Use of nicorandil is Associated with Increased Risk for Gastrointestinal Ulceration and Perforation- A Nationally Representative Population-based study

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Nicorandil is a vasodilatory drug used to relieve angina symptoms. Several healthcare products regulatory agencies have issued a warning associating the use of nicorandil and gastrointestinal (GI) ulceration. We aimed to evaluate the association between use of nicorandil and GI ulceration/perforation. A population-based cohort study involving 1 million randomly sampled participants in Taiwan’s National Health Insurance Research Database was carried out. We estimated the association between use of nicorandil and GI ulceration/perforation by a Cox proportional hazards regression model. A nicorandil-specific propensity score (PS) was also created for adjustment of 75 covariates and matching. 25.8% (183/710) of nicorandil-treated patients developed new GI ulcer events and 1.6% (20/1254) developed new GI perforation events in the three-year follow-up period, as compared to 9.3% (61,281/659,081) and 0.3% (2,488/770,537) in the general population comparator cohort. Patients treated with nicorandil were at significantly increased risk of GI ulcer (PS adjusted hazard ratio 1.43, 95% CI, 1.23 to 1.65, 6848 excess cases per 100,000 person years) or GI perforation (aHR 1.60, 95% CI 1.02–2.51, 315 excess cases per 100,000 person years) compared with the nicorandil unexposed population. Our finding may warn the clinicians to weigh the overall risk-benefit balance of nicorandil treatment in patients.

Gastrointestinal ulceration or perforation as a potential adverse effect of nicorandil treatment has received much attention recently. Since 1997, there were numerous case report or case series of nicorandil-induced ulcerations in skin and mucous tissue of gastrointestinal tract1–18. In almost all of these case reports, the ulcerations were reported to heal upon withdrawal of nicorandil treatment. Thus, several healthcare
products regulatory agencies have taken notice of this potential ulceration adverse effect and issued warnings on use of nicorandil.

Nicorandil is a common antianginal medication in Europe and Asia. UK’s 2008 annual prescription data suggested that over 100,000 people in the U.K. are prescribed with nicorandil. The pharmacological properties of nicorandil came from the nicotinamide ester, which can result in vasodilation of arteries and veins. In several randomized controlled trials, nicorandil has demonstrated equivalent efficacy to nitrate, calcium channel blockers, and beta-blockers in relieving angina symptoms. Unfortunately, these randomized controlled trials did not monitor gastrointestinal (GI) ulceration or perforation as one of the adverse effects.

Since there was no large-scale study conducted to quantify the observed association between nicorandil treatment and GI ulceration/perforation (as far as we were aware), case reports were the only supporting evidence for increased risk of GI ulceration/perforation. Evidence from case reports should be interpreted with caution, due to the limited sample size and the possibility of confounding bias. For example, nicorandil subjects who also took traditional non-steroidal anti-inflammatory drugs were predisposed to 3 fold higher risk of GI ulceration or perforation. Thus, there is a need to correct for the known risk factors for GI ulceration or perforation, before the association between nicorandil and GI ulceration/perforation can be suggested. With the limitation of the prior studies in mind, we used a 1 million national representative cohort to study the potential link between nicorandil treatment and risk of GI ulceration/perforation.

**Methods**

**Setting and Data Collection.** We carried out a population-based cohort study using the National Health Insurance Research Database (NHIRD) of Taiwan, done in accordance with STROBE guideline and under the approval of the institutional review board of National Taiwan University Hospital. The database contains de-identified secondary data, and met the requirements of the “Personal Information Protection Act” in Taiwan. Thus, the data were analyzed anonymously and the need for informed consent was waived.

Several studies have showed that the NHIRD is appropriate for use in pharmacoepidemiologic research. The demographics and complete claim history of 1 million representative Taiwanese can be found in the NHIRD database. Detailed claim history includes electronic claim records of outpatients, inpatients, pharmacy prescription, quantity of medications, route of administration, diagnoses, operations, and procedures.

