

Non-steroidal anti-inflammatory drug use and the risk of acute myocardial infarction in the general German population: A nested case-control study

Drugs- Real World Outcomes

Kathrin Thöne, Bianca Kollhorst, Tania Schink

Corresponding author:

Dr. Tania Schink

Leibniz Institute for Prevention Research and Epidemiology – BIPS, Bremen, Germany

schink@leibniz-bips.de

S1 Table: ATC-codes and definitions of the respective NSAIDs.

NSAID Description	ATC-Code
Aceclofenac	M01AB16
Acemetacin	M01AB11
Alclofenac	M01AB06
Alminoprofen	M01AE16
Azapropazone	M01AX04
Benoxaprofen	M01AE06
Benzydamine	M01AX07
Bufexamac	M01AB17
Bumadizone	M01AB07
Celecoxib	M01AH01
Clofezone	M01AA05
Dexibuprofen	M01AE14
Dexketoprofen	M01AE17
Diclofenac	M01AB05
Diclofenac, combinations	M01AB55
Difenpiramide	M01AB12
Droxicam	M01AC04
Etodolac	M01AB08
Etoricoxib	M01AH05
Fenbufen	M01AE05
Fenoprofen	M01AE04
Fentiazac	M01AB10
Feprazone	M01AX18
Feprazone, combinations	M01AX68
Flufenamic acid	M01AG03
Flunoxaprofen	M01AE15
Flurbiprofen	M01AE09
Ibuprofen	M01AE01
Ibuproxam	M01AE13
Ibuprofen, combinations	M01AE51
Indometacin	M01AB01
Indoprofen	M01AE10
Indometacin, combinations	M01AB51
Kebuzone	M01AA06
Ketorolac	M01AB15
Ketoprofen	M01AE03
Ketoprofen, combinations	M01AE53
Lonazolac	M01AB09
Lornoxicam	M01AC05
Lumiracoxib	M01AH06
Meclofenamic acid	M01AG04
Mefenamic acid	M01AG01

Meloxicam	M01AC06
Mofebutazone	M01AA02
Morniflumate	M01AX22
Nabumetone	M01AX01
Naproxen	M01AE02
Naproxcinod	M01AE18
Naproxen and esomeprazole	M01AE52
Niflumic acid	M01AX02
Nimesulide	M01AX17
Oxametacin	M01AB13
Oxaprozin	M01AE12
Oxyphenbutazone	M01AA03
Parecoxib	M01AH04
Phenylbutazone	M01AA01
Piroxicam	M01AC01
Pirprofen	M01AE08
Proglumetacin	M01AB14
Proquazone	M01AX13
Rofecoxib	M01AH02
Sulindac	M01AB02
Suprofen	M01AE07
Tenidap	M01AX23
Tenoxicam	M01AC02
Tiaprofenic acid	M01AE11
Tolfenamic acid	M01AG02
Tolmetin	M01AB03
Valdecoxib	M01AH03
Zomepirac	M01AB04

S2 Table: Comorbidities assessed in the 12 months (i.e., 365 days) before cohort entry.

