Clinical and Cost-Effectiveness of a Locking Versus Non-Locking Fixation Plate in Medial Opening Wedge High Tibial Osteotomy

Codie Primeau
The University of Western Ontario

Supervisor
Dr. Trevor Birmingham
The University of Western Ontario

Graduate Program in Kinesiology
A thesis submitted in partial fulfillment of the requirements for the degree in Master of Science
© Codie Primeau 2016

Follow this and additional works at: https://ir.lib.uwo.ca/etd

Part of the Orthopedics Commons

Recommended Citation
https://ir.lib.uwo.ca/etd/3986

This Dissertation/Thesis is brought to you for free and open access by Scholarship@Western. It has been accepted for inclusion in Electronic Thesis and Dissertation Repository by an authorized administrator of Scholarship@Western. For more information, please contact wlswadmin@uwo.ca.
Abstract

We investigated the clinical and cost-effectiveness of using a locking versus non-locking fixation plate in medial opening wedge high tibial osteotomy (HTO) for patients with medial compartment knee osteoarthritis. Medical charts were retrospectively reviewed up to 12 months following HTO for 144 patients who received a locking plate and 105 patients who received a non-locking plate. Surgeon notes provided the time to return to full weight-bearing. Participants had completed the Knee injury and Osteoarthritis Outcome Score (KOOS) preoperatively, six and 12 months postoperatively. Hospital and provincial administrative databases provided direct and indirect cost data. Improvements in KOOS scores were similar between groups. The locking plate was more expensive and therefore its use was not cost-effective from the healthcare payer perspective. However, the locking plate enabled statistically shorter time to return to full weight-bearing, translating to a faster return to work, and therefore its use was cost-effective from the societal perspective.

Keywords

Key terms: knee; osteoarthritis; high tibial osteotomy; locking plate; ContourLock; weight-bearing; patient reported outcomes; KOOS; cost-effectiveness; economic analysis
Co-Authorship Statement

Codie Primeau designed this study in collaboration with J. Robert Giffin, MD, Jacquelyn Marsh, PhD and Trevor Birmingham, PhD. Codie Primeau was solely responsible for patient screening and data extraction. He conducted the statistical analyses, interpreted the results and wrote the original draft of the thesis. Drs. Birmingham, Giffin and Marsh reviewed and revised drafts of the thesis. Codie Primeau received funding from the Bone & Joint Institute’s Collaborative Program in Musculoskeletal Health Research to support this project.
Acknowledgments

I would like to thank my supervisors, Drs. Trevor Birmingham, J. Robert Giffin and Jacquelyn Marsh, for their continuous guidance and support through this graduate experience and for contributing to my growth as an independent researcher. I am extremely grateful that you have all gone above and beyond to provide me with the best opportunities to make my graduate studies exceptionally enriching and for preparing me for future endeavors.

I would also like to thank Dr. Rebecca Moyer for her encouragement in the lab and for always being available to provide advice and guidance, along with Mr. Ian Jones for sharing his lab expertise and assistance. Thank you both for providing an extremely positive lab atmosphere and for helping me develop countless skills that I will carry with me in the future.

To my fellow WOBL and FKSMC students, thank you for all of the encouragement and laughs through my graduate studies. I am extremely grateful that we were able to share this experience and you all made it enjoyable for me. I would like to extend a special thank you to Ryan Pinto for always being there to lend a helping hand and for being a great friend.

Cheryl Pollard, Cathy Cuthbert and MarSHA Yerema, thank you all for all of your assistance, support, good company and humor in the clinic.

To the Bone & Joint Institute for providing me with the opportunity to expand my MSK research knowledge and apply this knowledge in a transdisciplinary manner through the Collaborative Program in Musculoskeletal Health Research.

Finally, thank you to my friends and family for their continuous support. Thank you, Mom, Dad & Connor, for always being patient with me and for providing constant words of love, encouragement and motivation. I could not have done any of this without you.
# Table of Contents

Abstract ........................................................................................................................... i  
Co-Authorship Statement ............................................................................................... ii  
Acknowledgments ......................................................................................................... iii  
Table of Contents ......................................................................................................... iv  
List of Tables ................................................................................................................ viii  
List of Figures ............................................................................................................... ix  
List of Appendices ....................................................................................................... xi  
List of Abbreviations ................................................................................................... xii  
Chapter 1 ..................................................................................................................... 1  
  1 Introduction ............................................................................................................... 1  
    1.1 Background & Rationale ..................................................................................... 1  
    1.2 Study Objectives and Hypotheses ................................................................... 5  
    1.3 Review of Literature ......................................................................................... 6  
       1.3.1 Osteoarthritis .............................................................................................. 6  
          1.3.1.1 Epidemiology ..................................................................................... 6  
       1.3.2 Knee Osteoarthritis .................................................................................. 7  
          1.3.2.1 Knee Anatomy .................................................................................... 7  
          1.3.2.2 Pathophysiology ................................................................................ 8  
          1.3.2.3 Etiology ............................................................................................... 8  
          1.3.2.4 Risk Factors for Knee OA ................................................................. 9  
          1.3.2.5 Diagnosis and Clinical Manifestations .......................................... 18  
    1.3.3 Management of medial compartment knee OA ............................................ 19  
    1.3.4 Medial Opening Wedge High Tibial Osteotomy ........................................... 20  
       1.3.4.1 Preoperative Assessment ..................................................................... 22
1.3.4.2 Surgical Procedure................................................................. 23
1.3.4.3 Benefits of Medial Opening Wedge HTO................................. 24
1.3.4.4 Medial Opening Wedge HTO Success........................................ 25
1.3.4.5 Weight-bearing and Return to Work after HTO........................ 25
1.3.4.6 Locking Plate vs. Non-Locking Plate Designs........................... 26
1.3.5 The Arthrex ContourLock HTO Plate®........................................ 28
1.3.6 Health Economics .................................................................... 31
  1.3.6.1 Economic Evaluation............................................................ 31
  1.3.6.2 Economic Burden of Osteoarthritis....................................... 31
Chapter 2 ......................................................................................... 34
  2 Methods ....................................................................................... 34
    2.1 Study Design............................................................................ 34
    2.2 Eligibility Criteria..................................................................... 34
    2.3 Intervention.............................................................................. 35
      2.3.1 Operative Procedure........................................................... 35
      2.3.2 Post-operative Care............................................................ 35
    2.4 Radiographic Assessment.......................................................... 36
    2.5 Outcome Measures................................................................... 37
      2.5.1 Return to full weight-bearing................................................. 37
      2.5.2 Knee injury and Osteoarthritis Outcome Score........................ 38
      2.5.3 Cost.................................................................................... 39
        2.5.3.1 Surgical Costs............................................................... 39
        2.5.3.2 Healthcare Resource Use.............................................. 39
    2.6 Data Analysis............................................................................ 41
      2.6.1 Objective 1........................................................................ 41
      2.6.2 Objective 2........................................................................ 41
2.6.3 Objective 3 ........................................................................................................ 42
    2.6.3.1 Economic Analysis .................................................................................. 42
    2.6.3.2 Incremental Cost-Effectiveness Ratio .................................................... 42
    2.6.3.3 Net Benefit Regression .......................................................................... 42
    2.6.3.4 Uncertainty .......................................................................................... 43
    2.6.3.5 Sensitivity Analysis .............................................................................. 44

2.6.4 Missing Data .................................................................................................. 44

Chapter 3 .................................................................................................................. 45

3 Results ..................................................................................................................... 45
    3.1 Patient Flow ..................................................................................................... 45
    3.2 Demographics and Clinical Characteristics .................................................. 47
    3.3 Surgical Characteristics .................................................................................. 49
    3.4 Surgical and Post-operative Complications ................................................. 50

3.5 Outcome Measures ............................................................................................. 51
    3.5.1 Objective 1 ............................................................................................... 51
    3.5.2 Objective 2 ............................................................................................... 51
    3.5.3 Objective 3 ............................................................................................... 55
        3.5.3.1 ICER .................................................................................................. 55
        3.5.3.2 Net Benefit Regression ..................................................................... 55
        3.5.3.3 Sensitivity Analysis .......................................................................... 59

Chapter 4 ..................................................................................................................... 63

4 Discussion ............................................................................................................... 63
    4.1 Strengths & Limitations ............................................................................... 68

Chapter 5 ..................................................................................................................... 72

5 Conclusion ............................................................................................................... 72
    5.1 Future Directions ........................................................................................... 72
References .................................................................................................................. 74
Appendices .................................................................................................................. 95
Curriculum Vitae ........................................................................................................ 96
List of Tables

Table 1: Ideal patient criteria for a medial opening wedge HTO. ........................................ 22

Table 2: Baseline demographics and clinical characteristics (n = 249)................................. 48

Table 3: Adverse event rates within first 12 months after HTO (n = 249)............................. 50

Table 4: Time to return to weight-bearing and patient reported outcome measures (KOOS) for all patients (n = 244)........................................................................................................... 52

Table 5: Cost and effect outcomes.............................................................................................. 57

Table 6: Net benefit regression results.......................................................................................... 57

Table 7: Sensitivity analyses cost and effect outcomes.............................................................. 60

Table 8: Sensitivity analyses net benefit regression results......................................................... 61
List of Figures

Figure 1: Schematic representation of the interacting systemic (biochemical) and local (biomechanical) risk factors that are associated with the development of knee OA and progression of the disease. Also presented are the radiographic and clinical criteria used to diagnose knee OA according to Kellgren and Lawrence, 1957 and Altman et al., 1986. 11

Figure 2: A) The mechanical axis angle (MAA) of the lower limb is measured as the angle between the line connecting the center of the hip and knee joints and the line connecting the center of the knee and ankle joints. B) The weight-bearing line (WBL) is drawn from the center of the hip joint to the center of the ankle joint. 13

Figure 3: The “vicious cycle” of medial compartment knee osteoarthritis. Varus alignment leads to excess loading on the medial compartment, promotes articular cartilage breakdown, narrowing of medial joint space and further malalignment of the joint. 15

Figure 4: The external knee adduction moment (KAM) about the knee is the product of the perpendicular distance between the knee joint center and the ground reaction force (GRF) vector in the front plane, forming the lever arm, and the magnitude of the GRF vector. Figure adapted from Perry J Gait Analysis: Normal and Pathological Function 1992. 17

Figure 5: Patient radiographs (A) before and (B) 12 months after HTO surgery. The yellow lines provide an estimate of the weight-bearing line (WBL) to display the shift to a more neutral position. 21

Figure 6: A) The Arthrex ContourLock HTO Plate® design (Arthrex, Naples, FL) possesses a wide frame which lengthens the distance between fixation screws and provides additional stability. B) & C) Top and side views of the Arthrex ContourLock HTO Plate® illustrate the anatomically curved body of the implant. 29

Figure 7: Participant flow through the study. Asterisk represents a smaller sample size for the cost-effectiveness analysis from the societal perspective (n = 106 locking plate, n = 58 non-locking plate). 46
Figure 8: Mean time to return to full weight-bearing with complete discontinuation of gait aid use (in weeks with 95% confidence intervals) for patients undergoing a medial opening wedge high tibial osteotomy with a locking or non-locking internal fixation plate. Stars indicate a significant difference.

Figure 9: Mean Knee injury and Osteoarthritis Outcome Score (KOOS) total and subdomain change scores from baseline to six months postoperative (with 95% confidence intervals) for patients undergoing a medial opening wedge high tibial osteotomy with a locking or non-locking internal fixation plate.

Figure 10: Cost-effectiveness acceptability curves (CEAC) displaying the probability that the locking plate is cost-effective compared to the non-locking plate from A) the healthcare payer’s perspective and B) the societal perspective, over a range of willingness to pay values for an additional one-point improvement in the Knee injury and Osteoarthritis Outcome Score total change score (baseline to 12 months).

Figure 11: Sensitivity analysis cost-effectiveness acceptability curves (CEAC) displaying the probability that the locking plate is cost-effective compared to the non-locking plate from the societal perspective over a range of willingness to pay values for an additional one-point improvement in the Knee injury and Osteoarthritis Outcome Score total change score (baseline to 12 months). A) Adjusting the dollar value for retirement or home making time, B) Adjusting the time to return to work, C) Combining the two previous adjustments.
List of Appendices

Appendix A: Ethics Approval.................................................................................................................. 95
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADL</td>
<td>Activities of Daily Living</td>
</tr>
<tr>
<td>ACL</td>
<td>Anterior Cruciate Ligament</td>
</tr>
<tr>
<td>AP</td>
<td>Anteroposterior</td>
</tr>
<tr>
<td>ASA</td>
<td>American Society of Anesthesiologists</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>CEAC</td>
<td>Cost-effectiveness Acceptability Curve</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>HTO</td>
<td>High Tibial Osteotomy</td>
</tr>
<tr>
<td>ICER</td>
<td>Incremental Cost-effectiveness Ratio</td>
</tr>
<tr>
<td>INB</td>
<td>Incremental Net Benefit</td>
</tr>
<tr>
<td>KL</td>
<td>Kellgren-Lawrence (grading of OA severity)</td>
</tr>
<tr>
<td>KOOS</td>
<td>Knee injury and Osteoarthritis Outcome Score</td>
</tr>
<tr>
<td>MAA</td>
<td>Mechanical Axis Angle</td>
</tr>
<tr>
<td>NBR</td>
<td>Net Benefit Regression</td>
</tr>
<tr>
<td>OA</td>
<td>Osteoarthritis</td>
</tr>
<tr>
<td>PCL</td>
<td>Posterior Cruciate Ligament</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>TKA</td>
<td>Total Knee Arthroplasty</td>
</tr>
<tr>
<td>UKA</td>
<td>Unicompartmental Knee Arthroplasty</td>
</tr>
<tr>
<td>WBL</td>
<td>Weight-bearing Line</td>
</tr>
<tr>
<td>WTP</td>
<td>Willingness-to-pay</td>
</tr>
</tbody>
</table>
Chapter 1

1 Introduction

1.1 Background & Rationale

Osteoarthritis (OA) is a common degenerative health condition and a leading cause of pain, disability and reduced quality of life in adult populations worldwide\(^1\). As a chronic condition, the symptoms of the disease can persist for decades, resulting in substantial economic burden to healthcare systems. In Canada, arthritis accounted for $6.4 billion of direct and indirect healthcare costs in the year 2000, OA being responsible for the majority of these costs\(^2\). These costs are expected to continue to grow with the aging population and the rising rate of obesity\(^3\). Therefore, the identification of cost-effective treatments for OA is of utmost concern for public health strategists\(^2\).

Osteoarthritis commonly involves the knee, with an estimated 250 million people currently affected globally\(^4\). Although there is no known cure for knee OA, there are several identified risk factors for knee OA progression that form the targets of various interventions\(^5–8\). Varus alignment of the lower limb is a particularly strong risk factor for the progression of knee OA due to its effect on loading the medial tibiofemoral compartment\(^9–13\). Surgical and non-surgical treatments aimed at altering loads on the medial tibiofemoral compartment are therefore common\(^14–17\).