**Study population.** We used a study cohort of NHIRD that consists of a longitudinally followed up Taiwanese population from January 2005 to December 2009. All participants in the NHIRD who were aged 20 years and over at 1 January 2005 and had at least one inpatient or outpatient visit in the previous 6 months were eligible for inclusion. Considering the time-varying risk after initial exposure to nicorandil, we adopted a new user cohort design, in which previous users of nicorandil were excluded before cohort entry. We excluded all patients who received at least one prescription of nicorandil in 2005, and assessed the nicorandil exposure status in 2006. Nicorandil users were defined as subjects who redeemed one or more prescriptions for nicorandil. In Taiwan, the prescription length of nicorandil is usually between 14 and 28 days. Patients entered the cohort on the first day of year 2007 and were followed up for 3 years until the first occurrence of the either event: diagnosis of gastrointestinal ulcer/perforation, termination of health insurance coverage, death, or end of the study period, whichever came first. We do not aim to study the risk of GI ulceration/perforation recurrence; therefore, patients who had been diagnosed with GI ulceration or perforation before 2007 were excluded for analysis. Considering GI ulceration and GI perforation are two related but different diseases, we created two separate cohorts for analysis. Cohort 1 excluded prevalent cases of GI ulceration before 2007 and cohort 2 excluded prevalent cases of GI perforation before 2007. In addition, patients with the following special conditions that can lead to increase risk in GI ulceration/perforation were excluded: ingestion of corrosives (ICD-9 CM 533.5, 533.6, 534.1, 534.2, 534.5, 534.6) and small or large intestinal perforation (569.83) plus procedure code for esophagogastroduodenoscopy or colonoscopy. GI perforation was defined by ICD-9-CM with either one of the following type of perforation: gastric perforation (531.1, 531.2, 531.5, 531.6, 532.1, 532.2, 532.5, 532.6, 533.1, 533.2, 533.5, 533.6, 534.1, 534.2, 534.5, 534.6) and small or large intestinal perforation (569.83) plus procedure code for laparotomy or computed tomography. NHIRD prevents the linkage between claim database and medical records; therefore we could not perform the validation of outcome in these 2 cohorts. Instead, we tested the accuracy of our outcome definition by performing an independent validation on one hundred electronic medical records from a university hospital. The combined diagnostic and procedure code definition in this study have a positive predictive rate of 83% for GI ulceration and 89% for GI perforation.

**Outcomes.** Cohort 1 was assessed for GI ulceration and cohort 2 was assessed for GI perforation. GI ulceration was defined by ICD-9-CM codes associated with either upper GI ulceration (530.2, 531.X, 532.X, 533.X, 534.X) or lower GI ulceration (569.41 and 569.82) plus procedure code for esophagogastroduodenoscopy or colonoscopy. GI perforation was defined by ICD-9-CM with either one of the following type of perforation: gastric perforation (531.1, 531.2, 531.5, 531.6, 532.1, 532.2, 532.5, 532.6, 533.1, 533.2, 533.5, 533.6, 534.1, 534.2, 534.5, 534.6) and small or large intestinal perforation (569.83) plus procedure code for laparotomy or computed tomography. NHIRD prevents the linkage between claim database and medical records; therefore we could not perform the validation of outcome in these 2 cohorts. Instead, we tested the accuracy of our outcome definition by performing an independent validation on one hundred electronic medical records from a university hospital. The combined diagnostic and procedure code definition in this study have a positive predictive rate of 83% for GI ulceration and 89% for GI perforation.
Covariates. In order to be as comprehensive as possible in adjusting for factors that might confound the drug-outcome association, we reviewed literature for covariates related to gastrointestinal ulceration/perforation and angina (the main indication for nicorandil). 75 relevant covariates (Table 1) were chose and assessed from January 2005 to December 2005. There are seven category of covariates: demographic variables, risk factors for intestinal ulceration/perforation, respiratory comorbidities, cardiovascular comorbidities, musculoskeletal comorbidities, healthcare service utilization, and use of specific medications. Each individual’s burden of comorbidity was quantified by a combined weighted comorbidity score. This index is an improved comorbidity index based on the Elixhauser system37. The score contains common comorbidities such as myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, liver disease, diabetes, hemiplegia, renal disease, neoplasms and AIDS.

Data Analysis. The baseline characteristics of participants were described and compared among nicorandil users and nonusers (Table 1). To examine differences in baseline characteristics between nicorandil users and nonusers, we used Pearson chi-square tests for comparison of dichotomous variables and Mann-Whitney U tests for continuous variables. For multivariate analysis, we constructed Cox proportional hazards models to derive hazard ratios and 95% confidence intervals. We tested the proportional hazards assumption by introducing an interaction term of exposure and follow-up time in the model. In addition, we confirmed the assumption of proportional hazards by an examination of the log (minus log) curves (appendix 1).