Confounder	ATC codes	ICD codes
Alcohol Abuse	N07BB01, N07BB02, N07BB03, N07BB04	F10.-, G31.2, G62.1, G72.1, I42.6, K70.-, K86.0, Z50.2
Obesity	A08AA01, A08AA02, A08AA03, A08AA04, A08AA05, A08AA06, A08AA07, A08AA08, A08AA09, A08AA10, A08AA56, A08AB01, A08AX01	E66.0, E66.2, E66.8, E66.9
Myocardial infarction** (acute, recurrent, silent, complication and old)		I21.-, I22.-, I23.-, I25.2, I25.20, I25.21, I25.22, I25.29
Chronic ischemic heart disease**		I20.-, I23.0, I23.1, I23.4, I23.5, I23.6, I23.8, I24.0, I24.8, I24.9, I25.0, I25.1, I25.10, I25.11, I25.12, I25.13, I25.14, I25.15, I25.19, I25.3, I25.5, I25.6, I25.8, I25.9
Heart failure**	C07AG02	I11.0, I11.00, I11.01, I13.0, I13.00, I13.01, I13.2, I13.20, I13.21, I50,-
Stroke** (haemorrhagic, ischemic, subarachnoid, and unspecified)		F01.-, G46.3, G46.4, G46.5, G46.6, I60.-, I61.-, I62.-, I63.-, I64, I69.-, P10.3, S06.6
Arterial hypertension and hypertensive disease**		I10.-, I11.-, I12.-, I13.-, I14.-, I15.-
Arterial fibrillation and flutter		I48.-
Peripheral arterial disease		I25.0, I70.-
Other cardiovascular diseases (cardiac arrhythmia/conduction disorders and arrest, cardiomyopathies, valvular disorders and endocarditis, myocarditis and pericarditis, arterial embolism and thrombosis)	C01BA*, C01BB*, C01BC03, C01BC04, C01BC07, C01BC08, C01BD*, C01BG*	I26.-, O88.0, O88.1, O88.2, O88.8, T79.1, I44.-, I45.-, I46.0, I46.9, I47.-, I49.-, Q24.6, I25.5, I42.-, I43.-, O90.3, I01.0, I01.2, I09.0, I09.2, I30.-, I32.-, I40.-, I41.-, I51.4, I01.1, I05.-, I06.-, I07.-, I08.-, I09.1, I23.4, I23.5, I33.-, I34.-, I35.-, I36.-, I37.-, I38, I39.1, I39.3, I39.4, I39.8, Q22.0, Q22.1, Q22.2, Q22.3, Q22.4, Q23.0, Q23.1, Q23.2, Q23.3, Q25.3
Hyperlipidemia		E78.0, E78.1, E78.2, E78.3, E78.4, E78.5

Osteoarthritis		M12.1, M12.1-, M15.0, M15.1, M15.2, M15.4, M16.-, M18.-, M20.2, M47.0-, M47.1-, M47.2-, M47.8-, M47.9-
Rheumatoid arthritis	M01CA03, M01CB01, M01CB02, M01CB03, M01CB04, M01CB05, M01CC01, M01CC02, M01CX, L04AC03	J99.0, L40.5, L93.-, M05.-, M06.-, M07.-, M08.-, M09.-, M12.1-, M12.2-, M12.3-, M12.4-, M13.0, M13.80, M13.90, M14.3, M14.4, M32.-, M45.-, M46.0-, M49.4-
Diabetes Mellitus**	A10*	E10.0, E10.01, E10.1, E10.11, E10.2, E10.20, E10.21, E10.3, E10.30, E10.31, E10.4, E10.40, E10.41, E10.5, E10.50, E10.51, E10.6, E10.60, E10.61, E10.7, E10.70, E10.71, E10.8, E10.80, E10.81, E10.9, E10.90, E10.91, E11, E11.0, E11.01, E11.1, E11.11, E11.2, E11.21, E11.3, E11.30, E11.31, E11.4, E11.40, E11.41, E11.5, E11.50, E11.51, E11.6, E11.60, E11.61, E11.7, E11.70, E11.71, E11.8, E11.80, E11.81, E11.9, E11.90, E11.91, E12, E12.0, E12.91, E13, E13.0, E13.01, E13.1, E13.11, E13.2, E13.20, E13.21, E13.3, E13.30, E13.31, E13.4, E13.40, E13.41, E13.5, E13.50, E13.51, E13.6, E13.60, E13.61, E13.7, E13.70, E13.71, E13.8, E13.80, E13.81, E13.9, E13.90, E13.91, E14, E14.0, E14.01, E14.1, E14.11, E14.2, E14.20, E14.21, E14.3, E14.30, E14.31, E14.4, E14.40, E14.41, E14.5, E14.51, E14.6, E14.60, E14.61, E14.7, E14.70, E14.71, E14.8, E14.80, E14.81, E14.9, E14.90, E14.91, G59.0, G63.2, H28.0, H36.0, M14.2, N08.3, O24.-
Chronic liver diseases		B15.-, B16.-, B17.-, B18.-, B19.-, B25.1, B58.1, D55.0, E74.0, E76.1, I81, I82.0, K70.-, K71.-, K72.-, K73.-, K74.-,

		K75.9, K76.-, T86.4, T86.4-
Kidney failure		K76.7, N17.-, N18.-, N19.-, O90.4

*Including all following 7-digit ATC codes of the respective category.

**A priori specified confounders.

S3 Table: Co-mediations assessed in the 12 months (i.e., 365 days) before cohort entry.

