Original Contribution

Association of Short-Term Use of Nonsteroidal Anti-Inflammatory Drugs With Stroke in Patients With Hypertension

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Background and Purpose—Limited studies have investigated the risk of cerebrovascular events associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in subjects at high risk. We examined the short-term (defined as 30-day period) effect of selective and nonselective NSAIDs use on the risk of ischemic and hemorrhagic stroke in patients with hypertension.

Methods—We conducted a case-crossover study using the National Health Insurance Research Database in Taiwan. We identified 1653 hypertensive subjects with stroke (defined as *International Classification of Diseases-Ninth Revision*-CM-codes: 433.x, 434.x, and 436.x for ischemic stroke; 430 and 431 for hemorrhagic stroke) in 2010. We investigated the transient effect of NSAIDs use on stroke using conditional logistic regressions with the adjustment of potential confounders.

Results—The results suggested that NSAIDs use during the 30 days before stroke was associated with a 1.57-fold increased risk of ischemic stroke, but not of hemorrhagic stroke (adjusted odds ratio, 1.57; 95% confidence interval, 1.26–1.97 for ischemic stroke; and adjusted odds ratio, 1.38; 95% confidence interval, 0.79–2.40 for hemorrhagic stroke). When classifying NSAIDs into selective and nonselective groups, nonselective NSAIDs use significantly increased the risk of ischemic stroke (adjusted odds ratio, 1.55; 95% confidence interval, 1.24–1.94), but not of hemorrhagic stroke (adjusted odds ratio, 1.56; 95% confidence interval, 0.90–2.73).

Conclusions—The results demonstrate an increased risk of stroke, specifically ischemic stroke among hypertensive subjects with NSAIDs use. It would be important to closely monitor the transient effect of initial NSAIDs treatment, particularly in patients with hypertension. **(*Stroke*. 2015;46:00-00. DOI: 10.1161/STROKEAHA.114.007932.)**

Key Words: hypertension ■ pharmacoepidemiology ■ stroke

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used medications in the world. It has been known that NSAIDs inhibit the 2 recognized forms of prostaglandin G/H synthase referred to as cyclooxygenase (COX), namely COX-1 and COX-2, respectively.[1] Although NSAIDs provide symptomatic relief of pain and inflammation, the adverse effects of NSAIDs use have been a critical concern.

Previous studies have reported that COX-2 selective NSAIDs (known as coxibs) are associated with an increased risk of atherothrombotic vascular events.[2,3] A placebo-controlled trial also shows the association of nonselective NSAIDs with increased risk of cardiovascular and cerebrovascular events.[4] Moreover, similar findings related to increased cardiovascular risk have emerged in observational studies of NSAIDs.[5,6]

Although several studies have documented the association of NSAIDs use with increased risk of cerebrovascular events, little information exists on the cerebrovascular effects of NSAIDs (including selective and nonselective NSAIDs) in patients at increased risk of vascular disease, for example, elderly populations or patients with hypertension. In this study, we performed a case-crossover study to investigate the

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association of NSAIDs use with an increased risk of ischemic or hemorrhagic stroke in patients with hypertension using nationwide medical claims data in Taiwan.

Methods

Data Source

Data used in this study were obtained from the National Health Insurance Research Database (NHIRD) in Taiwan. Taiwan launched a single-payer National Health Insurance Program on March 1, 1995. Since then, the NHIRD, derived from the reimbursement medical claims of the National Health Insurance Program, has collected demographic characteristics, disease diagnoses, ambulatory care and inpatient claims data, and prescription records from National Health Insurance Program enrollees, who represent ≈98% of the total population in Taiwan.[7] In this study, we used 2 subsets derived from the NHIRD: (1) the Longitudinal Health Insurance Database for the year 2005 derived from the NHIRD of 2005; and (2) the Longitudinal Health Insurance Database for the year 2010 derived from the NHIRD of 2010. The Longitudinal Health Insurance Database for the year 2005 and Longitudinal Health Insurance Database for the year 2010 were constructed by randomly selecting 1 000 000 enrollees from the Registry for Beneficiaries of the NHI program in 2005 and 2010, separately. There were no significant differences in the sex or age distributions, or in the average insurable income between the random samples selected from the Longitudinal Health Insurance Database for the year 2005 (or Longitudinal Health Insurance Database for the year 2010) and the enrollees recorded in the original NHIRD. This study protocol was approved by the Institutional Review Board of the National Health Research Institutes, Taiwan.

