AS Project Analysis Notes

Monday, June 25, 2018

# AS case definition

* Denominator
  + At least 12 months of continuous enrollment
  + For annual prevalence (calendar year), continuous enrollment for at least 6 months of the calendar year
  + For overall, 12 months of continuous enrollment can span calendar years
  + Includes 65+ year-olds
* Numerator
  + At least 2 diagnosis codes of 720.xx
  + Both must be from a rheumatologist ambulatory visit
  + Both must be between 7-365 days apart
  + AS date is set as the date of the 2nd diagnosis
  + AS date must be within enrollment window (i.e., patient must also be in the denominator)
* Protocol states the numerator should be single diagnosis of 720.0, but this was considered (a posteriori) to be not specific

# Exposure ascertainment

* Follows protocol
* But DMARD, NSAID, and no exposure episodes are grouped together into a “no TNF” exposure category
* Comparisons are made between 2 groups: TNF vs no TNF (DMARD, NSAID, or no exposure)

# Prevalent condition ascertainment

* 12-month period prevalence (±6 months from exposure date)
  + Other time windows were calculated but only 12-month is reported

# Propensity score model

* Model was a logistic regression model
* TNF exposure was used as the reference exposure
* Model output is probability of exposure to TNF
* Model estimation performed separately for the 3 data sources: MPCD, Marketscan, and Medicare
* Inverse probability treatment weight (IPTW) for TNF exposure
* IPTW are stabilized to reduce oversized effect of large propensity scores
* The common support region lower bound is the maximum of the lowest TNF propensity score among the 2 exposure groups. The common support region upper bound is the minimum of the greatest TNF propensity score among the 2 exposure groups

# Incident outcome modeling

* Subjects with disease prior to exposure are excluded
  + Exception for hospitalized and opportunistic infections, and non-melanoma skin cancer
* Models are weighted using IPTW
* Subjects with propensity scores outside of common support region are excluded
* Additional covariates include
  + 6-month mean daily corticosteroid dose (5 level ordinal)
* Comparisons are between
  + TNF vs DMARD, NSAID, or no exposure

# Tables

## Prevalence of AS

Denominator:

* At least 12 months of continuous enrollment
* For annual prevalence, continuous enrollment for at least 6 months of the year
* For overall, 12 months of continuous enrollment can span calendar year
* Includes 65+ year-olds
* Excludes <65 year-olds

Numerator:

* At least 2 diagnosis codes of 720.xx
* Both must be from a rheumatologist ambulatory visit
* Both must be between 7-365 days apart
* AS date is set as the date of the 2nd diagnosis
* AS date must be within enrollment window (i.e., patient must also be in the denominator)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **year** | **numer5pct** | **denom5pct** | **numerEstimated** | **denomEstimated** | **prev** |
| **2006** | 118 | 637,960 | 2,360 | 12,759,200 | 0.018% |
| **2007** | 250 | 687,896 | 5,000 | 13,757,920 | 0.036% |
| **2008** | 350 | 687,227 | 7,000 | 13,744,540 | 0.051% |
| **2009** | 453 | 687,127 | 9,060 | 13,742,540 | 0.066% |
| **2010** | 525 | 695,742 | 10,500 | 13,914,840 | 0.075% |
| **2011** | 654 | 719,161 | 13,080 | 14,383,220 | 0.091% |
| **2012** | 772 | 756,610 | 15,440 | 15,132,200 | 0.102% |
| **2013** | 991 | 871,076 | 19,820 | 17,421,520 | 0.114% |
| **2014** | 1,100 | 873,627 | 22,000 | 17,472,540 | 0.126% |
| **OVERALL 2006-2014** | **898** | **1,212,058** | **17,960** | **24,241,160** | **0.074%** |

Differences from earlier estimates

* Numerator used single diagnosis code of 720.0 (determined to have low specificity)
* Numerator used 2 diagnosis codes of 720.0 (determined to have high specificity)