Medial opening wedge high tibial osteotomy (HTO) is a surgical realignment procedure for patients with varus malalignment and OA of the medial compartment of the tibiofemoral joint\(^15,18,19\). The goals of HTO are to correct lower limb malalignment, redistribute loads laterally across the knee to lessen the compressive force on the diseased medial compartment, and thereby improve pain and function. The medial opening wedge technique requires cutting into the medial proximal tibia, wedging the bone open to a predetermined correction size to correct the malalignment, and securing the osteotomy with a fixation device\(^18,20,21\).
Adequate fixation of the osteotomy, typically achieved using an internal fixation plate, is vital for bone healing and recovery during rehabilitation\(^{22,23}\), that involves progressive weight-bearing using ambulatory aids (i.e. crutches, canes, etc.). The patient’s weight-bearing status is progressed based on postoperative assessments of radiographic bone healing and pain. The suggested duration of return to full weight-bearing after medial opening wedge HTO ranges from 2 to 12 weeks, and highly depends on the type of fixation used\(^{24-30}\).

HTO fixation plates are similar to those used for fracture fixation and can generally be categorized as non-locking and locking. The mechanical principles are quite different for non-locking and locking plates, providing distinct mechanical environments for bone healing. Non-locking plates rely on bone-plate compression and high friction at the bone-plate interface to provide fracture site stability\(^{31}\). At higher loads, however, non-locking screws that are drilled into the bone can begin to loosen. This reduces bone-plate friction, may render the plate unstable and increases the risk of complications such as hardware failure, delayed union, non-union and loss of correction\(^{32}\). Locking plate designs address mechanical issues with threaded fixed-angle screws or interference washers that control the axial rotation between the screw and the plate, and eliminate screw-plate-bone motion\(^{33}\). The mechanism does not rely on high friction at the bone-plate interface, but rather maintains stability at the angular-stable screw-plate interface\(^{31}\). Locking plates also convert shear stresses to compressive stresses, improving fixation since bone has a stronger resistance to compressive stress compared to shear. The mechanical advantages of locking plates provide stronger implant stability and resistance to higher load-bearing, and are therefore suggested to be advantageous for healing after medial opening wedge HTO\(^{23,34}\).

\textit{In vitro} biomechanical studies have suggest that locking plates do provide greater mechanical stability in response to compression and torsion\(^{35,36}\). Clinical studies suggest locking plates maintain the osteotomy correction size better than non-locking plates\(^{37,38}\), provide faster improvements in patient-important outcomes\(^{37,38}\), enable faster time to
achieve bone healing\textsuperscript{37} and earlier return to full weight-bearing after surgery\textsuperscript{37,39,40}. Although results are mixed, some studies also suggest that the rates of delayed and non-union\textsuperscript{22,38}, loss of correction and hardware failure have decreased since the introduction of locking plates\textsuperscript{41}.

The Arthrex ContourLock HTO Plate\textsuperscript{®} (ContourLock) is a relatively new locking plate designed to enable a precise fit proximally and distally on the tibia. The locking plate is proposed to provide advantages when compared to the commonly used non-locking Arthrex Puddu Plate\textsuperscript{®} (Puddu). \textit{In-vitro} biomechanical studies suggest the locking plate provides greater stability under high physiological stress loading and cyclical testing when compared to other locking and non-locking plates due to the wider distance between its fixed-angle screws\textsuperscript{42,43}. Although the greater stability is proposed to permit faster recovery after surgery, there is currently no study evaluating clinical outcomes after HTO using the plate.

The cost associated with using different HTO fixation plates is another important consideration. Costs of HTO include direct (healthcare resources consumed and out-of-pocket expenses) and indirect (time and productivity losses) costs. If locking plates can limit the number of postoperative complications that require revision surgery (i.e. non-union), locking plates could provide direct cost savings. Additionally, if locking plates enable quicker return to weight-bearing, patients could also return to work sooner, thus financially benefiting society with indirect cost savings from productivity. Alternatively, the cost of locking plates are substantially greater than non-locking plates because of their more complex design and number of screws (typically six or more, compared to four) used to achieve fixation. If clinical results are similar regardless of plate design then the extra costs of locking plates may not be warranted. Furthermore, the relative bulkiness of locking plates may cause irritation to the patients and require the plate to be surgically removed\textsuperscript{40,44} which can increase direct costs associated with the procedure. Importantly, the cost-effectiveness of different HTO fixation plate designs is currently unknown and requires research. Therefore the purpose of the present study is to compare
the clinical and cost-effectiveness of a locking plate (i.e., Arthrex ContourLock HTO Plate®) versus a non-locking plate (i.e., Arthrex Puddu Plate®) used for medial opening wedge HTO. Specific objective and hypotheses are listed below.
1.2 Study Objectives and Hypotheses

1. To compare the time to return to full weight-bearing following medial opening wedge HTO in patients receiving a locking versus non-locking fixation plate. 
   *Hypothesis:* Patients receiving the locking plate will return to full weight-bearing sooner postoperatively.

2. To compare the change in patient-reported outcomes (Knee injury and Osteoarthritis Outcome Score – KOOS) following a medial opening wedge HTO in patients receiving a locking versus non-locking fixation plate. 
   *Hypothesis:* Patients receiving the locking plate will experience greater improvements in patient-reported outcomes from baseline to 6 months after the surgery.

3. To estimate the cost-effectiveness of a locking plate compared to a non-locking plate, from the healthcare payer (Ministry of Health) and societal perspectives, using change in KOOS total score at 12 months postoperative as the measure of effectiveness. 
   *Hypothesis:* The locking plate will be cost-effective compared to the non-locking plate from both the healthcare payer and societal perspectives.
1.3 Review of Literature

1.3.1 Osteoarthritis

Osteoarthritis (OA) is the most common form of arthritis and is rapidly becoming one of the most disabling health conditions worldwide\textsuperscript{4,45–47}. It is a chronic musculoskeletal disease that can affect single or multiple joints, and is characterized by localized joint pain, functional limitations and diminished quality of life\textsuperscript{1,48}. In Canada, there are more than 4.4 million people (1 in 8) living with OA and this number is projected to double by the year of 2040 due to the aging population and the obesity epidemic\textsuperscript{49}.

1.3.1.1 Epidemiology

According to the 2013 Global Burden of Disease (GBD) study, the prevalence of OA has grown 72\% from the year 1990 with approximately 240 million people burdened by the disease worldwide\textsuperscript{4}. The chronic nature of OA also makes it one of the fastest growing health conditions in terms of disability\textsuperscript{46}. It accounted for more than 17 million years living with disability (YLDs) globally in 2010, a 64\% increase from the year of 1990\textsuperscript{50}. The World Health Organization (WHO) projects OA to become the fourth leading cause of disability worldwide by the year 2020\textsuperscript{51}.

The disease is not isolated to a specific population group, but affects people of various ethnic backgrounds and in different geographical locations worldwide\textsuperscript{52}. Although OA can be seen in people as young as 15 years of age, the majority of people affected by the disease are older individuals\textsuperscript{3,53} with women being affected approximately twice as often as men\textsuperscript{48}.
1.3.2 Knee Osteoarthritis

OA develops more frequently in the knee than any other weight-bearing joint in the body\textsuperscript{54–56} with over 10\% of the adult population currently affected by symptomatic knee OA\textsuperscript{49}. Due to the high loading demands on the joint, knee OA specifically is considered one of the leading causes of physical disability worldwide\textsuperscript{57,58}. The lifetime risk of developing knee OA is estimated to be 45\% (47\% in women, 40\% in men) with increased odds seen in those who possess predisposing risk factors for the disease such as obesity and malalignment, among others\textsuperscript{59}.

1.3.2.1 Knee Anatomy

The knee is a complex synovial hinge joint between the patella, the distal femur and the proximal tibia\textsuperscript{60}. The bone surfaces are lined with hyaline (articular) cartilage which aids in dissipating forces within the joint and limiting friction between bones. The cartilage tissue is not innervated by pain receptors, nor is it well vascularized which limits the tissue’s ability to repair itself\textsuperscript{61}. Aside from the surfaces concealed by articular cartilage, the inner lining of the joint is covered by a layer of connective tissue called the synovial membrane, or synovium. Its cells secrete synovial fluid, a viscous substance which reduces the level of friction within the joint space and provides nutrients to surrounding tissues whose supply of blood is poor, such as the menisci. There is a meniscus for each knee compartment (medial and lateral) between the articulating surfaces of the femur and the tibia. Their function is to assist with force dissipation from within the joint, improve knee joint stability and help lubricate the knee joint. Knee support is also maintained by various muscles and ligaments. The surrounding networks of muscle are important for assisting with shock absorption and initiation of movement about the knee. Ligaments are arranged in a manner that provides stability mediolaterally (collateral ligaments) and anteroposteriorly (cruciate ligaments) to the knee joint.
1.3.2.2 Pathophysiology

Knee OA is a degenerative condition that affects the various tissues of the joint and is considered a whole-joint disease\textsuperscript{62}. It is characterized by the disruption of the natural cartilage remodeling process, ultimately leading to the fibrillation and softening of the articular cartilage and intensified degeneration of the tissue\textsuperscript{63}. As cartilage continues to breakdown, subchondral bone becomes exposed within the joint resulting in bone-on-bone articulation. Continuous friction between exposed bone leads to the development of osteophytes and subchondral cysts at the articulating bone extremities due to excessive bone remodeling\textsuperscript{48,64}. In later stages of the disease, the subchondral bone tissue will begin to thicken and become sclerotic. Additionally, it is common to see inflammation of the synovial lining of the joint\textsuperscript{46} as well of the overproduction of several proteolytic enzymes and cytokines that have been shown to promote cartilage degradation and breakdown of the extracellular matrix of the joint. These intra-articular changes and inflammatory responses ultimately lead to loss of joint space, destabilization of the joint, abnormal joint loading and a number of clinical symptoms for the affected individual.

1.3.2.3 Etiology

Similar to OA in other joints of the body, knee OA is a complex condition. The initial onset of the disease can be idiopathic in nature, developing naturally over time as a result of various interacting risk factors (known as primary OA), or can develop following excessive or repetitive trauma to the knee joint such as ligament tears, cartilage impact, etc. (known as secondary OA)\textsuperscript{47}. There are still quite a few uncertainties that surround the etiology of the disease. Knee OA is unpredictable in its method of initiation and its progression, with some individuals exhibiting mild degeneration of the joint sustained over an extended period of time, while others progress in disease severity very rapidly. The medial compartment is the most commonly affected area of the joint when compared to other compartments of the knee\textsuperscript{5,65–67}. The disease does not affect the entire joint uniformly.
1.3.2.4 Risk Factors for Knee OA

As a disease whose onset and progression is quite variable, it is important to better understand the multiple risk factors that predispose individuals to developing knee OA and accelerate the progression of the disease. These risk factors can act systemically or can be considered local by acting directly on the joint itself (Figure 1).

Systemic risk factors have a biochemical influence on the knee joint. These factors can cause direct damage to the joint tissues or limit the tissue’s ability to repair itself after being damaged, both of which make the affected individual susceptible to further injury. Systemic risk factors that have been associated with development of knee OA and its progression include age\textsuperscript{46,47}, genetics\textsuperscript{46,47,62}, gender\textsuperscript{6,46,62,68}, overweight/obesity (BMI \(\geq 25\))\textsuperscript{69,70}, nutritional deficiencies\textsuperscript{71,72}, inactivity\textsuperscript{72,73} and elevated bone mineral density\textsuperscript{74,75}.

Local risk factors influence the joint mechanically. These factors are associated with exposure to joint injury or excessive joint loading that leads to degeneration of tissues. Local risk factors that have been associated with development of knee OA and its progression include knee malalignment\textsuperscript{10,55,76,77}, congenital deformities of the joint\textsuperscript{78}, previous injuries to the tissue components of the joint\textsuperscript{6,62,79,80}, overweight/obesity (BMI \(\geq 25\))\textsuperscript{81–83}, occupation\textsuperscript{62,79,84}, muscle weakness\textsuperscript{85,86}, elevated peak knee adduction moment\textsuperscript{9–11,87,88}, elevated knee adduction impulse\textsuperscript{89}, and varus thrust\textsuperscript{90}.

Although risk factors have been shown to independently promote knee OA disease progression, the risks are intensified as individuals are exposed to multiple risk factors simultaneously. For example, mechanical varus alignment of the lower limb has been shown to increase the risk of medial compartment OA progression by a fourfold\textsuperscript{10,76} as a result of increased mechanical axial loading on the joint past a normal physiological range to maintain proper cartilage function. In overweight and obese individuals, the sheer excess weight increases this level of mechanical loading of the medial compartment leading to further articular cartilage breakdown. Various studies have suggested there is an interaction between lower limb alignment and obesity\textsuperscript{5,7}. Moreover, associated
symptoms of pain resulting from knee OA can promote immobility and sedentary lifestyles, risk factors for obesity, which can lead to further progression of OA as the individual’s weight increases. For this reason, it is in the individual’s best interest to tackle as many potential risk factors that are modifiable to minimize the risk of developing knee OA or slow down disease progression.
Figure 1: Schematic representation of the interacting systemic (biochemical) and local (biomechanical) risk factors that are associated with the development of knee OA and progression of the disease. Also presented are the radiographic and clinical criteria used to diagnose knee OA according to Kellgren and Lawrence, 1957 and Altman et al., 1986.
1.3.2.4.1 Varus Alignment

Lower limb alignment is typically determined using full-limb standing hip-knee-ankle (HKA) anteroposterior (AP) radiographs. The gold standard measure of lower limb alignment is the mechanical axis angle (MAA), defined as the angle formed between the line connecting the femoral head center of the hip and the knee joint center and the line connecting the knee joint center and the ankle joint center\textsuperscript{91,92} (Figure 2). It has been shown to provide excellent reliability when measured with digital software programs\textsuperscript{93,94}. 
Figure 2: A) The mechanical axis angle (MAA) of the lower limb is measured as the angle between the line connecting the center of the hip and knee joints and the line connecting the center of the knee and ankle joints. B) The weight-bearing line (WBL) is drawn from the center of the hip joint to the center of the ankle joint.
Based on the MAA measure, lower limb alignment can be assessed to identify patients with varus (“bow-legged”) or valgus (“knock-kneed”) alignment. Individuals with an inward angulation of the distal segment of the lower limb (tibia and fibula) and a negative MAA are considered varus aligned, while those with an outward angulation and a positive MAA are considered valgus aligned. Many epidemiological studies suggest that lower limb malalignment is an important risk factor for knee OA progression\textsuperscript{5,55,76,95,96} and that the direction of this malalignment will affect which compartment of the knee joint is most affected. Medial compartment knee OA is most often seen in individuals with varus alignment, whereas lateral compartment knee OA is more commonly seen in individuals with valgus alignment\textsuperscript{55,76,97,98}.

