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Summary of Study Results Using National Database of Health Insurance Claims and Specific Health Checkup of Japan (NDB)

October 8, 2024

Study title

Evaluation of the risk of cardiovascular events due to non-steroidal anti-inflammatory drugs using NDB

Products investigated

- **The following oral non-steroidal anti-inflammatory drugs (NSAIDs):**

Acemetacin, ampiroxicam, ibuprofen, indometacin farnesil, etodolac, oxaprozin, zaltoprofen, diclofenac sodium, sulindac, celecoxib, tiaprofenic acid, tiaramide hydrochloride, nabumetone, naproxen, piroxicam, bucolome, pranoprofen, flufenamate aluminum, flurbiprofen, proglumetacin maleate, mefenamic acid, meloxicam, mofezolac, loxoprofen sodium hydrate, and lornoxicam

- **The following oral drugs classified as antipyretics, analgesics and anti-inflammatory agents in the same way as NSAIDs:**

Aspirin (therapeutic category 114 only)

Background:

- In the United States, the Food and Drug Administration (FDA) instructed revision of labeling for all NSAIDs except aspirin to add "Cardiovascular Risk" in the Boxed Warning and Warnings and Precautions sections and to include specific precautions concerning cardiovascular events as described below.[1] Similarly in Europe, the European Medicines Agency (EMA) instructed revision of package inserts for all

[1] Food and Drug Administration. FDA strengthens warning that non-aspirin nonsteroidal antiinflammatory drugs (NSAIDs) can cause heart attacks or strokes. https://www.fda.gov/media/92768/download. Accessed 2024/8/1.

NSAIDs to include precautions on cardiovascular events.[2]

- The risk of heart attack or stroke can occur as early as the first weeks of using an NSAID.
- The risk may increase with longer use of the NSAID.
- The risk appears greater at higher doses.

■ In Japan, the package inserts of celecoxib and diclofenac sodium, among NSAIDs, include precautions on cardiovascular events, while those of other NSAIDs do not. Thus, the status of issuance of precautions on cardiovascular events differs among NSAIDs.

Purpose of the study

The purpose is to evaluate the relationship of the time of NSAIDs use and number of days of prescription period with cardiovascular events in patients with chronic diseases (rheumatoid arthritis, osteoarthritis, lumbago, periarthritis scapulohumeralis, neck-shoulder-arm syndrome, or tendinitis/tenosynovitis).

Reason for selection of NDB for the study and data period

Reason for selection: It was selected because it is the nationwide database in Japan, and it is possible to collect medical information nationwide multiple different medical institutions.

Data period: April 1, 2012 to March 31, 2020

Outline of method

■ **Study population**

Patients who were diagnosed with a chronic diseases (rheumatoid arthritis, osteoarthritis, lumbago, periarthritis scapulohumeralis, neck-shoulder-arm syndrome, or tendinitis/tenosynovitis) and were prescribed or dispensed NSAIDs in the same month or by the end of the next month during the period between January 1, 2013 and March 31, 2020 (inclusion period) were identified. The earlier date of dispensing or prescribing the NSAIDs during the inclusion period was defined as t_0. Of these patients, those who (1) were under 20

[2] European Medicines Agency. PRAC recommends the same cardiovascular precautions for diclofenac as for selective COX-2 inhibitors. https://www.ema.europa.eu/en/documents/press-release/prac-recommends-same-cardiovascular-precautions-diclofenac-selective-cox-2-inhibitors_en.pdf. Accessed 2024/8/1.

years of age at t_0, (2) had no claim data 270 days or more before t_0, or (3) had a start date or end date of prescription period[3] of NSAIDs during 180 days before t_0 were excluded, and the remaining patients were included in the study population. t_0 was the start date of follow-up, and the end date of follow-up was the date of occurrence of cardiovascular events or the end date of the month of the last claim data, whichever comes earlier.

■ **Analysis population**

Based on the nested case-control design, patients who met the following definitions of case or control were included in the analysis population.

- Case: Patients with occurrence of cardiovascular events (composite outcome of acute coronary syndromes,[4] cerebral infarction[5] and cerebral hemorrhage[6]) during the follow-up period (the earliest date of hospitalization was defined as the index date).
- Control: Among patients who were non-cases at the time of the index date, those with matching factors (sex, age, calendar year of follow-up start, and presence/absence of history of cardiovascular events) that are consistent with each case (random sampling of up to 10 patients per 1 case)

■ **Exposure or non-exposure**

- Exposure category 1: Among NSAIDs with a start date of a prescription period before or on the index date, with a focus on an NSAID with an end date of the prescription period closest to the index date, patients were classified[7] as follows based on the temporal

[3] Period obtained by adding the number of days of prescription to the date of prescription or dispensing of NSAIDs. If the end date of the preceding prescription period and the start date of the following prescription period were within 14 days, both were combined as one prescription period.

[4] The date of hospitalization with an injury/disease named "acute coronary syndrome" must be recorded, and at least one of "percutaneous coronary intervention," "coronary artery bypass surgery," "intra-aortic balloon pumping," "percutaneous cardiopulmonary support," or "thrombolysis" must be performed during the period between the day before the date of hospitalization and 30 days after the date of hospitalization.

