Nonsteroidal anti-inflammatory drug choice and adverse outcomes in clopidogrel users: A retrospective cohort study

Young Hee Nam, Colleen M. Brensinger, Warren B. Bilker, Charles E. Leonard, Scott E. Kasner, Tilo Grosser, Xuanwen Li, Sean Hennessy

1 Center for Pharmacoepidemiology Research and Training, Department of Biostatistics, Epidemiology and Informatics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States of America, 2 Center for Clinical Epidemiology and Biostatistics, Department of Biostatistics, Epidemiology and Informatics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States of America, 3 Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States of America, 4 Department of Systems Pharmacology and Translational Therapeutics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States of America

Abstract

Objective

To examine the comparative safety of individual NSAIDs when given concomitantly with clopidogrel.

Methods

We conducted a retrospective cohort study using Medicaid claims from five US states during 1999–2010, supplemented with Medicare claims for dual-enrollees. The exposure of interest was the first concomitant use of clopidogrel and one of the 10 selected NSAIDs after a 1-year baseline period. The outcomes were: all-cause mortality; acute myocardial infarction (AMI)/ischemic stroke; and gastrointestinal bleeding (GIB)/intracranial hemorrhage (ICH). We calculated the hazard ratio of each NSAID for each outcome, with ibuprofen as the reference drug, using high-dimensional propensity score-adjusted proportional-hazards regression models.

Results

Of 1,060,412 clopidogrel users, 268,114 concomitant NSAID users met inclusion/exclusion criteria, contributing 48,483 person-years. We observed 2,463 deaths, 2,822 AMI/ischemic stroke outcomes, and 2,620 GIB/ICH outcomes, for unadjusted incidence rates of 50.8, 58.6, and 54.3 per 1,000 person-years, respectively. Compared with ibuprofen and controlling for potential confounders, rofecoxib (hazard ratio [HR] = 1.22; 95% confidence interval [CI]: 1.04, 1.43) and valdecoxib (HR = 0.66; 95% CI: 0.48, 0.92) showed higher and lower hazards of mortality, respectively. Indomethacin showed an increased AMI/ischemic stroke hazard (HR = 1.38; 95% CI: 1.09, 1.74). For GIB/ICH, indomethacin (HR = 2.18; 95% CI: 1.74, 2.73), diclofenac (HR = 1.65; 95% CI: 1.39, 1.97), naproxen (HR = 1.47; 95% CI: 1.28, 1.70), and rofecoxib (HR = 1.26; 95% CI: 1.08, 1.48) showed higher hazards, and valdecoxib (HR = 0.73; 95% CI: 0.55, 0.98) showed a lower hazard.
Conclusion
The bleeding risks of individual NSAIDs varied more markedly than thrombotic risks when used concomitantly with clopidogrel. Moreover, bleeding risk and thrombotic risk among individual NSAIDs did not appear to be inversely related to each other in the presence of clopidogrel. Further studies are needed to elucidate underlying biological mechanisms and help clinical decision-making for a better NSAID choice in clopidogrel users.

Introduction
Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used to treat pain and inflammation. In 2010, more than 29 million adults in the United States used an NSAID at least three times a week for at least three months [1]. Recent studies have suggested that individual NSAIDs may differ substantially with regard to the risk of acute myocardial infarction (AMI) [2–12], stroke [2–3,7–9,13–14], bleeding [8–9,15], and cardiovascular and all-cause death [2–3,6–9]. Since some NSAIDs may reduce the antiplatelet benefits of aspirin by competing directly for the same binding site on platelet cyclooxygenase (COX)-1 [16], other antiplatelet agents such as clopidogrel have been proposed for patients requiring both platelet inhibition and an NSAID [16–17]. Clopidogrel is widely used to reduce the risk of atherosclerotic events in patients who have had a recent AMI or stroke, and those with peripheral artery disease or acute coronary syndrome [18–19]. Clopidogrel needs to be converted to an active metabolite through a multistep process mediated by multiple cytochrome P450 (CYP) isozymes [20]. Although this need for activation has been hypothesized to result in drug-drug interactions with other CYP enzyme-metabolized drugs (including some NSAIDs), the clinical impact of such interactions is uncertain. In addition to potential CYP-based mechanisms, clopidogrel and NSAIDs might also interact through effects on the function of platelets [21], which is important to both atherothrombosis and hemostasis [22]. In particular, NSAIDs can either promote or suppress platelet aggregation through various mechanisms, and therefore might either increase or reduce the risk of thrombotic and/or hemorrhagic events. For example, NSAIDs can reduce platelet aggregation by inhibiting thromboxane [21] or reducing inflammation [23]. On the other hand, NSAIDs can promote platelet aggregation by suppressing the synthesis of prostacyclin, a potent endogenous platelet inhibitor [24]. Clopidogrel's antiplatelet activity may also increase the risk of bleeding complications [25–26]. How these multiple mechanisms interact with each other is unknown, and the current lack of knowledge about the comparative safety of NSAIDs in those who take clopidogrel can complicate treatment decisions for many patients with cardiovascular conditions who need to manage pain and/or inflammation. Our study therefore aimed to examine the comparative safety of NSAIDs with regard to all-cause mortality, AMI/ischemic stroke (as a composite endpoint), and gastrointestinal bleeding (GIB)/intracranial hemorrhage (ICH, which includes hemorrhagic stroke) (as a composite endpoint) among users of clopidogrel, using large-scale real-world data.

Methods
Study design, population, and data
We conducted a retrospective cohort study using Medicaid claims data from five US states (California, Florida, New York, Ohio, and Pennsylvania) from 1999–2010 [27]. Medicaid is a health insurance program funded by the federal and state governments that provides health coverage to nearly 70 million Americans, including eligible people with low-income or
disabilities [28]. Nationwide, approximately 43%, 34%, 14%, and 9% of the Medicaid enrollees account for children, adults (under age 65 years), people with disability (under age 65 years), and older people (age 65 years and older), respectively [29]. About 15% of the Medicaid enrollees are dually enrolled in Medicare [30], and among Medicaid-Medicare dual-enrollees, about 2.4% has end-stage renal disease [31]. Our five states comprise about 40% of the national Medicaid population [32]. The 12-year Medicaid data from these five states include about 65 million cumulative enrollees and 200 million person-years of records. For those also enrolled in Medicare, we also used Medicare claims data from 1999–2010, including Part D data from 2006–2010. Medicare is the federal program providing health insurance for about 58 million beneficiaries, including people who are age 65 years and older, certain younger people with disabilities, and people with end-stage renal disease [33–34]. Part D is an outpatient prescription drug coverage program of Medicare [35]. Our study population was defined as adults (18 ≤ age ≤ 100 years) with continuous enrollment in Medicaid during a one-year baseline period before the cohort entry date (explained below).

