,223 revision THAs. Furthermore, in that study the incidences of mortality following revision THA due to PPF in the highest risk group (males, ≥75 years, ASA ≥3) were 9% at 90 days, 21% at 1 year, and 60% at 5 years after revision surgery, contrary to reported incidences in the lowest risk group (females, <75 years, ASA classification ≤2) which were 0.6%, 1.4%, and 5.5%, respectively. (Khan et al. 2020) A slightly lower incidence (13.8%) of mortality at 1 year after revision surgery due to PPF was reported by Gibbs et al., who reviewed 203 patients with PPF from 2011 to 2018 (Gibbs et al. 2020). Lindahl et al. (2007) estimated the risk of death after PPF among patients whose primary diagnosis for THA was OA, based on SHAR data, from 1979 to 2000. They found a significantly higher risk of mortality at 14 days and 2 years after surgery due to PPF compared to THAs with no fractures. (Lindahl et al. 2007) Previous studies have also found that patients who have had revision THA due to PJI have higher mortality (Zmistowski et al. 2013, Gundtoft et al. 2017b). It has been reported that PJI increases the risk of mortality five-fold compared to revision operations done for aseptic reasons (Zmistowski et al. 2013). Yao et al. (2018) reported that the risk of mortality after revision THA due to PJI increased within the first postoperative year but persisted for several years after that (Yao et al. 2018).

2.6 Risk prediction models in total joint arthroplasty (TJA)

It is important that both patients and doctors understand the risks and benefits associated with surgery (Bilimoria et al. 2013). A process that provides appropriate and sufficient information on the procedure for the patient is part of so called shared decision-making (Clark et al. 2004). In shared decision-making, the potential risks of surgery are essential for the patient to understand thoroughly before giving informed consent. Previously, the assessment of postoperative risks was traditionally based on the experience of the individual surgeon and on published results in the literature. Risk factors for complications following total joint arthroplasty (TJA) have been studied widely. However, the reasons for complications are usually multifactorial. Therefore, an individual’s risk of complications cannot be estimated directly using only reported risk factors, which are largely based on average rates of risk for a diverse population of patients from the literature. (Bilimoria et al. 2013, Bozic et al. 2013, Kunutsor et al. 2017) Thus, these estimations of risk factors may not have been at the level of an individual patient and were also prone to subjective bias. Nowadays, preoperative risk prediction models have been developed to simplify the identification of patients at higher risk of complications. (Bilimoria et al. 2013, Kunze et al. 2018, 2023, Garland et al. 2021, Pakarinen et al. 2022)

Risk calculators can predict the likelihood of complications and mortality after THA based on the relative weight of patient demographic characteristics, comorbidities, and treatment methods. Therefore, the premise of these risk calculators is to preoperatively assist the surgeon's clinical decision-making, but universal generalization of these calculators has been lacking. (Klemt et al. 2021, Shah et al. 2021) Traditionally, the development of risk calculators has relied on the use of multivariable regression techniques (Shah et al. 2021). By using the multivariable regression technique with an adequate variable selection method it is possible to determine which of the variables from the data are important predictors of studied outcome. Furthermore, based on the fitted model coefficients, the multivariable regression technique can make estimations of probabilities for studied outcomes.

In medicine, risk calculators are usually used to inform patients about their prognosis of developing illness or complications after the operation. Further, with the reported data from risk calculators, doctors can minimize the risks of complications after surgery by optimizing the treatment options for each individual. (Moons et al. 2009) Risk prediction scores were first used in cardiology. In 1976, the Framingham study introduced the Framingham cardiovascular risk score to identify patients at high risk of cardiovascular disease who need preventive treatment. (Kannel et al. 1976) Some modifications were later made to the risk score, and it is still widely used globally in primary care (Moons et al. 2009, Cook et al. 2012). Further, risk prediction models predicting the risk of peri-operative mortality in non-cardiac surgery have achieved the recommendation for the use from the European Society for Cardiology, the American College of Cardiologists, the American Heart Association and the Canadian Society of Anesthesiologists (Kristensen et al. 2014, Duceppe et al. 2017, De Hert et al. 2018, Halvorsen et al. 2022). Over the last decade, risk calculators have also emerged in the area of orthopedics to estimate the risk of specific complications following TJA (Geubbels et al. 2006, Paxton et al. 2015, Kunutsor et al. 2017).

2.6.1 Overview of the developed risk calculators in TJA

Several risk calculators have been developed for various complications following THA such as PJI and death (Paxton et al. 2015, Kunutsor et al. 2017, Tan et al. 2018, Harris et al. 2019).

Tan et al. (2018) developed a preoperative risk calculator for PJI based on retrospective data from 31,167 total hip and 12,086 knee arthroplasties from a single institution from 2000 to 2014. There were 1,035 reported PJIs, and 42 risk factors including patient and surgical variables were analyzed. The logistic regression model, with variables selected based on statistical significance, was used to estimate the predicted risk of PJI. For external validation 29,252 patients were included in the developed models. They reached strong validity in both internal and external validated groups for any PJIs (areas under the receiver operating characteristic curve [AUROCs] of 0.83 and 0.84, respectively). The rate of PJI per person was 3.7% and 3.5% for the internal validation and external validation groups, respectively. (Tan et al. 2018)

The American Joint Replacement Registry (AJRR) Risk Calculator is an online risk calculator based on logistic regression that estimates the risk of mortality at 90 days and PJI at 2 years postoperatively (Harris et al. 2018a). The development of this risk calculator was based on Medicare patient data consisting of 65,499 primary THAs and 137,546 primary total knee arthroplasties (TKAs) with a total of 30 patient demographics and clinical variables. However, the AJRR risk calculator has not been internally or externally validated. (Harris et al. 2018b)

In 2014, the American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) developed an online risk calculator predicting the risk of various complications following surgical treatments based on regression models. This calculator is publicly available and was based on data covering over 1.4 million patients and different surgical subspecialties. Twelve percent of all the cases were referred as orthopedic, including THAs and TKAs. For 21 preoperative factors including demographics, comorbidities, and procedures, the ACS risk calculator provides risk estimations for 11 various complications within 30 postoperative days. The ACS risk calculator is updated regularly every 2 years with new data from ACS NSQIP hospitals. (Bilimoria et al. 2013, Manning et al. 2016) Edelstein et al. (2015) used Medicare patient data on over 1000 patients treated with THAs and TKAs to estimate the performance of the developed ACS risk calculator. They reported only poor predictability of the estimated probabilities for all the studied outcomes (AUROC=0.59 for any complication) (Edelstein et al. 2015).

Bozic et al. used a logistic regression model to create an electronic risk calculator for predicting patient-specific probabilities for 2-year risk of PJI and 90-day risk of mortality following primary THA. They used the Medicare 5% sample claims database covering 53,252 patients treated with primary THA between 1998 and 2009. They included 29 comorbidity variables and patient demographics in the logistic regression model. The overall rate of PJI at 2 postoperative years was 2.1% and 1.3% for mortality at 90 postoperative days. However, the developed risk calculator was neither internally nor externally validated. (Bozic et al. 2013)

The developed risk calculators are not yet globally accepted due to a lack of external validation (Tan et al. 2018). Therefore, it is unknown how they would perform outside the training cohort, such as in large integrated healthcare systems (Paxton et al. 2015). Furthermore, many of these risk calculators do not have information on surgery-related factors such as implants used and their characteristics

(Paxton et al. 2015, Harris et al. 2018a, Tan et al. 2018). Also, a lack of uniform diagnostic criteria for specific complications may create challenges to the globally accepted use of these prior risk calculators, especially the diagnosis of PJI (Kunutsor et al. 2017).

2.6.2 Data pre-processing

Several points require special attention when developing risk prediction models. Pre-processing is the phase where raw data is transformed so that it can be used in statistical analyses. It involves multiple series of steps and rules that must be taken into account, such as visualizing the distribution of variables and outliers. (Dreiseitl and Ohno-Machado 2002, Malley et al. 2016) Some of the risk prediction models require data with no missing values, but arthroplasty registers are usually missing some data. This can generally be managed by excluding those patients from the prediction models, but doing so may cause confounding bias to the estimated potential predictors and produce incorrect probabilities of studied outcome. To avoid excluding these patients, it is possible to exclude only the variables with missing data, but again this risks excluding variables associated with the outcome of interest. Hence, such exclusions should be done with caution. (Moons et al. 2012, Manning et al. 2016) Another method for analyzing datasets with missing values is multiple imputation. With this approach it is possible to replace the missing value with a new value, which is usually the result of various estimates of the distribution of the variable. (Donders et al. 2006) However, more quality studies are needed if the use of imputation is augmented to the development of risk prediction methods.

When data for external model validation is not available, it is often randomly split into two groups, training and test cohorts, for the model training and internal validation. The most commonly used and also recommended split ratio is 2:1. It assigns two thirds of the data to the training cohort and one third to a separate test cohort. (Dobbin and Simon 2011, Wu et al. 2019)

2.6.3 Variable and model selection

Variable selection for the analyses was conventionally performed using either backward elimination or forward selection. Because forward selection may cause selection bias and overfitting of risks, a preferable method for variable selection is backward elimination. After the selection, multivariable regression methods are used to develop a risk prediction model for estimating the coefficient (relative weight) of each selected variable for the predicted outcome. (Moons et al. 2012, Manning et al. 2016)

Standard logistic and Cox regressions can be classified as conventional risk prediction methods that are easy to use and intuitive. However, it has been said that the low number of events in relation to the number of included variables can easily result in overfitting of the model in both these approaches. In such cases a preferable method is shrinking, also known as penalization, to produce more accurate predictions. When developing risk prediction models, assessment of the included variables in relation to the number of studied events should be done. (Ambler et al. 2012, Pavlou et al. 2015, Van Calster et al. 2020)

The most commonly used penalized regression methods are the Ridge and the least absolute shrinkage and selection operator (Lasso) regressions (Pavlou et al. 2015). Penalized regression is an effective method to penalize a model for having too many variables compared to the number of events. The penalization procedure reduces the regression coefficients of some of the variables towards zero, meaning that those variables have zero influence on the model predictions and can hence be excluded from the final prediction model. The key difference between Lasso and Ridge regressions is the penalty term. With Lasso the variable selection is more effective due to L1 regularization that penalizes more variables towards zero, whereas with Ridge there might be some minor variables with a coefficient close to zero and not excluded from the model. (Ambler et al. 2012, Van Calster et al. 2020) As penalization techniques rely on the optimization of hyperparameters via cross-validation and random subsampling, the results may vary between different modeling runs. Hence, methods for stabilizing the end result, for example by applying a stable iterative variable selection (SIVS) procedure, have been introduced. (Mahmoudian et al. 2021) By applying this stabilizing method in model development, the prediction performance is maximized with only minor changes to it, even though the number of variables is effectively reduced (Venäläinen et al. 2020).

In addition to conventional and penalized regression approaches, various machine learning (ML) techniques have shown great promise in a range of prediction tasks. The benefit of ML techniques is that they can automatically detect complex, nonlinear relationships and inter-variable interactions. However, at the same time, they are prone to overfitting and require a great amount of training data to achieve good generalizability. Examples of ML methods include gradient boosting machine (GBM), random forest (RF), and neural networks. (Breiman 2001, Dreiseitl and Ohno-Machado 2002, Weng et al. 2017, Zhang et al. 2019) These, however, have not yet been extensively tested in the predictions of adverse outcomes following THAs.

2.6.4 Performance evaluation

Prior to clinical use, both internal and external validation should be performed for all risk prediction models. Internal validation means that the performances of the developed risk prediction model are tested with the dataset used for developing the models. This may lead to overly optimistic results. For this reason, external validation is performed using data on a new study population with similar characteristics that have not been used for the development of models. External validation is the most accurate method for evaluating the generalizability of the developed models for a diverse population. (Moons et al. 2012, Manning et al. 2016)

At the development stage of a risk prediction model, its generalization capabilities should be estimated, for example, with cross-validation or bootstrapping. Both methods estimate the generalizability of the model to new data that has not yet been used for the development of a risk prediction model. (Bernau et al. 2014, Pavlou et al. 2015)

When assessing the performances of a risk prediction model, both its calibration and discrimination performances should be evaluated (Altman et al. 2009). Optimally, initially good performance in the training dataset, supported by internal validation methods, should be reproducible in an external validation dataset for the model to be fully internally and externally validated. (Royston et al. 2009)

Calibration of predicted risk is the extent to which the observed incidence of an outcome of interest in the study population corresponds to the model's predictions. Plotting can be used to estimate the calibration between observed and predicted outcomes. An ideal line on the plot is the line of identity (45 degrees), which indicates perfect calibration. (Moons et al. 2012, Shah et al. 2021)

Discrimination describes the ability of developed model to distinguish patients into two groups, either with or without the studied outcome. It determines the reliability of the results from the risk prediction model concerning which patients will develop postoperative complications and which will not. (Steyerberg et al. 2010, Pavlou et al. 2015, Manning et al. 2016, Shah et al. 2021) A Receiver Operating Characteristic (ROC) curve plots the sensitivity (true positive rate) and specificity (false positive rate, 1-specificity) for the probability of an outcome of interest with all possible thresholds (Heagerty and Zheng 2005, Steyerberg et al. 2010). The discrimination can be evaluated in terms of the C-index, that is, the area under the ROC curve (AUROC). Discrimination performance in terms of the AUROC can be classified as random (0.5), strong (0.8), and perfect (1.0) predictions. (Manning et al. 2016)

During the internal validation phase of model development, there is a risk of overfitting if the risk prediction model is too specifically developed to predict the outcome of interest among its data, leading to reduced generalizability of the risk prediction model to external validation data. (Grant et al. 2018) Poor calibration may also cause overfitting despite good discrimination performances. This means that the predictions can be inaccurate, leading to over- or undertreatments. (Van Calster et al. 2019)

3 Aims

The aims of this thesis were to assess risk factors for dislocation and PJI revisions following primary THA based on FAR data, and to develop patient-specific risk calculators for clinical practice based on FAR and NARA data. Specifically:

1. To determine risk factors for revision for dislocation after primary THA based on FAR data.

2. To determine risk factors for PJI revision during the first year after primary THA based on FAR data.

3. To develop simple-to-use risk prediction models to assess the risk of the most common adverse outcomes after primary THA based on FAR data.

