공학박사 학위논문

Risk of severe cutaneous adverse reactions associated with different urate lowering therapies: a population-based cohort study

통풍 환자에서 요산강하요법에 따른 중증 피부 이상 반응의 위험: 인구 기반 코호트 연구

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한 민 지

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이 논문을 공학박사 학위논문으로 제출함

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한민지의 공학박사 학위논문을 인준함

2025년 7월

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ABSTRACT

Risk of severe cutaneous adverse reactions associated with different urate lowering therapies: a population-based cohort study

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BACKGROUND: Allopurinol, a commonly prescribed urate-lowering therapy (ULT) for gout, has been associated with rare but serious severe cutaneous adverse reactions (SCARs). However, comparative evidence on SCAR risk across different ULTs and associated risk factors remains limited.

OBJECTIVES: To compare the risk of SCAR among new users of allopurinol, febuxostat, and benzbromarone in patients aged 40 and older with gout, and to identify clinical risk factors for allopurinol-associated SCAR.

METHODS: We conducted a nationwide population-based cohort study using data from the Korean National Health Insurance Service (NHIS) between 2010 and 2020. The primary outcome was hospitalization for SCAR, including Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug

reaction with eosinophilia and systemic symptoms (DRESS). Poisson regression models adjusted for age, sex, income, liver and kidney function, diuretic use, and comorbidity burden were used to estimate adjusted relative risks (RRs). Time-specific and subgroup analyses were performed to evaluate SCAR onset timing and associated risk factors.

RESULTS: Among 1,243,819 new ULT users (allopurinol: 673,638; febuxostat: 570,181; benzbromarone: 31,072), 185 SCAR cases occurred within one year, with 99.5% occurring within 180 days of drug initiation. SCAR incidence rates (per 1,000 person-years) were 0.22 (95% CI: 0.18−0.27) for allopurinol, 0.01 (0.00-0.04) for febuxostat, and 0.05 (0.00−0.29) for benzbromarone. The adjusted RR was 16.35 (8.60−40.55) for allopurinol vs. febuxostat and 4.19 (0.92−133.35) vs. benzbromarone. SCAR onset peaked at 31−60 days post-initiation (IR 0.31, 95% CI: 0.25−0.38), with the highest mortality observed at 61−90 days (52.6%). Female sex, diuretic use, high starting dose, and impaired renal function were identified as significant risk factors.

CONCLUSION: Allopurinol users had a significantly higher risk of SCAR compared to those using febuxostat or benzbromarone. The findings support the need for careful drug selection, dose adjustment, and risk-based monitoring, especially among high-risk patients. This study provides real-world evidence to guide safer prescribing practices and SCAR prevention strategies.

KEYWORDS: severe cutaneous adverse reactions, gout, Urate lowering therapies, allopurinol, febuxostat, benzbromarone, a population-based cohort study (Student Number: 2022-31063)

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LIST OF ABBREVIATIONS

ACEI: Angiotensin-Converting Enzyme Inhibitor

ARB: Angiotensin II Receptor Blocker

ATC: Anatomical Therapeutic Chemical (classification)

CI: Confidence Interval

CKD: Chronic Kidney Disease

CV: Cardiovascular

DB: Database

DRESS: Drug Reaction with Eosinophilia and Systemic Symptoms

DRI: Drug-Immune Receptor Interaction

eGFR: Estimated Glomerular Filtration Rate

EM: Erythema Multiforme

ER: Emergency Room

HR: Hazard Ratio

ICD-10: International Classification of Diseases, 10th Revision

KNHIS: Korean National Health Insurance Service

MDRD: Modification of Diet in Renal Disease (Equation)

MI: Myocardial Infarction

NHSP: National Health Screening Program

NSAID: Nonsteroidal Anti-Inflammatory Drug

PY: Person-Years

RR: Relative Risk

SCAR: Severe Cutaneous Adverse Reaction

SD: Standard Deviation

SJS: Stevens-Johnson Syndrome

TEN: Toxic Epidermal Necrolysis

TIA: Transient Ischemic Attack

ULT: Urate-Lowering Thera

CHAPTER 1. INTRODUCTION

1.1. STUDY BACKGROUND

Gout is a common chronic inflammatory arthritis caused by the deposition of monosodium urate (MSU) crystals in synovial joints and surrounding soft tissues, resulting from longstanding hyperuricemia (Kuo et al., 2015). The prevalence of gout has been increasing globally, including in Korea (Kang et al., 2024; Krishnan & Chen, 2013), largely due to aging populations, dietary patterns, and comorbid conditions such as hypertension, obesity, and chronic kidney disease (Kuo et al., 2015). In South Korea, the prevalence of gout increased from 0.35% in 2008 to 0.76% in 2019 (J. W. Kim et al., 2017). Along with this rising trend, the prescription of urate-lowering therapy (ULT) has steadily increased. According to data from the Health Insurance Review and Assessment Service (HIRA), allopurinol was prescribed to approximately 670,000 patients in 2019 (HIRA, 2019).

International guidelines for the management of gout recommend the use of allopurinol as the first-line urate-lowering therapy (ULT), with a switch to alternative

ULT drugs, such as febuxostat or uricosurics, in cases of inefficacy or intolerance (FitzGerald et al., 2020; Richette et al., 2017). As such, allopurinol is the most widely prescribed medication for patients with gout worldwide (Kang et al., 2024; Krishnan & Chen, 2013). Its long clinical history, cost-effectiveness and safety for a wide range of patients make it the preferred choice for most. However, febuxostat is gradually becoming the first-line urate-lowering agent in Asian countries due to the risk of allopurinol associated adverse events, greater potency, and real-world clinical experience (Kang et al., 2024; Lin et al., 2019).

Meanwhile, the risk of severe cutaneous adverse reactions (SCAR) associated with allopurinol has been well documented in numerous studies (Hung et al., 2005). Reflecting this, the Korean National Health Insurance began reimbursing HLA-B*58:01 genotyping as of July 1, 2019 (Ministry of Health and Welfare, 2019). However, newer agents such as febuxostat and benzbromarone have been used for a shorter period and lack sufficient cumulative evidence, leaving the comparative risk of SCAR among the three urate-lowering therapies still insufficiently established (Lin et al., 2019; O’ Dell et al., 2022).

In this context, it is critically important to investigate and compare the risk of severe cutaneous adverse reactions associated with different urate lowering therapies that are currently used in real world clinical practice in Korea. It is also important to explore the clinical and immunological basis for any differences in risk. This study aims to provide evidence regarding the relative risk of each agent and to offer foundational data that can support safe and patient

centered prescribing decisions. This study may ultimately serve as a basis for developing personalized screening strategies for SCAR risk and support clinical decision-making for the safe selection of urate-lowering therapies.

1.2. MOLECULAR MECHANISMS OF GOUT AND URIC ACID METABOLISM

Uric acid is the final product of purine metabolism. It is generated through a two-step oxidation process in which hypoxanthine is converted to xanthine, and then to uric acid, both catalyzed by the enzyme xanthine oxidase (Cicero et al., 2023; Pacher et al., 2006). Unlike most mammals, humans lack the enzyme uricase, which converts uric acid to allantoin, a more soluble metabolite. This absence leads to a predisposition to hyperuricemia and urate crystal deposition, particularly in joints and renal tissues, resulting in inflammation and gout flares (Maiuolo et al., 2016).

The serum urate concentration is tightly regulated by a balance between production and renal excretion. The proximal tubule of the kidney plays a pivotal role in uric acid reabsorption and secretion, primarily via several key transporters such as GLUT9, URAT1 (SLC22A12), and OAT1/3 (SLC22A6/8) (Dalbeth et al., 2019; Dalbeth et al., 2021). Among them, URAT1 is considered a major reabsorptive transporter and a target of uricosuric therapies.

Currently, the ULTs widely used in South Korea differ in their molecular targets and

mechanisms of action:

Allopurinol is a purine analog that inhibits xanthine oxidase, thereby blocking the conversion of hypoxanthine and xanthine into uric acid. Its active metabolite, oxypurinol, binds irreversibly to the enzyme (Pacher et al., 2006).

Febuxostat is a non-purine selective xanthine oxidase inhibitor, which inhibits both the oxidized and reduced forms of the enzyme with high specificity. Unlike allopurinol, it does not interfere with other enzymes involved in purine or pyrimidine metabolism, which may result in fewer off-target effects (Dalbeth et al., 2021).

Benzbromarone acts as a uricosuric agent by inhibiting URAT1 in the renal tubules, thus enhancing uric acid excretion. It is metabolized by CYP2C9 and has been associated with hepatotoxicity, leading to restrictions in some countries. However, it remains in clinical use in South Korea (Maiuolo et al., 2016).

As illustrated in Figure 1, urate-lowering therapies exert their effects at distinct points in purine metabolism and urate handling. Xanthine oxidase inhibitors such as allopurinol and febuxostat reduce uric acid synthesis, whereas benzbromarone increases renal excretion by inhibiting URAT1 (Burns & Wortmann, 2011). These mechanistic differences may underlie varying risks of SCAR associated with each agent. In particular, the interaction between xanthine oxidase inhibitors and immune pathways is a key hypothesis guiding the investigation in this study.

These mechanistic distinctions among urate-lowering therapies not only underlie their clinical pharmacology but may also modulate immune activation pathways implicated in severe cutaneous adverse reactions. In particular, differences in metabolic transformation and enzyme interaction could contribute to drug-specific

hypersensitivity risks, which will be examined further in the next section.

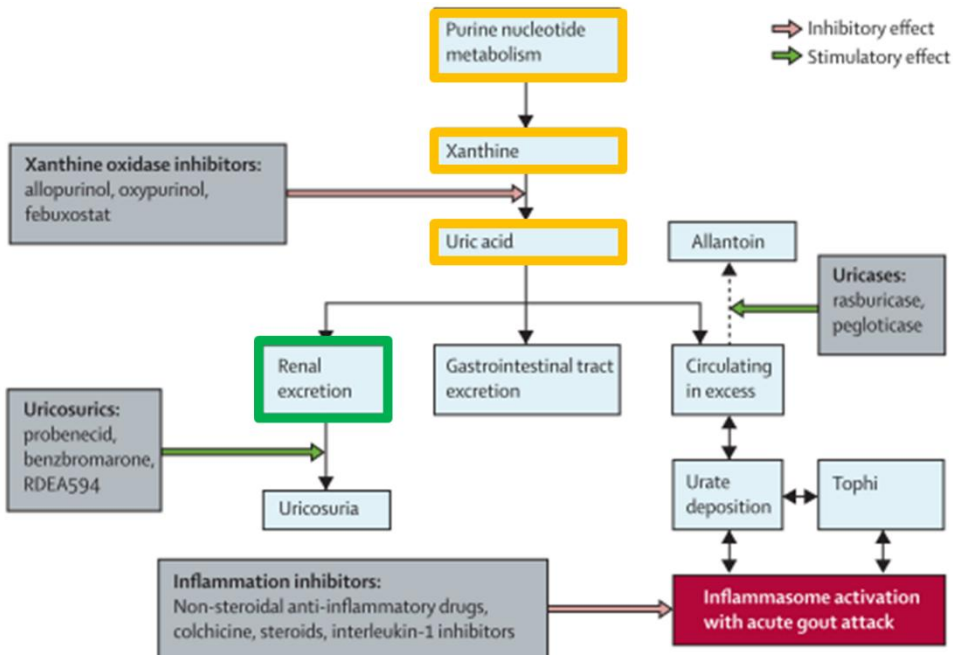


Figure 1. Targets for intervention in the treatment and prophylaxis of gout

Purine nucleotide degradation leads to uric acid production via xanthine oxidase. Urate-lowering therapies act at different stages: allopurinol and febuxostat inhibit xanthine oxidase; benzbromarone enhances renal uric acid excretion by targeting URAT1; and uricase agents promote urate conversion to allantoin. These mechanisms serve as key targets for controlling hyperuricemia and preventing gout flares.
Adapted from Burns and Wortmann (2011), The Lancet (Burns & Wortmann, 2011).

1.3. IMMUNOLOGICAL MECHANISMS OF SCAR

SCAR are rare but potentially fatal T cell–mediated drug hypersensitivity syndromes. Clinically, SCAR encompasses distinct phenotypes such as Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), and generalized bullous fixed drug eruption (GBFDE) (Duong et al., 2017; Hung et al., 2024; Mockenhaupt, 2012). Among these, SJS/TEN and DRESS are the most severe and are associated with significant long-term complications and mortality (Halevy et al., 2008; Roujeau et al., 1995; Wang et al., 2019; Wasuwanich et al., 2023).

As illustrated in Figure 2, SCAR pathogenesis is driven by a multistep immune process beginning with drug presentation by HLA molecules to clonotypic T cell receptors (TCRs) on cytotoxic or helper T cells (Chang et al., 2020). This interaction can occur via multiple mechanisms including the p-i concept (pharmacological interaction with immune receptors), altered peptide repertoire, or hapten hypothesis (Ostrov et al., 2012).

Well-established pharmacogenetic associations include HLA-B*15:02 with carbamazepine-induced SJS/TEN (Chang et al., 2020; Cheng et al., 2014), HLA-B*57:01 with abacavir hypersensitivity (Chessman et al., 2008; Mallal et al., 2008), and HLA-B*58:01 with allopurinol-induced SCAR, particularly SJS/TEN (Hung et al., 2005). These associations have led to clinical implementation of genetic screening in several countries, including Korea, where HLA-B*58:01 testing is reimbursed for patients initiating allopurinol (Kang et al., 2019).

In SJS/TEN, activated CD8+ cytotoxic T lymphocytes (Tc1) release high levels of granulysin, granzyme B, and perforin, leading to keratinocyte apoptosis and widespread epidermal detachment (Hung et al., 2024). Granulysin, in particular, has been identified as the central mediator of tissue necrosis and is abundant in blister fluid. Additional mediators such as IL-15, FasL, TRAIL, and TNF amplify the inflammatory cascade (Chung et al., 2015).

By contrast, DRESS is characterized by a Th2/Tc2-skewed immune response, involving cytokines such as IL-4, IL-5, IL-13, and eosinophilia. It frequently involves visceral organs (liver, lungs, kidneys) and may be exacerbated by viral reactivation (HHV-6, EBV, CMV) and JAK−STAT signaling (Chen et al., 2010; Kardaun et al., 2013). Innate lymphoid cells (ILC2), TARC, and other cytokine pathways contribute to inflammation amplification. Non−T cell components such as macrophages, dendritic cells, neutrophils, and NK/NKT cells further propagate tissue injury in both phenotypes (Mockenhaupt, 2012).

Among urate-lowering agents, allopurinol has the most clearly established pharmacogenetic link to SCAR via HLA-B*58:01 (Hung et al., 2005; Lonjou et al., 2008). The mechanism is thought to involve the presentation of oxypurinol-modified peptides or direct pharmacologic interaction with TCRs (Hung et al., 2024). In contrast, febuxostat and benzbromarone have not demonstrated definitive HLA associations, but isolated SCAR cases (e.g., SJS or DRESS) have been reported, suggesting alternative pathways such as reactive metabolite formation, CYP polymorphism, or non-HLA immune activation.

In summary, SCAR reflects a complex immunogenetic process involving drug metabolism, antigen processing, genetic predisposition (HLA), TCR repertoire,

and cytokine-mediated tissue damage. The allopurinol–HLA-B*58:01–Tc1 axis provides a model for understanding how molecular specificity translates to clinical immunotoxicity, as visualized in Figure 2 (Hung et al., 2024). Whether similar mechanisms or distinct ones are involved in SCAR induced by febuxostat or benzbromarone remains a critical question that this study aims to address.

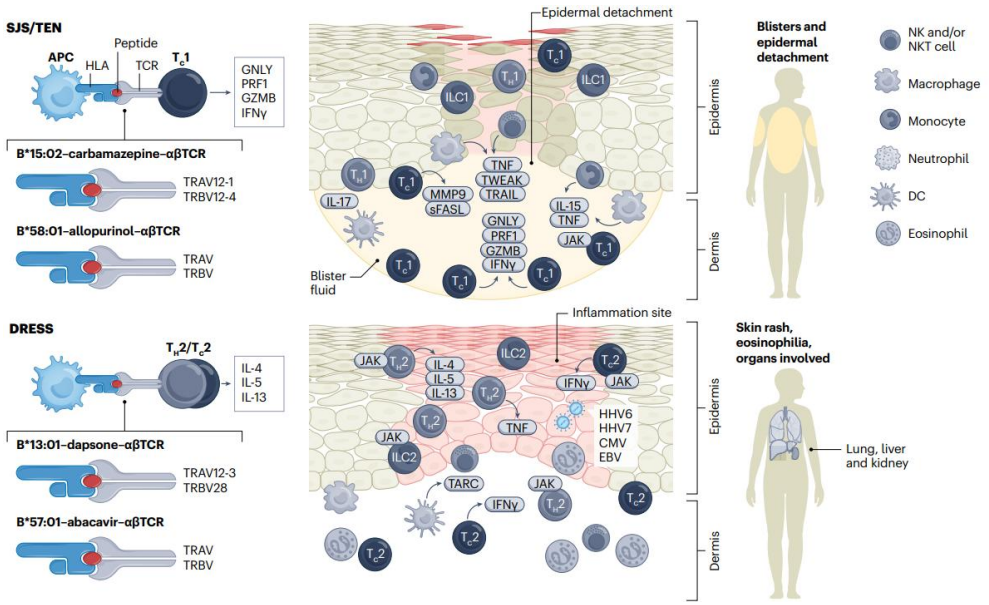


Figure 2. Pathophysiological mechanisms in SCARs

This figure illustrates the molecular and immunological mechanisms underlying different phenotypes of severe cutaneous adverse reactions (SCAR). In SJS/TEN (top panel), drug antigens are presented by HLA molecules (e.g., HLA–B15:02, HLA–B58:01) and recognized by clonotypic cytotoxic CD8+ T cells (Tc1), leading to the release of granulysin, perforin, and granzyme B, which induce keratinocyte apoptosis and epidermal detachment. Innate immune cells and cytokines such as IL–15, TRAIL, TNF, and sFASL amplify the inflammatory response. In DRESS (bottom panel), the immune response is dominated by Th2/Tc2 cells and innate lymphoid cells (ILC2), which produce cytokines including IL–4, IL–5, and IL–13, promoting eosinophilic inflammation, viral reactivation (e.g., HHV–6, EBV, CMV), and multiorgan involvement. JAK–STAT signaling and other mediators such as TARC and IFN–γ further contribute to systemic inflammation.