**Study cohort**

The study cohort consisted of apparently new concomitant users of clopidogrel and one of the following NSAIDs, which were the ten most frequently prescribed NSAIDs in the study population: ibuprofen, celecoxib, naproxen, rofecoxib, meloxicam, diclofenac, indomethacin, valdecoxib, nabumetone, and etodolac (in descending order by the number of users); these ten NSAIDs accounted for about 98% of all NSAID users in our data. Although rofecoxib and valdecoxib were withdrawn from the US market during our study period (in 2004 and 2005, respectively), we included these drugs since their inclusion might contribute to mechanistic insights. The cohort entry date was defined as the first date of concomitant use of clopidogrel plus an NSAID, irrespective of the initiation order of clopidogrel and NSAID [36]. Dates of drug use were estimated by the dispensing date and the days’ supply field. The one year prior to the cohort entry date defined the baseline period. Therefore, the earliest possible cohort entry in our data was in 2000. Since we did not intend to study only incident events, we did not exclude persons with a prior AMI, ischemic stroke, or GIB/ICH. Procedures for the identification of study cohorts and the application of inclusion and exclusion criteria are presented in S1 Fig.

**Exposure and follow-up time**

The exposure of interest was defined as the first concomitant use of clopidogrel plus one of the ten study NSAIDs dispensed as orally-administered, solid dosage forms, identified by the outpatient prescription drug claims. Prescriptions drug use was identified by using National drug Codes and days’ supply on prescription claims. We allowed a 15-day gap between contiguous prescriptions and at the end of the last prescription, to allow for potential incomplete adherence. Each NSAID defined a different exposure group. Ibuprofen was selected as the reference exposure because it was the most commonly used NSAID in the cohort. We excluded person-time during which more than one NSAID were used. Among the ten NSAIDs, over-the-counter formulations were available for lower strengths of ibuprofen and naproxen. Thus, it is possible that some exposures to these drugs were not captured. However, it seems that it would be uncommon for a clopidogrel user to take both a prescription and a nonprescription NSAID, particularly since prescription NSAIDs are paid for by Medicaid.

Follow-up time began on the cohort entry date and ended on the date of the first-occurring of the following events: 1) outcome of interest; 2) end of the days’ supply of clopidogrel or the exposure-defining NSAID (allowing for a 15-day grace period); 3) dispensing of an NSAID.
other than the exposure-defining NSAID (suggestive of switching to a different drug), for which the cohort end date was set to be the day before the non-exposure-defining NSAID prescription was dispensed; 4) disenrollment from Medicaid; and 5) end of the dataset, which was December 31, 2010. The follow-up time was independently determined for each of our three outcomes (i.e., all-cause mortality, AMI/ischemic stroke, or GIB/ICH), and each patient contributed person-time to only one NSAID. In a sensitivity analysis that restricted the follow-up period to the first 180 days after cohort entry, the 180th day from the cohort entry also served to censor follow-up time.

Ascertainment of outcomes

The outcomes of interest were all-cause mortality and two composite outcomes: 1) AMI/ischemic stroke and 2) GIB/ICH. All-cause mortality was ascertained by linkage to the Social Security Administration Death Master File. The definition of the components of our composite outcomes and the performance measures of the ascertainment algorithms are presented in Table 1. Based on prior studies, the positive predictive values of the outcome-specific algorithms range from 81% to 98% [37–40].

Statistical analysis

We first calculated descriptive statistics, including the baseline characteristics of the study cohort and unadjusted incidence rates and hazard ratios of the outcomes by NSAID exposure group. To assess balance in measured baseline covariates between the different NSAID-exposure groups, we calculated the standardized difference and the weighted conditional standardized difference (WCSD), before and after calculating propensity scores, respectively. The standardized difference represents the mean difference of a variable between the two groups in

| Outcome                                      | Discharge diagnosis position and claim type | ICD-9-CM\(^1\) discharge diagnosis code(s) | Performance metrics / validity measures of the algorithm |
|----------------------------------------------|--------------------------------------------|-------------------------------------------|--------------------------------------------------------|
| Acute myocardial infarction                  | Principal or non-principal diagnosis, inpatient claims | 410. '1                                  | PPV\(^\dagger\) ≈ 94% [37]                              |
| Ischemic stroke                              | Principal diagnosis, inpatient claims; excluding patients with intracranial injury diagnosis (ICD-9-CM codes, 800°-804°, 850°-854°) as secondary diagnosis on the same admission | 433. '1, 434° (excluding 434°.0), or 436° | PPV ≈ 88% [38] Specificity ≈ 95% Sensitivity ≈ 74% |
| Gastrointestinal bleeding                    | Principal or non-principal diagnosis, inpatient claims | 530.21, 531.0°, 531.2°, 531.4°, 531.6°, 532.0°, 532.2°, 532.4°, 532.6°, 533.0°, 533.2°, 533.4°, 533.6°, 534.0°, 534.2°, 534.4°, 534.6°, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 537.83, 537.84, 562.02, 562.03, 562.1, 562.13, 569.85, 569.86, or 578° | PPV ≈ 81% [39] |
| Intracranial hemorrhage (including hemorrhagic stroke) | Principal or non-principal diagnosis, inpatient or ED\(^\dagger\) claims; excluding patients with intracranial injury diagnosis (ICD-9-CM codes, 800°-804°, 850°-854°) on the same admission | 430 or 431 | PPV ≈ 97% (ICH\(^\dagger\)), 98% (SAH\(^\dagger\)) [40] |

\(^1\)ICD-9-CM: International Classification of Diseases 9th Revision Clinical Modification.

\(^\dagger\)PPV: positive predictive value.

\(\dagger\)ED: emergency department.

\(\dagger\)ICH: intracerebral hemorrhage.

\(\dagger\)SAH: subarachnoid hemorrhage.
units of the estimated common standard deviation of that variable in the two groups [41].
After calculating propensity scores, we used the WCSD to assess whether two comparison
groups had similar distributions of measured baseline covariates conditional on the propensity
score [41]. Literature suggests that standardized difference and WCSD values exceeding 0.1
may indicate potentially meaningful imbalance between groups [41].