The role alignment plays in the degenerative process of medial knee OA is related to increased loading of the knee joint\textsuperscript{10,96,99}. The distribution of loading within the joint is related to the lower limb weight-bearing line (WBL), a line drawn from the center of the femoral head to the center of the ankle (Figure 2). Individuals who are neutrally aligned will bear 75\% of the overall knee load in the medial compartment while standing on one leg\textsuperscript{91} with a WBL passing through the medial compartment of the joint. As alignment steers away from neutral and the WBL is shifted medially, the load distribution within the knee joint will undergo aberrant changes. Individuals with varus alignment will experience an increase in medial compartment loading\textsuperscript{9,91,100}. This in turn, will lead to a heightened degree of articular cartilage degeneration. In fact, a longitudinal study found that for every additional 1 degree of varus, patients will lose 17.7\(\mu\)l of femoral articular cartilage on average annually, with similar losses seen in the tibial cartilage volume\textsuperscript{97}.

Overall, the increase in compartmental loading associated with varus alignment promotes progression of medial compartment knee OA. The additional loading intensifies medial articular degeneration and loss which results in medial joint space narrowing, a further degree of varus alignment and additional loading in the medial compartment, creating a vicious cycle of medial compartment knee OA progression (Figure 3).
Figure 3: The “vicious cycle” of medial compartment knee osteoarthritis. Varus alignment leads to excess loading on the medial compartment, promotes articular cartilage breakdown, narrowing of medial joint space and further malalignment of the joint.
1.3.2.4.2 Gait and Knee Osteoarthritis

For the general population, one of the most common daily activities performed is walking, with thousands of steps taken per day\textsuperscript{101}. Three-dimensional (3D) motion analysis of gait kinematics and kinetics has been used extensively in the literature to better understand biomechanical factors associated with knee OA. Specifically, authors have investigated the role of the external knee adduction moment (KAM) (Figure 4) on increased loading of the medial compartment\textsuperscript{10,102,103}. During stance phase of gait, individuals will generate a ground reaction force (GRF) vector that projects upwards and medial to the knee joint’s center of rotation. The perpendicular line that connects the GRF to the knee joint center is known as the lever arm and the product of this lever arm and the GRF vector generates what is known as the external KAM. The external KAM creates a torque force that causes the tibia to adduct in relation to the femur, which results in greater compressive loading to the medial compartment of the joint. As the GRF is projected more medially, the lever arm grows longer and thus, increases the magnitude of the external KAM suggesting that the increase in external KAM is also related to alignment. Halder at al. suggest that the magnitude of medial compartment loading increases 5\% for every 1 degree increase in varus while walking\textsuperscript{104}.

Several studies have shown that the external KAM is strongly associated with characteristics of knee OA such as knee pain in previously asymptomatic knees\textsuperscript{88} and measures of OA disease severity\textsuperscript{87,105}. It has also been proven to be a reliable, valid and clinically meaningful proxy measure of medial compartment loading during gait\textsuperscript{9,106,107} and more importantly, a predictor for OA disease progression\textsuperscript{10,89}. Thus, treatment strategies have been geared towards decreasing the magnitude of external KAM during walking in an attempt to slow disease progression.
Figure 4: The external knee adduction moment (KAM) about the knee is the product of the perpendicular distance between the knee joint center and the ground reaction force (GRF) vector in the front plane, forming the lever arm, and the magnitude of the GRF vector. Figure adapted from Perry J *Gait Analysis: Normal and Pathological Function* 1992.
1.3.2.5 Diagnosis and Clinical Manifestations

Knee OA can develop in one or more of the three knee joint compartments: the medial tibiofemoral joint, the lateral tibiofemoral joint or the patellofemoral joint. Clinicians will use both clinical and radiographic assessment to diagnose patients with knee OA. Often, clinical assessment follows the guidelines set by Altman et al.\textsuperscript{109}, while radiographic assessment follows the criteria set by Kellgren and Lawrence\textsuperscript{110} (Figure 1). According to Altman et al., the required clinical criteria to diagnose a patient with knee OA includes knee pain, as well as one of the following; crepitus (popping sound/sensation or cracking) of the joint, over 50 years of age, or morning stiffness that lasts no longer than 30 minutes. For radiographic assessment, Kellgren and Lawrence developed a four point joint degeneration rating scale (1 = mild OA, 4 = severe OA) to assess OA disease severity in the knee joint by evaluating the presence or absence of osteophytic bone, sclerosis of subchondral bone and whether marked joint space narrowing is present on anteroposterior radiographs. Lateral and skyline radiographic views can also be helpful in confirming compartment disease severity\textsuperscript{111}.

Patients diagnosed with knee OA can exhibit a number of clinical symptoms which include recurrent joint pain (frequently activity-induced and persistent), stiffness, and swelling, reduced function, reduced range of motion, crepitus and deformity\textsuperscript{109,112}. Often, these symptoms will limit individuals and restrict participation in their daily activities\textsuperscript{113} and often makes them more dependent on others when it comes to walking, climbing stairs and performing lower extremity activities. Therefore, it is of utmost importance to identify treatment interventions that are geared towards minimizing pain, symptoms and function for patients with knee OA.
1.3.3 Management of medial compartment knee OA

Currently, there is no established cure for OA. However, a number of treatment modalities are available to aid patients in the management of associated pain and symptoms. Clinical guidelines outline non-surgical and surgical treatment interventions for patients with symptomatic knee OA\textsuperscript{1,114}. Available non-surgical interventions include physiotherapy, pharmacotherapy, foot orthoses, bracing, lifestyle modifications and activity management. These modalities typically target symptom management, but do not alter joint anatomy and benefits are not considered to be permanent. Surgical interventions include high tibial osteotomy (HTO), unicompartmental knee arthroplasty (UKA) and total knee arthroplasty (TKA). These modalities physically alter joint bony structures with permanent anatomical changes which modify risk factors that promote knee OA disease progression such as knee malalignment. Ultimately, selection of management method is decided upon mutually between the clinician and the patient based on the patient’s personal characteristics, physical functional limitations, symptom severity and the current level of disease severity.

For patients in earlier stages of the disease, clinicians typically attempt non-surgical interventions before opting for surgery. However, patients who are at more progressed stages of the disease often display substantial mobility restrictions, severe pain, decreases in quality of life and severe degenerative changes in a single or multiple compartments of the knee warranting a referral to an orthopaedic surgeon. The surgeon may recommend a UKA or a TKA to replace the articular components of the joint or the surgeon may recommend a HTO to correct malalignment of the lower limb, a risk factor for progression of OA, while preserving the components of the joint. All three surgical procedures have shown evidence of long-term benefits for pain management, improved quality of life and mobility, but differ in terms of recovery time, invasiveness, potential adverse events, limitations in activity participation following surgery and costs associated with the procedures\textsuperscript{115–119}. Thus, selection of the appropriate surgical intervention must be done carefully in order to maximize the probability of successful outcomes following surgery.
1.3.4 Medial Opening Wedge High Tibial Osteotomy

Medial opening-wedge high tibial osteotomy is a surgical treatment for patients with varus alignment of the lower limb and medial compartment knee OA\textsuperscript{15,19,20,120}. The procedure corrects knee malalignment by shifting the weight-bearing load of the joint laterally to a more neutral position (usually slight valgus) and away from the affected portion of the knee (Figure 5)\textsuperscript{121}. The redistribution of load decreases the magnitude of both static (standing) and dynamic (during walking) loading in the medial compartment with the goal of relieving patient symptoms and slowing the progression of the disease\textsuperscript{95,122}. 
Figure 5: Patient radiographs (A) before and (B) 12 months after HTO surgery. The yellow lines provide an estimate of the weight-bearing line (WBL) to display the shift to a more neutral position.
1.3.4.1 Preoperative Assessment

Similar to consideration in other surgical procedures, surgeons take a thorough patient history that identifies previous lower limb injuries or comorbidities that would contraindicate the patient from undergoing surgery and help ensure patient compliance during the post-operative period. A physical examination is then conducted to identify ligamentous instabilities of the joint and to provide additional information to aid the surgeon in establishing an appropriate treatment plan. Previous authors suggest the surgery is ideally performed on healthy young, active patients, where the level of joint degeneration is isolated to the medial compartment with associated varus alignment as determined by the mechanical axis angle\textsuperscript{19,111,121}. It is usually recommended to patients whose activities of daily living are typically more physically demanding. Inactive patients with tricompartmental disease, have complaints of rest/night pain and those who are above 60 years of age may be better suited for a TKA\textsuperscript{121}. Appropriate patient selection is considered crucial to maximize the likelihood that the procedure will be successful\textsuperscript{120}. Ideal patient criteria for medial opening wedge HTO is presented in Table 1.

Table 1: Ideal patient criteria for a medial opening wedge HTO.

<table>
<thead>
<tr>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varus deformity of the lower limb</td>
</tr>
<tr>
<td>Pronounced degeneration in the medial compartment of the tibiofemoral joint</td>
</tr>
<tr>
<td>Moderate to high activity levels</td>
</tr>
<tr>
<td>Younger than 60 years of age</td>
</tr>
<tr>
<td>A certain degree of pain tolerance</td>
</tr>
<tr>
<td>Symptoms of instability are not considered a contra-indication</td>
</tr>
</tbody>
</table>
Radiographic assessment is considered an important component for preoperative planning \(^{20,120}\) with full-limb standing anteroposterior (AP) radiographs \(^{111,123}\). Radiographs are used to determine the patient’s MAA and anatomical axes of the femur and tibia, as well as identifying the degree of arthritic joint degeneration in both the medial and lateral compartments of the joint. Ultimately, the AP radiographs are used to calculate the suggested degree of surgical correction for the procedure. Using the technique described by Dudgale et al., the desired correction has the WBL shifting laterally to a maximum position of 62.5% of the medial-to-lateral tibial plateau width, otherwise known as the “Fujisawa point” \(^{124}\).

### 1.3.4.2 Surgical Procedure

The classic technique for a medial opening wedge HTO has previously been described by Amendola and Fowler \(^{20,120}\). First, a guide pin is drilled medially into the proximal tibia at an angle approximately 3cm below the medial joint line. An oscillating saw is then used to make surgical cuts medially, anteriorly and posteriorly into the proximal tibia where both flexible and rigid osteotomes are used to complete the osteotomy and open the wedge to a predetermined correction size. Once achieved, the proximal and distal portions of the bone are fixed with an internal fixation plate using both cancellous and cortical screws. Bone graft or a synthetic substitute is typically used to fill in the wedge space for corrections larger than 7.5mm to assist with the bone healing process \(^{20,125}\). The surgery is done under fluoroscopic control to ensure that the desired correction is accurately achieved and to avoid breaching the lateral tibial cortex when making the cut.

Often, surgeons will also perform knee arthroscopy preceding the HTO to investigate OA severity in both the medial and lateral compartments of the tibiofemoral joint. The degree of degeneration in the lateral compartment is important to consider as shifting the loading from the affected medial compartment to a lateral compartment that is equally as degenerated may affect the success or longevity of the procedure. In such cases, surgeons
must decide whether proceeding with the HTO is in the best interest for the patient. Arthroscopy also allows a full visual inspection of the joint entirely to examine the overall knee condition and to surgically treat unstable chondral or meniscal tissue if the surgeon feels that it is indicated\textsuperscript{120}.

Following surgery, patients are monitored during their rehabilitation and given early joint exercises. These exercises are geared towards retraining patient gait, improving their range of motion, managing pain and improving overall function. Patients undergo a progressive returning to weight-bearing protocol based on evidence of radiographic bone healing and subsidized pain.

\textbf{1.3.4.3 Benefits of Medial Opening Wedge HTO}

The most common surgical methods of HTO reported in the literature are the medial opening wedge HTO and the lateral closing wedge HTO. Between these techniques, medial opening wedge HTO has grown in popularity over the last few years\textsuperscript{126}. The method easily allows simultaneous bi-planar correction of the frontal and sagittal planes to correct limb alignment. The ability to increase the wedge opening gradually to the desired correction also allows for a more precise adjustment in both the frontal and sagittal planes and makes it easier to achieve smaller corrections (< 5 degrees) than in a lateral closing wedge HTO\textsuperscript{20}. Moreover, the lateral closing wedge HTO requires two cuts to be made in the bone which can make it difficult to achieve the proper correction size and to form opposing bone surfaces that easily articulate to facilitate bone healing\textsuperscript{127}. 
1.3.4.4 Medial Opening Wedge HTO Success

Many studies have shown that medial opening wedge HTO is beneficial to the patient both clinically and biomechanically. Measures of pain, symptoms, function and quality of life have all been shown to improve significantly at one to five year follow-up assessments after the procedure\textsuperscript{27,28,122,128–130}. It has also been shown to reduce the level of loading on the medial compartment of the knee joint by significantly decreasing the degree of malalignment\textsuperscript{122,131} and reducing the external knee adduction moment during ambulation\textsuperscript{28,95,122,128,131} as well as other relevant kinematic and kinetic measures such as varus thrust\textsuperscript{90} that promote disease progression. Overall, medial opening wedge HTO is suggested to be a successful procedure with survival rates reported as high as 98% after five years\textsuperscript{132}, 90% after ten years\textsuperscript{133} and 71% after 15 years\textsuperscript{132} following the HTO.

Despite the many benefits of HTO, there are a number of complications associated with the surgery. Reports of surgical complications vary between authors, ranging from 1% to 45% of cases\textsuperscript{24,126,134–139}. The most frequently reported are lateral cortex hinge fractures, hardware failure often resulting in loss of correction, delayed and non-union of the bone (insufficient healing of the fracture site after a given time lapse) and hardware failure. However, many authors suggest that the rate of complication is dependent on the type of internal fixation used for the procedure\textsuperscript{37,38,126,134,140,141}.

1.3.4.5 Weight-bearing and Return to Work after HTO

Postoperative care following medial opening wedge HTO typically involves a 2 week period of toe-touch or feather weight -bearing with limb stabilization from a tracker brace, followed by a progressive increase in weight-bearing to the surgeon’s discretion based on radiographic healing of the bone and knee pain. The typical progression would have patients graduate to toe-touch or feather-touch weight-bearing, followed by protective (or partial, progressive) weight-bearing with crutches, to weight-bearing as tolerated and finally, full weight-bearing without crutches.
The length of time for protected weight-bearing ranges between two and 12 weeks\textsuperscript{24–30,142}. A return to full weight-bearing without gait aid (i.e. crutches, cane, walker, etc.) after HTO surgery is dependent on the ability of the bone to consolidate enough to safely bear weight on the limb. This is a major concern for surgeons, as allowing patients to early weight-bear after HTO has the potential to increase complication rates if the plate does not provide enough stability. As a result, studies have shown that the return to weight-bearing process can be related to the type of fixation hardware used for the HTO\textsuperscript{37}. Optimized stable implant designs are therefore essential to warrant a safe earlier return to weight-bear.

Another important factor to consider associated with the time to return to weight-bearing is the time to return to work following the HTO. Time lost from employment and leisure accounts for an estimated 80% of the overall annual costs for OA in Canada\textsuperscript{143}. It is important for healthcare providers to target OA treatment interventions that minimize these productivity losses to society and help reduce the overall OA burden worldwide. Previous studies have reported that the time to return to work following medial opening wedge HTO ranges between three to six months\textsuperscript{142,144–146}. It is important that more stable plate designs are developed to allow patients to return to weight-bearing earlier, translating to a faster return to work which will benefit society as a whole.