APC = Antigen−Presenting Cell, HLA = Human Leukocyte Antigen, TCR = T Cell Receptor, T_1 /T_2 = T helper cell subsets, DC = Dendritic Cell, NK = Natural Killer cell, IL = Interleukin, IFN γ = Interferon gamma, TNF = Tumor Necrosis Factor, PRF1 = Perforin 1, GZMB = Granzyme B, TRAV/TRBV = TCR α/β variable region genes, JAK = Janus Kinase, HHV6/7 = Human Herpesvirus 6/7, CMV = Cytomegalovirus, EBV = Epstein–Barr Virus, TARC = Thymus and Activation−Regulated Chemokine Adapted from Hung S.I., Mockenhaupt M., Blumenthal K.G., et al. Nat Rev Dis Primers. 2024; 10:30 (Hung et al., 2024).

1.4. REAL-WORLD COMPARATIVE EVIDENCE REVIEW

While the immunological mechanisms of SCAR, including the role of HLA-B*58:01 and CD8+ T cell–mediated cytotoxicity, have been described in previous sections, population-level epidemiological data and clinical outcome comparisons between urate-lowering therapies remain limited. This section summarizes existing evidence regarding the incidence, severity, and clinical significance of SCAR associated with allopurinol, febuxostat, and benzbromarone, highlighting major gaps in real-world data.

The HLA-B*58:01 allele is more prevalent in specific ethnic populations such as Han Chinese (approximately 7-8%) (Kurose et al., 2012; Stamp et al., 2016), Taiwan (20-25%) (Ko et al., 2015; Kurose et al., 2012), Thai (8-15%) (Sukasem et al., 2016), and Koreans (6-12%) (Kang et al., 2024; Kurose et al., 2012) correlating with the higher incidence of allopurinol-induced SCAR in these groups. In contrast, its frequency is significantly lower in Europeans (0.7-0.8%) (Kurose et al., 2012; Lonjou et al., 2008) and Japanese (0.4-0.6%) (Kaniwa et al., 2008; Kurose et al., 2012; Stamp et al., 2016) These ethnic disparities in allele prevalence directly

contribute to varying risks of allopurinol-induced SCAR across populations. The strong association between HLA-B58:01 and allopurinol-induced SCAR has led to the recommendation of genetic testing in high-risk ethnic populations prior to the initiation of allopurinol treatment, with the aim of reducing the incidence of these reactions (Tse et al., 2022). A study in Taiwan demonstrated that pre-testing for HLA-B58:01 significantly reduced the incidence of allopurinol-induced SCAR, with no cases observed among HLA-B58:01 negative participants who received allopurinol (Ko et al., 2015; Lin et al., 2019). Although HLA-B*58:01 is a major risk factor, SCAR can occur in its absence, suggesting that other genetic and non-genetic factors contribute to susceptibility (Stamp & Barclay, 2018; Stamp et al., 2016; Stamp et al., 2012). In fact, clinical factors such as chronic kidney disease (CKD) and the initial allopurinol dose have also been found to increase the risk of allopurinol-induced SCAR (Chung et al., 2015; Stamp et al., 2012; Yokose et al., 2019).

Febuxostat was considered as an alternative to allopurinol, particularly for patients with a history of allopurinol hypersensitivity or impaired renal function (Stamp & Barclay, 2018). The non-purine structure of the drug theoretically indicates a different and safer immunological profile (Afinogenova et al., 2022). However, febuxostat-induced SCAR has been, albeit rarely, reported in post-marketing surveillance (Chou et al., 2015; Tsai et al., 2023). The mechanism of febuxostat-induced SCAR is not fully understood, but it has been postulated that immunogenetic pathways similar to allopurinol-induced SCAR are involved (Lin et al., 2019; Paschou et al., 2016).

Benzbromarone, a highly effective uricosuric, was not approved in the U.S. due to rare but fatal hepatotoxicity (Zhang et al., 2006), with an estimated risk of one in

17,000 (Afinogenova et al., 2022; Castrejon et al., 2015). The incidence of SCAR induced by benzbromarone is not well defined, but appears to be lower than by allopurinol. However, no population-based study has quantified the SCAR risk associated with benzbromarone.

Despite the increasing prevalence of gout in population ageing and inevitable increase in ULT use, there is a need to study these rare but potentially fatal SCARs. Population-based comparisons of ULTs are still lacking. Robust real-world clinical evidence regarding SCARs associated with febuxostat and benzbromarone is also lacking, particularly with regard to their incidence, severity, and timing of occurrence. Furthermore, no previous study has integrated multiple SCAR definitions, subgroup risk stratification and temporal risk distribution analysis using a large national cohort.

1.5. CO-MEDICATIONS ASSOCIATED WITH SCAR RISK

In a Korean multicenter registry of 745 SCAR cases fulfilling the RegiSCAR criteria, allopurinol was identified as the most common causative drug (14.0%), followed by carbamazepine and vancomycin. Notably, allopurinol was associated predominantly with SJS/TEN rather than DRESS, confirming its high-risk status in East Asian populations (Kang et al., 2021)

Among the various drug classes associated with SCARs, two

pharmacological categories account for the majority of reported cases: neuropsychiatric agents and anti-infective agents.

First, neuropsychiatric agents, especially aromatic anticonvulsants such as carbamazepine, phenytoin, lamotrigine, and valproic acid, have been consistently implicated in both SJS/TEN and DRESS. These agents are widely used for epilepsy (ICD-10: G40), trigeminal neuralgia (G50.0), and bipolar disorder (F31), and are known to interact with specific HLA alleles—most notably HLA-B*15:02 in East Asian populations—to trigger SCAR through T-cell-mediated delayed hypersensitivity mechanisms. Even commonly used analgesics such as acetaminophen have been linked to SJS/TEN in observational studies, although with a lower incidence rate (Kang et al., 2021; Kang et al., 2019).

Second, a broad array of anti-infective agents is frequently associated with SCAR. These include: β-lactam antibiotics such as amoxicillin, cefaclor, ceftriaxone, and piperacillin-tazobactam; antituberculous agents like isoniazid and rifampicin; sulfonamide derivatives, particularly sulfamethoxazole-trimethoprim and dapsone; glycopeptides such as vancomycin; and fluoroquinolones including ciprofloxacin and levofloxacin (Kang et al., 2021; Kang et al., 2019).

These agents are primarily used for respiratory, urinary, and systemic infections (ICD-10: J18, N39.0, A15), and are thought to induce SCAR either through reactive metabolites or by stimulating cytotoxic T cells in genetically susceptible individuals. Some drugs, such as methazolamide, although less frequently used, have shown high specificity for SJS/TEN (Kang et al., 2021; Roujeau et al., 1995).

Taken together, the concentration of SCAR risk in these two therapeutic domains (neuropsychiatric and anti-infective) underscores the need to consider these co-medications as potential confounders in pharmacoepidemiological analyses of drug-induced SCAR. In real-world settings, patients prescribed urate-lowering therapy may concomitantly use these high-risk agents, particularly among those with comorbid epilepsy, infectious diseases, or immune suppression. Therefore, appropriate adjustment or stratification for these co-medications is essential to ensure valid risk estimation in comparative safety studies.

1.6. OBJECTIVES AND RESEARCH QUESTIONS

Objectives:

In this context, we aim to provide an overview for SCARs associated with different ULT drugs by comparing the population-based risk between allopurinol, febuxostat, and benzbromarone initiators. We also seek to identify SCAR risk factors using the nationally representative Korean National Health Insurance Service (KNHIS) database.

Research Questions:

1. How does the risk of SCAR differ among new users of allopurinol, febuxostat, and benzbromarone in a real-world population of gout patients?
2. Does this difference persist across various outcome definitions and analysis strategies?
3. What is the time distribution of SCARs and related mortality following individual ULT?
4. What patient- and treatment-related factors contribute to the increased risk of allopurinol-induced SCAR, and how do renal function and dosage interact to modify this risk?

The risk of SCAR varies depending on the urate-lowering therapy used, yet current evidence is predominantly limited to allopurinol. In particular, there is a lack of robust population-based data on SCAR risk associated with newer agents such as febuxostat and benzbromarone, especially in real-world clinical settings.

This dissertation aims to compare the risk of SCAR associated with three major urate-lowering therapies in patients with gout and to identify clinically and immunologically relevant factors that may explain observed differences.

Chapter 1 introduces the clinical and molecular background of gout, reviews the mechanisms of urate-lowering therapies, outlines the immunopathogenesis of SCAR, and identifies research gaps based on prior evidence.

Chapter 2 describes the study design, data sources, cohort construction, outcome definition, and statistical analysis strategies using a nationwide Korean healthcare database.

Chapter 3 presents the incidence rates and risk estimates of SCAR for each drug, including subgroup and heterogeneity analyses.

Chapter 4 discusses the clinical, epidemiological, and mechanistic implications of the findings, as well as public health and regulatory relevance.

Finally, **Chapter 5** summarizes the study's limitations and contributions, and proposes directions for future research.

CHAPTER 2. METHODS

2.1. STUDY DESIGN

A population-based cohort study was conducted using a new user design to evaluate the risk of severe cutaneous adverse reactions (SCARs) associated with different urate-lowering therapies (ULTs) in patients with gout. This approach was adopted to minimize bias related to confounding by indication or treatment failure to previous drug use and to ensure temporal clarity between drug initiation and outcome occurrence.

2.2. DATA SOURCE

The present study utilised data from the KNHIS, a nationwide, government-operated, mandatory health insurance system that covers approximately 97% of the South Korean population (Cheol Seong et al., 2017). The KNHIS database has been found to comprehensively capture real-world healthcare data, including sociodemographic information (age, sex, income level), medical records (the International Classification of Diseases, 10th revision (ICD-10) diagnoses, procedures, prescriptions), prescription information, and healthcare utilization data (outpatient visits, hospitalizations, and emergency visits). KNHIS can be linked to the National health screening programme (NHSP) data (Kang, 2022), which offers to all insured adults aged ≥40 years or employees aged ≥20 years. The NHSP datasets comprise self-reported questionnaires on lifestyle behaviours (e.g. smoking, alcohol consumption, physical activity), anthropometric measurements (height, weight, waist circumference, and BMI), cardiometabolic (e.g., blood pressure (BP), fasting blood glucose, and lipid profile), hepatic and renal parameters, chest radiography, and visual and hearing acuity (Kang, 2022). The participation rate for NHSP during 2010-2015 was beyond 70%.

2.3. STUDY POPULATION

The study population consisted of gout patents identified based on the ICD-10 diagnosis codes (M10.x) and aged ≥40 years, who initiated allopurinol, febuxostat or benzbromarone between 2011 and 2020. The index date was defined as the first prescription date of the study drug free of a previous prescription of the given drug for the pre-index 365 days (= baseline period). Individual patients were allowed to enter the study cohort only single time at an earliest qualification. Patients with a prior history of SCARs during the 365-day baseline period preceding the index date were excluded to ensure incident SCARs. Individuals with end-stage renal disease (ESRD) were excluded at baseline. This is defined by diagnostic codes for chronic kidney disease stage 5, ESRD, or procedure codes indicating hemodialysis or peritoneal dialysis. The selection process for the study cohort is shown in **Figure 3**. The ICD-10 and procedural codes and medications used to define the study population are detailed in **Table 1** and **Table 2**.

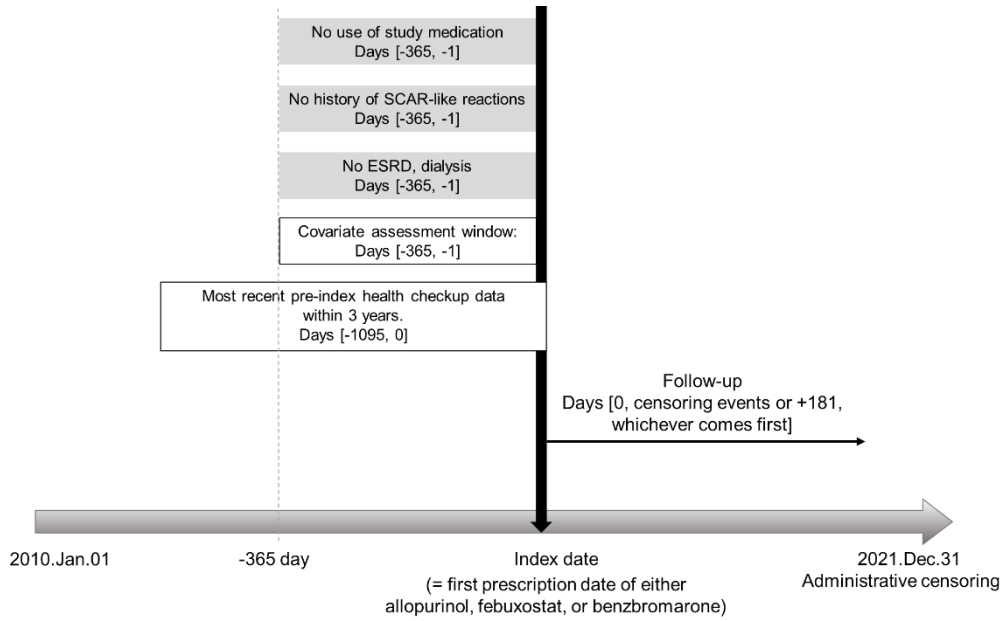


Figure 3. Schematic study design

ESRD = End Stage Renal Disease, SCAR = Severe Cutaneous Adverse Reactions, ULT = Urate Lowering Therapy, DB = Database

Table 1. Definitions of the study population based on ICD-10 and procedure codes

(A) Definitions of ICD-10 codes

Category	ICD-10 codes	ICD-10 item names
Inclusion criteria		
Gout	M10.x	Gout
Exclusion criteria		
SCAR-like reactions	L51.x	Erythema multiforme
	L53.x	Other erythematous conditions
	L27.x*	Dermatitis due to substances taken internally
ESRD	N18.5	Chronic kidney disease, stage 5
	N18.6	End stage renal disease
	Z99.2	Dependence on renal dialysis

ESRD = End Stage Renal Disease, * L27.2 (dermatitis due to ingested food) and L27.8 (dermatitis due to other substances taken internally) were excluded from the L27.x category.

(B) Definitions of Procedure codes

Category	Procedure codes
Exclusion criteria	
Dialysis	O7011-O7018, O7020, O7021, O7031-O7035, O7040, O7041, O7051-O7055, O7061, O7062, O7071-O7075, O7080, O7081

Table 2. Medication codes related to measure of exposure

Medications	Codes	Dose
Allopurinol	105001ATB	100mg
	105002ATB	200mg
	105003ATB	300mg
Febuxostat	567401ATB	80mg
	567403ATB	40mg
benzbromarone	115601ATB	50mg

2.4. OUTCOMES

The primary outcome was a composite of hospitalized cases of Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), erythema multiforme (EM), and DRESS, with the requirement of no further use of the index drug after the hospitalization episode. We used the ICD-10 diagnosis codes in a primary position among the discharge diagnoses to ascertain the outcome: L51.1 for SJS, L51.2 for TEN, L51.0, L51.8, L51.9 for EM, and L27.0 for DRESS (**Table 3** for ICD-10 diagnoses codes used to define study outcome). Secondary outcomes were defined as SJS/TEN combined, EM, and DRESS, based on the concept that SJS and TEN are all on the same spectrum and that there is a frequent overlap between the two (Halevy et al., 2008). In order to enhance the specificity of the study, other erythematous conditions (L53.x) and localized skin eruptions due to drugs and medicaments (L27.1) that had been used in other studies (Halevy et al., 2008; Keller et al., 2018; Lin et al., 2019) were excluded.

Table 3. ICD-10 codes used to define outcomes

Subtypes of SCAR	ICD-10 codes	ICD-10 item names
SJS	L51.1	Bullous erythema multiforme
TEN	L51.2	Toxic epidermal necrolysis [Lyell]
EM	L51.0	Non-bullous erythema multiforme
	L51.8	Other erythema multiforme
	L51.9	Erythema multiforme, unspecified
DRESS	L27.0	Generalized skin eruption due to drugs and medicaments
Dermatitis due to substances taken internally	L27.1	Localized skin eruption due to drugs and medicaments taken internally
Other specified erythematous conditions	L26.x	Exfoliative dermatitis
	L30.4	Erythema intertrigo
	L53.8	Other specified erythematous conditions
	L92.0	Granuloma annulare
	L95.1	Erythema elevatum diutinum
	L98.2	Febrile neutrophilic dermatosis [Sweet]
Unspecified erythematous condition	L53.9	Erythematous condition, unspecified

DRESS = drug reaction with eosinophilia and systemic symptoms, EM = erythema multiforme, SJS = Stevens-Johnson Syndrome, TEN = Toxic epidermal necrolysis

2.5. COVARIATES

We collected demographic and socioeconomic information, gout and non-gout medications, cardiovascular (CV) and non-CV comorbidities, and healthcare utilization measures (hospitalizations, emergency room visits, and outpatient visits) for the baseline period. **Table 4** for ICD-10 diagnoses codes used to comorbidities. Charlson-Deyo comorbidity scores were also obtained to assess comorbidities (Sundararajan et al., 2004).

To account for potential confounding by high risk medications known to induce SCAR, such as anticonvulsants and anti-infective agents, we constructed proxy variables based on underlying diseases that are commonly treated with these drugs. Due to data limitations, we were unable to obtain prescription records for these drug categories, as anticonvulsants and anti-infective agents were not included in the original data request submitted to the National Health Insurance Service. Therefore, instead of directly adjusting for medication use, we defined and adjusted for high risk disease categories for which such drugs are frequently prescribed.

For anticonvulsants, we included the following diagnostic codes recorded within 1 year before the index date: (1) epilepsy (G40), (2) trigeminal neuralgia (G500), (3) bipolar disorder (F313-F315). For anti-infective agents, we identified common infection types including (1) bacterial gastroenteritis (A00-A09), (2) bacterial pneumonia (J12-J18), (3) influenza and secondary bacterial pneumonia (J09-J18), (4) urinary tract infections including pyelonephritis and cystitis (N10, N12, N30, N390), and (5) skin infections (L00-L08). These diagnostic categories were included as binary covariates in the multivariable Poisson regression models to

mitigate confounding related to underlying risk of SCAR associated drug exposure.

