Increased the risk of heart failure and comorbidities in patients with gout treatment: a population-based cohort study

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Background: To investigate the association between gout treatment and heart failure (HF).

Methods: Patients with gout between 2000 and 2010 constituted the gout cohort. The main outcome was a new diagnosis of HF. Multivariable Cox proportional hazard regression models were used to measure the effect of gout on the risk of developing HF. The Kaplan-Meier method was used to estimate the cumulative HF incidence curve for the gout and nongout cohorts.

Results: The cohort study included 50,166 patients with gout. The incidence of HF was 1.96 times higher in the gout cohort than the non-gout cohort (7.11 vs. 3.63 per 10,000 person-years). The adjusted HR of developing HF was a 1.06-fold increase (95% CI: 1.06–1.07) with age and a 1.08-fold increase for women compared with men (95% CI: 1.02–1.14). HF incidence was higher in patients with receiving any two or more types of anti-gout drug treatment.

Conclusions: Our study revealed that gout could increase the risk of HF. Gout treatment in Taiwan cannot improve HF and actually increase the risk for HF after combination therapy for gout. The public health burden of gout should be resolved in the future.

Keywords: Gout treatment; heart failure (HF); cohort study

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Introduction

Because of its unique geographical and racial distribution, the rate of hyperuricemia is high in Taiwan, with a prevalence of 43.7% in men and 27.4% in women (1). Many studies have suggested that hyperuricemia is an independent risk factor for cardiovascular morbidity and mortality (2-4). According to nutritional and health surveys in Taiwan, research, including that on medical history, physical activity, food frequency, and fasting blood parameters,
has revealed that the uric acid levels and prevalence of hyperuricemia decreased in 1993–1996 and 2005–2008 but not the prevalence of gout (5). Although the nature of the relationship between gout and cardiovascular disease (CVD) remains unclear due to shared risk factors, such as diabetes, metabolic syndrome, and obesity (6–8), several epidemiologic reports concerning populations in America or Asia have mentioned that gout has an independent role in CVD (9–11). One review article suggested that patients with HF also suffered from hyperuricemia and gout (12). A case-control study showed the occurrence of gouty arthritis in HF patients (13). The Cameroon HF study revealed gout was one of the co-morbidities around 16.4% of HF subjects (14). HF is an important public health problem that affects an estimated 26 million individuals and results in more than 1 million hospitalizations each year. HF also causes an enormous economic burden worldwide (15). The Framingham Offspring Study suggested that hyperuricemia was an independent predictor for HF, and the other cohort also confirmed the relationship between serum uric acid and HF hospitalization in both sexes (16,17). Because of limited studies on the association between gout treatment and HF (7,18,19), we designed the present study to investigate the association between gout treatment and HF.

Methods

Data source

The National Health Insurance (NHI) program was launched in 1995 and has since covered over 99% of the 23.74 million people residing in Taiwan (http://www.nhi.gov.tw/english/index.aspx). We obtained data files of electronic claims from the Longitudinal Health Insurance Database (LHID), which contains the claims data of 1 million people randomly selected from the insured population. The LHID makes available linked data from 1996 to 2011 for every insurant in the NHI program. The identification numbers of all patients and their reimbursement data from the LHID are encrypted to protect their privacy. Diseases in the claims data were coded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). This study was exempted from a full ethical review by China Medical University and Hospital Research Ethics Committee (IRB permit number: CMUH104-REC2-115-R4).

Sampled participants

Patients 20 years of age and older who were newly diagnosed with gout (ICD-9-CM code 274) between 2000 and 2010 constituted the gout cohort. The index date for the patients was the date of their first medical visit for gout. Patients who were diagnosed with HF (ICD-9-CM code 428) at baseline or who were missing information were excluded. The nongout control cohort consisted of patients randomly selected from the LHID without a history of gout. For each gout case, we randomly selected two control persons through frequency matching based on sex, age (5-year periods), and year of index date. The same exclusion criteria were also applied to the nongout controls.

