RESEARCH

Heart disease and the risk of allopurinol-associated severe cutaneous adverse reactions: a general population–based cohort study

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ABSTRACT

BACKGROUND: Allopurinol is commonly prescribed for gout, and its clinical use may expand with ongoing trials assessing its potential cardiorenal benefits. Because heart disease has been suggested to be a risk factor for allopurinol-associated severe cutaneous adverse reactions, we sought to confirm this association in a Canadian general population cohort.

METHODS: We used population data from British Columbia, Canada, to identify all incident allopurinol users between 1997 and 2015. We examined the association between heart disease (ischemic heart disease and heart failure) and the risk of hospital admission for severe cutaneous adverse reactions, adjusting for known and purported risk factors. We also evaluated the joint effects of combined clinical and demographic risk factors.

RESULTS: Among 130 325 allopurinol initiators, 109 hospital admissions occurred for allopurinol-associated severe cutaneous adverse reactions. The multivariable relative risk among those with heart disease was 1.55 (95% confidence interval 1.01–2.37). Patients with heart disease and chronic kidney disease who were started on an allopurinol dosage of greater than 100 mg/d had an 11-fold higher risk. Allopurinol initiation at a lower dosage among patients with heart disease and chronic kidney disease resulted in a fivefold reduction in risk. Older women with heart disease from regions with large Asian populations had a 23-fold higher risk of allopurinol-associated severe cutaneous adverse reactions than younger men without heart disease from other regions.

INTERPRETATION: Heart disease is independently associated with risk of allopurinol-associated severe cutaneous adverse reactions, similar to chronic kidney disease, and low-dosage allopurinol initiation may substantially mitigate this risk. Risk factors for these rare but serious reactions should be considered when initiating allopurinol.

The global burden of gout continues to grow.[1] Amid concerns regarding possible cardiovascular adverse effects with febuxostat,[2] the number of patients with gout prescribed allopurinol may increase. Furthermore, as clinical trials[3] investigate allopurinol's purported cardiorenal benefits,[4,5] use of allopurinol among those without gout may also increase. Although generally safe and well-tolerated, allopurinol has been associated with severe cutaneous adverse reactions, including Stevens–Johnson syndrome and toxic epidermal necrolysis, which are collectively referred to as allopurinol-associated severe cutaneous adverse reactions.

A Taiwanese population–based study found that heart disease was independently associated with increased risk of hospital admission for allopurinol-associated severe cutaneous adverse reactions.[6] However, this finding has not been replicated in a non-Asian cohort. We sought to fill this knowledge gap by investigating the association in a Canadian general population cohort. Moreover, we investigated the potential joint impact of heart disease and other risk factors, including chronic kidney disease,[6–8] higher starting allopurinol dosage[6,8,9] and demographic factors.[6,8,10,11]

Methods

Population and study design

We conducted a cohort study using Population Data BC, an administrative database with de-identified patient-level data on hospital discharge records,[12] outpatient dispensed prescriptions[13] and vital statistics for nearly all of British Columbia's 4.7 million residents.[14] We used hospital admission and

prescription data, available from 1990, to identify incident allopurinol users between 1997 and 2015, excluding individuals with a history of severe cutaneous adverse reactions before allopurinol initiation.