Table 4. Definitions of the comorbidities based on ICD-10 codes

Diseases	ICD-10 codes	ICD-10 item names
Myocardial infarction		
	I21.x	Acute myocardial infarction
Other heart diseases		
	I26.x-I28.x	Pulmonary heart disease and diseases of pulmonary circulation
	I30.x-I52.x	Other forms of heart disease
Stroke		
	I60.x	Subarachnoid haemorrhage
	I61.x	Intracerebral haemorrhage
	I62.x	Other nontraumatic intracranial haemorrhage
	I63.x	Cerebral infarction
	I64.x	Stroke, not specified as haemorrhage or infarction
Diabetes mellitus		
	E10.x-E14.x	Diabetes mellitus
Dyslipidemia		
	E78.0	Pure hypercholesterolaemia
	E78.1	Pure hyperglyceridaemia
	E78.2	Mixed hyperlipidaemia
	E78.3	Hyperchylomicronaemia
	E78.4	Other hyperlipidaemia
	E78.5	Hyperlipidaemia, unspecified
Hypertension		
	I10.x -I15.x	Hypertensive diseases
Heart failure		
	I50.x	Heart failure
Chronic kidney disease		
	N03.x	Chronic nephritic syndrome

	N08.x	Glomerular disorders in diseases classified elsewhere
	N18.1–N18.4	Chronic kidney disease, stage 1–4
	N19.x	Unspecified kidney failure
	N25.x	Disorders resulting from impaired renal tubular function
	N26.x	Unspecified contracted kidney
Liver disease		
	K70.x–K77.x	Diseases of liver
	B18.x	Chronic viral hepatitis
Neurologic disease		
	G40.x	Epilepsy and recurrent seizures
	G50.0	Trigeminal neuralgia
	F31.3	Bipolar disorder, current episode depressed, mild or moderate severity
	F31.4	Bipolar disorder, current episode depressed, severe, without psychotic features
	F31.5	Bipolar disorder, current episode depressed, severe, with psychotic features
Respiratory tract infection disease		
	A00.x–A09.x	Intestinal infectious diseases
	J00.x–J06.x	Acute upper respiratory infections
	J09.x–J18.x	Influenza and pneumonia
	J20.x–J22.x	Other acute lower respiratory infections
	J85	Abscess of lung and mediastinum
Gastrointestinal infection disease		
	K57.x	Diverticular disease of intestine
	K60.x	Fissure and fistula of anal and rectal regions

	K63.0	Abscess of intestine
	K63.1	Perforation of intestine (nontraumatic)
	K63.2	Fistula of intestine
	J17.x	Pneumonia in diseases classified elsewhere
	J18.x	Pneumonia, unspecified organism
	J19.x	
Skin and soft tissue infection disease		
	L00.x–L08.x	Infections of the skin and subcutaneous tissue
Genitourinary infection disease		
	N10.x	Acute tubulo–interstitial nephritis
	N12.x	Tubulo–interstitial nephritis, not specified as acute or chronic
	N30.x	Cystitis
	N39.0	Urinary tract infection, site not specified

2.6. STATISTICAL ANALYSES

As our primary analysis, we performed a 180-day as-treated analysis. The observation period for each patient started from the day after the index date and was censored at the earliest of the following events: (a) the occurrence of SCARs; (b) the discontinuation of ULT; (c) the switching or addition of other ULTs; (d) death; or (e) 181th day after the index date.

This 180-day risk period was established based on existing literature reporting that >90% of all allopurinol hypersensitivity reactions occur within this time frame (Sato et al., 2021). Drug discontinuation was defined as no refills within 90 days from the last prescription date plus days' supply. Treatment changes included study drug discontinuation, adding of and switching to other ULT, which resulted in immediately censoring.

The event rate was calculated as the number of new cases of SCAR within a 180-day period per 1,000 new users of the study drug (Keller et al., 2018; Yang et al., 2015). Given that the vast majority of SCAR events occur early after drug initiation, with over 95 percent arising within the first 180 days (Kuo et al., 2015; Roujeau et al., 1995), a fixed follow up period allows for clinically meaningful estimation of absolute risk. This approach is particularly relevant for drug safety evaluation, where the focus lies in understanding how many adverse events occur among patients exposed over a standardized treatment window.

The relative risks (RRs) and 95% confidence intervals (CIs) were estimated by Poisson regression models with a log link and robust standard errors (Greenland, 2004; Zou, 2004). Poisson models were selected as the primary

analytic framework to directly compare event rates across treatment groups, offering a more interpretable measure than hazard ratios in contexts with short follow up and rare outcomes (McNutt et al., 2003). Additionally, the method avoids interpretive complexity associated with person time metrics and allows direct estimation of the cumulative probability of adverse events within the defined time frame (Zou, 2004). Four sequential models were constructed:

1) a crude model with no covariate adjustment,
2) a model adjusted for age, sex, income level, liver disease, estimated glomerular filtration rate (≥60, ≥30 and <60, <30), diuretic use, and comorbidity score,
3) Model 2 plus adjustment for psychiatric conditions commonly treated with anticonvulsants (e.g., epilepsy [G40], trigeminal neuralgia [G50.0], bipolar disorder [F31.3−F31.5]),
4) Model 3 plus adjustment for infectious conditions likely requiring anti-infective agents (e.g., bacterial gastroenteritis [A00−A09], acute upper respiratory infections [J00-J06], influenza and pneumonia [J09−J18], Other acute lower respiratory infections [J20−J22], abscess of lung and mediastinum [J85], Gastrointestinal infections [K57, K60, K61, K63.0, K63.1, K63.2], skin and soft tissue infections [L00−L08], and genitourinary infections [N10, N12, N30, N39.0]).

Secondary analyses were conducted using Cox regression models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Prior to

interpreting the results, we conducted statistical tests to verify the proportional hazards assumption of the Cox regression model. Given the robust correlation between drug hypersensitivity reactions and specific HLA genotypes, such as HLA-B*58:01 for allopurinol (Cheng et al., 2014; Chessman et al., 2008; Fricke-Galindo et al., 2017; Hung et al., 2005; E. Y. Kim et al., 2017; Stamp et al., 2016), the primary determinant of risk is genetic predisposition rather than disease severity. Consequently, disparities in gout severity between allopurinol and other ULT users are less likely to result in substantial confounding in hypersensitivity risk comparisons.

To account for the early clustering of SCAR events following study drug initiation, we assessed the proportional hazards assumption prior to model selection. Given that nearly all SCAR cases occurred within 180 days, and the proportional hazards assumption was violated during this risk window, we employed Poisson regression models as the primary analytical method. These models were used to estimate relative risks (RRs) and 95% confidence intervals, incorporating person-time as an offset term. Cox proportional hazards models were conducted as secondary analyses and presented in the appendix for comparison purposes (Bradburn et al., 2003).

Thus, we adjusted mainly for potential SCAR risk factors including age, sex, income, liver disease, ordinal level (<30, ≥30 & <60, ≥60) of estimated glomerular filtration rate (eGFR) per mL/min/1.73m^2 by modification of diet in renal disease (MDRD) equation, diuretics use, and comorbidity scores (Levey et al., 2009). A Wald test for linear trend was applied in order to evaluate the presence of a statistically significant trend across the ordered categories of ordinal variables.

This approach involves the testing of a consistent increase or decrease in the outcome as the level of the ordinal variable increases.

2.7. SUBGROUP ANALYSES

Due to the limited number of SCAR cases in the non-allopurinol groups, subgroup analyses were restricted to patients receiving allopurinol. These analyses were stratified by age (<60 vs. ≥60 years), sex, presence of high cardiovascular risk, diuretic use, initial allopurinol dose (≤100 mg, >100 to ≤300 mg, and >300 mg), and levels of renal function categorized by eGFR (≥60, ≥30 to <60, ≥10 to <30, and <10

2.8. SENSITIVITY ANALYSIS

First, the 180 day follow up analysis without censoring for drug discontinuation or adding/switching analysis was conducted in order to assess the short-term risk of SCARs following initiation of ULT. The follow-up period for each participant in

commenced on the day following the index date and continued until the earliest of the following censoring events: the 181st day, the occurrence of an outcome, death, or end of database.

Second, we applied a more stringent definition of SCAR by requiring both a diagnostic code for SCAR and the prescription of systemic corticosteroids at a daily dose equivalent to ≥30 mg of prednisone within 30 days of the SCAR diagnosis, regardless of hospitalization status.

Third, to evaluate the robustness of our primary findings and to understand the potential reasons for the difference in SCAR incidence compared to a prior Taiwanese study (Yang et al., 2015), we conducted a series of sensitivity analyses that applied modified definitions of SCAR and alternative follow-up and censoring strategies. Specifically, four analysis scenarios were constructed as follows:

Scenario 1: Broad SCAR ICD Codes, No Censoring, Any Diagnosis Position

This analysis applied an expanded definition of SCAR by including all ICD-10 codes that correspond to those used in the Taiwanese study, converted from ICD-9-CM codes (693.0, 695.1, 695.9, 695.89) to ICD-10 (L27.0, L27.1, L51.0–L51.9, L53.9, L26, L30.4, L53.8, L92.0, L95.1, L98.2) ((CMS), 2025) (**Table 5**), thereby capturing broader dermatologic reactions. Diagnosis codes in any diagnostic position (not limited to primary) were included, and follow-up continued for 90 days without censoring for drug discontinuation, addition, or switching.

Table 5. Conversion of SCAR ICD-9 Codes to ICD-10

ICD−9 codes: item names	Converted ICD−10 codes: item names
693: Dermatitis due to substances taken internally	L27.0*: Generalized skin eruption due to drugs and medicaments L27.1: Localized skin eruption due to drugs and medicaments taken internally
695.1: Erythema multiforme	L51.0*: Non−bullous erythema multiforme L51.1*: Stevens−Johnson syndrome L51.2*: Toxic epidermal necrolysis [Lyell] L51.8*: Other erythema multiforme L51.9*: Erythema multiforme, unspecified
695.89: Other specified erythematous conditions	L26.x: Exfoliative dermatitis L30.4: Erythema intertrigo L53.8: Other specified erythematous conditions L92.0: Granuloma annulare L95.1: Erythema elevatum diutinum L98.2: Febrile neutrophilic dermatosis [Sweet]
695.9: Unspecified erythematous condition	L53.9: Erythematous condition, unspecified

* ICD−10 codes marked with an asterisk were used in the primary case definition of SCAR in this dissertation, corresponding to severe cutaneous adverse reactions such as Stevens−Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme.
ICD−9 to ICD−10 mapping was informed by the CMS General Equivalence Mappings (GEMs).

Scenario 2: Study-Specific SCAR ICD Codes, No Censoring, Any Diagnosis Position

To isolate the effect of diagnosis code specificity, we used only the predefined SCAR ICD-10 codes from our main analysis (i.e., L51.1, L51.2, L27.0) while maintaining the same follow-up strategy as in Scenario 1. This allowed us to evaluate the contribution of code expansion to SCAR incidence while holding other conditions constant.

Scenario 3: Broad SCAR ICD Codes, Censoring Applied, Any Diagnosis Position

This scenario applied the same broad ICD-10 definition used in Scenario 1 but incorporated censoring for drug discontinuation or switching to mimic the treatment exposure definition of the main analysis. Censoring occurred at the date of drug discontinuation, switching, death, or the end of the 90-day follow-up period.

Scenario 4: Broad SCAR ICD Codes, No Censoring, Primary Diagnosis Only

In this final scenario, we retained the broad SCAR definition and uncensored follow-up strategy but restricted outcome ascertainment to cases where SCAR was recorded as the primary hospital diagnosis. This approach allowed for comparison of the impact of diagnosis position (primary vs. any) on the outcome estimates.

CHAPTER 3. RESULTS

3.1. BASELINE PATIENT CHARACTERISTICS

Figure 4 shows the study cohort selection process. A total of 1,274,891 new users of three different ULTs (n=673,638 for allopurinol, n=570,181 for febuxostat, and n=31,072 for benzbromarone) were included in the study, whose baseline characteristics are presented in **Table 6** and **Table 7**. Febuxostat (58.8 years of age, 86.4% male) and benzbromarone (57.4 years of age, 85.5% male) users showed a higher prevalence of comorbidities (mean comorbidity score of 2.0 and 1.8, respectively) than allopurinol users (57.3 years of age, 82.8% male, mean comorbidity score of 1.6): 35.8%, 31.0%, and 27.8% for DM, 58.6%, 54.7%, and 49.7% for hypertension, 45.7%, 42.3%, and 36.0% for liver disease, and 11.2%, 9.9%, and 5.0% for chronic kidney disease (CKD), respectively. Approximately 63% of the ULT new users (61.6% of allopurinol users, 65.4% of febuxostat users, 61.5% of benzbromarone users) underwent national health screening, and were included in the adjusted analysis.

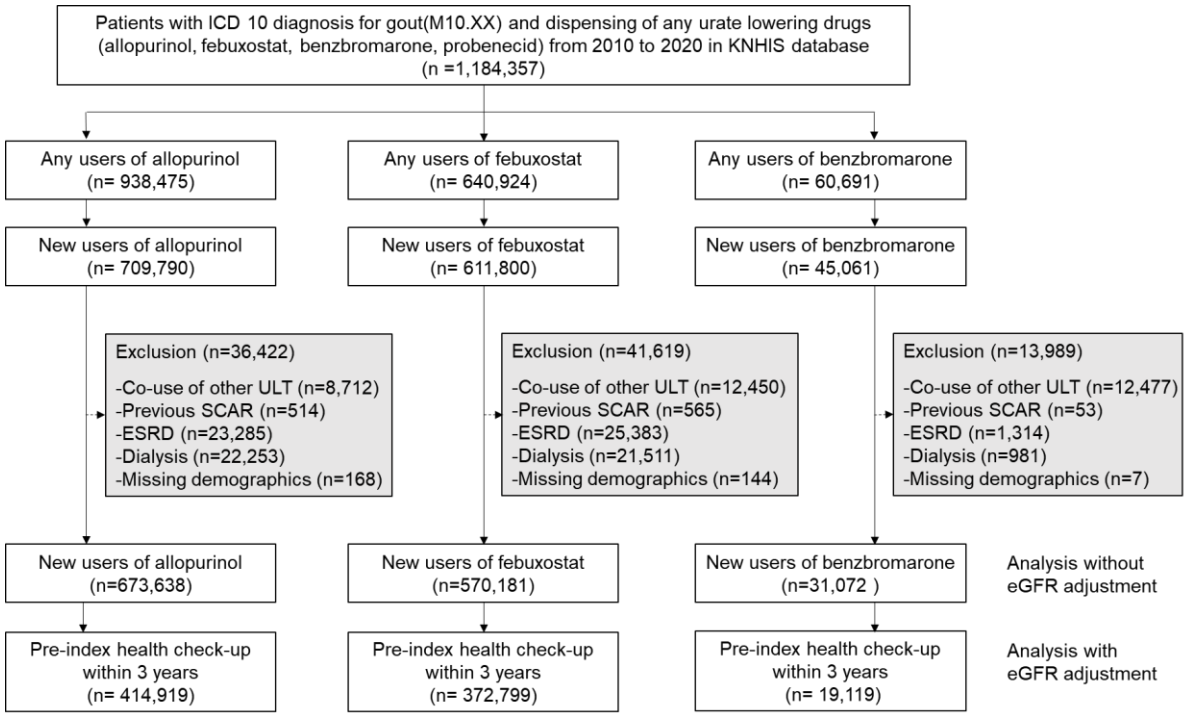


Figure 4. Study Cohort Selection Flow

This figure illustrates the inclusion and exclusion criteria applied to identify new users of ULTs between 2010 and 2021. Patients were excluded if they had co-use of other ULTs at baseline, had a prior diagnosis of SCAR, ESRD, received dialysis, or had missing demographic information. The final study cohorts consisted of 673,638 allopurinol users, 570,181 febuxostat users, and 31,072 benzbromarone users. ULT = urate-lowering therapies, SCAR = severe cutaneous adverse reaction, ESRD = end-stage renal disease

Table 6. Baseline Characteristics of Study Participants

Variables	Allopurinol	Febuxostat	Benzbromarone
N	673,638	570,181	31,072
Demographics			
Age, mean (SD)	57.3 (13.7)	58.8 (13.4)	57.4 (13.5)
Male, %	82.8	86.4	85.5
Income levels, %			
Medical aid	5.3	5.2	4.9
Poorest Q1	16.9	16.6	16.2
Lower−middle Q2	18.1	17.0	17.7
Upper−middle Q3	24.6	23.8	24.6
Wealthiest Q4	35.1	37.4	36.6
Index year,%			
2011	13.1	0	14.9
2012	11.8	4.7	13.9
2013	11.4	6.0	12.3
2014	11.4	3.8	11.7
2015	11.8	4.2	10.9
2016	11.0	12.8	9.8
2017	8.1	17.1	7.1
2018	7.5	18.9	5.9
2019	7.6	16.7	7.6
2020	6.3	15.8	5.9
Comorbidities			
Myocardial infarction, %	1.6	2.1	2.2
Other Heart Disease, %	11.3	14.6	12.8
Stroke, %	5.3	5.9	5.8
Diabetes Mellitus, %	27.8	35.8	31.0
Dyslipidemia, %	44.4	60.0	53.4
Hypertension, %	49.7	58.6	54.7
Heart failure, %	6.3	9.2	6.9
CKD, %	5.0	11.2	9.9
Liver disease, %	36.0	45.7	42.3
Comorbidity score, mean (SD)	1.6 (1.9)	2.0 (2.2)	1.8 (2.0)
Gout medications, %			
Colchicine	20.6	41.4	38.1
NSAID	65.0	66.6	69.1
Coxibs	6.5	10.1	6.9
Opioids	13.9	10.9	14.1
Steroid use	57.0	65.1	64.4
Other medications, %			
ACEI/ARBs	39.2	49.1	44.1

Beta blockers	15.4	17.9	18.5
Calcium channel blockers	23.4	24.8	26.8
Anti−arrhythmic agents	7.6	7.5	7.8
Diuretics	18.9	20.8	20.8
Insulin	4.1	5.3	4.8
Non−insulin glucose−lowering agents	14.5	17.6	15.4
Lipid lowering agents	23.4	30.5	27.9
Antiplatelet agents	20.7	21.3	22.9
Anticoagulant	4.9	6.1	5.9
Proton pump inhibitors	26.8	33.6	28.1
Healthcare service utilization, %			
Hospitalizations	23.6	25.8	24.4
ER visit	24.6	26.4	25.3
Initial dose of allopurinol, %			
≤ 100 mg	33.8		
>100, ≤300 mg	63.5		
>300 mg	2.7		

Data are presented as % for binary variables, and mean (standard deviation, SD) for continuous variables.

eGFR = estimated Glomerular Filtration Rate per ml/min/1.73m2, CKD = Chronic Kidney Disease, ER = Emergency Room, NSAID = Non−Steroidal Anti−Inflammatory Drug, ACE = Angiotensin−Converting Enzyme, ARBs = Angiotensin II Receptor Blockers.

The missing variables for income levels (13,567 individuals in the allopurinol group and 8,968 individuals in the febuxostat group) were imputed using the other baseline characteristics presented in this Table.

