



LEARNING OBJECTIVES

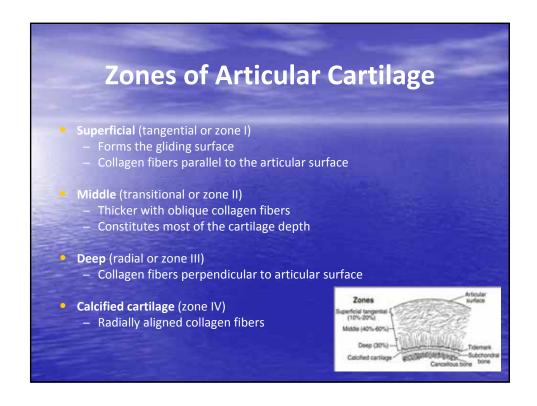
- Understanding the natural history of osteoarthritis of the knee
- Recognizing the signs and symptoms of knee osteoarthritis
- Become familiar with the knee physical exam
- Learn what studies to order to help diagnose knee osteoarthritis
- Understanding the treatment algorithm for knee osteoarthritis

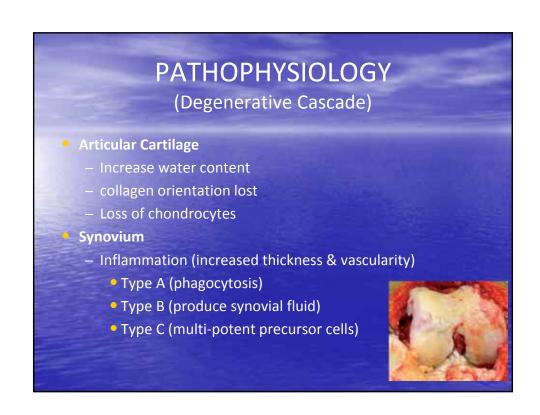
Knee Osteoarthritis

- 52 million Americans suffer from arthritis
- Most common joint disorder in the US
- Knee OA affects 37% of Americans >60 yo
 - 42% Females: 31% Males
- Estimated costs due to hospital expenditures of total knee replacements \$28.5 billion (2009)

KNEE ARTHRITIS Arthritis is a degenerative joint disease Knee arthritis is one of the most common joints effected Results in destruction of cartilage progressing to bone on bone in moderate/severe disease

General Principles • Knee is composed of three joint compartments - Medial, lateral and patellofemoral compartments • Normal knee functions as a complex hinge allowing - Flexion, extension, rotation, and gliding • Weight distribution across the knee with normal alignment - 60% through medial compartment - 40% through lateral compartment





PATHOPHYSIOLOGY (Degenerative Cascade) Meniscus Increasing congruency Increases contact area leads to decreased point loading Shock-absorption Meniscus is more elastic than articular cartilage, and therefore absorbs shock Synovial fluid Decrease of hyaluronin and lubricin Medial Meniscus PCL Ligament Meniscus Ligament

PATHOPHYSIOLOGY (Degenerative Cascade) In summary: • Articular cartilage degeneration • Meniscus degeneration • Synovial inflammation • Synovial fluid with diminished lubrication • Kidney failure, Heart failure, why not Joint failure?

Presentation

- Patients c/o knee pain worse with walking up or down steps
- Patellofemoral articulation reaction force
 - 2-3x body weight while descending stairs
- Tibiofemoral articulation reaction force
 - 3x body weight with walking

Presentation

- Symptoms may wax & wane often in correlation with recent activities or body stressors (illness)
- Not uncommon for OA exacerbation to occur during hospital admission for unrelated event
 - Surgery, CHF, COPD, pneumonia, viral illness

Physical Examination

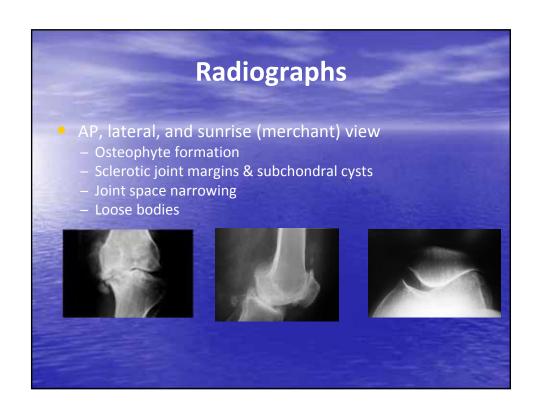
- Joint line tenderness to palpation
 - Degenerative compartment will often correlate to overall alignment
 - Varus deformity = medial joint space narrowing
 - Valgus deformity = lateral joint space narrowing
- Effusion
 - Persistent large/tense effusion may represent degenerative meniscus tear (without specific event)