Confounder	ATC codes
ACE inhibitors + AT II Antagonists**	C09AA*, C09CA01, C09CA02, C09CA03, C09CA04, C09CA05, C09CA06, C09CA07, C09CA08
Calcium channel blockers**	C08CA*, C08CX01, C08DA*, C08DB01, C08EA*, C08EX*
Beta blocking agents**	C07AA*, C07AB*, C07AG*
Diuretics**	C03AA*, C03AB*, C03AH*, C03AX01, C03BA*, C03BB*, C03BC01, C03BD01, C03BK, C03BX03, C03CA*, C03CB*, C03CC*, C03CD01, C03CX01, C03DA*, C03DB*, C03EA*, C03EB*, C03XA*
Other antihypertensive drugs**	C02LA*, C02LB01, C02LC*, , C02LE01, C02LF01, C02AA*, C02AB*, C02AC*, C02LG*, C02LK01, C02LL01, C02LN, C02LX01, C02N, C07BA*, C07BB*, C07BG01, C07CA*, C07CB*, C07CG01, C07DA06, C07DB01, C07EA, C07EB, C07FA05, C07FB*, C08GA01, C09BA*, C09BB*, C09DA*, C09DB*, C09DX01, C09DX02, C09DX03, C09XA52, C09XA53, C09XA54

*Including all following 7-digit ATC codes of the respective category.

**A priori specified confounders.

S4 Table: Co-medications assessed in the 3 months (i.e., 90 days) before the index date.

Confounder	ATC codes
Aspirin**	B01AC06, B01AC08, B01AC56
Glucocorticoids**	H02AB*, H02BX01
Anticoagulants	B01AA01, B01AA02, B01AA03, B01AA04, B01AA07, B01AA08, B01AA09, B01AA10, B01AA11, B01AB*, B01AE*, B01AX*
Statins**	C10AA*, C10BA01, C10BA02, C10BA03, C10BX01, C10BX02, C10BX03, C10BX04
Nitrates**	C01DA*
Platelet aggregation inhibitors**	B01AC*
Oral contraceptives**	G03AA*, G03AB*, G03AC*,
Postmenopausal hormone therapy**	G03CA*, G03CB*, G03CC*, G03CX01, G03DA*, G03DB*, G03DC*, G03FA*, G03FB*, G03HB01

*Including all following 7-digit ATC codes of the respective category.

**A priori specified confounders.

S5 Table: Co-medication assessed in the 1 month (i.e., 30 days) before the index date.

Confounder	ATC codes
Aspirin**	N02BA01, N02BA51, N02BA71, A01AD05, M01BA03

**A priori specified confounders.

S6 Table: Adjusted risk of acute myocardial infarction associated with use of NSAIDs by subgroups of major cardiovascular risk factors.

	With prior use of aspirin, anticoagulants, or platelet aggregation inhibitors (N=170,060)		Without prior use of aspirin, anticoagulants, or platelet aggregation inhibitors (N=165,1182)	
	Cases (n)/Controls (n)	Adjusted OR** (95% CI)	Cases (n)/Controls (n)	Adjusted OR** (95% CI)
	2,928/167,132		14,308/1,546,874	
Current use of				
Diclofenac	260/12,841	1.31 (1.12-1.53)	1,180/101,583	1.44 (1.35-1.55)
Diclofenac, combinations	6/314	1.20 (0.5-2.88)	30/1,859	1.99 (1.38-2.87)
Etoricoxib	24/955	1.63 (1.02-2.58)	73/5,452	1.47 (1.16-1.87)
Ibuprofen	185/8,825	1.37 (1.14-1.64)	801/61,483	1.56 (1.44-1.69)
Indometacin	11/312	2.27 (1.14-4.49)	26/1,859	1.59 (1.07-2.35)
	With prior use of ACE inhibitors, AT II antagonists, calcium channel blockers, beta-blockers, other antihypertensive drugs or diagnosis of hypertension (N=997,281)		Without prior use of ACE inhibitors, AT II antagonists, calcium channel blockers, beta-blockers, other antihypertensive drugs or diagnosis of hypertension (N=733,961)	
	Cases (n)/Controls (n)	Adjusted OR** (95% CI)	Cases (n)/Controls (n)	Adjusted OR** (95% CI)
	12,012/985,269		5,224/728,737	
Current use of				
Diclofenac	1026/71,856	1.32 (1.22-1.42)	414/42,568	1.72 (1.53-1.94)
Diclofenac, combinations	27/1,501	1.55 (1.06-2.29)	9/672	2.59 (1.3-5.14)
Etoricoxib	74/4,140	1.53 (1.21-1.94)	23/2,267	1.61 (1.05-2.46)
Ibuprofen	748/44,521	1.50 (1.38-1.64)	238/25,787	1.61 (1.38-1.87)
Indometacin	32/1,444	1.83 (1.27-2.62)	5/727	1.09 (0.44-2.68)
	With prior atrial fibrillation, myocardial infarction or heart failure (N=288,829)		Without prior atrial fibrillation, myocardial infarction or heart failure (N=1,442,413)	
	Cases (n)/Controls (n)	Adjusted OR** (95% CI)	Cases (n)/Controls (n)	Adjusted OR** (95% CI)