Table 7. Baseline Characteristics of Participants with Health Screening Records

Variables	Allopurinol	Febuxostat	Benzbromarone
N	414,919	327,799	19,119
Demographics			
Age, mean (SD)	57.2 (12.8)	58.1 (12.5)	57.4 (12.7)
Male, %	84.2	88.8	87.4
Income levels, %			
Medical aid	2.3	2.5	2.1
Poorest Q1	15.7	15.4	15.0
Lower−middle Q2	17.2	16.4	16.8
Upper−middle Q3	26.0	25.0	25.8
Wealthiest Q4	38.8	40.7	40.3
Index year,%			
2011	9.4	0	11.0
2012	11.3	4.3	13.6
2013	12.0	6.0	13.3
2014	12.0	3.9	12.5
2015	12.5	4.3	11.9
2016	11.9	13.5	10.5
2017	8.9	18.0	7.8
2018	8.4	20.2	6.8
2019	8.2	17.1	7.9
2020	5.4	12.8	4.7
Comorbidities			
Myocardial infarction, %	1.4	1.8	1.9
Other Heart Disease, %	10.2	12.7	11.6
Stroke, %	4.6	5.0	4.9
Diabetes Mellitus, %	27.4	34.2	30.2
Dyslipidemia, %	46.3	60.6	54.8
Hypertension, %	50.0	57.7	54.6
Heart failure, %	5.3	7.5	6.0
CKD, %	4.6	10.2	9.4
Liver disease, %	37.2	46.5	43.9
psychiatric diseases, %	2.3	2.7	2.5
Epilepsy, %	1.8	2.0	1.9
Trigeminal neuralgia, %	0.5	0.6	0.6
Bipolar disorder, %	0.1	0.2	0.1
Infectious disease, %	43.6	50.1	41.2
Bactrial gastroenteritis, %	13.8	16.7	13.4
Influenza and pneumonia, %	6.9	8.2	6.8
Pneumonia, %	5.6	6.1	5.7
Urinary tract infections, %	9.5	12.3	9.4

Skin infections, %	25.9	28.5	23.0
Comorbidity score, mean (SD)	1.6 (1.9)	1.9 (2.1)	1.8 (1.9)
Gout medications, %			
Colchicine	21.0	42.9	39.6
NSAID	67.2	68.8	71.4
Coxibs	6.6	9.9	6.8
Opioids	14.2	11.0	14.2
Steroid use	59.8	67.1	66.9
Other medications, %			
ACEI/ARBs	39.3	48.2	44.0
Beta blockers	14.2	16.2	17.1
Calcium channel blockers	22.8	23.6	25.7
Anti-arrhythmic agents	7.5	7.2	7.6
Diuretics	17.1	18.1	18.7
Insulin	3.4	4.3	3.9
Non-insulin glucose-lowering agents	13.9	16.2	14.6
Lipid lowering agents	24.6	30.6	28.7
Antiplatelet agents	20.4	20.6	22.6
Anticoagulant	4.4	5.3	5.1
Proton pump inhibitors	30.7	36.1	31.8
Healthcare service utilization, %			
Hospitalizations	22.8	24.5	23.5
ER visit	24.6	26.0	25.5
Initial dose of allopurinol, %			
≤ 100 mg	33.0		
>100, ≤300 mg	64.3		
>300 mg	2.7		
Health screening examination, %	100.0	100.0	100.0
eGFR, mean (SD)	76.1 (42.4)	72.3 (42.2)	72.4 (37.0)
eGFR level, %			
≥ 60	78.4	71.2	72.1
≥30, <60	19.8	25.5	25.5
≥10, <30	1.5	3.2	2.1
<10	0.3	0.1	0.3

Data are presented as % for binary variables, and mean (standard deviation, SD) for continuous variables.
eGFR = estimated Glomerular Filtration Rate per ml/min/1.73m2, CKD = Chronic Kidney Disease, ER = Emergency Room, NSAID = Non-Steroidal Anti-Inflammatory Drug, ACE = Angiotensin-Converting Enzyme, ARBs = Angiotensin II Receptor Blockers.

3.2. TEMPORAL TRENDS IN URATE-LOWERING DRUG USE

The distribution of urate-lowering therapies changed considerably over the study period. **Figure 5** presents the annual proportion of allopurinol, febuxostat, and benzbromarone prescriptions among new users. Allopurinol accounted for over 70 percent of use until 2015, but its share declined markedly thereafter. Febuxostat, which was approved for use in Korea in 2012 and became widely adopted by 2015, gradually replaced allopurinol as the most prescribed agent. Benzbromarone remained consistently below 5 percent throughout the study period.

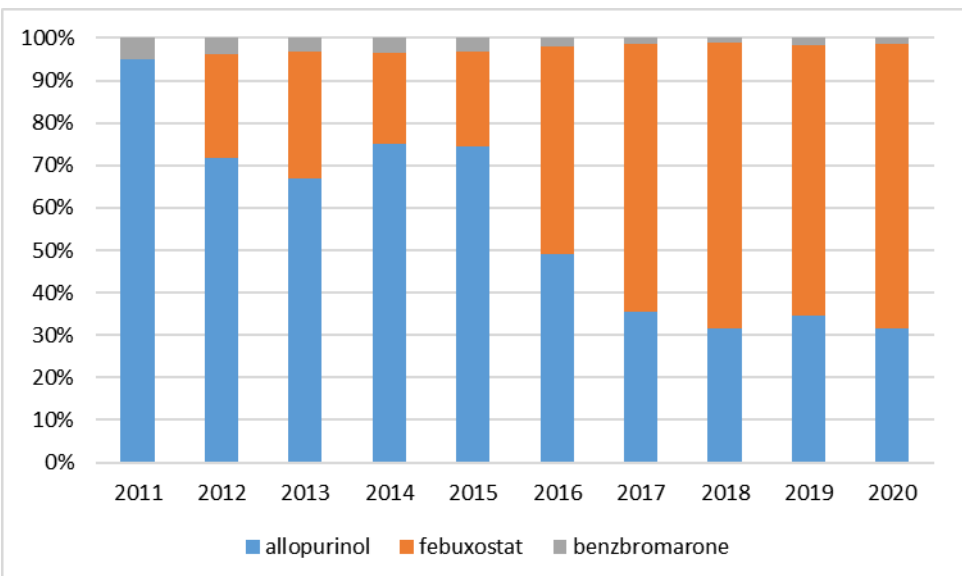
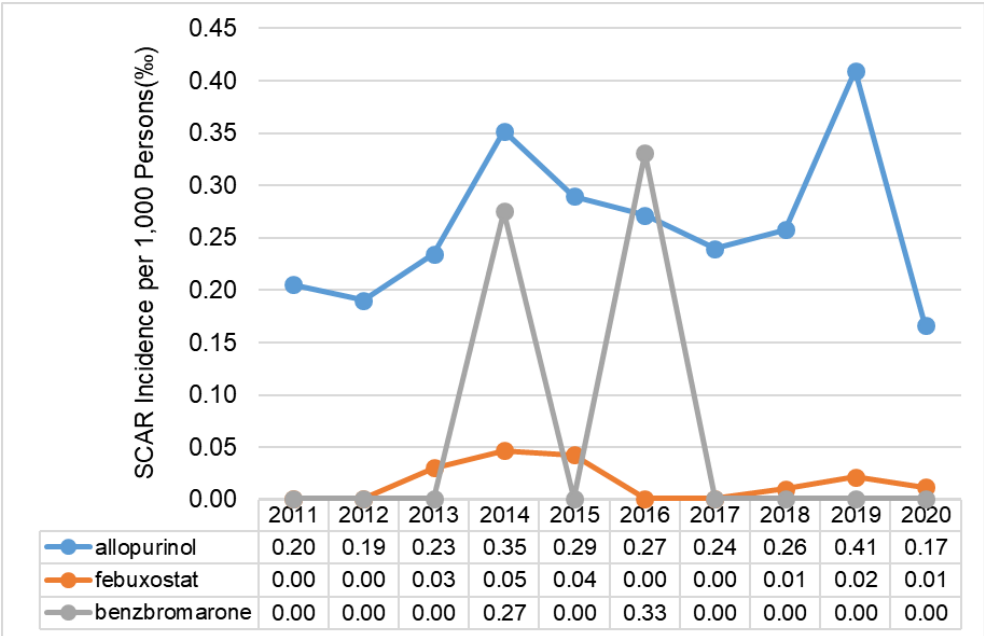


Figure 5. Annual proportion of urate-lowering drug use among new users (2011–2020)

Febuxostat was introduced in Korea in 2012 and gradually replaced

allopurinol as the dominant therapy.

Figure 6. Annual Incidence of SCAR per 1,000 Users by Urate-Lowering Therapy (2011–2020)**Figure 6** displays the annual incidence of SCAR per 1,000 persons by drug from 2011 to 2020. Allopurinol was consistently associated with a higher incidence of SCAR compared to the other agents. While a notable decrease was observed in 2020 following the national reimbursement of HLA−B*58:01 screening in 2019, trend tests revealed no statistically significant changes over time ($p > 0.05$ for all). Based on the Cochran−Armitage trend test, we did not observe a statistically significant trend in SCAR incidence across calendar years for any of the study drugs. The two−sided p−values were 0.252 for allopurinol, 0.689 for febuxostat, and 0.8528 for benzbromarone, indicating that the annual variation in SCAR cases was not statistically significant for any group.



	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
allopurinol	0.20	0.19	0.23	0.35	0.29	0.27	0.24	0.26	0.41	0.17
febuxostat	0.00	0.00	0.03	0.05	0.04	0.00	0.00	0.01	0.02	0.01
benzbromarone	0.00	0.00	0.00	0.27	0.00	0.33	0.00	0.00	0.00	0.00

Figure 6. Annual Incidence of SCAR per 1,000 Users by Urate-Lowering Therapy (2011–2020)

Yearly incidence rates of severe cutaneous adverse reactions (SCAR) per 1,000 users of each urate-lowering therapy between 2011 and 2020. Allopurinol consistently showed higher SCAR incidence than febuxostat and benzbromarone. Despite a visible drop in allopurinol-related SCAR in 2020, trend tests did not yield statistically significant changes over time (two-sided $p > 0.05$ for all drug groups).

3.3. RELATIVE RISK OF SCAR BETWEEN ALLOPURINOL VERSUS OTHER URATE LOWERING THERAPIES

Within 365 days, almost all SCAR cases (184/185, 99.5%) occurred within 180 days after the study drug initiation. Thus, we confined our analysis to 186 cases during the 180-day risk window (175 cases among allopurinol users, 7 among febuxostat, and 2 among benzbromarone) in Table 8.

The most common type of SCARs was SJS/TEN (n=105) followed by DRESS (n=78), and EM (n=4). EM cases were observed only among allopurinol users. The crude event rate (95% CI) of SCAR per 1000 new users was 0.26 (0.22-0.30) in the allopurinol group, 0.01 (0.00-0.03) in the febuxostat group, and 0.06 (0.01-0.23) in the benzbromarone group.

The adjusted RR (95% CI) was 26.33 (10.68-64.94) comparing allopurinol and febuxostat initiators, and 4.50 (0.77-139.46) comparing allopurinol and benzbromarone initiators. We observed a similar finding across secondary outcomes: 1) RR (95% CI) for SJS/TEN was 30.34 (8.82-149.71) comparing allopurinol and febuxostat and 3.07 (0.42-22.27) comparing allopurinol and benzbromarone, 2) RR (95% CI) for DRESS was 19.19 (5.91-62.89) comparing allopurinol and febuxostat. Only crude RR (95% CI) was

available comparing allopurinol and benzbromarone, corresponding to 3.73 (0.52–26.89) (Table 8).

Compared to febuxostat, the use of allopurinol was consistently associated with a markedly increased risk of severe cutaneous adverse reactions (SCARs) within 180 days after treatment initiation. The adjusted relative risk (RR) remained stable across models, with values of 26.33 (95% CI, 10.68–64.94) in Model 2 and 26.43 (95% CI, 10.72–65.19) in Model 3, which further adjusted for psychiatric and infectious conditions. These results indicate a strong and robust association that was not materially influenced by potential confounding due to underlying diseases commonly treated with high-risk co-medications, such as anticonvulsants and antibiotics (Table 8).

In contrast, when using benzbromarone as the reference, the estimated RR for allopurinol was approximately 4.5; however, the 95% confidence intervals were wide (Model 2: 0.77–139.46; Model 3: 0.77–139.72) and included the null value. This lack of statistical significance is likely attributable to the small number of SCAR cases in the benzbromarone group (n = 1), resulting in unstable estimates and limited power to detect a meaningful difference. Nonetheless, the direction of the association remained consistent with the febuxostat

comparison, suggesting a higher relative risk of SCARs associated with allopurinol use regardless of the comparator.

As the SCAR events occurred predominantly during the early risk period and the proportional hazards assumption was violated, Cox model results were not presented in the main text. Instead, consistent findings from Cox proportional hazards models are available in **Appendix Table A 1**.

Table 8. Comparative risk of SCAR in ULTs

(A) Crude analysis for all study participants

Type of SCAR	N	Events	Days from Index to SCAR Median (range)	SCAR event per 1,000 persons (95% CI)	RR (95% CI)	
					Ref=Febuxostat	Ref=Benzbromarone
Primary outcome						
Allopurinol	673,638	175	39 (4–149)	0.26 (0.22–0.30)	29.72 (13.96–63.29)	4.56 (1.13–18.39)
Febuxostat	570,181	7	7 (1–59)	0.01 (0.00–0.03)	Ref (1.00)	
Benzbromarone	31,072	2	25 (10–40)	0.06 (0.01–0.23)		Ref (1.00)
Secondary outcomes						
SJS/TEN						
Allopurinol	673,638	102	37 (4–124)	0.15 (0.12–0.18)	40.56 (12.86–127.88)	5.34 (0.74–38.25)
Febuxostat	570,181	2	2 (1–50)	0.00 (0.00–0.01)	Ref (1.00)	
Benzbromarone	31,072	1	40 (40–40)	0.03 (0.00–0.18)		Ref (1.00)
EM						
Allopurinol	673,638	4	28 (26–40)	0.01 (0.00–0.02)	NA	NA
Febuxostat	570,181	0	0	0.00 (0.00–0.00)	Ref (1.00)	
Benzbromarone	31,072	0	0	0.00 (0.00–0.00)		Ref (1.00)
DRESS						
Allopurinol	673,638	72	42 (5–149)	0.11 (0.08–0.13)	17.03 (6.87–42.20)	3.73 (0.52–26.89)
Febuxostat	570,181	5	7.5 (1–59)	0.01 (0.00–0.02)	Ref (1.00)	
Benzbromarone	31,072	1	10 (10–10)	0.03 (0.00–0.18)		Ref (1.00)

CI = Confidence Interval, NA = Not Applicable, RR = Relative Risk, SCAR = Severe Cutaneous Adverse Reaction, SJS = Stevens–Johnson Syndrome, TEN = Toxic Epidermal Necrolysis, EM = Erythema Multiforme, DRESS = Drug Reaction with Eosinophilia and Systemic Symptoms

(B) Adjusted analysis for those with eGFR values

Type of SCAR	n	Events	Days from Index to SCAR Median (range)	SCAR event per 1,000 persons (95% CI)	Model 1: Adjusted* RR (95% CI)	
					Ref=Febuxostat	Ref=Benzbromarone
Primary outcome						
Allopurinol	414,919	91	37 (13–149)	0.22 (0.18–0.27)	26.33 (10.68–64.94)	5.50 (0.77–39.51)
Febuxostat	372,799	5	7.5 (1–59)	0.01 (0.00–0.04)	Ref (1.00)	
Benzbromarone	19,119	1	40 (40–40)	0.05 (0.00–0.29)		Ref (1.00)
Secondary outcomes						
SJS/TEN						
Allopurinol	414,919	51	32 (17–124)	0.12 (0.09–0.16)	30.34 (8.82–149.71)	3.07 (0.42–22.27)
Febuxostat	372,799	2	26 (2–50)	0.01 (0.00–0.02)	Ref (1.00)	
Benzbromarone	19,119	1	40 (40–40)	0.05 (0.00–0.29)		Ref (1.00)
EM						
Allopurinol	414,919	2	33 (26–40)	0.01 (0.00–0.02)	NA	NA
Febuxostat	372,799	0	0	0.00 (0.00–0.00)	Ref (1.00)	
Benzbromarone	19,119	0	0	0.00 (0.00–0.00)		Ref (1.00)
DRESS						
Allopurinol	414,919	39	39 (13–149)	0.09 (0.07–0.13)	19.19 (5.91–62.36)	NA
Febuxostat	372,799	3	7.5 (1–59)	0.01 (0.00–0.03)	Ref (1.00)	
Benzbromarone	19,119	0	0	0.00 (0.00–0.00)		Ref (1.00)

CI = Confidence Interval, NA = Not Applicable, RR = Relative Risk, SCAR = Severe Cutaneous Adverse Reaction, SJS = Stevens–Johnson Syndrome, TEN = Toxic Epidermal Necrolysis, EM = Erythema Multiforme, DRESS = Drug Reaction with Eosinophilia and Systemic Symptoms

* Model 1: Adjusted for age, sex, income level, liver disease, eGFR (≥60, ≥30 and <60, <30 ml/min/1.73m2), diuretics use, and comorbidity score. NA, not applicable.

(C) Multivariable Poisson Regression Models for SCAR Risk Within 180 Days

Type of SCAR	n	Events	Model 2: Adjusted RR (95% CI)		Model 3: Adjusted RR (95% CI)	
			Ref=Febuxostat	Ref=Benzbromarone	Ref=Febuxostat	Ref=Benzbromarone
Primary outcome						
Allopurinol	414,919	91	26.33 (10.68−64.94)	4.50 (0.77−139.46)	26.43 (10.72−65.19)	4.53 (0.77−139.72)
Febuxostat	372,799	5	Ref (1.00)		Ref (1.00)	
Benzbromarone	19,119	1		Ref (1.00)		Ref (1.00)

CI = Confidence Interval, NA = Not Applicable, RR = Relative Risk, SCAR = Severe Cutaneous Adverse Reaction

Model 1: Adjusted for age, sex, income level, liver disease, estimated glomerular filtration rate (eGFR), diuretic use, and comorbidity score.

Model 2: Model 2 + adjustment for psychiatric conditions commonly treated with anticonvulsants (epilepsy, trigeminal neuralgia, bipolar disorder, and neuropathic pain).

Model 3: Model 3 + adjustment for infections likely requiring anti−infective agents (bacterial gastroenteritis, pneumonia, influenza−related infections, urinary tract infections, and skin infections).

3.4. INTERVAL SPECIFIC ANALYSIS ON OCCURRENCE AND PROGNOSIS OF ULT-INDUCED SCAR

For allopurinol initiators, the highest risk of SCAR was observed during the 31-60 days following treatment initiation, the crude event rate (95% CI) of SCAR per 1000 new users was 0.31 (0.25-0.38) (**Figure 7** and **Table 9**). Following a 60-day period, a significant decrease in risk was observed. Between 61-90 days, 0.074 (0.045-0.116), and further to 0.019 (0.005-0.049) during 91-180 days. The observation period was concluded after a duration of 60 days, and no further EM was detected. The majority of SCAR events (86.9%, 151/174) occurred within the first 60 days, indicating this period as a critical risk window.

In the group of patients treated with febuxostat, cases of SCAR were rare and occurred only within the first 60 days (n = 7 in total). The crude event rate (95% CI) of SCAR per 1000 new users was found to be highest in the initial 30-day period 0.009 (0.003-0.020), with a median onset of 2 days. All cases occurring after day 30 were observed within the 31-60-day interval, with no events recorded beyond this timeframe.