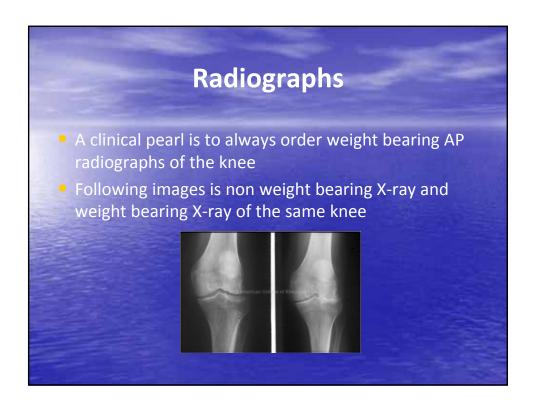
Physical Examination

- McMurray's test
 - Flex knee & place one hand on medial side of knee
 - Gently externally rotate leg & bring knee into extension
 - Palpable click is a positive test (medial meniscus tear)
- Lachman's test
 - Most sensitive exam to detect ACL tear



Physical Examination • Flexion contracture - Persistent synovitis and progressive immobility will lead to tight hamstrings • Joint widening - Osteophyte formation is the body's attempt to heal the progressive destruction of cartilage • Crepitus - Patella should glide smoothly over femoral trochlea



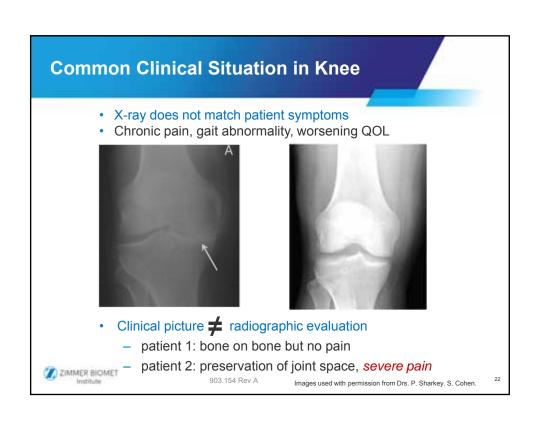




Degenerative tears in older patients are most commonly found in the posterior horn of the medial meniscus Correlation to physical exam findings and/or mechanical symptoms is critical to confirm diagnosis

MRI has been shown to find asymptomatic degenerative meniscus tears in over 60% of patients > 65 y.o. Diagnosis of symptomatic meniscus tear becomes difficult in the setting of concomitant OA Articular cartilage destruction may be the root cause of the patients symptoms





MRI Changes the Picture

- Bone damage not appreciated on radiographs
- As MRI technology improves helps us better understand this scenario
- MRI demonstrates:
 - Soft tissue causes of pain (meniscal tear, synovitis, etc.)
 - The primary reported source of pain: chronic subchondral bone marrow lesions (BML)





903.154 Rev A

Images used with permission from Dr. S. Cohen..

Rothman/Cohen Retrospective Case Series

Cohen, SB, Sharkey, PF. Subchondroplasty for Treating Bone Marrow Lesions, Journal of Knee Surgery, Dec. 2015.

Retrospective Review of 1st 66 Consecutive Patients

General Study Protocol

Patient profile

- Chronic, aching pain (VAS ≥ 4/10)
- ↑ pain with load bearing
- · Pain localized to compartment of subchondral bone defect
- · Failed conservative care
- Typical candidate for knee replacement

Clinical diagnosis of BML bone defect could be in combination with

- Meniscal tear / extrusion
- · Cartilage thinning / fraying / loss
- · Mechanical symptoms / loose bodies

Surgical care

- 1 surgeon, 1 center
- SCP® procedure + arthroscopy

Postop management

- WBAT w/ crutches 1 wk
- PT started 10-14 d post
- Full activity 4-8 wk post



Cohen Clinical Series -Results

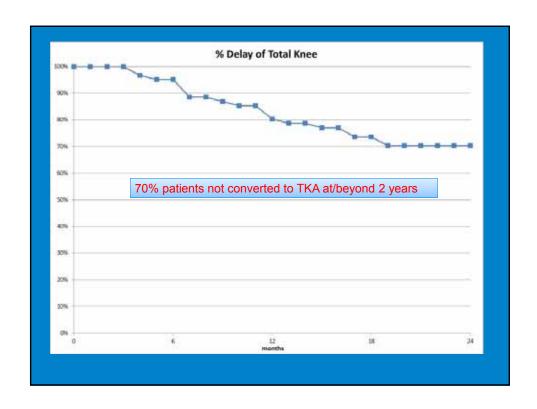
Patients followed ≥ 2 years

- · Regular follow up visits
- · Data points collected
- VAS Pain
- Change from baselineDuration of change (years postop at final VAS)
- IKDC
- · Change from baseline
- Duration of change
- Kaplan-Meier survivorship
- · Not converted to TKA/UKA