To consolidate the strength of our findings, we calculated the hazard ratios by three different methods. The first method obtains an unadjusted crude estimate. The second method obtains an adjusted effect estimate by entering the propensity score (PS) into the Cox regression model as a continuous covariate plus a quadratic term to allow nonlinearity. The PS was built by a multivariate logistic model using the prescription of nicorandil as the dependent variable, and the 75 covariates as the independent variables. The PS model (appendix 2, 3) showed high predictability (c-statistic: 0.91, appendix 4) of nicorandil prescription. Finally, using the COX-model, we carried out stratiifying on the matched pairs. The matching was done using the greedy matching algorithm without any trimming38. We examined the distribution of PS in the study population and checked the balance of each covariate after PS matching by using absolute standardized difference (appendix 5). Standardized differences between the two treatment groups were calculated as the differences in the either the means or the percentage, divided by the pooled standard deviation.

To assess the robustness of the hazard ratios for risk of GI ulceration/perforation in relation to the duration of follow-up, we carried out a subgroup analysis. Predefined subgroups included sex and age of 75 years. To find out if nicorandil users and PS-matched non-users have different cumulative hazard of GI ulceration/perforation, we used the Nelson-Aalen estimators to generate a cumulative hazard function and plot it over time. All analyses were carried out with SAS 9.3 for Windows (SAS Institute Inc, Cary, NC) and the data are reported in accordance with STROBE guideline.

Results

Participant Enrollment and Baseline Characteristics. The baseline characteristics of the two cohorts were displayed on Table 1. The source population comprises of 1 million participants with 3 years of follow-up. After exclusion of existing users of nicorandil and prevalent cases of GI ulceration/perforation in the pre-enrollment period, there were 710 nicorandil users in the GI ulceration cohort and 1,254 nicorandil users in the GI perforation cohort. In both cohorts, there were significant differences in the baseline characteristics between nicorandil users and nonusers. Users of nicorandil represented a group of patients with older age, more urban and suburban residents, higher burden of comorbidity, and used more anti-inflammatory, cardiovascular, and antipsychotics medications. We used PS for matching nicorandil users and nonusers. After matching, there were negligible standardized differences in the baseline covariates between nicorandil users and nonusers (appendix 5).

Outcome- GI ulceration. To investigate whether use of nicorandil has differential effects on different part of the GI system, we classified the location of GI ulceration as either upper GI (esophagus, stomach, and small intestine) or lower GI ulceration (large intestine and anus). There are more outcomes of upper GI ulceration outcome (N = 181) as compared to lower GI ulceration (N = 2). (Table 2).

During a 3 year follow-up period, nicorandil users were found to have higher incidence of upper GI ulceration (25.5%) as compared to nonusers (9.1%) and propensity score (PS) matched nonusers (18.9%). However, there was no significant difference in the incidence of lower GI ulceration (0.3%) among nicorandil users as compared to nonusers (0.2%).

Unadjusted analysis showed that nicorandil therapy was associated with an increased risk of overall GI ulceration (HR 3.10; 95%CI, 2.68-3.59). (Table 3) After adjusting for potential confounders using the PS in the Cox model, nicorandil therapy was still significantly associated with GI ulceration (HR 1.43; 95%CI, 1.23-1.65). PS-matched analysis yielded a similar effect size (HR 1.41, 95%CI 1.13-1.76). The adverse effects of nicorandil therapy were found in the upper GI tract but not in the lower GI tract.
| Cohort 1: GI ulcer | Cohort 2: GI perforation |
|--------------------|--------------------------|
| Nicorandil User (N = 710) | Non-user (N = 659,081) | P-value | Nicorandil User (N = 1,254) | Non-user (N = 770,537) | P-value |
| Gender male (%) | 412 (58.0) | 345387 (52.4) | 0.003 | 703 (56.1) | 397156 (51.5) | 0.0014 |
| Age | 65.1 ± 12.3 | 44.3 ± 17.4 | <.0001 | 65.9 ± 12.2 | 45.1 ± 17.5 | <.0001 |

### Area

| Urban Area | 212 (29.9) | 202929 (31.0) | <.02 | 357 (28.6) | 236290 (31.7) | 0.0002 |
| Metro Area | 195 (27.5) | 189394 (28.9) | 0.046 | 346 (27.7) | 222360 (29.1) | <.0001 |
| Suburban Area | 220 (31.1) | 207883 (31.8) | 0.0011 | 400 (32.0) | 242374 (31.7) | <.0001 |
| Countryside Area | 81 (11.4) | 54300 (8.3) | 0.0001 | 147 (11.8) | 64496 (8.4) | <.0001 |