For benzbromarone, merely 2 SCAR events were observed (one within 30 days and another during 31-60 days). The initial occurrence was DRESS (day 10), and the subsequent manifestation was a SJS/TEN case on day 40. The corresponding incidence rates were 0.032 (95% CI, 0.001-0.179) and 0.057 (95% CI, 0.001-0.318), respectively. No events occurred beyond 60 days.

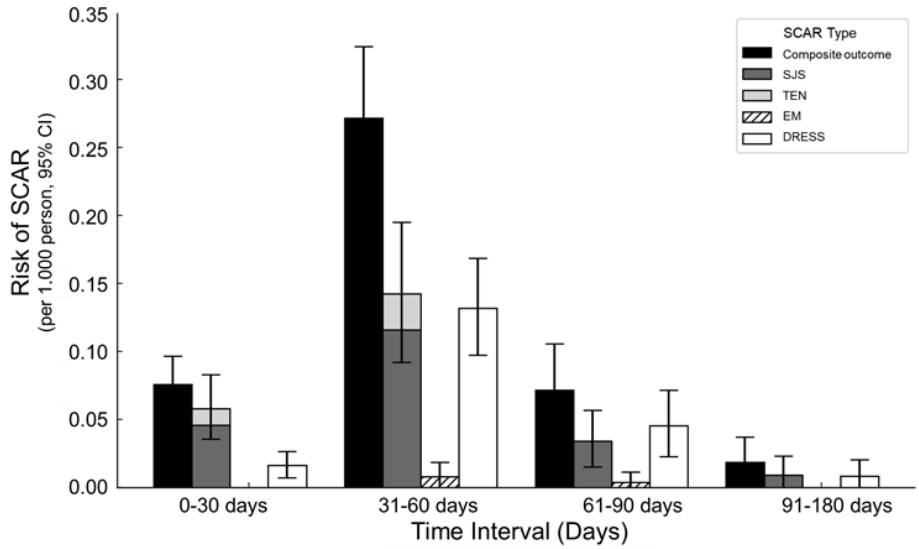


Figure 7. Risk of allopurinol-induced SCARs over time intervals

Bar heights indicate the risk per 1,000 persons, and error bars represent 95% confidence intervals. Composite SCAR includes any of the SCAR type events. The highest incidence was observed during the 31–60day period after allopurinol initiation, with SJS/TEN and DRESS accounting for most cases.

SCAR = Severe Cutaneous Adverse Reaction, SJS = Stevens–Johnson Syndrome, TEN = Toxic Epidermal Necrolysis, EM = Erythema Multiforme, DRESS = Drug Reaction With Eosinophilia And Systemic Symptoms.

Table 9. Interval-specific incidence rate of SCAR among new users of ULT

Time interval	Events	SCAR event per 1,000 persons (95% CI)	Days from Index to SCAR Median (range)
Allopurinol (n=673,638)			
Up to 30 days			
Composite outcome	50	0.074 (0.055−0.098)	25.5 (4−30)
SJS/TEN	37	0.055 (0.039−0.076)	25 (4−30)
EM	3	0.004 (0.001−0.013)	28 (26−28)
DRESS	10	0.015 (0.007−0.027)	26.5 (5−29)
31−60 days			
Composite outcome	102	0.151 (0.123−0.184)	41 (31−60)
SJS/TEN	54	0.080 (0.060−0.105)	41 (31−60)
EM	1	0.001 (0.000−0.008)	40
DRESS	48	0.071 (0.053−0.094)	41 (31−60)
61−90 days			
Composite outcome	19	0.135 (0.109−0.166)	68 (61−88)
SJS/TEN	9	0.013 (0.006−0.025)	68 (62−88)
EM	0	0	NA
DRESS	12	0.018 (0.009−0.031)	68.5 (61−83)
91−180 days			
Composite outcome	4	0.006 (0.002−0.015)	110.5 (91−149)
SJS/TEN	2	0.003 (0.000−0.011)	107.5 (91−124)
EM	0	0	NA
DRESS	2	0.003 (0.000−0.011)	123 (97−149)

Table 9. (continued)

Time interval	Events	SCAR event per 1,000 persons (95% CI)	Days from Index to SCAR Median (range)
Febuxostat (n=570,181)			
Up to 30 days			
Composite outcome	5	0.009 (0.003−0.020)	2 (1−22)
SJS/TEN	1	0.002 (0.000−0.013)	1 (1−2)
EM	0	0	NA
DRESS	4	0.007 (0.002−0.018)	7 (1−22)
31−60 days			
Composite outcome	2	0.004 (0.000−0.013)	54.5 (50−59)
SJS/TEN	1	0.002 (0.000−0.013)	50 (50−50)
EM	0	0	NA
DRESS	1	0.002 (0.000−0.013)	59 (59−59)
Benzbromarone (n=31,072)			
Up to 30 days			
Composite outcome	1	0.032 (0.001−0.179)	10 (10−10)
SJS/TEN	0	0	NA
EM	0	0	NA
DRESS	1	0.032 (0.001−0.179)	10 (10−10)
31−60 days			
Composite outcome	1	0.032 (0.001−0.179)	40 (40−40)
SJS/TEN	1	0.032 (0.001−0.179)	40 (40−40)
EM	0	0	NA
DRESS	0	0	NA

SCAR = Severe Cutaneous Adverse Reaction, SJS = Stevens−Johnson Syndrome, TEN = Toxic Epidermal Necrolysis, EM = Erythema Multiforme, DRESS = Drug Reaction with Eosinophilia and Systemic Symptoms.
CI = Confidence Interval, NA, Not Applicable.

3.5. SCAR-ASSOCIATED MORTALITY AND HOSPITALIZATION FOLLOWING ULT INITIATION

Among the 175 cases of SCAR in allopurinol users, 37 deaths (21.1%) were reported (Table 10). The median time from the onset of SCAR to death was 18 days (range, 1-54). Length of hospitalization among patients with SCAR differed by ULT. The median duration was 13 days (range, 8−24) for allopurinol users and 18 days (range, 9−29) for those with SJS/TEN. In the febuxostat group, the median hospitalization was 25 days (range, 14−29) overall and 27 days (range, 25−29) for SJS/TEN. Benzbromarone users had shorter stays, with a median of 9.5 days (range, 8−11). The highest mortality rate was observed in patients with SJS/TEN (27.5%, 28 out of 102), followed by EM (25.0%, 1 out of 4) and DRESS (13.9%, 10 out of 72). The median SCAR-to-death interval was shortest in EM (4 days), followed by SJS/TEN (17 days) and DRESS (24 days). Hospitalization duration was defined as the length of stay during the first SCAR-related admission, identified based on the primary diagnosis code. Recurrent or subsequent hospitalizations were not included in the duration calculation.

In contrast, no deaths associated with SCAR occurred in the febuxostat or benzbromarone groups. The hospitalization duration for febuxostat-related SCAR events was found to be significantly longer (median 29 days, range 7-70) than for benzbromarone (median 9.5 days, range 8-11), though it should be noted that the number of cases in each group was limited.

Table 10 shows the number and percentage of deaths by time interval from the occurrence of SCAR, as well as the median period in days from SCAR

occurrence to death among allopurinol initiators. The number of deaths indicates patients who died following a SCAR event that occurred during the specified interval period after ULT initiation. The median time to SCAR onset is shown in days, with the range in parentheses. Peak mortality rates of allopurinol-associated SCARs were found in 61-90 days (52.6%, 10/19), followed by 91-180 days (25.0%, 1/4), 31-60 days (22.5%, 23/102), and 1-30 days (10.0%, 5/50). Among the 19 patients who developed SCAR within the 61-90 days period, 10 died. These deaths occurred between 1 and 54 days after SCAR onset.

Table 11 presents the comparison of baseline characteristics between the two groups. Compared to survivors, non-survivors were older and had higher comorbidity scores. Hypertension, heart failure, diabetes mellitus, and other heart disease were more prevalent in the death group. Use of beta blockers, calcium channel blockers, and diuretics was also more common among deaths. Additionally, d

e

aths had lower mean eGFR, and none had preserved renal function (eGFR $\geq$60 although the distribution across dose groups differed.

Table 10. SCAR-related mortality and hospitalization duration by type of ULT

Type of ULT	Events	Death n (%)	SCAR to death (days) median (range)	Hospitalization (days) median (range)
Allopurinol (n=673,638)				
Primary outcome	175	37 (21.1)	18 (1–54)	13 (8–24)
SJS/TEN	102	28 (27.5)	17 (1–54)	18 (9–29)
EM	4	1 (25.0)	4	9 (6.5–20)
DRESS	72	10 (13.9)	25 (2–54)	11 (8–17.5)
Febuxostat (n=570,181)				
Primary outcome	7	0	NA	25 (14–29)
SJS/TEN	2	0	NA	27 (25–29)
EM	0	0	NA	NA
DRESS	5	0	NA	21 (14–29)
Benzbromarone (n=31,072)				
Primary outcome	2	0	NA	9.5 (8–11)
SJS/TEN	1	0	NA	8
EM	0	0	NA	NA
DRESS	1	0	NA	11

SCAR = Severe Cutaneous Adverse Reactions, ULT = Urate Lowering Therapy, SJS = Stevens–Johnson Syndrome, TEN = Toxic Epidermal Necrolysis, EM = Erythema Multiforme, DRESS = Drug Reaction with Eosinophilia and Systemic Symptoms, CI = Confidence Interval, NA = Not Applicable

Table 11. Interval-specific SCAR mortality in allopurinol new users

Time interval	Events	Death, n (%)	SCAR to death (days) median (range)
Up to 30 days (n=673,806)			
Primary outcome	50	5 (10.0)	23 (3–54)
SJS/TEN	37	3 (8.1)	7 (3–23)
EM	3	0	NA
DRESS	10	2 (20.0)	39 (24–54)
31–60 days (n=673,806)			
Primary outcome	102	23 (22.5)	17 (2–54)
SJS/TEN	54	17 (32.1)	17 (4–54)
EM	1	1 (100.0)	4
DRESS	48	5 (10.4)	26 (2–35)
61–90 days (n=673,806)			
Primary outcome	19	8 (52.6)	23.5 (1–54)
SJS/TEN	9	7 (77.8)	28 (1–54)
EM	0	0	NA
DRESS	12	3 (25.0)	19 (15–28)
91–180 days (n=673,806)			
Primary outcome	4	1 (25.0)	25
SJS/TEN	2	1 (50.0)	25
EM	0	0	NA
DRESS	2	0	NA

SCAR = Severe Cutaneous Adverse Reactions, ULT = Urate Lowering Therapy, SJS = Stevens–Johnson Syndrome, TEN = Toxic Epidermal Necrolysis, EM = Erythema Multiforme, DRESS = Drug Reaction with Eosinophilia and Systemic Symptoms, CI = Confidence Interval, NA = Not Applicable

Table 12. Comparison of baseline characteristics between survivors and death of SCAR among allopurinol initiators

Variables	Allopurinol induced SCAR (n=175)		
	Survivors (n=138)	Deaths (n=37)	p-value
Demographics			
Age, mean (SD)	66.7 (15.0)	76.1 (10.5)	<0.0001
Male, n (%)	79 (57.2)	20 (54.1)	0.728
Income levels, %			0.805
Medical aid	12 (8.7)	4 (10.8)	
Poorest Q1	35 (25.4)	6 (16.2)	
Lower-middle Q2	17 (12.3)	4 (10.8)	
Upper-middle Q3	29 (21.0)	9 (24.3)	
Wealthiest Q4	45 (32.6)	14 (37.8)	
Comorbidities			
Myocardial infarction, n (%)	8 (5.8)	3 (8.1)	0.607
Other Heart Disease, n (%)	36 (26.1)	19 (51.4)	0.003
Stroke, n (%)	12 (8.7)	5 (13.5)	0.380
Diabetes Mellitus, n (%)	56 (40.6)	23 (62.2)	0.019
Dyslipidemia, n (%)	76 (55.1)	22 (59.5)	0.633
Hypertension, n (%)	109 (79.0)	36 (97.3)	0.009
Heart failure, n (%)	25 (18.1)	15 (40.5)	0.004
Chronic kidney disease, n (%)	19 (13.8)	7 (18.9)	0.434
Liver disease, n (%)	49 (35.5)	18 (48.6)	0.144
Comorbidity score, mean (SD)	2.3 (2.3)	3.9 (2.0)	0.0003
Gout medications, n (%)			
Colchicine	31 (22.5)	5 (13.5)	0.232
NSAID	82 (59.4)	24 (64.9)	0.547
Coxibs	23 (16.7)	8 (21.6)	0.483
Opioids	25 (18.1)	5 (13.5)	0.510
Steroid use	77 (55.8)	23 (62.2)	0.487
Other medications, n (%)			
ACEI/ARBs	92 (66.7)	29 (78.4)	0.171
Beta blockers	38 (27.5)	22 (59.5)	<0.0001
Calcium channel blockers	42 (30.4)	21 (56.8)	0.003
Anti-arrhythmic agents	15 (10.9)	5 (13.5)	0.654
Diuretics	62 (44.9)	28 (75.7)	0.001
Insulin	15 (10.9)	6 (16.2)	0.374
Non-insulin glucose-lowering	37 (26.8)	16 (43.2)	0.053

agents			
Lipid lowering agents	43 (31.2)	11 (29.7)	0.867
Antiplatelet agents	56 (40.6)	19 (51.4)	0.240
Anticoagulant	20 (14.5)	6 (16.2)	0.794
Proton pump inhibitors	36 (26.1)	14 (37.8)	0.160
Healthcare service utilization, n (%)			
Hospitalizations	50 (36.2)	17 (45.9)	0.280
ER visit	46 (33.3)	14 (37.8)	0.604
Initial dose of allopurinol, n (%)			0.054
≤ 100 mg	53 (38.4)	22 (59.5)	
>100, ≤300 mg	81 (58.7)	15 (40.5)	
>300 mg	4 (2.9)	0 (0.0)	
Health screening examination	(n=78)	(n=13)	
eGFR, mean (SD)	58.8 (21.7)	40.5 (10.0)	<0.001
eGFR level, %			0.015
≥ 60	36 (26.1)	0 (0.0)	
≥30, <60	36 (26.1)	11 (84.6)	
≥10, <30	5 (3.6)	2 (15.4)	
<10	1 (0.7)	0 (0.0)	

Data are presented as % for binary variables, and mean (standard deviation, SD) for continuous variables.

eGFR = estimated Glomerular Filtration Rate per ml/min/1.73m^2, CKD = Chronic Kidney Disease, ER = Emergency Room, NSAID = Non-Steroidal Anti-Inflammatory Drug, ACE = Angiotensin-Converting Enzyme, ARBs = Angiotensin II Receptor Blockers.

3.6. RISK FACTOR ANALYSIS FOR ALLOPURINOL-ASSOCIATED SCAR

Baseline characteristics of allopurinol users according to SCAR development are summarized in Table 13. Patients who developed SCARs tended to be older and less frequently male, with a higher proportion of individuals in the lowest income quartile or receiving medical aid. Several comorbidities, including myocardial infarction, heart failure, stroke, diabetes mellitus, dyslipidemia, hypertension, and chronic kidney disease, were more prevalent in the SCAR group. The use of certain medications (such as coxibs, ACE inhibitors/ARBs, beta blockers, calcium channel blockers, diuretics, insulin, and antiplatelet agents) was also more common among SCAR cases. SCAR patients showed higher healthcare utilization, including hospitalizations and emergency room visits. A higher proportion of SCAR cases initiated allopurinol at a lower dose (≤100 mg). Among participants with available health screening data, impaired renal function was significantly associated with SCAR development.

Allopurinol users were stratified according to patient characteristics potentially associated with an elevated risk of SCARs. Comparative analyses were conducted between individuals with and without each risk factor. The adjusted RR was significantly higher among females compared to males (RR 2.02, 95% CI 1.29-3.20), diuretic users compared to non-users (RR 1.96, 95% CI 1.21-3.17), and those receiving moderate doses of allopurinol (>100 to ≤300 mg/day) compared to ≤100 mg/day (RR 2.30, 95% CI 1.48-3.60). Although a higher dose of allopurinol (>300 mg/day) was also associated with elevated risk, the estimate was imprecise (RR 1.70, 95% CI 0.41-7.09), likely due to limited sample size. A significant gradient in risk

was observed with declining eGFR (p for trend <0.0001): compared to those with an eGFR ≥60, RRs were 3.22 (95% CI 2.01-5.15) for eGFR of ≥30 and <60, 4.22 (95% CI 1.79-9.94) for eGFR of ≥10 and <30, and 5.84 (95% CI 0.80−42.66) for eGFR of <10. In contrast, older age (≥60 vs <60 years) and CV risk status (high vs non-high) were not significantly associated with SCARs.

