1

INTRODUCTION
Osteoarthritis (OA) is a degenerative joint disease involving cartilage, joint lining, ligaments and underlying bone. The reported prevalence of knee OA of patients ≥45 years is 19.2-27.8%, and 37.4% of patients ≥60 years in the United States [26]. OA of the knee that does not respond to conservative treatment, such as non-steroidal anti-inflammatory drugs, weight loss, physiotherapy, and intra-articular corticosteroid injections, can be treated surgically by total knee arthroplasty (TKA) [17]. The goal of TKA is to create a painless, stable, long-lasting, artificial knee joint with a large range of motion to perform the activities of daily life. In the Netherlands, 21,654 primary TKA procedures have been registered in 2013 [15]. It is highly likely that the incidence of TKA will rise in the future [12].

The first designs of the current total knee prostheses (TKP) have been developed forty to fifty years ago. Thereafter, changes have been made in response to problems encountered. The modern TKP consists of a femoral component, a tibial component and a polyethylene insert (Fig. 1). The femoral and tibial components are made of a metal alloy with a high wear resistance, low coefficient of friction and high hardness to reduce wear. Fixation of the femoral and tibial component can be done either cemented with PMMA, or uncemented which requires surface treatment of the prosthesis’ bone-implant interface. An attempt to obtain longer component fixation in younger patients lead to the design of uncemented TKA [5]. The insert is made of ultra-high molecular weight polyethylene (UHMWPE), and can be either a fixed or a mobile bearing. Mobile bearing TKA has been designed to create a dual surface articulation, and to reduce surface and subsurface stress states at the bearing and the bone implant surfaces [10]. The anterior cruciate ligament is usually sacrificed in TKA, but the posterior cruciate ligament can be retained or sacrificed depending on the type of TKA design. The TKA design is often strictly related to the surgical technique, whether the TKP is placed using the collateral ligaments or bone as a reference. All these variables have been subject to alterations to improve the outcome of TKA.

<table>
<thead>
<tr>
<th>Abbreviations</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMMA</td>
<td>poly-methyl-methacrylate</td>
</tr>
<tr>
<td>UHMWPE</td>
<td>ultra-high molecular weight poly-ethylene</td>
</tr>
<tr>
<td>TiN</td>
<td>titanium-nitride coating</td>
</tr>
<tr>
<td>CoCrMo</td>
<td>cobalt-chromium-molybdenum alloy</td>
</tr>
<tr>
<td>TKA</td>
<td>total knee arthroplasty</td>
</tr>
<tr>
<td>TKP</td>
<td>total knee prosthesis</td>
</tr>
<tr>
<td>PSI</td>
<td>patient specific instrumentation</td>
</tr>
<tr>
<td>OKS</td>
<td>Oxford Knee Score</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual Analogue Scale score</td>
</tr>
<tr>
<td>KSS</td>
<td>Knee Society Score</td>
</tr>
<tr>
<td>DKS</td>
<td>DynaPort® Knee Score</td>
</tr>
</tbody>
</table>

Introduction | 9
One of the TKA designs of special interest in this thesis is the Low Contact Stress, LCS, total knee prosthesis by DePuy Orthopaedics (Warsaw, Indiana, USA). This knee system has been introduced in 1977 as the New Jersey Low Contact Stress total knee prosthesis by Buechel and Pappas [19]. The LCS design was the first mobile bearing, tri-compartmental knee system, and was also unique because of a common articulating geometry for the tibia and patella on the distal femoral surface [19]. The LCS Classic has been succeeded by the LCS Universal, while since 2001 the LCS Complete is used. Each version of the LCS has been altered, however the geometry of the LCS system was kept the same. This LCS system showed good results with 94-97% survivorship at 12 years, and survival rates up to 96-98% at 18 years [21]. Since 2014, revision rates of TKP as provided by the manufacturers, are assessed by the Orthopaedic Data Evaluation Panel (ODEP, www.odep.org.uk) according to the National Institute for Health and Care Excellence (NICE, www.nice.org.uk) guidance. The LCS system has the highest ODEP rating (10A) i.e. there is evidence obtained during 10 years which is fully compliant with NICE benchmark and strong evidence.

