Tzu Chi Medical Journal 2019; 31(4): 276–279

Original Article

Allopurinol use associated with increased risk of acute myocardial infarction in older people in a case–control study

*Kuan-Fu Liao[a,b], Cheng-Li Lin[c,d], Shih-Wei Lai[c,e]**

[a]College of Medicine, Tzu Chi University, Hualien, Taiwan, [b]Department of Internal Medicine, Division of Hepatogastroenterology, Taichung Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Taichung, Taiwan, [c]College of Medicine, China Medical University, Taichung, Taiwan, [d]Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan, [e]Department of Family Medicine, China Medical University Hospital, Taichung, Taiwan

Received : 12-Jun-2018
Revised : 16-Jul-2018
Accepted : 13-Aug-2018

Abstract

Objective: There is controversy about the association between the allopurinol use and the risk of acute myocardial infarction. The aim of the study was to examine the association between allopurinol use and acute myocardial infarction in older people in Taiwan. **Materials and Methods:** We used the 2000–2013 database of the Taiwan National Health Insurance Program to conduct a case–control study. Cases were assigned as subjects aged 65 years and older with the first incident acute myocardial infarction. Matched controls were assigned as subjects aged 65 years and older without any type of coronary artery disease. Ever use of allopurinol was defined as subjects who had at least a prescription of allopurinol before the diagnosis date of first incident acute myocardial infarction. The odds ratio (OR) and the 95% confidence interval (CI) for acute myocardial infarction associated with allopurinol use were estimated by the multivariable logistic regression model. **Results:** There were 4701 cases with the first incident acute myocardial infarction and 9369 matched controls. The adjusted OR of acute myocardial infarction was 2.2 (95% CI 1.7– 2.7) for subjects with ever use of allopurinol, compared with never use. The adjusted ORs of acute myocardial infarction were 2.0 (95% CI 1.5–2.6) for subjects with average daily dosage of allopurinol <200 mg and 2.5 (95% CI 1.6–4.0) for subjects with average daily dosage of allopurinol ≥200 mg. **Conclusion:** Allopurinol use is associated with increased odds of acute myocardial infarction in older people, which is dosage dependent.

Keywords: *Acute myocardial infarction, Allopurinol, Case–control, Older people, Taiwan National Health Insurance Program*

Introduction

Hyperuricemia has been found to be associated with cardiovascular disease [1,2]. Thus, whether lowering serum uric acid can reduce the risk of cardiovascular disease is an important issue. Allopurinol, a uric acid-lowering drug mediated by the pathway of inhibition of xanthine oxidase, is frequently used to treat hyperuricemia [3]. Moreover, the association between allopurinol use and acute myocardial infarction remains to be controversial. Some studies revealed that allopurinol use could reduce the risk of acute myocardial infarction [4-7], but another study revealed that allopurinol use could increase the risk [8]. One study even revealed that allopurinol use should be considered as a contraindication among patients with ischemic heart disease [9].

Cardiovascular disease was the second leading cause of total death in Taiwan in 2016. Totally, 20,812 deaths were related to cardiovascular disease, accounting for 12.07% of total death in Taiwan in 2016 [10]. One study in Taiwan revealed that the prevalence rates of hyperuricemia were 39.4% in men and 17.4% in women [11]. However, there is no definite conclusion about whether allopurinol use can reduce or increase the risk of acute myocardial infarction in older people in Taiwan. If the association can be established, more clinical information can be added to the care of older people. Therefore, we conducted a population-based case–control study to examine the following questions: (1) What association can be found between allopurinol use and acute myocardial infarction? (2) Whether there is a dosage-dependent relationship of allopurinol use on the risk of acute myocardial infarction?

Access this article online

Quick Response Code:

Website: www.tcmjmed.com

DOI: 10.4103/tcmj.tcmj_144_18

**Address for correspondence:*
Dr. Shih-Wei Lai,
Department of Family Medicine, China Medical University Hospital, 2, Yuh-Der Road, Taichung, Taiwan.
E-mail: wei@mail.cmuh.org.tw

How to cite this article: Liao KF, Lin CL, Lai SW. Allopurinol use associated with increased risk of acute myocardial infarction in older people in a case–control study. Tzu Chi Med J 2019;31(4):276-9.

