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Association between topical beta-blockers and risks of cardiovascular and respiratory disease in patients with glaucoma: a retrospective cohort study

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ABSTRACT

Objective To determine if topical beta-blocker use is associated with increased risks of cardiovascular and respiratory diseases in patients with glaucoma.

Setting A retrospective cohort analysis was conducted using the database from Taiwan's National Health Insurance programme.

Participants In total, 12 336 newly diagnosed patients with glaucoma from January 2000 to December 2010 were included. The patients with glaucoma were subdivided into two cohorts according to whether they used topical beta-blockers or combination drugs (BBCDs).

Primary outcome measures The study endpoints included pneumonia, acute respiratory failure, stroke and coronary artery disease (CAD). Univariable and multivariable Cox proportional hazards regression models were used to estimate HRs and 95% CIs for the endpoints of both cohorts.

Results The BBCD cohort had a slightly higher risk of acute respiratory failure (adjusted HRs=1.16, 95% CI 1.00 to 1.34) and lower risk of CAD (aHR=0.93, 95% CI 0.87 to 0.99) than the non-BBCD cohort. Additionally, the risk of stroke was significantly higher in BBCD cohort than in the non-BBCD cohort (aHR=1.39, 95% CI 1.23 to 1.58), especially the ischaemic stroke (aHR=1.44, 95% CI 1.26 to 1.64; aHR=1.44, 98.75% CI 1.21 to 1.71). After considering the multiplicative interaction of age and sex, the BBCD cohort do not have higher risk of all outcomes than the non-BBCD cohort. Further time-dependent regression analysis revealed BBCD cohort had higher risk of acute respiratory failure (aHR=1.17, 95% CI 1.01 to 1.35) and ischaemic stroke (aHR=1.44, 95% CI 1.26 to 1.65) than non-BBCD cohort. However, after considering the multiplicative interaction of age and sex, the BBCD cohort had no significantly higher risk of all outcomes than the non-BBCD cohort.

Conclusion Topical beta-blocker is not associated with increased risks of cardiovascular and respiratory diseases in patients with glaucoma.

INTRODUCTION

Glaucoma is the leading cause of irreversible blindness worldwide.[1] In Taiwan, the prevalence and the incidence of open angle glaucoma (OAG) and angle closure glaucoma (ACG) are the highest among people

Strengths and limitations of this study

► The study has a large sample size because of its population-based design.
► National Health Insurance Research Database covers a highly representative sample of Taiwan's general population.
► All insurance claims should be scrutinised by medical reimbursement specialists and peer review.
► Lack of individual laboratory data and related exposure history.
► There may have some uncontrolled confounding factors and potential biases in this retrospective cohort study.

of advanced age.[2] There are various commercially available glaucoma medications that can be prescribed by a clinician.[3] In the past three decades, topical beta-blockers have served as first-line drugs for glaucoma treatment.[4] According to the policy of the National Health Insurance (NHI) of Taiwan, topical beta-blockers constitute first-line treatment for patients with glaucoma without contraindication to beta-blockers.[5] Patients with glaucoma in Taiwan are highly comorbid with cardiovascular disease of either the OAG or ACG type.[6 7] Several studies have reported on the cardiovascular and respiratory safety of the long-term use of topical beta-blockers.[8–10] However, their findings have been conflicting. For example, both the Barbados Eye Study and Blue Mountains Eye Study have observed an association between mortality and beta-blockers.[8 9] Similarly, a retrospective cohort analysis also observed a relationship between adverse outcomes and the use of topical beta-blockers for glaucoma therapy.[10] Conversely, the Rotterdam Study and EPIC-Norfolk Cohort Study have reported that topical beta-blockers do not appear to be associated with excess cardiovascular mortality.[4 11]

To clarify this important issue, we conducted a nationwide population-based cohort study by analysing data from Taiwan's NHI Research Database (NHIRD) to determine the relationship between topical beta-blocker use and risks of cardiovascular and respiratory diseases in patients with glaucoma in the population of Taiwan. To the best of our knowledge, this is the first study to use a large claims database from an Asian country to examine the long-term potential complications of cardiovascular and respiratory diseases among patients with glaucoma using topical beta-blockers.