Study Subjects

We first identified patients with an incident stroke in 2010 as those with a hospitalized record for a primary diagnosis of a stroke event under *International Classification of Diseases-Ninth Revision*-CM codes: 433.x, 434.x, and 436.x for ischemic stroke and 430 and 431 for hemorrhagic stroke. The index date was defined as the date that the subjects were diagnosed as having a hospitalized medical record of a stroke. Among those, we furthermore defined the study subjects as patients with diagnosis of hypertension (*International Classification of Diseases-Ninth Revision*-CM codes: 401–404 from either 2 inpatient claims records or 1 outpatient claims record during 1 year before the index date) and with antihypertensive prescription records during 1 year before the index date. The exclusion criteria were described as follows: (1) subjects aged <20 years in 2010; (2) subjects who had a prior inpatient admission or outpatient visits for stroke in 2009; (3) subjects with concurrent diagnosis of trauma or acute myocardial infarction at the same hospitalization; and (4) subjects who were hospitalized for any reason 120 days before the index date. As a result, a total of 1653 study subjects with hypertension were identified for further analyses in this study. Figure 1 presents the detailed flow chart on subject selection for this study.

Exposure to NSAIDs

We identified information on NSAIDs use from prescription records in the NHIRD. In addition to overall NSAIDs use, we also investigated the short-term effect of NSAIDs use on the risk of stroke in patients with hypertension based on NSAIDs classification (selective versus nonselective). Of note, short term was defined as 30-day period in this study. Therefore, the NSAIDs investigated in this study is as follows: selective NSAIDs—selective COX-2 inhibitors (celecoxib and etoricoxib)—and nonselective NSAIDs—propionic acid derivatives (ibuprofen, ketoprofen, naproxen, flurbiprofen, tiaprofenic acid, fenoprofen, and fenbufen); acetic acid derivatives (ketorolac, indomethacin, tolmetin, sulindac, etodolac, diclofenac, aceclofenac, and acemetacin); fenamic acid derivatives (mefenamic acid); enolic acid derivatives (piroxicam, meloxicam, and tenoxicam); and others (difunisal, nabumetone, nefopam, and nimesulide). Of note, celecoxib and etoricoxib were the 2 selective NSAIDs on the market in Taiwan in 2010.

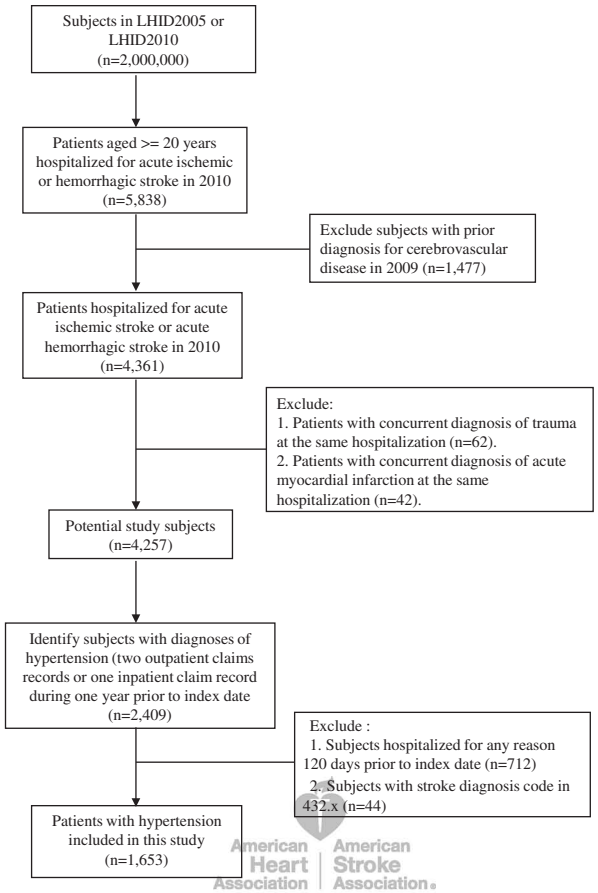

Figure 1. Flow diagram of inclusion/exclusion criteria for study population. LHID2005 indicates Longitudinal Health Insurance Database for the year 2005; and LHID2010, Longitudinal Health Insurance Database for the year 2010.

Time-Varying Confounding Factors

The time-varying confounding factors in the subsequent analyses included upper respiratory tract infections and medications related to stroke, which were defined if there were prescription records for any of the following medications: statins, antidiabetic agents (insulin, sulfonylurea, thiazolidinediones, and glinides), β-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, calcium channel blockers, diuretics, vitamin K antagonists, nonaspirin antiplatelet agents, aspirin, and number of outpatient visits.