Outcome

The main outcome was outpatient visits or hospitalization with a new diagnosis of HF during the follow-up period. Both cohorts were followed from the index date until diagnosis with HF, withdrawal from the NHI program, or the end date of December 31, 2011.

Comorbidities and medications

The baseline comorbidities and medications considered in this study were diabetes (ICD-9-CM code 250), hypertension (ICD-9-CM codes 401–405), hyperlipidemia (ICD-9-CM code 272), chronic kidney disease (ICD-9-CM 580–589), stroke (ICD-9-CM codes 430–438), chronic obstructive pulmonary disease (ICD-9-CM codes 491, 492, 496), asthma (ICD-9-CM code 493), alcohol-related illness (ICD-9-CM codes 291, 303, 305, 571.0, 571.1, 571.2, 571.3), coronary artery disease (ICD-9-CM codes 410–414), prednisolone, and nonsteroid anti-inflammatory drugs (NSAIDs). We hypothesized that antigout drugs, including allopurinol, benz bromarone, probenecid, sulfapyrazine, and colchicine, have different effects on HF in patients with gout.

Statistical analysis

We first compared the distributions of age (≤34, 35–49, 50–64, and 65+ years), sex, comorbidities, and medications between patients with and without gout using a chi-square test for the categorical variables and a t-test for the
Table 1 Demographic characteristics and comorbidities in cohorts with and without gout

| Variable                      | No, N=100,332 | Yes, N=50,166 | P value |
|-------------------------------|---------------|---------------|---------|
| Age, year                     |               |               | 0.99    |
| ≤34, n (%)                    | 18,224 (18.2) | 9,112 (18.2)  |         |
| 35–49, n (%)                  | 30,504 (30.4) | 15,252 (30.4) |         |
| 50–64, n (%)                  | 28,758 (28.7) | 14,379 (28.7) |         |
| 65+, n (%)                    | 22,846 (22.8) | 11,423 (22.8) |         |
| Mean ± SD†                    | 50.6±16.4     | 51.2±16.2     | <0.001  |
| Sex, n (%)                    |               |               | 0.99    |
| Female                        | 26,752 (26.7) | 13,376 (26.7) |         |
| Male                          | 73,580 (73.3) | 36,790 (73.3) |         |
| Comorbidity, n (%)            |               |               |         |
| Diabetes                      | 6,545 (6.52)  | 5,231 (10.4)  | <0.001  |
| Hypertension                  | 22,945 (22.9) | 21,582 (43.0) | <0.001  |
| Hyperlipidemia                | 11,425 (11.4) | 17,480 (34.8) | <0.001  |
| Chronic kidney disease        | 4,167 (4.15)  | 5,005 (9.98)  | <0.001  |
| Stroke                        | 2,889 (2.88)  | 1,673 (3.33)  | <0.001  |
| Chronic obstructive pulmonary diseases | 7,746 (7.72) | 5,408 (10.8) | <0.001  |
| Asthma                        | 4,203 (4.19)  | 3,306 (6.59)  | <0.001  |
| Alcohol-related illness       | 6,492 (6.47)  | 5,438 (10.8)  | <0.001  |
| Coronary artery disease       | 10,143 (10.1) | 8,911 (17.8)  | <0.001  |
| Medication, n (%)             |               |               |         |
| Prednisolone                  | 4,984 (4.97)  | 3,982 (7.94)  | <0.001  |
| NSAID                         | 32,009 (31.9) | 27,123 (54.1) | <0.001  |

Chi-square test: †, t-test. NSAID, nonsteroid anti-inflammatory drug.

