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**Title:** Prognostics of outcome of total knee replacement: on patient selection and intraoperative issues
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Chapter 9

Summary and discussion
The number of Total Knee Replacement (TKR) surgeries performed in the Netherlands per year is growing, from about 20,000 in 2010 to about 28,000 in 2016, an increase of 40% (www.lroi.nl). TKR is the end-stage treatment for symptomatic osteoarthritis (OA) of the knee. The performance of orthopedic implants is traditionally measured by a mean survival rate after a certain period of time. Since survival rates for TKR are quite good in general (i.e. mean survival after 10 years is about 90% for the endpoint “revision surgery”), other patient related outcome measures, such as patient satisfaction or quality of life, are becoming increasingly important.1 In chapter 2 long-term patient satisfaction and quality of life (where long term is considered ten years or more after primary surgery) are reported after total knee or hip replacement (THR). Interestingly, patients are less satisfied after TKR (up to 20-25%) than after THR. The latter might be related to the indication for surgery. Patients with little preoperative radiological osteoarthritis of the knee (Kellgren & Lawrence grade 1 or 2) perform in general less compared to patients with more severe radiological OA of the knee. Other factors, like pain sensitization are important to take in consideration too, when indicating for total joint replacement during the shared decision making process with the patient.

This thesis can be divided into two parts; in the first part we analyzed which patient receives a TKR and which patient does not, what is the timing and what is the outcome at patient level. In the second part we studied how to improve the TKR surgery as a procedure; what can be done (or not) to improve TKR treatment.

**Part 1 – on patient selection**

The indication, and thus patient selection, to perform TKR is a major driver for outcome and thus for differences in postoperative patient satisfaction. No clear guidelines exist for the indication of TKR, except the presence of “enough pain”.2 In order to get an idea when TKR is recommended in the Netherlands we performed a study asking all Dutch orthopedic surgeons whether they would perform TKR or not in three different cases (chapter 3). It seemed that radiological OA grade and old age were important factors to recommend TKR in daily clinical practice. For Dutch orthopedic surgeons, pain level as such (according to literature more important than
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In chapter 5 results from the Leiden 85+ study are reported on functional performance of the oldest old patients (i.e. 85 years and older) who had a TKR or THR in the past. The functional level and health status of the oldest old with total joint replacement was comparable with the oldest old patients without joint replacement surgery at twelve years of follow-up.

Osteoarthritis

The development of OA is a complex process, involving genomics, metabolomics and environmental risk factors invoking molecular changes- and structural changes of cartilage and subchondral bone, with subsequent destruction of the joint. Molecular interactions between cartilage, subchondral bone and synovial membrane play an important role in the pathogenesis of OA. Metalloproteases (MMP’s) are believed to play an important role in cartilage degeneration (e.g. MMP-13). Furthermore several pro-inflammatory cytokines (i.e. IL-1β) and cartilage regeneration factors such as tumor growth factor β (TGF-β), insulin-like growth factor (IGF-1) and bone morphogenic proteins (BMPs) are extensively studied for their role in the development of OA. Also other cell types, like mast cells, are suggested to play a role in OA. Another factor contributing to the development of knee OA is overweight, via not entirely clear mechanisms. Limb alignment is also a factor, where valgus alignment increases the odds of lateral progression of OA and varus alignment medial progression. The presence of intra-articular damage in the history of the knee, ranging from isolated meniscal tear to anterior cruciate ligament rupture to major intra-articular knee injuries, contributes to the odds of developing knee OA too.
Resurfacing the knee joint with a TKR is the final step in the treatment of OA of the knee. First, conservative (i.e. non-operative) treatment (like stepped care treatment) should be used exhaustively.\textsuperscript{8,9}

\textit{Disease modifying OA drugs (DMOADs)}

Oral diacerein, an IL-1\(\beta\) inhibitor, showed significant improvement of symptoms in patients with knee or hip OA.\textsuperscript{10} Also an agent like chondroitin sulphate has proved to have DMOAD potential. Several placebo controlled trials showed more radiographic joint space narrowing in placebo users compared to chondroitin sulphate users.\textsuperscript{11,12} Tetracycline analogues, like doxycycline, inhibit some MMPs. A placebo controlled study showed less joint space narrowing in patients who received doxycycline versus placebo.\textsuperscript{13} However it seems that the symptomatic benefit of doxycycline is minimal, while the small benefit in terms of reduction of joint space narrowing is of questionable clinical relevance and outweighed by safety issues.\textsuperscript{14} Other agents, like (oral) bisphosphonates, calcitonin (i.e. second generation calcitonin peptides), strontium, cathepsin K inhibitors, and sprifermin are promising and are currently under investigation in different phases of trials.\textsuperscript{15}

