Effect on Risk of Stroke and Acute Myocardial Infarction of Nonselective Nonsteroidal Anti-Inflammatory Drugs in Patients With Rheumatoid Arthritis

Yih-Ru Chen, PhD[a], Fang-I Hsieh, PhD[a], Chi-Ching Chang, MD, PhD[b,c], Nai-Fang Chi, MD, PhD[d], Hsin-Chiao Wu, MS[a], and Hung-Yi Chiou, PhD[a,*]

There are still debates on the association of increased cardiovascular risk with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in patients with rheumatoid arthritis (RA) because of inconsistent results. Therefore, our study aims to evaluate the transient effects of selective and nonselective NSAIDs on the risk of stroke and acute myocardial infarction (AMI) in patients with RA. We conducted a case-crossover study of 5,921 stroke or AMI patients with co-morbidity of RA. All cases were identified from the Taiwan National Health Insurance Database between January 1, 2006, and December 31, 2011, according to the *International Classification of Diseases, 9th Revision and Clinical Modification* diagnosis codes from inpatient claims. The index date was defined as the date of hospitalization for stroke or AMI. Exposure to NSAIDs was compared during a case period (1 to 30 days before the index date) with a control period (91 to 120 days before the index date). The adjusted odds ratios (ORs) of stroke and AMI were estimated using conditional logistic regression models. Our results showed that overall NSAIDs use increased the risk of stroke by 1.40-fold (95% confidence interval [CI] 1.25 to 1.56) and risk of AMI by 1.73-fold (95% CI 1.29 to 2.32). After classifying NSAIDs into selective and nonselective groups, only nonselective NSAIDs use significantly increased the risks of stroke (adjusted OR 1.39; 95% CI 1.25 to 1.55) and AMI (adjusted OR 1.82; 95% CI 1.37 to 2.41), respectively. In conclusion, nonselective NSAIDs were associated with an increased risk of both stroke and AMI in patients with RA. **(Am J Cardiol 2018;121:1271–1277)**

Commonly used nonsteroidal anti-inflammatory drugs (NSAIDs) have been given increased attention to cardiovascular safety over the past decade.[1] Both nonselective and selective cyclooxygenase inhibitors may increase blood pressure (BP), leading to short- and long-term increases in cardiovascular and cerebrovascular events.[2–5] However, the relation between NSAIDs use and risk of cardiovascular disease (CVD) among patients with rheumatoid arthritis (RA) is inconsistent in previous studies.[6–11] NSAIDs were widely used in RA population and only a few study evaluated the transient effect of NSAIDs on the risk of acute cardiovascular events such as stroke and acute myocardial infarction (AMI) in this population. Therefore, we performed a case-crossover study design to explore the association of transient use of NSAIDs with the risk of stroke and AMI among patients with RA using nationwide medical claims data in Taiwan.

Methods

In 1995, Taiwan established a single-payer National Health Insurance (NHI) program. This program covers more than 99% of the population of Taiwan and provides one of the largest and most comprehensive databases in the world.[12] The demographics of the subjects, diagnosis of the disease, and the records of the prescription (including the type of medication, time of prescription, duration of drug supply, and dosage) are included in the NHI database.

We first identified 766,562 patients admitted to hospital for stroke or AMI between January 1, 2006, and December 31, 2011, and a primary diagnosis was based on the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* codes: 430 to 431 (hemorrhagic stroke), 433 to 437 (ischemic stroke) for stroke, and 410 for AMI. The date which the subject was diagnosed with a hospitalized medical record of stroke or AMI was defined as the index date. Among those patients, 7,122 had more than 2 RA diagnostic codes (*ICD-9-CM* code 714.0) at least 1 year before

[a]School of Public Health, College of Public Health, Taipei Medical University, Taipei, Taiwan; [b]Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan; [c]Division of Rheumatology, Immunology and Allergy, Department of Internal Medicine, Taipei Medical University Hospital, Taipei, Taiwan; and [d]Department of Neurology, Shuang Ho Hospital, Taipei, Taiwan. Manuscript received October 3, 2017; revised manuscript received and accepted January 30, 2018.

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See page 1277 for disclosure information.

*Corresponding author: Tel: +886 2 27361661; fax: +886 2 23779188.
E-mail address: hychiou@tmu.edu.tw (H.-Y. Chiou).

