

Supplementary Online Content

Bouck Z, Mecredy GC, Ivers NM, et al. Frequency and associations of prescription nonsteroidal anti-inflammatory drug use among patients with a musculoskeletal disorder and hypertension, heart failure, or chronic kidney disease. *JAMA Intern Med*. Published online October 8, 2018. doi:10.1001/jamainternmed.2018.4273

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Inclusion Criteria and Index Event Definitions

Description	Definition(s)			
Primary care outpatient visit for a musculoskeletal (MSK) disorder (index event)	At least one OHIP claim for an in-office physician visit (i.e. LOCATION=O='Office') with a general practitioner (SPEC=00='general practitioner/family physician) and any of the following diagnostic codes:			
	MSK type	Subcategory	Descriptions	OHIP diagnostic codes
<i>Injury and related conditions</i>	<i>Injury and related conditions</i>	Fractures/dislocations	Fractures: facial bones, skull, vertebral column without spinal damage, vertebral column with spinal damage, ribs, pelvis, clavicle, humerus, radius/ulna, carpal bones, metacarpals, phalanges, femur, fibula/tibia, ankle, leg, other; Dislocations: shoulder, elbow, finger, other	802, 803, 805, 806, 807, 808, 810, 812, 813, 814, 815, 816, 821, 823, 824, 827, 829, 831, 832, 834, 839
		Strains/sprains	shoulder/upper arm, elbow, wrist/hand and fingers, knee/leg, ankle/foot & toes, coccyx/neck, other	840, 841, 842, 843, 844, 845, 847, 848
	<i>Arthritis and related conditions</i>	Inflammatory arthritis	rheumatoid arthritis, Still's disease; ankylosing spondylitis; disseminated lupus erythematosus, scleroderma, polyarteritis nodosa, temporal arteritis; pyogenic arthritis	714, 720, 710, 446, 711
		Other arthritis	osteoarthritis; injurytic arthritis; gout	715, 716, 274, 712
		Soft tissue disorders	synovitis, tenosynovitis, bursitis, bunion, ganglion; Dupuytren's contracture; fibrositis, myositis, muscular rheumatism	727, 728, 729
		Joint derangement	joint derangement, recurrent dislocation, ankylosis, meniscus or cartilage tear, loose body in joint	717, 718
	<i>Bone and spinal conditions</i>	Unspecified arthritis		739
		Bone	osteomyelitis, osteochondritis, Legg-Perthes disease, osteoporosis, spontaneous fracture, oth. dis. of bone & cart., flat foot, pes planus, hallux valgus, hallux varus, hammer toe	730, 731, 732, 733, 734, 735
		Spine	cervical arthritis, intervertebral disc	721, 722, 723, 724, 725, 737

		disorders, pain neck, lumbar strain, lumbago, coccydynia, sciatica, lumbar disc disease (degenerative), scoliosis	
	<i>Congenital anomalies</i>	club foot, other congenital anomalies of limbs, other musculoskeletal anomalies	754, 755, 756
	<i>Unspecified</i>	Include ill-defined symptoms such as leg or joint pain	781
History of heart failure* (inclusion criteria)	At least one claim in OHIP with one of the following diagnostic codes in 365 days prior to index event: 428 (congestive heart failure) OR At least one emergency department visit [NACRS] or hospital discharge [DAD] record with ICD-10 code = I50 (heart failure)		
History of hypertension* (inclusion criteria)	At least one claim in OHIP with one of the following diagnostic codes in 365 days prior to index event: o 401 = Essential hypertension o 402 = Hypertensive heart disease o 403 = Hypertensive renal disease OR One claim for an outpatient visit or hospital stay with one of the following diagnostic codes [NACRS, DAD]: o I10 = essential hypertension o I11 = hypertensive heart disease (could be with or without heart failure) o I12 = hypertensive renal (chronic kidney) disease o I13 = hypertensive heart and renal disease (could be with or without heart failure) o I15 = secondary hypertension		
History of chronic kidney disease (CKD)* (inclusion criteria)	At least one claim in OHIP with one of the following diagnostic codes in 365 days prior to index event: 403, 585 OR At least one hospital admission in CIHI DAD or an outpatient visit in NACRS with one of the following codes: E102, E112, E132, E142, I12, I13, N08, N18, N19		

Notes: * In defining the **primary exposure variables**, there is some overlap among the operational definitions of these diseases across both ICD-10-CA and OHIP diagnostic codes.