Data Analysis

In this study, we analyzed the effect of NSAIDs on stroke using a case-crossover design, an approach applied to investigate the effect of transient exposures on acute outcomes/events.[8,9] In detail, in accordance with the case-crossover design model, each study patient served as his/her own control, and as such, time-unvarying confounding factors were not adjusted in the subsequent analytic models. The odds ratios were computed using a pair-matched approach to evaluate the effect of NSAIDs use within the period right before the occurrence of stroke (case period) with a comparable period (control period). On the basis of this design, an increased risk of stroke can be identified if the case period including NSAIDs use was followed by more stroke events than what would be expected because of chance. Specifically, the case period was defined as 1 to 30 days before the

Table 1. Demographic and Clinical Characteristics of the Study Subjects

Characteristics	n	%
Demographics		
Age group, y		
20–64	470	28.4
≥65	1183	71.6
Sex		
Women	750	45.4
Men	903	54.6
Clinical characteristics		
Medical comorbid disorders (yes, %)		
Cerebrovascular disease	480	29.0
Chronic pulmonary disease	233	14.1
Type 2 diabetes mellitus	680	41.1
Heart failure	185	11.2
Conduction disorder	8	0.5
Valve heart disorders	61	3.7
Malignant neoplasm	88	5.3
Peripheral vascular disease	66	4.0
Upper respiratory tract infections	862	52.2
Osteoarthritis	404	24.4
Rheumatoid arthritis	13	0.8
Gout	217	13.1
Psychiatric comorbidity (yes, %)*	343	20.8
Concomitant medication		
Antidiabetes agents†	589	35.6
Antihypertensive agents		
ACE or ARB	1232	74.5
β-Blockers	985	59.6
Calcium channel blockers	1353	81.9
Diuretics	1034	62.6
Vitamin K antagonists	117	7.08
Others	394	23.8
Statins	600	36.3
Charlson comorbidity index score		
0–1	525	31.8
2–3	650	39.3
≥4	478	28.9
Healthcare use during 1 year before stroke		
No. of outpatient visits		
0	0	0.0
1–20	577	34.9
≥21	1076	65.1
No. of inpatient visits		
0	1393	84.3
≥1	260	15.7

ACE indicates angiotensin-converting enzyme; and ARB, angiotensin receptor blocker.

*Examined psychiatric comorbidities include dementia, mood disorder, schizophrenia and other psychosis, anxiety, and organic brain syndrome.

†Antidiabetic agents include insulin, sulfonylurea, thiazolidinediones, and glinides.

index date, and the control period was defined as 91 to 120 days before the index date.

We applied conditional logistic regression models to examine the effect of NSAIDs use on stroke comparing between the case and control periods. Crude and adjusted odds ratios (AORs) were calculated, respectively, after controlling for the above time-varying confounding medication factors. In addition to overall NSAIDs use, we also classified NSAIDs into selective, nonselective, and each individual nonselective NSAID, and examined their effects on stroke, separately. We then performed subgroup analyses to examine the modifying effect of various characteristics, such as age, sex, Charlson comorbidity index score,[10] heart disease (yes/no), type 2 diabetic mellitus (yes/no), and anticoagulants use (yes/no).

In addition to stroke, we also compared the odds of NSAIDs use between the case and control periods after the onset of stroke for ischemic or hemorrhagic stroke, separately. Of note, sensitivity analyses using (1) 1 to 14 days before the index date as the case period and 15 to 28 days before the index date as the control period; and (2) 1 to 30 days before the index date as the case period and 31 to 60 days before the index date as the control period were performed to test for the robustness of the results.

Statistical significance was determined using 95% confidence intervals (CIs) or a P value <0.05. All of the analyses were conducted using SAS version 9.2 for Windows (SAS Institute, Cary, NC).

Results

We identified a total of 1653 hypertensive patients aged ≥20 years, who were hospitalized for ischemic or hemorrhagic stroke in 2010. The mean age at the onset of stroke was 70.9 years (SD, 11.9); 45.4% of the study subjects were women. Among them, 84% of hypertensive patients were hospitalized for ischemic stroke and 16% were hospitalized for hemorrhagic stroke, which were consistent with previous studies.[11] Demographic characteristics, medical and psychiatric comorbidity, concomitant medication use, Charlson comorbidity index score, and healthcare use are summarized in Table 1. In addition, top 3 frequent primary diagnoses for study subjects given NSAIDs were acute upper respiratory infections, lumbago, and osteoarthritis. The detailed information related to NSAIDs use, concomitant medication use, and outpatient medical use between case and control periods in the study subjects is provided in Table 2. We observed that the exposure proportion of concomitant medication and outpatient medical use during the case period were higher than that during the control period, except for subjects with hemorrhagic stroke (Table 2).