Materials and methods

Study design and data source

The study design and data source were adapted from previous studies [12-14]. We conducted a population-based case–control study using the 2000–2013 database of the Taiwan National Health Insurance Program. The program began in March 1995 and has covered 99.6% of 23 million people living on an independent country of Taiwan [15-17].

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki. The study was approved by the Research Ethics Committee of China Medical University and Hospital in Taiwan (CMUH-104-REC2-115). Informed written consent was waived because the study was retrospective data.

Study subjects

Subjects aged 65 years or older with the first incident acute myocardial infarction (based on the International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9] code 410) were assigned as cases. The date of subjects being diagnosed with the first incident acute myocardial infarction was defined as the index date. For every one case with acute myocardial infarction, approximately two subjects aged 65 years or older without any type of coronary artery disease (ICD-9 codes 410–414) were assigned as matched controls. Both cases and matched controls were matched with sex, age (every 5 years), and the year of index date [Figure 1].

Definition of allopurinol exposure

To reduce the biased results, subjects whose final prescriptions of allopurinol were filled ≥6 months before the index date were excluded. Therefore, only those subjects whose final prescriptions of allopurinol were filled <6 months before the index date could be included. The definition of allopurinol use was adapted from previous studies [18,19]. Briefly speaking, ever use of allopurinol was defined as subjects who had at least a prescription of allopurinol before index date. Never use of allopurinol was defined as subjects who did not have a prescription of allopurinol before the index date.

Comorbidities studied

Based on ICD-9 codes, comorbidities were selected as follows: alcohol-related disease (ICD-9 codes 291, 303, 305.00, 305.01, 305.02, 305.03, 571.0–571.3, 790.3, and V11.3), cerebrovascular disease (ICD-9 codes 430–438), chronic kidney disease (ICD-9 codes 581–583, 585–587, and 588.8–588.9), chronic obstructive pulmonary disease (ICD-9 codes 491, 492, 493, and 496), diabetes mellitus (ICD-9 codes 250), hyperlipidemia (ICD-9 codes 272.0, 272.1, 272.2, 272.3, and 272.4), and hypertension (ICD-9 codes 401–405).

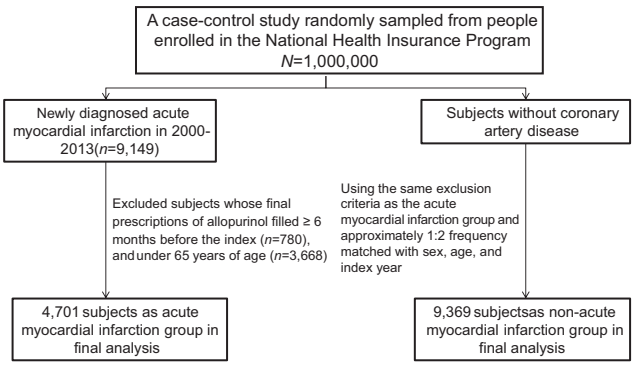

Figure 1: Flowchart showing selection process of study subjects

Statistical analysis

First, we compared the distributions of demographic information, allopurinol use, and comorbidities between cases and matched controls using the Chi-square test for categorical variables and the *t*-test for continuous variables. Second, the multivariable logistic regression model was used to estimate the odds ratio (OR) and the 95% confidence interval (CI) for acute myocardial infarction associated with allopurinol use. Third, we conducted an analysis about the risk of acute myocardial infarction associated with average daily dosage of allopurinol use. The average daily dose of allopurinol use was calculated using the total quantity of allopurinol divided by total number of days supplied. The average daily dose was divided into two levels according to the third quartile dose, <200 mg and ≥200 mg. All analyses were performed using the SAS Statistical Software (version 9.2; SAS Institute, Inc., Cary, NA, USA). The results were considered statistically significant when two-tailed $P < 0.05$.