[5] The date of hospitalization with an injury/disease named "cerebral infarction" must be recorded. At least one of "computed tomography," "magnetic resonance angiography," or "magnetic resonance computed tomography" must be performed during the period between the day before the date of hospitalization and 30 days after the date of hospitalization, and at least one of "cerebro- protective agents," "antiplatelet drugs (injection)," "anticoagulant drugs (injection)," "thrombolytic drugs," "anti-edema drugs," "craniotomy," or "thrombectomy" must be prescribed or performed.

[6] The date of hospitalization with an injury/disease named "cerebral hemorrhage" must be recorded. At least one of "computed tomography," "magnetic resonance angiography," or "magnetic resonance computed tomography" must be performed, and at least one of "anti-edematous drugs," "antihypertensive drugs (injection)," or "hematoma removal surgery" must be prescribed or performed during the period between the day before the date of hospitalization and 30 days after the date of hospitalization.

[7] If the end date of prescription period of different NSAIDs was also present within the exposure categories, the name of the NSAIDs for the patient was defined as "combinations".

relationship between the end date of the prescription period of the NSAID and the index date.

(1) Current use: The end date of the prescription period was within 14 days before the index date, or the prescription period started before the index date and ended after the index date.

(2) Recent use: The end date of the prescription period was between 15 days and 90 days before the index date.

(3) Past use: The end date of the prescription period was between 91 days and 180 days before the index date.

- Exposure category 2: Based on the number of days of the prescription period classified as current use,[8] patients of current use in exposure category 1 were classified as follows.[9]

  (1) Short use: Number of days of the prescription period of < 30 days

  (2) Medium use: Number of days of the prescription period of ≥ 30 and < 90 days

  (3) Long use: Number of days of the prescription period of ≥ 90 days

- Non-exposure (nonuse): No prescription period for any NSAIDs within 180 days before the index date

■ **Analysis methods**

Conditional logistic regression[10] was used to estimate the adjusted odds ratio and 95% confidence interval (95% CI) for each NSAID in exposure category 1 and exposure category 2 in comparison with nonuse. The pooled adjusted odds ratio and 95% CI for each exposure category were estimated using the contrast method.

Outline of results

■ **Analysis population**

- Of the 31,403,138 patients in the study population, 833,757 cases and 8,337,570 controls were identified.

[8] If the prescription period started before the index date and ended after the index date, the number of days of prescription period for the patient was calculated as the number of days from the start date of the prescription period to the index date.

[9] In exposure category 2, combinations were excluded from evaluation.

[10] The matched pairs were used as stratification factors, and hypertension, diabetes mellitus, dyslipidemia, arrhythmia, antiplatelet drugs, anticoagulant drugs, heart failure, chronic kidney disease, chronic obstructive pulmonary disease, and rheumatoid arthritis were used as adjustment factors.

- As for the patient background in the case and control groups, standardized differences exceeding 0.1 were observed in the distribution of hypertension (case: 62.55%, control: 55.21%; the same order applies hereinafter), diabetes mellitus (21.26%, 14.15%), arrhythmia (14.48%, 10.11%), heart failure (34.96%, 28.42%), history of chronic kidney disease (7.64%, 4.72%), and prescription of antiplatelet drugs (32.61%, 22.64%) and anticoagulant drugs (11.95%, 7.50%).

■ **Relationship between the time of NSAIDs use and cardiovascular events (exposure category 1)**

- The results of evaluation of the relationship between the time of NSAIDs use and cardiovascular events were as shown in Appendix Figure 1. The pooled adjusted odds ratios (95% CI) of each exposure category in comparison with nonuse were 1.41 (1.36-1.46) for current use, 1.00 (0.96-1.04) for recent use, and 0.96 (0.91-1.01) in past use. In current use, aspirin was the NSAID with the highest adjusted odds ratio of 20.47 (19.79-21.18). The point estimates of adjusted odds ratios exceeded 1.00 for all NSAIDs except oxaprozin and flurbiprofen. The adjusted odds ratio for combinations was 2.63 (2.57-2.69). The pooled adjusted odds ratio for current use in comparison with nonuse excluding aspirin and combinations was 1.24 (1.19-1.28).
- As for NSAIDs used for assessment of exposure category 1, the results of a same analysis focusing on an NSAID with the end date of a prescription period closest to the index date after excluding NSAIDs with a start date of prescription period on the index date are shown in Appendix Figure 2. The pooled adjusted odds ratio (95% CI) for current use in comparison with nonuse was 1.20 (1.16-1.25). In current use, the adjusted odds ratio for aspirin was 1.22 (1.13-1.33) and that of combinations was 1.61 (1.57-1.66), showing a great decrease compared with the results focusing on NSAIDs including those with a start date of a prescription period on the index date.

■ **Relationship between the number of days of prescription period of NSAIDs and cardiovascular events (exposure category 2)**

The results of evaluation of the relationship between the number of days of prescription period of NSAIDs and cardiovascular events are shown in Appendix Figure 3. The pooled adjusted odds ratios (95% CI) for each exposure category in comparison with nonuse were 1.50 (1.43-1.58) for short use, 1.15 (1.01-1.31) for medium use, and 1.10 (0.96-1.25) for long use.