We examined the association between the short-term effect of NSAIDs use and the risk of stroke, ischemic stroke, and hemorrhagic stroke, respectively. The results in Table 3 show that NSAIDs use during the 30 days before stroke was associated with a 1.51-fold increased risk of stroke and 1.57-fold increased risk of ischemic stroke, after controlling for the confounding medication factors. When we classified NSAIDs into selective and nonselective NSAIDs, we found that nonselective NSAIDs use significantly increased the risk of stroke (AOR, 1.51; 95% CI, 1.24–1.86), ischemic stroke (AOR, 1.55; 95% CI, 1.24–1.94), and hemorrhagic stroke (AOR, 1.56; 95% CI, 0.90–2.73), respectively (Table 3). Among each nonselective NSAID individual, the use of diclofenac significantly increased the risk of stroke (AOR, 1.43; 95% CI, 1.10–1.87) and ischemic stroke (AOR, 1.48; 95% CI, 1.10–1.98), but not of hemorrhagic stroke. Interestingly, the results in

Table 2. Information Related to NSAIDs Use, Concomitant Medication Use, and Medical Use Between Case and Control Periods in the Study Subjects

	Case Period (1–30 d)		Control Period (91–120 d)	
Concomitant Medication	n*	%	n	%
Stroke (n=1653)				
NSAIDs use	529	32.0	395	23.9
Antidiabetes agents	462	27.95	413	24.98
Antihypertensive agents				
ACE or ARB	922	55.78	818	49.49
β-Blockers	742	44.89	649	39.26
Calcium channel blockers	1010	61.1	895	54.14
Diuretics	793	47.97	709	42.89
Vitamin K antagonists	93	5.63	77	4.66
Others	303	18.33	277	16.76
Statins	460	27.83	403	24.38
No. of outpatient visits				
0	200	12.1	363	21.96
1–2	662	40.05	720	43.56
≥3	791	47.85	570	34.48
Ischemic stroke (n=1395)				
NSAIDs use	453	32.47	329	23.58
Antidiabetes agents	411	29.46	360	25.81
Antihypertensive agents				
ACE or ARB	801	57.42	698	50.04
β-Blockers	624	44.73	538	38.57
Calcium channel blockers	862	61.79	748	53.62
Diuretics	685	49.10	600	43.01
Vitamin K antagonists	85	6.09	71	5.09
Others	262	18.78	236	16.92
Statins	416	29.82	361	25.88
No. of outpatient visits				
0	143	10.25	299	21.43
1–2	548	39.28	602	43.15
≥3	704	50.47	494	35.41
Hemorrhagic stroke (n=258)				
NSAIDs use	76	29.46	66	25.58
Antidiabetes agents	51	19.77	53	20.54
Antihypertensive agents				
ACE or ARB	121	46.9	120	46.51
β-blockers	118	45.74	111	43.02
Calcium channel blockers	148	57.36	147	56.98
Diuretics	108	41.86	109	42.25
Vitamin K antagonists	8	3.10	6	2.33
Others	41	15.89	41	15.89
Statins	44	17.05	42	16.28
No. of outpatient visits				
0	57	22.09	64	24.81
1–2	114	44.19	118	45.74
≥3	87	33.72	76	29.46

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; and NSAIDs, nonsteroidal anti-inflammatory drugs.

*The study subjects are counted in both case period and control period, respectively.

Table 3 indicate that ketorolac significantly increased the risk of stroke, including both ischemic and hemorrhagic stroke (AOR, 4.79; 95% CI, 2.24–10.23 for stroke; AOR, 4.31; 95% CI, 1.89–9.84 for ischemic stroke; and AOR, 12.98; 95% CI, 1.49–112.77 for hemorrhagic stroke) in this population. However, because of the issues of multiple assessment and small sample size for most examined individual NSAIDs, the observed results should be interpreted with caution, and further investigation would be needed to validate the observed results of the examined individual NSAIDs in this study.

Figure 2 presents the relationship between NSAIDs use and the risk of stroke in patients with hypertension, stratified by various demographic and clinical characteristics. The results suggest that subjects without anticoagulants use had a higher risk of stroke, specifically ischemic stroke, than those with anticoagulants use (AOR, 1.90; 95% CI, 1.39–2.60 for stroke and AOR, 2.07; 95% CI, 1.44–2.98 for ischemic stroke in subjects without anticoagulants use). Moreover, we found a significant interaction between anticoagulants and NSAIDs use ($P<0.0001$ for both stroke and ischemic stroke, respectively). Similarly, compared with subjects without heart disease or type 2 diabetic mellitus, subjects with heart disease or type 2 diabetic mellitus had a higher risk of stroke, specifically ischemic stroke, but the association of heart disease or type 2 diabetic mellitus with hemorrhagic stroke was not statistically significant. We also found that hypertensive women aged 20 to 64 years with anticoagulants use were highly associated with the risk of ischemic and hemorrhagic stroke, separately. Therefore, we defined hypertensive women aged 20 to 64 years with anticoagulants use as the high-risk group. Interestingly, we found that this high-risk group had a higher risk of stroke and ischemic stroke than subjects not in the high-risk group, but the observed results should be interpreted with caution because of small sample size.