Assessment of end points

The primary end point was incident cases of hospital admission for allopurinol-associated severe cutaneous adverse reactions, identified based on principal hospital discharge diagnosis of a relevant *International Classification of Diseases*, *9th Revision, Clinical Modification* (ICD-9-CM) or *International Classification of Diseases*, *10th Revision, Clinical Modification* (ICD-10-CM) code, occurring within 3 months after filling the first prescription for allopurinol, followed by discontinuation of the drug after the hospital admission. The relevant ICD-9-CM codes included dermatitis due to drugs and medicines (693.0), erythema multiforme (695.1X) (which includes Stevens–Johnson syndrome [695.13] and toxic epidermal necrolysis [695.15]), unspecified erythematous conditions (695.9) and other specified erythematous conditions (695.89), and are consistent with those used in other claims database studies.[6,8] Two expert dermatologists previously found that this method had a positive predictive value of 100% after manual chart review of 33 patients identified through a national database.[6] We used a 3-month window between the first prescription for allopurinol and hospital admission for allopurinol-associated severe cutaneous adverse reactions because most of these reactions develop within 3 months of drug initiation.[6,8,15] Deaths from allopurinol-associated severe cutaneous adverse reactions were defined as deaths from any cause within 60 days of hospital admission with a diagnosis of allopurinol-associated severe cutaneous adverse reaction.[6,8]

Assessment of exposure and covariates

The exposure of interest was heart disease (defined as ischemic heart disease and heart failure, ICD-9-CM codes 410–414 and 402, 404, 428, respectively) before allopurinol initiation. Covariates of interest consisted of known or purported risk factors, including age, sex, region (as surrogate for high-risk Asian race), presence of chronic kidney disease (ICD-9-CM codes 580–586), diabetes (ICD-9-CM code 250) and gout (ICD-9-CM code 274), use of diuretics (loop and thiazide) within 1 year before allopurinol initiation, and initial allopurinol dosage greater than 100 mg/d. Age was analyzed as both a continuous variable and a categorical variable (< 60 yr, 60–70 yr and ≥ 70 yr).

Population Data BC does not include race or ethnicity, or genetic information such as *HLA-B*5801*. The *HLA-B*5801* allele is an important predictor of allopurinol-associated severe cutaneous adverse reactions; according to a meta-analysis, the risk of allopurinol-associated severe cutaneous adverse reactions among carriers of the allele was 97 times higher than among those who did not carry the allele.[16] The allele is more prevalent among Asian and black patients than among white or Hispanic patients, thus explaining the racial and ethnic differences in the risk of allopurinol-associated severe cutaneous adverse reactions.[15,17–22] Therefore, given the strong association between the *HLA-B*5801* allele and the risk of allopurinol-associated severe cutaneous adverse reactions, and the high prevalence of *HLA-B*5801* among Asian populations, the 16 health regions within BC were grouped into 4 region groups (Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.190339/-/DC1) based on the prevalence of Asian populations according to the 2016 Canadian Census data.[23] This was then used as a surrogate for Asian race, which has the highest prevalence of *HLA-B*5801*.[17,20,24,25] Secondarily, we analyzed regional prevalence of Asian populations as a continuous variable. Although black people also have an increased risk of allopurinol-associated severe cutaneous adverse reactions,[8,11] with a high prevalence of *HLA-B*5801*,[25] they constitute only 1.3% of the population of BC (v. 28.8% for Asian people).[23] However, to assess the specificity of our surrogate measure, we similarly analyzed the regional prevalence of North American Aboriginal populations, the third largest racial or ethnic group (6.6%) in BC after white (82.9%) and Asian (28.8%) populations.

Statistical analysis

We followed the study cohort members from the initiation of allopurinol until 1) hospital admission for allopurinol-associated severe cutaneous adverse reaction, 2) end of study period (Mar. 31, 2015), 3) end of the first 3 months of allopurinol exposure or 4) death, whichever came first. We calculated the overall risk of hospital admission for allopurinol-associated severe cutaneous adverse reactions per 1000 allopurinol initiators and the corresponding 95% confidence interval (CI). We estimated the risk of hospital admission for allopurinol-associated severe cutaneous adverse reactions per 1000 allopurinol initiators according to history of heart disease as well as the aforementioned known and purported risk factors. We then calculated the relative risk (RR) associated with heart disease in Poisson regression models (with sandwich robust estimators), adjusting for demographic factors alone and additionally for known and purported risk factors for allopurinol-associated severe cutaneous adverse reactions. We confirmed the absence of collinearity among variables using the variance inflation factor.