## Demographic characteristics

AS and non-AS cohorts

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| cohort | database | denom | age | female |
| AS | MPCD | 4,831 | 44.5 (15.0) | 49.0% (n = 2,369) |
| AS | Marketscan | 19,687 | 46.4 (14.1) | 50.9% (n = 10,025) |
| AS | Medicare | 14,370 | 74.4 (6.8) | 67.2% (n = 9,656) |
| Non-AS | MPCD | 1,139,225 | 50.1 (16.6) | 55.8% (n = 635,972) |
| Non-AS | Medicare | 1,447,192 | 74.5 (8.3) | 64.4% (n = 931,837) |

Exposed among AS cohort

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| cohort | database | denom | age | female |
| Exposed | MPCD | 2,384 | 46.4 (15.8) | 54.3% (n = 1,295) |
| Exposed | Marketscan | 9,032 | 46.3 (14.6) | 55.6% (n = 5,022) |
| Exposed | Medicare | 9,044 | 74.8 (6.9) | 68.8% (n = 6,218) |
| Non-AS | MPCD | 1,139,225 | 50.1 (16.6) | 55.8% (n = 635,972) |
| Non-AS | Medicare | 1,447,192 | 74.5 (8.3) | 64.4% (n = 931,837) |

Exposure cohorts

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| database | exposure | denom | age | female |
| MPCD | DMARD | 381 | 42.8 (14.9) | 59.6% (n = 227) |
| MPCD | NSAID | 587 | 44.0 (15.0) | 61.3% (n = 360) |
| MPCD | No exposure | 1,160 | 52.0 (15.7) | 57.5% (n = 667) |
| MPCD | TNF | 856 | 40.1 (13.0) | 46.4% (n = 397) |
| Marketscan | DMARD | 1,550 | 46.1 (14.1) | 63.6% (n = 986) |
| Marketscan | NSAID | 2,700 | 46.2 (15.1) | 60.9% (n = 1,643) |
| Marketscan | No exposure | 3,368 | 49.0 (15.5) | 55.6% (n = 1,871) |
| Marketscan | TNF | 3,936 | 43.6 (13.3) | 51.1% (n = 2,011) |
| Medicare | DMARD | 1,599 | 72.9 (5.8) | 70.1% (n = 1,121) |
| Medicare | NSAID | 4,448 | 74.6 (6.7) | 72.0% (n = 3,204) |
| Medicare | No exposure | 5,221 | 76.1 (7.2) | 69.6% (n = 3,635) |
| Medicare | TNF | 1,112 | 71.3 (5.2) | 55.7% (n = 619) |