Furthermore, in addition to the defined case and control periods, we conducted sensitivity analysis using different time windows (1–14 days for the case period and 15–28 days for the control period; and 1–30 days for the case period and 31–60 days for the control period, separately). No overt change was found in the stroke risk (including ischemic and hemorrhagic stroke) associated with NSAIDs use across different time windows (Table 4). Similar results were observed in the stroke risk of selective and nonselective NSAIDs use.

Discussion

Findings from this study demonstrate that short-term use of NSAIDs was associated with an increased risk of stroke and ischemic stroke in patients with hypertension. When classifying NSAIDs into selective and nonselective groups, an increased risk of stroke, specifically ischemic stroke was significant for nonselective NSAIDs, but not for coxibs.

Previous observational studies have investigated the effect of NSAIDs on stroke.[12–16] However, limited studies have conducted an evaluation of the cerebrovascular effects of NSAIDs (including selective and nonselective NSAIDs) use in high-risk patients. To our knowledge, this is one of the first observational studies to assess the risk of ischemic and hemorrhagic stroke associated with the short-term use of

Table 3. Risk of Stroke, Ischemic Stroke and Hemorrhagic Stroke, Respectively, in Relation to NSAIDs Use Among Patients With Hypertension

	Case Period		Control Period			
	With NSAIDs Use (n)	Without NSAIDs Use (n)	With NSAIDs Use (n)	Without NSAIDs Use (n)	COR (95% CI)	AOR (95% CI)*
Stroke (n=1653)						
Overall NSAIDs use	529	1124	395	1258	1.83† (1.51–2.21)	1.51† (1.23–1.85)
Selective NSAIDs	65	1588	55	1598	1.32 (0.83–2.11)	1.07 (0.65–1.76)
Nonselective NSAIDs	493	1160	361	1292	1.82† (1.50–2.21)	1.51† (1.24–1.86)
Diclofenac	217	1436	156	1497	1.64† (1.27–2.12)	1.43† (1.10–1.87)
Ibuprofen	69	1584	64	1589	1.10 (0.75–1.63)	0.91 (0.61–1.37)
Melenamic acid	104	1549	83	1570	1.36 (0.97–1.91)	1.19 (0.84–1.69)
Indomethacin	27	1626	19	1643	1.67 (0.82–3.41)	1.53 (0.74–3.19)
Sulindac	27	1626	19	1634	1.73 (0.82–3.93)	1.42 (0.66–3.04)
Ketorolac	47	1606	9	1644	5.75† (2.71–12.18)	4.79† (2.24–10.23)
Piroxicam	52	1601	49	1604	1.08 (0.69–1.70)	0.90 (0.56–1.44)
Meloxicam	69	1584	46	1607	2.00† (1.21–3.30)	1.59 (0.94–2.68)
Naproxen	19	1634	13	1640	1.86 (0.74–4.65)	1.55 (0.61–3.96)
Ketoprofen	12	1641	8	1645	1.67 (0.61–4.59)	1.22 (0.43–3.47)
Ischemic stroke (n=1395)						
Overall NSAIDs use	453	942	329	1066	1.94† (1.57–2.39)	1.57† (1.26–1.97)
Selective NSAIDs	59	1336	48	1347	1.42 (0.86–2.35)	1.08 (0.62–1.86)
Nonselective NSAIDs	420	975	301	1094	1.90† (1.54–2.34)	1.55† (1.24–1.94)
Diclofenac	181	1214	126	1269	1.71† (1.29–2.27)	1.48† (1.10–1.98)
Ibuprofen	59	1336	52	1343	1.18 (0.77–1.81)	0.99 (0.63–1.54)
Melenamic acid	93	1302	69	1326	1.48† (1.03–2.12)	1.31 (0.90–1.90)
Indomethacin	21	1374	11	1384	2.25 (0.98–5.17)	2.08 (0.88–4.89)
Sulindac	24	1371	14	1381	2.43† (1.01–2.85)	1.89 (0.77–4.67)
Ketorolac	36	1359	8	1387	5.00† (2.22–11.25)	4.31† (1.89–9.84)
Piroxicam	46	1349	42	1353	1.13 (0.69–1.85)	0.94 (0.56–1.57)
Meloxicam	61	1334	40	1355	2.00† (1.18–3.38)	1.50 (0.87–2.60)
Naproxen	16	1379	11	1384	1.83 (0.68–4.96)	1.54 (0.56–4.26)
Ketoprofen	11	1384	6	1389	2.00 (0.68–5.85)	1.48 (0.49–4.49)
Hemorrhagic stroke (n=258)						
Overall NSAIDs use	76	182	66	192	1.33 (0.83–2.14)	1.38 (0.79–2.40)
Selective NSAIDs	6	252	7	251	0.8 (0.22–2.98)	0.83 (0.21–3.36)
Nonselective NSAIDs	73	185	60	198	1.46 (0.91–2.37)	1.56 (0.90–2.73)
Diclofenac	36	222	30	228	1.33 (0.72–2.46)	1.33 (0.67–2.62)
Ibuprofen	10	248	12	246	0.78 (0.29–2.09)	0.73 (0.25–2.19)
Melenamic acid	11	247	14	244	0.63 (0.20–1.91)	0.58 (0.19–1.82)
Indomethacin	6	252	8	250	0.5 (0.09–2.73)	0.63 (0.10–4.10)
Sulindac	3	255	5	253	0.5 (0.09–2.73)	0.53 (0.10–3.03)
Ketorolac	11	247	1	257	11.00† (1.42–85.19)	12.98† (1.49–112.77)
Piroxicam	6	252	7	251	0.83 (0.25–2.73)	1.00 (0.28–3.63)
Meloxicam	8	250	6	252	2.00 (0.37–10.92)	3.92 (0.51–29.87)
Naproxen	3	255	2	256	2.00 (0.18–22.05)	1.76 (0.14–21.49)
Ketoprofen	1	257	2	256	NA	NA