■ **Discussion based on the results**

- The results of an evaluation of the relationship between the time of NSAIDs use and cardiovascular events indicated an increased risk of cardiovascular events in current use of NSAIDs (excluding aspirin) in comparison with nonuse. Although the point estimates of the adjusted odds ratios for oxaprozin and flurbiprofen in current use were less than 1.00, the number of cases was limited to 48 and 79, respectively, therefore it was difficult to conclude based on the results that only these two drugs have a low risk of cardiovascular events.
- As for aspirin, although a high adjusted odds ratio was observed in current use, the adjusted odds ratio greatly decreased by excluding NSAIDs whose prescription period started on the index date. This result suggests that the selection of aspirin based on the drug therapeutic classification did not completely exclude aspirin prescribed for the treatment of cardiovascular events, and hence the high adjusted odds ratio was observed. Although the adjusted odds ratio of aspirin exceeded 1.00, even excluding NSAIDs whose prescription period started on the index date, it was difficult to conclude the relationship between aspirin and cardiovascular events from the results, because the possibility that aspirin was prescribed prophylactically in patients at a high risk of cardiovascular events could not be ruled out.
- The results of an evaluation of the relationship between the number of days of prescription period of NSAIDs and cardiovascular events indicated an increased risk of cardiovascular events in short use of NSAIDs (excluding aspirin) in comparison with nonuse. There was no tendency toward an increase in the risk of cardiovascular events associated with an extension of prescription period, but that the number of cardiovascular events was small and the 95% CI was wide in medium use and long use, therefore interpretation of the result was limited.
- It should be noted that there are some limitations in the evaluation of the results, including the following: The outcome definition of cardiovascular events was set based on previous studies and clinical perspectives. However, the validation study in the NDB has been unachievable due to the prohibition of identifying patients and linking to the other electronic health records; the possibility that other potential confounders (e.g., history of drinking, body mass index) and changes in confounders during the follow-up period, which could affect the exposure situation, may have affected the results. Lastly, the use of NSAIDs as over-the-counter drugs could not be captured.

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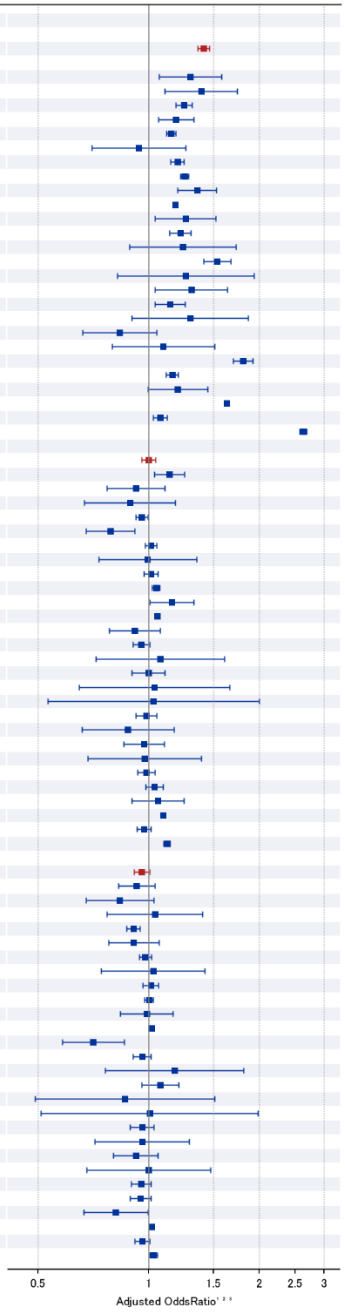
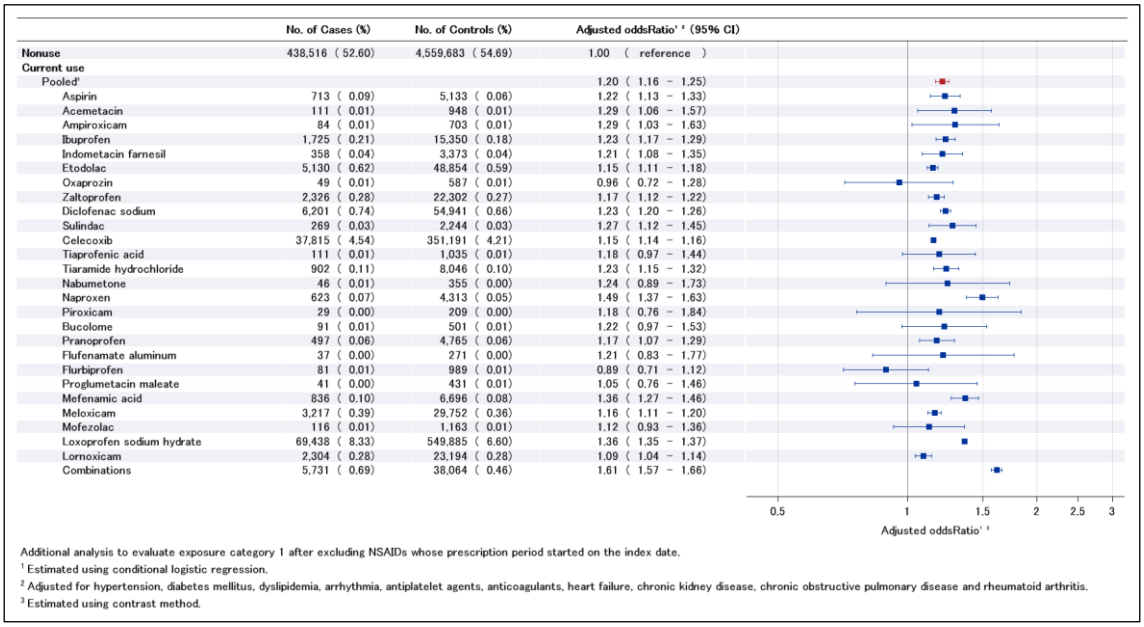
Appendix