Next, we used a high-dimensional propensity score (hdPS)-adjusted [42–46] propor-
tional-hazards models to calculate the hazard ratio of each NSAID for each outcome, with
ibuprofen as the reference drug. For the propensity score calculation, we used a multinom-
ial logistic regression model that included pre-specified covariates (N = 135), as well as
covariates identified empirically by the hdPS method (N = 596). The pre-specified covari-
ates were chosen based on potential association with both exposure and outcomes of inter-
est, including: a) demographic factors (e.g., age, sex, race/ethnicity, state of residence, etc.);
b) healthcare services utilization intensity (e.g., number of circulatory system hospitaliza-
tions, number of circulatory system emergency department visits, number of unique
outpatient diagnosis codes, number of outpatient ICD-9 procedure codes, number of pre-
scription dispensing, etc.); c) diseases (e.g., hypertension, diabetes mellitus, cancer, conduc-
tion disorders, lipid metabolism disorder, osteoarthritis, rheumatoid arthritis, etc.); and d)
prescription drugs (e.g., anticoagulants, aspirin, statins, fibrates, etc.) (S1 Table). These
covariates were measured as binary variables during the baseline period, except for age at
cohort entry, a continuous variable. The specifications used in the hdPS method are pre-
sented in S2 Table, and the hdPS-identified covariates are presented in S3 Table. As shown
in S2 Table, we specified 9 dimensions of data (inpatient ICD-9 diagnoses; inpatient ICD-9
procedures; inpatient CPT/HCPCS procedures; outpatient ICD-9 diagnoses; outpatient
ICD-9 procedures; outpatient CPT/HCPCS procedures; other setting ICD-9 diagnoses;
other setting ICD-9 procedures; and outpatient medication active ingredients), and identi-
fied 200 covariates with the highest frequencies in the claims data for each dimension
(N = 1,800), and selected top 500 covariates with the largest likelihood of confounding
(N = 500). We performed this procedure for each of the 9 pairs of NSAID of interest vs. ibu-
profen, separately (N = 4,500). Of these, we excluded overlapping (identical) covariates
(N = 3,856), covariates with the number of persons exposed less than 10 (N = 42), and
covariates overlapping with pre-specified covariates (N = 6). Thus, 596 empirically identi-
fied covariates, along with 135 pre-specified covariates, were used in the multinomial logis-
tic regression model to calculate propensity scores. In the proportional hazards models, we
included the propensity scores as continuous variables, as well as covariates with the WCSD
greater than 0.1 (presented in S1 and S4 Tables). We tested the proportional-hazard
assumption of the each model, and based on the results, we included a time-by-NSAID
interaction term. We also performed subgroup analysis as secondary analysis, stratified by:
a) age (18 ≤ age < 65 years; 65 ≤ age ≤ 100 years); b) sex (male; female); and c) concomi-
tancy-triggering drug (NSAID-triggered group; clopidogrel-triggered group and combina-
tion-triggered group), separately [36]. When an NSAID was added to the clopidogrel
therapy, it is called NSAID-triggered concomitancy; when clopidogrel was added to an
NSAID, it is called clopidogrel-triggered concomitancy; and when clopidogrel and an
NSAID started on the same date, it is called combination-triggered concomitancy [36].

Sensitivity analysis
In addition, we conducted two sensitivity analyses. In the first sensitivity analysis, we censored
the follow-up time at 180 days after the cohort entry date. In the second sensitivity analysis, we
excluded patients who had potentially incomplete data, such as those in managed care plans.
Data were analyzed using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina). This study was approved by the institutional review board of the University of Pennsylvania, which waived the requirement for obtaining informed consent.

**Results**

**Cohort characteristics and unadjusted incidence rates and hazard ratios of outcomes**

The numbers of unique users of clopidogrel and any NSAIDs were 1,060,412 and 11,825,916, respectively (S1 Fig). Of these, 403,833 patients had overlapping prescriptions of clopidogrel and any NSAID. After applying inclusion and exclusion criteria, the study cohort consisted of 268,114 patients who contributed 48,483 person-years of concomitant exposure to clopidogrel plus one of the ten study NSAIDs. Selected baseline characteristics of the study cohort are presented in Table 2. S4 Table shows a complete table of the pre-specified baseline characteristics, including demographic characteristics, healthcare utilization factors, diseases, and prescription drugs, in addition to the outcomes of interest during the baseline period. The median age at cohort entry was about 66.2–73.4 years, depending on the NSAID exposure group, with 53.7–76.9% being 65 years of age or older.

In the primary analysis (Table 3), we identified 2,463 deaths, 2,822 AMI/ischemic stroke events (AMI: 1,812; ischemic stroke: 1,030; both: 19), and 2,620 GIB/ICH events (GIB: 2,441; ICH: 182; both: 3); the proportion of the number of ICH events was relatively small (about 7% of the composite outcome). The median follow-up time was 46 days for each of the three outcomes. Table 3 shows the unadjusted incidence rates and hazard ratios of each outcome by NSAID exposure group. In the primary analysis, the overall incidence rates (in events per 1,000 person-years) for all-cause mortality, AMI/ischemic stroke, and GIB/ICH were about 50.8 (95% confidence interval [CI]: 48.8, 52.9), 58.6 (95% CI: 56.4, 60.8), and 54.3 (95% CI: 52.3, 56.5), respectively. The unadjusted incidence rates in the sensitivity analysis are presented in S5 Table.

**Adjusted hazard ratios of outcomes**

Fig 1 presents the propensity score-adjusted hazard ratios (HRs) of each NSAID vs. ibuprofen in the primary analysis. Compared with ibuprofen, rofecoxib (HR = 1.22; 95% CI: 1.04, 1.43) and valdecoxib (HR = 0.66; 95% CI: 0.48, 0.92) were associated with increased and reduced hazard for all-cause mortality, respectively. Indomethacin (HR = 1.38; 95% CI: 1.09, 1.74) was associated with an increased hazard for AMI/ischemic stroke. For GIB/ICH, indomethacin (HR = 2.18; 95% CI: 1.74, 2.73), diclofenac (HR = 1.65; 95% CI: 1.39, 1.97), naproxen (HR = 1.47; 95% CI: 1.28, 1.70), and rofecoxib (HR = 1.26; 95% CI: 1.08, 1.48) were associated with increased hazards, and valdecoxib (HR = 0.73; 95% CI: 0.55, 0.98) was associated with a reduced hazard. The results of the secondary analysis stratified by a) age (detailed results presented in S6 Table and S2 Fig), b) sex (S6 Table and S3 Fig), and c) concomitancy triggering drug (S6 Table and S4 Fig) were not substantially different. The propensity score-adjusted hazard ratios of each NSAID from the sensitivity analyses are presented in S5 Fig. The results were similar to the primary analysis results.

