Systemic Alpha1-Adrenoceptor Antagonists and Increased Risk of Open-Angle Glaucoma: A Nationwide Population-Based Cohort Study

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Purpose. To examine the risk of open-angle glaucoma (OAG) among patients receiving alpha1-adrenoceptor (α1-AR) antagonists for lower urinary tract symptoms (LUTS).

Methods. This was a nationwide, population-based, retrospective cohort study from Asia/Taiwan. One million beneficiaries were randomly sampled from among 27.38 million individuals enrolled in the National Health Insurance program, and subjects with a diagnosis of LUTS from 2001 to 2012 were identified ($N = 105{,}341$). After 1:1 propensity score matching by gender, age, comorbid medical diseases, number of all medical visits during the observational period, and index date, 4081 patients were enrolled in the study group, comprised of patients who had taken α1-AR antagonists, and 4081 patients were enrolled in the control group, comprised of patients who had never taken α1-AR antagonists. The incidence and risk of OAG (defined as two ambulatory visits with a ICD-9 diagnosis code 365, excluding ICD-9 diagnosis codes 365.2–365.6, 365.02, 365.03, 365.13, 365.14, and 365.8) were calculated.

Results. Patients taking α1-AR antagonists had a higher incidence ratio of 1.86 (95% confidence interval [CI], 1.30–2.65) for developing OAG. After adjusting for age, gender, and comorbidities, the hazard ratio (HR) for OAG for patients taking α1-AR antagonists was 1.66 (95% CI, 1.16–2.39; $P = 0.006$). Among patients with hypertension, the hazard ratio for OAG associated with taking α1-AR antagonists increased to 1.79 (95% CI, 1.07–2.99; $P = 0.003$). On the other hand, the association of α1-AR antagonists with OAG was not significant among patients with diabetes mellitus, hyperlipidemia, or older age.

Conclusions. The findings of our study suggest an increased risk for OAG among patients taking α1-AR antagonists for LUTS, especially in patients with hypertension.

Keywords: alpha-adrenoceptor antagonists, open-angle glaucoma, hypertension, ocular perfusion pressure, lower urinary tract symptoms

Glaucoma is the leading cause of irreversible blindness. It has been estimated that the number of people with glaucoma worldwide will increase to 111.8 million in 2040.[1] Investigation of the risk factors is essential for the prevention and treatment of glaucoma. Low ocular perfusion pressure (OPP) and hypoperfusion of the optic nerve head (ONH) are important mechanisms of glaucoma[2–5] that could be caused by systemic medications.

With aging of the worldwide population, lower urinary tract symptoms (LUTS) have become highly prevalent,[6] and alpha1-adrenoceptor (α1-AR) antagonists rank among the primary treatments for LUTS.[7] α1-AR antagonists decrease tone in the smooth muscle of the bladder neck and prostate, thus improving urinary flow. The adverse effects of α1-AR antagonists include asthenia, nasal congestion, dizziness, orthostatic hypotension, and intraoperative floppy iris syndrome (IFIS).[7] Dizziness and orthostatic hypotension suggest impairment of dynamic cerebral perfusion. Because ocular circulation shares a similar blood supply with cerebral flow, impaired cerebral perfusion might imply insufficient ocular perfusion. By using a nationwide, population-based dataset from Taiwan, this study investigated the relationship between α1-AR antagonists for LUTS and the risk of open-angle glaucoma (OAG).

Materials and Methods

Database

The National Health Insurance Research Database (NHIRD) contains registration files and original claims data for 27.38 million individuals. We randomly sampled the NHIRD registration data for 1 million individuals who were registered in the National Health Insurance program from

January 1, 2000, to December 31, 2012. All data in the database are encrypted to protect the privacy of individuals. The database provides detailed outpatient and inpatient claims data including patient identification number; birth date; sex; diagnostic codes according to the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM); treatment information; medical costs; dates of admission and discharge; and date of death. All datasets are interlinked through the patient identification number.