Results

Basic characteristics of the study population

There were 4701 cases with acute myocardial infarction and 9369 matched controls, with similar distributions of sex and age [Table 1]. The mean ages (standard deviation) were 77.1 (7.2)

Table 1: Characteristics between cases with acute myocardial infarction and matched controls

Variable	Matched controls (*n*=9369), *n* (%)	Cases with acute myocardial infarction (*n*=4701), *n* (%)	*P**
Sex			
Female	3967 (42.3)	1992 (42.4)	0.97
Male	5402 (57.7)	2709 (57.6)	
Age group (years)			
65-74	3944 (42.0)	1972 (42.0)	0.90
75-84	4024 (43.0)	2012 (42.8)	
≥85	1401 (15.0)	717 (15.2)	
Age (years), mean±SD†	76.9±7.2	77.1±7.2	0.16
Ever use of allopurinol use	144 (1.5)	282 (6.0)	<0.001
Comorbidities*			
Alcohol-related disease	216 (2.3)	163 (3.5)	<0.001
Cerebrovascular disease	812 (8.7)	1365 (29.0)	<0.001
Chronic kidney disease	566 (6.0)	944 (20.1)	<0.001
Chronic obstructive pulmonary disease	2192 (23.4)	2023 (43.0)	<0.001
Diabetes mellitus	878 (9.4)	1543 (32.8)	<0.001
Hyperlipidemia	1566 (16.7)	1705 (36.3)	<0.001
Hypertension	4697 (50.1)	4035 (85.8)	<0.001

Data are presented as the number of subjects in each group with percentages given in parentheses. *Chi-square test and, †*T*-test comparing subjects with and without acute myocardial infarction. SD: Standard deviation

years in cases and 76.9 (7.2) years in matched controls, without statistical significance (*t*-test, $P = 0.16$). Cases were more likely to have a higher proportion of ever use of allopurinol than matched controls, with statistical significance (6.0% vs. 1.54%, Chi-square test, $P < 0.001$). Cases had higher proportions of alcohol-related disease, cerebrovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, diabetes mellitus, hyperlipidemia, and hypertension than matched controls, with statistical significance (Chi-square test, $P < 0.001$ for all).

Risk of acute myocardial infarction associated with allopurinol use

After adjusting for potential covariables, the multivariable logistic regression model revealed that the adjusted OR of acute myocardial infarction was 2.2 (95% CI 1.7–2.7) for subjects with ever use of allopurinol, compared with never use of allopurinol [Table 2]. In addition, cerebrovascular disease (adjusted OR 2.5, 95% CI 2.2–2.7), chronic kidney disease (adjusted OR 2.0, 95% CI 1.7–2.2), chronic obstructive pulmonary disease (adjusted OR 2.0, 95% CI 1.8–2.1), diabetes mellitus (adjusted OR 2.5, 95% CI 2.3–2.8), hyperlipidemia (adjusted OR 1.6, 95% CI 1.4–1.7), and hypertension (adjusted OR 3.5, 95% CI 3.2–3.8) were associated with acute myocardial infarction.

Risk of acute myocardial infarction associated with average daily dosage of allopurinol use

We conducted an analysis about the risk of acute myocardial infarction associated with average daily dosage of allopurinol use. The adjusted ORs of acute myocardial infarction were 2.0 (95% CI 1.5–2.6) for subjects with average daily dosage of allopurinol <200 mg and 2.5 (95% CI 1.6–4.0) for subjects with average daily dosage of allopurinol use ≥200 mg, compared with never use of allopurinol [Table 3].