Conservative Treatment

- Weight Loss
 - Indications: symptomatic OA and BMI > 25
 - Improvement in joint pain and function
 - Reducing the risk of progression of OA
 - Each pound of weight loss results in a fourfold reduction in the load exerted on the knee per step during daily activities

Conservative Treatment

- Exercise / Physical therapy
 - First line treatment for all patients with symptomatic arthritis
 - Low impact aerobic exercise
 - Swimming
 - Bicycling
 - Improving flexibility and strengthening muscles improve functional outcome and pain scores

Conservative Treatment

- Exercise / Physical therapy
 - Quadriceps strengthening
 - Improve stability of joints and lessens pain
 - Hamstring stretching
 - Prevention of flexion contracture
 - Combination of supervised exercises and home program show the best results
 - Benefits often lost after 6 months if exercises are stopped

Conservative Treatment

- Viscosupplement intra-articular injections
 - Hyaluronic acid (HA) forms the backbone of aggrecans
 - The macromolecule that makes up cartilage matrix
 - HA at low load speeds acts as a lubricant and faster movements as a shock absorber
 - In OA the concentration of HA is reduced by half to one third of normal

Pharmacologic Treatment

- Acetaminophen at doses of up to 4 g per day have demonstrated to be superior to placebo in relief of pain resulting form OA
- Acetaminophen less effective than NSAIDs
- Tramadol
 - Strongly recommended by AAOS

Pharmacologic Treatment

- NSAIDS
 - First line treatment for all patients with symptomatic arthritis
 - Risk factors for adverse reaction
 - Age > 60
 - Multiple medical comorbidities
 - H/o PUD
 - H/o GI bleeding
 - Concurrent corticosteroid use
 - Anticoagulant use

Pharmacologic Treatment NSAIDS Cox-2 inhibitors limit inflammation without interfering with normal production of protective prostaglandins and thromboxane Decrease the potential gastric toxicity of NSAIDs Cox-2 inhibitors along with all NSAIDs may cause cardiovascular and renal side effects to varying degrees



Orthotics Padded shoe inserts Decrease in joint impact forces to joints Varus knee deformity - Lateral heel wedges

\$ 8-22

Hyaluronic Acid vs Corticosteroid Injections Meta-analysis, Randomized trial Reported effects of intra-articular hyaluronic acid vs corticosteroids on knee osteoarthritis 7 eligible trials included 606 patients ● 0 – 4 weeks: – Intraarticular corticosteroids appear to be more effective for pain than intraarticular hyaluronic acid 4 − 8 weeks: The 2 approaches have equal efficacy > 8 weeks: Hyaluronic acid has greater efficacy

Conservative Treatment

- Intra-articular corticosteroid injection
 - Limits inflammation of the joint
 - Injections given typically no closer than Q3 months
 - Useful in controlling acute exacerbation of OA
 - Often injection given in combination with Lidocaine

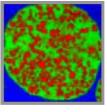
Microsphere Technology: Background

Pain relief associated with IA corticosteroid administration to patients with knee osteoarthritis (OA):

- Can diminish within 1-6 weeks following injection¹⁻⁴
- Is transient due to efflux of drug from the joint within hours of injection⁵

TA-ER is an extended-release formulation of the corticosteroid TA⁶⁻⁷

- Small crystals of TA are embedded in a PLGA co-polymer matrix
- Designed with the goal to extend TA joint residency time and reduce systemic exposure to TA following IA injection



Raman Microscopy cross-sectional view of a single microsphere. Green: PLGA matrix; Red: TA crystals

- IA, intraarticular; OA, osteoarthritis; PLGA, poly (lactic-co-glycolic acid); TA, triamcinolone acetonide;
 TA-ER, triamcinolone acetonide extended-release injectable suspension.

 1. Jinin P et al. Cochrane Dortobase Syst Rev. 2015; Oct 22;(10): CD005328. doi: 10.1002/14651858.CD005328.

 2. Ayhan E, et al. Vord J Orthop, 2014(5)]3531–61.

 3. Bjordal JM, et al. BMC Musculoskeler Disord. 2007;85:1.

 4. Godwin M, Dawes M. Can Fam Physician. 2004;50:241–8.

 5. Derendorf H, et al. Clin Pharmacol Ther. 1986;39(3):313–7.

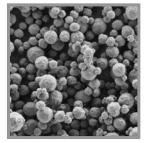
 6. Data on File. Fleion Therapeutics.