4. To develop risk prediction models for early revisions and death and to evaluate the predictive potential of various risk prediction models for complications following primary THA using the NARA dataset.

4 Materials and Methods

4.1 Patients

4.1.1 Studies I, II and III

Studies I, II, and III are based on data extracted from the FAR. The FAR was established in 1980 and since then has been collecting information on THA surgeries. The Finnish Institute for Health and Welfare is currently responsible for managing the FAR. All orthopedic units are obliged to deliver data to the FAR, and the Population Register Center also delivers information on dates of death. All Finnish citizens have a unique identification number that connects the person with the primary and possible revision THA performed on them. In 2021, data completeness in the FAR was >95% for primary THA and 84% for revision THA (FAR 2021). In 2014, the data contents of the FAR were thoroughly revised to include several new variables such as surgical approach, BMI, ASA classification, intraoperative bleeding, and duration of surgery.

The patient demographics and surgical characteristics were the same in Studies I, II, and III. Data on 33,337 primary THAs were extracted from all patient and surgical FAR data on primary and revision THAs performed in Finland between May 2014 and January 2018. Only the studied primary outcome differed between the studies. Most of the patients were aged 66 to 75 years and were women. Most of the treated patients had ASA class II or combined III and IV and underwent THA with uncemented fixation, bearing couples of metal on UHXLPE or ceramic on UHXLPE, and femoral head size 36 mm. The main reason for primary elective THA was OA and the most commonly used approach to the hip joint was posterior. Most of these patients had a BMI of 26–30 kg/m^2 and the operation was done under spinal anesthesia and lasted 60 to 89 minutes (Table 2).

Table 2. Patient and procedure characteristics of Studies I, II, and III.

Characteristics		No. of total	No. of available	%
No. of hips		33,337		
Age (years)		33,330		
	≤55		4,507	13.5
	56–65		8,333	25.0
	66–75		12,399	37.2
	≥76		8,091	24.3
Sex		33,319		
	Male		14,317	43.0
	Female		19,002	57.0
Operated side		33,337		
	Right		18,500	55.5
	Left		14,837	44.5
Simultaneous bilateral operation		33,337		
	No		32,425	97.3
	Yes		912	2.7
ASA physical status classification		32,697		
	ASA I		4,013	12.3
	ASA II		16,117	49.3
	ASA III–IV		12,567	38.4
Body mass index (kg/m^2)		30,382		
	≤20		716	2.3
	21–25		7,715	25.4
	26–30		12,450	41.0
	31–35		6,832	22.5
	>35		2,669	8.8
Preoperative diagnosis		32,315		
	Primary osteoarthritis		27,965	86.6
	Fracture		1,366	4.2
	Inflammatory arthritis		591	1.8
	Other		2,393	7.4
Hospital volume (per year)		33,333		
	Low (<240)		13,042	39.1
	Medium (240–480)		10,279	30.9
	High (>480)		10,012	30.0
Level of education of surgeon		29,853		
	Orthopedic specialist		28,438	95.3
	Resident		1,415	4.7
Level of education of assistant		29,003		
	Orthopedic specialist		2,877	9.9
	Resident		8,162	28.2
	Other		16,775	57.8
	None		1,189	4.1
Surgical approach		32,652		
	Anterolateral (modified Hardinge)		6,151	18.8
	Posterior		26,203	80.3
	Anterior (Smith-Peterson)		298	0.9

Characteristics	No. of total	No. of available	%
Intraoperative bleeding	31,381		
<500 ml		21,839	69.6
≥500 ml		9,542	30.4
Duration (min)	27,645		
<45		1,987	7.2
45–59		5,045	18.3
60–89		13,498	48.8
90–120		5,404	19.5
>120		1,711	6.2
Spinal anesthesia	32,604		
No		2,485	7.6
Yes		30,119	92.4
Epidural anesthesia	32,604		
No		31,813	97.6
Yes		791	2.4
General anesthesia	32,604		
No		30,072	92.2
Yes		2,532	7.8
Use of nerve blocks	32,604		
No		32,598	100.0
Yes		6	0.0
Use of LIA	32,604		
No		26,367	80.9
Yes		6,237	19.1
Fractures during surgery	31,395		
No		30,993	98.7
Yes		402	1.3
Previous operations on the same joint	28,071		
No		27,466	97.8
Yes		605	2.2
Antibiotic prophylaxis	32,898		
Cefuroxime		31,115	94.6
Clindamycin		1,043	3.2
Vancomycin		81	0.2
Other antibiotic prophylaxis		585	1.8
Not used		74	0.2
Antithrombotic prophylaxis	32,633		
Enoxaparin		23,874	73.2
Rivaroxaban		5,808	17.8
Tinzaparin		1,308	4.0
Warfarin		103	0.3
Other		1,230	3.8
Not used		310	0.9
Antifibrinolytic medications	31,873		
Tranexamic acid		28,703	90.0
None		2,856	9.0
Other		314	1.0

Characteristics		No. of total	No. of available	%
Mechanic postoperative antithrombotic prophylaxis		2,7137		
	Not used		15,873	58.5
	Calf muscle pump		61	0.2
	Surgical stocking		11,203	41.3
Antimicrobial incise drape		8,818		
	No		426	4.8
	Yes		8,392	95.2
Fixation		30,150		
	Uncemented		18,655	61.9
	Cemented		3,008	10.0
	Hybrid		6,837	22.7
	Reverse hybrid		1,650	5.4
Bearing couple		25,107		
	Metal on UHXLPE		12,652	50.4
	Ceramic on ceramic		2,786	11.1
	Ceramic on UHXLPE		7,063	28.1
	Ceramized metal on UHXLPE		1,445	5.8
	Other		1,161	4.6
Oblique liner		30,228		
	No		23,658	78.3
	Yes		6,570	21.7
Femoral head size (mm)		32,452		
	28		347	1.1
	32		7,836	24.1
	36		23,958	73.8
	>36		311	1.0

ASA = American Society of Anesthesiologists, LIA = Local infiltrative anesthesia, UHXLPE = ultra-highly crosslinked polyethylene.

Hospital volume is based on the average number of primary THAs performed annually during the study period.

4.1.2 Study IV

Study IV is based on the NARA dataset. This arthroplasty register collaboration was established in 2007 by the arthroplasty registers from Sweden, Norway, and Denmark to improve the quality and results of research after joint replacements. Finland joined the NARA collaboration in 2010. (Havelin et al. 2009, Mäkelä et al. 2014b) In Study IV, the initial dataset consisted of 841,855 primary THAs reported to the NARA between 1995 and 2018. Due to time-dependent changes in clinical practice regarding implant materials, fixation methods, and femoral head size, we restricted our analyses to primary THAs performed since 2010, leaving 251,438 primary THAs without any missing data. (Figure 11)

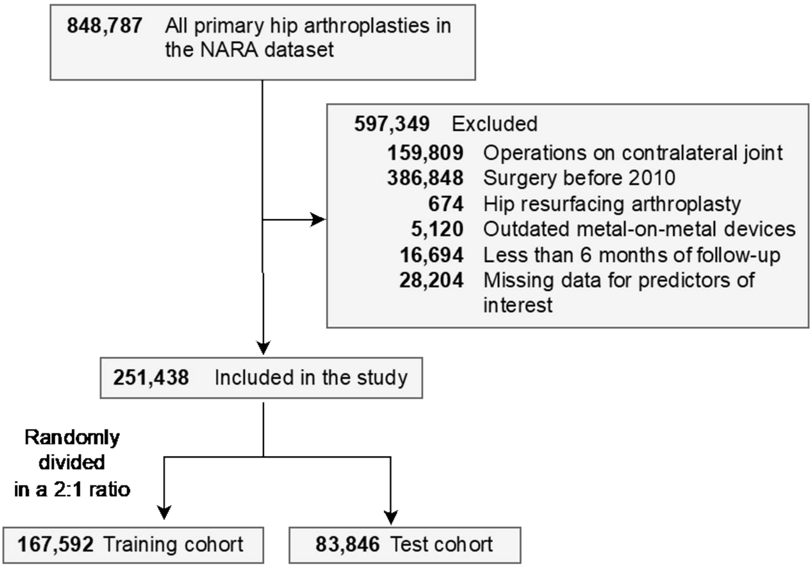


Figure 11. Selection of patients into the Study IV.

Patients were on average 67.8 years old and most of them were women whose right hip had been operated on. The main diagnosis for primary THA was OA. Most of the patients received unilateral THA with uncemented fixation with a metal-on-crosslinked-polyethylene bearing surface and 32 mm femoral head size and no hydroxyapatite coating on the cup or stem. The most commonly used approach to the hip joint was posterior (Table 3).

Table 3. Patient and procedure characteristics of Study IV.

Characteristics	No. of available	%
Country, N (%)		
Denmark	48,453	19.3
Norway	45,563	18.1
Sweden	109,559	43.6
Finland	47,863	19.0
Age [years], mean (SD)	67.8	11.0
Sex, N (%)		
Female	146,000	58.1
Male	105,438	41.9
Laterality, N (%)		
Right	142,621	56.7
Left	108,817	43.3
Simultaneous bilateral operation, N (%)		
No	249,292	99.1
Yes	2,146	0.9

Characteristics	No. of available	%
Preoperative diagnosis, N (%)		
Primary osteoarthritis	200,686	79.8
Hip fracture	25,640	10.2
Nontraumatic femoral head necrosis	5,818	2.3
Rheumatoid arthritis	2,559	1.0
Ankylosing spondylitis	252	0.1
Developmental dysplasia of the hip	7,653	3.0
Slipped capital femoral epiphysis	282	0.1
Perthes disease	918	0.4
Combination of slipped capital femoral epiphysis and Perthes	112	<0.1
Other inflammatory	696	0.3
Others	6,822	2.7
Fixation, N (%)		
Cemented	95,641	38.0
Hybrid	15,208	6.0
Inverse hybrid	30,187	12.0
Uncemented	110,402	44.0
Surgical approach, N (%)		
Anterior, anterolateral and others	116,068	46.2
Posterior	135,370	53.8
Bearing couple, N (%)		
CoC	13,387	5.3
CoX	40,021	15.9
CoP	5,618	2.2
MoP	35,718	14.2
MoX	154,826	61.6
Other	1,868	0.7
Hydroxyapatite coating (cup), N (%)		
No	215,017	85.5
Yes	36,421	14.5
Hydroxyapatite coating (stem), N (%)		
No	150,745	60.0
Yes	100,693	40.0
Femoral head size [mm], N (%)		
22	1,535	0.6
28	43,902	17.5
32	126,101	50.2
36	77,039	30.6
>36	2,772	1.1
Other	89	<0.1
Trochanteric osteotomy, N (%)		
No	250,947	99.8
Yes	491	0.2

SD = standard deviation, MoX = metal on polyethylene crosslink, MoP = metal on conventional (non-crosslinked) polyethylene, CoX = ceramic on crosslinked polyethylene, CoC = ceramic on ceramic, CoP = ceramic on conventional (non-crosslinked) polyethylene.

4.2 Covariates, candidate predictors, and study outcomes

4.2.1 Study I

The following risk factors were considered as covariates, with the used groupings or units given in parentheses: age group (≤55, 56–65, 66–75, ≥76 years), sex, diagnosis (primary OA, fracture, other), hospital volume (low, medium, high), surgical approach (posterior, anterolateral, anterior), head size (28, 32, 36, >36 mm), BMI (<25, 25–30, >30 kg/m^2), ASA class (I, II, III–IV), fixation method (uncemented, cemented, hybrid, reverse hybrid), previous operation on the same joint, like osteotomy or osteosynthesis (yes, no), level of education of the surgeon (specialist, resident), level of education of the first assistant (specialist, resident, other), bleeding (<500ml, ≥500ml), duration of the operation (minutes), anesthesia form (spinal, epidural, general), local infiltrative anesthesia (LIA) (yes, no), perioperative fracture during surgery (no complication, calcar fracture, trochanteric fracture, femoral shaft fracture, acetabular fracture), bearing surface used (CoC, ceramic on UHXLPE, metal on UHXLPE, ceramized metal on UHXLPE, other), and use of an oblique liner (yes, no). Classification of hospitals into volume groups was based on the average number of primary THAs performed annually during the study period: less than 240 (low), 240–480 (medium) and more than 480 (high).

In Study I, primary uni- and bilateral THAs reported to the FAR were included. Follow-up ended in January 2018. The survival endpoint was defined as the first revision where any component, including isolated liner exchange, was removed or exchanged due to dislocation, and these were linked to the primary operation through a patient-specific personal identification number and laterality. During follow-up there were 264 first-time revisions due to dislocation.