Fig 2 displays the hazard ratios and 95% confidence intervals of GIB/ICH vs. AMI/ischemic stroke of NSAIDs when concomitantly used with clopidogrel. Celecoxib, nabumetone, and valdecoxib were associated with reduced hazards for both composite outcomes than ibuprofen, and rofecoxib, etodolac, diclofenac, and indomethacin were associated with increased hazards.
Table 2. Baseline characteristics of clopidogrel users by NSAID exposure group.

| Characteristic | ibuprofen (N = 69,779) | celecoxib (N = 66,317) | diclofenac (N = 18,593) | etodolac (N = 2,807) | indomethacin (N = 7,651) | meloxicam (N = 25,459) |
|---------------|------------------------|------------------------|------------------------|----------------------|------------------------|------------------------|
| Age at cohort entry (continuous; years) | Median (Q3-Q1) | Age = 66.7 (56.1–75.4) | 73.4 (65.9–80.3) | 0.54 | 0.25 | 71.0 (62.2–78.2) | 0.31 | 0.17 | 66.2 (55.6–74.7) | 0.03 | 0.10 | 70.1 (60.1–77.9) | 0.23 | 0.19 | 72.3 (64.2–79.4) | 0.43 | 0.25 |
| Age group at cohort entry | 18 to <35 | 1.1 | 0.2 | 0.11 | 0.03 | 0.04 | 0.09 | 0.02 | 0.9 | 0.02 | 0.03 | 0.6 | 0.06 | 0.02 | 0.2 | 0.11 | 0.02 |
| | 35 to <50 | 12.3 | 4.0 | 0.31 | 0.07 | 6.6 | 0.19 | 0.05 | 12.8 | 0.02 | 0.05 | 8.1 | 0.14 | 0.07 | 4.7 | 0.27 | 0.04 |
| | 50 to <65 | 32.0 | 18.8 | 0.31 | 0.17 | 23.5 | 0.19 | 0.12 | 32.6 | 0.01 | 0.08 | 26.7 | 0.12 | 0.13 | 21.5 | 0.24 | 0.09 |
| | 65 to <80 | 40.2 | 50.9 | 0.22 | 0.14 | 49.6 | 0.19 | 0.14 | 39.5 | 0.01 | 0.07 | 45.4 | 0.11 | 0.09 | 50.2 | 0.20 | 0.13 |
| | 80 to ≤100 | 14.4 | 26.0 | 0.29 | 0.13 | 19.9 | 0.15 | 0.06 | 14.2 | 0.01 | 0.11 | 19.3 | 0.13 | 0.11 | 23.4 | 0.23 | 0.13 |
| Sex | Female | 56.3 | 67.2 | 0.23 | 0.08 | 64.3 | 0.16 | 0.06 | 63.8 | 0.15 | 0.11 | 45.5 | 0.22 | 0.24 | 65.9 | 0.20 | 0.07 |
| | Race/ethnicity | White | 40.4 | 42.6 | 0.05 | 0.10 | 42.2 | 0.04 | 0.09 | 57.5 | 0.35 | 0.10 | 46.4 | 0.12 | 0.14 | 41.7 | 0.03 | 0.12 |
| | | Black | 16.6 | 10.9 | 0.17 | 0.09 | 10.5 | 0.18 | 0.12 | 14.5 | 0.06 | 0.08 | 17.9 | 0.03 | 0.07 | 10.0 | 0.20 | 0.08 |
| | | Hispanic/Latino | 21.2 | 14.6 | 0.17 | 0.15 | 25.8 | 0.11 | 0.29 | 11.6 | 0.26 | 0.14 | 10.1 | 0.31 | 0.25 | 15.0 | 0.16 | 0.14 |
| | | Other/Unknown | 21.7 | 31.8 | 0.23 | 0.13 | 21.6 | 0.00 | 0.17 | 16.3 | 0.14 | 0.12 | 25.6 | 0.09 | 0.14 | 33.3 | 0.26 | 0.11 |

The full table of the characteristics of clopidogrel users by NSAID exposure group is presented in S4 Table.

S.Diff: standardized difference vs. ibuprofen.
WCSD: weighted conditional standardized difference vs. ibuprofen.

https://doi.org/10.1371/journal.pone.0193800.t002
for both outcomes. NSAIDs that had higher thrombotic risks than ibuprofen also showed a tendency of having higher hemorrhagic risks.

### Discussion

This study examined the comparative safety of individual NSAIDs relative to ibuprofen in patients receiving clopidogrel. We found that in the presence of clopidogrel, the differences in the bleeding risk, measured as a composite outcome of GIB and ICH, among individual

#### Table 3. Primary analysis: Unadjusted incidence rates and hazard ratios of outcomes by NSAID exposure group.

| Outcome                  | NSAID        | Number of users | Number of events | Person-years | Incidence rate (per 1,000 p-ys) | 95% CI of incidence rate | Hazard ratio | 95% CI of hazard ratio |
|--------------------------|--------------|-----------------|------------------|--------------|---------------------------------|--------------------------|--------------|------------------------|
| **All-cause mortality**  | Overall      | 268,114         | 2,463            | 48,483       | 50.8                            | 48.8–52.9                | 1.28         | 1.14–1.44              |
|                          | celecoxib    | 66,317          | 901              | 15,930       | 56.6                            | 52.9–60.4                | 1.28         | 1.14–1.44              |
|                          | diclofenac   | 18,593          | 138              | 3,379        | 40.8                            | 34.3–48.3                | 0.90         | 0.74–1.09              |
|                          | etodolac     | 2,807           | 20               | 536          | 37.3                            | 22.8–57.7                | 0.83         | 0.53–1.30              |
|                          | ibuprofen    | 69,779          | 414              | 8,667        | 47.8                            | 43.3–52.6                | Reference    | Drug                   |
|                          | indomethacin | 7,651           | 57               | 834          | 68.3                            | 51.8–88.5                | 1.40         | 1.06–1.85              |
|                          | meloxicam    | 25,459          | 191              | 5,277        | 36.2                            | 31.2–41.7                | 0.81         | 0.68–0.96              |
|                          | nabumetone   | 7,060           | 54               | 1,392        | 38.8                            | 29.1–50.6                | 0.86         | 0.65–1.15              |
|                          | naproxen     | 36,577          | 245              | 5,695        | 43.0                            | 37.8–48.8                | 0.93         | 0.79–1.09              |
|                          | rofecoxib    | 26,247          | 398              | 5,303        | 75.0                            | 67.9–82.8                | 1.66         | 1.45–1.91              |
|                          | valdecoxib   | 7,624           | 45               | 1,470        | 30.6                            | 22.3–41.0                | 0.67         | 0.50–0.92              |