 7. Conaghan PG et al. In Press. NCT02357459.

TA-ER Microsphere Characteristics

TA-ER is prepared as an injectable suspension of ~45 µm microspheres1

- Active Ingredient: TA
 - FDA-approved for use via multiple routes of administration (including IA)2
 - FDA-approved for several diseases/conditions (including OA)²
 - One of the most prescribed IA corticosteroids3
- Microsphere Scaffold: PLGA4
 - Biodegradable polymer
 - Used in several FDA-approved extended-release therapeutics (>20-year history)



Electron micrograph of PLGA microspheres.

FDA, US Food and Drug Administration; IA, intraarticular; OA, osteoarthritis; PLGA, poly (lactic-co-glycolic acid); TA, triamcinolone acetonide extended-release injectable suspension.

1. Data on File: Flosion Therapeutics, Inc.

2. Kenalogs*-40 injection (triamcinolone acetonide injectable suspension) Prescribing Information. Bristol-Myers Squibb. Jan 2016.

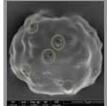
3. Data on File: Flosion Therapeutics, Inc.

4. Makadia HK and Siegel SJ. Polymers. 2011;3(3);1377.

TA-ER Microsphere Function

PLGA microsphere technology allows for extended-release of TA¹

- Initial TA release: TA crystals near the surface of the microsphere dissolve upon contact with synovial fluid
- Extended TA release: TA crystals that are more deeply embedded within the microsphere are slower to dissolve
 - Small pores on the surface of the microsphere are created by the dissolving TA crystals
 - ~500 nm channels appear throughout the microsphere; enable TA release from the interior through the surface pores
 - PLGA eventually degrades into lactic acid and glycolic acid, which ultimately metabolize into CO₂ and H₂O

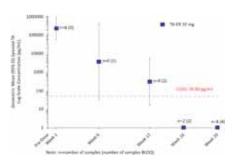


Electron micrograph of PLGA microsphere pores

TA-ER Microsphere Characteristics in a Pharmacokinetic Study: Synovial Fluid TA Concentrations

Patients with knee OA received a single IA injection; synovial fluid TA concentrations were measured¹

- **TA-ER 32 mg:** most patients had quantifiable TA through Week 12
 - Week 1: 231,328.9 pg/mL
 - Week 6: 3590.0 pg/mL
 - Week 12: 290.6 pg/mL



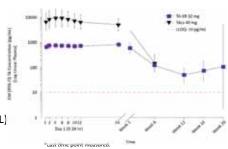
BLOQ, below limit of quantification; CI, confidence interval; LLOQ, lower limit of quantification; TA, triamcinolone acetonide; TAcs, triamcinolone acetonide extended-release injectable suspension.
TAEB, triamcinolone acetonide extended-release injectable suspension.
1. Adapted from Karsu's Ret al. Osernatrins's Carrilage. 2018;26(1):34-42.

4

TA-ER Microsphere Characteristics in a Pharmacokinetic Study: Plasma TA Concentrations

Patients with knee OA received a single IA injection; blood plasma TA concentrations were measured¹

- TA-ER 32 mg: plasma TA
 - Gradually increased to peak (836.4 pg/mL) over 24 hours
 - Slowly declined to <110 pg/mL over Weeks 12-20
- TAcs 40 mg: plasma TA
 - Peaked at 4 hours (9,628.8 pg/mL)
 - Decreased to 4,991.1 pg/mL at 24 hours
 - Was 149.4 pg/mL at Week 6*