4.2.2 Study II

Based on the previously reported associations with PJI and prior clinical knowledge, altogether 25 risk factors were considered as covariates. Most of these are the same as in Study I, but additional covariates were antibiotic prophylaxis (cefuroxime, clindamycin, vancomycin, other, not used), antithrombotic prophylaxis (enoxaparin, rivaroxaban, tinzaparin, warfarin, other, not used), antifibrinolytic medications (tranexamic acid, none, other), mechanical postoperative antithrombotic prophylaxis (calf muscle pump, surgical stocking, not used) and antimicrobial incise drape (yes, no) (Table 2).

In Study II, the time point at which at least one component was removed, exchanged, or inserted due to PJI was classified as the survival endpoint of the follow-up. There were 350 revision operations due to PJI reported to the FAR. Diagnosis of PJI as an indication for revision operation was based on preoperative evaluation and the clinical presentation evaluated by the operating surgeon. Ideally, diagnosis of PJI should be based on the recommended guidelines (Parvizi et al. 2016). The FAR does not currently collect data, for example, on intraoperative bacterial cultures. Follow-up ended in January 2018. Most of the THAs (334 of 350) were revised due to PJI during the first postoperative year.

4.2.3 Study III

All the variables included in this study are the same as in Studies I and II (Table 2). Both patient demographics and surgical variables were used as candidate predictors of the primary outcome.

For each operation, the first reported adverse outcome leading to revision surgery during which at least one component was removed, exchanged, or inserted for any reason, or after which the patient died within the first 6 months, was regarded as the primary outcome of this study. We chose to use the time frame of 6 months for all outcomes to simplify the analyses, even though shorter (e.g. 90 days) (Bülow et al. 2022) or longer time frames (e.g. 1 year) (Peters et al. 2020) could have been used. In total, 25,919 primary THAs fulfilled all the criteria above and were included in the analyses.

For model training and validation, data on 25,919 primary THAs were randomly divided into a separate training cohort (N=17,279; two thirds of the data) and an independent test cohort (N=8,640; one third of the data) based on the commonly used split ratio of 2:1 (Li et al. 2014, Bisaso et al. 2017, Wu et al. 2019). In each of these cohorts the patients were unique. No crossover of data was allowed at any stage of the model development and validation.

4.2.4 Study IV

The patient characteristics and surgical parameters available in all four countries were used as candidate predictors for each outcome. The patient characteristics included age, sex, laterality, simultaneous bilateral operation, and primary diagnosis, whereas the surgical characteristics included fixation type, use of trochanteric osteotomy, surgical approach (posterior or non-posterior including anterior, anterolateral and others), bearing couple (determined based on the combination of cup and caput materials), femoral head size, and hydroxyapatite (HA) coating of cup and stem (Table 3).

Inclusion criteria were the same as in Study III concerning follow-up time, outcomes, and bilateral surgery. Otherwise, the inclusion criteria of this study are reported more precisely in Figure 11. We also excluded from the study some of the prostheses such as those with MoM bearing surfaces to avoid outdated prostheses. Finally, only patients without any missing data were included in the analyses, as some of the risk prediction models require complete data, which left us with 251,438 primary THAs (Table 2). For model training and internal validation, the data (251,438 primary THAs) were divided into separate training (N=167,592, random sample of 67% of the population) and test (N=83,846, random sample of 33% of the population) cohorts based on the same split ratio as used in Study III.

4.3 Statistical analyses and mathematical modeling

4.3.1 Studies I and II

In Studies I and II, cumulative survival in terms of first-time revisions due to dislocation or PJI with 95% confidence intervals (CIs) was first estimated with Kaplan-Meier (KM) analysis. Next, univariable and multivariable Cox proportional hazards regression models were used for identification of possible risk factors and estimation of HRs with 95% CIs. The operations without the primary survival endpoint were censored at the time of revision for other reasons, death, or time of data extraction, whichever occurred first. Visual inspection of KM curves and a statistical test based on the scaled Schoenfeld residuals were used to assess the proportional hazards assumption of the Cox model (Grambsch and Therneau 1994, Ranstam et al. 2011). All statistical analyses were carried out using R versions 3.4.1 and 3.4.2 (R Development Core Team, http://www.r-project.org). Survival analyses were performed using R package survival (Therneau T. 2015). The level of significance was set at $P<0.05$.

In Study I, only operations without missing data were used (N=21,706) in the final multivariable model. All statistically significant ($P<0.05$) variables from the univariable analysis were included in the multivariable model. This was done due to identification of independent risk factors that retain the statistically significance association with the studied primary outcome in the presence of other relevant risk factors. To verify findings regarding the effect of different surgical approaches on dislocation risk, we performed sensitivity analysis consisting only of patients considered to be healthy standard patients (primary OA, ASA class I–II, uncemented or hybrid THA, metal-on-UHXLPE or ceramic-on-UHXLPE bearing surface, and head size 36 mm), using univariable Cox proportional hazard regression analysis in that subpopulation. As use of the posterior approach and patients with a diagnosis of femoral neck fracture have a similar risk trend for revision due to dislocation, we assessed the occurrence of revision for dislocation and the used surgical approaches among patients with a diagnosis of femoral neck fracture. The proportional hazards assumption was not fulfilled by the sex of the patient. Therefore, it was used as a stratification variable. Next, only minor violation of proportional hazards according to the Schoenfeld residuals (P=0.04) was reported for comparison of ASA class I vs. ASA class II. To make our results easier to comprehend, we did not divide the follow-up time into different time periods.

In Study II, directed acyclic graph (DAG) analysis was used to organize variables according to their supposed relation to PJI revision and other variables based on the previous medical literature and clinical practice (Figure 12). Multivariable analysis was performed by choosing the adjusting variables based on the DAG for all the variables that had potential confounding bias in the univariable analysis. In the multivariable analysis, the following eight risk factors were adjusted with associated covariates identified on the DAG: ASA class (adjusted for age), intraoperative bleeding [adjusted for BMI, previous operation on the same joint, complications during surgery and level of education (surgeon)], duration of operation [adjusted for previous operation on the same joint, level of education (surgeon), intraoperative bleeding, BMI, and complications during surgery], anesthesia mode (adjusted for age and ASA class), bearing couple (adjusted for age and ASA class), fixation (adjusted for sex and age), simultaneous bilateral operation (adjusted for age and ASA class), and complications during surgery (adjusted for BMI). A long duration of surgery >120 min did not fulfill the proportional hazard assumption in the multivariable analysis. Furthermore, in the univariable analysis, LIA, simultaneous bilateral operation, and complication during surgery did not fulfil the assumption of proportional hazards. Therefore, the follow-up time of these variables was divided into suitable time intervals based on the KM analyses. We then performed uni- and multivariable analyses for these variables separately. There were 2,839 patients with both hips operated on, of which 456 were done simultaneously. As in Study I, bilateral THAs were treated as two independent observations due to reported negligible associations between bilaterality and PJI and dislocation risk (Ranstam and Robertsson 2010).

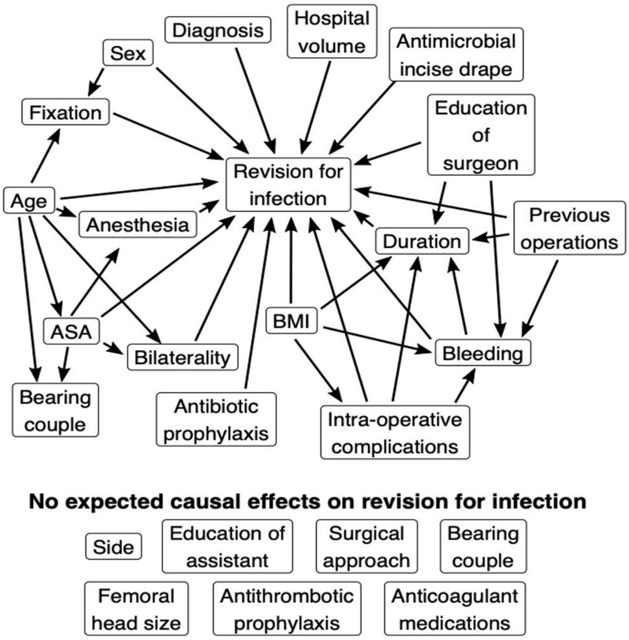


Figure 12. Directed acyclic graph (DAG) constructed under the following assumptions: **1)** THA 'revision for infection' is dependent on 'patient age', 'sex', 'bilaterality', 'ASA class', 'BMI', 'diagnosis', 'hospital volume', 'education of surgery', 'bleeding', 'duration', 'intra-operative complications', 'previous operations', 'antimicrobial incise drape', 'anesthesia', 'antibiotic prophylaxis', and type of THA 'fixation'. Choice of 'side', 'education of assistant', 'surgical approach', 'bearing couple', 'antithrombotic prophylaxis`, 'antifibrinolytic medications', and 'femoral head size' are not expected to affect 'revision for infection' according to clinical experience. **2)** 'Fixation' is dependent on 'age' and 'sex', because older and female patients have probably received a cemented or hybrid THA due to their poorer bone quality. 'Bearing couple' may be dependent on age, because surgeons have probably chosen a CoC bearing couple for younger patients. 'Bearing couple' may also be dependent on ASA class for the same reason. ASA class is partly dependent on age by definition. 'Bilaterality' is dependent on 'age' and 'ASA class', because both hips are seldom operated on in elderly or high-ASA-class patients. **3)** 'BMI' may be affected by 'duration' and `intra-operative complications` due to more difficult operation with high BMI. 'Duration' may be dependent on 'education of surgeon' due to the experience factor. 'Bleeding', 'duration', and `previous operations` may be dependent on clinical basis. **4)** 'Anesthesia' is dependent on 'ASA class' and 'age', because general anesthesia is usually avoided in the oldest patients.

4.3.2 Studies III and IV

In Studies III and IV, all statistical analyses and mathematical modeling were carried out using R statistical computing environment version 3.4.1 and 4.0.3, respectively (R Core Team, 2016. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/). In study III, R packages *glmnet* (Friedman et al. 2010), *survival* (Therneau 2015), *ggplot2* (Wickham 2016), and *pROC* (Robin et al. 2011) were used for penalized regression, survival analysis, visualization of results, and evaluation of AUROC values, respectively.

In Study III, ASA physical status classification was treated as a continuous variable due to improved model performance after it was first tested both as a categorical and continuous variable. In the case of bilateral THA, only the first reported THA was included in the analysis.

Further, in Study IV, the method-specific packages reported in Table 4 (Liaw and Wiener 2002, Friedman et al. 2010, Fritsch et al. 2019, Majka 2019, Therneau and Atkinson 2019, Greenwell and Boehmke 2020, Venäläinen et al. 2020, Mahmoudian et al. 2021), R packages *ggplot2* (Wickham 2016), and *pROC* (Robin et al. 2011) were used for visualization of the results and evaluation of AUROC values, respectively. Comparisons between the training and test cohorts were performed using the Mann-Whitney test for continuous variables and the chi-squared test for categorical variables. The level of significance was set at P<0.05.

Table 4. Applied machine learning algorithms and corresponding R packages used in Study IV.

Method	R package	Version
Logistic regression	stats	4.0.3
Penalized regression (Ridge)	glmnet	4.1-1
Penalized regression (Lasso)	glmnet	4.1-1
Lasso regression with stable iterative variable selection	sivs	0.2.5
Classification tree	rpart	4.1-15
Random forest	randomForest	4.6-14
Gradient boosting machines	gbm	2.1.8
Naïve Bayes	naivebayes	0.9.7
Neural network	neuralnet	1.44.2

4.3.3 Model development in Study III

We applied penalized logistic regression to the patient and surgery related factors in the training cohort to construct multivariable models for predicting the individualized risk of revision or death. The Lasso penalty was used for the variable selection. The five-fold cross-validation was used to maximize the prediction accuracy of the coefficient with the amount of penalty applied to it. Similarly to the SIVS protocol, the cross-validation was repeated 100 times to account for the effect of random subsampling during cross-validation resulting in model variability (Bovelstad et al. 2007, Roberts and Nowak 2014, Venäläinen et al. 2020). The evaluation and optimization of the discrimination performance of the risk assessment models was done in terms of AUROC.

The number of missing values among all the candidate predictors in the data was relatively small. We did not perform multiple imputation, even though the BMI had the highest number of missing variable data in primary THAs (10.8%). As the penalized regression requires complete input data, the final models were constructed and evaluated on the subset of patients with complete information on all candidate variables (N=13,585 for the training cohort) identified as important by the iterative variable selection procedure.

The obtained penalized regression models use the fitted regression coefficients and patient-specific data to produce estimations of risk scores for an individual. To achieve this, raw risk estimates should first be calculated as the sum of patient-specific risk factors weighted with the regression coefficients. Finally, the individualized risk scores in percentages can be obtained as the inverse logit of the sum of the model intercept (constant term) and the raw risk score as:

$$Risk = \frac{1}{1 + \exp\left(-(Intercept + Raw\ score)\right)} \times 100\%$$

In addition, to explore model calibration with a limited number of outcome events, patients were stratified into low-, intermediate-, and high-risk subgroups based on tertiles of the individualized risk score distributions in the training cohort. Finally, to estimate HRs and inspect the implant survival between subgroups, Cox proportional hazards regression and KM plots were used, respectively.

4.3.4 Model development in Study IV

For the training data we applied a range of ML algorithms [logistic regression, classification tree modeling, RF, GBM, penalized regression (with Ridge and Lasso penalty), Naïve Bayes, and neural networks] to identify which of these is the best for predicting the risk of revision and death. In addition, we applied Lasso regression in combination with the SIVS procedure (Venäläinen et al. 2020, Mahmoudian et al. 2021) and repeated model training and cross-validation to produce simple-to-use risk prediction models similarly to Study III. AUROC was used to estimate the discrimination performances of the ML models. Further, the DeLong test was used to compare those discrimination performances to each other (DeLong et al. 1988). Evaluation of the calibration for the predicted risks was done by grouping individuals by deciles of predicted risk.