AOR indicates adjusted odds ratio; CI, confidence interval; COR, crude odds ratio; NA, not available because of small sample size; and NSAIDs, nonsteroidal anti-inflammatory drugs.

*Covariates adjusted in the conditional logistic regression models include: upper respiratory tract infections, statins, antidiabetic agents, β-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, calcium channel blockers, diuretics, vitamin K antagonists, nonaspirin antiplatelet agents, aspirin, and number of outpatient visits.

†*P* value <0.05.

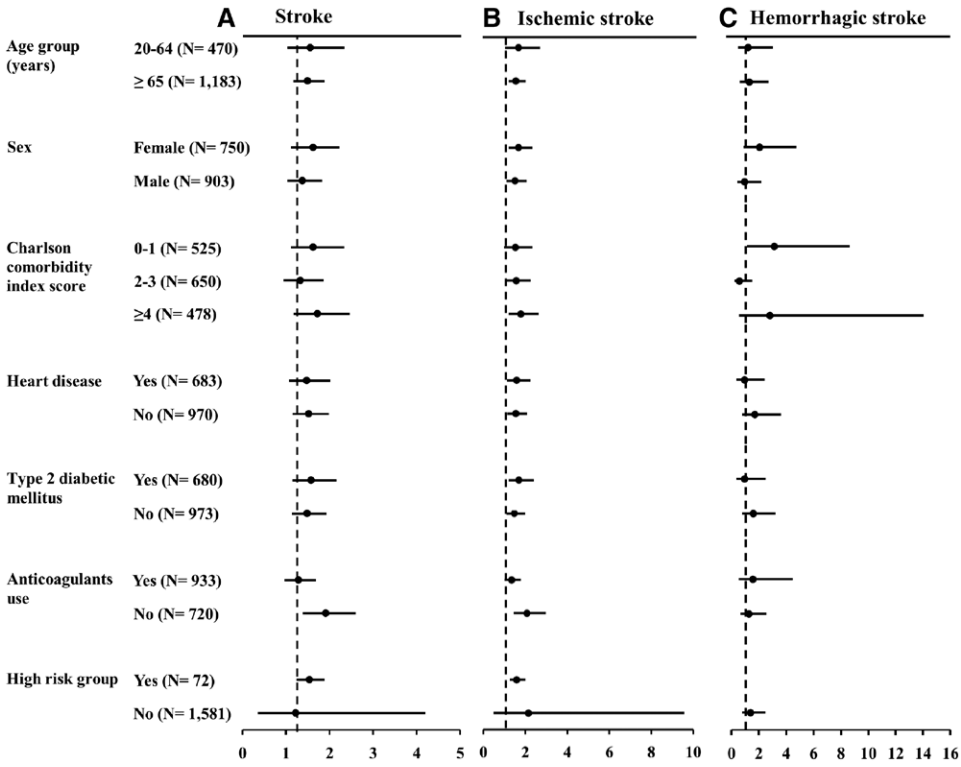

Figure 2. Risk of stroke in relation to nonsteroidal anti-inflammatory drugs use among patients with hypertension, stratified by various demographic and clinical characteristics.

selective and nonselective NSAIDs, respectively, in patients with hypertension.