We further examined the joint effects of combined demographic and clinical risk factors, including heart disease, on the risk of hospital admission for allopurinol-associated severe cutaneous adverse reactions following the approach taken by Keller and colleagues in their analysis of the US Medicaid population.[8] We first investigated joint effects of heart disease and clinical covariates, chronic kidney disease and initial allopurinol dosage, as chronic kidney disease and heart disease often coexist[26,27] and allopurinol dosage is the key modifiable factor in patients with chronic kidney disease to reduce the risk of allopurinol-associated severe cutaneous adverse reactions.[8,9,28] We then repeated the analysis with heart disease and demographic covariates. Region was categorized as a binary variable, with region groups 1 and 2 constituting high-risk regions with large Asian populations and region groups 3 and 4 constituting low-risk regions (Appendix 1). We also categorized age in the joint effects analysis as a binary variable, using age 70 as the cut-off point.

Ethics approval

This study was exempted by the Partners Human Research Committee.

Results

Cohort characteristics

We identified 130 325 allopurinol initiators in the database. The characteristics of patients with and without heart disease are shown in Table 1. Patients with heart disease tended to be older and had higher prevalence of chronic kidney disease, diabetes and diuretic use.

Incidence, timing of hospital admission and mortality

Among the 130 325 allopurinol initiators, we identified 109 cases of hospital admission for allopurinol-associated severe cutaneous adverse reactions occurring within 3 months of allopurinol initiation (Table 2). The overall risk of hospital admission for allopurinol-associated severe cutaneous adverse reactions was 1 out of 1196 allopurinol initiators. The risk of hospital admission for allopurinol-associated severe cutaneous adverse reactions became apparent within 10 days of allopurinol initiation, peaked around 1 month after initiation and declined progressively thereafter until the end of the 3-month period (Appendix 2, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.190339/-/DC1). Among the patients admitted to hospital for allopurinol-associated severe cutaneous adverse reactions, 13 died within 60 days of the hospital admission, yielding a mortality rate of 12%.

Risk of hospital admission by heart disease status

Among patients with heart disease, 1 in 655 allopurinol initiators (1.53, 95% CI 1.10–2.06, per 1000) were admitted to the hospital for allopurinol-associated severe cutaneous adverse reactions, versus 1 in 1548 allopurinol initiators (0.65, 95% CI 0.50–0.82, per 1000) among those without heart disease. In the age- and sex-adjusted analysis, heart disease was associated with an 84% higher risk of hospital admission for allopurinol-associated severe cutaneous adverse reactions (RR 1.84, 95% CI 1.23–2.76). After adjustment for other covariates, the RR attenuated but remained significant (multivariable RR 1.55, 95% CI 1.01–2.37).

Table 1: Characteristics of 130 325 patients who started allopurinol during the study period, by presence of heart disease

Characteristic	No. (%) of patients*		Standardized mean difference†
	Heart disease *n* = 28 176	No heart disease *n* = 102 149	
Age, yr			0.80
Mean ± SD	70.2 ± 11.6	59.9 ± 14.0	
< 60	5401 (19.2)	48 494 (47.5)	
60–70	7301 (25.9)	27 271 (26.7)	
≥ 70	15 454 (54.9)	26 384 (25.8)	
Sex, female	9328 (33.1)	27 870 (27.3)	0.13
Region‡			0.21
Richmond	1010 (3.6)	4574 (4.5)	
Vancouver and Fraser North	9414 (33.4)	24 994 (24.5)	
North Shore and Fraser South	5687 (20.2)	20 998 (20.6)	
Remainder	12 065 (42.8)	51 583 (50.5)	
Comorbidities			
Ischemic heart disease	24 537 (87.1)	0	3.67
Heart failure	10 076 (35.8)	0	1.06
Chronic kidney disease	7138 (25.3)	8736 (8.6)	0.46
Diabetes	12 111 (43.0)	20 759 (20.3)	0.50
Gout	18 104 (64.3)	61 660 (60.4)	0.08
Medications			
Diuretics	16 415 (58.3)	26 124 (25.6)	0.70
Initial allopurinol dosage > 100 mg/d	16 333 (58.0)	66 520 (65.1)	0.15