METHODS

Patient and public involvement

This population-based retrospective cohort study was conducted using the database of Taiwan's NHI programme. The NHI programme was launched on March 1995, and it covers approximately 99% of the 23.74 million people living in Taiwan.[12] The NHIRD was set up on 1 March 1995 by the NIH Administration and is maintained by the National Health Research Institute of Taiwan. The Longitudinal Health Insurance Database (LHID) is a part of the NHIRD. The NHIRD is a large computerised database that contains the data of all insured persons. It includes data on background conditions and diagnoses as well as data on detailed health services such as those on medications, examinations and operations. The LHID includes all medical claims data from 1996 to 2011 of 1 million beneficiaries who were randomly selected from the 23.74 million beneficiaries of the NHI. More details on the NHI programme and the LHID are available from other sources.[13 14]

Sample participants

The study population comprised patients who were newly diagnosed with glaucoma. They were identified from the LHID2000 (International Classification of Diseases (ICD)-9-CM code 365) data obtained from January 2000 to December 2010. The patients with glaucoma were divided into two cohorts according to whether they used a beta-blocker or combination drug (BBCD). The BBCD cohort included patients who had received a BBCD therapy for at least 28 days; the non-BBCD cohort included patients who had not received a BBCD before and during follow-up. The index date of the BBCD cohort was the 28th day; the index date for non-BBCD patients was a randomly selected month and day with the same index year of the matched BBCD patents. Patients aged less than 20 years who had incomplete age or sex information were excluded from both cohorts. Individuals without BBCD use were selected from the LHID2000 and matched to the BBCD cohort at a ratio of 1:1 based on the propensity score through nearest neighbour matching, initially to the eighth digit and then as required to the first digit.[15] Therefore, matches were first made within a calliper width of 0.0000001, and then the calliper width was increased for unmatched cases to 0.1. We reconsidered

the matching criteria and performed a rematch (greedy algorithm). For each glaucoma patient on BBCD use, the corresponding comparisons were selected based on the nearest propensity score. The propensity score was calculated using a logistic regression model to estimate the probability of the BBCD status. The model was based on the baseline variables of age, gender, index year and comorbidities of hypertension, hyperlipidaemia, diabetes mellitus, chronic obstructive pulmonary disease (COPD), asthma, chronic kidney disease, pneumonia (ICD-9-CM code 486), acute respiratory failure (ICD-9-CM code 518.81), stroke (ICD-9-CM codes 430–438) and coronary artery disease (CAD) (ICD-9-CM codes 410–414), and glaucoma medications of prostaglandin analogue (PGA), carbonic anhydrase inhibitor (CAI), alpha (α)-agonists and pilocarpine.

Outcome measurement

The study endpoints were pneumonia, acute respiratory failure, stroke (including haemorrhagic and ischaemic stroke) and CAD. All included patients were followed up from the index date until death, withdrawal from the NHI programme, the end of 2011 or the occurrence of the endpoint.

Statistical analysis

We compared the proportions of demographic data, comorbidities and medications between the BBCD and non-BBCD cohorts using Pearson's χ^2 test for categorical variables and Mann-Whitney U test for continuous variables. The overall incidence densities of the endpoints (including pneumonia, acute respiratory failure, stroke and CAD) were measured for both cohorts. To address the concern of constant proportionality, we examined the proportional hazard model assumption by using a test of scaled Schoenfeld residuals. The results showed that there was no significant relationship between Schoenfeld residuals for BBCD and follow-up time (p value =0.05, 0.08, 0.66, 0.10, 0.57, respectively) in the model evaluating the pneumonia, stroke, haemorrhagic stroke, ischaemic stroke and CAD risk. The proportional hazard model assumption was also applied by using a test of scaled Schoenfeld residuals. In the model evaluating the acute respiratory failure risk throughout overall follow-up period, the test results revealed a significant relationship between Schoenfeld residuals for BBCD and follow-up time, suggesting the proportionality assumption was violated (p value =0.02). In the subsequent analyses, we stratified the follow-up duration to deal with the violation of proportional hazard assumption. Univariable and multivariable Cox proportional hazards regression models were used to estimate the HRs, 95% CIs and 98.75% CIs of endpoints of the BBCD cohort in relation to the non-BBCD cohort. The multivariable models were also used by adjustment of age, gender and comorbidities of hypertension, hyperlipidaemia, diabetes mellitus, COPD, asthma, CKD, pneumonia, acute respiratory failure, stroke and CAD, and the use of glaucoma