	No. of Cases (%)	No. of Controls (%)	Adjusted oddsRatio[1,2] (95% CI)
Nonuse	419,443 (50.31)	4,498,164 (53.95)	1.00 (reference)
Current use			
Pooled[4]			1.41 (1.36 - 1.46)
Aspirin	10,437 (1.25)	5,365 (0.06)	20.47 (19.79 - 21.18)
Acemetacin	110 (0.01)	1,019 (0.01)	1.30 (1.07 - 1.58)
Ampiroxicam	85 (0.01)	745 (0.01)	1.39 (1.11 - 1.74)
Ibuprofen	1,772 (0.21)	16,757 (0.20)	1.25 (1.19 - 1.31)
Indometacin farnesil	358 (0.04)	3,541 (0.04)	1.19 (1.06 - 1.32)
Etodolac	5,110 (0.61)	51,591 (0.62)	1.15 (1.12 - 1.19)
Oxaprozin	48 (0.01)	620 (0.01)	0.94 (0.70 - 1.26)
Zaltoprofen	2,389 (0.29)	23,908 (0.29)	1.20 (1.15 - 1.25)
Diclofenac sodium	6,383 (0.77)	58,844 (0.71)	1.25 (1.22 - 1.29)
Sulindac	300 (0.04)	2,396 (0.03)	1.35 (1.20 - 1.53)
Celecoxib	38,230 (4.59)	366,404 (4.39)	1.18 (1.17 - 1.19)
Tiaprofenic acid	117 (0.01)	1,122 (0.01)	1.26 (1.04 - 1.52)
Tiaramide hydrochloride	911 (0.11)	8,756 (0.11)	1.22 (1.14 - 1.30)
Nabumetone	42 (0.01)	375 (0.00)	1.24 (0.89 - 1.73)
Naproxen	619 (0.07)	4,578 (0.05)	1.54 (1.41 - 1.67)
Piroxicam	29 (0.00)	223 (0.00)	1.26 (0.82 - 1.94)
Bucolome	91 (0.01)	511 (0.01)	1.31 (1.04 - 1.64)
Pranoprofen	495 (0.06)	5,229 (0.06)	1.14 (1.04 - 1.25)
Flufenamate aluminum	38 (0.00)	295 (0.00)	1.30 (0.90 - 1.86)
Flurbiprofen	79 (0.01)	1,041 (0.01)	0.83 (0.66 - 1.05)
Proglumetacin maleate	43 (0.01)	465 (0.01)	1.10 (0.80 - 1.51)
Mefenamic acid	1,141 (0.14)	7,214 (0.09)	1.81 (1.69 - 1.92)
Meloxicam	3,144 (0.38)	30,769 (0.37)	1.16 (1.12 - 1.20)
Mofezolac	122 (0.01)	1,239 (0.01)	1.20 (1.00 - 1.45)
Loxoprofen sodium hydrate	84,061 (10.08)	592,007 (7.10)	1.63 (1.62 - 1.65)
Lornoxicam	2,287 (0.27)	24,979 (0.30)	1.07 (1.03 - 1.12)
Combinations	9,499 (1.14)	41,018 (0.49)	2.63 (2.57 - 2.69)
Recent use			
Pooled[4]			1.00 (0.96 - 1.04)
Aspirin	498 (0.06)	4,491 (0.05)	1.14 (1.04 - 1.25)
Acemetacin	131 (0.02)	1,575 (0.02)	0.92 (0.77 - 1.11)
Ampiroxicam	51 (0.01)	671 (0.01)	0.89 (0.67 - 1.18)
Ibuprofen	3,042 (0.36)	35,324 (0.42)	0.96 (0.92 - 1.00)
Indometacin farnesil	184 (0.02)	2,636 (0.03)	0.79 (0.68 - 0.92)
Etodolac	3,518 (0.42)	39,177 (0.47)	1.01 (0.98 - 1.05)
Oxaprozin	45 (0.01)	525 (0.01)	0.99 (0.73 - 1.35)
Zaltoprofen	2,230 (0.27)	25,183 (0.30)	1.01 (0.97 - 1.06)
Diclofenac sodium	7,973 (0.96)	84,548 (1.01)	1.05 (1.02 - 1.07)
Sulindac	230 (0.03)	2,061 (0.02)	1.16 (1.01 - 1.33)
Celecoxib	22,108 (2.65)	232,857 (2.79)	1.06 (1.04 - 1.07)
Tiaprofenic acid	169 (0.02)	2,049 (0.02)	0.92 (0.78 - 1.07)