### Insurance premium level

| Dependent | 55 (7.8) | 33719 (5.1) | <.001 | 106 (8.5) | 39484 (5.1) | <.0001 |
| < 666 USD | 211 (29.7) | 164281 (24.9) | 0.0011 | 391 (31.2) | 185753 (24.1) | <.0001 |
| 666-1331 USD | 308 (43.4) | 292151 (44.3) | 0.0001 | 557 (44.4) | 345439 (44.8) | <.0001 |
| > = 1331 USD | 136 (19.2) | 168930 (25.6) | 0.0001 | 200 (16.0) | 199861 (25.9) | <.0001 |

### Comorbidity score

| Comorbidity score | 0.52 ± 1.42 | 0.1 ± 0.57 | <.0001 | 0.65 ± 1.47 | 0.13 ± 0.65 | <.0001 |

### Baseline comorbidities

| Diabetes | 202 (28.5) | 30904 (4.7) | <.0001 | 381 (28.5) | 43487 (5.6) | <.0001 |
| Disease related to use of alcohol | 14 (1.9) | 4736 (0.7) | <.0001 | 23 (1.8) | 6532 (0.9) | <.0001 |
| Disease related to use of tobacco | 8 (1.1) | 2948 (0.5) | 0.0011 | 13 (1.0) | 3930 (0.5) | 0.007 |
| Psychiatric disorder | 141 (19.9) | 40667 (6.2) | <.0001 | 329 (26.2) | 60376 (7.8) | <.0001 |
| Neurologic disorder and spinal cord injury | 28 (3.9) | 5537 (0.8) | <.0001 | 58 (4.6) | 7814 (1.0) | <.0001 |
| Immunocompromised states | 64 (9.0) | 13871 (2.1) | <.0001 | 128 (10.2) | 20766 (2.7) | <.0001 |
| Cancer (excluding GI cancer) | 32 (4.5) | 9869 (1.4) | <.0001 | 66 (5.3) | 14818 (1.9) | <.0001 |
| Congenital renal disease and acquired renal disease | 37 (5.2) | 5873 (0.9) | <.0001 | 92 (7.3) | 8888 (1.2) | <.0001 |
| Renal failure and hemodialysis | 42 (5.9) | 3619 (0.6) | <.0001 | 93 (7.4) | 5717 (0.7) | <.0001 |
| Benign prostatic hyperplasia | 87 (12.3) | 9034 (1.4) | <.0001 | 177 (14.1) | 14333 (1.9) | <.0001 |
| Anemia | 27 (3.8) | 9180 (1.4) | <.0001 | 69 (5.5) | 14044 (1.8) | <.0001 |
| Bed-ridden status | 11 (1.6) | 3538 (0.5) | <.0001 | 25 (1.9) | 5030 (0.6) | <.0001 |
| Aortic dissection and aortic aneurysm | 0 | 197 (0.0) | 0.64 | 1 (0.1) | 279 (0.1) | 0.64 |
| Obesity, diagnosed, not morbid | 5 (0.7) | 1356 (0.2) | <.0001 | 6 (0.5) | 1733 (0.2) | <.0001 |
| Malnutrition and postgastric surgery | 6 (0.9) | 1298 (0.2) | <.0001 | 14 (1.1) | 2249 (0.3) | <.0001 |
| Amputation | 0 | 46 (0.02) | <.0001 | 0 | 65 (0.01) | <.0001 |
| Chronic liver disease and cirrhosis | 86 (12.1) | 28279 (4.3) | <.0001 | 179 (14.3) | 43355 (5.6) | <.0001 |
| Organ transplant | 0 | 140 (0.0) | 0.69 | 1 (0.1) | 196 (0.0) | 0.22 |
| Serious neuromuscular | 3 | 499 (0.1) | 0.001 | 4 (0.3) | 688 (0.1) | 0.006 |

### Gastrointestinal Risk factors

| Appendicitis | 1 (0.1) | 878 (0.1) | 0.96 | 23 (1.8) | 6532 (0.9) | 0.41 |
| Colorectal cancer | 8 (1.1) | 1381 (0.2) | <.0001 | 13 (1.0) | 3930 (0.5) | <.0001 |
| Esophageal cancer | 0 | 96 (0.0) | 0.74 | 329 (26.2) | 60376 (7.8) | 0.19 |
| Stomach cancer (also called gastric cancer) | 2 (0.3) | 282 (0.0) | 0.0022 | 58 (4.6) | 7814 (1.0) | <.0001 |
| Inflammatory Bowel Disease (chronic) | 6 (0.9) | 3478 (0.5) | 0.24 | 128 (10.2) | 20766 (2.7) | <.0001 |
| Ulcerative Enterocolitis | 1 (0.1) | 237 (0.0) | 0.14 | 66 (5.3) | 14818 (1.9) | 0.62 |
| Superior mesenteric artery syndrome | 0 | 6 (0.0) | 0.93 | 92 (7.3) | 8888 (1.2) | 0.89 |
| Trauma (as exclusion for the intestinal perforation at the same time) | 58 (8.2) | 35034 (5.3) | 0.0007 | 93 (7.4) | 5717 (0.7) | <.0001 |
| Crushing Injury | 4 (0.6) | 2807 (0.4) | 0.57 | 177 (14.1) | 14333 (1.9) | 0.03 |
| Ascaris | 0 | 108 (0.0) | 0.73 | 69 (5.5) | 14044 (1.8) | 0.12 |