Results

The cohort study included 50,166 patients with gout and 100,332 patients without gout. Table 1 shows the baseline demographic data, comorbidities, and medications of the continuous variables. The follow-up person-years were used to estimate the incidence density for each cohort. Univariable and multivariable Cox proportional hazard regression models were used to measure the effect of gout on the risk of developing HF. The multivariable models were simultaneously adjusted for age; sex; and the comorbidities of diabetes, hypertension, hyperlipidemia, chronic kidney disease, stroke, chronic obstructive pulmonary disease, asthma, alcohol-related illness, and coronary artery disease; and the medications of prednisolone and NSAIDs. The hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using the Cox model. Further analysis was performed to assess whether antigout drug treatment played a role in the HF outcomes. The Kaplan–Meier method was used to estimate the cumulative HF incidence curve for the gout and nongout cohorts, and the log-rank test was conducted to determine the difference in these curves. All analyses were performed using SAS (version 9.3; SAS Institute Inc., Cary, NC, USA). A two-tailed P value <0.05 was considered statistically significant.
Figure 1 Cumulative incidence comparison of heart failure for patients with (dashed line) or without (solid line) gout disease.

cohorts. Most patients were ≥50 years of age (51.5%) and men (73.3%). The mean ages of the patients in the gout and nongout cohorts were 51.2 (SD =16.2) and 50.6 (SD = 16.4) years, respectively. The patients in the gout cohort were more likely to have comorbidities and medications than those in the nongout cohort (all P values <0.001). During the mean follow-up periods of 7.40 [standard deviation (SD) =3.22] and 7.28 (SD =3.26) years in the gout and nongout cohorts (data not shown), respectively, the cumulative incidence of HF was 3.16% higher among the patients with gout than among those without gout (log-rank P<0.001) by the end of follow-up (Figure 1).

Overall, the incidence densities of HF were 1.96 times higher in the gout cohort than in the nongout cohort (7.11 vs. 3.63 per 10,000 person-years), with an adjusted HR of 1.57 (95% CI: 1.49–1.67; Table 2). The age-specific incidence of HF increased with age in both cohorts. The age-specific gout cohort to nongout cohort adjusted HR of HF was significantly higher for all age groups. Within both cohorts, a higher incidence of HF occurred among women than among men. The comorbidity-specific adjusted HR of HF indicated that the gout cohort had higher risk than patients in the nongout cohort both without a comorbidity (HR =2.15, 95% CI: 1.85–2.51) and with comorbidity (HR =1.54, 95% CI: 1.28–1.85). In both cohorts, those receiving prednisolone or NSAID treatment displayed a higher incidence of HF than did those without prednisolone or NSAID treatment.

Table 3 shows the rates of gout and the other risk factors for HF in the study participants. The adjusted HR of developing HF was a 1.06-fold increase (95% CI: 1.06–1.07) with age (every 1 year) and a 1.08-fold increase for women compared with men (95% CI: 1.02–1.14). As expected, patients with diabetes, hypertension, hyperlipidemia, chronic kidney disease, stroke, chronic obstructive pulmonary disease, asthma, alcohol-related illness, and coronary artery disease were more likely to have HF.

Table 4 shows the analysis of treatment associated with HF risk among gout patients. Compared with gout patients who did not receive any treatment, gout patients who received any two or more types of anti-gout drugs exhibited a significantly higher risk for HF (adjusted HR =1.64, 95% CI: 1.46–1.85).

The risk of HF were 1.82 times higher in the gout cohort than in the nongout cohort among women patients age <50 years (adjusted HR =1.82, 95% CI: 1.15–2.87) (Table 5). The risk of HF were 1.56 times higher in the gout cohort than in the nongout cohort among women patients age >50 years (adjusted HR =1.56, 95% CI: 1.42–1.72).

Table 6 presented the risk of HF among different drug exposure (cumulative exposure dose). Relative to the prednisolone non-users, the risk of HF was significantly associated with decreased risk in higher prednisolone exposure. The results also demonstrated, compared with NSAID non-users, HRs of HF risk was 0.53 (95% CI: 0.35–0.81) for NSAID users with >28,500 mg exposure. The HF risk were still significantly associated with higher risk for ULTs users >1,200 mg compared with ULTs non-users (adjusted HR =1.13, 95% CI: 1.05–1.20) and for ULTs users ≤1,200 mg compared with ULTs non-users (adjusted HR =1.93, 95% CI: 1.63–2.27).