Note: SD = standard deviation.
*Unless stated otherwise.
†Standardized mean differences > 0.1 are considered meaningful.
‡Regions are grouped by proportion of Asian people in the population according to data from the 2016 Canadian Census (Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.190339/-/DC1) and are used here as a surrogate for Asian race, which has the highest prevalence of the *HLA-B*5801* polymorphism.

Table 2: Risk of hospital admission for allopurinol-associated severe cutaneous adverse reactions, by purported risk factor

Risk factor	No. (%)		Risk of hospital admission for allopurinol-associated severe cutaneous adverse reactions per 1000 patients (95% CI)	Relative risk (95% CI)		
	Allopurinol initiators	Hospital admissions for severe cutaneous adverse reactions		Age- and sex-adjusted	Primary multivariable*	Secondary multivariable†
All	130 325 (100)	109	0.84 (0.69–1.01)	–	–	–
Sex						
Male	93 127 (71.5)	49 (45.0)	0.53 (0.39–0.70)	1.0	1.0	1.0
Female	37 198 (28.5)	60 (55.0)	1.61 (1.23–2.08)	2.45 (1.67–3.61)	2.48 (1.67–3.70)	2.45 (1.65–3.65)
Age, yr						
Continuous, 1-year age increase	–	–	–	–	1.02 (1.00–1.04)	–
< 60	53 895 (41.4)	23 (21.1)	0.43 (0.27–0.64)	1.0	–	1.0
60–70	34 572 (26.5)	21 (19.3)	0.61 (0.38–0.93)	1.76 (1.37–2.25)	–	2.24 (1.33–3.78)
≥ 70	41 858 (32.1)	65 (59.6)	1.55 (1.20–1.98)	3.09 (1.89–5.06)	–	5.04 (1.77–14.30)
Region‡						
Continuous, per 1% Asian increase	–	–	–	–	1.03 (1.02–1.04)	–
Richmond	5584 (4.3)	8 (7.3)	1.43 (0.62–2.82)	4.66 (2.66–8.15)	–	4.67 (2.65–8.25)
Vancouver and Fraser North	34 408 (26.4)	54 (49.5)	1.57 (1.18–2.05)	2.79 (1.92–4.05)	–	2.80 (1.92–4.08)
North Shore and Fraser South	26 685 (20.5)	15 (13.8)	0.56 (0.31–0.93)	1.67 (1.39–2.01)	–	1.67 (1.38–2.02)
Remainder	63 648 (48.8)	32 (29.4)	0.50 (0.34–0.71)	1.0	–	1.0
Heart disease						
Yes	28 176 (21.6)	43 (39.4)	1.53 (1.10–2.06)	1.84 (1.23–2.76)	1.60 (1.04–2.44)	1.55 (1.01–2.37)
No	102 149 (78.4)	66 (60.6)	0.65 (0.50–0.82)	1.0	1.0	1.0
Chronic kidney disease						
Yes	15 874 (12.2)	26 (23.9)	1.64 (1.07–2.40)	1.70 (1.08–2.67)	1.86 (1.16–2.99)	1.88 (1.17–3.02)
No	114 451 (87.8)	83 (76.1)	0.73 (0.58–0.90)	1.0	1.0	1.0
Diabetes						
Yes	32 870 (25.2)	36 (33.0)	1.10 (0.77–1.52)	1.12 (0.75–1.68)	0.96 (0.63–1.46)	0.95 (0.62–1.45)
No	97 455 (74.8)	73 (67.0)	0.75 (0.59–0.94)	1.0	1.0	1.0
Gout						
Yes	79 764 (61.2)	57 (52.3)	0.71 (0.54–0.93)	0.80 (0.55–1.16)	0.80 (0.54–1.16)	0.80 (0.55–1.17)
No	50 561 (38.8)	52 (47.7)	1.03 (0.77–1.35)	1.0	1.0	1.0
Diuretic use						
Yes	42 539 (32.6)	55 (50.5)	1.29 (0.97–1.68)	1.32 (0.88–1.98)	1.27 (0.84–1.94)	1.26 (0.83–1.92)
No	87 786 (67.4)	54 (49.5)	0.62 (0.46–0.80)	1.0	1.0	1.0
Initial allopurinol dosage						
> 100 mg/d	82 853 (63.6)	86 (78.9)	1.04 (0.83–1.28)	2.53 (1.59–4.02)	2.79 (1.75–4.45)	2.78 (1.75–4.43)
≤ 100 mg/d	47 472 (36.4)	23 (21.1)	0.48 (0.31–0.73)	1.0	1.0	1.0