\textit{Clinical relevant OA}

Patients’ main complaint when seeking clinical help for knee OA is pain. Radiographic OA is only weakly associated with pain.\textsuperscript{16} This suggests that other features, such as biochemical, cellular or structural changes, but also pain sensitization are important factors in pain perception.\textsuperscript{17} Although the link between radiological OA and pain is weak, some authors show an association between pain and structural, subchondral bone changes.\textsuperscript{18} Other studies, using contrast enhanced MRI, suggest an association between synovitis and pain.\textsuperscript{19-21} The cause of synovitis is not fully understood.\textsuperscript{17} A connection with nerve growth factor (NGF) has been proposed in the literature.\textsuperscript{22} NGF is identified to mediate in inflammatory joint pain and NGF blocking agents showed pain reduction in patient with knee OA.\textsuperscript{22} Research in this direction can add pain reducing agents to the traditional acetaminophen, NSAIDs and opioids currently in use in the treatment of OA.
Summary and discussion

Resurfacing the knee joint with a TKR is the final step in the treatment of OA of the knee. First, conservative (i.e. non-operative) treatment (like stepped care treatment) should be used exhaustively. Disease modifying OA drugs (DMOADs) Oral diacerein, an IL-1β inhibitor, showed significant improvement of symptoms in patients with knee or hip OA. Also an agent like chondroitin sulphate has proved to have DMOAD potential. Several placebo controlled trials showed more radiographic joint space narrowing in placebo users compared to chondroitin sulphate users. Tetracycline analogues, like doxycycline, inhibit some MMPs. A placebo controlled study showed less joint space narrowing in patients who received doxycycline versus placebo. However it seems that the symptomatic benefit of doxycycline is minimal, while the small benefit in terms of reduction of joint space narrowing is of questionable clinical relevance and outweighed by safety issues. Other agents, like (oral) bisphosphonates, calcitonin (i.e. second generation calcitonin peptides), strontium, cathepsin K inhibitors, and sprifermin are promising and are currently under investigation in different phases of trials.

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Total knee replacement; expectations and satisfaction

Patient satisfaction after TKR is important since its goals is to improve quality of life. In Sweden 17% of over 25,000 patients after primary TKR were dissatisfied or uncertain on their outcome after TKR. Comparable results were found by our group in two cohort studies. This Swedish study showed also that satisfaction was related to the chronicity of the disease; those who suffered longer (e.g. in rheumatoid arthritis) were more satisfied after TKR than those who suffered from knee OA of more recent onset. Also preoperative radiological OA was associated with postoperative satisfaction. The largest risk factor for dissatisfaction are unmet preoperative expectations (Risk Ratio, RR, of 10.8), which is even higher compared to a RR of 1.9 for postoperative complications requiring re-admission to the hospital. Furthermore satisfaction is most strongly associated with improvement of pain scores after TKR. Other studies showed that, despite not all expectations are fulfilled, patients seem to be good to reasonably satisfied after TKR. Recently the ICHOM working group on hip and knee OA defined a ‘Standard Set’ of outcome measures intended for evaluating the treatment of hip and knee OA hereby facilitating international comparisons of treatment and benchmarking on outcome and patient values across health care systems.

Implications for the future

An important part of research in the field of osteoarthritis the coming years will focus on the prevention of OA. The step by step revelation how OA develops and how pain originates from the joint or acts as a centrally modulated entity will be important. Postponing and possibly preventing TKR surgery by conservative treatment options is only feasible if the patient has good functional results with high quality of life. Therapeutic intervention should focus on a combination of pain relief and functional improvement. With the end-goal in future to stop disease progression. For that matter, selective targeting IL-1β drugs are currently one of the most promising OA treatment strategies but many other disease modifying and pain reducing agents are currently being investigated.

Focus should shift away from fixing radiological OA to treating and counseling patients. As part of the patient informed consent procedure on TKR surgery,
assessment of patients’ expectations is important. If a mismatch between expectations of patient and orthopedic surgeon exists, TKR surgery should be postponed and expectations should be managed.

A more uniform approach in the treatment of knee OA will benefit not only research, education and economic analyses in knee OA patients between centers and between countries, but will mainly benefit patient perceived and expected outcome. Tools as the ICHOM Standard Set or the OECD (organization for economic collaboration and development, www.OECD.org) should be used.\textsuperscript{30}

Overall, treatment of knee OA should be more holistic, which means taking the patient and not only the “knee” into account. The latter implies to take also lifestyle interventions, patient education, physical exercises, oral medication, intra-articular injections with steroid derivatives to TKR into account as possible treatment options.