	4,694/284,135		12,542/1,429,871	
Current use of				
Diclofenac	448/21,311	1.23 (1.09-1.39)	992/93,113	1.51 (1.4-1.63)
Diclofenac, combinations	12/558	1.36 (0.74-2.49)	24/1,615	2.06 (1.37-3.1)
Etoricoxib	34/1,396	1.59 (1.1-2.29)	63/5,011	1.52 (1.18-1.96)
Ibuprofen	365/14,893	1.48 (1.29-1.68)	621/55,415	1.55 (1.41-1.69)
Indometacin	13/432	1.49 (0.82-2.71)	24/1,739	1.69 (1.22-2.54)
	With prior history of chronic ischemic heart disease or other cardiovascular disease (N=511,763)		Without prior history of chronic ischemic heart disease or other cardiovascular disease (N=1,219,479)	
	Cases (n)/Controls (n) 7076/504687	Adjusted OR** (95% CI)	Cases (n)/Controls (n) 10160/1209319	Adjusted OR** (95% CI)
Current use of				
Diclofenac	640/35,857	1.34 (1.21-1.47)	800/78,567	1.51 (1.39-1.64)
Diclofenac, combinations	18/844	1.67 (1.03-2.71)	18/1,329	1.96 (1.22-3.15)
Etoricoxib	50/2,234	1.63 (1.21-2.19)	47/4,173	1.47 (1.09-1.97)
Ibuprofen	488/23,469	1.53 (1.37-1.71)	498/46,839	1.56 (1.41-1.72)
Indometacin	19/755	1.64 (1.02-2.64)	18/1,416	1.65 (1.03-2.65)
	With prior history of peripheral atrial diseases or stroke (N=182,021)		Without prior history of peripheral atrial diseases or stroke (N=1,549,221)	
	Cases (n)/Controls (n) 2850/179171	Adjusted OR** (95% CI)	Cases (n)/Controls (n) 14386/1534835	Adjusted OR** (95% CI)
Current use of				
Diclofenac	245/13,430	1.2 (1.02-1.41)	1,195/100,994	1.47 (1.37-1.57)
Diclofenac, combinations	4/308	0.72 (0.26-2.01)	32/1,865	2.03 (1.42-2.9)
Etoricoxib	22/859	1.29 (0.79-2.11)	75/5,548	1.47 (1.17-1.86)

Ibuprofen	213/9,747	1.45 (1.22-1.72)	773/60,561	1.54 (1.41-1.67)
Indometacin	11/265	1.98 (0.97-4.02)	26/1,906	1.48 (1.00-2.19)

Values are numbers unless stated otherwise.

* Adjusted for the following respective covariates: obesity, hypertension, chronic liver diseases, heart failure, diabetes mellitus, myocardial infarction, chronic ischemic heart disease , stroke, atrial fibrillation and flutter, peripheral arterial diseases, other cardiovascular diseases, hyperlipidemia, ACE inhibitors + AT II antagonists, calcium channel blockers, beta blocking agents, diuretics, other antihypertensive drugs, aspirin (90 days prior index date), glucocorticoids, platelet aggregation inhibitors, oral contraceptives, postmenopausal hormone therapy, statins, nitrates, aspirin (30 days prior index date).

S7 Table: Adjusted risk of acute myocardial infarction associated with use of NSAIDs of major cardiovascular risk factors.