Note: CI = confidence interval
*Adjusted for sex, age (continuous), % Asian (continuous), heart disease, chronic kidney disease, diabetes, gout, diuretic use and initial allopurinol dosage.
†Adjusted for sex, age, region, heart disease, chronic kidney disease, diabetes, gout, diuretic use and initial allopurinol dosage.
‡Regions are grouped by proportion of Asian people in the population according to data from the 2016 Canadian Census (Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.190339/-/DC1) and are used here as a surrogate for Asian race, which has the highest prevalence of the *HLA-B*5801* polymorphism.

Risk of hospital admission by demographic and clinical risk factors

Female sex (multivariable RR 2.45, 95% CI 1.65–3.65), older age (age 60–70 yr: multivariable RR 2.24, 95% CI 1.33–3.78; age ≥ 70 yr: multivariable RR 5.04, 95% CI 1.77–14.30) and residence in regions with a higher proportion of people of Asian ethnicity (Richmond: multivariable RR 4.67, 95% CI 2.65–8.25; Vancouver and Fraser North: multivariable RR 2.80, 95% CI 1.92–4.08; North Shore and Fraser South: multivariable RR 1.67, 95% CI 1.38–2.02) were the demographic variables independently associated with risk of hospital admission for allopurinol-associated severe cutaneous adverse reactions in the multivariable analysis (Table 2).

We also analyzed age as a continuous variable and found that each 1-year increase in age was associated with a multivariable RR of 1.02 (95% CI 1.00–1.04), with other associations remaining similar. We considered prevalence of Asian population within a health region as a continuous variable and found that each 1% increase in Asian prevalence was associated with a multivariable RR of 1.03 (95% CI 1.02–1.04). We also considered the prevalence of North American Aboriginal populations and found a null association (RR 0.97, 95% CI 0.91–1.04), without affecting the remainder of results.

Chronic kidney disease (multivariable RR 1.88, 95% CI 1.17–3.02) and initial allopurinol dosage greater than 100 mg/d (multivariable RR 2.78, 95% CI 1.75–4.43) were the clinical variables independently associated with risk of hospital admission for allopurinol-associated severe cutaneous adverse reactions in the multivariable analysis. Gout and diabetes were not associated with increased risk of hospital admission for these reactions. Additionally, diuretic use, a previously suspected risk factor, was not associated with an increased risk of hospital admission for allopurinol-associated severe cutaneous adverse reactions (multivariable RR 1.26, 95% CI 0.83–1.92) (Table 2). Overall event rates were low, even among those with chronic kidney disease, who had the highest absolute event rate observed (1.64 per 1000 patients).

We tested the interactions terms for heart disease and each of the other risk factors for allopurinol-associated severe cutaneous adverse reactions and found no significant interactions, with *p* values ranging from 0.1 to 0.8.