All scenarios where multiple conditions (at least two of three) can be indicated on a single claim:

1. IF [DAD, NACRS] claim with DX10CODE I11 AND I50 then
History of heart failure = 1 AND history of hypertension = 1
2. IF [DAD, NACRS] claim with DX10CODE (I12 OR I13) AND DX10CODE N18 then
History of hypertension = 1 AND history of chronic kidney disease = 1
Same is true IF one [OHIP] claim with DXCODE = 403 then
History of hypertension = 1 AND history of chronic kidney disease = 1
3. IF [DAD, NACRS] claim with DX10CODE = I13 AND N18 AND I50 then
History of hypertension = 1 AND history of chronic kidney disease = 1 AND history of heart failure = 1

eTable 2. Primary and Secondary Outcome Definitions

Description (type) and definition	Generic drug name	DINs
Prescription NSAID use (primary) - Receipt of one or more ODB claims for any DIN ^a (corresponding with any of the listed generic drugs) within 7 days ^b after patient's index visit date.	Celecoxib**	2239941, 2239942, 2288915, 2288923, 2291975, 2291983, 2321246, 2321254, 2355442, 2355450, 2399881, 2412373, 2412381, 2412497, 2412500, 2418932, 2418940, 2420058, 2420066, 2420155, 2420163, 2423278, 2424533, 2424541, 2426382, 2426390, 2435632, 2435640, 2442639, 2442647, 2445670, 2445689
	Diclofenac potassium	881635, 2239355, 2239753, 2243433, 2261774
	Diclofenac sodium***	514004, 514012, 590827, 632724, 632732, 782459, 808539, 808547, 839175, 839183, 2048698, 2091194, 2158582, 2162814, 2231504, 2231505, 2231506, 2231508, 2261901, 2261928, 2261936, 2261944, 2261960, 2302616, 2302624
	Diclofenac sodium & misoprostol	1917056, 2229837, 2341689, 2341697, 2397145, 2397153
	Etodolac	2142023, 2142031, 2232317, 2232318
	Floctafenine	2017628, 2017636, 2244680, 2244681
	Flurbiprofen	600792, 647942, 1912038, 1912046, 2100509, 2100517
	Ibuprofen	252409, 327794, 364142, 441643, 441651, 484911, 506052, 585114, 629324, 629340, 629359
	Indomethacin	16039, 16047, 16233, 337420, 337439, 594466, 2231799, 2231800, 2461536, 2461811
	Ketoprofen	761680, 790427, 790435, 842664, 1926365, 1926373, 1926381, 1926403, 1926411, 2015951, 2172577
	Ketorolac tromethamine	2162660, 2229080, 2465124
	Mefenamic acid	155225, 2229452
	Meloxicam	2242785, 2242786, 2248267, 2248268, 2248973, 2248974, 2250012, 2250020, 2255987, 2255995, 2258315, 2258323, 2390884, 2390892
	Nabumetone	2083531, 2083558, 2238639, 2240868
	Naproxen	299413, 522651, 522678, 565350, 589861, 592277, 600806, 627097, 2017237, 2162415, 2162423, 2162431, 2162458, 2162474, 2162482, 2162490, 2162792, 2241024, 2243312, 2243313, 2243314, 2243432, 2246699, 2246700, 2246701, 2294702, 2294710
	Naproxen sodium	784354, 1940309, 2162717, 2162725
	Naproxen & esomeprazole magnesium	2361701, 2361728, 2443449, 2458608
	Oxaprozin	2027860, 2243661
	Piroxicam	525596, 525618, 632716, 642886, 642894, 695696, 695718, 2154463
	Sulindac	432369, 456888, 745588, 745596
Tiaprofenic acid	1989782, 2179679, 2179687, 2221950, 2230828	