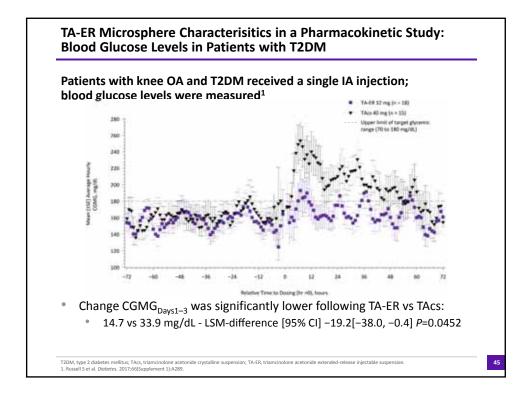


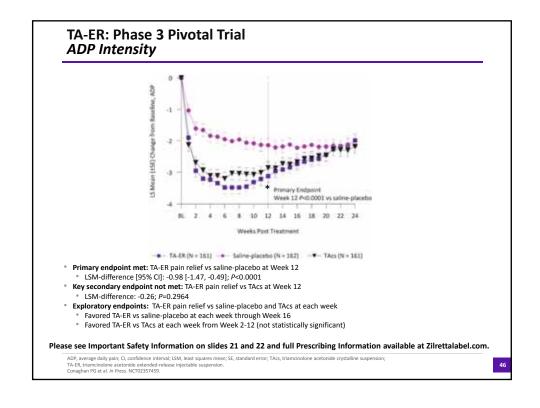
Please see Important Safety Information on slides 21 and 22 and full Prescribing Information available at Zilrettalabel.com.

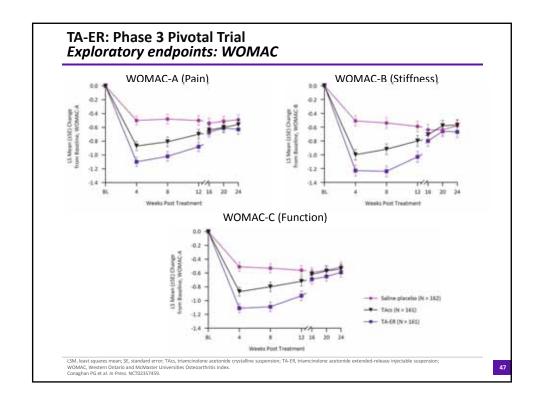
CI, confidence interval; GM, geometric mean; LLOQ, lower limit of quantification; OA, osteoarthritis; TA, triamcinolone acetonide; TAcs, triamcinolone acetonide crystalline suspension. TA-ER, triamcinolone acetonide extended-release injectable suspension.

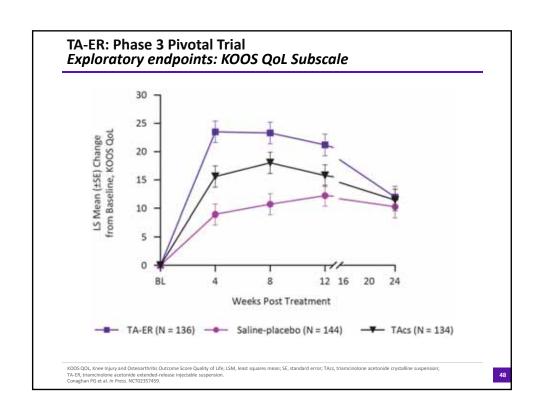
1. Adapted from Kraus VB et al. Sixcoorthrist Cardings 2.018;26(1):34-42.

44

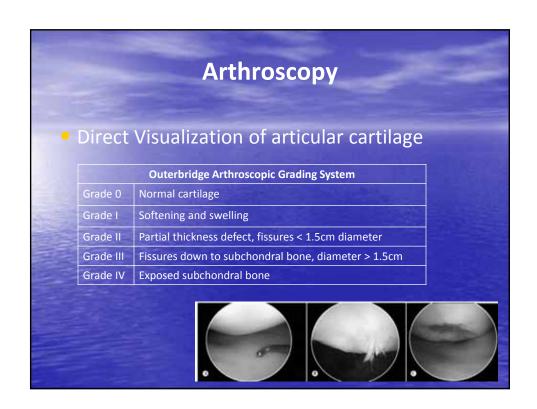












Evidence Based Medicine for Arthroscopic Debridement of Knee Osteoarthritis

- Study published in New England Journal of Med (2002)
- 180 patients with knee OA who received arthroscopic débridement, arthroscopic lavage, or placebo surgery (skin incisions)
- Outcomes were assessed at multiple points over a 24-month period
 - Use of 5 self-reported scores for pain, function, walking, and stair climbing
- The outcomes after arthroscopic lavage or arthroscopic debridement were no better than those after a placebo procedure

Arthroscopy

- Partial meniscectomy
 - >80% satisfactory function at minimum follow-up
 - Predictors of success
 - Age <40yo
 - Normal alignment
 - Minimal or no arthritis
 - Single tear

Arthroscopy Total meniscectomy 70% have arthritic X-ray changes 3 years after surgery 100% have arthrosis at 20 years Severity of degenerative changes is proportional to percent of the meniscus removed