Risk of hospital admission by heart disease combined with chronic kidney disease and initial allopurinol dosage

Patients with heart disease and chronic kidney disease who were started on allopurinol at a dosage of greater than 100 mg/d had an 11-fold higher risk of hospital admission for allopurinol-associated severe cutaneous adverse reactions than patients without heart disease or chronic kidney disease who were started at a dosage of 100 mg/d or less (multivariable RR 11.13, 95% CI 4.66–26.58) (Table 3). Among high-risk patients with both heart disease and chronic kidney disease, a lower initial allopurinol dosage of 100 mg/d or less reduced the multivariable adjusted RR from 11.13 to 2.28 (95% CI 0.68–7.58). Even among patients without chronic kidney disease, patients with heart disease who were started on allopurinol at a dosage of greater than 100 mg/d had a threefold increased risk of hospital admission for allopurinol-associated severe cutaneous adverse reactions (multivariable RR 3.44, 95% CI 1.52–7.81).

Risk of hospital admission by heart disease combined with demographic factors

Older women (≥ 70 yr) with heart disease living in a high-risk region (i.e., region with a large Asian population) had a 23-fold higher risk of hospital admission for allopurinol-associated severe cutaneous adverse reactions than younger men (< 70 yr) without heart disease living in a low-risk region (multivariable RR 22.61, 95% CI 7.57–67.60) (Table 4). Presence of comorbid heart disease was consistently associated with higher multivariable adjusted RRs than no heart disease across all combinations of demographic factors, with the exception of 2 categories (women aged < 70 yr living in a high-risk region and men aged ≥ 70 yr living in a high-risk region), where the sample sizes for the cases were low.

Interpretation

In this general population–based study, heart disease was independently associated with an increased risk of hospital admission for allopurinol-associated severe cutaneous adverse reactions. Furthermore, heart disease in combination with other risk factors significantly augmented the risk of hospital admission for these reactions. For example, patients with heart disease and chronic kidney disease who were started on allopurinol at an initial dosage of greater than 100 mg/d had an 11-fold increased risk of hospital admission for allopurinol-associated severe cutaneous adverse reactions compared with patients without heart disease or chronic kidney disease who were started on allopurinol at an initial dosage of 100 mg/d or less. Additionally, when allopurinol is prescribed to patients with cardiorenal

Table 3: Heart disease and risk of hospital admission for allopurinol-associated severe cutaneous adverse reactions, by presence of chronic kidney disease and initial allopurinol dosage

		(+) Heart disease		(–) Heart disease	
Variable	Initial allopurinol dosage	Risk of hospital admission for allopurinol-associated severe cutaneous adverse reactions per 1000 patients (95% CI)	Multivariable relative risk* (95% CI)	Risk of hospital admission for allopurinol-associated severe cutaneous adverse reactions per 1000 patients (95% CI)	Multivariable relative risk* (95% CI)
(+) Chronic kidney disease	> 100 mg/d	4.45 (2.44–7.47)	11.13 (4.66–26.58)	1.41 (0.52–3.06)	4.52 (1.60–12.78)
	≤ 100 mg/d	1.00 (0.27–2.56)	2.28 (0.68–7.58)	0.45 (0.05–1.61)	1.24 (0.27–5.80)
(–) Chronic kidney disease	> 100 mg/d	1.29 (0.75–2.06)	3.44 (1.52–7.81)	0.79 (0.58–1.04)	3.06 (1.50–6.23)
	≤ 100 mg/d	1.02 (0.44–2.01)	2.41 (0.92–6.64)	0.29 (0.13–0.55)	1.00 (Ref.)

Note: CI = confidence interval, Ref. = reference category
*Adjusted for age, sex, region, diabetes, diuretics and gout.