Tiaramide hydrochloride	1,553 (0.19)	17,914 (0.21)	0.95 (0.91 - 1.01)
Nabumetone	28 (0.00)	277 (0.00)	1.07 (0.72 - 1.61)
Naproxen	390 (0.05)	4,276 (0.05)	1.00 (0.90 - 1.11)
Piroxicam	20 (0.00)	220 (0.00)	1.04 (0.65 - 1.66)
Bucolome	<15	81 (0.00)	1.03 (0.53 - 2.00)
Pranoprofen	964 (0.12)	11,071 (0.13)	0.99 (0.92 - 1.05)
Flufenamate aluminum	50 (0.01)	640 (0.01)	0.88 (0.66 - 1.17)
Flurbiprofen	265 (0.03)	2,971 (0.04)	0.97 (0.86 - 1.10)
Proglumetacin maleate	33 (0.00)	392 (0.00)	0.97 (0.68 - 1.39)
Mefenamic acid	1,421 (0.17)	15,859 (0.19)	0.98 (0.93 - 1.04)
Meloxicam	1,394 (0.17)	15,120 (0.18)	1.04 (0.98 - 1.10)
Mofezolac	159 (0.02)	1,723 (0.02)	1.06 (0.90 - 1.25)
Loxoprofen sodium hydrate	81,156 (9.73)	813,627 (9.76)	1.09 (1.09 - 1.10)
Lornoxicam	2,331 (0.28)	27,163 (0.33)	0.97 (0.93 - 1.01)
Combinations	10,065 (1.21)	99,446 (1.19)	1.12 (1.10 - 1.14)
Past use			
Pooled[4]			0.96 (0.91 - 1.01)
Aspirin	318 (0.04)	3,452 (0.04)	0.93 (0.83 - 1.04)
Acemetacin	95 (0.01)	1,227 (0.01)	0.84 (0.68 - 1.03)
Ampiroxicam	48 (0.01)	497 (0.01)	1.04 (0.77 - 1.40)
Ibuprofen	2,412 (0.29)	29,010 (0.35)	0.91 (0.87 - 0.95)
Indometacin farnesil	171 (0.02)	2,082 (0.02)	0.91 (0.78 - 1.07)
Etodolac	2,801 (0.34)	31,699 (0.38)	0.98 (0.94 - 1.02)
Oxaprozin	41 (0.00)	430 (0.01)	1.03 (0.74 - 1.42)
Zaltoprofen	1,836 (0.22)	20,368 (0.24)	1.01 (0.97 - 1.06)
Diclofenac sodium	6,123 (0.73)	67,116 (0.80)	1.00 (0.98 - 1.03)
Sulindac	159 (0.02)	1,610 (0.02)	0.99 (0.84 - 1.16)
Celecoxib	17,280 (2.07)	186,129 (2.23)	1.02 (1.00 - 1.03)
Tiaprofenic acid	114 (0.01)	1,694 (0.02)	0.71 (0.58 - 0.86)
Tiaramide hydrochloride	1,343 (0.16)	15,198 (0.18)	0.96 (0.91 - 1.01)
Nabumetone	27 (0.00)	209 (0.00)	1.18 (0.76 - 1.81)
Naproxen	322 (0.04)	3,214 (0.04)	1.08 (0.96 - 1.21)
Piroxicam	<15	174 (0.00)	0.86 (0.49 - 1.51)
Bucolome	<15	72 (0.00)	1.01 (0.51 - 1.99)
Pranoprofen	793 (0.10)	9,216 (0.11)	0.96 (0.89 - 1.03)
Flufenamate aluminum	48 (0.01)	556 (0.01)	0.96 (0.71 - 1.29)
Flurbiprofen	218 (0.03)	2,586 (0.03)	0.92 (0.80 - 1.06)
Proglumetacin maleate	28 (0.00)	324 (0.00)	1.00 (0.68 - 1.47)
Mefenamic acid	1,129 (0.14)	12,817 (0.15)	0.95 (0.90 - 1.01)
Meloxicam	1,018 (0.12)	11,818 (0.14)	0.95 (0.89 - 1.01)
Mofezolac	105 (0.01)	1,414 (0.02)	0.81 (0.67 - 1.00)
Loxoprofen sodium hydrate	60,210 (7.22)	638,947 (7.66)	1.02 (1.01 - 1.03)
Lornoxicam	1,923 (0.23)	22,157 (0.27)	0.96 (0.92 - 1.01)
Combinations	7,774 (0.93)	82,502 (0.99)	1.03 (1.01 - 1.06)



