

## Online Supplementary Material

**Online Supplementary Table S1.** Sensitivity analyses for crude incidence rates by varying the definition of hypersensitivity reactions

	Person-days of follow up	#Cases	Incidence rate /100,000 person-days	Incidence Rate /1,000 person-years
Wright et al. definition <b>with</b> E code exclusion				
Allopurinol	11,167,791	731	6.5	23.91
Febuxostat	610,115	51	8.4	30.53
Colchicine	2,400,483	169	7.0	25.71
Allopurinol + colchicine	946,440	71	7.5	27.40
Allopurinol + febuxostat	34,789	3	8.6	31.50
Febuxostat + colchicine	70,719	11	15.6	56.81
Allopurinol + febuxostat + colchicine	8,191	2	24.4	89.18
Wright et al. definition <b>without</b> E code exclusion				
Allopurinol	11,739,499	819	7.0	25.48
Febuxostat	645,955	56	8.7	31.66
Colchicine	2,496,083	178	7.1	26.05
Allopurinol + colchicine	998,189	75	7.5	27.44
Allopurinol + febuxostat	36,022	3	8.3	30.42
Febuxostat + colchicine	78,869	11	13.9	50.94
Allopurinol + febuxostat + colchicine	9,058	2	22.1	80.65
Strom et al. definition <b>with</b> E code exclusion				
Allopurinol	10,966,738	418	3.8	13.92
Febuxostat	597,884	28	4.7	17.11
Colchicine	2,355,230	87	3.7	13.49
Allopurinol + colchicine	929,754	42	4.5	16.50
Allopurinol + febuxostat	33,404	0	0.0	0.00
Febuxostat + colchicine	69,618	5	7.2	26.23
Allopurinol + febuxostat + colchicine	7,950	1	12.6	45.94
Strom et al. definition <b>without</b> E code exclusion				
Allopurinol	11,492,392	472	4.1	15.00
Febuxostat	628,140	32	5.1	18.61
Colchicine	2,445,432	96	3.9	14.34
Allopurinol + colchicine	979,014	45	4.6	16.79
Allopurinol + febuxostat	34,287	0	0.0	0.00
Febuxostat + colchicine	76,635	5	6.5	23.83
Allopurinol + febuxostat + colchicine	8,601	1	11.6	42.47
Wright et al. definition included the following ICD-codes: 288.3, 713.6, 995.0, 995.2, 995.3				
Strom et al. definition included the following ICD-codes: 995.0, 995.2, 995.3				
E codes used for additional baseline exclusion: E930-E949				

**Online Supplementary Table S2.** Comparison of all variables used in propensity matching before and after 5:1 propensity-matching