## Prevalence of comorbidities

12-month prevalence

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **outcomeCategory** | **disease** | **MPCD AS cohort**  **N = 4,831** | **Marketscan AS cohort**  **N =19,687** | **Medicare AS cohort**  **N =14,370** |
| Cancer | Hematologic Cancer | 0.7 (0.4-1.1) | 0.5 (0.3-0.6) | 1.5 (1.3-1.8) |
| Cancer | Non Melanoma Skin Cancer | 0 | 0.5 (0.4-0.7) | 1.8 (1.6-2.1) |
| Cancer | Solid Cancer | 3.8 (3.1-4.6) | 2.9 (2.5-3.2) | 11.7 (11.1-12.4) |
| Cardiac disease | Aortic Insufficiency/Aortic Regurgitation | 1.8 (1.3-2.4) | 1.1 (0.9-1.3) | 6.2 (5.8-6.7) |
| Cardiac disease | Conduction Block | 0.6 (0.4-1.0) | 0.8 (0.6-1.0) | 3.8 (3.4-4.2) |
| Cardiac disease | Myocardial infarction | 0.0 (0.0-0.2) | 0.2 (0.1-0.3) | 1.0 (0.8-1.3) |
| Infection | Hospitalized infection | 1.4 (1.0-1.9) | 3.0 (2.7-3.4) | 10.0 (9.3-10.6) |
| Infection | Opportunistic infection | 0.8 (0.5-1.3) | 1.0 (0.8-1.2) | 1.7 (1.4-2.0) |
| Inflammatory bowel disease | Crohn’s Disease | 3.3 (2.7-4.1) | 3.7 (3.3-4.1) | 1.9 (1.6-2.2) |
| Inflammatory bowel disease | Ulcerative Colitis | 2.5 (1.9-3.2) | 2.9 (2.6-3.3) | 1.6 (1.3-1.8) |
| Kidney disease | Amyloidosis | 0.1 (0.0-0.3) | 0.0 (0.0-0.1) | 0.0 (0.0-0.1) |
| Kidney disease | IgA nephropathy | 0.3 (0.1-0.5) | 0.1 (0.1-0.2) | 0.1 (0.0-0.2) |
| Kidney disease | Nephrotic syndrome | 0.0 (0.0-0.2) | 0.0 (0.0-0.1) | 0.1 (0.1-0.2) |
| Lung disease | Apical Pulmonary fibrosis | 0.0 (0.0-0.1) | 0 | 0.0 (0.0-0.1) |
| Lung disease | Interstitial lung disease | 0 | 0.1 (0.1-0.2) | 0.4 (0.3-0.6) |
| Lung disease | Restrictive lung disease | 1.0 (0.7-1.5) | 0.9 (0.7-1.1) | 3.1 (2.7-3.5) |
| Neurological Disease | Cauda Equina syndrome | 0.0 (0.0-0.2) | 0.0 (0.0-0.1) | 0.1 (0.0-0.2) |
| Neurological Disease | Spinal Cord compression | 0.1 (0.0-0.3) | 0.1 (0.0-0.2) | 0.2 (0.1-0.3) |
| Osteoporotic fracture | Clinical vertebral fracture | 1.4 (1.0-2.0) | 0.7 (0.6-0.9) | 4.0 (3.6-4.4) |
| Osteoporotic fracture | Non-vertebral osteoporotic fracture | 1.8 (1.4-2.4) | 1.0 (0.8-1.2) | 4.2 (3.8-4.7) |
| PsO/PsA | Psoriasis | 2.7 (2.1-3.4) | 3.5 (3.1-3.9) | 3.3 (2.9-3.6) |
| PsO/PsA | Psoriatic arthritis | 5.0 (4.2-6.0) | 5.3 (4.9-5.8) | 3.4 (3.1-3.8) |
| Uveitis | Uveitis | 5.5 (4.7-6.5) | 6.4 (5.9-6.9) | 2.1 (1.9-2.5) |

## Crude incidence

* Subjects with disease prior to exposure are excluded
  + Exception for hospitalized and opportunistic infections, and non-melanoma skin cancer