| AMI/Ischemic stroke      | Overall      | 268,113         | 2,822            | 48,176       | 58.6                            | 56.4–60.8                | 1.07         | 0.96–1.20              |
|                          | celecoxib    | 66,316          | 888              | 15,807       | 56.2                            | 52.5–60.0                | 1.07         | 0.96–1.20              |
|                          | diclofenac   | 18,593          | 183              | 3,360        | 54.5                            | 46.9–63.0                | 0.97         | 0.82–1.14              |
|                          | etodolac     | 2,807           | 33               | 531          | 62.2                            | 42.8–87.3                | 1.13         | 0.79–1.60              |
|                          | ibuprofen    | 69,779          | 538              | 8,623        | 62.4                            | 57.2–67.9                | Reference    | Drug                   |
|                          | indomethacin | 7,651           | 93               | 828          | 112.4                           | 90.7–137.6               | 1.72         | 1.38–2.15              |
|                          | meloxicam    | 25,459          | 225              | 5,245        | 42.9                            | 37.5–48.9                | 0.78         | 0.67–0.92              |
|                          | nabumetone   | 7,060           | 59               | 1,386        | 42.6                            | 32.4–54.9                | 0.78         | 0.59–1.02              |
|                          | naproxen     | 36,577          | 311              | 5,670        | 54.9                            | 48.9–61.3                | 0.94         | 0.81–1.08              |
|                          | rofecoxib    | 26,247          | 417              | 5,264        | 79.2                            | 71.8–87.2                | 1.44         | 1.27–1.64              |
|                          | valdecoxib   | 7,624           | 75               | 1,463        | 51.3                            | 40.3–64.3                | 0.91         | 0.72–1.16              |

| GIB/ICH                   | Overall      | 268,087         | 2,620            | 48,225       | 54.3                            | 52.3–56.5                | 1.11         | 0.98–1.26              |
|                          | celecoxib    | 66,310          | 736              | 15,846       | 46.4                            | 43.2–49.9                | 1.11         | 0.98–1.26              |
|                          | diclofenac   | 18,592          | 207              | 3,354        | 61.7                            | 53.6–70.7                | 1.39         | 1.17–1.64              |
|                          | etodolac     | 2,806           | 29               | 533          | 54.5                            | 36.5–78.2                | 1.25         | 0.86–1.83              |
|                          | ibuprofen    | 69,775          | 416              | 8,635        | 48.2                            | 43.7–53.0                | Reference    | Drug                   |
|                          | indomethacin | 7,651           | 108              | 829          | 130.3                           | 106.9–157.4              | 2.62         | 2.12–3.23              |
|                          | meloxicam    | 25,455          | 246              | 5,252        | 46.8                            | 41.2–53.1                | 1.08         | 0.92–1.27              |
|                          | nabumetone   | 7,060           | 45               | 1,385        | 32.5                            | 23.7–43.5                | 0.75         | 0.55–1.02              |
|                          | naproxen     | 36,576          | 365              | 5,668        | 64.4                            | 58.0–71.4                | 1.41         | 1.22–1.62              |
|                          | rofecoxib    | 26,240          | 411              | 5,259        | 78.1                            | 70.8–86.1                | 1.79         | 1.56–2.06              |
|                          | valdecoxib   | 7,622           | 57               | 1,463        | 39.0                            | 29.5–50.5                | 0.88         | 0.67–1.16              |

*p-ys: person-years.

CI: confidence interval.

AMI: acute myocardial infarction.

GIB/ICH: gastrointestinal bleeding/intracranial hemorrhage.

https://doi.org/10.1371/journal.pone.0193800.t003
NSAIDs varied more markedly than in the thrombotic risk, measured as a composite outcome of AMI and ischemic stroke. Indomethacin, diclofenac, naproxen, and rofecoxib showed a statistically significantly higher bleeding risk than ibuprofen, while valdecoxib showed a significantly reduced bleeding risk. In contrast, no statistically significant differences in the thrombotic risk were found, except for indomethacin that showed significantly increased risk. In all-cause mortality, rofecoxib and valdecoxib were associated with a significantly increased and reduced risk, respectively. In addition, unlike what one might anticipate from the results of prior studies in patients not receiving clopidogrel [47–48], our results suggest that the thrombotic risks might not be inversely related to the bleeding risks of NSAIDs in patients also using clopidogrel. In particular, the combined results of randomized controlled trials in the absence of clopidogrel have suggested that the cardiovascular risk and GI risk have an inverse relationship, which is thought to be related to the degree of COX-2 or COX-1 selectivity [47–48]. Our results, however, suggest the absence of an inverse relationship in persons taking clopidogrel, as illustrated in Fig 2.

The underlying mechanisms for these results have remained to be elucidated. Yet, this observational study provides epidemiological insights suggesting that the known safety profiles of individual NSAIDs might differ in the presence of clopidogrel. For example, the molecular mechanisms that underlie differences in the safety profiles of distinct NSAIDs (related to factors such as COX-1 or COX-2 selectivity, inhibition of CYP enzymes or platelet aggregation) or their potencies might be different when NSAIDs are given concomitantly with clopidogrel. Drug-drug interactions might exist at the functional level (such as reduction of the cardiovascular risk by clopidogrel) and potentially also at the molecular level (such as alterations of the metabolism of some, but not all, NSAIDs due to CYP inhibition). Further studies are needed to shed light on the underlying mechanisms related to potential interactions between individual NSAIDs and clopidogrel. In addition, the risk of the individual components of our composite outcomes will need further investigation.

A direct comparison of our findings with the results of prior observational studies in patients receiving clopidogrel plus NSAIDs is difficult because of differences in the data, study population, definitions of exposure and outcomes, and methods, among others. For instance, a recent cohort study that analyzed the Danish nationwide administrative data reported increased risks of a composite cardiovascular outcomes (cardiovascular death, nonfatal recurrent MI, and stroke) and bleeding associated with the concomitant use of clopidogrel and NSAIDs (rofecoxib, celecoxib, diclofenac, ibuprofen, and naproxen) after MI, vs. non-NSAID-exposure as the referent [49]. They found that the risks of serious bleeding and cardiovascular events were higher with the use of any NSAID compared to non-use of NSAIDs among...
clopidogrel users. In that Danish study, the serious bleeding risk was higher for diclofenac, naproxen, and celecoxib than for ibuprofen, and the cardiovascular risk was lower for rofecoxib, celecoxib, diclofenac, and naproxen than for ibuprofen. The findings in the Danish study that the highest cardiovascular risk was with ibuprofen, and that bleeding risk was higher for celecoxib than for ibuprofen are not consistent with our results. Potentially important differences between two studies include that the prior study was restricted to the patients who were admitted with first-time MI and alive 30 days after discharge; the definitions of outcomes of interest differed; and that our study had a much larger number of users of clopidogrel and NSAIDs.

Our study has several important strengths. First, we studied a large, vulnerable population. Medicaid covers nearly 70 million people nationwide, or 1 in 5 Americans. This large, vulnerable population is therefore important to study in its own right. Second, this study compared individual NSAIDs, which helps reduce the potential for confounding by indication that can arise in the comparison of NSAID users vs. non-users. Third, the algorithms we used to ascertain outcomes of interest have been found to perform well. Lastly, this study reflects safety profile of NSAIDs in a real world setting, unlike clinical trials that are conducted under strictly regulated protocols generally among highly selected populations at specialized centers and much smaller numbers of patients.