Continued
Outcome- GI perforation. The association between nicorandil therapy and GI perforation is summarized in Tables 2 and 3. GI perforation was classified as either upper GI (gastric) perforation or lower GI (small or large intestinal) perforation. There are more outcomes of upper GI perforation (N = 19) as compared to lower GI perforation (N = 1).

### Table 1. Participant Enrollment and Baseline Characteristics.

|                          | Cohort 1: GI ulcer | Cohort 2: GI perforation |
|--------------------------|--------------------|--------------------------|
|                          | Nicorandil User (N = 710) | Non-user (N = 659,081) | P-value | Nicorandil User (N = 1254) | Non-user (N = 770,537) | P-value |
| Typhoid fever (acute)    | 0                  | 23 (0.0)                | 0.87     | 25 (1.9)                   | 5030 (0.6)                | 0.83     |
| Respiratory comorbidities|                    |                         |          |                            |                          |          |
| Chronic obstructive pulmonary disease (COPD) | 99 (13.9) | 16225 (2.5) | <.0001 | 217 (17.3)                   | 24935 (3.2)                | <.0001 |
| Asthma                   | 56 (7.9)           | 12617 (1.9)             | <.0001   | 115 (9.2)                   | 18204 (2.4)                | <.0001 |
| Pulmonary heart disease  | 3 (0.4)            | 308 (0.1)               | <.0001   | 7 (0.6)                     | 480 (0.1)                  | <.0001 |
| Cardiovascular comorbidities|                  |                         |          |                            |                          |          |
| Congestive heart failure | 96 (13.5)          | 6077 (0.9)              | <.0001   | 180 (14.4)                  | 9242 (1.2)                 | <.0001 |
| Cerebrovascular disease  | 83 (11.7)          | 10477 (1.6)             | <.0001   | 158 (12.6)                  | 15355 (2.0)                | <.0001 |
| Myocardial infarction/acute coronary syndromes | 22 (3.1) | 1087 (0.2) | <.0001 | 45 (3.6)                     | 15588 (0.2)                | <.0001 |
| Stroke or transient ischemic attack | 39 (5.5) | 5017 (0.8) | <.0001 | 72 (5.7)                    | 7501 (0.9)                 | <.0001 |
| Peripheral arterial disease | 16 (2.3) | 2075 (0.3) | <.0001 | 27 (2.2)                    | 3180 (0.4)                 | <.0001 |
| Angina                   | 84 (11.8)          | 4592 (0.7)              | <.0001   | 180 (14.4)                  | 7343 (0.9)                 | <.0001 |
| Other ischemic heart disease | 238 (33.5) | 14647 (2.2) | <.0001 | 450 (35.9)                  | 22766 (2.9)                | <.0001 |
| Cerebral atherosclerosis | 11 (1.6)           | 1041 (0.2)              | <.0001   | 19 (1.5)                    | 1674 (0.2)                 | <.0001 |
| Cardiac valve disease    | 29 (4.1)           | 4924 (0.8)              | <.0001   | 67 (5.3)                    | 7236 (0.9)                 | <.0001 |
| Conduction disorder      | 5 (0.7)            | 337 (0.1)               | <.0001   | 8 (0.6)                     | 521 (0.1)                  | <.0001 |
| Arrhythmia               | 89 (12.5)          | 10001 (1.5)             | <.0001   | 183 (14.6)                  | 14955 (1.9)                | <.0001 |
| Hypertension             | 349 (49.2)         | 56224 (8.5)             | <.0001   | 660 (52.6)                  | 78657 (10.2)               | <.0001 |
| Hyperlipidemia           | 173 (23.4)         | 31328 (4.8)             | <.0001   | 337 (26.9)                  | 44519 (5.8)                | <.0001 |
| CV congenital anomalies (CA) | 0               | 35 (0.01)               | 0.84     | 1 (0.1)                     | 44 (0.0)                   | <.0001 |
| Baseline musculoskeletal comorbidities |              |                         |          |                            |                          |          |
| Ankylosing spondylitis   | 8 (1.1)            | 1931 (0.3)              | <.0001   | 13 (1.0)                    | 2774 (0.4)                 | <.0001 |
| Congenital musculoskeletal anomalies | 0 | 1 | 0.97 | 0 | 1 | 0.97 |
| Gouty arthritis          | 91 (12.8)          | 19500 (2.9)             | <.0001   | 173 (13.8)                  | 27022 (3.5)                | <.0001 |
| Arthropathy associated with systemic disorders | 253 (35.6) | 66198 (10.0) | <.0001 | 502 (40.0)                  | 94417 (12.3)               | <.0001 |
| Healthcare Service Utilization |            |                         |          |                            |                          |          |
| Number of OPD visit      | 30.7 ± 22.2        | 11.5 ± 13.8             | <.0001   | 30.6 ± 22.1                 | 11.5 ± 13.8                | <.0001 |
| Number of emergency department visit | 0.42 ± 1.10 | 0.11 ± 0.52 | <.0001 | 0.42 ± 1.13 | 0.11 ± 0.52 | <.0001 |
| Number of hospitalization| 0.47 ± 1.06        | 0.11 ± 0.51             | <.0001   | 0.48 ± 1.06                 | 0.11 ± 0.51                | <.0001 |
| Medication               |                    |                         |          |                            |                          |          |
| NSAIDs                   | 319 (44.9)         | 125692 (19.1)           | <.0001   | 629 (50.2)                  | 169687 (22.0)              | <.0001 |
| Aspirin                  | 295 (41.6)         | 25270 (3.8)             | <.0001   | 523 (41.7)                  | 36556 (4.7)                | <.0001 |
| Systemic immunosuppressive agents and biologics | 0 | 422 (0.06) | 0.50 | 1 (0.1) | 579 (0.1) | 0.95 |
| Systemic corticosteroids | 113 (15.9)         | 34786 (5.3)             | <.0001   | 219 (17.5)                  | 48200 (6.3)                | <.0001 |
| DMARDs                   | 4 (0.6)            | 4774 (0.7)              | 0.61     | 10 (0.8)                    | 6122 (0.8)                 | 0.99     |
| Statin                   | 131 (18.5)         | 15719 (2.4)             | <.0001   | 260 (20.7)                  | 22385 (2.9)                | <.0001 |
| ACE inhibitors           | 146 (20.6)         | 20466 (3.1)             | <.0001   | 276 (22.0)                  | 28890 (3.8)                | <.0001 |
| Oral hypoglycemic        | 156 (21.9)         | 23220 (3.5)             | <.0001   | 309 (24.6)                  | 32074 (4.2)                | <.0001 |
| Antipsychotic            | 81 (11.4)          | 19433 (2.9)             | <.0001   | 205 (16.4)                  | 29368 (3.8)                | <.0001 |
| Antidepressants          | 1 (0.1)            | 1890 (0.3)              | 0.46     | 6 (0.5)                     | 2439 (0.3)                 | 0.31     |
The crude incidence of upper GI perforation was higher in nicorandil users (1.5%) as compared to nonusers (0.2%) and PS matched non-users (1.2%). There was no significant difference in the crude incidence of lower GI perforation between nicorandil users (0.08%) and PS matched non-users (0.08%).