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **type** | **outcomeCategory** | **disease** | **MPCD**  **TNF** | **MPCD**  **DMARD, NSAID, or no exposure** | **Marketscan**  **TNF** | **Marketscan**  **DMARD, NSAID, or no exposure** | **Medicare**  **TNF** | **Medicare**  **DMARD, NSAID, or no exposure** |
| Comorbidity | Cancer | Hematologic Cancer | 0.09 (0.00-0.50) | 0.41 (0.20-0.76) | 0.16 (0.07-0.31) | 0.49 (0.35-0.66) | 0.58 (0.37-0.86) | 0.46 (0.36-0.57) |
| Comorbidity | Cancer | Non Melanoma Skin Cancer | 1.46 (0.83-2.37) | 1.38 (0.95-1.94) | 0.84 (0.61-1.11) | 0.96 (0.76-1.20) | 3.13 (2.60-3.74) | 2.89 (2.63-3.17) |
| Comorbidity | Cancer | Solid Cancer | 1.10 (0.57-1.92) | 3.87 (3.11-4.76) | 1.37 (1.07-1.72) | 2.52 (2.19-2.90) | 3.08 (2.53-3.71) | 4.58 (4.24-4.95) |
| Comorbidity | Cardiac disease | Aortic Insufficiency/Aortic Regurgitation | 0.45 (0.15-1.06) | 1.17 (0.78-1.70) | 0.51 (0.34-0.74) | 0.82 (0.63-1.04) | 2.27 (1.81-2.80) | 2.91 (2.64-3.19) |
| Comorbidity | Cardiac disease | Conduction Block | 0.18 (0.02-0.65) | 0.79 (0.47-1.23) | 0.49 (0.32-0.71) | 1.00 (0.80-1.24) | 2.22 (1.78-2.75) | 2.54 (2.30-2.81) |
| Comorbidity | Cardiac disease | Myocardial infarction | 0.27 (0.06-0.79) | 0.04 (0.00-0.23) | 0.22 (0.11-0.38) | 0.24 (0.15-0.37) | 0.83 (0.57-1.16) | 0.98 (0.84-1.14) |
| Comorbidity | Infection | Hospitalized infection | 2.84 (1.93-4.03) | 3.45 (2.74-4.28) | 5.38 (4.77-6.05) | 5.68 (5.17-6.23) | 9.93 (8.90-11.06) | 11.48 (10.93-12.06) |
| Comorbidity | Infection | Opportunistic infection | 0.63 (0.25-1.30) | 0.29 (0.12-0.59) | 1.16 (0.90-1.49) | 0.56 (0.41-0.74) | 1.05 (0.76-1.42) | 0.48 (0.38-0.60) |
| Comorbidity | Kidney disease | Amyloidosis | 0.00 (0.00-0.33) | 0.12 (0.03-0.36) | 0.04 (0.00-0.13) | 0.01 (0.00-0.07) | 0.02 (0.00-0.13) | 0.01 (0.00-0.03) |
| Comorbidity | Kidney disease | IgA nephropathy | 0.18 (0.02-0.65) | 0.04 (0.00-0.23) | 0.05 (0.01-0.16) | 0.05 (0.01-0.12) | 0.12 (0.04-0.28) | 0.05 (0.02-0.10) |
| Comorbidity | Kidney disease | Nephrotic syndrome | 0.18 (0.02-0.65) | 0.00 (0.00-0.15) | 0.04 (0.00-0.13) | 0.04 (0.01-0.11) | 0.05 (0.01-0.17) | 0.02 (0.01-0.06) |
| Comorbidity | Lung disease | Apical Pulmonary fibrosis | 0.00 (0.00-0.33) | 0.04 (0.00-0.23) | 0.00 (0.00-0.07) | 0.00 (0.00-0.04) | 0.00 (0.00-0.09) | 0.00 (0.00-0.02) |
| Comorbidity | Lung disease | Interstitial lung disease | 0.00 (0.00-0.33) | 0.00 (0.00-0.15) | 0.07 (0.02-0.18) | 0.07 (0.03-0.16) | 0.50 (0.31-0.77) | 0.20 (0.14-0.28) |
| Comorbidity | Lung disease | Restrictive lung disease | 0.45 (0.15-1.06) | 0.87 (0.54-1.33) | 0.69 (0.49-0.95) | 0.72 (0.55-0.93) | 1.71 (1.33-2.17) | 1.51 (1.32-1.71) |
| Comorbidity | Neurological Disease | Cauda Equina syndrome | 0.00 (0.00-0.33) | 0.04 (0.00-0.23) | 0.02 (0.00-0.10) | 0.02 (0.00-0.09) | 0.02 (0.00-0.13) | 0.05 (0.02-0.09) |
| Comorbidity | Neurological Disease | Spinal Cord compression | 0.00 (0.00-0.33) | 0.08 (0.01-0.30) | 0.22 (0.11-0.38) | 0.14 (0.07-0.25) | 0.09 (0.03-0.24) | 0.13 (0.08-0.19) |
| Comorbidity | Osteoporotic fracture | Clinical vertebral fracture | 0.54 (0.20-1.18) | 1.12 (0.74-1.64) | 0.43 (0.28-0.65) | 0.75 (0.58-0.97) | 2.00 (1.58-2.49) | 2.44 (2.20-2.70) |
| Comorbidity | Osteoporotic fracture | Non-vertebral osteoporotic fracture | 1.27 (0.69-2.13) | 1.85 (1.34-2.48) | 1.14 (0.87-1.46) | 1.05 (0.84-1.30) | 2.28 (1.83-2.82) | 3.16 (2.89-3.46) |
| Disease manifestation | Inflammatory bowel disease | Crohn’s Disease | 1.71 (1.01-2.70) | 1.09 (0.71-1.59) | 1.58 (1.26-1.96) | 1.11 (0.89-1.37) | 0.69 (0.45-1.00) | 0.40 (0.31-0.50) |
| Disease manifestation | Inflammatory bowel disease | Ulcerative Colitis | 0.74 (0.32-1.46) | 0.87 (0.54-1.33) | 1.31 (1.02-1.65) | 1.29 (1.06-1.56) | 0.86 (0.60-1.21) | 0.47 (0.37-0.59) |
| Disease manifestation | PsO/PsA | Psoriasis | 2.07 (1.30-3.13) | 1.13 (0.75-1.65) | 2.39 (1.99-2.84) | 1.40 (1.15-1.68) | 1.46 (1.10-1.89) | 0.94 (0.79-1.10) |
| Disease manifestation | PsO/PsA | Psoriatic arthritis | 2.96 (2.00-4.22) | 1.40 (0.97-1.97) | 2.79 (2.35-3.29) | 1.71 (1.43-2.02) | 1.36 (1.01-1.79) | 0.45 (0.35-0.56) |
| Disease manifestation | Uveitis | Uveitis | 2.44 (1.58-3.60) | 2.55 (1.94-3.28) | 3.24 (2.77-3.78) | 2.60 (2.26-2.98) | 1.26 (0.93-1.67) | 0.47 (0.37-0.59) |