	Females (N=589,459)		Males (N=1,141,783)	
	Cases (n)/Controls (n) 5,869/583,590	Adjusted OR* (95% CI)	Cases (n)/Controls (n) 11,367/1,130,416	Adjusted OR* (95% CI)
Current use of				
Diclofenac	529/40,688	1.40 (1.29-1.52)	911/73,736	1.48 (1.33-1.63)
Diclofenac, combinations	15/965	1.83 (1.18-2.84)	21/1,208	1.65 (0.98-2.76)
Etoricoxib	57/2,722	1.56 (1.19-2.04)	40/3,685	1.47 (1.07-2.03)
Ibuprofen	405/29,324	1.55 (1.41-1.71)	581/40,984	1.52 (1.36-1.70)
Indometacin	15/676	1.47 (0.96-2.25)	22/1,495	2.16 (1.28-3.64)
	Younger than 60 years (N= 513,125)		60 years and older (N= 1,218,117)	
	Cases (n)/Controls (n) 5,083/508,042	Adjusted OR* (95% CI)	Cases (n)/Controls (n) 12,153/1,205,964	Adjusted OR* (95% CI)
Current use of				
Diclofenac	396/29,055	1.67 (1.48-1.89)	1,044/85,369	1.33 (1.23-1.43)
Diclofenac, combinations	8/320	2.82 (1.39-5.76)	28/1,853	1.47 (1.00-2.18)
Etoricoxib	29/1,419	2.13 (1.46-3.12)	68/4,988	1.38 (1.08-1.77)
Ibuprofen	263/18,661	1.67 (1.44-1.93)	723/51,647	1.48 (1.36-1.61)
Indometacin	6/477	1.26 (0.55-2.86)	31/1,694	1.76 (1.22-2.55)
	With prior use of calcium channel blocker (N=238,850)		Without prior use of calcium channel blocker (N=1,492,392)	
	Cases (n)/Controls (n) 3,405/235,445	Adjusted OR* (95% CI)	Cases (n)/Controls (n) 13,831/1,478,561	Adjusted OR* (95% CI)
Current use of				
Diclofenac	270/17,889	1.21 (1.05-1.41)	1,170/96,535	1.50 (1.40-1.61)
Diclofenac, combinations	7/352	1.38 (0.62-3.05)	29/1,821	1.84 (1.27-2.67)
Etoricoxib	18/1,067	1.39 (0.84-2.30)	79/5,340	1.62 (1.29-2.04)
Ibuprofen	211/11,327	1.38 (1.17-1.63)	775/58,981	1.57 (1.44-1.70)
Indometacin	11/371	2.06 (1.08-3.93)	26/1,800	1.58 (1.07-2.35)
	With prior use of beta blocker (N=441,397)		Without prior use of beta blocker (N=1,289,845)	
	Cases (n)/Controls (n) 6,063/435,334	Adjusted OR* (95% CI)	Cases (n)/Controls (n) 14,883/1,631,432	Adjusted OR* (95% CI)
Current use of				
Diclofenac	512/31,439	1.34 (1.20-1.49)	928/82,985	1.50 (1.38-1.62)
Diclofenac, combinations	13/653	1.51 (0.85-2.66)	23/1,520	1.94 (1.27-2.95)
Etoricoxib	31/1,855	1.18 (0.81-1.72)	66/4,552	1.70 (1.32-2.19)
Ibuprofen	369/19,726	1.47 (1.30-1.66)	617/50,582	1.59 (1.45-1.74)
Indometacin	17/646	1.94 (1.16-3.25)	20/1,525	1.64 (1.05-2.57)
	With prior use of other antihypertensive		Without prior use of other antihypertensive	