Discussion

Gout and HF

Outside of Europe and America (20,21), the highest prevalence of gout is in Taiwan (1,22). Our analysis showed the same results as those of previous studies conducted in Taiwan regarding the higher prevalence of gout in men than women (23). A higher HF rate was also noted in our gout group. One Crystal-proven Gout study showed the analysis of relationship between gout and other 8 different CVD. Except transient ischemic attack, significant higher prevalence of other CVD including HF around 14% was noted (24). However, we found that females with gout were more at risk for HF than were males were gout,
Table 2 Incidence of heart failure by sex, age, comorbidity and medication and Cox model measured hazards ratio for patients with gout compared those without gout

| Variables       | Gout          |                 | Gout to non-gout |                 |
|-----------------|---------------|-----------------|------------------|-----------------|
|                 | No            | Yes             |                  |                 |
|                 | Event PY Rate | Event PY Rate   | Crude HR (95% CI)| Adjusted HR (95% CI) |
| All             | 2,652 730,327 3.63 | 2,637 371,006 7.11 | 1.96 (1.86, 2.07)*** | 1.57 (1.49, 1.67)*** |
| Stratify age    |               |                 |                  |                 |
| ≤34             | 26 136,815 0.19 | 62 70,424 0.88  | 4.61 (2.91, 7.28)*** | 2.84 (1.73, 4.67)*** |
| 35–49           | 200 239,297 0.84 | 278 121,706 2.28 | 2.73 (2.28, 3.27)*** | 1.80 (1.47, 2.20)*** |
| 50–64           | 702 212,356 3.31 | 746 106,272 7.02  | 2.13 (1.92, 2.36)*** | 1.54 (1.38, 1.73)*** |
| 65+             | 1,724 141,860 12.2 | 1,551 72,604 21.4 | 1.76 (1.64, 1.89)*** | 1.53 (1.42, 1.65)*** |
| Sex             |               |                 |                  |                 |
| Female          | 1,009 193,190 5.22 | 1,026 96,189 10.7 | 2.04 (1.87, 2.23)*** | 1.59 (1.45, 1.74)*** |
| Male            | 1,643 537,137 3.06 | 1,611 274,818 5.86 | 1.92 (1.79, 2.06)*** | 1.56 (1.45, 1.68)*** |
| Comorbidity†    |               |                 |                  |                 |
| No              | 589 463,965 1.27 | 252 128,576 1.96  | 1.54 (1.33, 1.79)*** | 2.15 (1.85, 2.51)*** |
| Yes             | 2,063 266,362 7.75 | 2,385 242,431 9.84 | 1.28 (1.21, 1.36)*** | 1.54 (1.45, 1.63)*** |
| Medication      |               |                 |                  |                 |
| Prednisolone    |               |                 |                  |                 |
| No              | 2,443 701,120 3.48 | 2,342 345,993 6.77 | 1.95 (1.84, 2.06)*** | 1.57 (1.48, 1.67)*** |
| Yes             | 209 29,208 7.16  | 295 25,013 11.8  | 1.66 (1.39, 1.98)*** | 1.54 (1.28, 1.85)*** |
| NSAID           |               |                 |                  |                 |
| No              | 1,502 526,980 2.85 | 963 180,626 5.33  | 1.87 (1.73, 2.03)*** | 1.55 (1.42, 1.69)*** |
| Yes             | 1,150 203,348 5.66 | 1,674 190,380 8.79 | 1.57 (1.46, 1.70)*** | 1.57 (1.45, 1.70)*** |

Rate, incidence rate, per 10,000 person-years; crude HR*, relative hazard ratio; adjusted HR†, multivariable analysis including age, sex, and comorbidities of diabetes, hypertension, hyperlipidemia, chronic kidney disease, stroke, chronic obstructive pulmonary diseases, asthma, alcohol-related illness, and coronary artery disease and medication of prednisolone and NSAID. †, patients with any one of the comorbidities (diabetes, hypertension, hyperlipidemia, chronic kidney disease, stroke, chronic obstructive pulmonary diseases, asthma, alcohol-related illness, and coronary artery disease) were classified as the comorbidity group. ***P<0.001. NSAID, nonsteroid anti-inflammatory drug.