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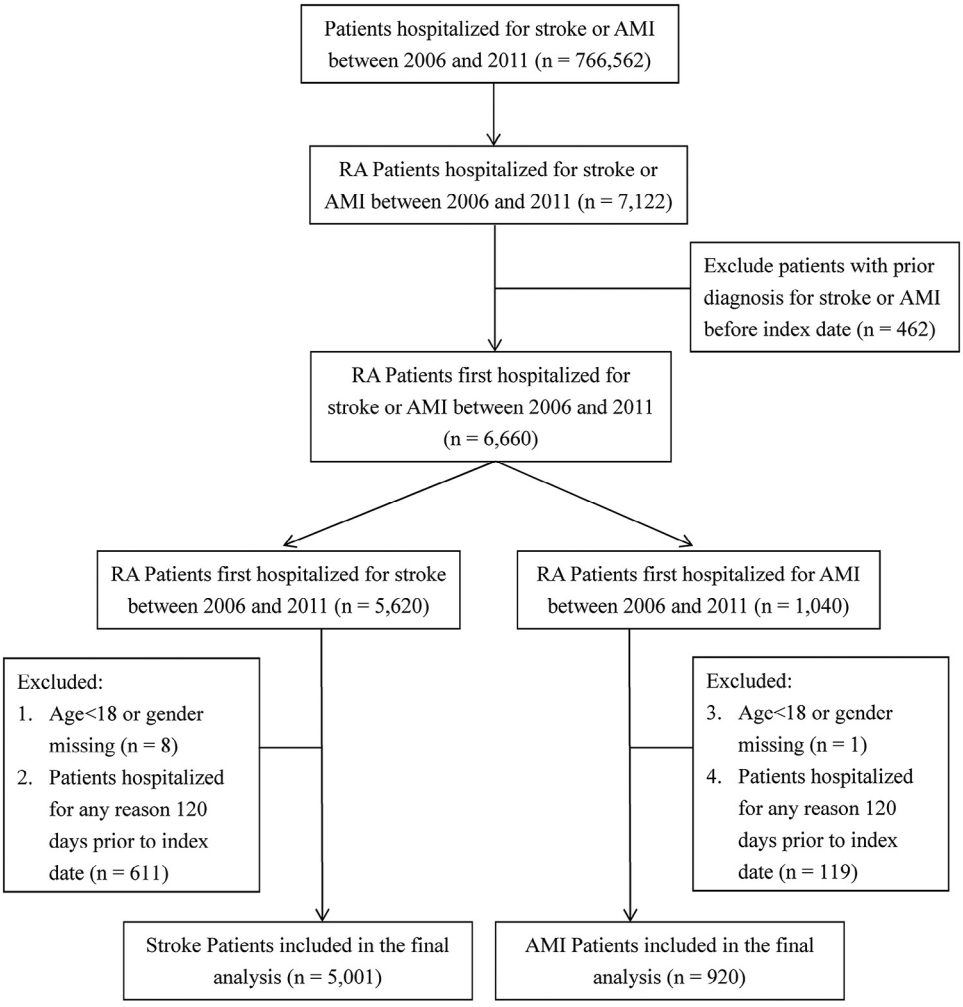

Figure 1. Flow diagram of study population selection.

the index date. The details of exclusion procedure were listed in Figure 1. Eventually, 5,001 stroke patients and 920 AMI patients with RA entered the final analysis. This study protocol was approved by the Taipei Medical University Joint Institutional Review Board (Approval No. 201411004).

NSAIDs use was determined from prescriptions dispensed for the following NSAIDs in Taiwan during the study period (2006 to 2011): (1) selective NSAIDs: celecoxib and etoricoxib; (2) nonselective NSAIDs: ibuprofen, ketoprofen, naproxen, flurbiprofen, tiaprofenic acid, fenoprofen, fenbufen, ketorolac, indomethacin, tolmetin, sulindac, etodolac, diclofenac, aceclofenac, acemetacin, flufenamic acid, mefenamic acid, niflumic acid, piroxicam, meloxicam, tenoxicam, difunisal, nabumetone, nefopam, and nimesulide. Data regarding dates of the prescriptions, daily dose, number of days supplied, and number of pills per prescription were collected. We used the defined daily doses (DDD); different drugs could be compared given the same standard unit. The average daily dose was determined by multiplying the number of pills dispensed by dose per pill, divided by days supply for the prescription episode. Age, sex, co-morbidities, including hypertension, diabetes, dyslipidemia, chronic kidney disease, cancer, peripheral vascular disease, dementia, mild liver disease, chronic obstructive pulmonary disease, gout, osteoarthritis, and migraine were also collected based on *ICD-9-CM* codes (Supplemental Table S1). Concomitant medication including antidiabetes agents, angiotensin-converting enzyme, angiotensin receptor blockers, β blockers, calcium channel blockers, diuretics, lipid-lowering drugs, anticoagulants, antiplatelet, disease-modifying antirheumatic drugs, glucocorticoids, and biologics were defined as the time-varying confounding factors.

We used a case-crossover design to assess the effect of transient exposure of NSAIDs on the risk of acute outcomes, as described previously.[13] This type of study is self-matched. For each person, there is a 'case period' that is immediately before the event, and a 'control period' that is more remote from the event. We compared the NSAIDs exposure status of study subjects between the case period and the control period. A case period was defined as 1 to 30 days before the index date and the control period was 91 to 120 days before the index date. Based on pharmacological properties of NSAIDs, we used the same definition of case and control periods as described in previous studies.[14,15] The categorical and continuous variables were calculated by percentage and mean ± SD, respectively. Conditional logistic regressions were used to cal-