This study also has limitations. First, data on genetic factors related to the CYP enzymes responsible for clopidogrel metabolism were unavailable in our dataset. Second, since we used
administrative claims data, complete information on drug ingestion (including P.R.N., i.e.,
administration as needed, or other intermittent use of drug), lifestyle, or health behaviors
(including smoking) was unavailable. It is notable, however, randomized clinical trials in
ambulatory settings often have incomplete or unreliable drug adherence data [50] as well. We
controlled for tobacco use as a pre-specified covariate (S4 Table), as a prior study documented
that ICD-9 codes for tobacco use had a specificity of 100%, a sensitivity of 32%, and showed lit-
tle evidence of documentation bias [51]. Third, this study does not provide information on the
effect of dose on risk or risk of NSAID use vs. non-use. Future research that examines dose-
response relationship will enable comparison of dose-dependent risk. Also, because our study
compared the outcomes of interest among NSAIDs, the estimated risks in this study does not
represent risks of NSAID users compared to NSAID non-users, in the presence of clopidogrel.
Fourth, although we controlled for many potential confounders, residual confounding may
remain, as is the case with observational pharmacoepidemiologic studies in general. For exam-
ple, we controlled for prescription aspirin use in the propensity score model, but we may not
have captured all aspirin use because aspirin is available over-the-counter. The proportion of
the subjects in this study with a recorded prescription for aspirin dispensed in the 60-day
period before cohort entry was 13–23%, depending on NSAID. Given that aspirin use may
influence comparative risk of NSAIDs, it will be important to control for over-the-counter
aspirin use in future research provided that the data are available. Also, selection bias or
channeling effect may be part of residual confounding. This study employed statistical meth-
ods to control for these potential confounders as much as possible, but we cannot rule out the
possibility of residual confounding. Fifth, our results were obtained from the Medicaid enroll-
ees, who tend to be vulnerable. Therefore, magnitude of the associations identified here may
not be generalizable to other populations.

Conclusions
In users of clopidogrel, the differences in the bleeding risk (GIB/ICH) among individual
NSAIDs relative to ibuprofen were more pronounced than in the thrombotic risk (AMI/ische-
mic stroke). Bleeding risks and thrombotic risks among individual NSAIDs did not appear to
be inversely related to each other, unlike the results from prior studies conducted in the
absence of clopidogrel. Although these findings are not definitive, bleeding risk might need a
relatively greater attention in the NSAID therapy among clopidogrel users, weighing antici-
pated benefits and risks. Further studies are needed to better understand the comparative
safety of NSAIDs in the concomitant use of clopidogrel and underlying mechanisms to help
clinical decision-making for a better NSAID choice, and thereby proactively reduce prevent-
able serious adverse outcomes.

Supporting information
S1 Fig. Identification of study cohorts and application of inclusion and exclusion criteria.
(TIF)
S2 Fig. Secondary analysis stratified by age: Adjusted hazard ratios (with 95% confidence
intervals) of AMI/Ischemic Stroke and GIB/ICH of NSAIDs when concomitantly used
with clopidogrel. A. 18 ≤ Age < 65 years.
B. 65 ≤ Age ≤ 100 years.
(TIF)
S3 Fig. Secondary analysis stratified by sex: Adjusted hazard ratios (with 95% confidence
intervals) of AMI/Ischemic Stroke and GIB/ICH of NSAIDs when concomitantly used
with clopidogrel. A. Male.
B. Female.

S4 Fig. Secondary analysis stratified by concomitancy triggering drug: Adjusted hazard ratios (with 95% confidence intervals) of AMI/Ischemic Stroke and GIB/ICH of NSAIDs when concomitantly used with clopidogrel. A. NSAID-triggered group.
B. Clopidogrel-triggered and combination-triggered group.

S5 Fig. Sensitivity analysis: Adjusted hazard ratios of outcomes by NSAID exposure group. A. Whole cohort with the follow-up time up to 180 days after cohort entry date. B. Excluding potential incomplete-data patients, without a restriction on the follow-up time.

S1 Table. Pre-specified covariates included in the propensity score model.

S2 Table. Specifications used in the high-dimensional propensity score method.

S3 Table. Covariates empirically identified by the high-dimensional propensity score method.

S4 Table. Characteristics of clopidogrel users by NSAID exposure group.

S5 Table. Sensitivity analysis: Unadjusted incidence rates of outcomes by NSAID exposure group. A. Whole cohort with the follow-up time up to 180 days after cohort entry date. B. Excluding potential incomplete-data patients, without a restriction on the follow-up time.

S6 Table. Secondary analysis stratified by age, sex, and concomitancy triggering drug: Adjusted hazard ratios of outcomes by NSAID exposure group.

Acknowledgments
The authors thank Ms. Qing Liu and Ms. Min Du of the Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, for their assistance with biostatistics computer programming, as well as Ms. Margaret J. Mangaali of the Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, for her research assistance.

Author Contributions
Conceptualization: Young Hee Nam, Colleen M. Brensinger, Warren B. Bilker, Charles E. Leonard, Sean Hennessy.
Formal analysis: Colleen M. Brensinger.
Funding acquisition: Sean Hennessy.
Methodology: Colleen M. Brensinger, Warren B. Bilker.
Writing – original draft: Young Hee Nam.
Writing – review & editing: Young Hee Nam, Colleen M. Brensinger, Warren B. Bilker, Charles E. Leonard, Scott E. Kasner, Tilo Grosser, Xuanwen Li, Sean Hennessy.