We found that hypertensive women aged 20 to 64 years with anticoagulants use were highly associated with the risk of ischemic and hemorrhagic strokes, separately. More importantly, when further defining hypertensive women aged 20 to 64 years with anticoagulants use as the high-risk group, we found that this high-risk group had a higher risk of both ischemic stroke and hemorrhagic stroke than those who were not in the high-risk group, even though the results were not statistically significant. However, this finding may be because of the small sample size of the high-risk group in this study.

Table 4. Risk of Stroke in Relation to NSAIDs Use Among Patients With Hypertension, Based on Different Lengths for Case and Control Periods

	Case Period 1–14 d Control Period 15–28 d		Case Period 1–30 d Control Period 31–60 d		Case Period 1–30 d Control Period 91–120 d	
	COR (95% CI)	AOR (95% CI)*	COR (95% CI)	AOR (95% CI)	COR (95% CI)	AOR (95% CI)
Stroke						
Overall NSAIDs use	2.21† (1.72–2.82)	1.54† (1.18–2.00)	1.98† (1.60–2.46)	1.70† (1.36–2.13)	1.83† (1.51–2.21)	1.51† (1.23–1.85)
Selective NSAIDs	1.46 (0.72–2.96)	1.33 (0.63–2.82)	1.65 (0.90–3.01)	1.57 (0.84–2.96)	1.32 (0.83–2.11)	1.07 (0.65–1.76)
Nonselective NSAIDs	2.17† (1.70–2.78)	1.52† (1.16–1.98)	1.97† (1.59–2.44)	1.67† (1.34–2.10)	1.82† (1.50–2.21)	1.51† (1.24–1.86)
Ischemic stroke						
Overall NSAIDs use	2.19† (1.68–2.85)	1.52† (1.14–2.02)	2.03† (1.61–2.55)	1.74† (1.36–2.21)	1.94† (1.57–2.39)	1.57† (1.26–1.97)
Selective NSAIDs	1.80 (0.83–3.90)	1.71 (0.75–3.88)	1.69 (0.91–3.13)	1.49 (0.78–2.87)	1.42 (0.86–2.35)	1.08 (0.62–1.86)
Nonselective NSAIDs	2.15† (1.65–2.80)	1.49† (1.12–1.98)	1.98† (1.57–2.50)	1.69† (1.33–2.16)	1.90† (1.54–2.34)	1.55† (1.24–1.94)
Hemorrhagic stroke						
Overall NSAIDs use	2.33† (1.19–4.59)	1.86 (0.83–4.19)	1.72† (0.96–3.08)	1.40 (0.72–2.69)	1.33 (0.83–2.14)	1.38 (0.79–2.40)
Selective NSAIDs	0.33 (0.04–3.21)	NA	1.00 (0.06–16.00)	1.13 (0.06–20.71)	0.8 (0.22–2.98)	0.83 (0.21–3.36)
Nonselective NSAIDs	2.33† (1.19–4.59)	1.85 (0.83–4.13)	1.88† (1.05–3.39)	1.57 (0.81–3.04)	1.46 (0.91–2.37)	1.56 (0.90–2.73)

AOR indicates adjusted odds ratio; CI, confidence interval; COR, crude odds ratio; and NSAIDs, nonsteroidal anti-inflammatory drugs.

*Covariates adjusted in the conditional logistic regression models include: upper respiratory tract infections, statins, antidiabetic agents, β-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, calcium channel blockers, diuretics, vitamin K antagonists, nonaspirin antiplatelet agents, aspirin, and number of outpatient visits.

†*P* value <0.05.

Our results are supported by recent previous studies conducted in white populations.[14,17,18] For example, Haag et al[18] reported that current use of nonselective and selective NSAIDs increased the risk of stroke (hazard ratio, 1.68; 95% CI, 1.05–2.69 for ischemic stroke in nonselective NSAIDs; and hazard ratio, 4.54; 95% CI, 2.06–9.98 for ischemic stroke in selective NSAIDs users). In addition, another nested case–control study suggested that the use of selective NSAIDs was associated with a significantly increased risk of ischemic stroke.[17] However, no association results have been reported previously.[19,20] When comparing others' findings with those of the present study, the inconsistent conclusions reported in those studies may have been because of different enrollment criteria and study designs.

Several plausible mechanisms might explain the observed adverse effect of NSAIDs use on stroke in patients with hypertension. First, previous studies have documented that NSAIDs, to some extent, have an impact on vasoconstriction and sodium excretion, which can increase blood pressure and subsequently lead to an increased risk of cerebrovascular events.[21–23] Second, NSAIDs inhibit the activity of the COX isozymes (COX-1 and COX-2) and block prostanoid biosynthesis. As a result, NSAIDs decrease total renal perfusion and lead to redistribution of renal blood flow, particularly in vulnerable populations, which may cause medullary ischemia and even acute renal failure.[24,25] Third, several reports have provided evidence that the COX-1–dependent generation of thromboxane A_2 may play a role in the regulation of platelet activation.[26,27] For example, Davì and Patrono[26] have reported that thromboxane A_2 is synthesized by activating platelets from arachidonic acid via the COX pathway. In turn, the release of thromboxane A_2 further induces platelet aggregation and activation.