Table 1 Demographic characteristics of study patients and the propensity score-matched sample by medicine use

	Beta-blocker or combination drug use			
	No (n=6168)		Yes (n=6168)	
	n	%	n	%
Age, median (IQR)	60.6 (47.7–71.4)		60.5 (47.7–70.4)	
Stratify age				
20–49	1772	28.7	1812	29.4
50–64	1928	31.3	1949	31.6
65+	2468	40	2407	39
Gender				
Women	3112	50.5	3135	50.8
Men	3056	49.6	3033	49.2
Comorbidity				
Hypertension	3240	52.5	3058	49.6
Hyperlipidaemia	2313	37.5	2207	35.8
Diabetes mellitus	1452	23.5	1363	22.1
COPD	1038	16.8	1013	16.4
Asthma	588	9.53	561	9.1
CKD	535	8.67	493	7.99
History of pneumonia	206	3.34	204	3.31
History of acute respiratory failure	38	0.62	41	0.66
History of coronary artery disease	1642	26.6	1588	25.8
History of stroke	474	7.68	426	6.91
Other glaucoma medications				
PGA	421	6.83	504	8.17
CAI	366	5.93	412	6.68
Alpha agonist	575	9.32	593	9.61
Pilocarpine	909	14.7	818	13.3

CAI, carbonic anhydrase inhibitor; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; PGA, prostaglandin analogue.

medications (PGA, CAI, α-agonist and pilocarpine). The Bonferroni method of multiple comparisons was set the p value at 0.0125. The BBCD use was quantified as a binary variable every 6 months. Due to frequency variations in BBCD use among patients with glaucoma during the study period, BBCD were considered as time-dependent covariates in the Cox proportional hazards models to compute the HRs and their 95% CI and 98.75% CI for outcome in BBCD cohort when compared with non-BBCD cohort. All data analyses were performed using SAS V.9.4 software. The level of significance was set at 0.05, and the tests were two-tailed.

RESULTS

We included 6168 patients with glaucoma in both the BBCD and non-BBCD cohorts; the distributions of age, gender and comorbidities were similar in both cohorts (table 1). The median (IQR) ages in the BBCD cohort

and the non-BBCD cohort were 60.5 (IQR=47.7–70.4) and 60.6 (IQR=47.7–71.4) years, respectively. In both cohorts, approximately 29% patients were aged ≤49 years, and approximately 51% of the patients were women. In both cohorts, the major comorbidity was hypertension (52.5% vs 49.6%), followed by hyperlipidaemia (37.5% vs 35.8%) and history of CAD (26.6% vs 25.8%). The use of the medications PGA, CAI, α-agonist and pilocarpine was also similar in the BBCD cohort than in the non-BBCD cohort.

The BBCD cohort had a slightly higher incidence rate of acute respiratory failure (10.8 per 1000 person-years) than the non-BBCD cohort (9.79 per 1000 person-years; adjusted HR (aHR)=1.16, 95% CI 1.00 to 1.34) (table 2). The multivariable analyses also showed that the BBCD cohort had a lower risk of CAD (aHR=0.93, 95% CI 0.87 to 0.99) than the non-BBCD cohort. Additionally, regarding the risk of the endpoints, the aHR was significantly higher