5 Results

5.1 Risk factors for dislocation leading to revision surgery after primary THA

The overall KM survival for revision due to dislocation at 3.5 years was 98.9% (CI: 98.8–99.1).

5.1.1 Surgical approach associated to dislocation revision risk

Statistical analyses revealed that patients operated on with the posterior approach were associated with an increased risk of revision for dislocation compared to the anterolateral (modified Hardinge) approach in both univariable [HR 2.6 (95% CI 1.7–4.1, P<0.001)] and multivariable analyses [HR 3.1 (95% CI 1.7–5.5, P<0.001)]. Further, anterior approach was associated with an increased dislocation revision risk but only in the multivariable analysis [HR 3.6 (95% CI 1.0–13.1), P=0.05] (Table 5).

Table 5. Statistically significant predictors for revision for dislocation in the multivariable analysis. Only patients without any missing data for variables of interest (N=21,706) were included in the final multivariable model.

Variable		Hazard ratio (95% CI)	P value
ASA class			0.09
	ASA I	Reference	
	ASA II	1.7 (0.9–3.3)	0.09
	ASA III–IV	2.0 (1.0–3.9)	0.04
Surgical approach			<0.001
	Anterolateral (modified Hardinge)	Reference	
	Posterior	3.1 (1.7–5.5)	<0.001
	Anterior (Smith-Petersen)	3.6 (1.0–13.1)	0.05
Femoral head size			0.004
	28	0.5 (0.1–3.4)	0.4
	32	Reference	
	36	0.5 (0.4–0.7)	<0.001
	>36	0.4 (0.0–2.6)	0.3
Preoperative diagnosis			<0.001
	Osteoarthritis	Reference	
	Femoral neck fracture	3.0 (1.9–4.7)	<0.001
	Other	1.4 (0.9–2.2)	0.2

ASA = American Society of Anesthesiologists, UHXLPE = ultra-highly crosslinked polyethylene.
In addition, these variables were included in the multivariable analysis: age (≤55, 56–65, 66–75, ≥76 years), intraoperative bleeding (<500ml, ≥500ml), anesthesia form (spinal, epidural, general), local infiltrative anesthesia (yes, no), fixation method (uncemented, cemented, hybrid, reverse hybrid), bearing surface used (ceramic on ceramic, ceramic on UHXLPE, metal on UHXLPE, ceramized metal on UHXLPE, other), and hospital volume (per year) low, medium, and high.

5.1.2 Sensitivity analysis estimating the effect of different surgical approaches on dislocation revision risk among healthy standard patients

Sensitivity analysis was performed on the findings for different surgical approaches on so-called healthy standard patients (N=7,108) (primary OA, ASA class I–II, uncemented or hybrid THA, metal-on-UHXLPE or ceramic-on-UHXLPE bearing surface, and head size 36 mm). The analysis revealed that the posterior approach subpopulation was not associated with more dislocation revision than the anterolateral approach [HR 2.1 (95% CI 0.7–5.8, P=0.2)].

5.1.3 Subpopulation: Femoral neck fracture patients

The effect of surgical approach on dislocation revision risk among patients who had received THA due to femoral neck fracture was also estimated in a subpopulation analysis (N=1,366). This analysis revealed that there were dislocation revisions only among patients who had been operated on using the posterior approach. Therefore, we were not able to perform further statistical analyses on the subject (Table 6).

Table 6. Used surgical approaches and occurrence of revision due to dislocation among patients with femoral neck fracture diagnosis (N=1,366).

Characteristic	Total number of patients with preoperative femoral neck fracture	Number of revisions due to dislocation	Number of patients without subsequent dislocation
Number of hips	1,366	33	1,333
Surgical approach, N (%)	1,341	33	1,308
Anterolateral (modified Hardinge)	247 (18%)	0 (0%)	247 (19%)
Posterior	1,083 (81%)	33 (100%)	1,050 (80%)
Anterior (Smith-Petersen)	11 (1%)	0 (0%)	11 (1%)

5.1.4 Operative diagnosis and American Society of Anesthesiologists classification increase the risk of revision for dislocation

Patients who received THA for femoral neck fracture were associated with an increased risk of revision for dislocation compared to patients with operative diagnosis of primary OA in both univariable [HR 3.6 (95% CI 2.5–5.2, P<0.001)] and multivariable analyses [HR 3.0 (95% CI 1.9–4.7, P<0.001)]. Patients operated on for other reasons did not have an increased risk of dislocation revision in univariable [HR 1.5 (95% CI 1.0–2.1), P=0.05] or multivariable [HR 1.4 (95% CI 0.9–2.2), P=0.2] analyses.

There were more dislocation revisions in patients with advanced ASA classification in both univariable [ASA II vs. ASA I HR 1.8 (95% CI 1.0–3.0, P=0.03) and ASA III–IV vs. ASA I HR 2.7 (95% CI 1.6–4.5, P<0.001)] and multivariable analyses [ASA III–IV vs. ASA I HR 2.0 (95% CI 1.0–3.9, P=0.04)]. ASA class II was a risk factor only in the univariable analysis but diminished in the multivariable analysis [HR 1.7 (95% CI 0.9–3.3, P=0.09)] (Table 5).

5.1.5 Small femoral head size increase the risk of revision due to dislocation

Statistical analysis revealed that the use of a 36 mm femoral head size was associated with a decreased risk of revision for dislocation compared to a head size of 32 mm in both univariable [HR 0.6 (95% CI 0.5–0.8, P<0.001)] and multivariable analyses [HR 0.5 (95% CI 0.4–0.7, P<0.001)]. The use of other femoral head sizes of 28 mm and >36 mm was not associated with dislocation revision risk compared to a head size of 32 mm (Table 5).

5.1.6 Statistically significant findings observed only in univariable analysis

High hospital volume vs. low hospital volume, intraoperative bleeding of ≥500 ml vs. <500ml, use of epidural anesthesia, and cemented or hybrid fixation vs. uncemented fixation were associated with an increased risk of revision for dislocation in univariable analysis but not in multivariable analysis. Additionally, the use of LIA and CoC, ceramic-on-UHXLPE, or ceramized metal-on-UHXLPE vs. metal-on-UHXLPE were associated with a decreased risk of revision for dislocation, but this was only found in univariable, not multivariable, analysis.

5.2 Risk factors for revision surgery due to PJI after primary THA

The overall KM probability of no PJI revision at 3.7 years was 98.8% (95% CI: 98.7–98.9).

5.2.1 Increased risk of revision for PJI

Statistical analyses revealed an increased risk of revision for PJI with high BMI, advanced ASA classification, bleeding ≥500 ml during surgery, and the use of epidural or general anesthesias. A high BMI was associated with an increased risk of revision for PJI compared to normal weight patients in univariable analysis [BMI 31–35 vs. BMI 21–25 HR 2.3 (95% CI 1.7–3.3, P<0.001) and BMI >35 vs. BMI 21–25 HR 5.0 (95% CI 3.5–7.1, P<0.001)].

Patients who had ASA class II or combined III–IV were associated with an increased PJI revision risk compared to ASA class I in both univariable [ASA class II vs. ASA class I HR 1.7 (95% CI 1.1–2.7, P=0.02) and ASA class III–IV vs. ASA class I HR 2.5 (95% CI 1.6–3.9, P<0.001)] and multivariable analyses [ASA class II vs. ASA class I HR 2.0 (95% CI 1.3–3.2, P=0.003) and ASA class III–IV vs. ASA class I HR 3.2 (95% CI 2.0–5.1, P<0.001)].

Blood loss ≥500 ml during surgery compared to less bleeding was associated with an increased risk of revision for PJI in both univariable [HR 1.5(95% CI 1.2–1.9, P<0.001)] and multivariable analyses [HR 1.4 (95% CI 1.1–1.7, P=0.008)].

Patients who were operated under epidural or general anesthesias were associated with an increased risk of revision for PJI in both univariable [HR 2.2 (95% CI 1.4–3.5, P=0.001) and HR 1.7 (95% CI 1.2–2.3, P=0.002), respectively] and multivariable analyses [HR 2.1 (95% CI 1.3–3.4, P=0.002) and HR 1.6 (95% CI 1.2–2.3, P=0.003), respectively] (Table 7).

Further, increased risk of revision due to PJI was reported in univariable analysis for preoperative diagnosis (other) vs. primary OA (HR 1.6 (95% CI 1.1–2.2, P=0.006)), high volume hospitals vs. low volume hospitals (HR 1.3 (95% CI 1.0–1.7, P=0.05)), previous operation on the same joint (HR 1.8 (95% CI 1.0–3.2, P=0.05)), antithrombotic prophylaxis not used vs. enoxaparin (HR 2.8 (95% CI 1.5–5.3, P=0.001)), femoral head size 36 mm vs. 32 mm (HR 1.9 (95% CI 1.4–2.6, P<0.001)), and 28 mm vs. 32 mm heads (HR 2.8 (95% CI 1.2–6.5, P=0.02)).

5.2.2 Decreased risk of revision for PJI

Patients who received THA with CoC or the other group of bearing couples and who were operated on under spinal anesthesia had a decreased risk of revision due to PJI based on the statistical analyses. The use of CoC and the other group of bearing couples decreased the risk of revision for infection in both univariable [CoC vs. metal-on-UHXLPE HR 0.4 (95% CI 0.2–0.7, P<0.001) and other vs. metal-on-UHXLPE HR 0.1 (95% CI 0.0–0.6, P=0.006)] and in multivariable analyses [CoC vs. metal-on-UHXLPE HR 0.4 (95% CI 0.2–0.7, P=0.003) and other vs. metal-on-UHXLPE HR 0.1 (95% 0.0–0.6, P=0.007)].

For the use of spinal anesthesia the HR was 0.6 in both univariable and multivariable analyses [(95% CI 0.4–0.8, P<0.001) and (95% CI 0.4–0.8, P<0.001), respectively] (Table 7).

Also, in univariable analysis females had a decreased risk of revision due to infection when compared to males [HR 0.6 (95% CI 0.5–0.7, P<0.001)].

Table 7. Adjusted multivariable analysis for revision for PJI.

Variable		Hazard ratio (95% CI)	P value
ASA class			<0.001
	ASA I	Reference	
	ASA II	2.0 (1.3–3.2)	0.003
	ASA III–IV	3.2 (2.0–5.1)	<0.001
Intraoperative bleeding			0.009
	<500 ml	Reference	
	≥500 ml	1.4 (1.1–1.7)	0.008
Spinal anesthesia			0.002
	No	Reference	
	Yes	0.6 (0.4–0.8)	0.001
Epidural anesthesia			0.005
	No	Reference	
	Yes	2.1 (1.3–3.4)	0.002
General anesthesia			0.005
	No	Reference	
	Yes	1.6 (1.2–2.3)	0.003
Bearing couple			<0.001
	Metal on UHXLPE	Reference	
	Ceramic on ceramic	0.4 (0.2–0.7)	0.003
	Ceramic on UHXLPE	0.9 (0.7–1.2)	0.5
	Ceramized metal on UHXLPE	0.9 (0.5–1.6)	0.7
	Other	0.1 (0.0–0.6)	0.007
Fixation			0.4
	Uncemented	Reference	
	Cemented	1.1 (0.7–1.7)	0.7
	Hybrid	1.3 (0.9–1.7)	0.1
	Reverse hybrid	0.9 (0.5–1.5)	0.6

ASA = American Society of Anesthesiologists, UHXLPE = ultra-highly crosslinked polyethylene. *ASA class was adjusted for age. Intraoperative bleeding was adjusted for body mass index, previous operation on the same joint, complications during surgery, and level of education (surgeon). Spinal, epidural, and general anesthesias and bearing couples were adjusted for age and ASA class. Fixation was adjusted for sex and age.*

5.2.3 Risk of revision for PJI for variables that did not fulfill the assumption of proportional hazards

The follow-up time was divided into suitable time intervals for duration of surgery, LIA, simultaneous bilateral operation and complication during the surgery due to not fulfilling the proportional hazard assumption ($P<0.05$). For the first three postoperative weeks simultaneous bilateral operation and duration of the operation over 120 min were associated with an increased risk of revision for PJI in both univariable [HR 2.2 (95% CI 1.2–4.2, P=0.01) and HR 3.3 (95% CI 1.8–6.0, P<0.001), respectively] and multivariable analyses [HR 2.6 (95% CI 1.4–4.9, P=0.004) and HR 3.0 (95% CI 1.6–5.6, P<0.001), respectively] (Table 8).

Table 8. Unadjusted univariable analyses and adjusted multivariable analyses divided into suitable time intervals for the duration, simultaneous bilateral operation, anesthesia (LIA), and fractures during surgery due to not fulfilling the assumption of proportional hazards.

