Sensitivity analyses: effect of adherence and cumulative use of HRT on implant survival

Therefore, we assessed whether HRT use is associated with reduced implant failure rates in a community-based cohort.

**Methods:** Study population: Female participants in the General Practice Research Database undergoing a TKA or THA from 1986 to 2006 were included. Revision surgery was identified using READ codes. In order to identify arthroplasties indicated for osteoarthritis, we excluded patients aged <40 years at the date of surgery, and those with a history of either previous hip fracture or rheumatoid arthritis.

Exposure: Women with at least 6 prescriptions of HRT or 6 months on therapy with a high (>80%) adherence were identified as HRT users. Three sensitivity analyses were carried out, where we explored the association between HRT use for ≥12 months, HRT adherence and cumulative use, and time to failure. We used time varying Cox Models to account for the immortal time till definition of HRT use.

Statistical analysis: Time-varying Cox models were used to estimate hazard ratios (HR) for HRT users versus non-users matched by propensity score to minimize for confounding by indication. Potential confounders were: age, gender, body mass index, joint replaced (hip/knee), year of surgery, OA indication, fracture history, anti-osteoporosis medication use, oral glucocorticoids, smoking, alcohol intake, multiple deprivation index, UK region, comorbid conditions, and use of drugs which can affect bone metabolism.

**Results:** Of 24,733 eligible women included, 3,644 met the definition of HRT user and the remaining 21,089 were non-users. From the propensity-matching, 2,700 HRT users and 3 comparable controls (8,100 women) were selected. The median (interquartile range) follow-up was 3.3 (1.5-6.1) years after surgery. Despite matching, HRT users were more likely to be taking drugs with increase fracture risk.

A total of 168 (1.56%) participants underwent revision surgery during the period of followup. The cumulative failure rate was significantly lower in HRT users than non-users (27(1.00%) vs 141(1.74%), p=0.007). HRT use for ≥6 months was associated with a lower risk of revision (HR 0.61 (0.41 to 0.93)) [Figure]. Both higher adherence (p=0.007) and longer therapy duration (p=0.008) led to further reductions in revision rates. [Table].

**Conclusions:** HRT use for at least 6 months is associated with an up to 40% reduction in prosthesis failure after lower limb total joint arthroplasty. Hormone therapy for at least 1 year appeared related to further reduction in failure rates to about 50%. This supports evidence that there is a significant protective benefit of anti-resorptive drugs in patients undergoing lower limb arthroplasty. These findings require replication in formal randomized controlled trials.

## 350

**LATENT CLASS CLUSTER ANALYSIS SHOWS FOUR DISTINCT SUBTYPES OF KNEE OA: DATA FROM THE OSTEOARTHRITIS INITIATIVE.**

J.H. Waarsing, S.M. Bierma-Zeinstra, H. Weinans. Erasmus MC, Rotterdam, Netherlands

**Purpose:** A possible explanation for the seeming complexity of osteoarthritis is that it is not one disease, but a collection of disease sub-types with different aetiology and clinical characteristics. In this study we used latent class cluster analysis to find subtypes of knee osteoarthritis based on OA characteristics in the baseline data of the Osteoarthritis Initiative (OAI).

**Methods:** Latent class cluster analysis (LCA) is a model based clustering approach that assumes the existence of a latent variable (the various clusters) that influences a set of observed variables, in this case OA characteristics. The optimal number of clusters was determined based on the BIC (Bayesian Information Criterion) that informs about the goodness of fit of the model, and the AWE (Approximate Weight of Evidence) which informs on the ability to classify subjects into the various clusters.

The OA characteristics that served as input for the LCA was formed by the set of x-ray scores of different features, quantitative MRI cartilage measures and various clinical scores like WOMAC and VAS from 520 subjects of the OAI progression cohort at baseline.