## Hazard ratios

* Weighted using stabilized IPTW and adjusted for 6-month prednisone equivalent daily dose
* Comparisons are between
  + TNF vs DMARD, NSAID, or no exposure
* Only HRs significantly different from 1.0 are shown
* Full results for all outcomes and all models are in the Excel spreadsheet **phregHazardRatios.xlsx**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **disease** | **database** | **nTNF** | **nComparator** | **HazardRatio** | **RobustWaldLower** | **RobustWaldUpper** |
| Myocardial infarction | MPCD | 839 | 1,765 | 15.56 | 1.59 | 152.27 |
| Psoriatic arthritis | Medicare | 1,010 | 5,107 | 3.89 | 2.36 | 6.41 |
| Uveitis | Medicare | 1,069 | 5,143 | 3.33 | 1.98 | 5.60 |
| Hospitalized infection | MPCD | 840 | 1,765 | 2.25 | 1.12 | 4.50 |
| Hematologic Cancer | Medicare | 1,104 | 5,160 | 2.24 | 1.00 | 4.98 |
| Crohn’s Disease | Medicare | 1,060 | 5,159 | 2.00 | 1.07 | 3.73 |
| Opportunistic infection | Medicare | 1,110 | 5,191 | 1.78 | 1.04 | 3.05 |
| Psoriatic arthritis | Marketscan | 3,679 | 6,147 | 1.65 | 1.27 | 2.16 |
| Psoriasis | Marketscan | 3,785 | 6,207 | 1.61 | 1.20 | 2.16 |
| Crohn’s Disease | Marketscan | 3,751 | 6,196 | 1.57 | 1.13 | 2.20 |
| Solid Cancer | Marketscan | 3,883 | 6,221 | 0.71 | 0.52 | 0.97 |
| Clinical vertebral fracture | Medicare | 1,083 | 5,071 | 0.65 | 0.45 | 0.92 |
| Solid Cancer | Medicare | 1,030 | 4,908 | 0.62 | 0.47 | 0.83 |
| Solid Cancer | MPCD | 829 | 1,752 | 0.40 | 0.17 | 0.92 |
| Conduction Block | MPCD | 836 | 1,763 | 0.13 | 0.03 | 0.58 |