		Univariable		**Multivariable**	
		Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Duration (min)					
Time interval 0–3 weeks					
	45–59	Reference		Reference	
	<45	1.0 (0.5–2.3)	1.0	1.1 (0.5–2.5)	0.8
	60–89	1.4 (0.8–2.3)	0.2	1.3 (0.8–2.2)	0.3
	90–120	1.4 (0.8–2.5)	0.3	1.3 (0.7–2.3)	0.4
	>120	3.3 (1.8–6.0)	<0.001	3.0 (1.6–5.6)	<0.001
Time interval >3 weeks					
	45–59	Reference		Reference	
	<45	1.2 (0.4–3.7)	0.8	1.1 (0.3–3.4)	0.9
	60–89	1.1 (0.5–2.2)	0.8	1.0 (0.5–2.2)	0.9
	90–120	1.4 (0.6–3.1)	0.4	1.4 (0.6–3.1)	0.4
	>120	0.6 (0.2–1.5)	0.2	0.5 (0.2–1.4)	0.2
Simultaneous bilateral operation					
Time interval					
	0–3 weeks	2.2 (1.2–4.2)	0.01	2.6 (1.4–4.9)	0.004
	>3 weeks	0.3 (0.07–1.0)	0.05	0.3 (0.07–1.0)	0.05
Use of LIA					
Time interval					
	0–3 weeks	0.7 (0.5–1.1)	0.1	0.7 (0.5–1.1)	0.1
	>3 weeks	1.5 (0.9–2.6)	0.2	1.5 (0.8–2.5)	0.2
Fractures during the surgery					
Time interval					
	0–5 weeks	0.3 (0.04–2.2)	0.2	0.4 (0.05–2.6)	0.3
	>5 weeks	8.8 (0.9–86.2)	0.06	8.6 (0.9–84.1)	0.06

In the multivariable analysis simultaneous bilateral operations and LIA were adjusted for age and ASA classification. Fractures during surgery was adjusted for BMI. Duration was adjusted for previous operation on the same joint, level of education (surgeon), intraoperative bleeding, BMI, and complications during surgery. LIA = local infiltrative anesthesia, ASA = American Society of Anesthesiologists, BMI = Body mass index.

5.3 Development of preoperative risk prediction models for early revision and death after primary THA based on the Finnish Arthroplasty Register (FAR) dataset

During 6 postoperative months 789 revision operations were done, the most common reasons for revision operations were PJI, dislocation, or PPF. A total of 25,919 hips were included, 296 revised for PJI, 172 revised for dislocation, and 124 revised for PPF. For 172 of the primary THAs the first reported outcome was death. We included these abovementioned revision operations and cases where death occurred in the development of risk prediction models to have a large number of cases when applying the machine learning methodology (Table 9).

Table 9. Outcomes reported within the first 6 postoperative months.

Outcome	**All patients (N=25,919)**	**Training cohort (N=17,279)**	**Test cohort (N=8,640)**
	No. of events (%)	No. of events (%)	No. of events (%)
Revision	789 (3.0%)	538 (3.1%)	251 (2.9%)
Periprosthetic joint infection	296 (1.1%)	204 (1.2%)	92 (1.1%)
Dislocation	172 (0.7%)	116 (0.7%)	56 (0.6%)
Periprosthetic fracture	124 (0.5%)	76 (0.4%)	43 (0.5%)
Other*	102 (0.4%)	73 (0.4%)	34 (0.4%)
Reason missing	95 (0.4%)	69 (0.4%)	26 (0.3%)
Death	172 (0.7%)	111 (0.6%)	61 (0.7%)

**Includes the following revisions: breakdown of the liner; breakdown of the femoral head; free-floating, unstabilized femoral stem or non-ossified femoral stem; unclear pain; aseptic loosening of the femur; periprosthetic fracture of the acetabulum; unstabilized cup or non-ossified; repair of the lower limb length discrepancy; malposition of the femur component; malposition of the acetabulum component; aseptic loosening of the acetabulum; other reason*

5.3.1 Revision due to PJI

For revision operation due to PJI, the Lasso regression with iterative variable selection identified male sex, higher BMI, higher ASA classification, and the use of general anesthesia as increasing the PJI revision risk (Table 10). In terms of the AUROC, the risk prediction model developed for PJI reached good performance and was the most consistent between the training (AUROC 0.70, 95% CI: 0.67–0.74) and test cohorts (AUROC 0.68, 95% CI: 0.62–0.74) (Table 11).

5.3.2 Revision due to dislocation

To predict the risk of revision due to dislocation, the Lasso penalized regression identified high ASA classification, preoperative fracture diagnosis, previous operation on the same joint, 32 mm femoral head size (as compared to other head sizes, mainly 36 mm), and posterior approach as increasing the dislocation revision risk (Table 10). In terms of the AUROC, the risk prediction model for dislocation had the lowest discrimination performance in both the training (AUROC 0.65, 95% CI: 0.60–0.70) and test cohorts (AUROC 0.64, 95% CI: 0.56–0.72) (Table 11).

5.3.3 Revision due to PPF

High ASA classification, advanced age, and uncemented fixation were identified as increasing the risk of revision due to PPF in Lasso penalized regression (Table 10). In terms of the AUROC, the risk prediction model for PPF reached good performance in the training cohort (AUROC 0.70, 95% CI: 0.64–0.76), and moderate performance in the test cohort (AUROC 0.65, 95% CI: 0.58–0.72) (Table 11).

5.3.4 Death

For death, the Lasso penalized regression identified advanced age, preoperative fracture diagnosis, and higher ASA classification as predicting the risk of death after primary THA (Table 10). In terms of the AUROC, the risk prediction model developed for death had the highest discrimination performance in both the training (0.82, 95% CI: 0.78–0.86) and test (0.84, 95% CI: 0.78–0.90) cohorts (Table 11).

Table 10. The variables selected by Lasso penalized logistic regression and corresponding coefficients for predicting each of the outcomes*.

	Model			
Variable	**PJI**	**Dislocation**	**PPF**	**Death**
Intercept	8.576	6.801	9.138	7.017
ASA class (per class)	0.387	0.459	0.404	0.491
Male sex (1 if yes, 0 if no)	0.444	-	-	-
Age (per 10 years)	-	-	0.244	0.104
Body mass index (per kg/m^2)	0.103	-	-	-
Preoperative diagnosis: fracture (1 if yes, 0 if no)	-	0.861	-	0.878
Previous operation on the same joint (1 if any, 0 if no)	-	0.675	-	-
Surgical approach: posterior (1 if yes, 0 if no)	-	0.606	-	-
Anesthesia: general (1 if yes, 0 if no)	0.636	-	-	-
Fixation: uncemented (1 if yes, 0 if no)	-	-	1.479	-
Head diameter 32 mm (1 if yes, 0 if no)	-	0.355	-	-
Example calculations*				
Raw score (sum of patient value × coefficient)	4.681	2.844	4.350	3.058
Transformed score = $\frac{1}{1+e^{\text{Intercept}-\text{Raw score}}}$	0.020 or 2.0%	0.019 or 1.9%	0.008 or 0.8%	0.019 or 1.9%

*The coefficients indicate the impact of one unit change in a predictor variable, given in brackets, on the response variable when the other predictors are held constant. Fields without a numerical value indicates that the denoted variable is not needed for predicting the risk of designated outcome (i.e. regression coefficient equals zero).

PJI = periprosthetic joint infection, PPF = periprosthetic fracture, ASA = American Society of Anesthesiologists.

Example calculations are given for a 68 years old female patient with ASA class 3, body mass index of 28 kg/m^2, preoperative fracture diagnosis and no previous contributing operations for a surgery performed using posterior surgical approach, general anesthesia, uncemented fixation in order to install an implant with head diameter greater than 32 mm.

Table 11. Discrimination performances of the developed models in terms of the area under the receiver operating characteristic curve (AUROC), including number of primary operations available for predictions and corresponding number of events in both the training and test cohorts.

Model	**Training cohort (N=17,279)**			**Test cohort (N=8,640)**		
	No. of available	No. of events	AUROC (95% CI)	No. of available	No. of events	AUROC (95% CI)
Periprosthetic joint infection	15,127	199	0.70 (0.67–0.74)	7,506	86	0.68 (0.62–0.74)
Dislocation	15,907	109	0.65 (0.60–0.70)	7,929	51	0.64 (0.56–0.72)
Periprosthetic fracture	16,291	74	0.70 (0.64–0.76)	8,140	44	0.65 (0.58–0.72)
Death	16,466	109	0.82 (0.78–0.86)	8,226	56	0.84 (0.78–0.90)

5.3.5 Differences in hazard ratios between high- and low-risk subgroups

We stratified patients into different risk subgroups based on the estimated risk scores (Table 12). This revealed that belonging to a group with a higher estimated risk was also associated with higher observed rates of adverse outcomes. This was consistent in both training and test cohorts, meaning that the generalizability of these results was good. The highest difference in HRs between the high- and low-risk subgroups was observed for death (test cohort HR 14.0, 95% CI 5.6–35.2, P<0.001). Additionally, patients belonging to the high-risk subgroup for PJI (test cohort HR 3.5, 95% CI 2.06.2, P<0.001), dislocation (test cohort HR 3.5, 95% CI 1.4–8.5, P=0.001), and PPF (test cohort HR 4.4, 95% CI 1.9–10.0, P<0.001) had significantly higher observed revision rates compared to the low-risk subgroup (Table 13).

Table 12. Stratification of the patients into different subgroups based on the estimated risk scores.

			Training cohort			Test cohort	
Outcome	**Risk group**	**N total**	**N event**	**% event**	**N total**	**N event**	**% event**
PJI	Low	5296	27	0.5	2681	15	0.6
	Intermediate	4472	42	0.9	2175	20	0.9
	High	5359	129	2.4	2650	51	1.9
Dislocation	Low	4206	13	0.3	2100	6	0.3
	Intermediate	6202	36	0.6	3107	17	0.5
	High	5499	60	1.1	2722	27	1.0
PPF	Low	6631	10	0.2	3344	7	0.2
	Intermediate	3213	12	0.4	1638	7	0.4
	High	6447	52	0.8	3158	29	0.9
Death	Low	7127	6	0.1	3622	5	0.1
	Intermediate	4281	14	0.3	2155	4	0.2
	High	5058	96	1.9	2449	53	2.2

N = number, PJI = periprosthetic joint infection, PPF = periprosthetic fracture.

Table 13. Hazard ratios (HR) for different risk subgroups.

	Training cohort			Test cohort	
	Periprosthetic joint infection			**Periprosthetic joint infection**	
Risk group	Threshold	HR (95% CI)	P value	HR (95% CI)	P value
Low	0.0%	Reference	-	Reference	-
Intermediate	0.8%	1.8 (1.1–3.0)	0.01	1.6 (0.8–3.2)	0.04
High	1.3%	4.8 (3.2–7.3)	<0.001	3.5 (2.0–6.2)	<0.001
	Dislocation			**Dislocation**	
Risk group	Threshold	HR (95% CI)	P value	HR (95% CI)	P value
Low	0.0%	Reference	-	Reference	-
Intermediate	0.5%	1.8 (1.0–3.5)	0.05	2.0 (0.8–5.1)	0.1
High	0.8%	3.6 (2.0–6.5)	<0.001	3.5 (1.4–8.5)	0.001
	Periprosthetic fracture			**Periprosthetic fracture**	
Risk group	Threshold	HR (95% CI)	P value	HR (95% CI)	P value
Low	0.0%	Reference	-	Reference	-
Intermediate	0.3%	2.5 (1.1–5.8)	0.03	2.3 (0.8–6.4)	0.1
High	0.5%	5.4 (2.7–10.6)	<0.001	4.4 (1.9–10.0)	<0.001
	Death			**Death**	
Risk group	Threshold	HR (95% CI)	P value	HR (95% CI)	P value
Low	0.0%	Reference	-	Reference	-
Intermediate	0.5%	3.9 (1.5–10.1)	0.005	1.4 (0.3–5.0)	0.7
High	0.8%	21.3 (9.3–48.7)	<0.001	14.0 (5.6–35.2)	<0.001

** For each outcome, the thresholds for low, intermediate, and high risk were defined using tertiles of the risk score distribution in the training data, respectively. CI = confidence interval, HR = hazard ratio.*

5.4 Development of risk prediction models for early revision and death following THA using the Nordic Arthroplasty Register Association (NARA) dataset

Within the first 6 postoperative months, most of the revision operations were performed due to PJI, dislocation, or PPF. There were a total of 251,438 hips, of which 1,994 (0.8%) were revised due to PJI, 1,019 (0.4%) due to dislocation, and 738 (0.3%) due to PPF. For 2,658 (1.1%) hips the first reported outcome was death. There were also 705 (0.3%) revision operations for various other reasons than mentioned above (Table 14).

Table 14. Rates of early revision outcomes and death following primary total hip arthroplasty in the study population.

Outcome	**All patients (N=251,438)**	**Training cohort (N=167,592)**	**Test cohort (N=83,846)**
	No. of events (%)	No. of events (%)	No. of events (%)
Revision	4,530 (1.8%)	3,047 (1.8%)	1,483 (1.8%)
Periprosthetic joint infection	1,994 (0.8%)	1,342 (0.8%)	652 (0.8%)
Dislocation	1,019 (0.4%)	675 (0.4%)	344 (0.4%)
Periprosthetic fracture	738 (0.3%)	497 (0.3%)	241 (0.3%)
Aseptic loosening	276 (0.1%)	199 (0.1%)	77 (0.1%)
Other*	429 (0.2%)	281 (0.2%)	148 (0.2%)
Reason missing	74 (<0.1%)	53 (<0.1%)	21 (<0.1%)
Death	2,658 (1.1%)	1,803 (1.1%)	855 (1.0%)

5.4.1 Predictive performances of the developed models

Among all outcomes of interest, good discrimination performances were achieved for the models predicting the risk of PPF (AUROC 0.74, 95% CI: 0.71–0.77) and death (AUROC 0.85, 95% CI: 0.84–0.87), whereas the discrimination performances were moderate for the models predicting the risk of revision for PJIs (AUROC 0.61, 95% CI: 0.59–0.64) and dislocations (AUROC 0.67, 95% CI: 0.65–0.70). The abovementioned AUROC values are the results for the GBM, which was the best-performing ML algorithm. The six top-performing models were GBM, conventional logistic regression, Ridge regression, Lasso regression (with or without SIVS), and RF. Among these models the variation between discrimination performances ranged from little to no difference. For dislocation revision, slightly lower AUROCs were reported for Ridge regression (AUROC of 0.67, 95%: 0.64–0.70, P=0.004) and conventional Lasso regression (AUROC of 0.67, 95%: 0.64–0.70, P=0.03) compared to GBM. Also, slightly lower AUROCs were reported for the Lasso regression with SIVS (AUROC of 0.84, 95%: 0.83–0.86, P=0.001) and RF (AUROC of 0.83, 95%: 0.82–0.85, P<0.001) when compared to GBM for predicting death (Table 15).