References
1. Zhou Y, Boudreau DM, Freedman AN. Trends in the use of aspirin and nonsteroidal anti-inflammatory drugs in the general U.S. population. Pharmacoepidemiol Drug Saf. 2014; 23:43–50. https://doi.org/10.1002/pds.3463 PMID: 23723142
2. Fosbol EL, Folke F, Jacobsen S, Rasmussen JN, Sorensen R, Schramm TK, et al. Cause-specific cardiovascular risk associated with nonsteroidal anti-inflammatory drugs among healthy individuals. Circ Cardiovasc Qual Outcomes. 2010; 3:395–405. https://doi.org/10.1161/CIRCOUTCOMES.109.861104 PMID: 20530789
3. Varas-Lorenzo C, Riera-Guardia N, Calingaert B, Castellsague J, Salvo F, Nicotra F, et al. Myocardial infarction and individual nonsteroidal anti-inflammatory drugs meta-analysis of observational studies. Pharmacoepidemiol Drug Saf. 2013; 22:559–70. https://doi.org/10.1002/pds.3437 PMID: 23616423
4. Coxib and Traditional NSAID Trialists' (CNT) Collaboration; Bhala N, Emberson J, Merhi A, Abramson S, Arber N, Baron JA, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: Meta-analyses of individual participant data from randomised trials. Lancet. 2013; 382 (9894):769–79. https://doi.org/10.1016/S0140-6736(13)60900-9 PMID: 23726390
5. Caldwell B, Aldington S, Weatherall M, Shirtcliffe P, Beasley R. Risk of cardiovascular events and celecoxib: a systematic review and meta-analysis. J R Soc Med. 2006; 99:132–40. https://doi.org/10.1258/jrsm.99.3.132 PMID: 16508052
6. United States Food and Drug Administration. Advisory Committee Briefing Document: Celecoxib and valdecoxib cardiovascular safety. Arthritis Advisory Committee, USFDA. 2005 January. http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4090B1_03_Pfizer-Celebrex-Bextra.pdf. Last accessed: 12/10/2016.
7. Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclooxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. BMJ. 2006; 332:1302–8. https://doi.org/10.1136/bmj.332.7553.1302 PMID: 16740558
8. Chou R, Hellfand M, Peterson K, Dana T, Roberts C. Comparative effectiveness and safety of analgesics for osteoarthritis. Comparative Effectiveness Review Number 4. 2006. Agency for Healthcare Research and Quality. AHRQ Publication No. 06-EHC009-EF. http://www.effectivehealthcare.ahrq.gov/repFiles/AnalgesicsFinal.pdf. Last accessed: 12/10/2016.
9. Chou R, McDonagh MS, Nakamoto E, Griffin J. Analgesics for osteoarthritis: An update of the 2006 comparative effectiveness. Comparative Effectiveness Review Number 38. 2011. Agency for Healthcare Research and Quality. AHRQ Publication No. 11(12)-EHC076-EF. https://www.effectivehealthcare.ahrq.gov/ehc/products/180/795/Analgesics-Update_CER-38_20111007.pdf. Last accessed: 12/10/2016.
10. Kimmel SE, Berlin JA, Reilly M, Jaskowiak J, Kishel L, Chittams J, et al. Patients exposed to rofecoxib and celecoxib have different odds of nonfatal myocardial infarction. Ann Intern Med. 2005; 142:157–64. PMID: 15684203
11. Shau WY, Chen HC, Chen ST, Chou HW, Change CH, Kuo CW, et al. Risk of new acute myocardial infarction hospitalization associated with use of oral and parenteral non-steroidal anti-inflammation drugs (NSAIDs): a case-crossover study of Taiwan’s National Health Insurance claims database and review of current evidence. BMC Cardiovascular Disord. 2012; 12:4. https://doi.org/10.1186/1471-2261-12-4 PMID: 22297085
12. Solomon DH, Schneeweiss S, Glynn RJ, Kiyota Y, Levin R, Mogun H, et al. Relationship between selective cyclooxygenase-2 inhibitors and acute myocardial infarction in older adults. Circulation. 2004; 109: 2068–73. https://doi.org/10.1161/01.CIR.0000127578.21885.3E PMID: 15096449
13. Varas-Lorenzo C, Riera-Guardia N, Calingaert B, Castellsague J, Pariante C, Scotti L, et al. Stroke risk and NSAIDs: a systematic review of observational studies. Pharmacoepidemiol Drug Saf. 2011; 20:1225–36. https://doi.org/10.1002/pds.2227 PMID: 21971833
14. Chang CH, Shau WY, Kuo CW, Chen ST, Lai MS. Increased risk of stroke associated with nonsteroidal anti-inflammatory drugs. Stroke. 2010; 41:1884–90. https://doi.org/10.1161/STROKEAHA.110.585828 PMID: 20671253
15. Castellsague JC, Holick CN, Hoffman CC, Gimeno V, Stang M, Perez-Guthmann SP. Risk of upper gastrointestinal complications associated with cyclooxygenase-2 selective and nonselective nonsteroidal anti-inflammatory drugs. Pharmacotherapy. 2009; 29(12):1397–407. https://doi.org/10.1592/phco.29.12.1397 PMID: 19947799
16. Li X, Fries S, Li R, Lawson JA, Propert KJ, Diamond SL, et al. Differential impairment of aspirin-dependent platelet cyclooxygenase acetylation by nonsteroidal anti-inflammatory drugs. Proc Natl Acad Sci USA. 2014; 111(47):16830–5. https://doi.org/10.1073/pnas.1406979111 PMID: 25385584

17. Couzin J. Drug testing. Massive trial of Celebrex seeks to settle safety concerns. Science. 2005; 310(5756):1890–1.

18. Lip GY, Lane DA. Stroke prevention in atrial fibrillation: A systematic review. JAMA. 2015; 313(19):1950–62. https://doi.org/10.1001/jama.2015.4369 PMID: 25988464

19. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, et al. 2012 focused update of the ESC guidelines for the management of atrial fibrillation. Eur Heart J. 2012; 14:1385–413. https://doi.org/10.1093/eurheartj/eur305 PMID: 22923145

20. Shah BS, Parmar SA, Mahajan S, Mehta AA. An insight into the interaction between clopidogrel and proton pump inhibitors. Curr Drug Metab. 2012; 13:225–35. PMID: 22300021

21. Patrono C, Collard B, Dalen JE, FitzGerald GA, Fuster V, Gent M, et al. Platelet-Active Drugs. The relationships among dose, effectiveness, and side effects. Chest. 2001; 119:39S–63S. PMID: 11157642

22. Ruggeri ZM. Platelets in atherothrombosis. Nat Med. 2002; 8(11):1227–34. https://doi.org/10.1038/nm1102-1227 PMID: 12411949

23. Masfeer JL, Needlemann P. Anti-inflammatories for cardiovascular disease. Proc Natl Acad Sci USA. 2000; 97(23):12400–1. https://doi.org/10.1073/pnas.240459597 PMID: 11058172

24. McAdam BF, Catella-Lawson F, Mardini IA, Kapoor S, Lawson JA, FitzGerald GA. Systemic biosynthesis of prostacyclin by cyclooxygenase (COX)-2: The human pharmacology of a selective inhibitor of COX-2. Proc Natl Acad Sci USA. 1999; 96:272–7. PMID: 9874908

25. Patrono C, Coller B, FitzGerald GA, Hirsh J, Roth G. Platelet-active drugs: The relationships among dose, effectiveness, and side effects. The Seventh ACCP conference on antithrombotic and thrombolytic therapy. Chest. 2004; 126:234S–264S. https://doi.org/10.1378/chest.126.3_suppl.234S PMID: 15383474

26. Lamberts M, Olesen JB, Ruwald MH, Ruwald MH, Hansen CM, Karasoy D, et al. Bleeding after initiation of multiple antithrombotic drugs, including triple therapy, in atrial fibrillation patients following myocardial infarction and coronary intervention. A nationwide cohort study. Circulation. 2012; 126(10):1185–93. https://doi.org/10.1161/CIRCULATIONAHA.112.114967 PMID: 22869839

27. Hennessy S, Carson JL, Ray WA, Strom BL. Medicaid databases. In: Strom BL, ed. Pharmacoeconomics. 4th ed. Sussex, United Kingdom: John Wiley; 2005:281–94.