Unadjusted analysis showed that nicorandil therapy was associated with an increased risk of overall GI perforation (HR, 3.82; 95%CI, 2.46–5.93). PS adjustment decreased the effect size (HR, 1.60, 1.02–2.51), and PS matching further attenuates the effect (HR 1.25, 0.65–2.42). The effect estimates associated with the upper gastric perforation was very similar to the effect estimates obtained for overall GI perforation. Although the effect was not significant, we detected a 68% higher risk of lower GI perforation among the nicorandil treated anginal patients (PS-adjusted HR 1.68, 0.23–12.3).

Time-varying risk analysis. To describe the time-varying nature of nicorandil associated ulceration/perforation risk, we draw a hazard function plot over the three year follow-up period (Fig. 1). We found that the cumulative hazard increased at a faster rate for nicorandil users than nonusers for both the GI ulceration (Fig. 1A) and GI perforation (Fig. 1B) events. There was no apparent sign of the cumulative hazard plateauing for both nicorandil users and nonusers for both the GI ulcer/perforation cohort. To remove the confounding effect, we further plotted the cumulative hazard over time for 1:1 PS-matched cohort (Fig. 1 right panel). For GI ulceration, the cumulative hazard is consistently higher than PS matched nonusers. For GI perforation, the cumulative hazard was higher for nicorandil users in the first 800 days after exposure, and there is a trend toward undifferentiated risk between users and PS matched nonusers after 800 days (Fig. 1B right panel).