which is different from other studies that have identified a relationship between high renal excretion of urate and plasma estrogen in women with gout (25,26). In our analysis, the age of women was not the confounder for HF showed in Table 5. In our opinion, different race or gene might be the possible explanation. In the Framingham Offspring Study, gout was associated with poor cardiac pump function, resulting in clinical HF. Myocardial systolic dysfunction was noted in the follow-up analysis and caused elevated mortality in subjects with gout and HF. A higher incidence rate of HF was associated with older age in our study, which confirmed the results of the Quebec study (27). One basic research mentioned gout is also associated with a shorter telomere length which is associated with ageing and therefore with more cardiovascular diseases such as HF (28).

**Gout treatment and HF**

**Prednisolone and NSAIDs**

Gout is a low-grade chronic inflammatory condition that
### Table 3 Cox model with hazard ratios and 95% confidence intervals of heart failure associated with gout and covariates

| Variable                              | Crude* |                | Adjusted† |                |
|---------------------------------------|--------|---------------|-----------|---------------|
|                                       | HR     | (95% CI)      | HR        | (95% CI)      |
| Age, years                            | 1.08   | (1.07, 1.08)** | 1.06      | (1.06, 1.07)*** |
| Sex (female vs. male)                 | 1.75   | (1.66, 1.85)*** | 1.08      | (1.02, 1.14)*** |
| Baseline comorbidities (yes vs. no)   |        |               |           |               |
| Gout                                  | 1.96   | (1.86, 2.07)*** | 1.57      | (1.49, 1.67)*** |
| Diabetes                              | 2.96   | (2.76, 3.18)*** | 1.28      | (1.19, 1.38)*** |
| Hypertension                          | 5.72   | (5.40, 6.06)*** | 1.73      | (1.61, 1.85)*** |
| Hyperlipidemia                        | 2.11   | (1.99, 2.23)*** | 0.89      | (0.83, 0.94)*** |
| Chronic kidney disease                | 3.42   | (3.18, 3.67)*** | 1.34      | (1.25, 1.45)*** |
| Stroke                                | 3.57   | (3.22, 3.95)*** | 1.08      | (0.98, 1.20)   |
| Chronic obstructive pulmonary diseases| 3.67   | (3.44, 3.92)*** | 1.22      | (1.14, 1.31)*** |
| Asthma                                | 3.05   | (2.80, 3.31)*** | 1.31      | (1.19, 1.43)*** |
| Alcohol-related illness               | 1.21   | (1.08, 1.35)*** | 1.21      | (1.08, 1.35)*** |
| Coronary artery disease               | 5.22   | (4.94, 5.51)*** | 1.69      | (1.59, 1.80)*** |
| Medication                            |        |               |           |               |
| Prednisolone                          | 2.00   | (1.83, 2.20)*** | 0.93      | (0.88, 0.99)*  |
| NSAID                                 | 2.04   | (1.93, 2.15)*** | 0.96      | (0.87, 1.05)   |

Crude HR*, relative hazard ratio; adjusted HR†, multivariable analysis including age, sex and comorbidities of diabetes, hypertension, hyperlipidemia, chronic kidney disease, stroke, chronic obstructive pulmonary diseases, asthma, alcohol-related illness, and coronary artery disease and medication of prednisolone and NSAID. *P<0.05, **P<0.01, ***P<0.001. NSAID, nonsteroid anti-inflammatory drug.