1.3.4.6 Locking Plate vs. Non-Locking Plate Designs

Early studies suggest that an optimal balance between micro-motion and implant stability is needed to promote osteotomy healing\textsuperscript{147,148} by ensuring that the plate is not too stiff (suppresses micro-motion and healing\textsuperscript{149}) but is stable enough to evade non-union of the osteotomy site. Over the years, technological advancements have allowed manufacturers to design fixation plates that provide the required components to optimize HTO success.

Fixation plates used in HTO can generally be divided into non-locking and locking plate categories. Conventional non-locking plates were designed to provide stability to the
osteotomy with resistance to various types of loading. The force generated from the axial load is countered by the normal force of the plate (i.e. the product of the friction force between the plate and bone, and the force generated by screw torque) which forms a shear stress at the bone-plate interface. As the screw torque or the friction coefficient decreases however, bone-plate motion increases. Excessive motion results in mechanical environment that discourages primary or secondary bone healing. Furthermore, frictional forces that are overcome by axial loading rely on the axial stiffness of the screw most distal to the plate to maintain stability. The lack of axial control in non-locking screws forces it to be maintained by the bone at the bone-plate interface. Here, the bone is the load-determining factor in maintaining stability under compressive loads. The high mechanical shear stresses generated therefore leaves the bone vulnerable to failure under compressive load or susceptible to absorption of the bone that results in screw loosening.

Since, locking plate designs have been developed to address the mechanical pitfalls of conventional non-locking plates. Locking plates control the axial orientation of the screws to the plate, which improves bone-plate-screw stability. Locking screw-plate constructs act as fixed-angle devices that provide stability maintenance without relying on bone-plate friction and can convert shear stresses to compressive stresses when subject to loading. This improves the stability of the fixation as bone has a high resistance to compressive stress and a low tolerance for shear stress. The strength of the fixation also combines the strength of all bone-screw interfaces, as opposed to relying on the axial stiffness of a single screw (i.e. in non-locking plates), which further increases the stability of the implant. Additionally, threaded locking screws or interference washers provide angular and axial stability that optimize the rigidity of the fixation and optimized strain under loading conditions. The latter provides a favourable biological environment for secondary bone healing with callus formation, important for fractures located in the metaphysis (Schutz, 2003) such as the case in the proximal tibia after HTO. The lack of frictional forces between the bone and plate also allows blood supply under the plate to be preserved and is suggested to promote faster bone healing.
Although all fixation plate designs have the same goal of maintaining correction size and promoting bone healing, the mechanical and biological benefits that locking plates provide are suggested to optimize rehabilitation outcomes after HTO surgery\(^{27,127,152}\). Many studies have evaluated different plate designs through biomechanics and clinical outcomes\(^{23,29,34–38,42,43,140,141,153,154}\). General conclusions suggest that locking plates provide better stability for patients with a higher resistance to mechanical stresses\(^{35}\) and optimized micro-motion at the osteotomy site\(^{23}\). Locking plates are also suggested to allow patients to return to full weight-bearing and achieve consolidation of the osteotomy faster\(^ {37}\), improve clinical outcomes faster\(^ {37,141}\), and reduce the cases of delayed and non-union\(^ {22,38}\), hardware failure\(^ {41}\), loss of correction\(^ {41,155}\) and post-surgical lateral cortex fractures\(^ {38}\) than using a non-locking plate.

### 1.3.5 The Arthrex ContourLock HTO Plate®

The Arthrex ContourLock HTO Plate® is a new titanium fixation device designed with a locking construct (Figure 6), an anatomically curved body, a wider frame than previously introduced locking plates and screws that diverge proximally. To date, no studies have compared clinical outcomes between the Arthrex ContourLock HTO Plate® and other more conventionally used plate designs. However, a few studies have examined the biomechanical differences between the Arthrex ContourLock HTO Plate® and other implants.
Figure 6: A) The Arthrex ContourLock HTO Plate® design (Arthrex, Naples, FL) possesses a wide frame which lengthens the distance between fixation screws and provides additional stability. B) & C) Top and side views of the Arthrex ContourLock HTO Plate® illustrate the anatomically curved body of the implant.
Studies have shown that the Arthrex ContourLock HTO Plate® provides great stability under static loading, similar to other implant designs (Tomofix sm, Tomofix std, iBalance, Peek Power), while it provides superior stability under dynamic cyclic loading conditions, likely as a result of a wider frame and larger distance between fixation screws\(^{42,43}\). Although these studies suggest that the maximum forces at moment of failure are considered too low to warrant full dynamic loading (full weight-bearing) immediately after the surgery for all the plate designs studied, the maximum force at failure for the Arthrex ContourLock HTO Plate® is almost twice as high as other designs, suggesting that full dynamic loading may be achievable for patients much earlier and would require less healing of the osteotomy site to safely begin weight-bearing. Furthermore, a study using finite element modeling showed that at higher compressive loadings, the Arthrex ContourLock HTO Plate® experiences low hardware stresses and small wedge micromotion which can be beneficial for fracture site healing\(^{156}\).

Although there is currently only a small body of evidence to support the use of the Arthrex ContourLock HTO Plate® design, the aforementioned biomechanical studies suggest that the Arthrex ContourLock HTO Plate® is a great implant choice for patients who require a strong, stable locking construct for an early return to weight-bearing following the HTO surgery. A faster return to full weight-bearing could translate to faster improvements in clinical outcomes relating to pain, symptoms and quality of life for the patient, as well as faster returns to daily activity and sport. In turn, patients could return to work much earlier, which would provide socioeconomically benefit by reducing losses in productivity in the workforce.
1.3.6 Health Economics

Healthcare costs are rising at an alarming rate. The current economic climate requires a high level of accountability from budgetary decision-makers for expended healthcare dollars\textsuperscript{157}. As a result, decision-makers are seeking treatment interventions that provide the best quality of care for patients while minimizing dollars spent for the intervention. Programs are now requesting evidence-based research to support the economic efficiency of treatments to better judge the value for their money\textsuperscript{158}.

1.3.6.1 Economic Evaluation

Economic evaluation provides a framework to compare clinical and cost data simultaneously between competing interventions to assess value for money\textsuperscript{159}. In Canada, along with many other countries, economic analyses are a requirement for manufacturers wishing to make their products available as treatment options with Ontario’s Health Insurance Plan\textsuperscript{160}. They are also a useful evaluative tool for decision-makers operating on a given budget in order to make choices concerning the deployment of finances for maximum health benefit.

1.3.6.2 Economic Burden of Osteoarthritis

Symptoms of OA typically do not resolve, and are associated with chronic pain that can persist for decades, resulting in a substantial number of health-care visits over a lifetime, which poses a large economic burden on healthcare systems. In industrialized countries such as Canada, the US, UK, Australia and France, OA accounts for anywhere between 1 and 2.5\% of the country’s gross national product\textsuperscript{161}. In Canada alone, there is an average annual cost of $12,200 ($CAN) per patient with OA\textsuperscript{143} with the annual economic burden of OA estimated to increase to $405 billion dollars by 2020\textsuperscript{49}. As the burden of OA continues to grow around the world, health care systems are in critical need of identifying treatment interventions that limit OA progression at a minimal cost.
1.3.6.2.1 Cost-Effectiveness of Medial Opening Wedge HTO

Medial opening wedge HTO is a procedure that has been shown to benefit patients with varus alignment and medial compartment knee OA both clinically and biomechanically however, economic evaluation of the HTO procedure is an evolving area of research. Studies are beginning to examine the economic impact of medial opening wedge HTO in comparison to alternative treatment methods.

The first study to evaluate the cost-utility of HTO concluded that UKA is a more cost-effective treatment method for medial compartment knee OA than HTO\(^{162}\) (Brown, 2010). A study that soon followed found results favoring the KineSpring\(^ \text{®} \) Knee Implant System (an implantable load absorber)\(^ {163} \). However, the authors from this study claim to report an ICER when the values reported are in fact average cost-effectiveness ratios (ACERs). This incorrect use of terminology can lead to misinterpretation of results\(^ {164} \) and inaccurate conclusions.

More recently, two studies have investigated the cost-utility of HTO compared to both UKA and total knee arthroplasty (TKA) for younger patients with medial compartment knee OA\(^ {118,119} \). According to the results of these studies, HTO is the most cost-effective treatment for patients below 60 years of age and the authors strongly support the use of HTO as a first line treatment method for this younger patient population.

The aforementioned studies provide some evidence to suggest that HTO is a cost-effective treatment intervention for patients who are varus aligned and with medial compartment knee OA. However, no studies have been conducted to compare economic impact of using different internal hardware devices when performing a medial opening wedge HTO surgery. Locking plates have been suggested to provide functional and patient-important benefits when compared to non-locking plates for medial opening wedge HTO\(^ {35,36,43} \) and are thought to reduce the number of post-operative complications (i.e. non-union) that can result in revision surgery\(^ {37,38,141} \). Patients are also expected to
return to full weight-bearing sooner, and therefore productivity losses may be lessened by allowing patients to return to work sooner. In both cases, costs associated with the surgery can be minimized. However, locking plates and screws are generally more expensive than non-locking designs, and the bulkiness of locking plates can be irritating to the patient requiring surgical plate removal\textsuperscript{29,40,44} further increasing the costs associated with the procedure. Cost-effectiveness analysis is therefore warranted to justify using locking plates for medial opening wedge HTO.
Chapter 2

2 Methods

2.1 Study Design

We conducted a retrospective analysis using prospectively collected data from patients who had undergone medial opening wedge HTO at the Fowler Kennedy Sport Medicine Clinic between July 2005 and June 2015, performed by one fellowship-trained orthopaedic surgeon (JRG). All surgeries were completed using either a locking (Arthrex ContourLock HTO Plate®) or a non-locking (Arthrex Puddu Plate®) internal fixation plate. Patients at earlier time points of the study received the non-locking plate. Availability of the locking plate in 2009 resulted in a shift in clinical practice where most patients received the locking plate. The study was approved by the University of Western Ontario’s Research Ethics Board for Health Sciences Research Involving Human Subjects. All patients had provided informed consent prior to study enrollment to have their data entered into a research database.

2.2 Eligibility Criteria

We included patients who underwent a medial opening wedge HTO for mechanical varus alignment and had been diagnosed with knee OA according to the American College of Rheumatology classification criteria\textsuperscript{109} affecting primarily the medial compartment of the tibiofemoral joint. We did not exclude patients with evidence of lateral compartment knee OA as long as the patient’s symptoms and radiographic severity of OA was more pronounced in the medial compartment. We excluded patients who had a combined HTO and anterior cruciate ligament (ACL) reconstruction, as well as those who received a bilateral HTO. We also excluded patients that underwent a revision ACL reconstruction surgery on the same limb or an HTO on the contralateral limb within 12 months following surgery.
2.3 Intervention

2.3.1 Operative Procedure

Preoperative hip-knee-ankle full-limb standing anteroposterior radiographic views were used to calculate the desired correction size for the osteotomy using the method described by Dugdale et al.\textsuperscript{124} This technique suggests a shift in the weight-bearing line to 62.5% of the medial-to-lateral tibial plateau width. Other considerations for preoperative templating were the condition of the articular cartilage in the lateral compartment and the degree of correction required to achieve neutral alignment.

The HTO was performed using a medial opening wedge technique similar to the procedure described by Fowler et al.\textsuperscript{20} Fluoroscopy was used to insert a guide pin and osteotomes, both flexible and rigid, were used to perform the osteotomy. Once the tibia was opened to the desired width, fluoroscopy was again used to confirm correction size and limb alignment. If necessary, adjustments were made to the posterior tibial slope to provide address sagittal instability. One of two plate designs was used as an internal implant: a 4-hole Arthrex Puddu Plate® non-locking plate (Arthrex, Naples, FL, USA) or an Arthrex ContourLock HTO Plate® locking plate (Arthrex, Naples, FL, USA). Cortical and cancellous bone screws were used to fixate the osteotomy both proximally and distally and confirmed using fluoroscopy. For corrections larger than 7.5mm, cancellous bone allograft was used to fill in the osteotomy gap.

2.3.2 Post-operative Care

Following surgery, the operative limb was placed in a hinged knee brace. At this time, patients were instructed to feather-touch weight-bear (WB) with the assistance of crutches for a minimum of two weeks. Once the patient showed clinical and radiographic evidence of osteotomy healing, they progressed to protective WB. The decision to
progress the weight-bearing status of the patient during rehabilitation was decided by the surgeon using radiographic evidence of osteotomy healing (i.e. the extent of consolidation on x-ray), perceived stability of the fixation device and the level of pain or discomfort reported by the patient during ambulation.

Patients were also given a progressive rehabilitation protocol to allow them to re-establish full range of motion, strength and function, in addition to reducing swelling, and avoiding joint contracture and muscle atrophy from disuse. Patients began this program at three weeks postoperative with lighter exercises and progressed in exercise difficulty until they exhibited a normal gait pattern at the discretion of the physiotherapist. All patients followed the same rehabilitation protocol with slight modifications if deemed necessary.

All patients returned to clinic for a follow-up visit with the surgeon at two and six weeks and three, six and 12 months after surgery. Patients who experienced intraoperative or post-operative complications (i.e. infection, delayed union, etc.) were reviewed as needed.

2.4 Radiographic Assessment

A full-limb standing digital radiograph of the lower limb was obtained for each patient at baseline, three, six and 12 months following surgery. Patients stood with patellae centered over their femoral condyles with feet pointed straight ahead. The position controls for effects of foot rotation on alignment measures that could result in inaccurate frontal plane images\(^\text{165}\). Additional imaging was taken for patients who displayed delayed bone healing and/or suspected complication to monitor consolidation more closely.

Baseline radiographs were assessed using a customized computer software program (HTO Pro; Wolf Orthopaedic Biomechanics Laboratory, London, Ontario, Canada)\(^\text{93}\). Anteroposterior radiographs were measured to obtain the preoperative mechanical axis.
angle (MAA) and to assess OA severity in both the medial and lateral tibiofemoral compartments. The MAA was defined as the angle generated between the mechanical axis of the femur and the mechanical axis of the tibia. In other words, it is the angle formed by the lines connecting the center of the hip to center of the knee, and the center of the knee to the center of the ankle. The center of the hip was characterized as the center of a circular outline positioned over the femoral head. The center of the knee was characterized as the midpoint of a line drawn between the peaks of the tibial spines, extrapolated inferiorly to the surface of the intercondylar eminence. The center of the ankle was characterized as the midpoint between the fibula and tibia at the height of the tibial plafond. A negative MAA value indicated varus alignment. Previous studies conducted in our lab have shown excellent reliability for the MAA when using the HTOPro program ($ICC_{2,1} = 0.97$). Joint degeneration in the medial and lateral compartments of the tibiofemoral joint was measured using the Kellgren-Lawrence rating scale. Although the reliability of reporting the Kellgren-Lawrence grade using HTOPro has not yet been reported, evaluators were given original atlases of individual radiographic features for Kellgren-Lawrence grading of knee OA. These guidelines have proven to be reliable in measuring the severity of knee OA.