Subgroup analysis. To investigate whether there is a differential risk among different populations, we performed analyses on pre-defined age and gender subgroups (Table 4). The interaction term did not reach statistical significance (p-value < 0.05) for any of the subgroups. Compared with non-nicorandil user, the association between GI ulceration/perforation and use of nicorandil was consistent across the subgroups within their cohort. The only exception is the >75 years of age subgroup in the GI perforation cohort, which has a lower risk of GI perforation.

### Table 2. Gastrointestinal ulceration and perforation outcomes in users and nonusers of nicorandil. In the matched cohort, we were unable to find a non-user with ulceration of large intestine and anus.

|                          | Nicorandil User (N = 710) | Non-user (N = 659,081) | Matched Non-user (N = 708) |
|--------------------------|---------------------------|------------------------|-----------------------------|
| Ulceration of esophagus, stomach and small intestine | 181 (25.5%) | 60,126 (9.1%) | 134 (18.9%) |
| Ulceration of large intestine and anus | 2 (0.3%) | 1,155 (0.2%) | 0* |

### Table 3. Crude and adjusted effect measure for the association between use of Nicorandil and risk of incident gastrointestinal ulcer and perforation. HR refers to hazard ratio *refers to p < 0.05, **refers to p < 0.01, and ***refers to p < 0.001.

|                          | Crude effect estimate (HR, 95% confidence interval) | Propensity score adjusted (HR, 95% confidence interval) | Propensity score matched (HR, 95% confidence interval) |
|--------------------------|----------------------------------------------------|-------------------------------------------------------|-------------------------------------------------------|
| Overall gastrointestinal ulceration | 3.10 (2.68–3.59)*** | 1.43 (1.23–1.65)*** | 1.41 (1.13–1.76)*** |
| Ulceration of esophagus, stomach and small intestine | 3.13 (2.70–3.62)*** | 1.43 (1.23–1.66)*** | 1.40 (1.12–1.75)*** |
| Ulceration of large intestine and anus | 1.31 (0.18–9.28) | 1.11 (0.15–8.00) | NA |
| Overall gastrointestinal perforation | 3.82 (2.46–5.93)*** | 1.60 (1.02–2.51)* | 1.25 (0.65–2.42) |
| Gastric perforation | 3.78 (2.41–5.93)*** | 1.61 (1.02–2.55)* | 1.27 (0.65–2.50) |
| Small or large intestinal perforation | 6.22 (0.87–44.6) | 1.68 (0.23–12.3) | 1.00 (0.06–16.0) |
**A. Gastrointestinal ulceration cumulative hazard plots**

![Cumulative hazard plots for gastrointestinal ulceration](image)

**B. Gastrointestinal perforation cumulative hazard plots.**

![Cumulative hazard plots for gastrointestinal perforation](image)

Figure 1. Cumulative hazard plots for gastrointestinal ulceration (A) and gastrointestinal perforation (B). All the left panels display the combined cumulative hazard of all the nicorandil non-users. In the right panels, only the cumulative hazard of the propensity score matched nicorandil non-users are displayed. The p-values were calculated by log-rank test.

|                  | Patient subgroups | Propensity score adjusted HR (95% Confidence interval) | Interaction term P-value |
|------------------|-------------------|--------------------------------------------------------|--------------------------|
| Gastrointestinal ulcer |                   |                                                        |                          |
|                   | >75 years of age   | 1.54 (1.12–2.12)**                                    | 0.42                     |
|                   | <=75 years of age  | 1.42 (1.20–1.67)***                                   |                          |
|                   | Male               | 1.37 (1.11–1.68)**                                    | 0.40                     |
|                   | Female             | 1.46 (1.18–1.80)***                                   |                          |
| Gastrointestinal perforation |               |                                                        |                          |
|                   | >75 years of age   | 1.19 (0.44–3.21)                                      | 0.34                     |
|                   | <=75 years of age  | 1.78 (1.08–2.94)*                                     |                          |
|                   | Male               | 1.66 (0.91–3.03)                                      | 0.91                     |
|                   | Female             | 1.59 (0.82–3.10)                                      |                          |

Table 4. Effect of Nicorandil participant subgroups on risk of gastrointestinal ulcer and perforation. HR refers to hazard ratio. *refers to p < 0.05, **refers to p < 0.01, and ***refers to p < 0.001.
Discussion

We carried out a population-based study involving one million national representative participants. After adjustment for PS, use of nicorandil was associated with a 1.4 fold increase in risk for GI ulceration and 1.6 fold increase in risk for GI perforation. The risk of for GI ulceration was consistently higher in the entire three year follow-up period, but risk for GI perforation seemed to be higher only in the first 800 days after exposure.