Several limitations should be noted in this study. First, the accuracy of stroke was not validated by medical chart review. However, we defined stroke not only based on the *International Classification of Diseases-Ninth Revision*-CM codes (433.x, 434.x, and 436.x for ischemic stroke; 430 and 431 for hemorrhagic stroke) but also on hospitalization claim records. Second, several potential confounding factors that might affect the association between NSAIDs use and stroke, such as body mass index, smoking, and alcohol consumption, are not available in the NHIRD. However, because we used a case-crossover design for this study, these confounding factors were unlikely to have changed during such a relatively short study period. Third, we did not estimate the effect of overthe-counter NSAIDs use. However, this misclassification issue might be undifferentiated and thereby would reduce the estimated risk. Fourth, to account for potential confounding by indication, we have excluded subjects taking NSAIDs in the period of 121 to 365 days before stroke occurrence. We found that the results were similar with those without excluding subjects taking NSAIDs in the period of 121 to 365 days before stroke occurrence (Table I in the online-only data Supplement). In addition, we have applied a case-crossover study design, that is, each study subject serves as his/her own control, as such, time-unvarying confounding factors are not necessary to be adjusted in the subsequent analytic models. It is known that underlying indications required for NSAID prescription are those related to chronic physical conditions, such as rheumatoid arthritis, osteoarthritis, and systemic lupus erythematosus, these factors are usually not varied during the study period—1 to 120 days before the index date. However, it is likely that the observed increased risk of stroke might be still partially explained by potential confounding by indication. Fifth, because this study was based on the use of a case-crossover design, we were only able to investigate the transient effect of NSAIDs use. It would be of interest to further explore the long-term effect of NSAIDs use on ischemic and hemorrhagic stroke. Sixth, because of the constraints of a small sample size, we did not have sufficient power to evaluate the effect of dose response for selective and nonselective NSAIDs. Further investigation on dose response would be merited.

Taken together, these findings indicate that NSAIDs use can increase the risk of ischemic and hemorrhagic stroke in patients with hypertension, a high-risk population for cerebrovascular disease. Of importance, physicians should take caution when prescribing NSAIDs drugs to patients with hypertension. Their use should be based on a stringent clinical evaluation of benefits and risks, particularly in patients with hypertension.

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Disclosures

None.

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supplemental table I. Risk of stroke, ischemic and hemorrhagic stroke, individually, in relation to NSAIDs use[*] among patients with hypertension.

	Case period, *N*	Control period, *N*	COR (95% CI)[a]	AOR (95%CI)[a,b]
Stroke				
Overall NSAIDs use	85	34	**3.13** (1.97-4.95)[c]	**2.25** (1.36-3.72)
Selective NSAIDs	8	2	4.00 (0.85-18.84)	3.23 (0.57-18.30)
Nonselective NSAIDs	79	32	**2.88** (1.83-4.54)	**2.05** (1.25-3.36)
Ischemic stroke				
Overall NSAIDs use	74	27	**3.47** (2.09-5.79)[c]	**2.34** (1.34-4.04)
Selective NSAIDs	7	1	6.99 (0.86-56.76)	5.32 (0.44-63.80)
Nonselective NSAIDs	69	26	**3.26** (1.95-5.46)	**2.19** (1.27-3.79)
Hemorrhagic stroke				
Overall NSAIDs use	11	7	1.8 (0.60-5.37)	1.60 (0.39-6.61)
Selective NSAIDs	1	1	1.00 (0.06-15.99)	0.44 (0.02-12.87)
Nonselective NSAIDs	10	6	1.67 (0.61-4.59)	1.69 (0.46-6.25)

NOTE:

[*] Subjects taking NSAIDs in the period of 121-365 days prior to the index date are excluded.

[a] Abbreviations. COR: crude odds ratio; AOR: adjusted odds ratio.

[b] Covariates adjusted in the conditional logistic regression models include: upper respiratory tract infections, statins, antidiabetic agents, β-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, calcium channel blockers, diuretics, vitamin K antagonists, nonaspirin antiplatelet agents, aspirin and number of outpatient visits.

[c] p value < 0.05 is in bold.

Association of Short-Term Use of Nonsteroidal Anti-Inflammatory Drugs With Stroke in Patients With Hypertension

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