Since OA increases in severity over time, a cluster analysis can only be meaningful when performed independent of disease severity. To accomplish this we included a severity variable into the model, such that a model fit was obtained adjusted for severity. The severity variable was obtained by performing Latent Class Factor analysis, which is similar to principle component analysis, but works for both continuous and categorical data.

The same set of OA characteristics was used as input.

**Results:** Our method resulted in 4 clusters, of which the 1st contained 47% of the subjects, the 2nd 27%, the 3rd 15% and the 4th 12% of the subjects. Clusters 1, 2 and 4 showed mainly medial cartilage degeneration, while cartilage degeneration in the 3rd cluster occurred laterally. Interestingly, clusters 3 and 4 showed a strong increase in area of denuded bone with increasing OA severity as measured on MRI, while cluster 1 did not show any denuded bone, independent of OA severity. Cluster 2 showed a very mild increase in denuded bone area with increasing OA severity. Pain scores increased with increasing severity in all clusters. Pain scores were lower in the 3rd cluster, significantly so in the VAS scores reflecting pain in the last month (p<0.05).

We further examined if there were differences in the presence of risk-factors between the clusters. There were no differences in the presence of heberden’s nodes or BMI. However, clusters varied with respect to reported trauma. Prevalence of trauma was lowest in cluster 1 (33%) and highest in cluster 4 (56%).

Finally, using the x-ray scores at 48 months, we looked at differences in progression, characterized by the prevalence of subjects that increased in

### Sensitivity analyses: effect of adherence and cumulative use of HRT on implant survival

<table>
<thead>
<tr>
<th>Exposure</th>
<th>N (%)</th>
<th>Failure incidence (/1,000 py) [95%CI]</th>
<th>HR [95%CI]; p-val</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HRT MPR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 0.4</td>
<td>8,100 (75.0%)</td>
<td>4.25 [3.61 to 5.02]</td>
<td>0.70 [0.44 to 1.14]; p=0.15</td>
<td></td>
</tr>
<tr>
<td>0.4 to &lt; 0.8</td>
<td>1,631 (15.1%)</td>
<td>3.04 [1.94 to 4.76]</td>
<td>0.66 [0.29 to 1.50]; p=0.33</td>
<td></td>
</tr>
<tr>
<td>≥ 0.8</td>
<td>594 (5.5%)</td>
<td>2.98 [1.34 to 6.63]</td>
<td>0.22 [0.05 to 0.89]; p=0.033</td>
<td></td>
</tr>
<tr>
<td>p for trend</td>
<td></td>
<td>0.97 [0.24 to 3.86]</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td><strong>HRT Cumulative use (DDD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 365</td>
<td>8,100 (75.0%)</td>
<td>4.25 [3.61 to 5.02]</td>
<td>1.23 [0.63 to 2.42]; p=0.54</td>
<td></td>
</tr>
<tr>
<td>365 to 1,065</td>
<td>507 (4.7%)</td>
<td>5.24 [2.73 to 10.07]</td>
<td>0.40 [0.19 to 0.86]; p=0.019</td>
<td></td>
</tr>
<tr>
<td>&gt; 1,065</td>
<td>1,180 (10.9%)</td>
<td>1.74 [0.83 to 3.65]</td>
<td>0.53 [0.29 to 0.99]; p=0.046</td>
<td></td>
</tr>
<tr>
<td>p for trend</td>
<td></td>
<td>2.39 [1.33 to 4.32]</td>
<td>0.008</td>
<td></td>
</tr>
</tbody>
</table>
JSN scores, medially or laterally. Progression was compartment specific for the various clusters. Medial progression occurred only in clusters 1, 2 and 4, most dramatically so in cluster 4 (48%). Cluster 3 again only showed lateral progression (61%).