### Table 4 Cox proportional hazards regression analysis measured hazard ratio of heart failure among gout patients by treatment

| Variables                        | Event | PY     | Rate⁶ | Crude HR* (95% CI) | Adjusted HR† (95% CI) |
|----------------------------------|-------|--------|-------|---------------------|-----------------------|
| Gout                             |       |        |       |                     |                       |
| Without treatment                | 329   | 60,384 | 5.45  | 1 (reference)       | 1 (reference)         |
| With treatment                   |       |        |       |                     |                       |
| Only allopurinol                 | 41    | 5,423  | 7.56  | 1.40 (1.01, 1.93)*  | 0.97 (0.70, 1.35)     |
| Only benzbromarone               | 270   | 38,057 | 7.09  | 1.32 (1.12, 1.55)***| 1.09 (0.93, 1.28)     |
| Only probenecid                  | 2     | 268    | 7.46  | 1.38 (0.34, 5.54)   | 1.40 (0.35, 5.64)     |
| Only sulfinpyrazone              | 9     | 1,060  | 8.49  | 1.53 (0.79, 2.97)   | 1.02 (0.53, 1.98)     |
| Only colchicine                  | 407   | 73,268 | 5.55  | 1.02 (0.88, 1.18)   | 1.13 (0.97, 1.31)     |
| Any above medicine               | 1,579 | 192,546| 8.20  | 1.54 (1.37, 1.73)***| 1.64 (1.46, 1.85)***  |

Rate⁶, incidence rate, per 10,000 person-years; crude HR*, relative hazard ratio; adjusted HR†, multiple analysis including age, sex, and comorbidities of diabetes, hypertension, hyperlipidemia, chronic kidney disease, stroke, chronic obstructive pulmonary diseases, asthma, alcohol-related illness, and coronary artery disease and medication of prednisolone and NSAID. *P<0.05, ***P<0.001. PY, person-years.
### Table 5: Cox model with hazard ratios and 95% confidence intervals of heart failure associated with gout and covariates among women

| Variable                          | Women age <50 yrs | Women age ≥50 yrs |
|-----------------------------------|-------------------|-------------------|
|                                   | Crude, HR (95% CI) | Adjusted*, HR (95% CI) | Crude, HR (95% CI) | Adjusted*, HR (95% CI) |
| Gout                              | 4.31 (2.94, 6.33)** | 1.82 (1.15, 2.87)* | 1.96 (1.79, 2.14)*** | 1.56 (1.42, 1.72)*** |
| Age, years                        | 1.09 (1.05, 1.13)** | 1.04 (1.01, 1.08)* | 1.08 (1.06, 1.07)** | 1.06 (1.06, 1.07)** |
| Baseline comorbidities (yes vs. no) |                   |                   |                   |                   |
| Diabetes                          | 7.58 (4.91, 11.7)** | 2.95 (1.84, 4.72)*** | 1.81 (1.62, 2.02)*** | 1.25 (1.12, 1.40)*** |
| Hypertension                      | 7.72 (5.38, 11.1)** | 3.47 (2.26, 5.32)** | 3.15 (2.83, 3.50)** | 1.68 (1.49, 1.89)** |
| Hyperlipidemia                    | 4.31 (3.01, 6.18)** | 1.23 (0.80, 1.88)  | 1.41 (1.29, 1.55)** | 0.90 (0.81, 0.99)*  |
| Chronic kidney disease            | 3.84 (2.33, 6.34)** | 1.54 (0.91, 2.59)  | 2.29 (2.04, 2.56)** | 1.46 (1.30, 1.64)** |
| Stroke                            | 7.08 (2.25, 22.3)** | 1.67 (0.51, 5.40)  | 2.28 (1.94, 2.69)** | 1.15 (0.97, 1.36)  |
| Chronic obstructive pulmonary diseases | 1.25 (0.51, 3.07)  |                   | 1.99 (1.78, 2.23)** | 1.21 (1.07, 1.38)** |
| Asthma                            | 3.52 (2.02, 6.15)** | 2.16 (1.21, 3.86)** | 1.72 (1.50, 1.97)** | 1.22 (1.05, 1.42)** |
| Alcohol-related illness           | 0.50 (0.25, 0.98)*  | 1.12 (0.56, 2.25)  | 0.89 (0.66, 1.19)  | 1.12 (0.83, 1.50)  |
| Coronary artery disease           | 4.78 (3.06, 7.48)** | 1.46 (0.90, 2.36)  | 2.69 (2.45, 2.94)** | 1.56 (1.41, 1.72)** |
| Medication                        |                   |                   |                   |                   |
| Prednisolone                      | 1.54 (0.78, 3.05)  |                   | 1.27 (1.09, 1.48)** | 0.93 (0.79, 1.08)  |
| NSAID                             | 2.10 (1.47, 3.02)** | 1.09 (0.74, 1.60)  | 1.39 (1.26, 1.52)** | 0.93 (0.85, 1.03)  |