As demonstrated in Table 14, the risk of SCAR increased with higher allopurinol doses, particularly among patients with impaired renal function (eGFR <30 mL/min/1.73m). In this group, those receiving >300 mg/day had an adjusted RR of 18.64 (2.52-138.03) compared to the reference group (≤100 mg/day with eGFR ≥30), reflecting an approximately 31-fold higher crude risk. Among patients with eGFR

Table 13. Baseline Characteristics of Allopurinol Users by SCAR Occurrence

Variables	Allopurinol (n=673,638)		
	SCAR occurrence		p-value
	No (n=673,463)	Yes (n=175)	
Demographics			
Age, mean (SD)	57.25 (13.7)	68.7 (14.7)	<0.0001
Male, n (%)	557,517 (82.8)	99 (56.6)	<0.0001
Income levels, n (%)			0.008
Medical aid	35,435 (5.3)	16 (9.1)	
Poorest Q1	113,696 (16.9)	41 (23.4)	
Lower-middle Q2	122,131 (18.1)	21 (12.0)	
Upper-middle Q3	165,632 (24.6)	38 (21.7)	
Wealthiest Q4	236,569 (35.1)	59 (33.7)	
Comorbidities			
Myocardial infarction, n (%)	10,831 (1.6)	11 (6.3)	<0.0001
Other Heart Disease, n (%)	76,133 (11.3)	55 (31.4)	<0.0001
Stroke, n (%)	35,441 (5.3)	17 (9.7)	0.008
Diabetes Mellitus, n (%)	187,446 (27.8)	79 (45.1)	<0.0001
Dyslipidemia, n (%)	299,091 (44.4)	98 (56.0)	0.002
Hypertension, n (%)	334,733 (49.7)	145 (82.9)	<0.0001
Heart failure, n (%)	42,261 (6.3)	40 (22.9)	<0.0001
Chronic kidney disease, n (%)	33,311 (5.0)	26 (14.9)	<0.0001
Liver disease, n (%)	242,124 (36.0)	67 (38.3)	0.520
Comorbidity score, mean (SD)	1.6 (2.0)	2.7 (2.4)	<0.0001
Gout medications, n (%)			
Colchicine	138,476 (20.6)	36 (20.6)	0.908
NSAID	437,887 (65.0)	106 (60.6)	0.217
Steroid use	383,575 (57.0)	100 (57.1)	0.960
Coxibs	43,906 (6.5)	31 (17.7)	<0.0001
Opioids	93,866 (13.9)	30 (17.1)	0.221
Antihistamines	369,679 (54.9)	94 (53.7)	0.754
Other medications, n (%)			
ACEI/ARBs	264,133 (39.2)	121 (69.1)	<0.0001
Beta blockers	103,705 (15.4)	60 (34.3)	<0.0001
Calcium channel blockers	157,869 (23.4)	63 (36.0)	<0.0001

Anti−arrhythmic agents	51,215 (7.6)	20 (11.4)	0.056
Diuretics	127,463 (18.9)	90 (51.4)	<0.0001
Insulin	27,733 (4.1)	21 (12.0)	<0.0001
Non−insulin glucose−lowering agents	97,719 (14.5)	53 (30.3)	<0.0001
Lipid lowering agents	157,756 (23.4)	54 (30.9)	0.020
Antiplatelet agents	139,445 (20.7)	75 (42.9)	<0.0001
Anticoagulant	33,183 (4.9)	26 (14.9)	<0.0001
Proton pump inhibitors	180,563 (26.8)	50 (28.6)	<0.0001
Healthcare service utilization, n (%)			
Hospitalizations	50 (36.2)	17 (45.9)	<0.0001
ER visit	46 (33.3)	14 (37.8)	0.0031
Initial dose of allopurinol, n (%)			
Allopurinol initial dosage			0.039
≤ 100 mg	227,333 (33.8)	75 (42.9)	
>100, ≤300 mg	427,647 (63.5)	96 (54.9)	
>300 mg	18,483 (2.7)	4 (2.3)	
Hospital utilization pattern, n (%)			
Hospitalizations	50 (36.2)	17 (45.9)	<0.0001
ER visit	46 (33.3)	14 (37.8)	0.0031
Health screening examination	(n=414,828)	(n=91)	
eGFR, ml/min/1.73m^2, mean (SD)	76.1 (42.4)	56.2 (21.4)	<0.0001
eGFR level, n (%)			<0.0001
≥ 60	325,381 (48.3)	36(39.6)	
≥30, <60	82,021 (12.2)	47(51.7)	
≥10, <30	6,242 (0.9)	7(7.7)	
<10	1,184 (0.2)	1(1.1)	

Data are presented as % for binary variables, and mean (standard deviation, SD) for continuous variables.

eGFR = estimated Glomerular Filtration Rate per ml/min/1.73m^2, CKD = Chronic Kidney Disease, ER = Emergency Room, NSAID = Non−Steroidal Anti−Inflammatory Drug, ACE = Angiotensin−Converting Enzyme, ARBs = Angiotensin II Receptor Blockers.

Table 14. Identification of risk factors for allopurinol-induced SCAR

	Allopurinol (n=414,919)				
	N	Events	SCAR event per 1,000 persons (95% CI)	Crude RR (95%CI)	Adjusted* RR (95%CI)
Age					
<60	242,190	34	0.14 (0.10−0.20)	1.00	1.00
≥60	172,729	57	0.33 (0.25−0.43)	1.97 (1.29−3.02)	1.05 (0.65−1.71)
Sex					
Male	349,310	60	0.17 (0.13−0.22)	1.00	1.00
Female	65,609	31	0.47 (0.32−0.67)	2.92 (1.89−4.51)	2.02 (1.29−3.21)
High CV risk**					
No	248,318	32	0.13 (0.09−0.18)	1.00	1.00
Yes	166,601	63	0.38 (0.29−0.50)	1.67 (1.09−2.54)	0.98 (0.60−1.59)
Heart failure					
No	393,141	77	0.20 (0.15−0.24)	1.00	1.00
Yes	21,778	14	0.64 (0.35−1.08)	2.58 (1.46−4.57)	1.27 (0.67−2.39)
Diuretics					
No	343,927	50	0.15 (0.11−0.19)	1.00	1.00
Yes	70,992	41	0.58 (0.41−0.78)	3.07 (2.03−4.64)	1.86 (1.21−3.18)
Allopurinol initial dosage (mg/day)					
≤ 100	137,000	31	0.23 (0.15−0.32)	1.00	1.00
>100, ≤300	266,886	58	0.22 (0.17−0.28)	1.75 (1.13−2.71)	2.34 (1.50−3.65)
>300	11,033	2	0.18 (0.02−0.65)	1.49 (0.36−6.21)	1.69 (0.40−7.07)
eGFR (ml/min/1.73m^2)					
≥60	325,417	36	0.11 (0.08−0.15)	1.00	1.00
≥30, <60	82,068	47	0.57 (0.42−0.76)	3.78 (2.45−5.83)	3.16 (1.98−5.05)
≥10,	6,249	7	1.12	6.02	4.15

<30			(0.45−2.31)	(2.68−13.52)	(1.76−9.97)
<10	1,185	1	0.84 (0.02−4.70)	6.16 (0.84−44.95)	5.67 (0.78−41.41)

*Adjusted for variables presented in the table except the given stratifying factor: age, sex, CV risk, heart failure, diuretic use, initial dosage of allopurinol, and eGFR.

**The presence of at least one diagnosis of angina, MI, stroke/TIA, peripheral vascular disease, or diabetes at baseline. We also examined an interaction between index dose of allopurinol and eGFR.

CI = Confidence Interval, CV = Cardiovascular, eGFR = estimated Glomerular Filtration Rate, RR = Relative Risk, SCAR = Severe Cutaneous Adverse Reaction

Table 15. Interaction between allopurinol initial dosage and eGFR

	Allopurinol initial dosage (mg/day)	N	Events	SCAR events per 1,000 persons (95% CI)	Adjusted* RR (95% CI)
eGFR (≥30)	≤ 100	132,746	27	0.20 (0.13−0.30)	1.00
	>100, ≤300	263,890	56	0.21 (0.16−0.28)	2.23 (1.40−3.56)
	>300	10,849	1	0.09 (0.00−0.51)	0.91 (0.12−6.70)
eGFR (<30)	≤ 100	4,254	4	0.94 (0.26−2.41)	2.22 (0.77−6.40)
	>100, ≤300	2,996	3	1.00 (0.21−2.93)	4.02 (1.21−13.35)
	>300	184	1	5.43 (0.14−30.28)	18.64 (2.52−138.03)

CI=Confidence Interval, eGFR=estimated glomerular filtration rate

*Adjusted for variables presented in the table except the given stratifying factor: age, sex, CV risk, heart failure, diuretic use, initial dosage of allopurinol, and eGFR.

3.7. SENSITIVITY ANALYSIS

180 Day Follow-up Without Treatment Censoring

As shown in Table 16, the 180 day follow up analysis without censoring for drug discontinuation or adding/switching, produced results consistent with the primary analysis. The crude event rate (95% CI) of SCAR per 1,000 new users was 0.43 (0.38-0.48) for allopurinol, 0.04 (0.02-0.06) for febuxostat, and 0.23 (0.09-0.46) for benzbromarone, with corresponding RRs of 11.34 and 2.33 for allopurinol versus febuxostat and benzbromarone, respectively. For SJS/TEN and DRESS, the event rates remained highest in the allopurinol group, with RRs of 14.60 and 8.62 versus febuxostat. Although EM events were rare, they occurred only among allopurinol users. Similar patterns were observed in the subgroup with health screening data, reinforcing the robustness of the findings under a fixed 180-day follow up.

180 Day Follow-up Without Treatment Censoring Analysis Based on Steroid-Defined SCAR

As shown in Table 18, the 180-day follow-up without treatment censoring analysis evaluating SCAR risk based on diagnosis codes and systemic corticosteroid prescriptions (≥30 mg/day), regardless of hospitalization status, demonstrated consistently elevated risks associated with allopurinol use. The crude SCAR event rate (95% CI) per 1,000 new users for the composite outcome was 0.69 (0.63-0.76)

for allopurinol, 0.07 (0.05-0.09) for febuxostat, and 0.39 (0.20-0.67) for benzbromarone. The corresponding RRs were 14.60 and 6.74, respectively. Subtype-specific risks remained highest for SJS/TEN (RR 17.55) and DRESS (RR 14.40) with allopurinol use. In the health screening subgroup, the pattern persisted, with RRs of 16.04 and 7.45 for allopurinol versus febuxostat and benzbromarone, respectively. These results support the robustness of the association even under a more clinically stringent SCAR definition.

Effect of Case Definition Criteria on SCAR Risk Estimation

To assess the robustness of our findings and explore the sources of discrepancy between our study and a prior Taiwanese cohort (Yang et al., 2015), we conducted four scenario-based sensitivity analyses varying the SCAR definition, diagnosis code position, and censoring strategy (**Table 18 (A)**).

In Scenario 1, where a broad set of ICD-10 codes converted from the ICD-9-CM codes used in the Taiwanese study was applied, SCAR incidence per 1,000 persons was 1.01 in the allopurinol group, 0.11 in the febuxostat group, and 0.16 in the benzbromarone group. The relative risk (RR) of SCAR was 9.46 (95% CI, 7.24–12.30) for allopurinol compared to febuxostat, and 6.29 (2.61–15.16) compared to benzbromarone.

In Scenario 2, where our study’s stricter SCAR ICD-10 codes were used while maintaining uncensored follow-up and any-position diagnosis inclusion, SCAR incidence slightly declined across all groups. However, the RR estimates remained elevated: 11.14 (8.22–15.08) vs. febuxostat and 5.46 (2.26–13.17) vs. benzbromarone.

In Scenario 3, incorporating censoring for drug discontinuation or switching, SCAR incidence declined further (0.63 per 1,000 for allopurinol; 0.06 for febuxostat; 0.06 for benzbromarone). The RR for allopurinol was 11.21 (7.83−16.06) vs. febuxostat and 9.78 (2.44−39.23) vs. benzbromarone.

In Scenario 4, which limited outcome ascertainment to SCAR as the primary hospital diagnosis while excluding censoring, SCAR incidence was the lowest in the febuxostat group (0.02 per 1,000) and highest in the allopurinol group (0.43 per 1,000). The RR was 20.46 (11.48−36.44) vs. febuxostat and 3.34 (1.25−8.97) vs. benzbromarone.

Across all scenarios, allopurinol consistently showed higher SCAR incidence and relative risk compared to febuxostat and benzbromarone. This pattern remained robust across composite outcomes as well as SCAR subtypes, including Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), erythema multiforme (EM), and drug reaction with eosinophilia and systemic symptoms (DRESS), regardless of diagnostic code scope, censoring strategy, or diagnostic position **Table 18 (B)~(D)** .

Table 16. 180 Day Follow-up Without Treatment Censoring: SCAR risk by ULT

(A) Crude analysis for all study participants

Type of SCAR	N	Events	SCAR event per 1,000 persons (95% CI)	RR (95% CI) Ref=Febuxostat	RR (95% CI) Ref= Benzbromarone
Composite outcome					
Allopurinol	673,638	288	0.43 (0.38−0.48)	11.34 (6.30−20.41)	2.33 (0.74−7.30)
Febuxostat	570,181	22	0.04 (0.02−0.06)	Ref (1.00)	
Benzbromarone	31,072	7	0.23 (0.09−0.46)		Ref (1.00)
SJS/TEN					
Allopurinol	673,638	160	0.24 (0.20−0.28)	14.60 (5.92−36.01)	1.87 (0.46−7.61)
Febuxostat	570,181	8	0.01 (0.01−0.03)	Ref (1.00)	
Benzbromarone	31,072	2	0.06 (0.01−0.23)		Ref (1.00)
EM					
Allopurinol	673,638	11	0.02 (0.01−0.03)	NA	NA
Febuxostat	570,181	1	0.00 (0.00−0.01)	Ref (1.00)	
Benzbromarone	31,072	2	0.06 (0.01−0.23)		Ref (1.00)
DRESS					
Allopurinol	673,638	123	0.18 (0.15−0.22)	8.62 (3.96−18.78)	3.10 (0.43−22.31)
Febuxostat	570,181	13	0.02 (0.01−0.04)	Ref (1.00)	
Benzbromarone	31,072	3	0.10 (0.02−0.28)		Ref (1.00)

CI = Confidence Interval, DRESS = Drug Reaction with Eosinophilia and Systemic Symptoms, EM = Erythema Multiforme, NA = Not Applicable, RR = Relative Risk, SCAR = Severe Cutaneous Adverse Reaction, SJS = Stevens−Johnson Syndrome, TEN = Toxic Epidermal Necrolysis

(B) Adjusted analysis for those with health screening results

Type of SCAR	N	Events	SCAR event per 1,000 persons (95% CI)	RR (95% CI) Ref=Febuxostat	RR (95% CI) Ref= Benzbromarone
Composite outcome					
Allopurinol	414,919	151	0.36 (0.31−0.43)	12.54 (6.95−22.64)	2.58 (0.82−8.11)
Febuxostat	372,799	12	0.03 (0.02−0.06)	Ref (1.00)	
Benzbromarone	19,119	3	0.16 (0.03−0.46)		Ref (1.00)
SJS/TEN					
Allopurinol	414,919	81	0.20 (0.16−0.24)	15.92 (6.43−39.43)	2.07 (0.51−8.43)
Febuxostat	372,799	5	0.01 (0.00−0.03)	Ref (1.00)	
Benzbromarone	19,119	2	0.10 (0.01−0.38)		Ref (1.00)
EM					
Allopurinol	414,919	7	0.02 (0.01−0.02)	NA	NA
Febuxostat	372,799	0	0.00 (0.00−0.00)	Ref (1.00)	
Benzbromarone	19,119	0	0.00 (0.00−0.00)		Ref (1.00)
DRESS					
Allopurinol	414,919	67	0.16 (0.13−0.21)	9.73 (4.45−21.29)	3.46 (0.48−24.94)
Febuxostat	372,799	7	0.02 (0.01−0.04)	Ref (1.00)	
Benzbromarone	19,119	1	0.05 (0.00−0.29)		Ref (1.00)

*Adjusted for age, sex, income level, liver disease, eGFR (≥60, ≥30 and <60, <30 ml/min/1.73m^2), diuretics use, and comorbidity score.

CI = Confidence Interval, DRESS = Drug Reaction with Eosinophilia and Systemic Symptoms, EM = Erythema Multiforme, NA = Not Applicable, RR = Relative Risk, SCAR = Severe Cutaneous Adverse Reaction, SJS = Stevens−Johnson Syndrome, TEN = Toxic Epidermal Necrolysis

Table 17. 180 Day Follow-up Without Treatment Censoring using a steroid based SCAR Definition

(A) Crude analysis for all study participants

Type of SCAR	N	Events	SCAR event per 1,000 persons (95% CI)	RR (95% CI) Ref=Febuxostat	RR (95% CI) Ref= Benzbromarone
Composite outcome					
Allopurinol	673,638	466	0.69 (0.63−0.76)	14.60 (7.45−28.63)	6.74 (0.94−48.18)
Febuxostat	570,181	39	0.07 (0.05−0.09)	Ref (1.00)	
Benzbromarone	31,072	12	0.39 (0.20−0.67)		Ref (1.00)
SJS/TEN					
Allopurinol	673,638	162	0.24 (0.20−0.28)	17.55 (6.43−47.95)	3.60 (0.50−25.89)
Febuxostat	570,181	7	0.01 (0.00−0.03)	Ref (1.00)	
Benzbromarone	31,072	2	0.06 (0.01−0.23)		Ref (1.00)
EM					
Allopurinol	673,638	40	0.06 (0.04−0.08)	NA	NA
Febuxostat	570,181	4	0.01 (0.00−0.02)	Ref (1.00)	
Benzbromarone	31,072	2	0.06 (0.00−0.23)		Ref (1.00)
DRESS					
Allopurinol	673,638	264	0.39 (0.35−0.44)	14.40 (5.25−39.55)	NA
Febuxostat	570,181	28	0.05 (0.03−0.07)	Ref (1.00)	
Benzbromarone	31,072	8	0.26 (0.11−0.51)		Ref (1.00)

CI = Confidence Interval, DRESS = Drug Reaction with Eosinophilia and Systemic Symptoms, EM = Erythema Multiforme, NA = Not Applicable, RR = Relative Risk, SCAR = Severe Cutaneous Adverse Reaction, SJS = Stevens−Johnson Syndrome, TEN = Toxic Epidermal Necrolysis

(B) Adjusted analysis for those with health screening results

Type of SCAR	N	Events	SCAR event per 1,000 persons (95% CI)	RR (95% CI) Ref=Febuxostat	RR (95% CI) Ref=Benzbromarone
Composite outcome					
Allopurinol	414,919	260	0.63 (0.55−0.71)	16.04 (8.16−31.53)	7.45 (1.04−53.26)
Febuxostat	372,799	22	0.06 (0.04−0.09)	Ref (1.00)	
Benzbromarone	19,119	6	0.31 (0.12−0.68)		Ref (1.00)
SJS/TEN					
Allopurinol	414,919	83	0.20 (0.16−0.25)	19.15 (6.99−52.49)	3.97 (0.55−28.55)
Febuxostat	372,799	4	0.01 (0.00−0.03)	Ref (1.00)	
Benzbromarone	19,119	2	0.10 (0.01−0.38)		
EM					
Allopurinol	414,919	25	0.06 (0.04−0.09)	NA	NA
Febuxostat	372,799	3	0.01 (0.00−0.02)		
Benzbromarone	19,119	0	0		
DRESS					
Allopurinol	414,919	152	0.37 (0.31−0.43)	15.89 (5.76−43.79)	NA
Febuxostat	372,799	15	0.04 (0.02−0.07)	Ref (1.00)	
Benzbromarone	19,119	4	0.21 (0.06−0.54)		

*Adjusted for age, sex, income level, liver disease, eGFR (≥60, ≥30 and <60, <30 ml/min/1.73m2), diuretics use, and comorbidity score. CI = Confidence Interval, DRESS = Drug Reaction with Eosinophilia and Systemic Symptoms, EM = Erythema Multiforme, NA = Not Applicable, RR = Relative Risk, SCAR = Severe Cutaneous Adverse Reaction, SJS = Stevens−Johnson Syndrome, TEN = Toxic Epidermal Necrolysis

Table 18. SCAR Incidence and Relative Risks by Drug and Analysis Scenario

(A) Composite outcome

Type of analysis	N	Events	SCAR event per 1,000 persons (95% CI)	RR (95% CI) Ref=Febuxostat	RR (95% CI) Ref=Benzbromarone
Analysis Scenario 1: broad SCAR ICD code, no censored, diagnosis any position					
Allopurinol	673,638	682	1.01 (0.94–1.09)	9.46 (7.24–12.30)	6.29 (2.61–15.16)
Febuxostat	570,181	61	0.11 (0.08–0.14)	Ref (1.00)	
Benzbromarone	31,072	5	0.16 (0.07–0.38)		Ref (1.00)
Analysis Scenario 2: Study ICD code only, no censored, diagnosis any position					
Allopurinol	673,638	592	0.88 (0.81–0.95)	11.14 (8.22–15.08)	5.46 (2.26–13.17)
Febuxostat	570,181	45	0.08 (0.06–0.11)	Ref (1.00)	
Benzbromarone	31,072	5	0.16 (0.07–0.38)		Ref (1.00)
Analysis Scenario 3: broad SCAR ICD code, **censored**, diagnosis any position					
Allopurinol	673,638	424	0.63 (0.57–0.69)	11.21 (7.83–16.06)	9.78 (2.44–39.23)
Febuxostat	570,181	32	0.06 (0.04–0.08)	Ref (1.00)	
Benzbromarone	31,072	2	0.06 (0.02–0.23)		Ref (1.00)
Analysis Scenario 4: broad SCAR ICD code, no censored, **primary position only**					
Allopurinol	673,638	290	0.43 (0.38–0.48)	20.46 (11.48–36.44)	3.34 (1.25–8.97)
Febuxostat	570,181	12	0.02 (0.01–0.04)	Ref (1.00)	
Benzbromarone	31,072	4	0.13 (0.05–0.33)		Ref (1.00)

RR = Relative Risk, CI = Confidence Interval, SCAR = Severe Cutaneous Adverse Reaction

Incidence rates and relative risks (RRs) of SCAR are shown for four scenarios varying by diagnosis code set, censoring, and code position. Rates per 1,000 persons; Febuxostat used as primary reference.