Table 2 Comparison of incidence and HRs of outcomes by medication status

| | Beta-blocker or combination drug use | | | | | | Crude HR (95% CI) | Adjusted HR (95% CI)† | Adjusted HR (98.75% CI)† | Adjusted HR (95% CI)‡ |
| | No | | | Yes | | | | | | |
Outcomes	Event	PY	Rate*	Event	PY	Rate*				
Pneumonia	586	34399	17.0	595	34257	17.4	1.02 (0.91 to 1.15)	1.06 (0.94 to 1.19)	1.06 (0.92 to 1.23)	1.19 (0.58 to 2.45)
Acute respiratory failure	345	35242	9.79	377	35074	10.8	1.10 (0.95 to 1.27)	1.16 (1.00 to 1.34)	1.16 (0.96 to 1.39)	1.45 (0.54 to 3.85)
≤5	233	24591	9.48	241	24727	9.75	1.03 (0.86 to 1.23)	1.13 (0.94 to 1.36)	1.13 (0.90 to 1.43)	1.55 (0.46 to 5.20)
>5	112	10651	10.5	136	10346	13.1	1.25 (0.98 to 1.61)	1.19 (0.93 to 1.53)	1.19 (0.87 to 1.64)	1.27 (0.23 to 7.11)
Stroke	441	34316	12.9	549	33683	16.3	1.27 (1.12 to 1.44)	1.39 (1.23 to 1.58)	1.39 (1.19 to 1.64)	0.73 (0.34 to 1.57)
Haemorrhagic stroke	62		1.81	65		1.93	1.07 (0.75 to 1.51)	1.14 (0.80 to 1.61)	1.14 (0.73 to 1.77)	0.55 (0.09 to 3.33)
Ischaemic stroke	379		11.0	484		14.4	1.30 (1.14 to 1.49)	1.44 (1.26 to 1.64)	1.44 (1.21 to 1.71)	0.80 (0.35 to 1.86)
CAD	1930	27123	71.2	1823	27431	66.5	0.93 (0.88 to 1.00)	0.93 (0.87 to 0.99)	0.93 (0.86 to 1.01)	0.85 (0.61 to 1.18)

*p<0.05; **p<0.01; ***p<0.001; ****p<0.0125.

*Incidence rate, per 1000 person-years.

†Multivariable analysis includes age, gender and comorbidities of hypertension, hyperlipidaemia, diabetes mellitus, COPD, asthma, CKD, pneumonia, acute respiratory failure, stroke and CAD, and the use of the medications PGA, CAI, alpha agonist and pilocarpine.

‡Multivariable analysis includes age, gender, multiplicative interaction of age and sex and comorbidities of hypertension, hyperlipidaemia, diabetes mellitus, COPD, asthma, CKD, pneumonia, acute respiratory failure, stroke and CAD, and the use of the medications PGA, CAI, alpha agonist and pilocarpine.

CAD, coronary artery disease; CAI, carbonic anhydrase inhibitor; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; PGA, prostaglandin analogue; PY, person-years.

Table 3 Comparison of incidence and HRs of outcomes by medication status by Cox proportional hazard model with time-dependent covariates

Outcomes	Beta-blocker or combination drug use				
	No		Yes		
	Crude HR (95% CI)	Adjusted HR (95% CI)*	Crude HR (95% CI)	Adjusted HR (95% CI)*	Adjusted HR (95% CI)†
Pneumonia	1	1	1.02 (0.91 to 1.15)	1.06 (0.92 to 1.23)	1.11 (0.54 to 2.28)
Acute respiratory failure	1	1	1.10 (0.95 to 1.27)	1.17 (1.01 to 1.35)	1.37 (0.51 to 3.64)
Stroke	1	1	1.27 (1.12 to 1.44)	1.39 (1.23 to 1.58)	0.72 (0.34 to 1.56)
Haemorrhagic stroke	1	1	1.07 (0.75 to 1.51)	1.14 (0.80 to 1.62)	0.79 (0.34 to 1.83)
Ischaemic stroke	1	1	1.30 (1.14 to 1.49)	1.44 (1.26 to 1.65)	0.57 (0.10 to 3.46)
CAD	1	1	0.93 (0.88 to 1.00)	0.93 (0.87 to 0.99)	0.85 (0.61 to 1.17)