	Before Propensity matching			After 5:1 Propensity matching		
	Allopurinol	Febuxostat	P-value*	Allopurinol	Febuxostat	P-value*
Total episodes	28,501	2,513		9,765	1,953	
Age category						
65-75	12,815 (45.0%)	1147 (45.6%)	ref	4,478 (45.9%)	888 (45.5%)	0.69
75-85	10,966 (38.5%)	972 (37.7%)	0.52	3,712 (38.0%)	740 (37.9%)	0.89
>85	4,720 (16.6%)	394 (15.7%)	0.47	1,575 (16.1%)	325 (16.6%)	0.38
Gender						
Female	14,278 (50.1%)	1212 (48.2%)	0.65	4,766 (48.8%)	962 (49.3%)	0.65
Male	14,223 (49.9%)	1301 (51.8%)	Ref	4,999 (51.2%)	991 (50.7%)	0.66
Race						
White	22,525 (79.0%)	1911 (76.0%)	Ref	7,827 (80.2%)	1,578 (80.8%)	0.62
Black	3,475 (12.2%)	268 (10.7%)	<b>0.004</b>	1,086 (11.1%)	221 (11.3%)	0.68
Other	2,501 (8.8%)	334 (13.3%)	<b>&lt;.0001</b>	852 (8.7%)	154 (7.9%)	0.042
Charlson-Romano score, mean (SD)	1.49 (2.71)	2.73 (3.34)	<b>&lt;.0001</b>	2.03 (3.00)	2.13 (3.01)	<b>0.0002</b>
Cardiovascular medication use						
Beta-blockers	2,267 (8.0%)	201 (8.0%)	0.40	656 (6.7%)	142 (7.3%)	0.14
ACE- Inhibitors	1,614 (5.7%)	86 (3.4%)	<b>&lt;.0001</b>	376 (3.9%)	72 (3.7%)	0.56
Diuretics	2,591 (9.1%)	230 (9.2%)	0.08	746 (7.6%)	162 (8.3%)	0.10
Statins	2,100 (7.4%)	182 (7.2%)	0.40	556 (5.7%)	124 (6.4%)	0.062
Charlson-Romano score Comorbidities						
Myocardial infarction	762 (2.7%)	114 (4.5%)	<b>&lt;.0001</b>	355 (3.6%)	78 (4.0%)	0.20
Diabetes	11,651 (40.9%)	699 (27.8%)	<b>&lt;.0001</b>	2257 (23.1%)	484 (24.8%)	<b>0.020</b>
Diabetes with complications	1,819 (6.4%)	324 (12.9%)	<b>&lt;.0001</b>	822 (8.4%)	154 (7.9%)	0.19
Peripheral vascular disease	4,891 (17.2%)	323 (12.9%)	<b>&lt;.0001</b>	951 (9.7%)	209 (10.7%)	0.035
Cerebrovascular disease	3,645 (12.8%)	197 (7.8%)	<b>&lt;.0001</b>	647 (6.6%)	128 (6.6%)	0.85
Congestive heart failure	3,567 (18.5%)	509 (20.3%)	<b>&lt;.0001</b>	1670 (17.1%)	351 (18.0%)	0.15
Dementia	427 (1.5%)	53 (2.1%)	<b>&lt;.0001</b>	184 (1.9%)	39 (2.0%)	0.57
Chronic pulmonary disease	2,921 (10.3%)	424 (16.9%)	<b>&lt;.0001</b>	1378 (14.1%)	277 (14.2%)	0.89
Rheumatologic disease	502 (1.8%)	108 (4.3%)	<b>0.0001</b>	254 (2.6%)	49 (2.5%)	0.69
Peptic ulcer disease	238 (0.8%)	46 (1.8%)	0.24	109 (1.1%)	19 (1.0%)	0.33
Mild liver disease	138 (0.5%)	30 (1.2%)	<b>&lt;.0001</b>	61 (0.6%)	11 (0.6%)	0.58
Hemiplegia or paraplegia	97 (0.3%)	14 (0.6%)	<b>&lt;.0001</b>	49 (0.5%)	7 (0.4%)	0.13
Malignancy, including leukemia and lymphoma	1,470 (5.2%)	211 (8.4%)	<b>&lt;.0001</b>	679 (7.0%)	139 (7.1%)	0.67
Moderate or severe liver disease	34 (0.1%)	3 (0.1%)	<b>&lt;.0001</b>	10 (0.1%)	3 (0.2%)	0.32
Metastatic solid tumor	109 (0.4%)	9 (0.4%)	<b>&lt;.0001</b>	38 (0.4%)	8 (0.4%)	0.82

AIDS	8 (0.03%)	3 (0.1%)	<.0001	6 (0.1%)	0 (0.0%)	N/A
Renal disease	3,777 (13.3%)	766 (30.5%)	<.0001	1,832 (18.8%)	405 (20.7%)	<b>0.002</b>
Other common medical comorbidities						
Tobacco use disorder	814 (2.9%)	72 (2.9%)	0.57	255 (2.6%)	50 (2.6%)	0.82
Hypertension	24,121 (84.6%)	2,285 (90.9%)	<.0001	8,689 (89.0%)	1,741 (89.1%)	0.90
Hyperlipidemia	17,438 (61.2%)	1,683 (67.0%)	<.0001	6,211 (63.6%)	1,237 (63.3%)	0.82
Region						
Midwest	7,236 (25.4%)	466 (18.5%)	<.0001	2,021 (20.7%)	413 (21.2%)	0.49
Northeast	4,584 (16.1%)	448 (17.8%)	0.10	1,639 (16.8%)	327 (16.7%)	0.94
South	11,458 (40.2%)	1,023 (40.7%)	<b>0.018</b>	4,216 (43.2%)	845 (43.3%)	0.92
West	5,223 (18.3%)	576 (22.9%)	ref	1,889 (19.3%)	368 (18.8%)	0.42
Propensity score**, mean, SD	n/a	n/a		0.117 (0.04)	0.117 (0.04)	
<p><b>Bold font</b> indicates statistically significant difference with a p-value &lt;0.05  SD, standard deviation  *P-values are from logistic regression performed on all variables  **The mean propensity score was the same for allopurinol versus febuxostat groups after the 1:5 propensity matching</p>						

**Online Supplementary Table S3.** Association of allopurinol or febuxostat doses on the risk of incident hypersensitivity reactions in the 5:1 propensity-matched sample

Average Daily Dose	HR (95% CI)	P-value
Allopurinol <200 mg/day	Ref	
Allopurinol 200-299 mg/day	0.86 (0.62, 1.19)	0.35
Allopurinol ≥300 mg/day	1.25 (0.99, 1.58)	0.06
Febuxostat 40 mg/day	<b>1.43 (1.03, 1.98)</b>	<b>0.034</b>
Febuxostat 80 mg/day	0.84 (0.37, 1.90)	0.67
HR, Hazard ratio; CI, confidence interval; Ref, referent category *Propensity-matching was done for allopurinol versus febuxostat exposure, not dose of allopurinol or febuxostat		