Table 15. Discrimination performance of the applied machine learning methods and ranking according to area under the receiver operating characteristic curve (AUROC) in the independent test cohort. The P values were computed for comparisons with the best-performing method in predicting each outcome using the Delong method. CI denotes confidence interval.

Method	**Periprosthetic joint infection**			**Dislocation**			**Periprosthetic fracture**			**Death**		
	Rank	AUROC (95% CI)	P	Rank	AUROC (95% CI)	P	Rank	AUROC (95% CI)	P	Rank	AUROC (95% CI)	P
Gradient boosting machines	1	0.62 (0.59–0.64)		4	0.67 (0.65–0.70)	0.4	1	0.74 (0.71–0.77)		1	0.85 (0.84–0.87)	
Lasso regression with stable iterative variable selection (SIVS)	2	0.62 (0.59–0.64)	0.9	2	0.67 (0.65–0.70)	0.5	3	0.74 (0.71–0.77)	0.7	6	0.84 (0.83–0.86)	0.001
Logistic regression	7	0.61 (0.58–0.63)	0.5	1	0.67 (0.65–0.70)		5	0.74 (0.71–0.77)	0.5	2	0.85 (0.83–0.86)	0.5
Ridge regression	5	0.61 (0.59–0.63)	1.0	5	0.67 (0.64–0.70)	0.004	6	0.74 (0.71–0.76)	0.3	3	0.85 (0.83–0.86)	0.1
Lasso regression	6	0.61 (0.59–0.63)	1.0	7	0.67 (0.64–0.70)	0.03	2	0.74 (0.71–0.77)	1.0	4	0.85 (0.83–0.86)	0.2
Random forest	3	0.61 (0.59–0.63)	0.9	6	0.67 (0.64–0.70)	0.3	4	0.74 (0.71–0.76)	0.6	7	0.83 (0.82–0.85)	<0.001
Neural network	8	0.60 (0.58–0.62)	0.005	3	0.67 (0.65–0.70)	0.4	7	0.73 (0.70–0.76)	0.002	5	0.84 (0.83–0.86)	0.03
Naive Bayes	4	0.61 (0.59–0.63)	0.7	8	0.65 (0.62–0.67)	<0.001	9	0.70 (0.68–0.73)	0.007	8	0.83 (0.81–0.84)	<0.001
Classification tree	9	0.58 (0.56–0.61)	0.01	9	0.64 (0.62–0.67)	0.002	8	0.71 (0.68–0.74)	0.02	9	0.82 (0.81–0.84)	<0.001

5.4.2 Evaluation of the variables required for model predictions

When the accuracy of the top-performing models was analyzed, the Lasso regression with SIVS procedure had the same accuracy as the more complex models (maximum AUROC decrease of 0.01 for predicting death), even though it required the least input variables (Figure 13A). In terms of number of variables required for the model predictions, the Lasso with SIVS required only six inputs of variables (age, sex, preoperative diagnosis, bearing couple, fixation, and surgical approach) out of the available 32 variables for the models predicting the risk of revision due to PJI (5 variables, 16%), dislocation (5 variables, 16%), PPF (6 variables, 19%), and death (5 variables, 16%) (Figure 13B). To achieve the same accuracy as the Lasso with SIVS, GBM used all 32 variables as well as up to 55 additional model-generated inter-variable interactions. All the other competing models reached similar AUROCs to the Lasso with SIVS when using nearly all 11 available variable types and associated information. Logistic regression was excluded from this comparison due to having virtually the same performances and variables as the Ridge regression in all comparisons. The Lasso with SIVS procedure models were considered for further evaluation as simple-to-use risk prediction models for clinical practice due to the good performance with minimum number of input variables.

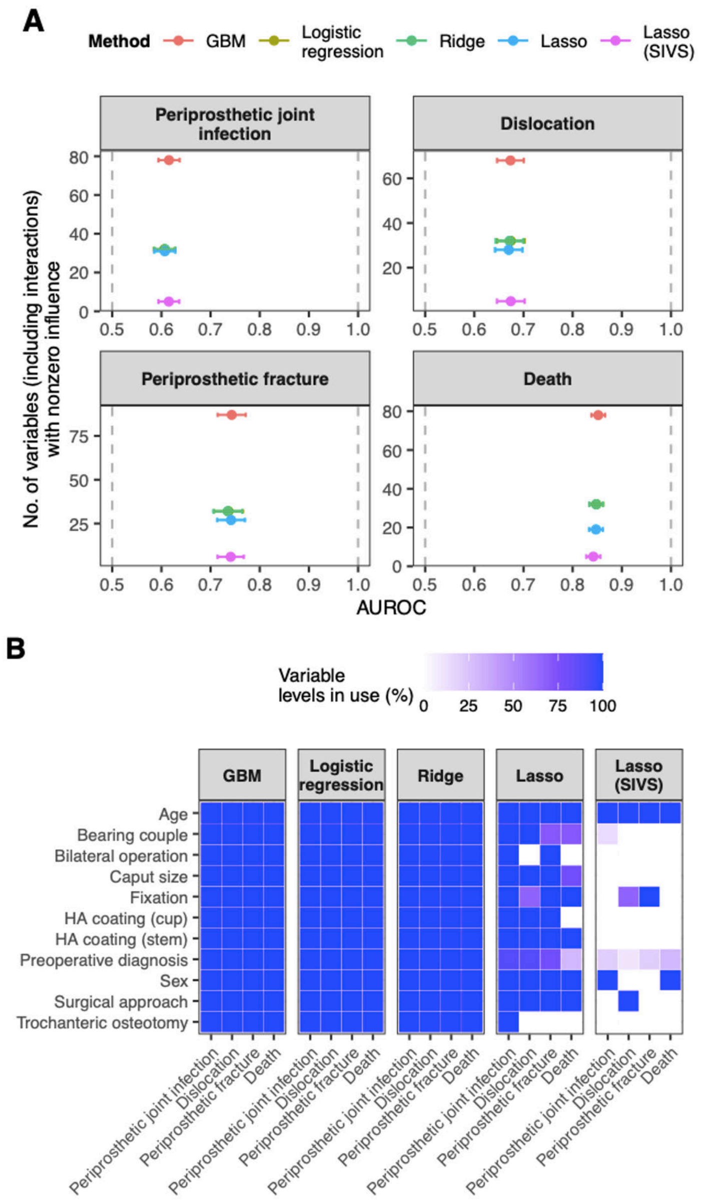


Figure 13. Evaluation of variables used by the four top-performing models. A) Complexity of the models in terms of number of variables (or also inter-variable interactions in gradient boosting machines, GBM) with non-zero influence on model predictions vs. discrimination performance in terms of area under the receiver operating characteristic curve (AUROC) in the test cohort. Horizontal lines indicate 95% confidence intervals. Ridge and logistic regressions had nearly identical performance. B) Summary of the variables with non-zero influence identified by different modeling approaches. The color indicates the fraction of variable levels with non-zero influence in the final models.

5.4.2.1 Least absolute shrinkage and selection operator with stable iterative variable selection procedure

The model predicting risk of death based on the Lasso with SIVS procedure identified several key variables that increase the risk: advanced age, male sex, and a preoperative diagnosis of hip fracture, nontraumatic femoral head necrosis, or other diagnosis. For PPF the key variables increasing the risk were advanced age, a preoperative diagnosis of hip fracture or nontraumatic femoral head necrosis, and the use of uncemented, hybrid, or reverse hybrid fixations. For PJIs advanced age, male sex, and a preoperative diagnosis of hip fracture or nontraumatic femoral head necrosis were key variables increasing the risk, whereas ceramic-on-ceramic (CoC) bearings decreased the risk compared to other bearing types. For dislocation, key variables increasing the risk were advanced age, a preoperative diagnosis of hip fracture, uncemented and hybrid fixations, and posterior approach. Risk prediction models based on the Lasso with SIVS procedure showed no signs of substantial over- or underfitting and all the risk predictions from these models were in good agreement with the observed outcome rates (Figure 14).

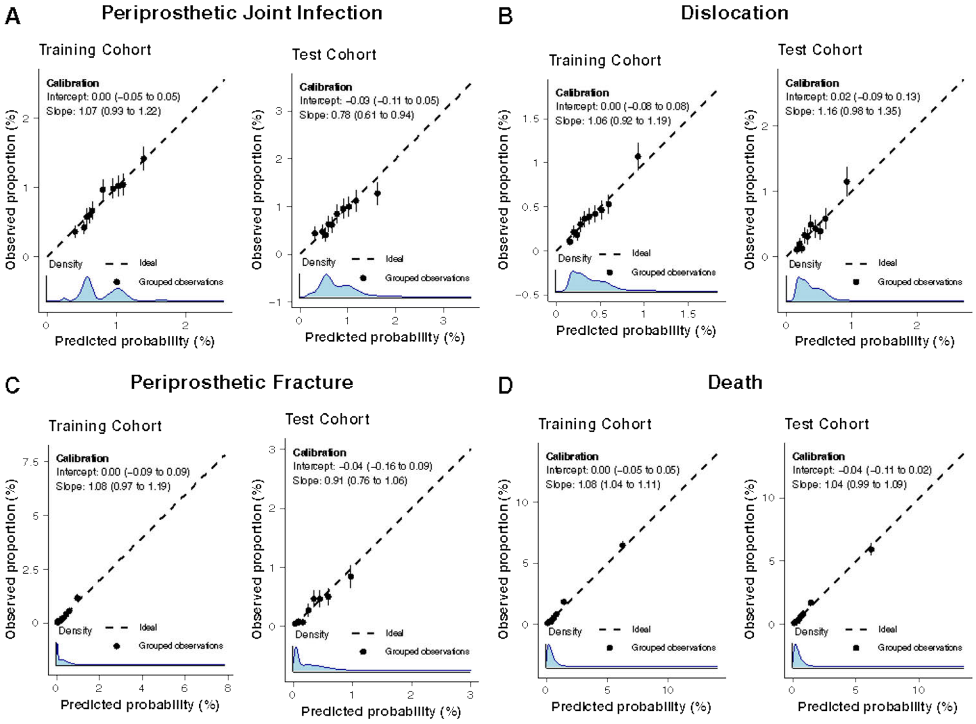


Figure 14. Calibration plots indicating agreement between observed outcome rates and predicted risks in different deciles of risk predicted using Lasso regression with stable iterative variable selection.

6 Discussion

Population-based data reported to arthroplasty registers make it possible to assess risk factors associated with failure of THA. The purpose of these registers is to collect patient- and surgery-related data to facilitate active research on the role of patient selection, surgeon's choice of pre- and perioperative management, and measurement of adherence to clinical guidelines, and to improve the quality of care for patients undergoing arthroplasty surgery. Preoperative risk prediction models have recently been developed to help surgeons identify high-risk patients at the earliest point of care and inform these patients about the expected outcomes of the surgery. Risk prediction models could have the potential to decrease the number of revision surgeries in the future and improve treatment outcomes overall. A shared decision-making process engages both the surgeon and the patient in deciding on the best treatment options given the patient's circumstances. The use of preoperative risk prediction models assists in this process and should be part of all future treatment of arthroplasty surgeries. The aim of this doctoral thesis was to identify the risk factors for revision operations and to develop risk prediction models for estimating the risks of complications following primary THA.

6.1 Dislocation revision risk in primary THA

One of the main reasons for revision after primary THA is dislocation (AOANJRR 2016, FAR 2017, NJR 2017). We used FAR data from 2014 to 2018 to assess risk factors for dislocation revisions after primary THA. In our material, posterior approach, fracture diagnosis, and ASA class III–IV increased the dislocation revision risk. In addition, using a 36 mm femoral head size decreased the dislocation revision risk.

We found that the posterior approach was associated with an increased risk of dislocation revision compared to the anterolateral approach. Similar results have been found in previous studies (Hailer et al. 2012, Higgins et al. 2015, Mjaaland et al. 2017). A prior study by Zijlstra et al. (2017) reported HRs of 0.5 to 0.6 for dislocation revision risk for the straight lateral, anterolateral, and anterior approaches compared to the posterior approach based on LROI data (Zijlstra et al. 2017). For the posterior approach, the dislocation revision risk was found to be 2.1-fold higher compared to the anterolateral approach in a Norwegian register study (Mjaaland et al. 2017). Previously, there has been a suggestion to use lateral surgical approaches when treating patients belonging to risk groups (Hailer et al. 2012). Our results support this proposal. The anterior approach had an increased risk of revision due to dislocation compared to the anterolateral approach in the current study, but the total amount of THAs performed using the anterior approach was very small. In sensitivity analysis the difference in the dislocation revision rate between the posterior and anterolateral approaches was no longer statistically significant. Sensitivity analysis included approximately 21% of all operations, so lower statistical power may be the reason for the non-significant result.

