AS Project Analysis Notes

Monday, June 25, 2018

AS case definition

- Change case definition to **spondyloarthritis** (720.xx)
- 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.~~0~~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
- ~~We also considered broadening the scope of ICD-9 diagnosis codes to 720.xx (at least two codes); but also considered this 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.~~0~~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.~~xx~~0 (determined to have ~~low~~ 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