Conclusions: We found clear differences between the various clusters. Cluster 1 could be described as a mild type of OA, with no denuded bone and limited OA progression. Cluster 3 and 4 were more severe and erosive types of OA, showing strong increases in area of denuded bone with increasing OA severity, and a high prevalence of progression. Interestingly, cluster 3 was purely a lateral type of OA, while cluster 4 was purely medial in all respects. The causes that led to differences between the clusters remain speculative. The higher prevalence of reported trauma in cluster 3 and 4, the more aggressive OA types might suggest a difference in OA initiation. We kept the complexity of the models low to reduce the risk of overfitting and increase the likelihood that our findings are generalizable to other cohorts. The fact that clusters also differed on data not included in cluster finding (trauma and progression) indicates that the found clusters are meaningful. In conclusion, latent class cluster analysis confirmed the suspected existence of distinct subtypes of knee OA.

352 BODYWEIGHT CHANGES AND CORRESPONDING CHANGES IN PAIN AND FUNCTION IN PERSONS WITH SYMPTOMATIC KNEE OSTEOARTHRITIS. A LONGITUDINAL ANALYSIS USING DATA FROM OAI AND MOST

D.L. Riddle 1, P.W. Stratford 2, 1 Virginia Commonwealth Univ., Richmond, VA, USA; 2 McMaster Univ., Hamilton, ON, Canada

Purpose: Osteoarthritis (OA) of the knee has multiple causes but one of the more powerful risk factors for OA onset and progression is excessive bodyweight. We found no studies that determined if a dose-response relationship existed between bodyweight changes, both gains and losses, and changes in knee related pain and functional status in a large sample of persons with symptomatic knee osteoarthritis. Trial evidence suggests that moderate to substantial weight loss of at least 5% of body weight would lead to improved function and that weight losses of 10% or more would lead to greater reductions in pain and substantially improved function. Recommendations based on trial findings on persons with knee OA are similar to federal government-based recommendations for weight loss to optimize health. The purpose of our study was to determine if a dose-response relationship exists between percentage bodyweight changes in persons with symptomatic knee osteoarthritis (OA) and self reported pain and function.

Methods: Data from persons in the Osteoarthritis Initiative (OAI) and the Multicenter Osteoarthritis (MOST) datasets (n=1410) with symptomatic knee limiting knee OA were studied. For the OAI, we used baseline and 3-year follow-up data while for the MOST, baseline and 30-month data were used. Key outcome variables were WOMAC Physical Function and Pain change scores. In addition to covariates, the predictor variable of interest was the extent of weight change over the study period and divided into 5 categories representing different percentages of bodyweight change.

Results: A significant dose-response relationship (p<0.001) was found between the extent of percentage change in bodyweight and the extent of change in WOMAC Physical Function and WOMAC Pain. For example, persons who gained >10% of bodyweight had WOMAC Physical Function score changes of -5.4 (95%CI, -8.7, -2.0) points indicating worsening relative to the reference group of persons with weight changes of between <5% weight gain and <5% weight loss.

Conclusions: Our data provide the first published evidence to suggest a dose-response relationship between changes in bodyweight and corresponding changes in pain and function. The threshold for this response gradient appears to be >10% bodyweight shifts. Clinicians can advise

In conclusion, latent class cluster analysis consolidation suggests that the found clusters are meaningful. The causes that led to differences between the clusters remain speculative. The higher prevalence of reported trauma in cluster 3 and 4, the more aggressive OA types might suggest a difference in OA initiation.

Cluster 1 could be described as a mild type of OA, with no denuded bone and limited OA progression. Cluster 3 and 4 were more severe and erosive types of OA, showing strong increases in area of denuded bone with increasing OA severity, and a high prevalence of progression. Interestingly, cluster 3 was purely a lateral type of OA, while cluster 4 was purely medial in all respects. The causes that led to differences between the clusters remain speculative. The higher prevalence of reported trauma in cluster 3 and 4, the more aggressive OA types might suggest a difference in OA initiation. We kept the complexity of the models low to reduce the risk of overfitting and increase the likelihood that our findings are generalizable to other cohorts. The fact that clusters also differed on data not included in cluster finding (trauma and progression) indicates that the found clusters are meaningful. In conclusion, latent class cluster analysis confirmed the suspected existence of distinct subtypes of knee OA.