Cardiac complication (secondary)- Defined as at least one claim with any of the following ICD-10 codes [DAD, NACRS]:	<i>Ischemic heart disease:</i> I20-I25 <i>Heart failure:</i> I50 <i>Other cardiovascular conditions:</i> I00-I02, I05-I13, I15, I26-I28, I30-I40, I44-I49, I51, I52, I60-I74, I77-I82, I95, I97, R02, R55, R57, and R96
Renal complication (secondary) - Defined as at least one claim with any of the following codes [DAD, NACRS]:	<i>Acute kidney injury:</i> <ul style="list-style-type: none"> • ICD code (primary or secondary) = N17, N170-N172, N178-N179 <i>Acute dialysis:</i> <ul style="list-style-type: none"> • ICD-10 code = G323, G325, G866, R849 (hemodialysis); G330, G331 (peritoneal dialysis); G082, G083, G085, G090-G093, G095, G294, G295 (continuous renal replacement therapy) • CCI code = 1PZ21HQBR (hemodialysis), 1PZ21HQBS (continuous renal replacement therapy), 1PZ21HPD4 (peritoneal dialysis) <i>Hyperkalemia</i> ICD-10 code = E875
Death (secondary) – all-cause mortality	Any claim in [RPDB] with DTHFLAG and DTHDATE
<i>Notes:</i> DINs = drug identification numbers; *=aspirin and topical formulations excluded; **only selective (COX-2 inhibitor) NSAID on e-formulary; ***only NSAID with topical formulations on e-formulary (excluded).	
^a All DINs had to be listed on the ODB formulary and covered during the study window.	
^b Please refer to Supplemental Table 3 for preliminary results that informed length of observation window.	

eTable 3. Preliminary Analysis of Distribution of NSAIDs Prescribed Within 30 Days of Musculoskeletal-Related Primary Care Visit by Number of Days Since Visit Occurred.

Days	n	%	Cumulative n	Cumulative %
0	148662	44.27	148662	44.27
1	23906	7.12	172568	51.39
2	11798	3.51	184366	54.90
3	8793	2.62	193159	57.52
4	7967	2.37	201126	59.89
5	7290	2.17	208416	62.06
6	7835	2.33	216251	64.39
7*	8574	2.55	224825	66.95
8	6586	1.96	231411	68.91
9	5282	1.57	236693	70.48
10	4831	1.44	241524	71.92
11	4920	1.47	246444	73.38
12	4881	1.45	251325	74.84
13	5604	1.67	256929	76.51
14	7063	2.10	263992	78.61
15	5418	1.61	269410	80.22
16	4453	1.33	273863	81.55
17	4088	1.22	277951	82.77
18	4067	1.21	282018	83.98
19	4166	1.24	286184	85.22
20	4794	1.43	290978	86.65
21	6240	1.86	297218	88.50
22	4883	1.45	302101	89.96
23	4004	1.19	306105	91.15
24	3716	1.11	309821	92.26
25	3700	1.10	313521	93.36
26	3871	1.15	317392	94.51
27	4345	1.29	321737	95.80
28	6002	1.79	327739	97.59
29	4514	1.34	332253	98.94
30	3574	1.06	335827	100.00

Notes: *As most NSAIDs (67.0%) dispensed within 30 days of a musculoskeletal-related visit were claimed within the first week, we set 7 days as our observation window (see eTable 2).

eTable 4. Distribution of Baseline Characteristics by Primary Outcome for Unmatched (n = 396,248) and Matched Samples (n = 71,104).