	drugs (N=308,612)		drugs (N=1,422,630)	
	Cases (n)/Controls (n) 3,821/304,791	Adjusted OR* (95% CI)	Cases (n)/Controls (n) 13,415/1,409,215	Adjusted OR* (95% CI)
Current use of				
Diclofenac	337/23,296	1.30 (1.14-1.49)	1,103/91,128	1.47 (1.36-1.58)
Diclofenac, combinations	9/478	1.24 (0.62-2.50)	27/1,695	1.82 (1.23-2.67)
Etoricoxib	26/1,450	1.38 (0.90-2.10)	71/4,957	1.56 (1.22-1.98)
Ibuprofen	210/13,852	1.30 (1.10-1.52)	776/56,456	1.62 (1.49-1.76)
Indometacin	12/510	1.64 (0.88-3.04)	25/1,661	1.68 (1.12-2.50)
	With prior use of postmenopausal hormone therapy (N=39,802)		Without prior use of postmenopausal hormone therapy (N=1,691,440)	
	Cases (n)/Controls (n) 291/39,511	Adjusted OR* (95% CI)	Cases (n)/Controls (n) 16,945/1,674,495	Adjusted OR* (95% CI)
Current use of				
Diclofenac	31/2,761	2.11 (1.27-3.50)	1,409/111,663	1.41 (1.33-1.51)
Diclofenac, combinations	0/56	NA	36/2,117	1.78 (1.28-2.49)
Etoricoxib	3/177	4.16 (1.07-16.22)	94/6,230	1.51 (1.22-1.86)
Ibuprofen	11/1,817	1.04 (0.48-2.24)	975/68,491	1.55 (1.43-1.66)
Indometacin	1/60	1.53 (0.07-34.45)	36/2,111	1.66 (1.19-2.32)
	With prior stroke (N=93,852)		Without prior stroke (N=1,637,390)	
	Cases (n)/Controls (n) 1,456/92,396	Adjusted OR* (95% CI)	Cases (n)/Controls (n) 15,780/1,621,610	Adjusted OR* (95% CI)
Current use of				
Diclofenac	132/6,977	1.18 (0.93-1.51)	1,308/107,447	1.45 (1.35-1.54)
Diclofenac, combinations	2/179	0.60 (0.14-2.69)	34/1,994	1.93 (1.37-2.71)
Etoricoxib	8/481	1.05 (0.48-2.30)	89/5,926	1.60 (1.29-1.98)
Ibuprofen	119/5,535	1.30 (1.01-1.67)	867/64,773	1.55 (1.43-1.67)
Indometacin	6/121	2.71 (0.93-7.84)	31/2,050	1.56 (1.09-2.24)
	With prior peripheral arterial disease (N=101,884)		Without prior peripheral arterial disease (N=1,629,358)	
	Cases (n)/Controls (n) 1,701/100,183	Adjusted OR* (95% CI)	Cases (n)/Controls (n) 15,535/1,613,823	Adjusted OR* (95% CI)
Current use of				
Diclofenac	141/7,505	1.16 (0.93-1.46)	1,293/106,919	1.45 (1.36-1.55)
Diclofenac, combinations	2/159	1.53 (0.32-7.23)	34/2,014	1.94 (1.38-2.74)
Etoricoxib	17/456	1.58 (0.85-2.95)	80/5,951	1.41 (1.12-1.77)
Ibuprofen	122/4,997	1.78 (1.39-2.27)	864/65,311	1.53 (1.42-1.66)
Indometacin	5/165	1.28 (0.44-3.66)	32/2,006	1.67 (1.17-2.38)
	With prior use of glucocorticoids (N=55,738)		Without prior use of glucocorticoids (N=1,675,504)	
	Cases (n)/Controls (n) 827/54,911	Adjusted OR* (95% CI)	Cases (n)/Controls (n) 16,409/1,659,095	Adjusted OR* (95% CI)
Current use of				
Diclofenac	88/5,922	1.11 (0.80-1.53)	1,352/108,502	1.46 (1.37-1.56)

Diclofenac, combinations	1/132	0.81 (0.08-7.81)	35/2,041	1.88 (1.34-2.63)
Etoricoxib	16/523	1.62 (0.80-3.28)	81/5,884	1.45 (1.16-1.82)
Ibuprofen	86/3,769	1.44 (1.01-2.06)	918/66,539	1.57 (1.45-1.69)
Indometacin	2/118	0.60 (0.11-3.27)	35/2,053	1.79 (1.27-2.51)
	With prior hypertension (N=904,993)		Without prior hypertension (N=826,249)	
	Cases (n)/Controls (n) 10,877/894,116	Adjusted OR* (95% CI)	Cases (n)/Controls (n) 6,359/819,890	Adjusted OR* (95% CI)
Current use of				
Diclofenac	933/65,341	1.33 (1.23-1.44)	507/49,083	1.63 (1.46-1.81)
Diclofenac, combinations	25/1,355	1.64 (1.10-2.45)	11/818	2.21 (1.19-4.07)
Etoricoxib	69/3,783	1.57 (1.23-2.01)	28/2,624	1.53 (1.04-2.25)
Ibuprofen	695/40,294	1.55 (1.42-1.70)	291/30,014	1.51 (1.32-1.73)
Indometacin	29/1,326	1.74 (1.19-2.54)	8/845	1.22 (0.60-2.50)
	With prior diabetes mellitus (N=304,099)		Without prior diabetes mellitus (N=1,427,143)	
	Cases (n)/Controls (n) 4,702/299,397	Adjusted OR* (95% CI)	Cases (n)/Controls (n) 12,534/1,414,609	Adjusted OR* (95% CI)
Current use of				
Diclofenac	435/91,444	1.34 (1.19-1.51)	1,005/22,980	1.45 (1.34-1.56)
Diclofenac, combinations	7/463	0.89 (0.41-1.93)	29/1,710	2.12 (1.46-3.08)
Etoricoxib	26/1,251	1.30 (0.86-1.97)	71/5,156	1.61 (1.26-2.05)
Ibuprofen	305/14,660	1.50 (1.31-1.72)	681/55,648	1.57 (1.44-1.72)
Indometacin	17/493	2.13 (1.27-3.58)	20/1,678	1.31 (0.84-2.06)
	With prior myocardial infarction (N=84,927)		Without prior myocardial infarction (N=1,646,315)	
	Cases (n)/Controls (n) 2,353/82,574	Adjusted OR* (95% CI)	Cases (n)/Controls (n) 14,883/1,631,432	Adjusted OR* (95% CI)
Current use of				
Diclofenac	245/6,076	1.16 (0.96-1.41)	1,195/108,348	1.47 (1.38-1.58)