### 2.5 Outcome Measures

#### 2.5.1 Return to full weight-bearing

We defined time to return to full weight-bearing as the time to discontinuation of gait aid use (i.e. crutches, cane, or walker), as documented in the medical record. A single reviewer (CAP) reviewed patient clinic follow-up reports from each follow up visit time point up to 12 months following the HTO. Identified weight-bearing status terms included non-weight-bearing, toe-touch (or touch-down, feather-touch) weight-bearing, partial (or progressive, protective) weight-bearing, weight-bearing as tolerated and full weight-bearing. Discontinuation of gait aid use (i.e. crutch, cane, or walker) was outlined as surgeon instruction to wean off of crutches (or slowly wean off) or a report that the
patient was ambulating without the use of crutches (or other gait aid). A weight-bearing status timeline was created for each patient to determine the total time it took for each patient to return to full weight-bearing without use of a gait aid. The total time to return to weight-bearing was expressed in weeks.

If the time to return to full weight-bearing was specified by the surgeon, the time from surgery to that appointment date was attributed as the total time to return to weight-bearing for the patient. For patients whose reports did not explicitly provide a value in weeks, we made assumptions to determine total return to weight-bearing time. Patients were given a time to return to full weight-bearing one week past the date of the follow-up visit if they were instructed to wean off of their crutches and were fully weight-bearing by their next appointment. Similarly, patients instructed to slowly wean off crutches were attributed a time to return to weight-bearing two weeks later than the date of the follow-up visit. A patient who was described as having already been off crutches was attributed a return to weight-bearing time one week earlier than said appointment as a conservative measure. If the surgeon specified exactly how many weeks earlier that they were off crutches, that value was assigned to the patient.

In cases where the patient missed an appointment visit and the time to return to weight-bearing was unclear, a conservative measure of worst possible outcome was attributed to that patient. For example, if a patient was still on crutches at 10 weeks, was not seen at 3 months, but was off crutches at a 4 month appointment visit, the given outcome value was one week earlier than the 4 month appointment date (i.e. 16 weeks).

2.5.2 Knee injury and Osteoarthritis Outcome Score

The Knee injury and Osteoarthritis Outcome Score (KOOS) is a 42-item self-administered knee and OA-specific questionnaire that addresses five domains of health: pain (9 items), other symptoms (7 items), function during activities of daily living (17 items), function during sport and recreational activities (5 items), and quality of life.
related to the knee (4 items). The tool uses a five-point ordinal scale for each item and generates a standardized mean value score to represent each of the five domains ranging from 0 (worst outcome) to 100 (best outcome). The KOOS has been shown to exhibit excellent test-retest reliability in each domain (range 0.75-0.93), face validity, construct validity and responsiveness to change for individuals with knee OA and ligamentous injuries\textsuperscript{167,168}. A change of ten points in a given KOOS domain is considered to be clinically meaningful\textsuperscript{169}.

2.5.3 Cost

2.5.3.1 Surgical Costs

All direct costs associated with the HTO procedure were reported using the average procedure cost from the Ontario Case Costing Initiative\textsuperscript{170} in addition to costs associated with any additional surgeries (e.g. revisions, hardware removals, irrigation and debridement for infection). These costs included operating room (OR) costs, equipment used, and other medical tests performed during the procedure, as well as the total length of stay in the hospital (outpatient or inpatient) following surgery. Surgeon and anaesthesiologist billing fees were obtained through the Ontario Ministry of Health Schedule of Benefits\textsuperscript{171}. The individual costs for the locking (Arthrex ContourLock HTO Plate\textsuperscript{®}) and non-locking (Arthrex Puddu Plate\textsuperscript{®}) plates and their associated fixation screws were obtained from our hospital’s cost report data.

2.5.3.2 Healthcare Resource Use

To account for possible postoperative complications, we recorded any additional healthcare resource use for 12 months following the HTO surgery by reviewing patient clinic charts and electronic hospital records. All clinic consultations, follow-up visits, emergency room visits and hospitalization, diagnostic imaging and laboratory tests
performed and additional procedures performed for postoperative complications were recorded. Costs were attributed using the Ontario Ministry of Health Schedule of Benefits\textsuperscript{171}.

Additionally, we recorded patient time to return to work. The time to return to work was defined as the time loss of employment, retirement or homemaking following surgery. The total time was determined in one of two ways. First, if patients returned to the clinic for a follow up visit during the study period, they were asked to indicate their employment status at the time of surgery, time off work from paid employment (or retirement, homemaking activities, etc.) as a result of the HTO, change in employment status (i.e. modified or restricted duties), and level of activity of employment. If patients did not return to the clinic during the study period, we reviewed the surgeon dictated clinic follow-up reports up to 12 months following the HTO to identify the patient’s occupation and references of date to return to employment. The total time was reported as either below 3 months (with specification of total time), 3-4 months, 5-6 months, 7-8 months, more than 8 months (with specification of total time) or “I did not return to work”.

The 2015 average Canadian wage reported by Statistics Canada was used to account for time off employment\textsuperscript{172}. We assigned the current value of minimum wage in Ontario to account for time off for patients who were retired, or who lost time from home making activities.

We estimated the total cost for each individual patient over the study period. All costs were reported in 2016 Canadian dollars.
2.6 Data Analysis

We used descriptive statistics to describe the demographic and clinical characteristics for each group. We report means and standard deviation (SD) for all continuous measures (age, height, mass, body mass index (BMI), mechanical axis angle (MAA)), and frequencies and proportions for categorical variables (sex, Kellgren-Lawrence grade and American Society of Anesthesiologists (ASA)) (Table1). All statistical measurements were performed using the Statistical Package for the Social Sciences (SPSS) version 23.0 (IBM SPSS Statistics v 23; IBM Corp, Armonk, New York, USA).

2.6.1 Objective 1

We conducted an independent t-test to compare the mean between group difference in time to return to full weight-bearing with 95% confidence intervals around the estimate.

2.6.2 Objective 2

We calculated KOOS change scores from baseline to six months after surgery and presented the mean and standard deviation (SD) by group for the total KOOS and for each KOOS subdomain. We used the six-month time point as our outcome measure since stability differences between the plates could affect patient-important outcomes shorter term; however, most patients have fully recovered regardless of the plate used by 12 months after surgery. We compared the mean between group difference in change score using an independent t-test and report 95% confidence intervals around the estimates.

For objectives 1 and 2, we tested the assumptions for independent samples t-test which include homogeneity of variance, random independent samples, and normality. Normality was tested by plotting a histogram for each outcome and all graphs were assessed for
kurtosis and skewness. A Mann-Whitney U non-parametric test was performed if the assumption of normality was not met.

2.6.3 Objective 3

2.6.3.1 Economic Analysis

We conducted a cost-effectiveness analysis from the healthcare payer and societal perspectives. The healthcare payer perspective includes the direct costs from healthcare resources consumed including the HTO surgery, any additional procedures (e.g. revision surgeries), diagnostic testing and inpatient hospitalizations. The societal perspective includes these same costs along with out-of-pocket patient costs (e.g. hyaluronic acid or corticosteroid injections) and indirect costs such as time off employment, retirement and homemaking activities as a result of the surgery. To capture all costs associated with return to work and additional surgical procedures, we included all costs up to 12 months following surgery and used the KOOS total change score from baseline to 12 months postoperative as our effectiveness measure.

2.6.3.2 Incremental Cost-Effectiveness Ratio

We calculated the incremental cost-effectiveness ratio (ICER) to consider the value of using the locking plate. The ICER is defined as the ratio between the incremental cost and the incremental effect (change in KOOS).

2.6.3.3 Net Benefit Regression

We also estimated the cost-effectiveness of the locking plate using the net benefit regression (NBR) framework, a statistical tool that considers both the incremental cost and effect of an intervention in addition to the maximum acceptable amount one is
willing-to-pay (WTP) in order to achieve one additional unit improvement in effect. In this framework, an intervention is deemed more cost-effective than the existing treatment if:

\[ INB = WTP \times (\Delta E - \Delta C) > 0 \]  \hspace{1cm} [1]

where INB represents the incremental net benefit, WTP is the willingness-to-pay value, \( \Delta E \) is the incremental effect and \( \Delta C \) is the incremental cost.

We conducted two individual NBR models to evaluate from both the payer and societal perspectives. The WTP values used varied between $0 and $2,000. The following covariates were included in our models: age, sex, BMI, comorbidities and baseline MAA.

We tested the assumptions for multiple linear regression which include a linear relationship between independent and dependent variables, multivariate normality, limited multicollinearity, no auto-correlation and homoscedasticity. Linear relationships were assessed with scatter plots. Multivariate normality was assessed by plotting histograms and all graphs were assessed for kurtosis and skewness. Homoscedasticity was assessed by plotting predicted values against the observed values and observing the proximity of points to the prediction line.

2.6.3.4 Uncertainty

To characterize the statistical uncertainty, we presented 95% CIs around our estimates of the incremental net benefit (INB) and with a cost-effectiveness acceptability curve (CEAC)\textsuperscript{174}. The CEAC provides a functional representation of probability that the treatment is cost-effective at various WTP values.
2.6.3.5 Sensitivity Analysis

We conducted one-way sensitivity analyses on the variables that were considered to have the most uncertainty because of the assumptions required to calculate the cost: 1) the dollar value for retired or home making time (ranging from $0 per hour to $11.25 per hour); 2) adding seven weeks to the return to weight-bearing time for patients where we were unable to collect a return to work time and using this value as their time to return to work, as seven weeks was the mean time to return to work from return to full weight-bearing in our sample; 3) combining the adjustments of sensitivity analyses 1 and 2.

2.6.4 Missing Data

We used Multiple Imputation methods to impute missing 6 and 12 month KOOS total change score data. A pooled score was generated from 5 individual imputations to provide a best estimate value. Covariates including age, sex, BMI, comorbidities, baseline MAA and baseline total KOOS were used in the model to increase the accuracy of the imputed values.
Chapter 3

3 Results

3.1 Patient Flow

We screened 502 HTO procedures that were captured in our database. Of these, 249 met the inclusion criteria and were included in the present analysis. From this sample, 144 patients underwent a medial opening wedge HTO using the locking plate, while 105 patients received the non-locking plate (Figure 7).
Number of surgeries by JRG between July 2005 and June 2015 (n = 502)

Included (n = 249)

Excluded (n = 253)
Reasons for exclusion:
- Combined HTO/ACL reconstruction (n = 112)
- Contralateral HTO within 12 months (n = 60)
- Alternative fixation plate (n = 32)
- Lost to follow-up in first 6 months (n = 22)
- Other HTO procedure performed (n = 21)
- Staged ACL reconstruction within 6 months (n = 6)

Locking Plate
(Arthrex ContourLock HTO Plate®, n = 144)

Baseline (n = 144)

6-month follow-up (n = 144)

12-month follow-up (n = 144)*

Non-locking Plate
(Arthrex Puddu Plate®, n = 105)

Baseline (n = 105)

6-month follow-up (n = 105)

12-month follow-up (n = 105)*

Figure 7: Participant flow through the study. Asterisk represents a smaller sample size for the cost-effectiveness analysis from the societal perspective (n = 106 locking plate, n = 58 non-locking plate).
3.2 Demographics and Clinical Characteristics

Baseline demographics and clinical characteristics were similar between groups (Table 2). Patients were typically male, middle-aged and categorized as overweight from their BMI. Patients were varus aligned as defined by their MAA and had large correction sizes. Most had advanced osteoarthritic degeneration in the medial compartment of the tibiofemoral joint, however, the degree of lateral compartment joint degeneration was slightly higher in the locking plate group. According to the American Society of Anesthesiologists (ASA) score, most patients were considered to have mild systemic disease.
Table 2: Baseline demographics and clinical characteristics (n = 249)*.

<table>
<thead>
<tr>
<th>Demographic/clinical characteristic</th>
<th>Group 1: Locking Plate (n = 144)</th>
<th>Group 2: Non-locking Plate (n = 105)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>108 (75.0)</td>
<td>79 (75.2)</td>
</tr>
<tr>
<td>Age, years</td>
<td>48.9 ± 8.0</td>
<td>46.7 ± 8.6</td>
</tr>
<tr>
<td>Height, cm</td>
<td>175.6 ± 8.3</td>
<td>175.7 ± 9.0</td>
</tr>
<tr>
<td>Mass, kg</td>
<td>92.5 ± 15.3</td>
<td>91.0 ± 17.0</td>
</tr>
<tr>
<td>Body mass index (BMI), kg/m²</td>
<td>30.1 ± 5.0</td>
<td>29.4 ± 4.4</td>
</tr>
<tr>
<td>Operative limb left, no. (%)</td>
<td>77 (53.5)</td>
<td>52 (49.5)</td>
</tr>
<tr>
<td>Mechanical axis angle, degrees a</td>
<td>-8.5 ± 2.8</td>
<td>-8.1 ± 3.4</td>
</tr>
<tr>
<td>Mean correction size ± SD (mm)</td>
<td>11.9 ± 2.7</td>
<td>12.3 ± 3.0</td>
</tr>
<tr>
<td>Medial Compartment K/L Grade, no. (%) b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>11 (7.6)</td>
<td>9 (8.6)</td>
</tr>
<tr>
<td>2</td>
<td>48 (33.3)</td>
<td>28 (26.7)</td>
</tr>
<tr>
<td>3</td>
<td>61 (42.4)</td>
<td>42 (40.0)</td>
</tr>
<tr>
<td>4</td>
<td>21 (14.6)</td>
<td>23 (21.9)</td>
</tr>
<tr>
<td>Lateral Compartment K/L Grade, no. (%) b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>25 (17.4)</td>
<td>53 (50.5)</td>
</tr>
<tr>
<td>2</td>
<td>82 (56.9)</td>
<td>31 (29.5)</td>
</tr>
<tr>
<td>3</td>
<td>31 (21.5)</td>
<td>10 (9.5)</td>
</tr>
<tr>
<td>4</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>American Society of Anesthesiologists score, no. (%) c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>47 (32.6)</td>
<td>37 (35.2)</td>
</tr>
<tr>
<td>2</td>
<td>83 (57.6)</td>
<td>54 (51.4)</td>
</tr>
<tr>
<td>3</td>
<td>14 (9.7)</td>
<td>14 (13.3)</td>
</tr>
</tbody>
</table>

*Values are reported as means with standard deviations unless otherwise specified

A negative mechanical axis value indicates varus alignment

Kellgren-Lawrence (K/L) grade of osteoarthritis severity

American Society of Anesthesiologists physical status classification system: 1 = healthy, normal patient; 2 = patient with mild systemic disease; 3 = patient with severe systemic disease
3.3 Surgical Characteristics

Diagnostic knee arthroscopy was performed on 246 (98.8%) patients. A tibial tubercle osteotomy (TTO) was performed on 130 (52.2%) patients in order to maintain patellar height. Cancellous bone allograft was used to fill the osteotomy for 238 (95.6%) patients. Substitute bone grafts used included: cancellous autograft for two patients, demineralized bone matrix for one patient and OsteoSet bone graft for one patient. The osteotomy was left unfilled in 7 cases (2.8%). Plate removal from a previous HTO on the contralateral limb was performed on nine (3.6%) patients (3 non-locking, 6 locking) during the procedure and removal of TTO hardware from a previous HTO was performed on two (0.8%) patients (2 non-locking). The surgery was an inpatient procedure for most cases (228 patients, 91.6%).