Crude HR, relative hazard ratio; *, variables found to be statistically significant in the univariable model were further tested by the multivariable model. *P<0.05, **P<0.01, ***P<0.001. NSAID, nonsteroid anti-inflammatory drug.

### Table 6: Incidence and adjusted hazard ratio of heart failure stratified by cumulative dose of prednisolone, NSAID or ULTs therapy

| Medication exposed | N  | Event | Person-year | Rate* | Adjusted HR† (95% CI)† |
|--------------------|----|-------|-------------|-------|-----------------------|
| Prednisolone       |    |       |             |       |                       |
| Non-prednisolone   | 51,455 | 1,740 | 366,166     | 4.75  | 1.00                  |
| ≤300 mg            | 60,942 | 1,919 | 451,277     | 4.25  | 0.77 (0.73, 0.83)**   |
| >300 mg            | 38,101 | 1,630 | 283,891     | 5.74  | 0.61 (0.56, 0.66)**   |
| NSAID              |    |       |             |       |                       |
| Non-NSAID          | 5,872  | 174   | 37,624      | 4.62  | 1.00                  |
| ≤28,500 mg         | 69,409 | 2,147 | 493,353     | 4.35  | 0.70 (0.60, 0.82)**   |
| >28,500 mg         | 75,217 | 2,968 | 570,357     | 5.20  | 0.45 (0.38, 0.53)**   |
| ULTs               |    |       |             |       |                       |
| Non-ULTs           | 123,162 | 3,945 | 885,551     | 4.45  | 1.00                  |
| ≤1,200 mg          | 2,328  | 146   | 17,510      | 8.34  | 1.93 (1.63, 2.27)**   |
| >1,200 mg          | 25,008 | 1,198 | 198,272     | 6.04  | 1.13 (1.05, 1.20)**   |

* the cumulative dose is partitioned in to 2 segments by median; rate*, incidence rate, per 10,000 person-years; adjusted HR†, multiple analysis including age, sex, and comorbidities of diabetes, hypertension, hyperlipidemia, chronic kidney disease, stroke, chronic obstructive pulmonary diseases, asthma, alcohol-related illness, and coronary artery disease and medication of prednisolone and NSAID. ***P<0.001. PY, person-years; NSAID, nonsteroid anti-inflammatory drug; ULT, urate lowering theraphy.
promotes thrombogenesis or atherogenesis (22,29). In our analysis for prednisolone, a higher HF rate was found in non-prednisolone user and higher dose of prednisolone could decrease the risk of HF which was consistent with the anti-inflammatory function of prednisolone. In our study, both groups with or without steroid use showed the higher HF risk. Insufficient dosage or poor compliance with steroid use might be the reason for this result (30,31). A relatively high HF rate was noted in those using NSAIDs in our study. Although NSAIDs can inhibit the pathway of cyclooxygenase-2 induced by inflammation and are effective for gout treatment. Unfortunately, in healthy subjects, NSAIDs can have a negative effect on renal function (causing sodium and volume retention), may worsen the condition of renal failure in elderly persons, and can increase HF (12,32).

**Colchicine**

Colchicine is a potent anti-inflammatory medication extracted from the autumn crocus that has been used for centuries. Its anti-inflammatory mechanism occurs through the inhibition of microtubule generation and tubulin polymerization. Colchicine could inhibit the inflammatory pathway resulting in the stability of native atherosclerotic plaques. The protein effects of colchicines could inhibit neutrophil chemotaxis and activation within a proinflammatory environment causing to reduce the levels of high sensitivity C-reactive protein (33). One randomized clinical trial of colchicine showed a significantly decreased risk of CVD (34), and others have revealed that colchicine can decrease ischemic cardiovascular events (35). In our analysis of colchicine and HF, gout treatment with colchicine was not found to decrease HF. This might be because of the high dose effect or the other mechanisms of colchicine, such as inhibition of spindle formation and cell division, that constrict blood vessels (12).