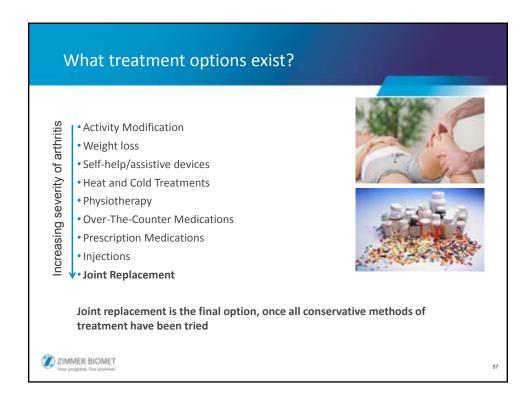
Unicompartmental Knee Arthroplasty Indications Isolated unicompartmental noninflammatory arthritis Deformity of less than 10 degrees Intact anterior cruciate ligament (ACL) Little or no joint subluxation Little or no patellofemoral disease Weight < 90 kg

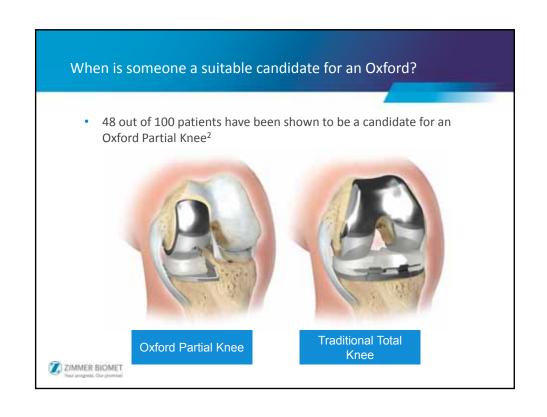
Unicompartmental Knee Arthroplasty

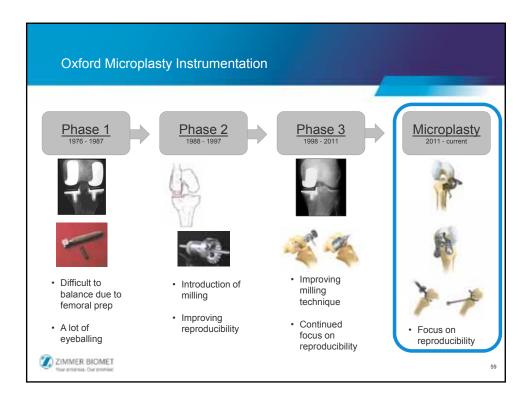
- Data suggests that only 6% of patients meet the criteria for whom knee arthroplasty is indicated
- Indications for this procedure have been expanded for younger patients
- 10 year survival rates range from 87 to 96%
- 15 year survival rates range from 79 to 90%
 - Survivorship declines rapidly in the second decade
- Late failure
 - Opposite compartment degeneration
 - Component loosening
 - Polyethylene wear

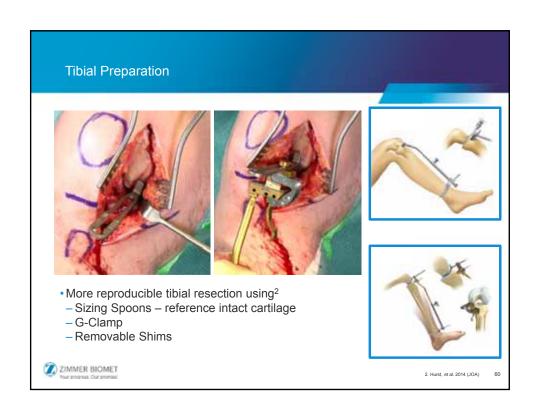


Table 1 American Academy of Orthopaedic Surgeons Evidence-Based Clinical Practice Guidelines for Osteoarthritis of the Knee ¹		
Strengthening exercises with neuromuscular education	Recommend	Strong
NSAIDs	Recommend	Strong
Total knee arthroplasty	Recommend	Strong
Appropriate weight loss (body mass index ≥25 kg/m²)	Recommend	Moderate
Valgus-producing proximal tibial osteotomy	Might recommend	Limited
Intra-articular corticosteroids	Cannot recommend for or against	Inconclusive
Acetaminophen (oral) or opioids (oral or transdermal patch)	Cannot recommend for or against	Inconclusive
Manual therapy	Cannot recommend for or against	Inconclusive
Physical agents, including electrotherapeutic modalities	Cannot recommend for or against	Inconclusive
Arthroscopic partial meniscectomy	Cannot recommend for or against	Inconclusive
Intra-articular hyaluronic acid	Cannot recommend	Strong
Braces (to unload medial compartment)	Cannot recommend	Strong
Arthroscopic intervention (eg. lavage, débridement)	Cannot recommend	Strong
Glucosamine and chondroitin	Cannot recommend	Strong
Acupuncture:	Cannot recommend	Strong
Insoles (eg. lateral wedge)	Cannot recommend	Moderate
Needle lavage	Cannot recommend	Moderate
Free-floating (unfixed) interpositional device	Cannot recommend	Consensus (no reliable evidence