Table 2: Crude and adjusted odds ratio and 95% confidence interval of acute myocardial infarction associated with allopurinol use and comorbidities by logistical regression model

Variable	Crude		Adjusted†	
	OR	95% CI	OR	95% CI
Sex (male vs. female)	1.0	0.9-1.1	-	-
Age (per 1 year)	1.0	0.9-1.0	-	-
Ever use of allopurinol use (never use as a reference)	4.1	3.3-5.0	2.2	1.7-2.7
Comorbidities (yes vs. no)				
Alcohol-related disease	1.5	1.2-1.9	1.2	0.9-1.6
Cerebrovascular disease	4.3	3.9-4.8	2.5	2.2-2.7
Chronic kidney disease	3.9	3.5-4.4	2.0	1.7-2.2
Chronic obstructive pulmonary disease	2.5	2.3-2.7	2.0	1.8-2.1
Diabetes mellitus	4.7	4.3-5.2	2.5	2.3-2.8
Hyperlipidemia	2.8	2.6-3.1	1.6	1.4-1.7
Hypertension	6.0	5.5-6.6	3.5	3.2-3.8

†Adjustment for alcohol-related disease, cerebrovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, diabetes mellitus, hyperlipidemia, and hypertension. OR: Odd ratio, CI: Confidence interval

Discussion

To date, there remains to be controversy about the association between allopurinol use and the risk of acute myocardial infarction. Based on the hypothesis that the inhibition of xanthine oxidase might reduce radical oxygen species and vascular oxidative stress, and ameliorate myocardial ischemia [20], that was why allopurinol, an inhibitor of xanthine oxidase, was proposed to be associated with reduced risk of acute myocardial infarction in previous studies [4-7].

In our case–control study, only those subjects whose final prescriptions of allopurinol were filled <6 months before the index date could be included. Thus, allopurinol use among these subjects could be regarded as current or recent use, rather than the past use, based on the definition of previous studies [14,21]. We noted that allopurinol use was associated with increased odds of acute myocardial infarction in older people [adjusted OR 2.15, Table 2]. This finding is partially compatible with a cohort study, revealing that allopurinol use could increase the cardiovascular risk, with a hazard ratio of 1.25 (95% CI 1.10–1.41) [8]. Although one double-blind study revealed that allopurinol use should be considered as a contraindication among patients with ischemic heart disease [9], our study was unable to give such a suggestion due to lack of a causal relationship.

We noted that there seemed to be a dosage-dependent relationship of allopurinol use on the risk of acute myocardial infarction. That is, the higher the average daily dosage of allopurinol use, the greater the risk of acute myocardial infarction. This finding is contrary to previous studies, revealing that the higher dose of allopurinol use (300 mg or higher daily) was associated with reduced risk of acute myocardial infarction, with an OR of 0.30 (95% CI 0.13–0.72) [5].

Conclusion

Our population-based case–control study does not support the hypothesis that allopurinol has a cardioprotective effect in older people, but allopurinol use might be associated with increased odds of acute myocardial infarction, particularly at higher dosage.

Financial support and sponsorship

This study was supported in part by the Ministry of Health and Welfare, Taiwan (MOHW107-TDU-

Table 3: Risk of acute myocardial infarction associated with average daily dosage of allopurinol use

Variable	Case number/control number	Crude OR	95% CI	Adjusted OR†	95% CI
Never use of allopurinol as a reference	4419/9225	1.0	Reference	1.0	Reference
Average daily dosage of allopurinol use (mg)					
<200	228/108	4.4	3.5-5.6	2.0	1.5-2.6
≥200	54/36	3.1	2.1-4.8	2.5	1.6-4.0

†Adjustment for alcohol-related disease, cerebrovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, diabetes mellitus, hyperlipidemia, and hypertension. OR: Odd ratio, CI: Confidence interval

B-212-123004), China Medical University Hospital, Taiwan (DMR-107-192), Academia Sinica Stroke Biosignature Project (BM10701010021), MOST Clinical Trial Consortium for Stroke (MOST 106-2321-B-039-005), Tseng-Lien Lin Foundation, Taichung, Taiwan, and Katsuzo and Kiyo Aoshima Memorial Funds, Japan. These funding agencies did not influence the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflicts of interest

There are no conflicts of interest.