To the best of our knowledge, the risk of GI ulceration/perforation among nicorandil users has not previously been examined in a large general population. Several randomized controlled trials (RCT) have shown nicorandil to be an effective and safe drug in relieving angina symptoms\(^{20-29,39}\). These RCTs, however, did not associate mucosal and cutaneous ulcerations with nicorandil treatment. The adverse effects of GI ulceration/perforation may be undetected in RCTs if ulceration was not listed as one of the actively surveyed safety endpoints. In addition, most RCTs have a small sample size and exclude elderly patients with multiple comorbidities\(^{40,41}\). It was not until the first case report in 1997 that nicorandil treatment was suspected to cause oral ulcers\(^{13,12}\). Since then, many case reports of nicorandil induced GI ulcerations and GI perforations associated with elderly patients have been published\(^{11,12,13,32-44}\). Although the increased incidence of GI ulceration/perforation in patients treated with nicorandil must be validated in other cohorts, evidences from existing clinical observation provide substantial support for our result.

Currently, the best biological hypothesis on how nicorandil might induce ulceration comes from a single patient study that showed ulceration might result from the increased concentrations of nicorandil metabolites in the edge of a previously injured area\(^{45}\). Since it is extremely difficult to conduct any large scale clinical studies involving injured subjects with use of nicorandil, it is hoped that scientists can use the animal model to decipher the biological mechanism of nicorandil induced GI ulcerations or GI perforation.

Despite the significant risk of nicorandil associated GI ulceration/perforation identified in this study, clinical decision on nicorandil treatment should consider the background incidence of GI ulceration and GI perforation in a similar (PS-matched) population. In this cohort, the observed risk in the nicorandil treated cohort corresponded to 6848 excess cases of GI ulceration and 315 excess cases of GI perforation per 100,000 person years. In other words, if the observed association were causal, there will be one additional case of nicorandil induced GI ulceration in every 15 nicorandil users, and one additional case of nicorandil induced GI perforation in every 317 nicorandil users. Given the high frequency of nicorandil induced GI ulceration and the high mortality associated with GI perforation, physicians should really weigh the overall risk-benefit balance of nicorandil treatment in patients at high risk for GI ulceration/perforation.

Results of study should be interpreted in light of both strengths and limitations. The use of a national representative database ensured minimal risk of selective population and related potential bias. In addition, excluding all existing users and cases from analysis may help to minimize the survivor bias. We constructed a highly discriminative PS (C-statistic, 0.91) and use it for matching users and nonusers, which we believe may greatly alleviate confounding by indication. Confounding by indication may have arisen if nicorandil was prescribed for patients at increased risk for GI ulceration/perforation.

Our study also bears some limitations. First, even though we tried to be as comprehensive as possible in adjusting/matching baseline characteristics, there will always be unmeasured confounders. Since we were studying on a claims database, many life style factors such as alcohol drinking and smoking are missing. Both of these factors pose an increase in risk for GI ulceration and GI perforation\(^{46-50}\). We used alcohol- or smoking-related diseases as a proxy for confounding adjustment; nevertheless, we cannot totally exclude the possibility of residual confounding. Secondly, we also cannot rule out the possibility of exposure misclassification. The claims database had no record on whether nicorandil was actually taken by patients. Non-compliance with nicorandil could result in misclassification of non-users to users, but could not misclassified users to non-users. Finally, an even larger study population will be required for answering whether use of nicorandil has differential effect on different parts of the GI system.

This study based on more than 600,000 randomly selected patients found a 43% increase in risk of GI ulceration and a 60% increase in the risk of GI perforation in nicorandil treated patients. The augmented risk of GI complications adds significantly to existing evidence. Given the high mortality and morbidity associated with GI complications, these findings may warn the clinicians to weigh the overall risk-benefit balance of nicorandil treatment in patients at high risk for GI ulceration or perforation.

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Author Contributions

C.-C.L. study design, data management, statistics, wrote first and final draft, and research funding. S.-S.C. statistics, data management, reviewed and approved final draft. S.-H.L statistics, data management and reviewed final draft. Y.-S.C. wrote the introduction section of the first draft. W.-T.H. reviewed final draft. M.-T.L. reviewed and approved final draft.

Additional Information

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