PROMs have been reported to be better for anterior and posterior approaches compared to anterolateral and direct lateral approaches (Smith et al. 2012, Amlie et al. 2014, Peters et al. 2018). When postoperative pain was measured on the Numeric Rating Scale (NRS), patients operated on using the posterior approach had less postoperative pain during activity and at rest compared to patients operated on using the anterolateral approach (Peters et al. 2018).

In the present study, there were dislocation revisions only among patients with a pre-operative femoral neck fracture diagnosis who were operated on using the posterior approach. This finding is consistent with those of prior studies (Enocson et al. 2009, Sköldenberg et al. 2010, Cebatorius et al. 2015). The Australian registry has reported a two-fold and the Swedish registry a four-fold dislocation revision risk for patients whose causative primary diagnosis for THA was femoral neck fracture, compared to patients whose primary diagnosis was OA (Conroy et al. 2008, Hailer et al. 2012). Our results are in accordance with these registry findings, showing a three-fold dislocation revision risk following a femoral neck fracture compared to OA. Special attention should be paid to implant choice and approach when treating fracture patients.

We also found that a high ASA class was associated with an increased risk of dislocation revisions. Zijlstra et al. (2017) analyzed LROI data and reported that patients with ASA class II or higher had an increased risk of dislocation (Zijlstra et al. 2017). In our data, ASA class II was a risk factor only in univariable analysis, but otherwise our results support the findings reported by Zijlstra et al. Patients with higher ASA class have more comorbidities and may be more fragile, which might predispose them to dislocations. In addition, the threshold for operating on these patients may be higher. The preoperative clinical situation may already be more demanding, which might increase the dislocation risk.

Previously, the use of larger femoral head sizes has been associated with a decreased dislocation revision risk. Based on FAR data on 42,379 THAs and HRAs, the use of 28 mm femoral heads has been reported to have a 10-fold dislocation revision risk compared to >36 mm femoral heads (Kostensalo et al. 2013). However, this previous study included several thousand large-head MoM THAs and HRAs and is therefore not directly comparable to the current study, which did not include any MoM bearings. In previous studies the dislocation revision risk has been reported to be equal for 32 and 36 mm heads (Hailer et al. 2012, Kostensalo et al. 2013). Previously, Tsikandylakis et al. (2018) analyzed NARA data from 2003 to 2014 and found no difference between 36 mm and 32 mm heads in relation to dislocation revision risk (Tsikandylakis et al. 2018), contrary to our current finding of a lower risk with 36 mm heads. A recent report by Zijlstra et al. (2017) stated that 36 mm heads reduced the risk of revision for dislocation compared to 32 mm heads, although this finding considered only THAs performed with the posterior approach (Zijlstra et al. 2017). Based on these most recent data, 36 mm femoral heads should be considered instead of 32 mm heads for patients with high dislocation risk.

6.1.1 Strengths and weaknesses of Study I

FAR includes an extensive number of variables which offers a good basis for retrospective studies. Further, FAR has a high data completeness of reported primary and revision THAs to the register. The methodology was carefully designed for the study. The dislocation rate was 1.1% after primary THA, which is similar as reported previously (Brooks 2013, Saiz et al. 2019). We acknowledge that our study has several limitations. First, from the methodology point of view, we did not perform DAG analysis, which may have led to an over adjustment in multivariable analyses. Second, comorbidity data on the patients were not available even though the ASA class is a crude estimation of a patient's medical condition. Additionally, PROMs were not available. Third, we were unable to assess radiographs and implant positioning. Fourth, we did not have data on closed repositions of dislocated THA. It is possible that some patients suffered one or two dislocations and their hip subsequently stabilized without revision surgery. Further, patients who have revision operation due to dislocation may have comorbidity factors that predisposes them for dislocations and in primary situation for femoral neck fractures. This may lead to residual confounding of the results especially when comorbidities are not included in the analyses.

6.2 PJI revision risk in primary THA

In our material, an increased risk of revision for PJI was found for BMI of 31–35 kg/m^2 and >35 kg/m^2, advanced ASA class, bleeding over 500 ml, and use of epidural or general anesthesias, whereas a CoC bearing couple and spinal anesthesia were associated with PJI with a decreased risk of revision. For the first 3 postoperative weeks the risk of revision for PJI was increased for simultaneous bilateral operation and duration of operation over 120 min. The cumulative rate of revision due to PJI was 1.04%, which is slightly higher than published previously at 1-year follow-up (ranging from 0.3% to 0.7%) (Gundtoft et al. 2017a, Kurtz et al. 2018, Perni et al. 2023). We reported a high incidence of PJI within the first six months after the primary THA in our Studies III and IV (1.1% and 0.8%, respectively). For PJI there are differences in definitions, time frame, surveillance systems, and data completeness of reporting to arthroplasty registers, which makes it more challenging to compare the reported incidences of PJIs with each other (Wilson et al. 2007).

We reported an increased risk of revision for PJI for high ASA class; numerous prior studies have found a similar association (Dale et al. 2011, Namba et al. 2012, Kong et al. 2017, Lenguerrand et al. 2018, Smith et al. 2018). ASA class is a crude estimate of a patient's medical condition. Comorbidity conditions such as depression, obesity, cardiac arrhythmia, and rheumatologic disease are important factors associated to PJI risk (Bozic et al. 2012, 2014b). Comorbidities also have a major role in determining ASA classification.

In our multivariable analysis, bleeding over 500 ml was associated with an increased risk of infection. We are not aware of previous studies concerning the association between intraoperative bleeding and PJI, but blood transfusion and PJI have been associated previously (Kim et al. 2017). In addition, as intraoperative bleeding is a common indication for blood transfusion, we consider our findings to support the pre-existing evidence. However, some association between intraoperative bleeding and PJI was found in a comprehensive literature review, but more quality studies are needed on the subject (Kwong et al. 2012).

In our material, male sex was a risk factor for revision due to PJI. This finding is consistent with those of prior studies (Pedersen et al. 2010, Dale et al. 2012, Lenguerrand et al. 2018, Smith et al. 2018). Furthermore, our results support the magnitude of risk presented earlier (1.2–1.7-fold). Only one study has reported that female sex was associated with a higher risk of revision for PJI (Namba et al. 2012). There might be some confounding factors that increase the risk of PJI among male patients, but that association is unclear. Possible factors not included in the FAR are smoking and alcohol abuse, both of which more common among males (WHO 2015, 2018). Previously it has been reported that skin metabolism, hair growth, sebum production, skin pH, and skin thickness differ between males and females. These differences may predispose male patients more than female patients to PJI. (Badawy et al. 2017). The increased PJI risk of male patients should be considered in detailed pre-operative patient counseling to manage modifiable surgery related risks.

It is widely known that obesity is associated with PJI risk and this is well documented in several prior studies and meta-analyses (Namba et al. 2012, Kunutsor et al. 2016, Kong et al. 2017, Lenguerrand et al. 2018, Smith et al. 2018, Triantafyllopoulos et al. 2018). Our findings are in accordance with those of these studies. In our material, the HR was 2.4 for patients with a BMI of 31–35 kg/m^2 and 5.1 for patients with a BMI of >35 kg/m^2. The PJI risk of those with BMI >35 kg/m^2 was even higher than reported previously (OR 1.9 for BMI 35–40 kg/m^2, OR 4 for BMI >40 kg/m^2) (Smith et al. 2018). Jämsen et al. (2012) reported that diabetes more than doubled the revision risk due to PJI independently of obesity when compared to patients without diagnosis of diabetes (OR of 2.3). However, the data included both hip and knee replacements. (Jämsen et al. 2012) Diabetes was also associated to PJI in a large meta-analysis by Kong et al. (Kong et al. 2017). Special preoperative attention should be paid to patients with a high BMI, as this might be an even more prominent risk factor than assessed previously. However, it is not clear how weight loss prior to THA affects the risk of PJI, and more quality studies are needed to clarify this issue (Lui et al. 2015, Li et al. 2019).

For the first 3 postoperative weeks, long duration of surgery has been associated an increased risk of PJI. Previous studies have reported the same association (Engesaeter et al. 2006, Pedersen et al. 2010): Pedersen et al. (2010) reported an increased PJI rate when the duration of surgery was 2 hours or more. On the other hand, Namba et al. (2012) found that duration of surgery was not an independent risk factor for PJI. Specializing in arthroplasty surgeries increases the numbers of performed THAs, which probably decreases operation time. Unfortunately, our data did not include surgeon volume data. In the current study, high hospital volume was associated with an increased PJI rate.

Simultaneous bilateral surgery increased the risk of revision due to PJI for the first 3 postoperative weeks. The same association was found also in previous studies, but with no regard to time from the operation (Namba et al. 2012, Kong et al. 2017). The risk of PJI should be considered in elective management of patients who require both hips to be operated on simultaneously.

We found that the use of spinal anesthesia decreased the risk of revision due to PJI, whereas epidural and general anesthesias increased the risk of PJI revision in comparison to other anesthesia options. The use of neuraxial anesthesia has been reported to have a decreased PJI rate compared to general anesthesia (Helwani et al. 2015, Johnson et al. 2016, Lenguerrand et al. 2018, Memtsoudis et al. 2019, Scholten et al. 2019), but we are unaware of any data showing that epidural anesthesia would be associated with an increased risk of revision due to PJI. Epidural anesthesia is often used in patients with an anticipated longer operation time and hence might be associated with an increased risk of complications. Further, comorbidity conditions have a major role in a selection of the used anesthesia mode for the patients.

The use of CoC bearing couples may be a protective factor against developing PJI, and this has been of interest in recent times (Lee et al. 2016, Pitto and Sedel 2016, Kurtz et al. 2017, Lenguerrand et al. 2018). Kurtz et al. (2017) found that receiving a THA with CoP and CoC bearings had a reduced risk of infection relative to MoP bearings (HRs of 0.9 and 0.7, respectively). Lenguerrand et al. (2018) found that the risk of revision for PJI was influenced by the type of bearing couples and varied according to the time period. In the early postoperative period, no differences were observed. For a long-term revision (from 12 months onwards for CoC and 24 months for CoP postoperatively), CoC and CoP bearings had lower PJI rates than did MoP bearings. (Lenguerrand et al. 2018) Contrary to previous studies, we found that CoC was associated with a lower rate of revision for PJI in the early postoperative period, as our study did not include long term infections. Further, ceramic on UHXLPE did not protect against PJI in our study. It is likely that this finding is affected by residual confounding, as the CoC population differs from other surface groups regarding patient-related factors. A CoC bearing couple tends to be used in younger and healthier patients with less co-morbidity. Also, surgeons using CoC may be more experienced. This residual confounding likely affects the results even after adjusting.

A high-volume hospital increased the risk of revision due to PJI. The preceding evidence concerning this association has been contradictory. A study from the US found no association between high-volume hospitals (>200 THAs performed annually) and PJI revisions (Namba et al. 2012). However, a study from the UK by Lenguerrand et al. (2018) reported that THAs performed in high-volume hospitals (>255 THAs in the previous 12 months) increased the incidence of early infections (Lenguerrand et al. 2018). In our study, a previous contributing operation was associated with increased risk of PJI in univariable analysis and a similar association has been presented earlier (Cordero-Ampuero and de Dios 2010).

Previously, a preoperative diagnosis for the THA has often been associated with PJI risk (Pedersen et al. 2010, Namba et al. 2012, Lenguerrand et al. 2018). In our study, “other” preoperative diagnosis vs. primary OA was a significant risk factor for PJI. Conditions that cause e.g. avascular necrosis, such as steroid use or irradiation, cause immunosuppression and predispose to PJI. Patients with preoperative diagnosis of femoral neck fracture have been associated with an increased PJI risk after primary THA compared to elective THAs with preoperative diagnosis of OA (Pedersen et al. 2010, Ren et al. 2021).

6.2.1 Strengths and weaknesses of Study II

The strengths of this study are similar as reported in Study I concerning analyzed data. In this study we used DAG analysis to limit over adjustment in multivariable analyses. We acknowledge that our study has several limitations. Although prospectively collected, our data are observational. Further, the FAR does not incorporate comprehensive data about possibly relevant patient-related factors such as socioeconomic status, smoking status, or comorbidities, and ASA class is just a crude measure of morbidity. Even though the FAR has included new variables since 2014, there might still be some confounding factors not included in the FAR that influenced our results, such as the lower risk of infection in CoC articulations. Furthermore, the completeness of revision surgery data in the FAR is only 81% compared to the discharge register; thus we are missing information on some PJI revisions (FAR 2021). Revision operations performed on-call (PJI, fractures, dislocations) are probably slightly underreported compared to elective revisions (wear). It is also possible that revision operations, which do not include implant change such as DAIR are underreported to the FAR. This means that data completeness of revision THA to the FAR may be depended on the indication for the revision operation and how the revision operation is performed. However, we do not think that this caused serious bias to our results.

The incidence of revision might be overestimated when death is considered as a competing risk. In our study the mortality rate was low. During the study period, 2.4% of the patients died. Our main focus was to estimate relative revision risk. More accurate results of relative revision risks are reported when Cox regression has been used (Ranstam and Robertsson 2010). Hence, we considered death not to be a significant competing event with PJI revision and we did not perform competing risk analysis between infection and death. A PJI diagnosis reflects a clinical judgment sufficient to lead the surgeon to conduct a revision operation. Our data are recorded in operating theatres based on clinical diagnosis and are not complemented later with e.g. microbiology data, which may lead to underestimation of the incidence of PJIs.