Study Design

This study was approved by the Ethics Committee and Human Subjects Institutional Review Board of Tzu Chi Hospital, Hualien, Taiwan. This retrospective cohort study was comprised of insured patients seeking ambulatory care between January 1, 2001, and December 31, 2012, and who received a diagnosis of bladder neck obstruction (ICD-9 code 596.0), neurogenic bladder (ICD-9 code 596.5, excluding 596.53 and 596.55), spastic urethral sphincter (ICD-9 code 599.84), benign prostate hyperplasia (ICD-9 code 600), stress urinary incontinence (ICD-9 code 625.6), dysuria (ICD-9 code 788.1), urinary retention (ICD-9 code 788.2), urinary incontinence (ICD-9 code 788.3), or frequency of urination and polyuria (ICD-9 code 788.4) (N = 105,341). The dates of patients receiving their first prescriptions of α1-AR antagonists (including phenoxybenzamine, terazosin, doxazosin, tamsulosin, and silodosin) were assigned as the index dates in the study group, and the dates of diagnosis of the above diseases were assigned as the index dates in the control group. The follow-up period of each subject was defined as the time interval from the index date to the last observation day. Subjects with OAG were defined as individuals who had two ambulatory visits from the index date with a diagnosis code of glaucoma (ICD-9 code 365), excluding primary angle-closure glaucoma (ICD-9 code 365.2), anatomical narrow angle borderline glaucoma (ICD-9 code 365.02), pigmentary open-angle glaucoma (ICD-9 code 365.13), glaucoma of childhood (ICD-9365.14), corticosteroid-induced glaucoma (ICD-9 code 365.3), steroid responders borderline glaucoma (ICD-9 code 365.03), glaucoma associated with congenital anomalies dystrophies and systemic syndromes (ICD-9 code 365.4), glaucoma associated with disorders of the lens (ICD-9 code 365.5), glaucoma associated with other ocular disorders (ICD-9 code 365.6), and other specified forms of glaucoma (ICD-9 code 365.8). The study excluded patients younger than 18 years of age or older than 70 years of age, as well as those with use of drugs for LUTS other than α1-AR antagonists (mainly anticholinergics and tricyclic antidepressants), with use of α1-AR antagonists for an unknown period or before the diagnosis of the above diseases, with an interval from the first diagnosis date of LUTS to starting α1-AR antagonists of more than 15 days, and with a previous diagnosis of OAG or angle-closure glaucoma prior to their index date.

Initially, the study group was comprised of 11,765 patients who received their first prescription of α1-AR antagonists between January 1, 2001, and December 31, 2012, and the control group was comprised of 18,273 patients who had the above diagnosis but had not received any medication. Both groups were selected by a 1:1 propensity score matching for age; gender; Charlson Comorbidity Index (CCI) scores and comorbid medical diseases including diabetes mellitus, hypertension, hyperlipidemia, chronic heart disease, and chronic renal disease; number of all medical visits during the follow-up period; and index date. After matching, 4081 patients were enrolled in the study group and 4081 patients were enrolled in the control group. The data flow for the study is illustrated in Figure 1.

Statistical Analysis

All statistical analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC, USA). Patient demographics were compared using standardized differences that reflect the mean difference as a percentage of the standard deviation (SD), as described by Mamdani et al.[8] A standardized difference measure is less sensitive to sample size than traditional hypothesis tests and estimates the relative magnitude of differences. The demographic variables with a standard difference of >0.1 between the study group and the control group were considered clinically meaningful differences. The 1000 person-year incidence of OAG with or without taking α1-AR antagonists, defined as 1000 × (number of newly diagnosed OAG)/(total follow-up years of the subjects), and their incidence ratios were calculated. The Kaplan–Meier estimator was used to examine the differences in OAG-free survival rates between the study and the control cohorts (time zero = index date). Competing risk regression was used to estimate the adjusted hazard ratio (HR) and 95% confidence interval (CI) for OAG, adjusting for age, gender, and comorbidities, including CCI scores, diabetes mellitus, hypertension, hyperlipidemia, chronic heart disease, and chronic renal disease. $P < 0.05$ was considered significant.

Results

The demographic characteristics and comorbidities for the study and control cohorts are presented in Table 1. The mean age of the study patients, gender, comorbidities (CCI scores, diabetes mellitus, hypertension, hyperlipidemia, chronic heart disease, and chronic renal disease), number of visits during the follow-up period, and mean follow-up period were well matched between the two groups, with all standardized differences being 0.02 or lower.