[1] Estimated using conditional logistic regression.
[2] Adjusted for hypertension, diabetes mellitus, dyslipidemia, arrhythmia, antiplatelet agents, anticoagulants, heart failure, chronic kidney disease, chronic obstructive pulmonary disease and rheumatoid arthritis.
[3] Adjusted oddsRatio for aspirin in current use is not shown.
[4] Estimated using contrast method.

Figure 1. Relationship between the time of NSAIDs use and cardiovascular events



	No. of Cases (%)	No. of Controls (%)	Adjusted oddsRatio[1] (95% CI)
Nonuse	438,516 (52.60)	4,559,683 (54.69)	1.00 (reference)
Current use			
Pooled[3]			1.20 (1.16 – 1.25)
Aspirin	713 (0.09)	5,133 (0.06)	1.22 (1.13 – 1.33)
Acemetacin	111 (0.01)	948 (0.01)	1.29 (1.06 – 1.57)
Ampiroxicam	84 (0.01)	703 (0.01)	1.29 (1.03 – 1.63)
Ibuprofen	1,725 (0.21)	15,350 (0.18)	1.23 (1.17 – 1.29)
Indometacin farnesil	358 (0.04)	3,373 (0.04)	1.21 (1.08 – 1.35)
Etodolac	5,130 (0.62)	48,854 (0.59)	1.15 (1.11 – 1.18)
Oxaprozin	49 (0.01)	587 (0.01)	0.96 (0.72 – 1.28)
Zaltoprofen	2,326 (0.28)	22,302 (0.27)	1.17 (1.12 – 1.22)
Diclofenac sodium	6,201 (0.74)	54,941 (0.66)	1.23 (1.20 – 1.26)
Sulindac	269 (0.03)	2,244 (0.03)	1.27 (1.12 – 1.45)
Celecoxib	37,815 (4.54)	351,191 (4.21)	1.15 (1.14 – 1.16)
Tiaprofenic acid	111 (0.01)	1,035 (0.01)	1.18 (0.97 – 1.44)
Tiaramide hydrochloride	902 (0.11)	8,046 (0.10)	1.23 (1.15 – 1.32)
Nabumetone	46 (0.01)	355 (0.00)	1.24 (0.89 – 1.73)
Naproxen	623 (0.07)	4,313 (0.05)	1.49 (1.37 – 1.63)
Piroxicam	29 (0.00)	209 (0.00)	1.18 (0.76 – 1.84)
Bucolome	91 (0.01)	501 (0.01)	1.22 (0.97 – 1.53)
Pranoprofen	497 (0.06)	4,765 (0.06)	1.17 (1.07 – 1.29)
Flufenamate aluminum	37 (0.00)	271 (0.00)	1.21 (0.83 – 1.77)
Flurbiprofen	81 (0.01)	989 (0.01)	0.89 (0.71 – 1.12)
Proglumetacin maleate	41 (0.00)	431 (0.01)	1.05 (0.76 – 1.46)
Mefenamic acid	836 (0.10)	6,696 (0.08)	1.36 (1.27 – 1.46)
Meloxicam	3,217 (0.39)	29,752 (0.36)	1.16 (1.11 – 1.20)
Mofezolac	116 (0.01)	1,163 (0.01)	1.12 (0.93 – 1.36)
Loxoprofen sodium hydrate	69,438 (8.33)	549,885 (6.60)	1.36 (1.35 – 1.37)
Lornoxicam	2,304 (0.28)	23,194 (0.28)	1.09 (1.04 – 1.14)
Combinations	5,731 (0.69)	38,064 (0.46)	1.61 (1.57 – 1.66)

Additional analysis to evaluate exposure category 1 after excluding NSAIDs whose prescription period started on the index date.

[1] Estimated using conditional logistic regression.

[2] Adjusted for hypertension, diabetes mellitus, dyslipidemia, arrhythmia, antiplatelet agents, anticoagulants, heart failure, chronic kidney disease, chronic obstructive pulmonary disease and rheumatoid arthritis.

[3] Estimated using contrast method.

Figure 2. Relationship between the time of NSAIDs use and cardiovascular events (excluding NSAIDs whose prescription period started on the index date)

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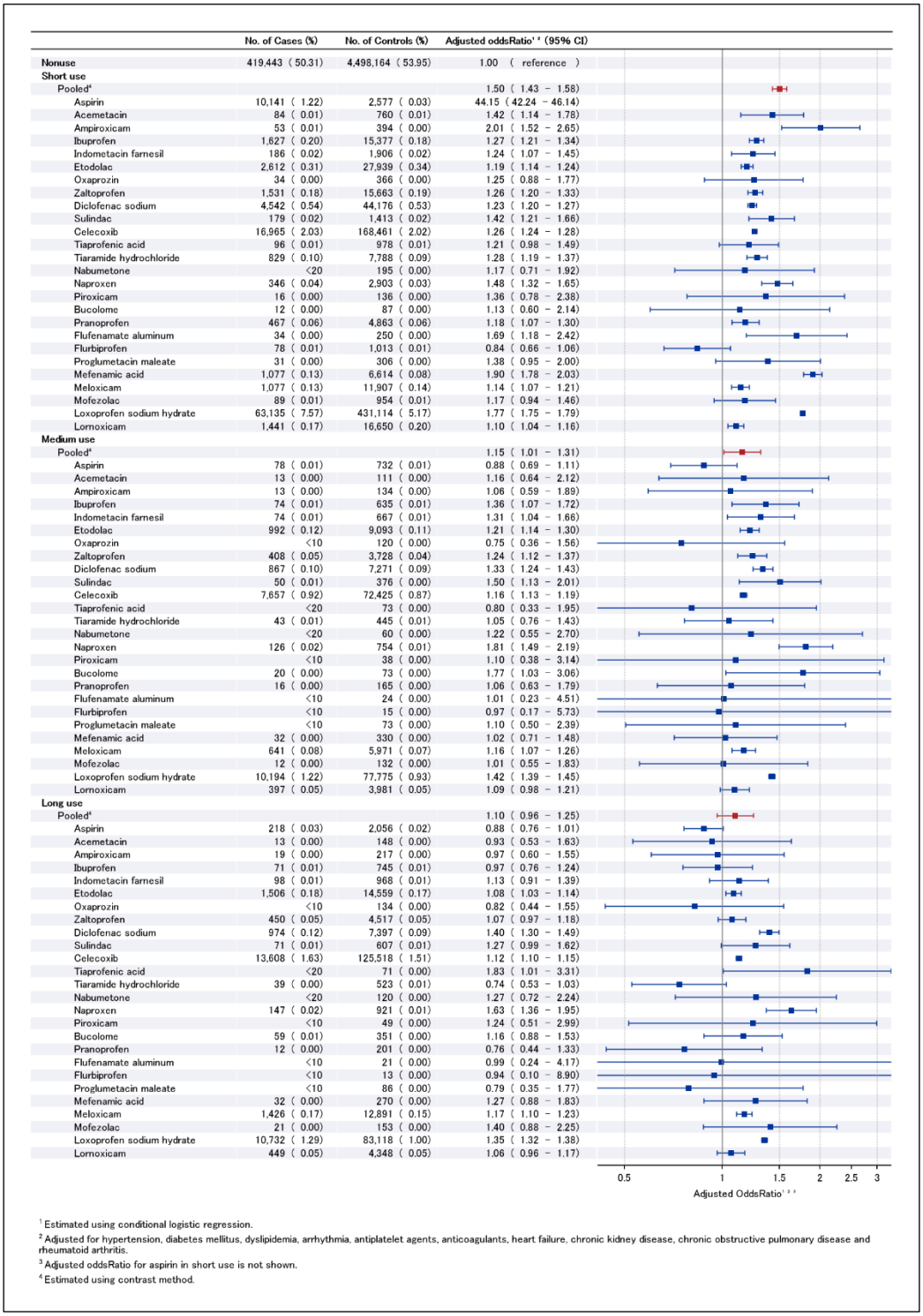

