The Comparative Safety of Analgesics in Older Adults with Arthritis (Solomon et al)\(^1\)

**Study Cohort:**
- Analysis of a large drug plan claims administrative database for Medicare beneficiaries from Pennsylvania and New Jersey who received a traditional NSAID, coxib or opioid between 1999 – 2005.
- **Included:** low income adults, either osteoarthritis (OA) or rheumatoid arthritis, with new Rx for 1 of the 3 classes of analgesics. Subjects had to use health care system consistently in previous 365 days.
- **Excluded:** recent analgesic use (<180days). >1 analgesic class used simultaneously, malignancy/hospice use, <1yr follow up.

**Study Validity:** Observational cohort, matched on high dimensional propensity scores (500 covariate) based on administrative database
- Matched for demographic, surgical & diagnosis (e.g. CV diagnosis/tx, osteoporosis/fractures, GI diagnosis/tx, liver & renal).
- Initial cohort = 163,714 subjects; & after exclusions = 23,647
- Cohort after propensity score matching = 12,840  (7.8% or 4,280 in each of the 3 tx groups)
- Well designed observational study; however, limited by the potential for unknown/expected confounders and impact of the inclusion/exclusion criteria on the population to which the results apply.
- Unknown/expected confounders [opiod group potentially sicker than other group (acute care hospital stay 2.4 days vs 1.9; higher comorbidity index 1.7 vs 1.6; falls, osteoporosis, renal insufficiency, chronic back pain, gout; ACEI, ARBs, BB, surgery; huge difference in baseline characteristics in eTable 1 before propensity score-matched); variance in dose/duration & ASA/OTC analgesic use not factored in. All opioids in one group.]

**Baseline population:**
- ~ 90% OA; ~ 10% RA; Age mean = 80; 84% \(\hat{=}\); on an average of 4.7 different drugs; 32% diabetes, 32% hypertensive, 6% MI, ~7% previous fractures; 24% on a PPI; 1-2% renal insufficiency; co-morbidity index = 1.5
- Note: this population represents a relatively healthy older (80yr) female OA population with <2 co-morbidities.

**Results:** Safety Events Among Propensity Score-Matched Older Arthritic Adults Initiating Rx Analgesics

<table>
<thead>
<tr>
<th>Adverse Events (AE)</th>
<th>NSAIDs</th>
<th>HR &amp; 95% CI</th>
<th>Coxibs</th>
<th>HR &amp; 95% CI</th>
<th>Opioids</th>
<th>HR &amp; 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite Cardiovascular (CV)(^a)</td>
<td>1 (reference)</td>
<td>1.28 (1.01-1.62)</td>
<td>1.77 (1.39-2.24); NNH=17/yr Author's estimate</td>
<td>1.87 (1.39-2.53); NNH=27/yr Author's estimate</td>
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<tr>
<td>Upper/Lower GI Tract Bleed</td>
<td>1 (reference)</td>
<td>0.60 (0.35-1.00)</td>
<td></td>
<td>0.67 (0.38-1.07)</td>
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<tr>
<td>Composite Fracture(^b)</td>
<td>1 (reference)</td>
<td>0.96 (0.62-1.49)</td>
<td></td>
<td>4.47 (3.12-6.41); NNH=26/yr Author's estimate</td>
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<tr>
<td>Hospitalized AE</td>
<td>1 (reference)</td>
<td>1.12 (0.91-1.38)</td>
<td></td>
<td>1.68 (1.37-2.07); NNH=19/yr Author's estimate</td>
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<tr>
<td>Death related to AE</td>
<td>1 (reference)</td>
<td>1.12 (0.62-2.02)</td>
<td></td>
<td>1.11 (0.58-2.10)</td>
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<tr>
<td>All-cause mortality</td>
<td>1 (reference)</td>
<td>1.16 (0.85-1.57)</td>
<td></td>
<td>1.87 (1.39-2.53); NNH=27/yr Author's estimate</td>
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</tr>
</tbody>
</table>

Individual AE HRs of note for opioid vs NSAID: **Bowel obstruction** 4.87 (1.40-17.02); Fracture: hip 3.02 (1.20-7.58); humerus 9.26 (1.45-60.18)

\(^a\) MI, stroke, hospitalization for HF, revascularization, CV death out of hospital. \(^b\) hip, numerus, pelvis & wrist.

**Considerations:**
- Very well done observational study; however, potential for unrecognized confounding leaves the results, especially those with more marginal HRs (e.g. CV & mortality) open to question.
- It is quite likely that opioid use in the elderly is associated with increased fracture risk and related morbidity/mortality as well as bowel obstruction. The HR for these outcomes is more convincing.
- The higher CV risk associated with opioids was unexpected and since HR is much smaller (<2), and since opioids are often chosen for those in whom NSAIDs/Coxibs are contraindicated, this result is open to question.

**Bottom Line (Opioids relative to NSAIDs & Coxibs):**
- Although opioids are sometimes considered “preferred” in elderly patients due to the well recognized GI, CV and renal risks of NSAIDs/Coxibs, opioids do present their own potential array of harms. One should be aware of the increased risk of falls/fractures and bowel obstruction, and carefully weigh this against any potential benefit.
- Opioids may be associated with an increase in CV events and mortality; however, given the limitations of the study and the modest hazard ratios, this may be the result of confounding and not represent true causality. (Opioids not usually associated with a direct adverse CV event (except for QT interval with methadone). Opioids may be an indirect cause of CV events 2° to other adverse events. NSAIDs appear to ↑ CV events (CV risk: rofecoxib, diclofenac > ibuprofen & celecoxib at low doses > naproxen appears safer).\(^1,2\) Opioid use has been indirectly associated with ↑ mortality and the recent ↑ in opioid utilization has occurred in association with a rise in opioid related deaths. Observational data, \(\hat{=}\)
- One should not extrapolate the findings of this study to elderly with several (>2) co-morbidities as NSAIDs & Coxibs may still present significant cardiovascular and renal risks relative to opioids.

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