The incidence of OAG diagnosis per 1000 person-years was 3.77 (95% CI, 2.97–4.57) for the study group and 2.03 (95% CI, 1.44–2.62) for the control group. Patients taking α1-AR antagonists had a significantly higher incidence of OAG, with an incidence ratio of 1.86 (95% CI, 1.30–2.65). After adjusting for age, gender, and comorbidities, the OAG HR for subjects taking α1-AR antagonists was 1.66 (95% CI, 1.16–2.39; P = 0.006) (Table 2). Kaplan–Meier survival analysis showed that patients taking α1-AR antagonists had significantly lower OAG-free survival rates than the controls during the follow-up period (Fig. 2). The competing risk regression analysis showed that the HR for OAG was 1.76 (95% CI, 1.15–2.69, P = 0.009) for patients with hyperlipidemia relative to those without hyperlipidemia. Age, gender, CCI scores, diabetes mellitus, hypertension, chronic heart disease, and chronic renal disease did not influence the development of OAG (Table 2).

Table 3 provides details regarding OAG and the use of α1-AR antagonists among patients older than 50 years of age with comorbid diabetes mellitus, hypertension, or hyperlipidemia. Among patients older than 50, the hazard ratio for OAG and the use of α1-AR antagonists was 1.40 (95% CI, 0.90–2.19; P = 0.14) compared to those not taking α1-AR antagonists, indicating that the risk was not

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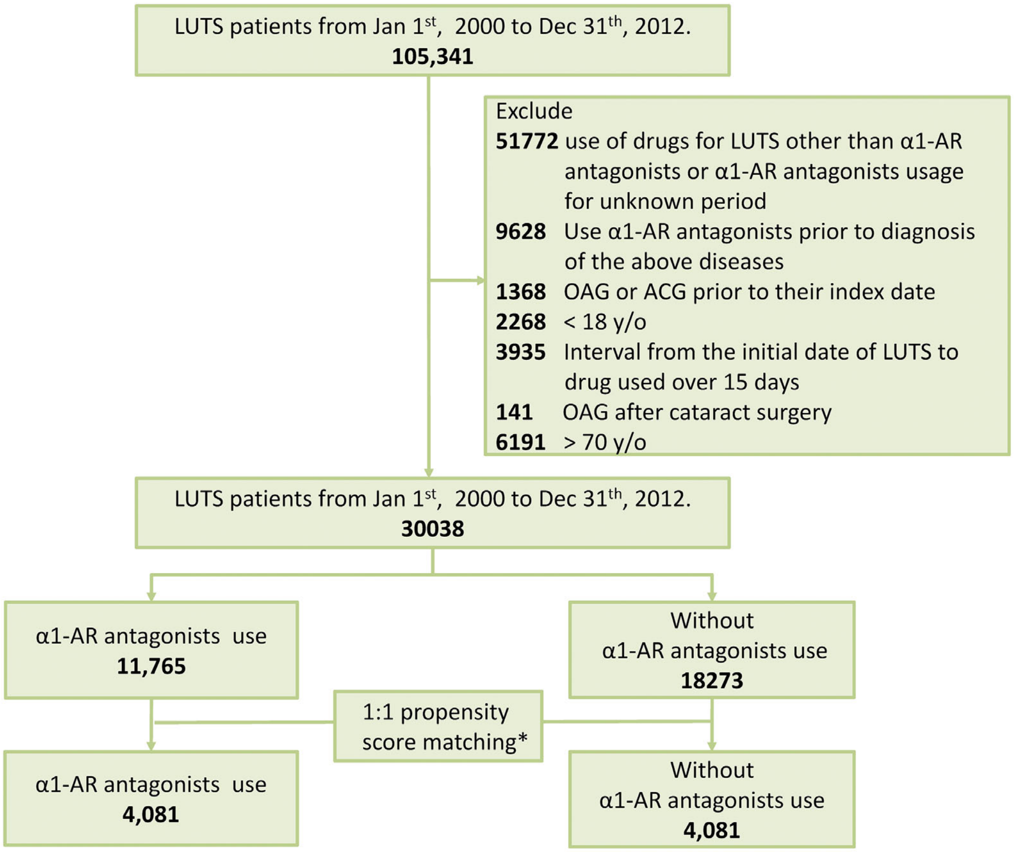

*1:1 propensity score matching by age, gender, diabetes mellitus, hypertension, hyperlipidemia, chronic heart disease, chronic renal disease, number of visits and duration from the index date.

Figure 1. Study protocol and profile. y/o, years old.