Incidence rate, per 1000 person-years.
*Multivariable analysis includes age, gender and comorbidities of hypertension, hyperlipidaemia, diabetes mellitus, COPD, asthma, CKD, pneumonia, acute respiratory failure, stroke and CAD, and the use of the medications PGA, CAI, alpha agonist and pilocarpine.
†Multivariable analysis includes age, gender, multiplicative interaction of age and sex and comorbidities of hypertension, hyperlipidaemia, diabetes mellitus, COPD, asthma, CKD, pneumonia, acute respiratory failure, stroke and CAD, and the use of the medications PGA, CAI, alpha agonist and pilocarpine.
CAD, coronary artery disease; CAI, carbonic anhydrase inhibitor; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; PGA, prostaglandin analogue; PY, person-years.

for stroke (aHR=1.39, 95% CI 1.23 to 1.58) and ischaemic stroke (aHR=1.44, 95% CI 1.26 to 1.64; aHR=1.44, 98.75% CI 1.21 to 1.71). After considering the multiplicative interaction of age and sex, the BBCD cohort do not have significantly higher risk of all outcomes than the non-BBCD cohort.

Moreover, the time-dependent regression analysis after adjustment for age, gender and comorbidities of hypertension, hyperlipidaemia, diabetes mellitus, COPD, asthma, CKD, pneumonia, acute respiratory failure, stroke and CAD and the use of the medications PGA, CAI, α-agonist and pilocarpine revealed that BBCD cohorts had higher risk of acute respiratory failure (aHR=1.17, 95% CI 1.01 to 1.35) and ischaemic stroke (aHR=1.44, 95% CI 1.26 to 1.65) (table 3). However, after considering the multiplicative interaction of age and sex, the BBCD cohort had no significantly risk of all outcomes than the non-BBCD cohort.

DISCUSSION
Our study demonstrated that in a large Taiwanese–Chinese population, topical beta-blocker use would not increase the risks of cardiovascular and respiratory diseases in patients with glaucoma. Topical beta-blockers remain a primary glaucoma medication.[16] It is contraindicated in individuals with a previous myocardial infarction, a history of arrhythmia or bradycardia and pulmonary issues such as COPD or emphysema.[11 16] Conflicting results on the association between topical beta-blocker use and cardiovascular mortality have been reported. The Blue Mountains Eye Study showed increased cardiovascular mortality in persons with previously diagnosed glaucoma.[8] The Barbados Eye Study demonstrated that cardiovascular mortality tended to increase in persons

with previously diagnosed or treated OAG and ocular hypertension in the black population; the excess mortality associated with timolol maleate treatment of OAG was also observed in a white population.[9] Similarly, a retrospective cohort study was conducted using data from the UK Clinical Practice Research Datalink database.[10] That study suggested that the introduction of beta-blockers in patients with glaucoma who later discontinue their use is associated with an increase in the use of healthcare resources (such as a higher number of general practitioner visits and hospitalisations). This may be indicative of a potential relationship between adverse outcomes and the use of topical beta-blockers for glaucoma therapy.[10] Conversely, the Rotterdam Study and the EPIC-Norfolk Cohort Study have showed that topical beta-blockers are not associated with excess cardiovascular mortality.[4 11] Our study corroborates the results of the Rotterdam Study and EPIC-Norfolk Cohort Study with regard to the risk of CAD.

With regard to topical beta-blockers and the risk of pulmonary disease, the aforementioned retrospective cohort study conducted using the UK database[10] reported a significant increase in respiratory event rates postindex versus preindex in patients who discontinued beta-blocker use and patients who did not use beta-blockers, but not in patients who continued using beta-blockers. Our results revealed that topical beta-blocker use might slightly increase the risk of acute respiratory failure (adjusted HRs=1.16, 95% CI 1.00 to 1.34); however, after considering the multiplicative interaction of all potential factors, topical beta-blocker is not associated with higher risk of respiratory disease. Nonetheless, our results cannot be directly compared with the aforementioned one because of our different study design. For

example, we included pneumonia and acute respiratory failure as comorbidities. A future longitudinal prospective study must be conducted for further clarification of this important issue-.

