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Allopurinol, benzbromarone and risk of coronary heart disease in gout patients: A population-based study

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ABSTRACT

Background: The effect of gout on the risk of developing coronary artery disease (CAD) is uncertain. Some studies have found that gout is a risk factor for acute myocardial infarction. This study examined the changes in risk of CAD in gout patients taking allopurinol and/or benzbromarone, and analyzed the dose-response relationship of both drugs with CAD incidence.

Methods: The medical records of one million subjects from 2000 to 2011 were provided by the Taiwan National Health Insurance Research Database. Cox proportional hazard ratio was used to compare the risk of CAD in gout patients taking allopurinol or/and benzbromarone with those taking neither drug. Hazard ratios (HR) were adjusted for possible confounding factors, including age, gender, hypertension, hyperlipidemia, diabetes mellitus, chronic kidney disease, and relevant medications.

Results: Of 8047 gout patients, 1422 were treated with allopurinol (Group A), 4141 with benzbromarone (Group B), and 2484 with both drugs (Group A/B) during the follow-up period. Our results showed the incidence of CAD after adjusting for covariates for Group A, Group B, and Group A/B did not significantly differ from the comparison group. However, after adjustment for covariates in dose-response analyses, treatment with over 270 defined daily doses (DDDs) of allopurinol, and over 360 DDDs of benzbromarone, was associated with a significantly reduced risk of CAD.

Conclusion: We found that the use of allopurinol and benzbromarone, whether alone or in combination, had a linear dose-response relationship between the numbers of defined daily doses and the risk of CAD, especially in higher DDDs.

1. Introduction

Coronary artery disease (CAD) results from narrowing of the lumen of one or more coronary arteries. Acute obstruction is usually caused by rupture or erosion of an atherosclerotic plaque with consequent thrombus formation, leading to obstruction of the vessel. According to a survey in 2001, the prevalence of angina in Taiwan is 15.0%, with 15.1% in males and 14.4% in females [1].

Gout manifesting in a variety of ways, such as recurrent acute arthritis with intense pain, is considered to be caused by hyperuricemia with monosodium urate (MSU) crystals becoming deposited in joints [2]. When investigated in the Nutrition and Health Survey in Taiwan, its prevalence during 2005–2008 was estimated to be 8.2% in males and 2.3% in females [3].

The role of gout or hyperuricemia in the risk of CAD is uncertain. Some studies concluded that the association of uric acid with CAD or other cardiovascular outcomes is not due to uric acid per se but to its association with other risk factors, and accordingly that it does not

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play a causal role in CAD development [4,5]. On the other hand, other studies found that hyperuricemia is a risk factor for acute myocardial infarction, and an independent risk factor for subclinical atherosclerosis in young adults [6,7]. Additionally, Taiwanese gout patients have been reported to have an increased risk for CAD whether or not other cardiovascular risk factors were present [8,9].

Medications for gout serve as urate-lowering agents for hyperuricemia or as anti-inflammatory agents for acute arthritis [2]. Urate-lowering therapy is of two mechanisms: inhibition of urate production, and promotion of urate excretion. The former includes xanthine oxidase (XO) inhibitors [10], and the latter relies on uricosurics [11]. Allopurinol and benzbromarone are two of the most commonly used urate-lowering drugs in Taiwan.

In randomized controlled trials, allopurinol appeared to improve endothelial dysfunction and reduce oxidative stress, prolong exercise time, and delay the onset of angina and ST depression during stress testing [12–14]. An open-label study indicated that coronary blood flow may improve in stable CAD patients with endothelial dysfunction after intravenous infusion of 200 mg oxypurinol (an active metabolite of allopurinol) [15]. However, research on the association of reduced CAD with allopurinol is limited, and all studies so far were conducted on small numbers of patients. Furthermore, although benzbromarone has been withdrawn from the market in several countries for over a decade, it is still prescribed in Taiwan, and to date there has been no research on the relationship between CAD and benzbromarone. Therefore, we conducted a study to observe how CAD risk changes with allopurinol and/or benzbromarone therapy in gout patients using the nationwide population-based database in Taiwan.

2. Methods

2.1. Data source

The primary data of this nationwide population-based retrospective cohort study were sourced from the Longitudinal Health Insurance Database 2000 (LHID 2000), which contains medical registration files and original claim data of one million beneficiaries randomly drawn from the National Health Insurance Research Database (NHIRD) in Taiwan from 2000 to 2011. Instituted in 1995, the National Health Insurance program is a compulsory social insurance that covers over 99% of the population of Taiwan, and diagnoses and medical interventions such as medication records are included. "The NHIRD contained all the claimed record for national health insurance payment. Therefore, it can provide complete information for medication prescription and dispensing for individual patient." It is not possible to identify an individual using the NHIRD, and hence the present study was exempted from full review by the Joint Institutional Review Board of Taipei Medical University.