Table 1. Demographics of Patients Taking and Not Taking α1-AR Antagonists for LUTS

Demographic	Patients Receiving α1-AR Antagonists ($N = 4081$)	Comparison Patients ($N = 4081$)	Standard Difference
Age, mean ± SD	50.5 ± 10.0	50.4 ± 10.0	0.01
<50 y, *n* (%)	1917 (47)	1927 (47.2)	0.00
≥50 y, *n* (%)	2164 (53)	2154 (52.8)	
Sex			
Male, *n* (%)	3719 (91.1)	3715 (91)	0.00
Female, *n* (%)	362 (8.9)	366 (9)	
CCI score	2.8 ± 2.0	2.8 ± 2.0	0.01
≤3, *n* (%)	2063 (50.6)	2054 (50.3)	0.00
>3, *n* (%)	2018 (49.4)	2027 (49.7)	
Diabetes mellitus, *n* (%)	912 (22.3)	905 (22.2)	0.00
Hypertension, *n* (%)	1611 (39.5)	1586 (38.9)	0.01
Hyperlipidemia, *n* (%)	1534 (37.6)	1537 (37.7)	0.00
Chronic heart disease, *n* (%)	761 (18.6)	754 (18.5)	0.00
Chronic renal disease, *n* (%)	514 (12.6)	489 (12)	0.02
Number of medical visits, mean ± SD	121.1 ± 118.9	121.4 ± 121.4	0.00
Follow-up period (y), mean ± SD	5.5 ± 3.5	5.6 ± 3.6	0.01

significant. Among patients with comorbid diabetes mellitus, the hazard ratio for OAG and the use of α1-AR antagonists was 1.64 (95% CI, 0.85–3.15) compared to those not taking α1-AR antagonists, again indicating that the risk was not significant ($P = 0.14$). However, among patients with comorbid hypertension, the hazard ratio for OAG and the use of α1-AR antagonists was 1.79 (95% CI, 1.07–2.99, $P = 0.03$) by competing risks regression analysis. Among patients with

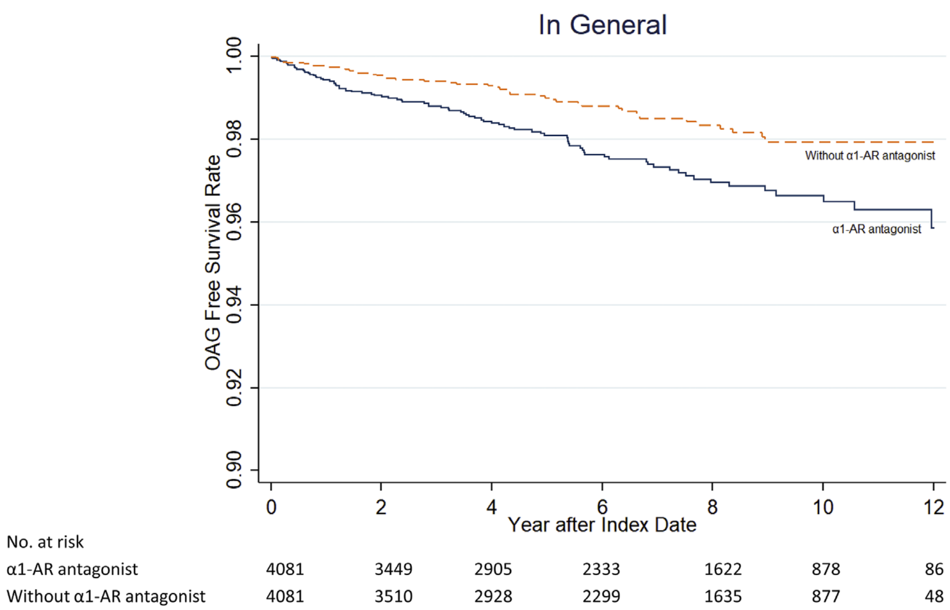

Figure 2. Kaplan–Meier survival curves for OAG-free survival for patients using and not using α1-AR antagonists for LUTS in the general population.