References

1. Borghi C, Verardi FM, Pareo I, Bentivenga C, Cicero AF. Hyperuricemia and cardiovascular disease risk. Expert Rev Cardiovasc Ther 2014;12:1219-25.
2. Gudiño Gomezjurado Á. Hyperuricemia as a risk factor for cardiovascular disease: Clinical review. Medwave 2016;16:e6606.
3. Seth R, Kydd AS, Buchbinder R, Bombardier C, Edwards CJ. Allopurinol for chronic gout. Cochrane Database Syst Rev 2014;10:CD006077.
4. Grimaldi-Bensouda L, Alpérovitch A, Aubrun E, Danchin N, Rossignol M, Abenhaim L, et al. Impact of allopurinol on risk of myocardial infarction. Ann Rheum Dis 2015;74:836-42.
5. de Abajo FJ, Gil MJ, Rodríguez A, García-Poza P, Álvarez A, Bryant V, et al. Allopurinol use and risk of non-fatal acute myocardial infarction. Heart 2015;101:679-85.
6. Singh JA, Yu S. Allopurinol reduces the risk of myocardial infarction (MI) in the elderly: A study of medicare claims. Arthritis Res Ther 2016;18:209.
7. Lin HC, Daimon M, Wang CH, Ho Y, Uang YS, Chiang SJ, et al. Allopurinol, benzbromarone and risk of coronary heart disease in gout patients: A population-based study. Int J Cardiol 2017;233:85-90.
8. Kok VC, Horng JT, Chang WS, Hong YF, Chang TH. Allopurinol therapy in gout patients does not associate with beneficial cardiovascular outcomes: A population-based matched-cohort study. PLoS One 2014;9:e99102.
9. Parmley LF, Mufti AG, Downey JM. Allopurinol therapy of ischemic heart disease with infarct extension. Can J Cardiol 1992;8:280-6.
10. Ministry of Health and Welfare T 2016 Statistics of Causes of Death; 2016. Available from: http://www.mohw.gov.tw/EN/Ministry/Index.aspx. [Last accessed on 2018 Jun 01].
11. Lai SW, Liu CS, Lin T, Lin CC, Lai HC, Liao KF, et al. Prevalence of gout and hyperuricemia in Taiwan: A hospital-based, cross-sectional study. South Med J 2009;102:772-3.
12. Lai SW, Liao KF, Liao CC, Muo CH, Liu CS, Sung FC, et al. Polypharmacy correlates with increased risk for hip fracture in the elderly: A population-based study. Medicine (Baltimore) 2010;89:295-9.
13. Liao KF, Cheng KC, Lin CL, Lai SW. Etodolac and the risk of acute pancreatitis. Biomedicine (Taipei) 2017;7:4.
14. Lai SW, Lin CL, Liao KF. Association between oral corticosteroid use and pyogenic liver abscesses in a case-control study. Biomedicine (Taipei) 2018;8:5.
15. Ministry of Health and Welfare T 2016 Taiwan Health and Welfare Report; 2016. Available from: http://www.mohw.gov.tw. [Last accessed on 2018 Jun 01].
16. Lai SW, Lin CL, Liao KF. Population-based cohort study investigating the association between weight loss and pyogenic liver abscesses. Biomedicine (Taipei) 2017;7:26.
17. Liao KF, Huang PT, Lin CC, Lin CL, Lai SW. Fluvastatin use and risk of acute pancreatitis: A population-based case-control study in Taiwan. Biomedicine (Taipei) 2017;7:17.
18. Hung SC, Liao KF, Hung HC, Lin CL, Lai SW, Lee PC, et al. Using proton pump inhibitors correlates with an increased risk of chronic kidney disease: A nationwide database-derived case-controlled study. Fam Pract 2018;35:166-71.
19. Lin HF, Liao KF, Chang CM, Lin CL, Lai SW. Tamoxifen usage correlates with increased risk of Parkinson's disease in older women with breast cancer: A case-control study in Taiwan. Eur J Clin Pharmacol 2018;74:99-107.
20. Lee BE, Toledo AH, Anaya-Prado R, Roach RR, Toledo-Pereyra LH. Allopurinol, xanthine oxidase, and cardiac ischemia. J Investig Med 2009;57:902-9.
21. Liao KF, Cheng KC, Lin CL, Lai SW. Statin use correlates with reduced risk of pyogenic liver abscess: A population-based case-control study. Basic Clin Pharmacol Toxicol 2017;121:144-9.