(B) SJS/TEN

Type of analysis	N	Events	SCAR event per 1,000 persons (95% CI)	RR (95% CI) Ref=Febuxostat	RR (95% CI) Ref=Benzbromarone
Analysis Scenario 1: broad SCAR ICD code, no censored, diagnosis any position					
Allopurinol	673,638	220	0.33 (0.29−0.37)	20.69 (12.44−39.47)	10.15 (2.08−349.59)
Febuxostat	570,181	9	0.02 (0.01−0.03)	Ref (1.00)	
Benzbromarone	31,072	1	0.03 (0.00−0.18)		Ref (1.00)
Analysis Scenario 2: Study ICD code only, no censored, diagnosis any position					
Allopurinol	673,638	220	0.33 (0.29−0.37)	20.69 (12.44−39.47)	10.15 (2.08−349.59
Febuxostat	570,181	9	0.02 (0.01−0.03)	Ref (1.00)	
Benzbromarone	31,072	1	0.03 (0.00−0.18)		Ref (1.00)
Analysis Scenario 3: broad SCAR ICD code, **censored**, diagnosis any position					
Allopurinol	673,638	165	0.24 (0.21−0.29)	34.91 (15.88−109.34)	7.61 (1.59−256.49)
Febuxostat	570,181	4	0.01 (0.00−0.02)	Ref (1.00)	
Benzbromarone	31,072	1	0.03 (0.00−0.18)		Ref (1.00)
Analysis Scenario 4: broad SCAR ICD code, no censored, **primary position only**					
Allopurinol	673,638	134	0.20 (0.17−0.24)	28.36 (13.12−87.19)	6.18 (1.31−204.55)
Febuxostat	570,181	4	0.01 (0.00−0.02)	Ref (1.00)	
Benzbromarone	31,072	1	0.03 (0.01−0.18)		Ref (1.00)

RR = Relative Risk, CI = Confidence Interval, SCAR = Severe Cutaneous Adverse Reaction, SJS = Stevens−Johnson Syndrome, TEN = Toxic Epidermal Necrolysis

Incidence rates and relative risks (RRs) of SCAR are shown for four scenarios varying by diagnosis code set, censoring, and code position. Rates per 1,000 persons; Febuxostat used as primary reference.

(C) EM

Type of analysis	N	Events	SCAR event per 1,000 persons (95% CI)	RR (95% CI) Ref=Febuxostat	RR (95% CI) Ref=Benzbromarone
Analysis Scenario 1: broad SCAR ICD code, no censored, diagnosis any position					
Allopurinol	673,638	35	0.05 (0.04–0.07)	29.62 (7.39–12.30)	1.61 (7.39–815.03)
Febuxostat	570,181	1	0.00 (0.00–0.01)	Ref (1.00)	
Benzbromarone	31,072	1	0.03 (0.01–0.18)		Ref (1.00)
Analysis Scenario 2: Study ICD code only, no censored, diagnosis any position					
Allopurinol	673,638	35	0.05 (0.04–0.07)	29.62 (7.39–12.30)	1.61 (7.39–815.03)
Febuxostat	570,181	1	0.00 (0.00–0.01)	Ref (1.00)	
Benzbromarone	31,072	1	0.03 (0.01–0.18)		Ref (1.00)
Analysis Scenario 3: broad SCAR ICD code, **censored**, diagnosis any position					
Allopurinol	673,638	12	0.02 (0.01–0.03)	10.16 (3.18–207.30)	0.55 (11.3–0.17)
Febuxostat	570,181	1	0.00 (0.00–0.01)	Ref (1.00)	
Benzbromarone	31,072	1	0.03 (0.01–0.18)		Ref (1.00)
Analysis Scenario 4: broad SCAR ICD code, no censored, **primary position only**					
Allopurinol	673,638	16	0.02 (0.01–0.01)	NA	0.74 (0.22–8.97)
Febuxostat	570,181	0	NA		
Benzbromarone	31,072	1	0.03 (0.01–0.18)		Ref (1.00)

RR = Relative Risk, CI = Confidence Interval, SCAR = Severe Cutaneous Adverse Reaction, EM = Erythema Multiforme
Incidence rates and relative risks (RRs) of SCAR are shown for four scenarios varying by diagnosis code set, censoring, and code position. Rates per 1,000 persons; Febuxostat used as primary reference.

(D) DRESS

Type of analysis	N	Events	SCAR event per 1,000 persons (95% CI)	RR (95% CI) Ref=Febuxostat	RR (95% CI) Ref=Benzbromarone
Analysis Scenario 1: broad SCAR ICD code, no censored, diagnosis any position					
Allopurinol	673,638	337	0.50 (0.45–0.56)	8.15 (6.52–10.48)	5.18 (1.97–22.51)
Febuxostat	570,181	35	0.06 (0.04–0.09)	Ref (1.00)	
Benzbromarone	31,072	3	0.10 (0.02–0.28)		Ref (1.00)
Analysis Scenario 2: Study ICD code only, no censored, diagnosis any position					
Allopurinol	673,638	337	0.50 (0.45–0.56)	8.15 (6.52–10.48)	5.18 (1.97–22.51)
Febuxostat	570,181	35	0.06 (0.04–0.09)	Ref (1.00)	
Benzbromarone	31,072	3	0.10 (0.02–0.28)		Ref (1.00)
Analysis Scenario 3: broad SCAR ICD code, **censored**, diagnosis any position					
Allopurinol	673,638	200	0.03 (0.26–0.34)	8.46 (6.29–12.00)	9.23 (1.90–315.62)
Febuxostat	570,181	20	0.04 (0.00–0.02)	Ref (1.00)	
Benzbromarone	31,072	1	0.03 (0.00–0.18)		Ref (1.00)
Analysis Scenario 4: broad SCAR ICD code, no censored, **primary position only**					
Allopurinol	673,638	129	0.19 (0.16–0.23)	2.98 (0.98–20.51)	15.60 (1.25–32.39)
Febuxostat	570,181	7	0.01 (0.00–0.03)	Ref (1.00)	
Benzbromarone	31,072	2	0.06 (0.01–0.23)		Ref (1.00)

RR = Relative Risk, CI = Confidence Interval, DRESS = Drug Reaction with Eosinophilia and Systemic Symptoms, SCAR = Severe Cutaneous Adverse Reaction, SJS = Stevens–Johnson Syndrome, TEN = Toxic Epidermal Necrolysis

Incidence rates and relative risks (RRs) of SCAR are shown for four scenarios varying by diagnosis code set, censoring, and code position. Rates per 1,000 persons; Febuxostat used as primary reference.

CHAPTER 4. DISCUSSION

4.1. SUMMARY OF KEY FINDINGS

This large, population-based cohort study utilizing Korean National Health Insurance Service data provides robust evidence of a substantially increased risk of severe cutaneous adverse reactions (SCARs) associated with allopurinol compared to febuxostat and benzbromarone among new users of urate-lowering therapy. The risk of SCAR was markedly elevated in the allopurinol group, with adjusted incidence rate ratios of 26.1 versus febuxostat and 4.97 versus benzbromarone, findings that remained consistent across multiple sensitivity analyses and alternative definitions of SCAR.

Temporal analysis revealed that the incidence of allopurinol-induced SCAR peaked within 31-60 days after initiation, with the highest mortality observed between 61-90 days. These results highlight a critical window for clinical vigilance during the early phase of therapy.

Multivariable analysis identified female sex, concomitant diuretic use,

higher initial doses of allopurinol (>100 mg/day), and impaired renal function (

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a These findings provide important insights into optimizing ULT selection in real-world settings, especially for patients at high risk of SCAR. While prior studies have also noted increased SCAR risk among allopurinol users with impaired renal function or higher doses (Krishnan & Chen, 2013; Stamp et al., 2012), few have jointly examined the interaction between the two factors. Our findings, which indicate a synergistic increase in SCAR risk among individuals prescribed higher initial doses of allopurinol in the context of reduced renal function, add important population-level evidence from routine clinical settings. This highlights the need for careful dose adjustment and renal function monitoring during the initiation of urate-lowering therapy in high-risk groups.

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4.2. INTERPRETATION AND CLINICAL IMPLICATIONS

ULT and SCAR Incidence

This study sought to address whether allopurinol remains a high-risk agent for SCARs in a contemporary Korean population-a question rooted in ongoing concerns about the drug’ s hypersensitivity potential. In response, our findings reaffirm the well-established risk of SCAR associated with allopurinol, with a 180-day risk of SCAR of 0.26 per 1,000 persons, which is substantially higher than that observed with febuxostat (0.01 per 1,000 person) or benzbromarone (0.06 per 1,000 person). In the 180-day analysis evaluating SCAR risk by ULT, the incidence of SCAR without censoring for treatment discontinuation or switching was 0.43 (95% CI: 0.38−0.48) per 1,000 allopurinol initiators, with 288 cases observed among 673,638 individuals. When applying a broader SCAR definition that included cases with high-dose systemic corticosteroid prescriptions (≥30 mg/day) regardless of hospitalization, the incidence further increased to 0.69 (95% CI: 0.63−0.76) per 1,000 initiators, with 466 cases identified, supporting the robustness of our primary results.

Although our observed incidence rates are consistent with the known risk of allopurinol-induced SCARs, they appear notably lower than those reported in other East Asian and Western populations. For example, Yang et al. reported a SCAR incidence of 2.02 per 1,000 users in a nationwide Taiwanese cohort using a broad SCAR definition (Yang et al., 2015), while Sato et al. found a 0.94 per 1,000 rate in Japanese patients using similar outcome criteria (Sato et al., 2021). In the United States, Keller et al. estimated an incidence of 0.51 per 1,000 among Medicaid

beneficiaries (Keller et al., 2018).

One potential explanation for the relatively low SCAR incidence observed in our Korean cohort is the conservative and clinically oriented outcome definition used in our study. We defined SCAR cases based on hospitalization records with primary discharge diagnoses, and excluded individuals who continued the index ULT even once after the SCAR diagnosis. In contrast, the Taiwanese study did not clearly specify whether SCAR cases were identified based on primary diagnoses. Moreover, it excluded only those who did not discontinue the index drug within 3 months after the SCAR event. In our dataset, we found that many patients continued or resumed the same urate-lowering therapy more than a year after the SCAR diagnosis. It is also likely that the Taiwanese study included secondary diagnoses in the outcome definition, which may have led to an overestimation of SCAR incidence (Yang et al., 2015).

To better understand the substantially lower SCAR incidence observed in the Korean cohort compared to a prior population based study, we conducted a series of sensitivity analyses across four scenarios in **Table 18**. These scenarios systematically varied three key components: the breadth of diagnostic code definitions, the position of diagnosis codes, and the application of censoring for drug discontinuation or switching (Yang et al., 2015). Among these, the diagnosis position had the most pronounced effect. When the analysis allowed SCAR diagnoses to appear in any diagnostic field rather than only as the principal diagnosis, the number of identified cases nearly doubled. This suggests that many SCAR events may be recorded as secondary rather than primary reasons for hospitalization in clinical practice.

Even in the most inclusive scenario that applied the broader ICD 10 code set used in the previous study, removed censoring rules, and accepted diagnoses in any position, the SCAR incidence among allopurinol users was only 1.01 per 1,000 persons. This was still lower than the reported incidence of 2.02 per 1,000 persons in the earlier study (Yang et al., 2015). These findings imply that other contextual factors may explain the difference.

It is likely that variations in diagnostic coding conventions, the earlier and more widespread implementation of HLA B*58:01 screening in Korea, and evolving prescribing practices such as the increased use of alternative urate lowering therapies have contributed to the lower SCAR incidence. Our scenario based comparisons support the conclusion that differences in case ascertainment methods and national healthcare practices are more influential than pharmacologic exposure definitions alone in explaining the discrepancies observed across populations (Yang et al., 2015).

Additionally, differences in patient characteristics may also contribute to the discrepancy. Compared to our cohort, the Taiwanese population had a higher proportion of female participants, a two-fold higher prevalence of chronic kidney disease (CKD), and a nearly double frequency of the HLA-B*58:01 allele-all of which are known risk factors for allopurinol-induced SCAR (Kurose et al., 2012).

Furthermore, demographic differences may partially account for the lower risk observed in Korea compared to international studies. For example, in the U.S. cohort reported by Keller et al. (Keller et al., 2018), the mean age was substantially higher (68.8 years vs. 57 years in our cohort), and the proportion of female patients and those with heart failure was also greater. These are all known risk factors for SCAR (Keller et al., 2018; Sato et al., 2021; Stamp et al., 2016; Stamp et al., 2012).

Older age is associated with reduced drug clearance and altered immune responses, while female sex and heart failure have been independently linked to increased risk of allopurinol hypersensitivity. Therefore, it is likely that the lower SCAR incidence in our Korean cohort reflects not only differences in outcome definitions and risk mitigation practices, but also underlying demographic and clinical risk profiles.

Importantly, while the incidence may be lower than in earlier or international studies, the risk remains clinically significant. Given that most events occurred within 60 days of therapy initiation and that mortality reached 21% among SCAR cases, these findings underscore the need for continued risk mitigation strategies, such as genetic screening, dose individualization, and early monitoring during the high-risk treatment window. Confirmation of the continued importance of risk stratification and early vigilance when prescribing allopurinol in real-world practice is provided by these findings.

Febuxostat has been considered relatively safe in terms of cutaneous adverse reactions, but it is not entirely without risk. In our study, SCAR events occurred at a rate of 0.01 per 1,000 febuxostat users. Although rare, this finding demonstrates that serious adverse reactions can still occur with febuxostat use.

A nationwide cohort study conducted in Taiwan (Lin et al., 2019) reported similar findings. Among 28,229 febuxostat users, 6 cases of SCAR were identified, corresponding to an incidence rate of 0.21 per 1,000 persons. In the same study, 212 SCAR cases occurred among 164,048 allopurinol users, with 42 SCAR-related deaths in the allopurinol group and 1 in the febuxostat group.

These findings suggest that while febuxostat is associated with a lower incidence of SCAR compared to allopurinol, the risk is not negligible. In the

Taiwanese study, the prevalence of chronic kidney disease was 12% among allopurinol users and 45% among febuxostat users. In contrast, our study population had a lower prevalence, with 5% in the allopurinol group and 12% in the febuxostat group. Since impaired renal function is known to increase the risk of SCAR, this difference may partially explain the higher SCAR incidence in the Taiwanese cohort.

Furthermore, another study (Ko et al., 2015) reported no recurrence of SCAR in patients who switched from allopurinol to febuxostat, even among those carrying the HLA-B*58:01 allele. This provides supporting evidence that febuxostat may be a safer option for high-risk individuals.

However, the low incidence of SCAR should not lead to an overly optimistic interpretation of febuxostat's safety profile. In real-world clinical settings, various underlying conditions, concomitant medications, and genetic factors can influence outcomes. Therefore, it is essential to carefully evaluate whether SCAR events observed in febuxostat users are truly attributable to the drug itself.

While these findings underscore the differential SCAR risks across urate-lowering therapies, it is important to assess whether residual confounding from co-medications may have influenced our results. Given that certain high-risk drugs such as anticonvulsants and anti-infective agents are known triggers for SCAR, we undertook additional adjustment strategies to account for these potential confounders.

Given that several high-risk medications—such as anticonvulsants and anti-infective agents—are well-known triggers of SCAR, we considered the possibility that differential use of these drugs across treatment groups may confound the observed associations. Since direct prescription data for these drug classes were not available in the dataset, we utilized proxy variables based on the presence of

underlying conditions typically managed with such medications (Kang et al., 2021). These included psychiatric disorders (e.g., epilepsy, trigeminal neuralgia, bipolar disorder, and neuropathic pain) and infectious diseases (e.g., gastroenteritis, pneumonia, urinary tract infections, and skin infections) within one year prior to index date.

Our multivariable models demonstrated that even after adjusting for these proxy comorbidity indicators, the relative risk of SCAR associated with allopurinol remained substantially elevated compared to febuxostat across all models. The magnitude and direction of risk estimates were nearly identical before and after adjustment for these high-risk conditions, suggesting that residual confounding by co-medications is unlikely to explain the observed association. This finding reinforces the intrinsic risk profile of allopurinol, particularly in populations without prior screening for HLA-B*58:01 (Hung et al., 2005; Somkrua et al., 2011).

While adjustments for co-medication-related conditions added analytic rigor, certain limitations persist. First, the inability to directly observe co-prescriptions of SCAR-inducing medications such as carbamazepine, lamotrigine, or vancomycin represents a structural limitation of the data. Second, the use of diagnosis codes as proxies does not capture the timing, dosage, or duration of actual drug exposure, possibly resulting in exposure misclassification. Nonetheless, the consistency of effect sizes despite this limitation provides indirect support for the robustness of our findings.

Overall, these results underscore the necessity of incorporating co-medication risk into SCAR pharmacoepidemiologic studies. Where direct data on drug exposure is lacking, comorbidity-based proxies can serve as valuable tools—

though researchers must interpret such analyses with awareness of their inherent limitations.

In conclusion, febuxostat presents a lower risk of SCAR compared to allopurinol, but the risk is not absent. Particularly in high-risk patients, careful risk assessment and early monitoring are warranted. Awareness of potential adverse events remains crucial to ensure the safe use of febuxostat in clinical practice.