Table 2. Adjusted Hazard Ratios for OAG and Factors Relative to Their Controls

	Competing Risks Regression	
Variable	**HR (95% CI)**	***P***
α1-AR antagonists	1.66 (1.16–2.39)	0.006
Older age (≥50 y)	1.33 (0.83–2.15)	0.236
Gender (female)	0.81 (0.40–1.65)	0.559
CCI score (>3)	1.04 (0.65–1.66)	0.872
Diabetes mellitus	1.09 (0.71–1.67)	0.702
Hypertension	1.13 (0.75–1.69)	0.560
Hyperlipidemia	1.76 (1.15–2.69)	0.009
Chronic heart disease	1.53 (1.01–2.34)	0.046
Chronic renal disease	0.85 (0.52–1.40)	0.532

Table 3. Hazard Ratios for OAG and α1-AR Antagonist Usage for LUTS in Older Patients with Comorbid Diabetes Mellitus, Hypertension, or Hyperlipidemia

	Competing Risks Regression	
Comorbidity	**HR (95% CI)**	***P***
Age ≥ 50 y	1.40 (0.90–2.19)	0.14
Diabetes mellitus	1.64 (0.85–3.15)	0.14
Hypertension	1.79 (1.07–2.99)	0.03
Hyperlipidemia	1.43 (0.90–2.29)	0.13

comorbid hyperlipidemia, taking α1-AR antagonists did not increase the risk of OAG. The Kaplan–Meier curves of each subgroup are displayed in Figure 3.

Discussion

In this population-based, retrospective cohort study in which the data for 4081 patients prescribed α1-AR antagonists and data for 4081 control subjects were analyzed, we found that patients taking α1-AR antagonists had a significantly higher incidence ratio of 1.86 (95% CI, 1.30–2.65) for developing OAG in the follow-up period. The adjusted hazard ratio for OAG and α1-AR antagonist use was 1.66 (95% CI, 1.16–2.39; $P = 0.006$). The hazard ratio increased to 1.79 (95% CI, 1.07–2.99; $P = 0.003$) in hypertensive patients. Diabetes mellitus, hyperlipidemia, and older age did not add to the risk of OAG in patients taking α1-AR antagonists.

In the current study, the competing risks regression approach was applied for analyzing the risk of α1-AR antagonist rather than the traditional Cox proportional model, because the rate of mortality during the follow-up period in the current study (α1-AR antagonist group: 316/4081, or 7.7%; comparison group: 260/4081, or 6.4%) was much higher than the rate of OAG (α1-AR antagonist group: 86/4081, or 2.1%; comparison group: 46/4081, or 1.1%). The impact of competing events (e.g., mortality) might be significant. When competing events such as mortality may preclude the occurrence or may substantially alter the study outcome (OAG in the current study), competing risks regression is the better approach.

The effects of α1-AR antagonists on glaucoma are interesting. Several topically applied α1-AR antagonists were reported to have an intraocular pressure (IOP)-lowering effect.[9–16] Bunazosin hydrochloride, a selective α1-AR antagonist used systemically as an antihypertensive drug, has been reported to reduce IOP when applied topically in monkeys by increasing uveoscleral outflow from ciliary muscle relaxation.[9] It is generally believed that lower IOP reduces the risk of glaucoma progression.[10] However, our study showed that systemic administration of α1-AR antagonists for LUTS was associated with an increased risk for OAG. The disparity might come from different study species or population, or different routes of drug administration. Although topically applied α1-AR antagonists have some IOP-lowering effect, the effect of systemically applied α1-AR antagonists on IOP has not yet been determined.

Intraoperative floppy iris syndrome is a notorious ocular complication of α1-AR antagonist use for LUTS, with a high rate of incidence ranging from 19% to 52% during cataract