6.3 Preoperative risk prediction models in primary THA based on the FAR data

In our third study, we developed simple-to-use preoperative risk prediction models for PJI, dislocation, PPF, and death within 6 postoperative months after primary THA. Preoperative risk prediction tools can be used to identify high-revision-risk patients at the earlier point of care and to analyze the estimated risk for adverse outcome. Furthermore, surgeons may ensure long-term prosthesis survival by minimizing the risk of adverse outcomes, for example with the selection of appropriate methods and devices for the operation.

For the model predicting the risk of PJI, penalized Lasso regression identified male sex, higher BMI, higher ASA class, and general anesthesia as important risk factors for PJI. Previously, all these risk factors have been associated with PJI after THA (Kunutsor et al. 2016, Smith et al. 2018, Scholten et al. 2019). We were not able to analyze the data on comorbidities due to unavailability in the FAR, even though previous analyses have suggested that comorbid conditions influence the risk of PJI (Bozic et al. 2014b, Kong et al. 2017). However, ASA class is a crude estimate of medical condition and hence was considered sufficient for representing patients' health status.

Our iterative variable selection procedure identified ASA class, fracture diagnosis, previous contributing operations, 32 mm femoral head size, and posterior approach as important factors in the final risk prediction model increasing the risk of dislocation. Based on the previous literature, all these risk factors for dislocation have already been described (Hailer et al. 2012, Mjaaland et al. 2017, Zijlstra et al. 2017, Ferguson et al. 2019, Ravi et al. 2019). There is an increased risk of dislocation and dislocation revisions among patients who have undergone failed cephalomedullary nailing (CMN) of hip fracture before THA (Smith et al. 2019). Conversion THAs (after sliding hip screw and side plate (SHS) or CMN) are more demanding and are associated with an increased risk of postoperative complications like dislocation (Pui et al. 2013).

Advanced age, higher ASA class, and uncemented fixation were identified as important risk factors in our risk prediction model for PPF. Prior studies have also identified these risk factors for PPF (Thien et al. 2014, Abdel et al. 2016, Lindberg-Larsen et al. 2017, Peters et al. 2019).

Finally, our risk prediction model for death identified advanced age, higher ASA class, and fracture diagnosis as important risk factors for death. These findings are in accordance with those of prior studies which have identified higher age (80 years or more) (Rhee et al. 2018), higher ASA class (≥III) (Belmont et al. 2014), and femoral neck fracture diagnosis (Sassoon et al. 2013, Charette et al. 2019) as strong risk factors for death after THA.

When the patients were stratified into different risk subgroups (low, intermediate, and high), those who were predicted to belong to the high-risk subgroup were also observed to have a higher incidence of adverse outcomes. Although the predicted patient-specific risks were relatively low in general, the incidence of adverse outcomes was found to be up to four to 14 times higher in the high-risk than in the low-risk subgroups. Therefore, from a clinical point of view, it may be most important to concentrate the use of developed models to identifying patients belonging to these high-risk subgroups. For these patients, the risk of adverse outcomes could potentially be reduced by optimizing the treatment-related modifiable risk factors with the aid of our risk prediction models. More intensive follow-up of high-risk patients could also be considered. It is also possible to inform patients about their predicted risks for adverse events, hence the patients can avoid specific situations that may predispose them for those adverse events. Finally, in addition to patient stratification, the risk prediction models can be used to estimate more detailed trends in risk, even within a certain risk subgroup.

6.3.1 Strengths and weaknesses of Study III

The strength of this registry-based study is a large and versatile, prospectively collected, dataset. However, the data completeness for revision THA in the FAR is 81% (FAR 2021), meaning that not all revision data are reported regularly to the register.

Even though all the developed models reached moderate to good performance and were able to stratify patients according to predicted risk, it should be noted that some individuals may still be misclassified as high or low risk for different outcomes due to prediction uncertainties. The performance of some models, such as the model for PJI, could still be improved, for example by including comorbid conditions, which were not available here but could be considered in the future when re-evaluating the models with larger amounts of data. Another limitation of the present study was the absence of factors describing surgeon experience, which could substantially reduce variability in the results. It is anticipated that by considering these additional variables and retraining the models with a greater number of operations as more data becomes available, even more accurate risk predictions could be achieved. An important feature that is also still missing is the possibility to evaluate error bounds for the predictions, which could be associated with the models once robust tools become available for evaluating them in Lasso regression.

In the present study, the incompleteness of revision data may have resulted in slight underestimation of the risk of revision compared to true incidence. For these reasons, it would be beneficial to further validate the performance of the developed models in additional patient cohorts.

6.4 Preoperative risk prediction models in primary THA based on the NARA data

In our fourth study, we were able to identify the best-performing ML model for predicting the risk of common early (6 months) adverse outcomes following THA among a range of ML models. Based on the NARA dataset, the most common adverse outcomes following THA were PJI, dislocation, PPF, and death which is in line with previously reported (AOANJRR 2020). When the discrimination performances of the applied ML models were compared with each other, we observed only very small differences between them. Further, it is possible to use simpler models to predict the risk for the outcome of interest without losing prediction accuracy, while effectively reducing the number of required variables in risk prediction models. Hence, these simpler models enable easier preoperative implementation of these simple-to-use risk prediction models in clinical decision-making. Finally, we developed a simple-to-use preoperative risk prediction models based on the Lasso with SIVS procedure, which may assist in clinical decision-making in the future by making estimations about the expected levels of risks preoperatively.

Our main finding in Study IV was that simpler modeling strategies can be used to produce accurate risk predictions despite large amounts of THA register data. The same prediction accuracy as that of the complex models was estimated for models based on the Lasso with SIVS procedure, even though the number of predictors were effectively reduced, leading to substantially simpler models. This implies that complex models which can also involve modeling of deep inter-variable interactions and complex nonlinear relationships may not necessarily be needed when estimating the risks of adverse outcomes following THA based on registry data. Therefore, careful selection of a few variables with simple linear relationships can lead to a capture of the most essential relationships with each outcome of interest. This finding is in line with those of prior studies that developed risk prediction models using the same modeling approach (Venäläinen et al. 2020, Mahmoudian et al. 2021). The use of simpler models for risk predictions also enables the use of simple risk equations, which means that dedicated computer software is not needed, thus the model is more practical. Finally, it is easier for the surgeon to use these models and their results, and with the information obtained communicate effectively with the patient about the expected results of the operation.

The highest discrimination performance in terms of the AUROC was achieved for the model predicting the risk of death within the first 6 postoperative months. This observation was comparable to our results from Study III, with excellent performance for the model predicting risk of death. Advanced age, male sex, preoperative hip fracture, nontraumatic femoral head necrosis, or other unspecified preoperative diagnosis were key variables identified for predicting the risk of death based on the Lasso with SIVS procedure. Prior studies support the selection of these input variables concerning advanced age (Belmont et al. 2014, Dagneaux et al. 2021), male sex (Belmont et al. 2014, Robinson et al. 2017), and hip fracture (Dale et al. 2020).

The discrimination performance in terms of the AUROC for the model predicting the risk of PPF was 0.74, which is substantially better when compared to our Study III with an AUROC of 0.65 for the model predicting the risk of PPF. However, the revision rates for PPF were quite similar in both studies (0.3% and 0.5% for Study IV and Study III, respectively). The development of ML models requires a large amount of data for training of the models, which may be the explanatory factor behind more accurate risk predictions from the PPF model in Study IV. The number of operations was 10 times higher in this study than in Study III and included more cases with cemented stems. Advanced age and preoperative hip fracture diagnosis, nontraumatic femoral head necrosis diagnosis, and use of uncemented, hybrid, and reverse hybrid fixations were identified as key variables for predicting the risk of

PPF in the Lasso with SIVS procedure. The same variables have been associated with the PPF also in previous studies (Franklin and Malchau 2007, Thien et al. 2014, Patsiogiannis et al. 2021, Bloemheuvel et al. 2022).

The model predicting the risk of revision due to dislocation had moderate discrimination performances in terms of the AUROC, which is similar to Study III (Study IV AUROC 0.67 vs. Study III AUROC 0.65). Advanced age, a preoperative diagnosis of hip fracture, uncemented and hybrid fixations, and posterior approach were identified as key variables increasing the risk of dislocation. Similar findings have been reported in prior studies (Hailer et al. 2012, Thoen et al. 2022). A recent study by Thoen et al. reported an increased dislocation risk with the use of uncemented fixation compared to cemented and reverse hybrid fixations. However, there might be some time-dependent confounding due to increased use of uncemented fixation more recently.

In Study IV, a slightly lower discrimination performance in terms of the AUROC compared to Study III was reported for the model predicting the risk of PJI (Study IV AUROC 0.62 vs. Study III AUROC 0.68) and also compared to the risk prediction model developed based on the SHAR (AUROC 0.68) (Bülow et al. 2022). The Lasso with SIVS procedure identified male sex and preoperative hip fracture or diagnosis of nontraumatic femoral head necrosis as increasing the risk of PJI. This is consistent with the findings of prior studies (Bergh et al. 2014, Lenguerrand et al. 2018). Additionally, the model for PJI identified CoC bearings as decreasing the risk of PJI compared to other bearing types. This association has also been reported in earlier studies (Lenguerrand et al. 2018, Madanat et al. 2018). There might be some residual confounding regarding the use of CoC bearings, because this bearing type tends to be used in younger patients with fewer comorbidities.

6.4.1 Strengths and weaknesses of Study IV

Some of the strengths and weaknesses of Study IV are the same as those reported for Study III; for example, not all revision operations are reported to the register and the NARA dataset is not collecting information on more detailed surgeon characteristics like annual number of operations performed. The NARA member countries have reported varying data completeness for revision THAs ranging from 85% to 94% (Mäkelä et al. 2019). Unfortunately, some of the key risk factors for each outcome are not included in the NARA dataset, due to the requirement that all included variables must be able to be delivered by all the participating countries. Prior studies have associated both BMI and ASA classification with infection risk (Kunutsor et al. 2017, Smith et al. 2018). Further, also in Study II an increased risk for PJI was reported for both high BMI and advanced ASA classification. The performance of our models might have been improved, and even simplified, if these had been included in the model predictions of infection revisions. Additionally, ASA classification is a known risk factor for mortality following THA (Belmont et al. 2014). If some of the variables had been replaced with the ASA classification in the model predicting risk of death, it might have led to the development of even more simplified models with improved model performances. As in Study III, the performances of the developed models should in future be externally validated in additional patient cohorts with similar characteristics, despite the large amounts of national register data in both the training and test cohorts.

6.5 Strengths and future perspectives

In the history of THAs, arthroplasty registers have played a major role in improving the results of both primary and revision THAs. New implants and surgical techniques are under continual development. The expansion of new inventions in clinical practice must be done with caution and should be strictly followed. The long-term results of all THA-related factors should be systemically analyzed and reported, for example in the annual reports of arthroplasty registers.

The strength of this thesis is that the data used in all the studies are national, extensive, and versatile. I personally think that all the reported results from the studies can be adapted to use in clinical practice. It is hugely important to be able to identify patients who are at increased risk of developing complications, allowing them to be followed up more intensively and also to inform them to avoid unnecessary things that predisposes them to complications.

The results from Studies I and II strengthen our understanding of the factors that increase, and those that decrease, the risk of dislocation and infection following primary THA. Based on Studies III and IV, we know how the developed risk prediction models perform with the data they were developed from. Therefore, in the future it will be essential to verify the performance of these models with additional patient cohorts whose data can be adapted from various national arthroplasty registers such as the AOANJRR. It will then be possible to produce online risk calculators which are universally available. Variables included in the risk prediction models should also be carefully interpreted i.e. is it possible to change the variables' effect to the outcome. There are some factors that cannot be changed such as sex or age. However, from the surgery method and devices point of view, there are factors which can be affected such as surgical approach and femoral head size.

Hopefully, in the future, the use of risk prediction models will also emerge in clinical orthopedic practice, reducing rates of complication and revision surgery and enabling even better and more precise care for individual patients. Much remains to be done, however, before the risk prediction models developed here can be expanded to predicting the risk of complications for patients universally. Collaboration between national arthroplasty registers will be essential to this end. Further, when the risk prediction models becomes available in the clinical practice, it should be evaluated how these risk prediction models affects to surgeons decision making process concerning the treatment of THA.

7 Conclusions

The current thesis leads to the following conclusions:

1. Posterior approach compared to anterolateral approach, femoral neck fracture compared to OA, and ASA class III-IV compared to ASA class I were associated with an increased dislocation revision risk after primary THA. Whereas, 36 mm femoral head size compared to 32 mm femoral head size was associated with a decreased dislocation revision risk. Special attention should be paid to patients belonging to high-risk groups for dislocation with a diagnosis of femoral neck fracture and ASA classification of III–IV. Additionally, for these patients, the use of the anterolateral approach and 36 mm femoral heads should be considered.

2. We found several modifiable variables that increase or decrease the risk of revision surgery due to PJI following primary THA during the first year after primary THA. Especially patients with a high BMI (31–35 kg/m^2 and >35 kg/m^2) may be at even higher risk of developing infection than previously reported.

3. The most common reasons for the revision operations after primary THA were dislocation, PJI, and PPF. Death was also an important outcome reported after primary THA. Risk prediction models can be used to estimate the risk of revision and death and guide the preoperative decision-making process.

4. Complex modeling strategies are not required to achieve maximum predictive potential of THA register data for predicting the risk of revisions and death. In the future simple-to-use risk prediction models based on Lasso regression and iterative variable selection are a promising approach to clinical risk predictions due to requiring the least amount of variables.

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