Slight between-group differences were seen in the number of concomitant tibial tubercle osteotomy (TTO) surgeries performed (91 patients, 63% locking plate; 39 patients, 37% non-locking plate), the number of outpatient cases (19 patients, 13% locking plate; 2 patients, 2% non-locking) and the number of osteotomies that were left unfilled, with no bone graft (1 patients, 1% locking plate; 6 patients, 6% non-locking). These most likely represent slight changes in clinical practice of JRG.
3.4 Surgical and Post-operative Complications

A hematoma was noted in 13 cases. Deep infection was identified in three patients requiring an irrigation and debridement surgical procedure to be performed. One patient experienced isolated anterior compartment syndrome (likely related to combined TTO), which was treated surgically with a fasciotomy. A pulmonary embolism was confirmed for one patient with chest radiographs and was treated with thrombolytic medication. A deep vein thrombosis (DVT) was documented for one patient through ultrasound and was treated with an anticoagulant. Partial implant failure was documented in the charts of 12 patients where ten patients had one broken screw and two patients had two broken screws. A partial loss of correction was identified for one patient. One patient experienced non-union of the osteotomy site that required a revision osteotomy surgery to be performed. A total of 19 patients complained of irritation at site of osteotomy following the surgery and had the hardware surgically removed within the first 12 months postoperatively. No patients experienced neurovascular injuries or cardiac complications. Adverse event rates are summarized in Table 3.

<table>
<thead>
<tr>
<th>Complication</th>
<th>Group 1: Locking Plate (n = 144)</th>
<th>Group 2: Non-locking Plate (n = 105)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematoma</td>
<td>3 (2.1%)</td>
<td>9 (8.6%)</td>
</tr>
<tr>
<td>Deep infection</td>
<td>3 (2.1%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Compartment syndrome</td>
<td>1 (0.7%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1 (0.7%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Deep vein thrombosis (documented)</td>
<td>1 (0.7%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Hardware failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 broken screw</td>
<td>3 (2.1%)</td>
<td>7 (6.7%)</td>
</tr>
<tr>
<td>2 broken screws</td>
<td>1 (0.7%)</td>
<td>1 (1.0%)</td>
</tr>
<tr>
<td>Partial loss of correction</td>
<td>1 (0.7%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Non-union/collapse</td>
<td>0 (0.0%)</td>
<td>1 (1.0%)</td>
</tr>
<tr>
<td>Hardware removal</td>
<td>11 (8.3%)</td>
<td>8 (7.6%)</td>
</tr>
<tr>
<td>Neurovascular injury</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Cardiac complications</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

*Values are reported as frequencies with proportions
3.5 Outcome Measures

3.5.1 Objective 1

There was a statistically significant difference between treatment groups in the time to return to full weight-bearing with discontinuation of gait aid (mean difference 6.1 weeks; 95% CI 4.5, 7.6), with a faster return to weight-bearing for the locking plate group (Table 4, Figure 8).

3.5.2 Objective 2

Although the KOOS total change score and subdomain change scores were slightly higher in the locking plate group from baseline to six months after surgery, no significant between-group differences were found (Table 4, Figure 9). Large improvements were seen for both groups from baseline to six months in the total KOOS and all subdomains, above the minimal clinically important difference (MCID) of ten points\textsuperscript{176}. Missing 6-month data values were imputed for 17 patients in the locking plate group (11.8%) and 11 patients in the non-locking plate group (10.5%).
Table 4: Time to return to weight-bearing and patient reported outcome measures (KOOS) for all patients (n = 244)*.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Time (weeks)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Locking Plate (n = 144)</td>
<td>Non-locking Plate (n = 105)</td>
</tr>
<tr>
<td>Time to return to WB</td>
<td>10.9 ± 5.8</td>
<td>17.0 ± 6.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>KOOS Outcome (range 0 – 100)</th>
<th>Time point</th>
<th>Treatment Group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Locking Plate (n = 144)</td>
<td>Non-locking Plate (n = 105)</td>
</tr>
<tr>
<td>Pain</td>
<td>Baseline</td>
<td>52.0 ± 19.9</td>
<td>52.6 ± 18.5</td>
</tr>
<tr>
<td></td>
<td>6-month</td>
<td>70.1 ± 17.7</td>
<td>68.5 ± 17.6</td>
</tr>
<tr>
<td>Change Score a</td>
<td></td>
<td>18.3 ± 20.7</td>
<td>15.9 ± 20.6</td>
</tr>
<tr>
<td>Other Symptoms</td>
<td>Baseline</td>
<td>49.9 ± 17.8</td>
<td>52.8 ± 19.9</td>
</tr>
<tr>
<td></td>
<td>6-month</td>
<td>69.6 ± 16.5</td>
<td>65.7 ± 20.5</td>
</tr>
<tr>
<td>Change Score a</td>
<td></td>
<td>18.0 ± 20.5</td>
<td>15.4 ± 20.4</td>
</tr>
<tr>
<td>ADL</td>
<td>Baseline</td>
<td>60.9 ± 21.0</td>
<td>61.8 ± 19.8</td>
</tr>
<tr>
<td></td>
<td>6-month</td>
<td>77.8 ± 18.0</td>
<td>74.2 ± 17.5</td>
</tr>
<tr>
<td>Change Score a</td>
<td></td>
<td>17.7 ± 22.5</td>
<td>12.6 ± 20.3</td>
</tr>
<tr>
<td>Sport and Recreation</td>
<td>Baseline</td>
<td>29.1 ± 22.8</td>
<td>28.0 ± 22.3</td>
</tr>
<tr>
<td></td>
<td>6-month</td>
<td>46.5 ± 24.1</td>
<td>43.1 ± 24.2</td>
</tr>
<tr>
<td>Change Score a</td>
<td></td>
<td>17.6 ± 28.5</td>
<td>14.5 ± 26.1</td>
</tr>
<tr>
<td>Quality of life</td>
<td>Baseline</td>
<td>30.2 ± 19.8</td>
<td>25.0 ± 30.1</td>
</tr>
<tr>
<td></td>
<td>6-month</td>
<td>49.0 ± 22.0</td>
<td>43.1 ± 24.2</td>
</tr>
<tr>
<td>Change Score a</td>
<td></td>
<td>18.4 ± 23.5</td>
<td>16.4 ± 22.2</td>
</tr>
<tr>
<td>KOOS Total</td>
<td>Baseline</td>
<td>50.9 ± 18.8</td>
<td>50.3 ± 17.2</td>
</tr>
<tr>
<td></td>
<td>6-month</td>
<td>68.3 ± 16.9</td>
<td>64.7 ± 17.1</td>
</tr>
<tr>
<td>Change Score a</td>
<td></td>
<td>17.9 ± 20.4</td>
<td>14.4 ± 19.1</td>
</tr>
</tbody>
</table>

*Values are reported as means with standard deviations

a The change in KOOS score between baseline and 6 months after surgery

b A positive mean difference favors the locking plate treatment group

c A negative mean difference favors the locking plate treatment group

† p < 0.05, ‡ p ≤ 0.001

Abbreviations: KOOS = Knee injury and Osteoarthritis Outcome Score, ADL = Activities of Daily Living, CI = confidence interval, WB = weight-bearing
Figure 8: Mean time to return to full weight-bearing with complete discontinuation of gait aid use (in weeks with 95% confidence intervals) for patients undergoing a medial opening wedge high tibial osteotomy with a locking or non-locking internal fixation plate. Stars indicate a significant difference.
Figure 9: Mean Knee injury and Osteoarthritis Outcome Score (KOOS) total and subdomain change scores from baseline to six months postoperative (with 95% confidence intervals) for patients undergoing a medial opening wedge high tibial osteotomy with a locking or non-locking internal fixation plate.
3.5.3 Objective 3

There was a statistically significant difference between groups in mean costs from the healthcare payer perspective favoring the non-locking plate group (Table 5). A statistically significant difference was also seen from the societal perspective, however favoring the locking plate group. The mean between group difference in effect (KOOS change score) was small and not statistically significant, but favored the locking plate group. Missing 12-month data values were imputed for 19 patients in the locking plate group (13.2%) and 12 patients in the non-locking plate group (11.4%).

3.5.3.1 ICER

The ICER was $472.00 per one point improvement in the total KOOS change score for the healthcare payer perspective (Table 5), translating to an additional $4,720 per patient for a clinically important improvement of ten KOOS points compared to patients who receive a non-locking plate. The ICER was -$3,892.63 for the societal perspective, indicating a cost saving of $3,892.63 per additional one point improvement in total KOOS change score in favor of the locking plate group. The negative incremental cost and positive incremental effect from the ICER suggest that, when incorporating indirect costs, the locking plate costs less for a better outcome compared to the non-locking plate.

3.5.3.2 Net Benefit Regression

From the healthcare payer perspective, the incremental net benefit (INB) was negative for WTP values <$1,000, indicating that the locking plate is not cost-effective compared to the non-locking plate below this WTP threshold (Table 6). At a WTP ≥ $1,000, the positive INB indicates that the locking plate is cost-effective compared to the non-locking plate at this threshold. From a societal perspective, the INB was positive for all WTP suggesting that the locking plate is cost-effective compared to the non-locking plate.
3.5.3.2.1  Uncertainty

From the healthcare payer perspective, the 95% confidence intervals (CI) around our estimate widen as WTP increases and at WTP values ≥$1,000, the lower bounds of the 95% CIs remain negative. The larger confidence intervals suggest a higher degree of uncertainty surrounding the cost-effectiveness of the locking plate as one is willing to pay more. From the societal perspective, the lower bounds of the CI remain positive up to a WTP of $500, however become negative at values >$500 and these CIs continue to widen as WTP increases also suggesting uncertainty.

To visually display this uncertainty, the probability of cost-effectiveness for the locking plate is displayed on the cost-effectiveness acceptability curve (CEAC) (Figure 10). From the healthcare payer perspective, the CEAC suggests that even at a WTP of $1,000 for a one point improvement in total KOOS change score (i.e. $10,000 for a clinically meaningful improvement), the probability that the locking plate is cost-effective is 50% (Figure 10A). From a societal perspective, the CEAC suggests with 99% certainty that the locking plate is cost-effective at a WTP value of $0 (Figure 10B). As WTP increases however, this certainty slowly declines as a result of cost savings with minimal improvement in effect (Fenwick, 2004).
Table 5: Cost and effect outcomes*.

| Healthcare payer (n = 249, CL = 144, PUD = 105) |  |
|-----------------------------------------------|--|---|
| **Plate** | **Cost** | **Δ Cost** | **CI, p-value** | **Effect** | **Δ Effect** | **CI, p-value** | **ICER** |
| Locking | 6876.74 | +755.2 | (304.2, 1206.3), 0.01‡ | 21.32 | +1.60 | (-6.1, 2.9), 0.49 | +472.00 |
| Non-locking | 6121.49 | | | | | | |
| Societal (n = 164, CL = 106, PUD = 58) |  |
| **Plate** | **Cost** | **Δ Cost** | **CI, p-value** | **Effect** | **Δ Effect** | **CI, p-value** | **ICER** |
| Locking | 23894.88 | -6228.21 | (-10549.7, -1906.7), <0.01‡ | 21.32 | +1.60 | (-6.1, 2.9), 0.49 | -3892.63 |
| Non-locking | 30123.09 | | | | | | |

*Values are reported as means
a 2016 Canadian dollars.
| Total change Knee injury and Osteoarthritis Outcome Score (KOOS) between baseline and 12 months
| p < 0.05, ‡ p ≤ 0.001

Abbreviations: ICER = Incremental cost-effectiveness ratio, CI = confidence interval

Table 6: Net benefit regression results.

| WTP* | Healthcare payer** |  |
|-----------------------------------------------|--|---|---|
| **Incremental net benefit** | **95% CI** | **p-value** | **Incremental net benefit** | **95% CI** | **p-value** |
| 0 | -812.26 (243.34) | -1291.6 to -332.9 | <0.001‡ | 5232.19 (2127.32) | 1029.9 to 9434.5 | 0.015† |
| 250 | -605.15 (654.95) | -1895.4 to 685.1 | 0.356 | 5599.82 (2324.64) | 1007.8 to 10191.9 | 0.017† |
| 500 | -398.05 (1236.74) | -2834.5 to 2038.4 | 0.748 | 5967.46 (3345.13) | 1007.8 to 10191.9 | 0.017† |
| 750 | -190.94 (1833.28) | -3802.5 to 3420.6 | 0.917 | 6335.09 (3743.13) | 1007.8 to 10191.9 | 0.017† |
| 1000 | 16.16 (2433.74) | -4778.4 to 4810.7 | 0.995 | 6702.72 (4012.16) | 1007.8 to 10191.9 | 0.017† |
| 1250 | 223.26 (3035.80) | -5757.3 to 6203.9 | 0.941 | 7070.35 (4727.36) | 1007.8 to 10191.9 | 0.017† |
| 1500 | 430.38 (3638.67) | -6737.9 to 7598.6 | 0.906 | 7437.98 (5471.88) | 1007.8 to 10191.9 | 0.017† |
| 1750 | 637.48 (4242.00) | -7719.4 to 8994.3 | 0.881 | 7805.61 (6235.22) | 1007.8 to 10191.9 | 0.017† |
| 2000 | 844.59 (4845.62) | -8701.4 to 10390.6 | 0.862 | 8173.24 (7011.24) | 1007.8 to 10191.9 | 0.017† |

* WTP for a one-point improvement on the KOOS total change score from baseline to 12 months
** Incremental net benefit with standard error (SE)
| A positive incremental net benefit favors the locking plate treatment group
| † p < 0.05, ‡ p ≤ 0.001

Abbreviations: WTP = willingness-to-pay, CI = confidence interval
Figure 10: Cost-effectiveness acceptability curves (CEAC) displaying the probability that the locking plate is cost-effective compared to the non-locking plate from A) the healthcare payer’s perspective and B) the societal perspective, over a range of willingness to pay values for an additional one-point improvement in the Knee injury and Osteoarthritis Outcome Score total change score (baseline to 12 months).
3.5.3.3 Sensitivity Analysis

Results from our sensitivity analysis suggest that, from the societal perspective, cost savings are 1) $3309.91, 2) $3747.08 and 3) $3595.41 per one point improvement of KOOS total change score after adjusting for 1) the dollar value for retired or homemaking time at 0$ per hour, 2) time to return to work = time to return to weight bearing plus seven weeks, and 3) both 1) and 2) (Table 7).