28. Medicaid.gov. Medicaid overview. https://www.medicaid.gov/medicaid/index.html. Last accessed 4/20/2017.

29. Kaiser Family Foundation. Medicaid enrollees by enrollment group. Available at https://www.kff.org/medicaid/state-indicator/distribution-of-medicaid-enrollees-by-enrollment-group/?currentTimeframe=0&sortModel=%7B%22sortId%22:%22Location%22,%22sort2%22:%22asc%22%7D Last accessed: 01/25/2018.

30. Kaiser Family Foundation. Dual eligible as a percent of total Medicaid beneficiaries. Available at https://www.kff.org/medicaid/state-indicator/duals-as-a-of-medicaid-beneficiaries/?currentTimeframe=0&sortModel=%7B%22sortId%22:%22Location%22,%22sort2%22:%22asc%22%7D Last accessed: 01/25/2018.

31. Centers for Medicare and Medicaid Services. National Profile of Medicare-Medicaid Enrollees (2012). Available at https://www.cms.gov/Medicare-Medicare-Coordination/Medicare-and-Medicaid-Coordination/Medicare-Medicaid-Coordination-Office/Analytics.html Last accessed: 02/03/2018.

32. Kaiser Family Foundation. Medicaid enrollment: June 2010 data snapshot. 2011. Report #8050–03. Available at: https://kaiserfamilyfoundation.files.wordpress.com/2013/01/8050-03.pdf. Last accessed: 08/12/2016.

33. Medicare.gov. What’s Medicare? https://www.medicare.gov/sign-up-change-plans/decide-how-to-get-medicare/whats-medicare/what-is-medicare.html. Last accessed 4/4/20/2017.

34. Centers for Medicare and Medicaid Services. Medicare enrollment dashboard. https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics/Trends-and-Reports/Dashboard/Medicare-Enrollment/Enrollment%20Dashboard.html Last accessed 4/20/2017.

35. Medicare.gov. Drug coverage (Part D). https://www.medicare.gov/part-d/index.html. Last accessed 4/20/2017.

36. Hennessy S, Leonard CE, Gagne JJ, Flory JH, Han X, Brensinger CM, et al. Pharmacoepidemiologic methods for studying the health effects of drug-drug interactions. Clin Pharmacol Ther. 2016; 99(1):92–100. https://doi.org/10.1002/cpt.277 PMID: 26479278

37. Kiyota Y, Schneeweiss S, Glynn RJ, Cannuscio CC, Avorn J, Solomon DH. Accuracy of Medicare claims-based diagnosis of acute myocardial infarction: Estimating positive predictive value on the basis
38. Tirschwell DL, Longstreth WT Jr. Validating administrative data in stroke research. Stroke. 2002; 33:2465–70. https://doi.org/10.1161/01.STR.0000032240.28636.BD PMID: 12364739

39. Schelleman H, Bliker WB, Brensinger CM, Wan F, Yang YX, Hennessy S. Fibrate/statin initiation in warfarin users and gastrointestinal bleeding risk. Am J Med. 2010; 123(2):151. https://doi.org/10.1016/j.amjmed.2009.07.020 PMID: 2013024

40. Kokotailo RA, Hill MD. Coding of stroke and stroke risk factors using International Classification of Diseases, Revisions 9 and 10. Stroke. 2005; 36:1776–81. https://doi.org/10.1161/01.STR.0000174293.17959.a1 PMID: 16020772

41. Austin PC. Goodness-of-fit diagnostics for the propensity score model when estimating treatment effects using covariate adjustment with the propensity score. Pharmacoepidemiol Drug Saf. 2008; 17:1202–17. https://doi.org/10.1002/pds.1673 PMID: 18972454

42. Schneeweiss S, Rassen JA, Glynn RJ, Avorn J, Mogun H, Brookhart MA. High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. Epidemiology 2009; 20:512–22. https://doi.org/10.1097/EDE.0b013e3181a663cc PMID: 19487948

43. Rassen JA, Doherty M, Huang W, Schneeweiss S. Pharmacoepidemiology toolbox. Boston, MA. Available at: http://www.drugepi.org/dope-downloads/#Pharmacoepidemiology%20Toolbox. Last accessed: 08/12/2016.

44. Rassen JA, Glynn RJ, Brookhart MA, Schneeweiss S. Covariate selection in high-dimensional propensity score analyses of treatment effects in small samples. Am J Epidemiol 2011; 173:1404–13. https://doi.org/10.1093/aje/kwr001 PMID: 21623001

45. Brookhart MA, Wyss R, Layton JB, Sturmer T. Propensity score methods for confounding control in nonexperimental research. Circ Cardiovasc Qual Outcomes. 2013; 6:604–11. https://doi.org/10.1161/CIRCOUTCOMES.113.000359 PMID: 24021692

46. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika. 1983:41–55.

47. Grosser T, Fries S, FitzGerald GA. Biological basis for the cardiovascular consequences of COX-2 inhibition: therapeutic challenges and opportunities. J Clin Invest. 2006; 116(1):4–15. https://doi.org/10.1172/JCI27291 PMID: 16395396

48. Grosser T, Yu Y, FitzGerald GA. Emotion recollected in tranquility: Lessons learned from the COX-2 saga. Annu Rev Med. 2010; 61:17–33. https://doi.org/10.1146/annurev-med-011209-153129 PMID: 20059330

49. Olsen AMS, Gislanon G, McGettigan P, Fosbol E, Sorensen R, Hansen ML, et al. Association of NSAID use with risk of bleeding and cardiovascular events in patients receiving antithrombotic therapy after myocardial infarction. JAMA. 2015; 313(8):805–14. https://doi.org/10.1001/jama.2015.0809 PMID: 25710657

50. Breckenridge A, Aronson JK, Blaschke TF, Hartman D, Peck CC, Vrijens B. Poor medication adherence in clinical trials: consequences and solutions. Nat Rev Drug Discov. 2017; 16(3):149–50. https://doi.org/10.1038/nrd.2017.1 PMID: 28154411

51. Wiley LK, Shah A, Xu H, Bush WS. ICD-9 tobacco use codes are effective identifiers of smoking status. J Am Med Inform Assoc. 2013; 20:652–658. https://doi.org/10.1136/amiainj-2012-001557 PMID: 23396545