Diclofenac, combinations	4/133	0.68 (0.20-2.30)	32/2,040	2.02 (1.42-2.88)
Etoricoxib	15/345	1.35 (0.72-2.50)	82/6,062	1.56 (1.25-1.95)
Ibuprofen	191/3,903	1.34 (1.08-1.67)	795/66,405	1.55 (1.43-1.68)
Indometacin	8/107	1.67 (0.70-4.01)	29/2,064	1.64 (1.13-2.38)
	With prior chronic ischemic heart disease (N=332,919)		Without prior chronic ischemic heart disease (N=1,398,323)	
	Cases (n)/Controls (n) 5,543/327,376	Adjusted OR* (95% CI)	Cases (n)/Controls (n) 11,693/1,386,630	Adjusted OR* (95% CI)
Current use of				
Diclofenac	521/23,649	1.32 (1.18-1.48)	919/90,775	1.48 (1.37-1.60)
Diclofenac, combinations	16/551	1.73 (1.02-2.94)	20/1,622	1.84 (1.17-2.87)
Etoricoxib	38/1,462	1.50 (1.06-2.12)	59/4,945	1.52 (1.17-1.98)
Ibuprofen	390/15,622	1.48 (1.30-1.68)	596/54,686	1.57 (1.43-1.72)
Indometacin	16/511	1.58 (0.93-2.66)	21/1,660	1.61 (1.04-2.49)
	With prior other cardiovascular disease (N=311,804)		Without prior other cardiovascular disease (N=1,419,438)	
	Cases (n)/Controls (n) 3,793/308,011	Adjusted OR* (95% CI)	Cases (n)/Controls (n) 13,443/1,405,995	Adjusted OR* (95% CI)
Current use of				
Diclofenac	325/21,561	1.35 (1.17-1.55)	1,115/92,863	1.47 (1.36-1.57)
Diclofenac, combinations	9/531	1.79 (0.90-3.56)	27/1,642	1.79 (1.22-2.64)
Etoricoxib	29/1,400	1.80 (1.21-2.69)	68/5,007	1.45 (1.13-1.85)
Ibuprofen	266/14,109	1.63 (1.40-1.89)	720/56,199	1.52 (1.40-1.66)
Indometacin	7/465	1.19 (0.54-2.62)	30/1,706	1.93 (1.33-2.78)
	With prior hyperlipidaemia (N=602,952)		Without prior hyperlipidaemia (N=1,128,290)	
	Cases (n)/Controls (n) 7,381/595,571	Adjusted OR* (95% CI)	Cases (n)/Controls (n) 9,855/1,118,435	Adjusted OR* (95% CI)