	No. of Cases (%)	No. of Controls (%)	Adjusted oddsRatio[1,2] (95% CI)
Nonuse	419,443 (50.31)	4,498,164 (53.95)	1.00 (reference)
Short use			
Pooled[4]			1.50 (1.43 - 1.58)
Aspirin	10,141 (1.22)	2,577 (0.03)	44.15 (42.24 - 46.14)
Acemetacin	84 (0.01)	760 (0.01)	1.42 (1.14 - 1.78)
Ampiroxicam	53 (0.01)	394 (0.00)	2.01 (1.52 - 2.65)
Ibuprofen	1,627 (0.20)	15,377 (0.18)	1.27 (1.21 - 1.34)
Indometacin farnesil	186 (0.02)	1,906 (0.02)	1.24 (1.07 - 1.45)
Etodolac	2,612 (0.31)	27,939 (0.34)	1.19 (1.14 - 1.24)
Oxaprozin	34 (0.00)	366 (0.00)	1.25 (0.88 - 1.77)
Zaltoprofen	1,531 (0.18)	15,663 (0.19)	1.26 (1.20 - 1.33)
Diclofenac sodium	4,542 (0.54)	44,176 (0.53)	1.23 (1.20 - 1.27)
Sulindac	179 (0.02)	1,413 (0.02)	1.42 (1.21 - 1.66)
Celecoxib	16,965 (2.03)	168,461 (2.02)	1.26 (1.24 - 1.28)
Tiaprofenic acid	96 (0.01)	978 (0.01)	1.21 (0.98 - 1.49)
Tiaramide hydrochloride	829 (0.10)	7,788 (0.09)	1.28 (1.19 - 1.37)
Nabumetone	<20	195 (0.00)	1.17 (0.71 - 1.92)
Naproxen	346 (0.04)	2,903 (0.03)	1.48 (1.32 - 1.65)
Piroxicam	16 (0.00)	136 (0.00)	1.36 (0.78 - 2.38)
Bucolome	12 (0.00)	87 (0.00)	1.13 (0.60 - 2.14)
Pranoprofen	467 (0.06)	4,863 (0.06)	1.18 (1.07 - 1.30)
Flufenamate aluminum	34 (0.00)	250 (0.00)	1.69 (1.18 - 2.42)
Flurbiprofen	78 (0.01)	1,013 (0.01)	0.84 (0.66 - 1.06)
Proglumetacin maleate	31 (0.00)	306 (0.00)	1.38 (0.95 - 2.00)
Mefenamic acid	1,077 (0.13)	6,614 (0.08)	1.90 (1.78 - 2.03)
Meloxicam	1,077 (0.13)	11,907 (0.14)	1.14 (1.07 - 1.21)
Mofezolac	89 (0.01)	954 (0.01)	1.17 (0.94 - 1.46)
Loxoprofen sodium hydrate	63,135 (7.57)	431,114 (5.17)	1.77 (1.75 - 1.79)
Lornoxicam	1,441 (0.17)	16,650 (0.20)	1.10 (1.04 - 1.16)
Medium use			
Pooled[4]			1.15 (1.01 - 1.31)
Aspirin	78 (0.01)	732 (0.01)	0.88 (0.69 - 1.11)
Acemetacin	13 (0.00)	111 (0.00)	1.16 (0.64 - 2.12)
Ampiroxicam	13 (0.00)	134 (0.00)	1.06 (0.59 - 1.89)
Ibuprofen	74 (0.01)	635 (0.01)	1.36 (1.07 - 1.72)
Indometacin farnesil	74 (0.01)	667 (0.01)	1.31 (1.04 - 1.66)
Etodolac	992 (0.12)	9,093 (0.11)	1.21 (1.14 - 1.30)
Oxaprozin	<10	120 (0.00)	0.75 (0.36 - 1.56)
Zaltoprofen	408 (0.05)	3,728 (0.04)	1.24 (1.12 - 1.37)
Diclofenac sodium	867 (0.10)	7,271 (0.09)	1.33 (1.24 - 1.43)
Sulindac	50 (0.01)	376 (0.00)	1.50 (1.13 - 2.01)
Celecoxib	7,657 (0.92)	72,425 (0.87)	1.16 (1.13 - 1.19)
Tiaprofenic acid	<20	73 (0.00)	0.80 (0.33 - 1.95)
Tiaramide hydrochloride	43 (0.01)	445 (0.01)	1.05 (0.76 - 1.43)
Nabumetone	<20	60 (0.00)	1.22 (0.55 - 2.70)
Naproxen	126 (0.02)	754 (0.01)	1.81 (1.49 - 2.19)
Piroxicam	<10	38 (0.00)	1.10 (0.38 - 3.14)