Similarly, the sensitivity analysis provided comparable results when conducting net benefit regression. In each of the three sensitivity conditions, the INB was positive for all WTP values indicating that the locking plate is cost-effective compared to non-locking plate (Table 8). As WTP increases however, the 95% CIs around our estimate widen suggesting uncertainty in the cost-effectiveness of the locking plate as one is willing to pay more. Visual display of CEACs indicates that at a WTP of $0, there is between 97% (Figure 11A) and 99% (Figures 11B and 11C) certainty that the locking plate is cost-effective compared to the non-locking plate with a slow decline in certainty as the WTP increases.
Table 5: Sensitivity analyses cost and effect outcomes*

<table>
<thead>
<tr>
<th>Societal Sensitivity Analysis 1 (n = 164, CL = 106, PUD = 58)</th>
<th>Plate</th>
<th>Cost*&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Δ Cost</th>
<th>CI, p-value</th>
<th>Effect*&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Δ Effect</th>
<th>CI, p-value</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locking</td>
<td>23679.56</td>
<td>-5295.86</td>
<td>(9873.7, -716.5), 0.02†</td>
<td>21.32</td>
<td>+1.60 (-6.1, 2.9), 0.49</td>
<td>-3309.91</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-locking</td>
<td>28975.42</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Societal Sensitivity Analysis 2 (n = 249, CL = 144, PUD = 105)</th>
<th>Plate</th>
<th>Cost*&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Δ Cost</th>
<th>CI, p-value</th>
<th>Effect*&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Δ Effect</th>
<th>CI, p-value</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locking</td>
<td>24214.74</td>
<td>-5995.32</td>
<td>(-8897.5, -3093.1), &lt;0.01‡</td>
<td>21.32</td>
<td>+1.60 (-6.1, 2.9), 0.49</td>
<td>-3747.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-locking</td>
<td>30210.06</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Societal Sensitivity Analysis 3 (n = 249, CL = 144, PUD = 105)</th>
<th>Plate</th>
<th>Cost*&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Δ Cost</th>
<th>CI, p-value</th>
<th>Effect*&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Δ Effect</th>
<th>CI, p-value</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locking</td>
<td>24056.14</td>
<td>-5752.66</td>
<td>(-8760.0, -2745.3), &lt;0.01‡</td>
<td>21.32</td>
<td>+1.60 (-6.1, 2.9), 0.49</td>
<td>-3595.41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-locking</td>
<td>29808.81</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Values are reported as means  
<sup>a</sup> 2016 Canadian dollars.  
<sup>b</sup> Total change Knee injury and Osteoarthritis Outcome Score (KOOS) between baseline and 12 months  
† p < 0.05, ‡ p ≤ 0.001  
Abbreviations: ICER = Incremental cost-effectiveness ratio, CI = confidence interval
Table 6: Sensitivity analyses net benefit regression results.

<table>
<thead>
<tr>
<th>WTP*</th>
<th>Incremental net benefit</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4238.26 (2240.09)</td>
<td>-186.6 to 8663.1</td>
<td>0.060</td>
</tr>
<tr>
<td>250</td>
<td>4609.59 (2419.84)</td>
<td>-170.3 to 9389.5</td>
<td>0.059</td>
</tr>
<tr>
<td>500</td>
<td>4980.91 (2832.09)</td>
<td>-613.3 to 10575.1</td>
<td>0.081</td>
</tr>
<tr>
<td>750</td>
<td>5352.24 (3393.11)</td>
<td>-1350.1 to 12054.6</td>
<td>0.117</td>
</tr>
<tr>
<td>1000</td>
<td>5723.56 (4041.43)</td>
<td>-2259.4 to 13706.5</td>
<td>0.159</td>
</tr>
<tr>
<td>1250</td>
<td>6094.89 (4741.36)</td>
<td>-3270.7 to 15460.4</td>
<td>0.201</td>
</tr>
<tr>
<td>1500</td>
<td>6466.22 (5473.14)</td>
<td>-4344.8 to 17277.2</td>
<td>0.239</td>
</tr>
<tr>
<td>1750</td>
<td>6837.54 (6225.55)</td>
<td>-5459.7 to 19134.8</td>
<td>0.274</td>
</tr>
<tr>
<td>2000</td>
<td>7208.87 (6991.93)</td>
<td>-6602.2 to 21019.9</td>
<td>0.304</td>
</tr>
</tbody>
</table>

Societal Sensitivity Analysis 1 (n = 164, CL = 106, PUD = 58)

<table>
<thead>
<tr>
<th>WTP*</th>
<th>Incremental net benefit</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5446.01 (1480.25)</td>
<td>2529.9 to 8362.3</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>250</td>
<td>5653.11 (1621.99)</td>
<td>2457.8 to 8848.5</td>
<td>0.001‡</td>
</tr>
<tr>
<td>500</td>
<td>5860.22 (1949.72)</td>
<td>2019.3 to 9701.2</td>
<td>0.003†</td>
</tr>
<tr>
<td>750</td>
<td>6067.32 (2388.05)</td>
<td>1362.8 to 10771.8</td>
<td>0.012†</td>
</tr>
<tr>
<td>1000</td>
<td>6274.43 (2887.03)</td>
<td>586.9 to 11961.9</td>
<td>0.031†</td>
</tr>
<tr>
<td>1250</td>
<td>6481.53 (3420.22)</td>
<td>-256.4 to 13219.5</td>
<td>0.059</td>
</tr>
<tr>
<td>1500</td>
<td>6688.64 (3973.88)</td>
<td>-1140.0 to 14517.3</td>
<td>0.094</td>
</tr>
<tr>
<td>1750</td>
<td>6895.75 (4540.52)</td>
<td>-2049.2 to 15840.7</td>
<td>0.130</td>
</tr>
<tr>
<td>2000</td>
<td>7102.85 (5115.84)</td>
<td>-2975.5 to 17181.2</td>
<td>0.166</td>
</tr>
</tbody>
</table>

Societal Sensitivity Analysis 2 (n = 249, CL = 144, PUD = 105)

<table>
<thead>
<tr>
<th>WTP*</th>
<th>Incremental net benefit</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5087.07 (1539.42)</td>
<td>2054.4 to 8119.8</td>
<td>0.001‡</td>
</tr>
<tr>
<td>250</td>
<td>5294.18 (1672.44)</td>
<td>1999.4 to 8588.9</td>
<td>0.002†</td>
</tr>
<tr>
<td>500</td>
<td>5501.28 (1988.74)</td>
<td>1583.4 to 9419.1</td>
<td>0.006†</td>
</tr>
<tr>
<td>750</td>
<td>5708.39 (2417.42)</td>
<td>946.0 to 10470.8</td>
<td>0.019†</td>
</tr>
<tr>
<td>1000</td>
<td>5915.50 (2909.23)</td>
<td>184.3 to 11646.7</td>
<td>0.043†</td>
</tr>
<tr>
<td>1250</td>
<td>6122.60 (3437.16)</td>
<td>-648.7 to 12893.9</td>
<td>0.076</td>
</tr>
<tr>
<td>1500</td>
<td>6329.71 (3986.90)</td>
<td>-1524.6 to 14184.0</td>
<td>0.114</td>
</tr>
<tr>
<td>1750</td>
<td>6536.81 (4550.55)</td>
<td>-2427.8 to 15501.5</td>
<td>0.152</td>
</tr>
<tr>
<td>2000</td>
<td>6743.92 (5123.52)</td>
<td>-3349.5 to 16837.4</td>
<td>0.189</td>
</tr>
</tbody>
</table>

* WTP for a one-point improvement on the KOOS total change score from baseline to 12 months
** Incremental net benefit with standard error (SE)
* A positive incremental net benefit favors the locking plate treatment group
† p < 0.05, ‡ p ≤ 0.001
Abbreviations: WTP = willingness-to-pay, CI = confidence interval
Figure 11: Sensitivity analysis cost-effectiveness acceptability curves (CEAC) displaying the probability that the locking plate is cost-effective compared to the non-locking plate from the societal perspective over a range of willingness to pay values for an additional one-point improvement in the Knee injury and Osteoarthritis Outcome Score total change score (baseline to 12 months). A) Adjusting the dollar value for retirement or home making time, B) Adjusting the time to return to work, C) Combining the two previous adjustments.
Chapter 4

4 Discussion

The present study is the first to investigate the clinical and cost-effectiveness of a locking plate compared to a non-locking plate in patients undergoing medial opening wedge HTO. We found statistically significant differences in time to return to full weight-bearing favoring the locking plate group, while there were no statistically significant differences in the KOOS total change score or any of its subdomains from baseline to six months between the two plate groups. Our results also suggest that the locking plate is unlikely to be cost-effective from the healthcare payer perspective, although it may be cost-effective from the societal perspective.

With the suggested additional stability that the locking plate provides, we expected these patients to return to full weight-bearing much faster than patients who received the non-locking plate. In line with our hypothesis, we found that patients who underwent HTO with the locking plate returned to full weight-bearing without gait aid use at a mean 10.9 ± 5.8 weeks after surgery, which was significantly sooner than patients receiving the locking plate whose return to full weight-bearing time was 17 ± 6.5 weeks (between group difference = 6.1 weeks, 95% CI 4.5, 7.6). The present findings are in line with those from Asik et al. who report return to full weight-bearing times of approximately three months after surgery among 65 patients who received a non-locking plate.\textsuperscript{24}

Reports in the literature for time to return to full weight-bearing in locking plates vary considerably. Lobenhoffer and Agneskirchner reported that patients who received a locking plate (Synthes TomoFix Plate\textsuperscript{®}) began full weight-bearing as early as six to nine weeks postoperative, however it is unclear whether this was with complete discontinuation of crutch use or if the patient was able to put full weight on the operative limb with assisted crutch use.\textsuperscript{177} Staubli et al. reported that patients returned to full weight-bearing without crutches at ten weeks after surgery on average when using a locking plate (Synthes TomoFix Plate\textsuperscript{®})\textsuperscript{178}, while Brosset et al. reported a mean 3
months to return to full weight-bearing without gait aid assistance among 51 patients using the same locking plate\(^3^9\).

Hernigou et al. also compared patients receiving locking and non-locking HTO plates (Limmed Plate\(^\circledR\)). They found that 80% of patients began full weight-bearing on the operative limb without crutches at a mere two weeks following the HTO when locking screws were used (n = 85), while matched control patients who received non-locking screws (n = 85) took three months to return to full weight-bearing. However, their patient sample is considered a healthy weight (BMI between 20 and 25 kg/m\(^2\))\(^3^7\), whereas our patient sample is considered borderline obese (BMI \(\approx 30\) kg/m\(^2\)). It is therefore difficult to compare our results with the results from Hernigou et al. as previous studies have emphasized the importance of handling the rehabilitation process after HTO in obese patients with care due to a longer period time required for healing\(^1^2^9,1^7^9,1^8^0\).

A recent study from Landsdaal et al. investigated the functional impacts of early weight-bearing for patients undergoing medial opening wedge HTO with a locking HTO plate (Synthes TomoFix Plate\(^\circledR\)) in a randomized control trial\(^3^0\). They found that although patients were able to immediately begin weight-bearing (45 days earlier than their delayed weight-bearing group), 29% of patients in the immediate weight-bearing group (n = 25) were still using crutches at three months compared to only 17% of the delayed weight-bearing group patients (n = 25). This suggests that goals should perhaps not be aimed at allowing patients to immediately begin weight-bearing after HTO surgery, but instead identifying the optimal time period to begin the weight-bearing process that promotes bone healing in a safe manner.

A primary concern for surgeons in allowing patients an early return to full weight-bearing without crutches is the risk of post-operative complications. However, we found that despite a much faster return to full weight-bearing for the locking plate patients, post-operative complications were generally similar between the two groups aside from hardware failures which occurred slightly more frequently in patients receiving the non-locking plate. This is likely because of the lack of primary stability that the non-locking
plate provides with excess motion to the osteotomy site and increased stress on the plate and screws$^{33,35}$. Although we expected to see higher rates of plate removal in the locking plate group, the number of cases between groups is similar. It is important to note however, that plate removals were only reported up to 12 months following the HTO to be included in our cost-effectiveness analysis.

Based on the suggested quicker return to full weight-bearing with the locking plate, we expected to see earlier improvements in patient-reported outcomes in these patients when compared to those receiving the non-locking plate. Although the KOOS total and subdomain change scores are slightly higher in the locking plate group from baseline to six months after surgery, the between-group differences are not statistically significant. No other studies have compared KOOS scores between the locking plate and non-locking plate, however the large improvements in KOOS seen for both treatment groups from baseline to six months after the surgery is similar to results found in the literature. Brinkman et al. found significant improvements for early weight-bearing patients when using a locking plate (Synthes TomoFix Plate®, n = 14), with a change score ranging between 8 and 35 points from baseline to six months in individual KOOS subdomains$^{27}$. Birmingham et al. also found significant improvements in all KOOS domains from baseline to six months when using a non-locking plate (Arthrex Puddu Plate®, n = 126), although the six month KOOS score mean values were not reported (primary outcomes were 24-month data)$^{122}$.

Results from our CEA suggest that the use of a locking plate for fixation in medial opening wedge HTO is unlikely to be cost-effective from the healthcare payer perspective, although it may be cost-effective from the societal perspective. In terms of effectiveness, we found statistical uncertainty surrounding the small difference in improvement seen in the KOOS total change score that favors the locking plate group (+1.60 KOOS total change point; 95% CI -1.8, 2.9) indicating that either intervention could be the favorable treatment. Therefore, our results are driven heavily by differences in costs between the two interventions.
In our sample, we found that the initial surgical costs are very similar between groups with similar rates of postoperative complications requiring additional intervention (i.e. revision surgery, etc.). The difference in overall cost between the two interventions (+$755.20 for the locking plate) is reflected in the raw plate and screw costs ($1,192.43 for the non-locking plate (Arthrex Puddu Plate®) and $1,827.43 for the locking plate (Arthrex ContourLock HTO Plate®)). The ICER value of +$472.00 per one additional point improvement in the KOOS total change score suggests that the Ministry of Health must be willing to pay almost $5,000 more per patient to achieve a clinically important improvement in KOOS score, however due to the similar outcomes between groups, it is unlikely to be cost-effective. This is further supported with the results from the NBR (Table 6) and the CEAC (Figure 10A) which show that the probability that the locking plate is cost-effective from the payer perspective plateaus at around 55% at a WTP of $1,000 (Figure 10A) with probabilities less than half of that when WTP < $1,000, making the non-locking plate a more attractive treatment option for institutional decision makers in terms of saving healthcare dollars.