351 INADEQUATE PAIN RELIEF (IPR) IN KNEE OSTEOARTHRITIS: WHAT DOES IT LOOK LIKE? A EUROPEAN SURVEY OF OSTEOARTHRITIS REAL WORLD THERAPIES (SORT)

P. Conaghan 1, F. Rannou 2, N. Arden 3, S.V. Everett 4, R. Balshaw 5, P.M. Peloso 6, D.J. Watson 7, S.S. Sen 8, S.D. Taylor 4, 1 Univ. of Leeds, Leeds, United Kingdom; 2 Cochin Hosp., Univ. Paris Descartes, Paris, France; 3 Univ. of Oxford, Oxford, United Kingdom; 4 Merck, Sharp & Dohme, Corp., Whitehouse Station, NJ, USA; 5 Syreon Corp., Vancouver, BC, Canada

Purpose: Osteoarthritis (OA) treatment is often unsatisfactory, with limited data suggesting that inadequate pain relief (IPR) is a major issue for people with OA. Despite multiple medication options, data on treatment patterns, adequacy of pain relief and quality of life are limited. SORT was designed to determine the adequacy of pain relief and compare clinical characteristics and patient-reported outcomes in patients with knee OA.

Methods: SORT, a 12-month prospective, observational study enrolled 1260 participants (across 6 EU countries) who used oral and/or topical agents. People > 50 years old with knee OA visiting a primary care physician and taking pain medications in the past 14 days were enrolled. Clinical history, medications, quality of life, treatment satisfaction and health care resource utilization were collected at baseline and months 1, 3, 6, 9 and 12. IPR was defined as an average Brief Pain Inventory pain score of “moderate or greater pain” (score >4). Baseline data are presented in this analysis.

Results: Evaluable baseline data are presented for 1025 participants: 68% women; median age 67 years; duration of knee OA for 5.5 years (SD=6.2) and 67% were taking oral pain medications, 14% were taking topical or a combination of oral and topical agents. Hypertension (50%) was the most common co-morbidity. IPR was reported by 54% of the cohort (558 of 1025). Participants reporting IPR were clinically different than non-IPR participants having greater BMI (30.3 vs. 28.7 kg/m², p<0.001); duration of disease (6.2 yrs vs. 4.8yrs, p<0.001) and proportion with OA of both knees (55% vs. 39%, p<0.001). Overall, the analgesics used most often were NSAIDs (64.1%); followed by paracetamol (39.8%), medications containing opioids (20.2%) and alternative therapies (12.6%). IPR participants (vs. non-IPR) used more opioid containing medications (24.7% vs. 14.8%, p<0.001).

IPR participants (vs. non-IPR) differed in their scoring on: WOMAC Stiffness (115 vs. 67, p<0.001), Pain (266 vs. 136, p<0.001), Physical Function (892 vs. 459, p<0.001); SF-12 General Health (fair/poor 47% vs. 27%, p<0.001); satisfaction with prescribed knee OA treatment (less than satisfied 58% vs. 36%, p<0.001) and satisfaction with treatment side effects (less than satisfied 41% vs. 23%, p<0.001). Additionally, there were significant differences in IPR participants’ report of response to prescribed medication (fair, poor and no response 67% vs. 43%, p<0.001) as compared to non-IPR. IPR vs. non-IPR participants differed significantly in the number of GP/family physician visits for knee OA (p<0.023) and number of physician visits for other reasons (p<0.011). More IPR participants reported having “more than one visit” to a physician for knee OA and other reasons than non-IPR participants.

Conclusions: SORT, an observation of real world clinical practice, found over half of those being treated for knee OA had persistent moderate to severe pain. IPR was associated with higher BMI, longer disease duration, multiple site OA, greater opioid use and more health-care resource utilization.