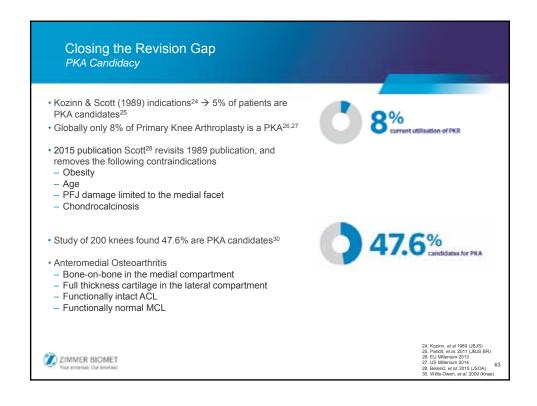


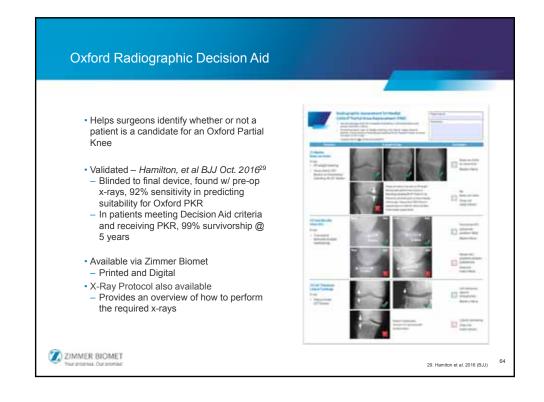




Globally Published Oxford Partial Knee Survivorship Non-designer results **Author** Year Published Cohort Follow-Up Survival Svard⁶ 2001 124 10-year 95% Rajasekhar⁷ 2004 135 94% 10-year Yoshida8 2013 1279 10-year 95% Jones⁹ 1000 10-year 2012 91% Lim¹⁰ 2012 400 10-year 94% Faour-Martin¹¹ 2013 416 10-year 95% Price¹² 2011 682 20-year 91% ZIMMER BIOMET







Benefits of PKA compared to TKA

Benefits

- Better range of motion³²⁻³⁴
- Preserving more healthy bone than TKA34
- More physiological functionality34 and near normal gait35 than TKA
- Faster return to a more functional level and shorter hospital stay than TKA³²
- \bullet Fewer and less severe postoperative complications including less morbidity compared with TKA 36,37

And for society...

- Substantial cost savings over TKA³⁰ (\$3,261 per knee)
- Registry data reports that TKAs are 2.6 times more likely to have risk of reoperation for infection37
- Average reduction in length of stay, at least 0.8 days in favour of PKA (variation between 0.8 4 days) $^{36.41}$
- Additional cost savings when associated with an accelerated recovery protocol⁴²



30. Willis-Owen, et al. 2009 (Knee) 32. Lombardi, et al. 2009 (CORR) 33. Amin, et al. (2006) 34. Deshmukh, et al. (2001) 35. Wilk, et al. (2013) 36. Brown, et al. (2012)

37. Robertsson, et al. 1999 (AOS) 38. Shakespeare, et al. 2003 (Knee) 39. Yang, et al. 2003 (SMJ) 40. Xie, et al. 2009 (EJHE) 41. Koskinen, et al. 2008 (AO) 42. Reilly, et al. 2005 (Knee)

Lifetime Warranty

- Every Oxford Partial Knee implanted on or after April 29, 2013 is covered under the only Lifetime Knee Implant Replacement Warranty in the US*
- If a patient receives an Oxford Partial Knee, and it has to be revised for any reason, Zimmer Biomet will cover the cost of the Zimmer Biomet replacement knee implant.



ZIMMER BIOMET





References

- Bannuru,R., Natov, N., Obadan, I., Price, L, Schmid, C., McAlindon, T. (2009). Therapeutic trajectory of hyaluronic acid versus corticosteroids in the treatment of knee osteoarthritis: a systematic review and metaanalysis. Journal of Arthritis Rheumatology. Dec 15;61(12):1704-11
- Boyer, M. (2014) Primary Knee Arthroplasty. Wellman, S., Bolognesi, M. AAOS Comprehensive Orthopaedic Review (pp 1289-1304) Rosemont, IL: American Academy of Orthopaedic Surgeons.
- Fischgrund, J. (2008). Knee Reconstruction and Replacement. Peters, C., Crofoot, C. *Orthopaedic Knowledge Update* (pp 457-472). Rosemont, IL: American Academy of Orthopaedic Surgeons.
- Hoshino, A., Wallace, W. (1987). Impact-absorbing properties of the human knee. Journal of Bone Joint Surgery British, 69(5), 807-811.
- Miller, M., Thompson, S., Hart, J. (2012). Total Knee Arthroplasty.
 Review of Orthopaedics (pp 394-398). Philadelphia, PA: Saunders Elsevier.