High long-term survival rates of more than 92% have been documented for TKA with revision for any reason [7, 18, 22, 23]. In the paradigm of disease-centered care, the focus on outcome after TKA has been restricted to complications and survival of the TKP until recently [36]. Since the paradigm shifted to patient-centered care, other outcome parameters became important as well [16]. Besides the clinical rating systems, e.g. the Knee Society Score, and patient-reported outcome measures, e.g. the Knee injury and Osteoarthritis Outcome Score and the Oxford Knee Score, and performance-based outcome measures, e.g. the six-minute-walk-test and the timed-up-and-go-test, are used to assess the outcome of TKA [14, 24]. These outcome measures will be used to determine the success of TKA and to evaluate the quality of care. Therefore, it is important to know how to interpret these outcome measures.
The outcome of several different designs of TKA has been compared [20, 28, 29, 30, 31, 39]. In a review of the literature on roentgen stereophotogrammetric analysis (RSA) studies concerning cemented and uncemented TKA with a follow-up of two years, smaller displacement of the cemented tibial component has been found, compared to the uncemented tibial component [30]. Nonetheless, a greater risk of future aseptic loosening has been documented with the cemented tibial component compared to the uncemented tibial component [30]. Although differences in RSA were observed, there were no differences in functional outcome scores [30]. Further, TKA showed the same functional and clinical results, whether the posterior cruciate ligament was either retained or sacrificed [39]. In a review on the use of a mobile or fixed bearing in posterior cruciate retaining TKA, the use of a mobile bearing showed the same results as the use of a fixed bearing [20]. Designs to improve postoperative knee flexion, the so-called high-flex TKA, showed no benefit over conventional TKA [29, 31]. To improve the outcome of TKA in women, based on the assumption that women have different anatomy of the knee, a gender-specific TKA has been designed [28]. No benefits of the use of gender-specific TKA designs have been shown [31]. Also, the hypothesis of inferior clinical outcome of conventional TKA in women was refuted [28].

To improve the outcome of TKA, modifications in the surgical approach have been made, and the use of computer navigation and patient-specific surgical instruments (PSI) has been explored. The standard approach for TKA is a medial parapatellar arthrotomy, but other approaches have been tried. Various minimal invasive approaches have been compared to the standard approach, but no differences have been observed in perioperative factors, clinical or radiographic outcomes, survivorship, or complication rates [11]. Patients receiving a minimal invasive approach showed a faster recovery of quadriceps muscle function [11]. With the use of computer navigation the alignment of the knee components improves, but it does not result in clinical benefits over conventional TKA [9, 38]. The use of PSI TKA does not improve the mechanical axis as measured with the hip-knee-angle, compared with TKA using conventional instrumentation [1]. Also, there is no difference in clinical outcome between PSI TKA and conventional TKA [1]. The aforementioned alterations to TKA have not resulted in a better clinical outcome compared with conventional TKA. To improve the clinical outcome of TKA other methods should be examined.

Optimization of the tribological aspects, i.e. wear, friction and lubrication of interacting surfaces, of the metal alloy surface of femoral and tibial components might improve clinical outcome. To enhance the tribological aspects of the metal alloy surface as well as the osteoconductive properties of this surface, several ceramic coatings have been developed. Ceramic coatings are inorganic and nonmetallic coatings, and can be applied to the articular surface of the bone-implant surface in case of uncemented TKP. Coating of the bone-implant surface is used to improve the osseointegration of the uncemented components. Bone-implant surface coatings are usually calcium-phosphate-based coatings, such as hydroxyapatite [40]. These coatings likely reduce instability of hydroxyapatite-coated tibial components between the first and second year after implantation, compared, and as opposed to, all other types of tibial implants [40].
Ceramic coatings applied to the articular surface are used to increase hardness, and to reduce wear, and friction on the implant surface [25]. Examples of articular surface ceramic coatings used in orthopaedic implants are chromium-nitride, chromium-carbon-nitride, titanium-nitride, titanium-niobium-nitride, zirconium-nitride, and zirconium-oxide [27, 33, 34, 35]. Most of these ceramic coatings are inert and can also be used on the bone-implant interface of uncemented TKP.