Current use of				
Diclofenac	597/41,876	1.26 (1.14-1.39)	843/72,548	1.54 (1.42-1.68)
Diclofenac, combinations	12/825	1.32 (0.73-2.37)	24/1,348	2.10 (1.38-3.17)
Etoricoxib	43/2,379	1.50 (1.09-2.06)	54/4,028	1.52 (1.15-2.00)
Ibuprofen	430/25,278	1.48 (1.32-1.65)	556/45,030	1.59 (1.44-1.76)
Indometacin	17/812	1.58 (0.96-2.60)	20/1,359	1.73 (1.10-2.72)
	With prior heart failure (N=178,792)		Without prior heart failure (N=1,552,450)	
	Cases (n)/Controls (n) 2,722/176,070	Adjusted OR* (95% CI)	Cases (n)/Controls (n) 14,514/1,537,936	Adjusted OR* (95% CI)
Current use of				
Diclofenac	251/13,762	1.20 (1.02-1.42)	1,189/100,662	1.47 (1.37-1.57)
Diclofenac, combinations	6/401	1.07 (0.45-2.56)	30/1,772	1.99 (1.38-2.87)
Etoricoxib	20/894	1.59 (0.97-2.60)	77/5,513	1.53 (1.21-1.93)
Ibuprofen	227/10,012	1.58 (1.33-1.87)	759/60,296	1.53 (1.40-1.66)
Indometacin	9/273	1.70 (0.77-3.74)	28/1,898	1.57 (1.07-2.29)
	With prior arterial fibrillation and flutter (N=94,941)		Without prior arterial fibrillation and flutter (N=1,636,301)	
	Cases (n)/Controls (n) 1,163/93,778	Adjusted OR* (95% CI)	Cases (n)/Controls (n) 16,073/1,620,228	Adjusted OR* (95% CI)
Current use of				
Diclofenac	102/6,696	1.39 (1.06-1.81)	1,338/107,728	1.43 (1.34-1.53)
Diclofenac, combinations	4/164	1.74 (0.55-5.47)	32/2,009	1.73 (1.21-2.46)
Etoricoxib	10/552	1.58 (0.78-3.18)	87/5,855	1.51 (1.21-1.87)
Ibuprofen	83/4,858	1.60 (1.20-2.12)	903/65,450	1.54 (1.43-1.67)
Indometacin	4/164	1.84 (0.56-6.00)	33/2,007	1.67 (1.18-2.37)
	With prior use of platelet aggregation inhibitors (N=104,816)		Without prior use of platelet aggregation inhibitors (N=1,626,426)	

	Cases (n)/Controls (n) 2,203/102,613	Adjusted OR* (95% CI)	Cases (n)/Controls (n) 15,033/1,611,393	Adjusted OR* (95% CI)
Current use of				
Diclofenac	197/7,635	1.31 (1.08-1.58)	1,243/106,789	1.44 (1.34-1.54)
Diclofenac, combinations	5/188	1.38 (0.51-3.77)	31/1,985	1.87 (1.30-2.68)
Etoricoxib	15/492	1.51 (0.83-2.75)	82/5,915	1.51 (1.21-1.89)
Ibuprofen	135/5,187	1.36 (1.09-1.70)	851/65,121	1.56 (1.44-1.68)
Indometacin	7/161	1.85 (0.75-4.55)	30/2,010	1.64 (1.14-2.37)
	With prior use of nitrates (N= 59,381)		Without prior use of nitrates (N=1,671,861)	
	Cases (n)/Controls (n) 1,928/57,453	Adjusted OR* (95% CI)	Cases (n)/Controls (n) 15,308/1,656,553	Adjusted OR* (95% CI)
Current use of				
Diclofenac	162/4,448	1.28 (1.03-1.60)	1,278/109,976	1.45 (1.35-1.55)
Diclofenac, combinations	4/132	1.00 (0.34-2.97)	32/2,050	1.91 (1.34-2.71)
Etoricoxib	10/300	0.87 (0.40-1.89)	87/6107	1.58 (1.27-1.96)
Ibuprofen	141/3,075	1.80 (1.42-2.29)	845/67,233	1.52 (1.40-1.64)
Indometacin	6/132	2.54 (0.93-6.98)	31/2,039	1.72 (1.20-2.47)

Values are numbers unless stated otherwise.

* Adjusted for the following respective covariates: obesity, hypertension, chronic liver diseases, heart failure, diabetes mellitus, myocardial infarction, chronic ischemic heart disease, stroke, atrial fibrillation and flutter, peripheral arterial diseases, other cardiovascular diseases, hyperlipidemia, ACE inhibitors + AT II antagonists, calcium channel blockers, beta blocking agents, diuretics, other antihypertensive drugs, aspirin (90 days prior index date), glucocorticoids, platelet aggregation inhibitors, oral contraceptives, postmenopausal hormone therapy, statins, nitrates, aspirin (30 days prior index date).