Variable	Value	Pre-matching sample (all eligible for matching, n = 396,248)			Post-matching sample (n = 71,704)		
		Prescription NSAID use		Std. difference	Prescription NSAID use		Std. difference
		Yes (n = 36,119)	No (n = 360,129)		Yes (n = 35,552)	No (n = 35,552)	
CKD	Yes	1,612 (4.5%)	32,790 (9.1%)	0.19	1,442 (4.1%)	1,442 (4.1%)	0
Hypertension	Yes	34,701 (96.1%)	332,066 (92.2%)	0.17	34,300 (96.5%)	34,300 (96.5%)	0
Heart failure	Yes	1,661 (4.6%)	32,463 (9.0%)	0.18	1,433 (4.0%)	1,433 (4.0%)	0
Back pain	Yes	6,074 (16.8%)	46,976 (13.0%)	0.11	5,975 (16.8%)	5,659 (15.9%)	0.02
Arthritis	No	22,147 (61.3%)	246,113 (68.3%)	0.15	21,949 (61.7%)	21,258 (59.8%)	0.04
Arthritis	Yes - Inflammatory	763 (2.1%)	14,131 (3.9%)	0.11	761 (2.1%)	819 (2.3%)	0.01
Arthritis	Yes - Other	13,209 (36.6%)	99,885 (27.7%)	0.19	12,842 (36.1%)	13,475 (37.9%)	0.04
Age group	65-69 y	12,138 (33.6%)	98,767 (27.4%)	0.13	11,997 (33.7%)	12,392 (34.9%)	0.02
Age group	70-74 y	9,099 (25.2%)	81,181 (22.5%)	0.06	8,953 (25.2%)	9,094 (25.6%)	0.01
Age group	75-79 y	7,073 (19.6%)	72,286 (20.1%)	0.01	6,946 (19.5%)	6,895 (19.4%)	0
Age group	80-84 y	4,650 (12.9%)	57,545 (16.0%)	0.09	4,579 (12.9%)	4,473 (12.6%)	0.01
Age group	85+ y	3,159 (8.7%)	50,350 (14.0%)	0.17	3,077 (8.7%)	2,698 (7.6%)	0.04
Male	Yes	16,223 (44.9%)	145,856 (40.5%)	0.09	15,916 (44.8%)	15,916 (44.8%)	0
Rural	Yes	3,152 (8.7%)	37,851 (10.5%)	0.06	2,969 (8.4%)	2,969 (8.4%)	0
Income quintile	1 (lowest)	7,193 (19.9%)	62,343 (17.3%)	0.07	7,066 (19.9%)	7,066 (19.9%)	0
Income quintile	2	7,837 (21.7%)	72,394 (20.1%)	0.04	7,709 (21.7%)	7,709 (21.7%)	0
Income quintile	3	7,490 (20.7%)	72,382 (20.1%)	0.02	7,346 (20.7%)	7,346 (20.7%)	0
Income quintile	4	7,289 (20.2%)	76,749 (21.3%)	0.03	7,197 (20.2%)	7,197 (20.2%)	0
Income quintile	5 (highest)	6,310 (17.5%)	76,261 (21.2%)	0.09	6,234 (17.5%)	6,234 (17.5%)	0
Hospitalization in past y	Yes	7,731 (21.4%)	116,673 (32.4%)	0.25	7,508 (21.1%)	7,441 (20.9%)	0
Cancer	Yes	5,751 (15.9%)	73,213 (20.3%)	0.11	5,640 (15.9%)	5,337 (15.0%)	0.02
Cardiovascular disease (other)	Yes	8,114 (22.5%)	105,901 (29.4%)	0.16	7,937 (22.3%)	7,372 (20.7%)	0.04
ACE-inhibitor or ARB	No use	10,848 (30.0%)	148,515 (41.2%)	0.24	10,731 (30.2%)	10,731 (30.2%)	0
ACE-inhibitor or ARB	Recent use	3,980 (11.0%)	31,725 (8.8%)	0.07	3,735 (10.5%)	3,735 (10.5%)	0
ACE-inhibitor or ARB	Current use	21,291 (58.9%)	179,889 (50.0%)	0.18	21,086 (59.3%)	21,086 (59.3%)	0
Diuretic	No use	27,477 (76.1%)	260,449 (72.3%)	0.09	27,333 (76.9%)	27,333 (76.9%)	0
Diuretic	Recent use	1,671 (4.6%)	19,252 (5.3%)	0.03	1,403 (3.9%)	1,403 (3.9%)	0
Diuretic	Current use	6,971 (19.3%)	80,428 (22.3%)	0.07	6,816 (19.2%)	6,816 (19.2%)	0
Liver disease	Yes	633 (1.8%)	7,740 (2.1%)	0.03	627 (1.8%)	538 (1.5%)	0.02
Prior NSAID use	Yes	8,243 (22.8%)	32,024 (8.9%)	0.39	7,822 (22.0%)	7,228 (20.3%)	0.04
Payment model	Fee-for-service	4,355 (12.1%)	39,055 (10.8%)	0.04	4,304 (12.1%)	4,099 (11.5%)	0.02
Payment model	FHG	12,999 (36.0%)	104,234 (28.9%)	0.15	12,786 (36.0%)	12,877 (36.2%)	0.01