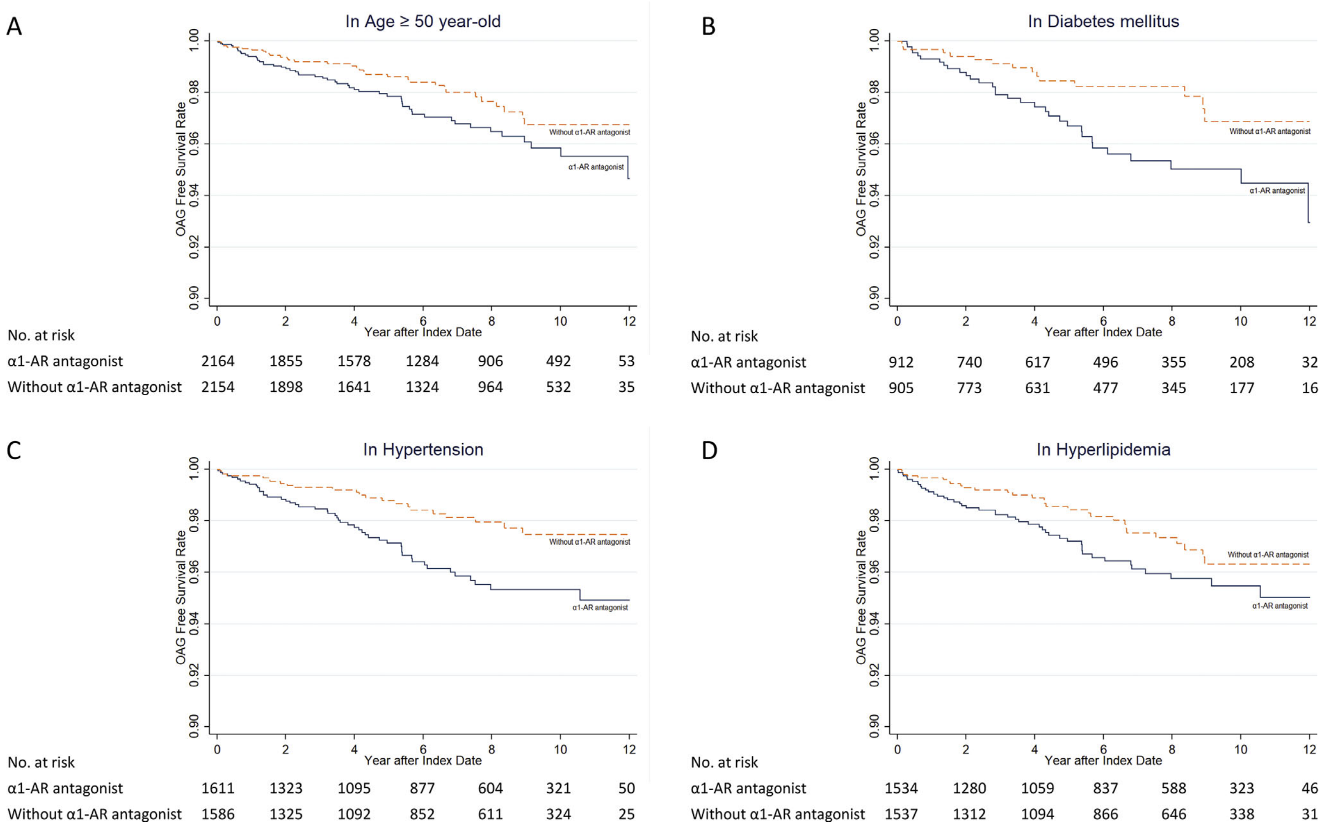

Figure 3. Kaplan–Meier survival curves for OAG-free survival for patients using and not using α1-AR antagonists. (A) Patients $\geq$ 50 years old. (B) Patients with diabetes mellitus. (C) Patients with hypertension. (D) Patients with hyperlipidemia.

surgery.[11,12] Morphologic changes, including small pupil diameter, iris stromal thinning, and depigmentation, have been described in IFIS eyes.[13] Pathological changes including iris dilator muscle atrophy and vacuolation, uneven iris pigment granules, and lipofuscin-like granules have also been found in IFIS.[14] α1-AR has been found in iris dilator smooth muscle and iris arteriole and may participate in IFIS development. We know that some of the ciliary muscle fibers attach to the scleral spur, and their contraction increases aqueous outflow by opening up the spaces of the trabecular meshwork. If α1-AR antagonists cause atrophy and vacuolation of not only the iris dilator muscle but also the ciliary muscle fibers, then increased IOP may be anticipated and hence development of OAG. However, this hypothesis remains unproven and requires further investigation.

Topical application of α1-AR antagonists either does not affect or minimally affects blood pressure (BP),[15] whereas systemic administration of all kinds of α1-AR antagonists for LUTS reduces systolic and diastolic BP by approximately 10%.[16–20] The vascular theory is considered one of the contributors to pathogenesis of OAG, especially in normal-tension glaucoma. Ocular perfusion pressure (OPP) is the difference between the mean arterial pressure and IOP. Due to the complex interactions among BP, IOP, and OPP, the association between BP and glaucoma remains controversial. Several studies have reported a higher risk of OAG in patients with hypertension.[2,21,22] The proposed pathophysiologic mechanisms include higher IOP associated with more elevated BP,[2,21] microvascular damage, increased vascular resistance, and impaired ocular perfusion to the optic nerve caused by sustained hypertension.[2,22] In contrast, other studies have reported that low BP can lead to low OPP and has been associated with new glaucoma development or with a progression of established glaucoma.[2–5,23]