References

- Moore, D. Orthobullets: Basic Science. Linage Medical. 2015. March, 29. www.orthobullets.com.
- Moore, D. Orthobullets: Adult Reconstruction. Linage Medical. 2015.
 March, 29. www.orthobullets.com.
- Moore, D. Orthobullets: Sports. Linage Medical. 2015. March, 29.
 www.orthobullets.com.
- Moseley, J., O'Malley, K., Petersen, N., Menke, T., Brody, B., Kuykendall, D., Hollingsworth, J., Ashton, C., Wray, N. (2002). A controlled trial of arthroscopic surgery for osteoarthritis of the knee. New England Journal of Medicine: 347(2):81-8
- Sheth, N., Lonner, J. (2009). Total Knee Arthroplasty. Pill, S. Gowned and Gloved Orthopaedics (pp 251-267). Philadelphia, PA: Saunders Elsevier

Which of the following non-operative treatments for osteoarthritis has the best evidence to support its use?

- 1. Combination of supervised and home exercise programs
- 2. Hyaluronic acid injections
- 3. Lateral heel wedge
- 4. Acetaminophen
- 5. Glucosamine

Question 1

Which of the following non-operative treatments for osteoarthritis has the best evidence to support its use?

- 1. Combination of supervised and home exercise programs
- 2. Hyaluronic acid injections
- 3. Lateral heel wedge
- 4. Acetaminophen
- 5. Glucosamine

A 62-year-old female undergoes an uncomplicated primary total knee replacement. Her knee range-of-motion pre-operatively was 0-135 degrees of flexion. Which of the following is true regarding the immediate post-operative use of a continuous passive motion machine in this patient?

- 1. Reduced risk of venous thromboembolism
- 2. No long-term difference in ROM compared to patients not using CPM
- 3. Increased passive knee flexion at 6 months
- 4. Increased length of hospitalization
- 5. Decreased risk of surgical site infection

Question 2

A 62-year-old female undergoes an uncomplicated primary total knee replacement. Her knee range-of-motion pre-operatively was 0-135 degrees of flexion. Which of the following is true regarding the immediate post-operative use of a continuous passive motion machine in this patient?

- 1. Reduced risk of venous thromboembolism
- 2. No long-term difference in ROM compared to patients not using CPM
- 3. Increased passive knee flexion at 6 months
- 4. Increased length of hospitalization
- 5. Decreased risk of surgical site infection

The following are risk factors for developing knee osteoarthritis EXCEPT:

- 1. Knee articular trauma
- 2. Metabolic syndrome
- 3. Female gender
- 4. Increased age
- 5. Participating in physical fitness

Question 3

The following are risk factors for developing knee osteoarthritis EXCEPT:

- 1. Knee articular trauma
- 2. Metabolic syndrome
- 3. Female gender
- 4. Increased age
- 5. Participating in physical fitness

- All the following are common complaints associated with knee osteoarthritis EXCEPT?
- 1. Knee pain at night
- 2. Knee pain while climbing stairs
- 3. Knee stiffness
- 4. Instability, clicking, or locking sensation
- 5. Numbness in the ankle or foot

Question 4

- All the following are common complaints associated with knee osteoarthritis EXCEPT?
- 1. Knee pain at night
- 2. Knee pain while climbing stairs
- 3. Knee stiffness
- 4. Instability, clicking, or locking sensation
- 5. Numbness in the ankle or foot

Which radiographic images are most commonly used to identify the degree of degenerative joint disease caused by knee osteoarthritis?

- 1. Knee MRI to identify meniscal pathology
- 2. Knee CT scan
- 3. X-ray images of knee with patient lying down
- 4. Ultrasound images of the knee joint
- 5. X-rays: Standing AP, lateral, and sunrise views of the knee

Question 5

Which radiographic images are most commonly used to identify the degree of degenerative joint disease caused by knee osteoarthritis?

- 1. Knee MRI to identify meniscal pathology
- 2. Knee CT scan
- 3. X-ray images of knee with patient lying down
- 4. Ultrasound images of the knee joint
- X-rays: Standing AP, lateral, and sunrise views of the knee