Payment model	FHN	65 (0.2%)	546 (0.2%)	0.01	60 (0.2%)	44 (0.1%)	0.01
Payment model	FHO	9,459 (26.2%)	103,862 (28.8%)	0.06	9,386 (26.4%)	9,509 (26.7%)	0.01
Payment model	FHT	7,379 (20.4%)	95,449 (26.5%)	0.14	7,197 (20.2%)	7,024 (19.8%)	0.01
Payment model	Other	1,862 (5.2%)	16,983 (4.7%)	0.02	1,819 (5.1%)	1,999 (5.6%)	0.02
April-June		9,502 (26.3%)	92,731 (25.7%)	0.01	9,393 (26.4%)	9,392 (26.4%)	0
July-September		9,227 (25.5%)	85,948 (23.9%)	0.04	8,990 (25.3%)	8,785 (24.7%)	0.01
October-November		8,057 (22.3%)	85,821 (23.8%)	0.04	7,958 (22.4%)	8,108 (22.8%)	0.01
CWC recommendation	Post-release	25,202 (69.8%)	253,234 (70.3%)	0.01	24,838 (69.9%)	25,206 (70.9%)	0.02
Quarter	1	1,084 (3.0%)	10,796 (3.0%)	0	1,077 (3.0%)	1,119 (3.1%)	0.01
Quarter	2	1,144 (3.2%)	9,868 (2.7%)	0.03	1,124 (3.2%)	1,040 (2.9%)	0.01
Quarter	3	981 (2.7%)	9,771 (2.7%)	0	941 (2.6%)	961 (2.7%)	0
Quarter	4	915 (2.5%)	8,645 (2.4%)	0.01	906 (2.5%)	901 (2.5%)	0
Quarter	5	1,164 (3.2%)	10,919 (3.0%)	0.01	1,148 (3.2%)	1,068 (3.0%)	0.01
Quarter	6	1,121 (3.1%)	10,363 (2.9%)	0.01	1,085 (3.1%)	1,005 (2.8%)	0.01
Quarter	7	980 (2.7%)	10,120 (2.8%)	0.01	970 (2.7%)	932 (2.6%)	0.01
Quarter	8	841 (2.3%)	9,231 (2.6%)	0.02	825 (2.3%)	808 (2.3%)	0
Quarter	9	1,097 (3.0%)	11,329 (3.1%)	0.01	1,101 (3.1%)	1,043 (2.9%)	0.01
Quarter	10	1,180 (3.3%)	11,386 (3.2%)	0.01	1,139 (3.2%)	1,069 (3.0%)	0.01
Quarter	11	1,043 (2.9%)	11,434 (3.2%)	0.02	1,029 (2.9%)	994 (2.8%)	0.01
Quarter	12	2,353 (6.5%)	24,805 (6.9%)	0.01	2,333 (6.6%)	2,421 (6.8%)	0.01
Quarter	13	6,157 (17.0%)	59,687 (16.6%)	0.01	6,067 (17.1%)	6,162 (17.3%)	0.01
Quarter	14	5,782 (16.0%)	54,331 (15.1%)	0.03	5,642 (15.9%)	5,671 (16.0%)	0
Quarter	15	5,053 (14.0%)	54,496 (15.1%)	0.03	5,018 (14.1%)	5,221 (14.7%)	0.02
Quarter	16	5,224 (14.5%)	52,948 (14.7%)	0.01	5,147 (14.5%)	5,137 (14.4%)	0
<20 y since graduation	1	9,187 (25.4%)	99,621 (27.7%)	0.05	9,043 (25.4%)	8,683 (24.4%)	0.02
20-30 y since graduation	2	10,202 (28.2%)	101,524 (28.2%)	0	10,023 (28.2%)	9,961 (28.0%)	0
>30 y since graduation	3	16,730 (46.3%)	158,984 (44.1%)	0.04	16,486 (46.4%)	16,908 (47.6%)	0.02
Male physician	Yes	26,056 (72.1%)	242,119 (67.2%)	0.11	25,721 (72.3%)	25,721 (72.3%)	0
IMG	Yes	11,636 (32.2%)	89,274 (24.8%)	0.17	11,451 (32.2%)	11,056 (31.1%)	0.02