Does this difference persist across various outcome definitions and analysis strategies?

To test the robustness of our findings, we examined whether the elevated risk of SCAR with allopurinol persisted under a variety of definitions and analytic strategies. Our results consistently affirmed this association across all approaches.

First, by applying both stricter (e.g., hospitalization plus corticosteroid $\geq$ 30 mg/day within 30 days first SCAR diagnosis) and broader (e.g., inclusion of less-specific rash codes) SCAR definitions, we sought to evaluate whether our observed risk differences could be attributed to outcome misclassification. The consistent signal of elevated SCAR risk with allopurinol-regardless of the definition-strengthens the causal interpretation and highlights the robustness of our findings.

Second, methodological triangulation via both as-treated and ITT frameworks allowed us to assess potential biases introduced by differential treatment discontinuation or switching. This was particularly important given the real-world setting, where patient adherence and clinical decisions may vary. The persistence of risk signals across both designs suggests that our conclusions are unlikely to be

artifacts of analytical choices.

Third, the broader definitions enabled comparative alignment with prior international studies, such as the Taiwanese cohort study (Yang et al., 2015), which used less restrictive SCAR criteria. Reproducing similar patterns under their definitions ensures external validity and facilitates cross-national interpretation.

Finally, these analyses allowed us to identify not only the most conservative estimates of risk but also the likely clinical spectrum of SCARs as encountered in practice-ranging from confirmed, hospitalized cases to potentially underdiagnosed or miscoded events.

Together, these layers of sensitivity testing show that the association between allopurinol and SCAR is not due to coding practices, statistical modelling or the follow-up approach, but is a reproducible signal that requires serious clinical attention.

Timing and Fatality of SCAR: The Critical Early Treatment Window

In our study, most SCAR events occurred within 60 days of initiating urate-lowering therapy, with the highest incidence during days 31−60 and peak mortality during days 61−90 (52.6%). Specifically, 86.9% of allopurinol-induced SCARs occurred within the first 60 days, underscoring a critical period for clinical monitoring.

This temporal pattern is consistent with the delayed-type hypersensitivity mechanism driven by drug-specific T-cell responses in genetically predisposed individuals. In particular, the strong link between HLA-B*58:01 and allopurinol-induced SCAR (especially SJS/TEN and DRESS) supports this immunopathological

process (Cheng et al., 2014; Chessman et al., 2008; Halevy et al., 2008).

The overall SCAR-related mortality in our cohort was 21.1%, with 27.5% mortality among patients with SJS/TEN, highlighting the severity of these reactions even in populations with relatively low incidence (Chessman et al., 2008; Halevy et al., 2008). Notably, all SCAR cases from febuxostat and benzbromarone also occurred within 60 days, reinforcing the importance of early-phase monitoring for all ULTs.

Importantly, SCAR cases associated with febuxostat and benzbromarone also occurred exclusively within the first 60 days, reinforcing the need for early monitoring of not only allopurinol, but other ULTs as well. Although rare, these events should not be overlooked, especially in high-risk individuals.

Taken together, these findings suggest that the first two months following ULT initiation represent a high-risk period, during which close observation is essential. Early detection of skin symptoms and prompt discontinuation of the suspected agent can significantly reduce morbidity and mortality. Therefore, clinicians should adopt short-term mitigation strategies, such as genetic screening, dose titration and risk-based patient education, particularly when prescribing allopurinol.

SCAR Mortality: Clinical Significance and Identification of High Risk Groups

In this study, the overall mortality among allopurinol-induced SCAR cases was 21.1%, with the highest death rate observed in SJS/TEN cases (27.5%). These findings align with prior literature, including mortality rates reported in Taiwan

(26.1%) (Yang et al., 2015), Japan (20–25%) (Sato et al., 2021), and Europe/Israel (24%) (Halevy et al., 2008), reinforcing the lethal nature of these conditions.

Most fatal cases occurred among older adults (mean age 76 years), those with impaired renal function (none had eGFR $\geq$60 mL/min/1.73m^2), and patients with substantial comorbidity burdens, particularly heart failure (40.5%) and diabetes mellitus (62.2%). These patients also exhibited higher usage of cardiovascular medications, including beta-blockers, calcium channel blockers, and diuretics as consistent with known SCAR risk enhancers (Cheng et al., 2014; Hung et al., 2005; Lin et al., 2019; Stamp et al., 2012).

Importantly, more than half (52.6%) of all SCAR-related deaths occurred between 61-90 days after allopurinol initiation, indicating a delayed but critical mortality window. This suggests that initial monitoring strategies that focus solely on the first month may miss later high-risk periods. These results highlight the need for tailored risk mitigation strategies, particularly among high risk groups. This includes: (a) Dose reduction in patients with renal impairment (Stamp et al., 2016), (b) Close clinical monitoring for at least 90 days after initiation, with special attention between 30–90 days.

While the incidence of SCAR may appear low, its consequences are profound. Identifying and protecting vulnerable patients is a critical public health and pharmacovigilance priority.

Furthermore, the selection of febuxostat as the primary reference group was based on both statistical stability and clinical rationale. Compared to benzbromarone, which had a limited number of SCAR cases and sparse supporting literature,

febuxostat allowed more robust estimation of relative risks. Although benzbromarone was also included as a secondary comparator, its use was primarily supplementary due to interpretative limitations from rare event counts and limited external validation.

4.3. STRENGTHS AND LIMITATIONS

Strengths:

This study has several important strengths. This study is the first large-scale, population-based cohort to compare SCAR risk across allopurinol, febuxostat, and benzbromarone using national data over 10 years, unlike many prior studies that were registry-based (D. Y. Kang et al., 2021; Kang et al., 2019; Kardaun et al., 2013; Lonjou et al., 2008), lacked population-level generalizability (Aatif et al., 2018; De La Cruz et al., 2021), or were limited to short observation periods (Yang et al., 2015) and focused solely on allopurinol (Keller et al., 2018). We applied multiple outcome definitions and analytic strategies (e.g., diagnosis position, no censoring, broad and strict SCAR definitions), and found consistent results-enhancing credibility. SCAR definitions based on primary inpatient diagnoses and corticosteroid use added clinical validity.

Limitations:

However, several limitations must be acknowledged. First, as with all claims-based studies, our outcome definitions relied on diagnostic codes, without access to

detailed clinical charts or pathology confirmation. While we applied conservative definitions to improve specificity, the absence of clinical adjudication may introduce misclassification bias. Second, we lacked data on genetic risk factors, particularly the presence of HLA-B*58:01, a known strong predictor of allopurinol-induced SCAR. As a result, we were unable to assess gene-drug interactions or the protective effects of preemptive screening. Although HLA-B*58:01 is a key risk factor for SCAR, fewer than 1% of patients had documented genetic screening, limiting our ability to assess gene-associated risk directly. Third, the number of SCAR cases for febuxostat and benzbromarone users was small, which may limit the precision and stability of risk estimates for these drugs. Fourth, we could not account for unmeasured confounders such as over-the-counter medication use, treatment adherence, or lifestyle factors that might influence SCAR risk.

Several directions can be considered to address the limitations of this study. First, while this study defined SCAR based on diagnostic codes from Korean administrative data, future studies should utilize datasets from other countries and apply broader definitions of SCAR (such as those including generalized rash in any body location) to enable cross-national comparisons and external validation of findings. Second, since SCAR cases in this study were identified solely by diagnostic codes, future research should incorporate detailed clinical information, including electronic medical records, pathology results, and clinical photographs, to improve the accuracy and interpretability of SCAR classification. Third, to improve prediction of rare but serious adverse drug reactions such as SCAR, artificial intelligence models should be developed using structured data (including

comorbidities, concomitant medications, dosage, and treatment duration，without relying on genetic testing. These models may serve as practical tools for real-world precision medicine, helping clinicians identify high-risk patients and implement tailored prevention strategies. Fourth, a key limitation of this study is that we restricted our cohort to patients with a confirmed diagnosis of gout (ICD-10: M10) who were newly prescribed urate-lowering therapy. This design choice was intended to reduce treatment indication heterogeneity and ensure that the index medications were prescribed for comparable clinical reasons. However, because of this restriction, we were unable to evaluate the risk of SCAR associated with allopurinol in patients without gout. In real-world clinical practice, allopurinol is frequently prescribed for non-gout indications such as uric acid nephrolithiasis or tumor lysis syndrome. Therefore, our findings may not be generalizable to these populations. Future studies should broaden the inclusion criteria to assess whether SCAR risk varies by treatment indication. Stratified analyses by clinical context may help refine risk estimates and enhance the safe prescribing of urate-lowering therapies across diverse patient populations.

CHAPTER 5. CONCLUSION

In this nationwide population-based cohort study, we found that allopurinol use was associated with a significantly higher risk of severe cutaneous adverse reactions (SCAR) compared to febuxostat and benzbromarone. This elevated risk persisted across multiple outcome definitions—including hospitalization, corticosteroid use, and RegiSCAR-based case ascertainment—and was robust to various sensitivity and stratified analyses. Notably, SCAR events clustered within the first 60 days after treatment initiation, emphasizing the need for vigilant monitoring during this early treatment window.

The risk of SCAR was further heightened among subgroups with renal impairment, higher initial allopurinol doses, female sex, and concomitant use of diuretics, supporting a multifactorial pathogenesis involving pharmacokinetic vulnerability and immunogenetic predisposition. These findings align with the established HLA-B*58:01–allopurinol–SCAR axis, but also suggest the contribution of non-genetic clinical factors that may act independently or synergistically.

In contrast, febuxostat and benzbromarone exhibited markedly lower SCAR incidence rates, with no consistent association with high-risk subgroups. This

provides real-world support for their use as safer alternatives in patients at elevated SCAR risk, particularly those unable to undergo or afford genetic testing. However, further investigation is warranted regarding their long-term immunologic safety and potential idiosyncratic reactions, given the limited evidence base.

Clinically, these findings underscore the importance of early screening, personalized drug selection, and cautious titration in initiating urate-lowering therapy. From a public health perspective, they reinforce the value of genetic screening policies and pharmacovigilance systems that monitor post-marketing drug safety using real-world evidence.

This study adds to the growing literature by integrating molecular pharmacology, immunogenetic mechanisms, and large-scale real-world data, offering one of the most comprehensive comparative risk assessments of SCAR across urate-lowering agents to date. The findings may inform future clinical guidelines, support shared decision-making, and guide the design of precision-based SCAR prevention strategies.

Future research should aim to elucidate the underlying immune pathways of febuxostat- and benzbromarone-associated SCAR, validate the findings in other ethnic populations, and explore multi-omics approaches to risk prediction that go beyond HLA typing. Continued effort in this domain is essential for ensuring safe, personalized, and equitable gout management in an era of precision medicine.

ABSTRACT IN KOREAN

통풍환자에서 요산강하요법에 따른 중증 피부 이상 반응 위험: 인구 기반 코호트 연구

배경: 통풍 환자에게 흔히 사용되는 요산강하제(Urate-Lowering Therapies, ULTs) 중 알로퓨리놀은 드물지만 심각한 피부 이상 반응(Severe Cutaneous Adverse Reactions, SCARs)과의 연관성이 다수 보고되어 왔다. 그러나 다양한 ULT 간 SCAR 발생 위험을 직접 비교하고, 알로퓨리놀 유발 SCAR의 개별 위험 요인을 규명한 연구는 부족하다.

목적: 본 연구는 40세 이상 통풍 환자에서 알로퓨리놀, 페북소스타트, 벤즈브로마론의 신규 사용자를 비교하여 SCAR 발생 위험을 추정하고, 알로퓨리놀 관련 SCAR의 시기별 위험도 및 위험 요인을 평가하고자 하였다.

방법: 2010년부터 2020년까지 국민건강보험공단(NHIS) 자료를 이용한 인구 기반 코호트 연구를 수행하였다. 알로퓨리놀(n=673,638), 페북소스타트(n=570,181), 벤즈브로마론(n=31,072) 신규 사용자를 대상으로, 입원이 필요한 SCAR(스티븐스-존슨 증후군, 독성표피괴사용해, 호산구증가 및 전신증상 약물반응)의 복합 발생을 주요 결과지표로 정의하였다. 연령, 성별, 소득 수준, 간질환, 신기능, 이뇨제 사용 여부, 동반질환 점수를 포함한 공변량을 보정한 포아송 회귀모형을 사용하여 약제 간 상대위험도(RR) 및 95% 신뢰구간(CI)을 산출하였다. 아울러, 알로퓨리놀 사용군 내에서 SCAR의 발

생 시기 및 사망률을 분석하고, 연령, 성별, 심혈관질환 위험, 이뇨제 사용, 알로퓨리놀 시작 용량, 신기능에 따른 하위그룹 분석을 통해 위험 요인을 평가하였다.

결과: 전체 1,243,819명의 신규 ULT 사용자 중 1년 이내 SCAR 발생 사례는 185건이었으며, 이 중 184건(99.5%)은 약물 복용 후 180일 이내에 발생하였다. SCAR 발생률(IR, 1,000인년당, 95% CI)은 알로퓨리놀 1.41(1.22–1.64), 페북소스타트 0.04(0.02–0.08), 벤즈브로마론 0.28(0.07–1.12)로 나타났다. 보정된 RR(95% CI)은 페북소스타트 대비 알로퓨리놀 16.35 (8.60–40.55), 벤즈브로마론 대비 알로퓨리놀 4.19(0.92–133.35)이었다. 알로퓨리놀 유발 SCAR 발생은 투약 후 31–60일 사이에서 가장 많이 나타났으며(IR 0.31, 95% CI 0.25–0.38), SCAR 관련 사망은 주로 61–90일 사이에서 발생하였다(사망률 52.6%). 여성, 이뇨제 병용, 높은 알로퓨리놀 시작 용량, 신기능 저하(GFR 분류 기반)가 SCAR 발생의 유의한 위험 요인으로 확인되었다.

결론: 알로퓨리놀은 페북소스타트 및 벤즈브로마론에 비해 SCAR 발생 위험이 현저히 높았으며, 약제 선택 시 초기 용량 조절, 신기능 평가 및 고위험 환자(여성, 이뇨제 병용 등)에 대한 주의가 필요하다. 본 연구는 실제 진료현장에서의 약제별 SCAR 위험을 비교한 국내 최초의 대규모 분석으로서, 환자 맞춤형 약제 선택과 사전 스크리닝 전략 수립에 기초자료를 제공한다.

주요어: 심각한 피부 이상 반응(SCARs), 통풍, 요산강하제(ULTs), 알로퓨

리놀, 페북소스타트, 벤즈브로마론, 인구 기반 코호트 연구

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APPENDIX

Appendix Table A 1. Comparative risk of SCAR in ULTs initiators by Cox models 19. Comparative risk of SCAR in ULTs initiators by Cox models

(A) Crude analysis for all study participants

Type of SCAR	n	Events	PY	IR (95% CI)	HR (95% CI)	
					Ref=Febuxostat	Ref=Benzbromarone
Composite outcome						
Allopurinol	673,638	175	124,306	1.41 (1.22−1.64)	31.55 (14.82−67.17)	4.77 (1.18−19.21)
Febuxostat	570,181	7	167,977	0.04 (0.02−0.08)	Ref (1.00)	
Benzbromarone	31,072	2	7,078	0.28 (0.07−1.12)		Ref (1.00)
SJS/TEN						
Allopurinol	673,638	102	124,309	0.82 (0.68−1.00)	63.78 (15.75−258.28)	5.52 (0.77−39.54)
Febuxostat	570,181	2	167,970	0.01 (0.00−0.04)	Ref (1.00)	
Benzbromarone	31,072	1	7,078	0.14 (0.02−0.99)		Ref (1.00)
EM						
Allopurinol	673,638	4	124,314	0.03 (0.01−0.08)	NA	NA
Febuxostat	570,181	0	167,970	0.00 (0.00−0.00)	Ref (1.00)	
Benzbromarone	31,072	0	7,078	0.00 (0.00−0.00)		Ref (1.00)
DRESS						
Allopurinol	673,638	72	124,314	0.58 (0.46−0.73)	18.44 (7.45−45.65)	3.97 (0.55−28.59)
Febuxostat	570,181	5	167,978	0.03 (0.01−0.07)	Ref (1.00)	
Benzbromarone	31,072	1	7,078	0.14 (0.02−0.99)		Ref (1.00)

PY = Person Year, IR = Incidence Rate, CI = Confidence Interval, HR = Hazard Risk, SCAR = Severe Cutaneous Adverse Reaction, SJS = Stevens−Johnson Syndrome, TEN = Toxic Epidermal Necrolysis, EM = Erythema Multiforme, DRESS = Drug Reaction with Eosinophilia And Systemic Symptoms. NA, Not Applicable.

(B) Adjusted analysis for those with eGFR values

Type of SCAR	n	Events	PY	IR (95% CI)	Adjusted* HR (95% CI)	
					Ref=Febuxostat	Ref=Benzbromarone
Composite outcome						
Allopurinol	414,919	91	75,717	1.20 (0.98−1.47)	24.62 (9.99−60.70)	5.29 (0.74−37.97)
Febuxostat	372,799	5	110,351	0.05 (0.02−0.12)	Ref (1.00)	
Benzbromarone	19,119	1	4,327	0.23 (0.03−1.63)		Ref (1.00)
SJS/TEN						
Allopurinol	414,919	51	75,719	0.67 (0.51−0.88)	33.82 (8.21−139.34)	2.94 (0.41−21.30)
Febuxostat	372,799	2	110,353	0.02 (0.01−0.08)	Ref (1.00)	
Benzbromarone	19,119	1	4,327	0.23 (0.03−1.63)		Ref (1.00)
EM						
Allopurinol	414,919	2	75,722	0.03 (0.01−0.12)	NA	NA
Febuxostat	372,799	0	110,354	0.00 (0.00−0.00)	Ref (1.00)	
Benzbromarone	19,119	0	4,327	0.00 (0.00−0.00)		Ref (1.00)
DRESS						
Allopurinol	414,919	39	75,721	0.52 (0.38−0.71)	18.09 (5.57−58.78)	NA
Febuxostat	372,799	3	110,351	0.04 (0.02−0.11)	Ref (1.00)	
Benzbromarone	19,119	0	4,327	0.00 (0.00−0.00)		Ref (1.00)

PY = Person Year, IR = Incidence Rate, CI = Confidence Interval, HR = Hazard Risk, SCAR = Severe Cutaneous Adverse Reaction, SJS = Stevens−Johnson Syndrome, TEN = Toxic Epidermal Necrolysis, EM = Erythema Multiforme, DRESS = Drug Reaction with Eosinophilia And Systemic Symptoms.

NA, Not Applicable.

*Adjusted for age, sex, income level, liver disease, eGFR (≥60, ≥30 and <60, <30 ml/min/1.73m2), diuretics use, and comorbidity score. NA, not applicable.

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