Bonomi et al.[2] showed that the prevalence of glaucoma increased inversely with diastolic OPP. Leske et al.[3] reported that reduced baseline BP (systolic BP < 101, diastolic BP < 55, or mean BP < 42 mm Hg) was associated with a threefold increased risk of developing OAG. The Barbados Eye Study showed that lower systolic BP and lower OPP doubled the risk of developing glaucoma.[5] In the Los Angeles Latino Eye Study, high systolic BP and mean BP, low diastolic BP, and low diastolic OPP, systolic OPP, and mean OPP were associated with increased risk of OAG.[23] Also, nocturnal arterial hypotension was found to play a critical role in the pathogenesis of glaucomatous optic neuropathy.[24–28] Most healthy people have a dip of 10% to 20% in nocturnal BP compared to daytime BP; however, others present extreme dipping (>20% dipping of nocturnal BP compared to daytime BP) or reverse dipping of BP.[29–31] In the Maracaibo Aging Study, extreme nighttime dipping of systolic pressure or diastolic pressure was a significant risk factor (odds ratios 19.78 and 5.55, respectively) for glaucomatous damage.[28] Charlson et al.[32] found that glaucoma progression was associated with the duration and magnitude of nocturnal BP reduction, especially with a decrease of more than 10 mm Hg. The rates of visual field progression were highest (24%) in extreme dippers in normal-tension glaucoma in a 3-year follow-up study.[27] We speculate that the association between α1-AR antagonists for LUTS and OAG might be partially due to their BP-lowering effect and hence decreased OPP. For those dippers and extreme dippers, taking α1-AR antagonists might cause a further decline of nocturnal BP to a critical point below which autoregulation of the ONH would lose its effect. If this is true, use of a 24-hour ambulatory BP monitor by patients taking α1-AR antagonists should perhaps be considered in order to adjust the α1-AR antagonist prescription accordingly. Taking α1-AR antagonists in the daytime, taking a minimum dose, and avoiding bedtime dosing may alleviate the risk; however, these suggested precautions require further study.

We found that the hazard ratio for OAG and the use of α1-AR antagonists for LUTS increased to 1.79 in hypertensive patients. Autoregulation of the ONH is disrupted in low BP,[33] especially in those with older age and chronic hypertension.[34] In the Early Manifest Glaucoma Trial, a lower systolic OPP increased the risk of glaucoma progression (HR = 1.55) in patients with higher baseline IOP.[4] In hypertensive patients with impaired autoregulation, a decreased OPP caused by the BP-lowering effect of α1-AR antagonists would cause more damage to the ONH and increase the risk of glaucoma.

Our study has several strengths. First, the NHIRD provided population-based and representative claims information for insured people in Taiwan and reduced selection bias. Second, the large sample size and longitudinal study design provided enough statistical power to detect differences between the study group and control cohorts. Third, the NHIRD contains all claims data that were recorded electronically, ensuring accuracy and avoiding recall bias.

This study has several limitations. First, the study used data retrieved from NHIRD, which lacks strict disease definitions for LUTS and glaucoma. Second, patients in this retrospective study did not receive a thorough ocular exam and might not have been free of glaucoma before the index day. The enrolled patients also did not receive regular ocular examinations; hence, glaucoma might be delayed or underdiagnosed. Such inaccuracy, however, existed similarly in both the study group and the control group; an extended period of observation might help compensate for that inaccuracy. Because the difference in the incidence of glaucoma persisted during the 12-year observation period (Figs. 2, 3), that difference should be accurate. Third, there were no data for BP or IOP in the NHIRD, let alone OPP or its circadian variation; thus, further exploration into these associations is lacking. Fourth, the database could not provide other clinical ocular details that were related to glaucoma development, such as refractive error, axial length, status of the lens, nerve fiber thickness, or progression of the visual field. Investigations into the pathophysiological mechanism are limited. Fifth, information regarding some of the potential risk factors for glaucoma could not be obtained, such as drinking, smoking habits, personal lifestyle, occupation, or the severity of comorbid diseases. Finally, most of the study subjects in the current study were ethnically Chinese people, and the study results might not apply to other races.

In conclusion, to the best of our knowledge, this population-based study is the first to determine that patients taking α1-AR antagonists for LUTS have a higher risk for OAG, especially among those with hypertension. A more detailed understanding of the possible pathogenesis of glaucoma with α1-AR antagonists for LUTS awaits future studies.

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