Another interesting finding of this study is that topical beta-blocker potentially increases the risk of stroke (aHR=1.39, 95% CI 1.23 to 1.58)—an association that has been rarely discussed in the literature. However, after considering the multiplicative interaction of age and sex, the BBCD cohort had no significantly higher risk of all outcomes than the non-BBCD cohort. The Rotterdam Study investigated associations between the long-term and short-term use of topical beta-blockers and mortality. The cause of mortality was stroke in 3/53 (5.7%) of beta-blocker users and in 58/656 (8.8%) of non-users. We believe that a different study will have a different outcome; thus, with regard to stroke, our results cannot be directly compared with the results of others. With regard to this problem, further observation is required.

Timolol, a non-selective beta-blocker that was approved for use in the USA in 1979, was one of the most frequently prescribed first-line topical therapies for the reduction of intraocular pressure (IOP) in the 1980s and 1990s.[17 18] Currently, beta-blockers are the first-line treatment facilitating IOP lowering in patients with glaucoma without contraindications in Taiwan. The labelling for timolol and any combination drug with timolol states that coexistent cardiovascular or respiratory disease is a contraindication to their use.[18 19] Timolol-induced interstitial lung disease was reported: a 76-year-old woman presented with productive cough and progressive dyspnoea and hypoxia after starting timolol eye drop use following glaucoma surgery.[20] It was also reported that an elderly patient was hospitalised with three side effects of timolol. His condition required intensive care unit admission with mechanical ventilation and temporary transvenous pacing.[21] This emphasises the need to raise awareness among clinicians regarding the potential side effects and drug interactions for timolol.

Although our study yielded some important findings, it has some limitations. First, the identification of glaucoma relied entirely on claims data (ICD-9 coding from clinicians), which may be less accurate than individually determined diagnoses by professional ophthalmologists using standardised procedures.[22 23] Second, selection bias was noted in this study. Because the NHIRD database only included patients who sought treatment, those who did not seek treatment may have been recruited into the control cohort.[22 23] However, it is the inherent limitation of this kind of claims database study. Third, most residents in Taiwan are of Chinese ethnicity. Thus, the current results may not directly apply to other ethnic groups. Fourth, preservative-free glaucoma medications are not included in the current health insurance system, and data on them are not available in the current database. Fifth, there is a high likelihood of residual confounding factors, such as smoking, body mass index, severity of glaucoma and systemic disease, were either not available or too complicated to be included in the analysis. Sixth, individuals with the endpoints of this study were more likely to die or withdraw from the study; this limitation is inherent to claims database studies such as ours. Finally, we believe that different study design and methodology might influence the outcomes. It is inadequate to directly compare our study result with others.

Despite the aforementioned limitations, our study has some notable strengths. First, the database is large and has effective sample randomisation[22 23] and we could follow patients over time to assess the relationship between topical beta-blocker use and subsequent onset of outcomes. Second, this dataset includes data on a diverse range of patients with different sociodemographic profiles, unlike some smaller studies that have recruited patients from a specific region, which might not represent the whole population.[22 23] Third, the large sample size of Taiwan's NHIRD database allows for statistically powerful assessments of the relative risk for diseases, including the potential risk factors. Fourth, because glaucoma medications are costly, most patients with glaucoma in Taiwan seek treatment from ophthalmologists. Therefore, the claims database for glaucoma medication usage that was used in this study appears to be reliable.[22 23] Finally, the current study is one of the few studies evaluating the association between topical beta-blocker use and the risk of cardiovascular and respiratory disease in patients with glaucoma by using a large claims database. We believe this finding could enrich the literature and remind the clinicians of the important issue.

CONCLUSIONS

Although our population-based cohort study indicate that topical beta-blocker is not associated with increased risks of cardiovascular and respiratory diseases in patients with glaucoma, ophthalmologists should still prescribe topical beta-blockers with caution.

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