Bucolome	20 (0.00)	73 (0.00)	1.77 (1.03 - 3.06)
Pranoprofen	16 (0.00)	165 (0.00)	1.06 (0.63 - 1.79)
Flufenamate aluminum	<10	24 (0.00)	1.01 (0.23 - 4.51)
Flurbiprofen	<10	15 (0.00)	0.97 (0.17 - 5.73)
Proglumetacin maleate	<10	73 (0.00)	1.10 (0.50 - 2.39)
Mefenamic acid	32 (0.00)	330 (0.00)	1.02 (0.71 - 1.48)
Meloxicam	641 (0.08)	5,971 (0.07)	1.16 (1.07 - 1.26)
Mofezolac	12 (0.00)	132 (0.00)	1.01 (0.55 - 1.83)
Loxoprofen sodium hydrate	10,194 (1.22)	77,775 (0.93)	1.42 (1.39 - 1.45)
Lornoxicam	397 (0.05)	3,981 (0.05)	1.09 (0.98 - 1.21)
Long use			
Pooled[4]			1.10 (0.96 - 1.25)
Aspirin	218 (0.03)	2,056 (0.02)	0.88 (0.76 - 1.01)
Acemetacin	13 (0.00)	148 (0.00)	0.93 (0.53 - 1.63)
Ampiroxicam	19 (0.00)	217 (0.00)	0.97 (0.60 - 1.55)
Ibuprofen	71 (0.01)	745 (0.01)	0.97 (0.76 - 1.24)
Indometacin farnesil	98 (0.01)	968 (0.01)	1.13 (0.91 - 1.39)
Etodolac	1,506 (0.18)	14,559 (0.17)	1.08 (1.03 - 1.14)
Oxaprozin	<10	134 (0.00)	0.82 (0.44 - 1.55)
Zaltoprofen	450 (0.05)	4,517 (0.05)	1.07 (0.97 - 1.18)
Diclofenac sodium	974 (0.12)	7,397 (0.09)	1.40 (1.30 - 1.49)
Sulindac	71 (0.01)	607 (0.01)	1.27 (0.99 - 1.62)
Celecoxib	13,608 (1.63)	125,518 (1.51)	1.12 (1.10 - 1.15)
Tiaprofenic acid	<20	71 (0.00)	1.83 (1.01 - 3.31)
Tiaramide hydrochloride	39 (0.00)	523 (0.01)	0.74 (0.53 - 1.03)
Nabumetone	<20	120 (0.00)	1.27 (0.72 - 2.24)
Naproxen	147 (0.02)	921 (0.01)	1.63 (1.36 - 1.95)
Piroxicam	<10	49 (0.00)	1.24 (0.51 - 2.99)
Bucolome	59 (0.01)	351 (0.00)	1.16 (0.88 - 1.53)
Pranoprofen	12 (0.00)	201 (0.00)	0.76 (0.44 - 1.33)
Flufenamate aluminum	<10	21 (0.00)	0.99 (0.24 - 4.17)
Flurbiprofen	<10	13 (0.00)	0.94 (0.10 - 8.90)
Proglumetacin maleate	<10	86 (0.00)	0.79 (0.35 - 1.77)
Mefenamic acid	32 (0.00)	270 (0.00)	1.27 (0.88 - 1.83)
Meloxicam	1,426 (0.17)	12,891 (0.15)	1.17 (1.10 - 1.23)
Mofezolac	21 (0.00)	153 (0.00)	1.40 (0.88 - 2.25)
Loxoprofen sodium hydrate	10,732 (1.29)	83,118 (1.00)	1.35 (1.32 - 1.38)
Lornoxicam	449 (0.05)	4,348 (0.05)	1.06 (0.96 - 1.17)

[1] Estimated using conditional logistic regression.
[2] Adjusted for hypertension, diabetes mellitus, dyslipidemia, arrhythmia, antiplatelet agents, anticoagulants, heart failure, chronic kidney disease, chronic obstructive pulmonary disease and rheumatoid arthritis.
[3] Adjusted oddsRatio for aspirin in short use is not shown.
[4] Estimated using contrast method.

Figure 3. Relationship between the number of days of prescription period of NSAIDs and cardiovascular events

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