\textbf{Part 2 – on intra-operative issues}

TKR is a rather successful treatment which is routinely performed by orthopedic surgeons worldwide. Several topics to improve TKR still remain under discussion. It has been suggested that topical application of a fibrin sealant (a locally applied hemostatic agent) could be beneficial in terms of reducing hemoglobin loss or the frequency of red blood cell transfusions. In \textbf{chapter 6} results of a large multi-center randomized controlled trial are reported. With current restrictive transfusion protocols, transfusion rates have diminished and are not as important an outcome as before. However it is suggested that after TKR surgery still 650-700 mL blood loss occurs. This volume of blood in the knee can impair postoperative function. In our study primary outcome was knee extension after TKR, this did not differ when fibrin sealant was applied during surgery. Also, when taking into account the use of vacuum drainage no difference in knee extension (or other functional outcomes) was identified.

An ongoing discussion in TKR is whether or not to sacrifice the posterior cruciate ligament (PCL). \textbf{Chapter 7} describes the results from a large systematic review and meta-analysis conducted within the Cochrane framework and published both in a journal and in the Cochrane library for systematic reviews. Because 2,347 knees were included in this analysis the identified mean difference in flexion angle, in favor
of PCL resection, of 2.1 degrees was statistically significant. This difference is clinically not relevant. So it can be concluded that no functional, clinical or radiological differences were found between TKR with or without PCL sacrifice.

After primary TKR or THR a prosthetic joint infection could develop. Hypothermia could raise the risk of infection. Heating the patient by forced-air can disrupt laminar airflow at the operation room (OR), potentially raising the risk of infection. In chapter 8 we aimed to study the occurrence of hypothermia in patients who received active heating or forced-air heating. In this study both warming blankets did not prevent hypothermia during the surgery. Although a difference of 0.2 °C was found between both groups at the end of TKR/THR surgery, we consider this difference not clinically relevant. The complication rate in both groups was the same.

**Surgical issues to consider**

In TKR surgery several issues can be considered, all of them having (strong) advocates and opponents. One of these issues is implant design. Besides the issue of retention or sacrifice the posterior cruciate ligament (as discussed in Chapter 7 of this thesis) another point of debate is the use of a fixed or mobile bearing for the tibial baseplate. Some authors report superior results of one of these bearings, however systematic reviews report no significant differences on a wide range of outcomes for either one of these bearings.31-33

A TKR can be placed either in a measured resection (i.e. bony referenced) or ligament balanced fashion. In both techniques the goal is to match flexion and extension gaps in order to produce a stable and mobile TKR, without resecting too much bone and without altering the joint line to a too great extent.34,35 In a systematic review and meta-analysis comparing both techniques clinical outcomes were reported to be similar, ligament balanced TKR showed slightly more femoral component external rotation and joint line elevation than measured resected TKRs.36

TKR can be placed using computer navigation. During the past twenty years computer navigation has improved (less outliers in alignment or component positioning), became less expensive, faster, but has failed to show improvement in patient reported outcomes in terms of functionality or satisfaction.37-39 It should be noted that, based on experiences in the past, a phased introduction of TKR and TKR
related techniques is important.\textsuperscript{40} Radiostereometric analysis might aid in this process, since it detects within two years whether the implant has good implant-bone fixation, a proxy for late loosening if continuous migration is present.\textsuperscript{41} In line with developments in computer assisted TKR, robotic-assisted TKR is developed. Several systems are on the market with names as Robodoc, Navio, iBlock, MAKO and PiGalileo. Results are promising, safety has improved greatly, yet the use of robotics is still expensive and its benefits have to be proven in studies.\textsuperscript{42,43}

The development of three-dimensional printing technology has enabled the development of patient-specific cutting blocks. Studies show no improvement in clinical and functional outcomes when patient specific instrumentation is used.\textsuperscript{44,45} The cutting block might be of use when extra-articular deformities are present, or when conventional placement is not possible (e.g. presence of osteosynthesis materials or an intramedullary tumor).\textsuperscript{46}

The frequency of red blood cell transfusions after TKR has significantly been decreased recent years.\textsuperscript{47} This is due to a more evidence based restrictive rationale on patient blood management. The use of tranexamic acid, intravenously, peri-operatively, significantly reduces blood loss. Because of the low price of tranexamic acid this intervention is highly cost-effective.\textsuperscript{48,49} Evidence suggest that the either intravenous registration or the topical application of tranexamic acid in TKR surgery yield similar results.\textsuperscript{50}