On the other hand, we did find the locking plate to be cost-effective from the societal perspective, which incorporates indirect costs such as time off work, retirement and home making and out-of-pocket expenses for the patient. The difference in overall societal costs between treatment groups favored the locking plate with an estimated $6,228.21 cost saving at 12 months following the HTO. The cost difference is largely due to a much sooner time to return to employment/activities and reduction in productivity losses for patients receiving the locking plate. These conclusions are supported from our NBR model (Table 6) and CEAC (Figure 10B) which suggest that there is a 99% probability that the locking plate is cost-effective at a WTP of $0, however this certainty slowly decreases as the WTP value increases (Figure 10B). This is explained by the uncertainty surrounding the incremental effect between the two treatment groups. The wide confidence intervals around our estimated incremental effect (95% CI -6.1, 2.9) indicate that using the locking plate does not always result in health gains and therefore, the CEAC is a slowly decreasing function of WTP.\(^{181}\)
Both perspectives provide valuable information in the process of decision-making. A few essential aspects specific to HTO are worth considering when making decisions. The rehabilitation period after HTO surgery is deemed fairly lengthy with a period of crutch ambulation that can continue several weeks after surgery as evidenced by numerous studies in the literature\textsuperscript{24,30,39,177,178} and results from our study (Table 3). Consequently, employed patients are often off work for extended periods of time and retired and home making patients are often limited in their everyday activities for many weeks which can generate large losses in productivity for society.

The viewpoint of institutional decision makers is often quite restrictive to direct system costs and sometimes fails to consider the overall societal impacts. From our results, the decision maker may opt for using the non-locking plate due to significantly lower cost; however considering solely the healthcare payer perspective could significantly undermine the true benefit the locking plate for society. Ignoring these important costs in CEA can lead to inefficient allocation of resources both short and long-term for society as a whole\textsuperscript{182}. The societal perspective theoretically includes all costs relating directly to the patient, their families, the public, and government expenditures as a whole, making for a more comprehensive analysis. Although much attention is given to the direct healthcare costs associated with OA in current economic analyses, workforce absenteeism has been shown to contribute considerably to the burden of OA in Canada\textsuperscript{182}. One study estimated that 80\% of the overall annual costs for OA result from time lost from employment and leisure by both participants and unpaid caregivers\textsuperscript{143}. Therefore, it is important for decision makers to consider the entire scope of incurred costs when allocating resources. It is important to consider both perspectives for decision making, however most organizations such as The Canadian Agency for Drugs and Technologies in Health advocate that the societal perspective holds the most importance for the entire population’s best interest\textsuperscript{160}. 
Our center performs approximately 75 to 100 HTO surgeries annually. In the eyes of the healthcare payer, using the non-locking (Arthrex Puddu Plate®) for HTO could save $755.20 for every patient (equivalent to approximately $56,500 cost saving annually). When examining from a societal perspective, the costs associated with using the locking (Arthrex ContourLock HTO Plate®) over the non-locking plate are offset by significant savings to society (equivalent to approximately $467,000 cost saving annually). Ultimately, it may require surgeons to advocate the use of socioeconomically favorable treatment interventions and offer perspective to governing boards who remain restrictive in the decision-making process. Potential solutions include the reallocation of funds for surgical equipment to offset the higher cost of locking plates and profit from its societal cost savings, benefiting from both perspectives. For example, bone graft and substitutes cost between $500 and $750 per HTO procedure. Recent evidence suggests that the use bone graft or substitutes may be unnecessary when using a stronger locking plates as patients experience similar improvements in clinical outcomes without an increase in complication rates\textsuperscript{125}. Eliminating the cost of graft could offset the higher cost of the locking plate designs; however this is a question that demands further research.

4.1 Strengths & Limitations

To our knowledge, our study is the first to investigate clinical outcomes for the Arthrex ContourLock HTO Plate® and also the first to compare the cost-effectiveness of plate design in medial opening wedge HTO. The strengths of this study include the use of validated disease/joint specific outcomes and a large sample size. Furthermore, the use of the net benefit regression framework in our CEA allowed us to control for baseline variables and to explore potential interaction terms for a richer understanding of the cost-effectiveness, which can be limited when solely exploring incremental cost-effectiveness ratios\textsuperscript{173}. 
Perhaps the biggest limitation in our study was the retrospective design. The decision to use a locking vs. non-locking plate resulted from a shift in clinical practice. The lack of group randomization makes our study susceptible to biases that could factor into patient improvement after surgery as a result of between-group differences in baseline characteristics. However, baseline demographic and clinical characteristics that were believed to influence outcomes in this study are similar between groups and were also controlled for in our cost-effectiveness analysis.

Slight between-group differences are seen in the degree of joint degeneration in the lateral compartment of the knee (more severe for the locking plate group). There are also between-group differences in the number of concomitant tibial tubercle osteotomy surgeries performed (more in the locking group), the number of outpatient procedures (more in the locking group) and the number of osteotomies that were left unfilled, with no bone graft (more in the non-locking group). For these characteristics, time was likely a factor contributing to between-group differences as a result of the shift in clinical practice. Differences in lateral compartment degeneration could have resulted from differences in measurement between radiographic assessors or surgeon expertise over time treating more advance OA cases. Differences in the number of TTOs, outpatient procedures performed and osteotomy gaps left unfilled could have resulted from changes in medical practice over time. However, these clinical and surgical characteristics are not thought to have influenced the outcomes investigated in this study.

Another large limitation in our study is the high volume of assumptions that were made when assessing patient charts such as identifying the exact time to return to full weight-bearing without crutches. Although data extraction methods were standardized for the two treatment groups, data collected prospectively (i.e. through questionnaires) may have been more precise. Prospective data collection would have also allowed us to address other relevant questions such as patient satisfaction following the surgery (i.e. related to return to weight-bearing rehabilitation process).
Further, patients who filled out cost questionnaires in our study were asked to recall how long they were off work after surgery, making our data susceptible to recall bias. To minimize this, response options were presented in 2-month increments (i.e. 3-4 months).

Another limitation to our study is that all surgeries were performed by a single surgeon. This presents the risk for expertise bias that could influence interpretation of bone consolidation and pain in deciding whether to allow the patient to begin full weight-bearing. Additionally, complication rates from our study are low when compared to previous studies. The surgeon’s expertise could have resulted in the lower complication rate from years of experience performing HTO procedures, which threatens the external validity (generalizability) of the results to other clinical practices. Specifically, the frequency of hardware removals reported for patients receiving a locking plate are quite low when compared to previous studies who report over 80% removal rate. Although we were unable to control for this in our cost-effectiveness analysis that uses trial-based data, alternative model-based analyses can use complication and plate removal rates reported in the literature to generate cost estimates.

The generalizability of this study is also threatened by the fact that all surgeries were performed at a single center. For example, our center receives a pro-rate on charges for some surgical equipment costs due to the high volume of HTO cases performed annually, which may not translate to costing at other centers. It is important also to note that this study was designed to evaluate the clinical and cost-effectiveness of using the Arthrex ContourLock HTO Plate® (locking) over the Arthrex Puddu Plate® (non-locking) for medial opening wedge HTO in patients with medial compartment knee OA and varus alignment and therefore conclusions should not be drawn for patients receiving variations of the osteotomy procedure (i.e. lateral closing wedge HTO, distal femoral osteotomy, etc.), who are valgus aligned or undergo HTO using a different internal fixation plate.

Another potential limitation for this study is the 12-month follow-up period. Previous studies have indicated that the survivorship of a HTO can exceed 15 years and the optimal economic analysis would incorporate all lifetime costing which includes
revision and co-interventions past the 12 month mark (i.e. revision HTO, conversion to TKA or UKA, etc.). However, the likelihood that large differences in cost exist between a locking plate and non-locking plate past the 12 month mark is low since the majority of post-operative complications occur within the first 12 months of surgery, as does the progression to full weight-bearing\textsuperscript{28,30,36,126,179}.

Finally, some costs typically included in CEAs to capture a more comprehensive societal perspective were omitted due to the retrospective nature of the study. Direct costs related to out-of-pocket expenses for the patient/caregivers and over-the-counter medication/aids, as well as indirect costs related to time lost from the caregiver were not available to be included in the study. Therefore, our total cost values are likely underestimated. However, we suspect that addition of these costs would increase the cost difference between groups as a result of a much quicker return to full weight-bearing for the locking plate group. Our estimate is therefore conservative.
Chapter 5

5 Conclusion

We found that patients who received a locking plate (Arthrex ContourLock HTO Plate®) for medial opening wedge HTO returned to full weight-bearing without assistance of gait aid significantly faster than patients who received a non-locking plate (Arthrex Puddu Plate®). No significant between-group differences were found for the change in KOOS from baseline to six months after surgery. Results from our CEA indicate that the locking plate is not cost-effective from the healthcare payer’s perspective as a result of higher initial plate and screw costs. The locking plate is however, cost-effective from the societal perspective as patients return to work much faster after the surgery.

5.1 Future Directions

The retrospective nature of this study required a high volume of assumptions to be made during data extraction, opening the opportunity for improved study design in future investigations. Prospective studies should aim to introduce more surgeons and orthopaedic centers to make results from this study (i.e. complication rates, cost, etc.) more generalizable to all medial opening wedge HTO procedures while including various different locking and non-locking plate designs. Time to return to weight-bearing and time to return to work should be collected prospectively, along with direct patient costs, caregiver costs and other out-of-pocket expenses that would generate a more complete CEA estimate.

Results from this study indicate that the locking plate allows patients to return to full weight-bearing much quicker after HTO. It would therefore be important to evaluate patient outcomes (i.e. change in muscle strength, functional outcomes, etc.) at shorter follow-up times (i.e. 3 months) to observe if the differences in return to full weight-bearing time could also affect the rate of improvement in patient activities of daily living,
quality of life and gait mechanics. Finally, studies should be conducted to determine whether costs can be minimized when eliminating bone graft or substitute in HTO procedures when a locking plate is used, as some studies have suggested that bone graft is not necessary for these cases\textsuperscript{125}. In turn, we could benefit from both the healthcare and societal viewpoints of cost when using a locking plate.
References


35. Stoffel K, Stachowiak G, Kuster M. Open wedge high tibial osteotomy:


42. Maas S, Diffo Kaze A, Dueck K, Pape D. Static and Dynamic Differences in Fixation Stability between a Spacer Plate and a Small Stature Plate Fixator Used


52. Felson DT, Zhang Y. An update on the epidemiology of knee and hip osteoarthritis


132. Schallberger A, Jacobi M, Wahl P, Maestretti G, Jakob RP. High tibial valgus


Appendices

Appendix A: Ethics Approval

Principal Investigator: Dr. Trevor Birmingham
File Number: 1187
Review Level: Delegated
Approved Local Adult Participants: 000
Approved Local Minor Participants: 0
Protocol Title: "Medial Opening Wedge High Tibial Osteotomy for the Treatment of Knee Osteoarthritis: Evaluation of Dynamic Joint Loads and Health-Related Quality of Life" - 029.12E
Department & Institution: Health Sciences/Physical Therapy, Western University
Sponsor: Canadian Institutes of Health Research

Ethics Approval Date: March 26, 2013 Expiry Date: April 30, 2017

Documents Reviewed & Approved & Documents Received for Information:

<table>
<thead>
<tr>
<th>Document Name</th>
<th>Comments</th>
<th>Version Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revised Letter of Information &amp; Consent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Revised Western University Protocol</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

This is to notify you that the University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced revision(s) or amendment(s) on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the University of Western Ontario Updated Approval Request Form.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

The Chair of the HSREB is Dr. Joseph Gilbert. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000960.

This is an official document. Please retain the original in your files.
Curriculum Vitae
Codie Alexander Primeau, BSc

EDUCATION

Master of Science  Kinesiology, Integrative Biosciences
Collaborative Program in Musculoskeletal Health Research
Western University, London, Ontario, Canada

Bachelor of Science  Sciences de l’activité physique (Human Kinetics)
University of Ottawa, Ottawa, Ontario, Canada
Sept. 2010 – Apr. 2014

RESEARCH EXPERIENCE

Western University  Clinical and Cost-Effectiveness of a Locking Versus Non-Locking Fixation Plate in Medial Opening Wedge High Tibial Osteotomy
Graduate Student  Supervisors: Drs. Trevor Birmingham, J. Robert Giffin & Jacquelyn Marsh
2014-2016

Western University  Effect of Congenital Versus Acquired Varus on Patient-Reported Outcomes after High Tibial Osteotomy
Graduate Student  Supervisors: Drs. Trevor Birmingham & J. Robert Giffin
2015-2016

Western University  A Randomized Trial Comparing High Tibial Osteotomy Plus Non-Surgical Treatment to Non-Surgical Treatment Alone
Graduate Student 2014-2016

University of Ottawa  Self-Controlled Feedback Is Effective If It Is Based on the Learner’s Performance: A Replication and Extension of Chiviacowsky & Wulf (2005)
Undergraduate Student  Supervisors: Michael Carter & Dr. Diane Ste-Marie
2013-2014

University of Ottawa  A Comparative Biomechanical Analysis of Mid-Foot and Heel Strike Running Patterns
Undergraduate Student  Supervisors: Adam Teav & Dr. Jing Xian Li
2013-2014
**HONOURS & AWARDS**

Western University

2016 Top Oral Presentation (KGSA Research Symposium)
2016 Top Poster Presentation (KGSA Research Symposium)
2015 Transdisciplinary Bone & Joint Training Award ($10,000)
2014-2016 Western Graduate Research Scholarship

University of Ottawa

2014 Maurice Jetté Student Leadership Award ($1,000)
2014 Graduate with Magna Cum Laude Distinction
2013 Undergraduate Research Opportunity Program Grant ($1,000)
2010-2014 Dean’s Honor List

**CONFERENCES**

London, ON 2nd Annual KGSA Symposium
*April 2016* 
*Oral Presentation*: High Tibial Osteotomy: A retrospective cohort comparing locking vs. non-locking plates
*Poster Presentation*: Effect of congenital vs. acquired varus on patient-reported outcomes after high tibial osteotomy

London, ON Canadian Bone & Joint Conference 2016
*April 2016* 
*Poster Presentation*: High Tibial Osteotomy: A retrospective cohort comparing locking vs. non-locking plates

Amsterdam, NED Osteoarthritis Research Society International (OARSI) World Congress on Osteoarthritis 2016
*April 2016* 
*Poster Presentation*: Effect of congenital vs. acquired varus on patient-reported outcomes after high tibial osteotomy

London, ON Faculty of Health Sciences Research Day
*March 2016* 
*Poster Presentation*: Effect of congenital vs. acquired varus on patient-reported outcomes after high tibial osteotomy

London, ON 1st Annual KGSA Symposium
*April 2015* 
*Oral Presentation*: High Tibial Osteotomy: A retrospective cohort comparing locking vs. non-locking plates

London, ON Faculty of Health Sciences Research Day
*March 2015* 
*Poster Presentation*: High Tibial Osteotomy: A retrospective cohort comparing locking vs. non-locking plates
TEACHING EXPERIENCE

Teaching Assistant
Western University

Winter 2016  KIN 2236B – Introduction to Athletic Injuries
Professor: Dave Humphreys

Fall 2015  KIN 3330 – Laboratory in Exercise Physiology
Professor: Mark Babcock

Winter 2015  KIN 3343: Biomechanical Analysis of Discrete Sport Skills
Professor: Volker Nolte

Fall 2014  KIN 4560: Advanced Topics in Musculoskeletal Rehab
Professor: Dave Humphreys

PEER-REVIEWED ABSTRACTS