Notes: CWC = Choosing Wisely Canada; FHG = family health group; FHN = family health network; FHO = family health organization; FHT = family health team; IMG = international medical graduate.

eTable 5. 2x2 Tables for McNemar’s Test of Correlated Binary Proportions for Overall Matched Sample and Sample Stratified by History of Hypertension.

a) All patients in the matched sample.

	NSAID within 7 d = No		Total
	Any secondary outcome = Yes	Any secondary outcome = No	
NSAID within 7 d = Yes	4	304	308
Any secondary outcome = Yes	296	34,948	35,344
Any secondary outcome = No			
Total	300	35,252	35,552

Absolute risk difference (exposed versus unexposed) = 0.0003.
 $X^2(1)=0.11$; p-value = 0.74.

b) Matched sample excluding patients without hypertension.

	NSAID within 7 d = No		Total
	Any secondary outcome = Yes	Any secondary outcome = No	
NSAID within 7 d = Yes	4	293	297
Any secondary outcome = Yes	271	33,732	34,003
Any secondary outcome = No			
Total	275	34,025	34,300

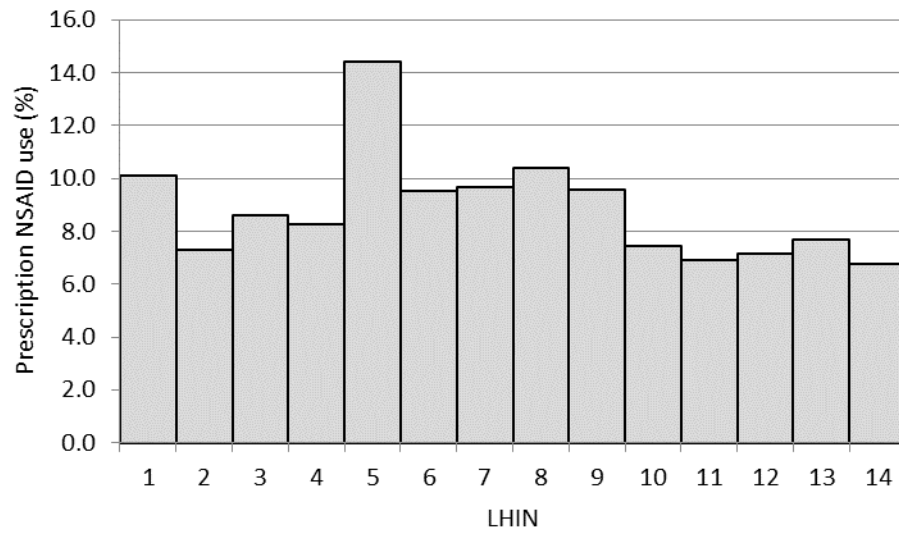
Absolute risk difference (exposed versus unexposed) = 0.0003; 95% CI (-0.001 to 0.002). $X^2(1)=0.20$; p-value = 0.65.

c) Matched sample excluding patients with hypertension.

	NSAID within 7 d = No		Total
	Any secondary outcome = Yes	Any secondary outcome = No	
NSAID within 7 d = Yes	0	11	11
Any secondary outcome = Yes	25	1,216	1,241
Any secondary outcome = No			
Total	25	1,227	1,252

Absolute risk difference (exposed versus unexposed) = -0.021; 95% CI (-0.021 to -0.002). $X^2(1)=5.4$; p-value = 0.02.

eFigure 1. Prescription Nonsteroidal Anti-inflammatory Drug (NSAID) Use by Health Region (LHIN), 2010-11 to 2015-16.



eFigure 2. Prescription Nonsteroidal Anti-inflammatory Drug (NSAID) Use by Primary Care Practice Group, 2010-11 to 2015-16.