Using a pneumatic tourniquet and its timing of release during TKR surgery remains a topic of debate. A tourniquet is said to reduce blood loss, facilitate optimal cementation and yield better visualization of the surgical field. However, neuromuscular injuries can occur, as well as postoperative pain, delayed wound healing and increased thrombotic events.\textsuperscript{51,52} Several systematic reviews on the timing of tourniquet release show reduced incidence of wound complications in early tourniquet release compared to late release, no other evident differences are seen.\textsuperscript{52,53}

Peri-operative pain management traditionally consisted of oral medication (acetaminophen, NSAIDs and/or opioids) in combination with spinal and/or epidural anesthetics with adjuncts such as long acting peripheral nerve blocks. These
modalities have multiple side-effects delaying rehabilitation after TKR surgery.\textsuperscript{54,55} Local infiltrative analgesia (LIA) during the TKR surgery is proved to be beneficial in both reducing pain and preventing the aforementioned side-effects.\textsuperscript{56} Several ‘cocktails’ are described, all containing ropivacaine and epinephrine. The solution is injected during several moments of the surgery, within the posterior capsule, the anterior capsule and the subcutaneous layer.\textsuperscript{55}

About two decades ago, first in the USA (Florida), later on in Denmark, the idea of fast track TKR started to spread across parts of the world.\textsuperscript{57} The program consists of patient education, the peroperative use of local infiltrative anesthesia (LIA) instead of postoperative opioids, no drains, standardized physiotherapy and the use of a skilled and dedicated surgical and rehabilitation team. This ultimately can result in daycare surgery for TKR in selected patients.\textsuperscript{57-59} A recent study from Denmark showed that 15\% of unselected TKR and total hip replacement patients can be discharged at the day of surgery.\textsuperscript{60} Although some studies report some a relapse of functional deficit once the patient is home in his or hers own social environment.

Analyzing and evaluating the outcome after TKR and all related issues can be done by clinical studies with respect to functional, clinical and/or radiological outcomes. On the other hand revision rates, infection rates, implant survival can be studied better using data from implant registries.\textsuperscript{61,62} Including PROMS in registry data might yield better understanding of (patient) factors that contribute to pain relief, functional improvement and patient satisfaction.\textsuperscript{63} There is some experience abroad.\textsuperscript{64,65} It is worth mentioning that valuable correlations can be identified using registry data, however confounding should be considered when analyzing these kind of datasets.\textsuperscript{66} An international working group published recommendations for choice of PROMS, survey logistics, timing, reporting missing values and analysis of data.\textsuperscript{67}

\textit{Implications for the future}

Some technical issues in TKR surgery could be left to the surgeons’ preference; whether to sacrifice the posterior cruciate ligament or not, whether to use a fixed or mobile bearing implant and whether to use a measured resection or ligament balanced technique since the surgical technique itself is individualized not only to the
patient but also for a specific surgeon. Orthopedic surgeons should think about the use of a pneumatic tourniquet (preferably not to use a tourniquet) and if still used the timing of release is important. Tranexamic acid should routinely be used perioperatively as well as local infiltrative analgesia (LIA) during surgery if not contraindicated otherwise.

Patient specific instrumentation could have a place in the future when used for strict indications (e.g. extra-articular deformities, intramedullary tumors), but not for routine use. Robotic assisted TKR might have a place in the future of TKR.

Patients should remain within the hospital as long as appropriate. Outpatient TKR on selected on unselected patients should be further evaluated. Both in terms of safety aspects and potential economic benefits.

PROMs need to be recorded in the Dutch registry LROI in order to understand and interpret registry data, but mainly as a quality control tool to monitor performance of the surgical procedure, indication for surgery and outcome. Preferably these data should be benchmarked with colleagues in order to improve outcome for patients. The Dutch Orthopedic Association (NOV), using national registry data (LROI data), has developed a protocol on how to deal with outlier clinical practices (i.e. 1% highest revision rate practices) since 2017. Since TKR is only one small step in the clinical pathway of OA treatment of the lower extremity, which is indicated by data showing that within one year after TKR/THR surgery, about 20% of patients will have severe clinical symptoms of the contralateral knee or hip or ipsilateral hip and are in need for a total joint replacement. Thus, a more holistic approach towards OA as a disease and not as a single joint problem is necessary. For that matter the orthopedic surgeon should have expertise on etiology and conservative treatment modalities in order to recommend optimal management, which can be both pharmacological as well as surgical or using physiotherapy. Only then shared decision making between patient and orthopedist (i.e. who is both surgeon as well as expert in conservative treatment options) is possible.
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