The femoral and tibial components of TKP need to be well fixed to bone to reduce the chance of failure due to aseptic loosening of the TKP. Aseptic TKP loosening is a disabling condition which requires revision surgery [2]. Cemented TKA has been suggested to increase the chance of aseptic loosening with time [32]. Therefore, for young patients, uncemented TKA has been designed with the philosophy that "osseointegrated" components are less susceptible to aseptic loosening [6]. In uncemented TKA, the bone-implant surface is treated to optimize osteoconduction and later osseointegration. After the femoral and tibial component are placed press-fit for short term fixation, the process of osteoconduction starts [3]. First, blood platelets get in contact with the implant and are activated, thereby secreting growth factors that cause migration of osteogenic cells through the blood clot to the implant surface [13]. These osteogenic cells differentiate to osteoblasts and form a collagenous bone matrix in which the osteoblasts are embedded and become osteocytes [13]. The osteocytes are the mechanosensors of bone and regulate bone formation according to the leading mechanical loading of bone [8]. The morphology and alignment of osteocytes influence their mechanosensitivity [4, 37]. Bone and its cells are important in uncemented TKA, because the long term fixation will also depend on cell activity.

**Aim of this thesis**

The aim of this thesis is threefold. First, the effect of TiN-coating is investigated on osteoconduction of CoCrMo implant material, and on the clinical outcome of cementless mobile bearing TKA. Also, the additional value of TiN coating used on orthopaedic implant material in clinical and preclinical studies is explored. Second, the influence of design changes to a cementless mobile bearing TKA on the clinical outcome is assessed as well as the correlation of a patient related outcome measure with pain and performance based functioning after cementless mobile bearing TKA. Third, the relationship between osteopetrotic bone and complications after cementless mobile bearing TKA is studied, and further the role of osteocyte morphology in different bone mineral densities encountered in cementless mobile bearing TKA is explored.
Outline of this thesis

In Chapter 2, an in-vitro study is performed to compare proliferation, differentiation, and cytokine production by mouse osteoblast-like cells seeded on TiN-coated and uncoated cobalt-chromium-molybdenum (CoCrMo) alloy to investigate whether osteoconduction is affected by TiN-coating of CoCrMo.

To examine whether the improved biomechanical properties of the CoCrMo implant material by TiN-coating results in a clinical benefit, a randomized clinical trial is performed to compare the postoperative outcome regarding pain, revision rate, range of motion, swelling and temperature of the knee of TiN-coated CoCrMo uncemented mobile bearing TKP with uncoated CoCrMo TKP in Chapter 3.

Chapter 4 assesses the effects of TiN-coating on orthopaedic implant material on wear and biocompatibility in preclinical studies, and the influence of these effects on the clinical outcome of TiN-coated orthopaedic implants to examine whether TiN-coating of implant material has an additional value in orthopaedics.

Chapter 5 aims to determine the correlation of the OKS, a knee specific self-report questionnaire, with the VAS for pain, the KSS, a clinical rating system and the DKS, a performance based function score to check whether the OKS is equally influenced by pain as performance based function.

In Chapter 6, the 5 year revision rate and midterm clinical performance before and after introduction of a new version of an uncemented mobile bearing TKP is compared to evaluate the consequences of this introduction on the postoperative outcome.

In Chapter 7, bone of patients with different bone mineral densities undergoing TKA is used to determine the differences in 3D morphology of osteocytes and their lacunae which are determinants of the mechanosensitivity of osteocytes.

Chapter 8 shows the problems encountered in a case of an uncemented TKP in a patient with osteosclerotic bone due to autosomal dominant type I osteopetrosis.

Chapter 9 discusses the results of the different studies and concludes on the work presented in this thesis.
References