Table 4: Heart disease and risk of hospital admission for allopurinol-associated severe cutaneous adverse reactions, by demographic profiles

Variable	(+) Heart disease		(–) Heart disease	
	Risk of hospital admission for allopurinol-associated severe cutaneous adverse reactions per 1000 patients (95% CI)	Multivariable relative risk* (95% CI)	Risk of hospital admission for allopurinol-associated severe cutaneous adverse reactions per 1000 patients (95% CI)	Multivariable relative risk* (95% CI)
Female sex, region with high Asian population†; age, yr				
≥ 70	3.65 (1.57–7.19)	22.61 (7.57–67.60)	3.12 (1.49–5.73)	20.61 (7.69–57.46)
< 70	1.44 (0.17–5.21)	9.13 (1.82–45.83)	2.60 (1.35–4.55)	17.52 (6.53–47.01)
Female sex, region with low Asian population†; age, yr				
≥ 70	2.30 (1.05–4.37)	13.76 (4.67–40.55)	0.99 (0.43–1.95)	6.42 (2.18–18.87)
< 70	1.63 (0.34–4.78)	9.68 (2.35–39.80)	0.67 (0.29–1.32)	4.38 (1.51–12.73)
Male sex, region with high Asian population†; age, yr				
≥ 70	2.72 (1.17–5.36)	17.10 (5.78–50.55)	2.77 (1.38–4.96)	18.28 (6.73–49.68)
< 70	1.28 (0.42–2.99)	8.43 (2.56–27.77)	0.34 (0.12–0.73)	2.33 (0.75–7.24)
Male sex, region with low Asian population†; age, yr				
≥ 70	0.93 (0.34–2.03)	5.48 (1.70–17.56)	0.45 (0.15–1.05)	2.92 (0.89–9.63)
< 70	0.36 (0.04–1.30)	2.27 (0.45–11.34)	0.14 (0.05–0.32)	1.00 (Ref.)

Note: CI = confidence interval, Ref. = reference category.
*Adjusted for chronic kidney disease, initial allopurinol dosage, diabetes, diuretics and gout.
†Proportion of Asian people in the population by region, according to data from the 2016 Canadian Census, is used here as a surrogate for Asian race, which has the highest prevalence of the *HLA-B*5801* polymorphism.

comorbidities, a starting dosage of 100 mg/d or less, as recommended by a guideline from the American College of Rheumatology,[29] may reduce the risk of hospital admission for allopurinol-associated severe cutaneous adverse reactions by nearly fivefold (from 11.13 to 2.28).

Our findings are applicable to patients with gout, in whom there is a high prevalence of comorbid heart disease[30–33] and chronic kidney disease.[34–36] In light of the US Food and Drug Administration's warning[2] regarding potential cardiovascular adverse effects related to febuxostat,[37] allopurinol use among patients receiving treatment for gout who also have chronic kidney disease and heart disease may be set to increase. These findings may also have implications for clinical trials of allopurinol among at-risk populations. For example, in the Preventing Early Renal Loss in Diabetes (PERL) trial involving patients with type 1 diabetes and chronic kidney disease,[38] all participants were screened for *HLA-B*5801* as a safety measure given the increased risk of allopurinol-associated severe cutaneous adverse reactions in patients with chronic kidney disease. In contrast, the ALL-HEART (Allopurinol and Cardiovascular Outcomes in Patients with Ischaemic Heart Disease) study, which aims to enroll thousands of patients with ischemic heart disease, including patients with chronic kidney disease, implemented no safety measures against allopurinol-associated severe cutaneous adverse reaction and rapidly escalated the allopurinol dosage in the study protocol.[39]

Our findings suggest that heart disease, like chronic kidney disease, is a risk factor for allopurinol-associated severe cutaneous adverse reactions that warrants adoption of precautionary measures against these reactions, such as low-dosage allopurinol initiation or screening for *HLA-B*5801*.