2.2. Study population

Diagnoses were defined by the International Classification of Diseases, Ninth Revision, and Clinical Modification (ICD-9-CM) code. Patients with gout (ICD-9-CM codes 274.0, 274.8, and 274.9) between January 1, 2001 and December 31, 2008 were enrolled, including both inpatients and outpatients. Patients were excluded if they had a history of CAD (ICD-9-CM codes 410, 411, 413, and 414), heart failure (HF) (ICD-9-CM code 428), or cancer (ICD-9-CM codes 140–239), or were taking either allopurinol or benzbromarone before the diagnosis of gout.

To ascertain the effects of allopurinol and benzbromarone on the risk of CAD, we excluded subjects who had been identified as having CAD before or within 180 days of taking either allopurinol or benzbromarone. We also excluded patients who had been taking either drug for fewer than 90 days within 180 days of starting either medication. In order to improve the accuracy of diagnosis, we included only those patients in whom the diagnosis of gout had been made either as an inpatient or at least twice as an outpatient. We excluded patients under 20 years of age to meet the requirement of the Institutional Review Board (IRB) of Taipei Medical University Hospital.

2.3. Primary and secondary outcomes

The primary purpose of the study was to ascertain whether allopurinol and benzbromarone are associated with a reduced risk of CAD in gout patients. The primary outcome was occurrence of CAD during the follow-up period. We also endeavored to analyze the dose-response relationship between risk of CAD and the use of allopurinol and/or benzbromarone. In order to calculate and compare the cumulative numbers of doses of different drugs, the concept of defined daily dose (DDD) was applied. The secondary outcomes were the hazard ratios of CAD in each case subgroup with different DDDs. According to the World Health Organization, one DDD of allopurinol corresponds to 400 mg allopurinol by oral or parenteral routes, and one DDD of benzbromarone corresponds to 100 g benzbromarone taken orally.

2.4. Adjustments for covariates

We adjusted for several confounding factors, which were decided by several cardiovascular risk evaluation score systems, [16–18] including age, gender, hypertension, hyperlipidemia, diabetes mellitus, chronic kidney disease, and related medications (including stratins, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), β-blockers, and antiplatelet drugs.

2.5. Statistical analyses

All data were analysed using the Statistics Analysis System® (SAS®) 9.1 statistical package (SAS Institute Inc., Cary, NC, USA). Student's *t*-test and Pearson's chi-squared (χ^2) test were used to examine differences in baseline characteristics and potential covariates among different groups of patients during the follow-up period. Cox proportional hazards regression was used to estimate the hazards of CAD for both the case and comparison groups with age, gender, and other covariates adjusted. Statistical significance was defined as a two-tailed *p*-value of <0.05.

3. Results

3.1. Baseline characteristics

As shown in Fig. 1, of the 52,693 gout patients who met the inclusion criteria, 36,499 were treated with either allopurinol or benzbromarone and 16,194 were treated with neither drug. A total of 8047 gout patients remained and were regarded as the case groups. We classified them into subgroups as only allopurinol-treated (Group A, $N = 1422$), only benzbromarone-treated (Group B, $N = 4141$), and both ever-treated (allopurinol and benzbromarone, i.e., Group A/B, $N = 2484$) during the follow-up period. Each of the 8047 patients was exclusively matched with one of the remaining 16,194 subjects (no allopurinol or benzbromarone) by age and gender in the ratio of 1:1.

Table 1 shows the differences in gender, age, comorbidities, and use of related medications. The average ages of all groups were between 50 and 60 years. Males accounted for more than three-fourths of the study population. After matching for age and gender, there were significant differences in the distributions of hypertension, hyperlipidemia, diabetes mellitus, chronic kidney disease and related medications between case groups A, B, and A/B and their comparison subjects. Therefore, the differences between the case groups and their comparison groups were adjusted in order to compare the incidences of CAD in the primary and secondary outcomes.

3.2. Primary outcome

Table 2 shows the incidence of CAD during the follow-up period. The risk of CAD for each study group is presented as the HR. The crude HRs indicated that the risk of CAD was significantly greater in Group A (HR = 1.27; 95% CI 1.02–1.57), Group B (HR = 1.27; 95% CI 1.12–1.45), and Group A/B (HR = 1.46; 95% CI 1.22–1.74) than in their respective comparison groups. However, our results show the incidence of CAD during the follow-up period, after adjusting for covariates, the HRs for Group A (allopurinol-treated, adjusted HR = 1.07, 95% CI 0.86–1.33), Group B (benzbromarone-treated, adjusted HR = 1.05, 95% CI 0.92–1.21), and Group A/B (allopurinol/ benzbromarone treated, adjusted HR = 0.86, 95% CI 0.71–1.03) did not differ significantly.

3.3. Secondary outcome

Patients of each case subgroup were stratified into five layers by number of DDDs to explore the relationships between CAD risk and doses of allopurinol, benzbromarone, and allopurinol plus benzbromarone. In Group A, the case subgroup receiving more than 270 DDDs of allopurinol showed a significant reduction of CAD risk after adjusting for covariates, the adjusted HR being 0.25 for the 271–360 DDD subgroup (95% CI 0.10–0.61) and 0.28 for the more

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