**Xanthine oxidase inhibitor**

After myocardial infarction, poor left ventricular remodeling causes the development of HF and myocardial reactive oxygen species (ROS) production, leading to cardiac hypertrophy and dysfunction (36). Xanthine oxidase, a potent enzymatic source of ROS, was demonstrated in HF and shown to promote cardiomyocyte hypertrophy (37). Febuxostat and allopurinol, a xanthine oxidase inhibitor, are usually prescribed for gout treatment. Febuxostat was not analyzed here because during our study period, this type of medicine could not be prescribed in Taiwan. However, one recent publication showed that compared with allopurinol, febuxostat might increase all-cause mortality and cardiovascular mortality (38). Many publications have suggested that long-term use (more than 300 mg/day) of allopurinol reduced cardiovascular hospitalizations and improved cardiovascular mortality (39,40). A study for different dose effect of allopurinol to forearm blood flow showed that higher dose of allopurinol could improve the endothelial function resulting in better myocardial perfusion and improving LV function. This study also mentioned the underlying mechanism for left ventricle remodeling could still be oxidative stress reduction. Different antioxidant effect of allopurinol was dose dependence. Allopurinol also improved endothelial-dependent vasodilatation by 52% compared with probenecid (39). Unfortunately, our results did not indicate improved HF rates. The dose response due to the habit of prescription or the adherence of patients is a possible reason.

**Uricosuric drugs**

These types of medicines, which include benzbromarone, probenecid, and sulfinpyrazone, block renal tubular urate reabsorption at the proximal renal tubule (41). One study showed that compared with allopurinol, probenecid decreased the risk of CVD, including HF exacerbation (42). But one study showed that compare to allopurinol in the same uric acid decreasing, probenecid could not improve endothelial-dependent vasodilatation (39). Probenecid promotes serum uric acid excretion through the kidneys and causes the inhibition of pannexin 1 channels and IL-1β. These inhibitions have been hypothesized to have potential beneficial effects on CVD. At present, however, using uricosuric drugs for a cardioprotective effect remains controversial (26,40). Our findings showed no benefits in HF.

**Combination therapy**

In our study, treating gout with combination therapy was found to worsen HF incidence. Our explanations for this outcome are as follows. First, poor compliance with or adherence to gout treatment (29,30) might have caused the higher levels or fluctuations of uric acid and gout flare, inducing persistent low-grade inflammation and HF. Second, combination therapy is associated with cases with a more severe or longer duration of gout treatment, which is concordant with previous findings regarding the association between gout and HF (18,27). Third, we need more basic research on the drug-drug interaction of these types of
antigout medications in gout treatment and HF.

Limitations
First, we could not obtain additional laboratory data, such as uric acid levels, images of joints, heart echoes, or functional evaluations, due to national principal restrictions. Second, we could not identify all other potential confounding factors in our database, such as smoking, alcohol consumption, or the nutritional status and environmental factors of the patients.

Conclusions
In Taiwan, the prevalence of hyperuricemia has decreased, but gout has increased gradually (5). To our knowledge, gout and hyperuricemia are not synonymous and have distinct pathophysiologic pathways. However, the inflammatory activity of gout might induce more CVD, such as HF. Our study revealed that gout treatment in Taiwan cannot improve HF and actually increase the risk for HF after combination therapy for gout. However, according to the results of our study, from the public health point of view, it is easy for patients with gout flare to obtain medical help and treatment for painful joints by primary physicians. This suggests that we should pay more attention to the gout treatment burden to decrease HF incidence.

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Footnote
Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm.2020.03.124). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was exempted from a full ethical review by China Medical University and Hospital Research Ethics Committee (IRB permit number: CMUH104-REC2-115-R4).

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