The mechanisms behind the independent association between heart disease and hospital admission for allopurinol-associated severe cutaneous adverse reactions remain unclear. Stevens–Johnson syndrome and toxic epidermal necrolysis are considered to be a delayed-type hypersensitivity reaction mediated by genetic predisposition (especially human leukocyte antigen alleles), drug metabolism, and T- and NK-cell mediated cytotoxicity.[40,41] Future research could clarify whether any of the genetic predispositions or immunologic milieu implicated in the development of Stevens–Johnson syndrome and toxic epidermal necrolysis may also be involved in heart disease pathogenesis. There are also a few case reports of a potential interaction between allopurinol and angiotensin-converting enzyme inhibitors; however, only one such case involved a cutaneous reaction.[42–44]

Our study also confirmed previously reported demographic and clinical risk factors associated with hospital admission for allopurinol-associated severe cutaneous adverse reactions using a Canadian general population database. Older age, female sex, presence of chronic kidney disease, and initial allopurinol dosage

of greater than 100 mg/d were all independently associated with hospital admission for allopurinol-associated severe cutaneous adverse reactions, consistent with those found in the Taiwanese[6] and US Medicaid[8] populations. Furthermore, our study did not find that diuretics were associated with increased risk of allopurinol-associated severe cutaneous adverse reactions, in contrast to prior studies which suggested a link.[45]

Although information on race was not available through Population Data BC, we used prevalence of Asian residents in a health region as a surrogate marker of at-risk race and observed results consistent with those obtained from the US Medicaid population.[8] We also evaluated and found a null association between North American Aboriginal populations and the risk of allopurinol-associated severe cutaneous adverse reactions. Overall low prevalence, lack of sufficient variation across the regions, and lack of association with this ethnicity group could all potentially explain this null association. To this end, while we do not know the specific prevalence of *HLA-B*5801* in North American Aboriginal populations in British Columbia, data on US Native Americans suggest that its frequency is similar to that in white populations. Similarly, the other racial and ethnic groups in BC are too small (< 2%) for meaningful analyses.

We used a comprehensive province-wide database from BC, which has universal health care and thus is expected to capture nearly all health care use among its residents. Thus, this study is more generalizable than the US Medicaid study, which represents more underserved populations. By limiting the time period of allopurinol-associated severe cutaneous adverse reaction development to within 3 months of the first allopurinol prescription, we minimized any potential issues related to early drug discontinuation.

Limitations

As this study relied on ICD codes, misclassification of allopurinol-associated severe cutaneous adverse reactions and relevant comorbidities is possible. Although a prior study found a high degree of accuracy of the ICD codes for these reactions based on dermatologists' review of the medical records,[6] validation of these codes has not been done in the BC database. However, any misclassification is expected to be nondifferential and thus bias the results toward the null, yielding conservative estimates of risk.

Another limitation of this study is the absence of objective data on patients' race. However, we incorporated census-derived prevalence of Asian populations as a surrogate marker of high-risk race and ethnicity reflecting underlying prevalence of *HLA-B*5801*,[25] and the results are closely consistent with what has been shown in other studies that incorporated either *HLA-B*5801* or data on race and ethnicity.[8,11,17,24]

Conclusion

We found that heart disease was independently associated with an increased risk of hospital admission for allopurinol-associated severe cutaneous adverse reactions. Additionally, combinations of heart disease and other risk factors significantly augment the risk of hospital admission for these reactions. However, allopurinol-associated severe cutaneous adverse reactions are notably rare, even among those with multiple risk factors (e.g., 4.45 per 1000 people for those with chronic kidney disease, heart disease and initial allopurinol dosage > 100 mg/d). We were also able to replicate previously reported associations between older age, female sex, chronic kidney disease, and higher initial allopurinol dosage on the risk of hospital admission for allopurinol-associated severe cutaneous adverse reactions in another general population–based database. Physicians who prescribe allopurinol should look for these risk factors so that they may consider initiating lower-dosage allopurinol and other precautions, which may prevent this rare but serious adverse reaction.

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