Increased risk of trigeminal neuralgia after hypertension
A population-based study

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ABSTRACT

Objective: Very few studies have explored the temporal relationship between hypertension and trigeminal neuralgia (TN). The aim of this population-based follow-up study was to investigate whether hypertension is associated with a higher risk of developing TN.

Methods: A total of 138,492 persons with at least 2 ambulatory visits with the principal diagnosis of hypertension in 2001 were enrolled in the hypertension group. The nonhypertension group consisted of 276,984 age- and sex-matched, randomly sampled subjects without hypertension. The 3-year TN-free survival rate and the cumulative incidence of TN were calculated using the Kaplan-Meier method. Cox proportional hazard regression was used to estimate the hazard ratio of TN.

Results: In the hypertension group, 121 patients developed TN during follow-up, while, in the nonhypertension group, 167 subjects developed TN. The crude hazard ratio for the hypertension group was 1.52 (95% confidence interval [CI] 1.20–1.92; \( p = 0.0005 \)), while, after adjustment for demographic characteristics and medical comorbidities, the adjusted hazard ratio was 1.51 (95% CI 1.19–1.90; \( p = 0.0006 \)).

Conclusions: This study shows a significantly increased risk of developing TN after hypertension. Further studies are needed to elucidate the underlying mechanism of the association between hypertension and TN. Neurology® 2011;77:1605–1610

GLOSSARY

\( \text{aHR} \) = adjusted hazard ratio; \( \text{CI} \) = confidence interval; \( \text{HFS} \) = hemifacial spasm; \( \text{HR} \) = hazard ratio; \( \text{ICD-9-CM} \) = International Classification of Diseases, ninth revision, Clinical Modification; \( \text{IQR} \) = interquartile range; \( \text{MS} \) = multiple sclerosis; \( \text{NHI} \) = National Health Insurance; \( \text{TN} \) = trigeminal neuralgia.

Trigeminal neuralgia (TN) is an uncommon disorder characterized by recurrent, paroxysmal, lancinating, or electric shock–like pain within the trigeminal nerve distribution,\(^1\) with an estimated annual incidence of 4–27 per 100,000 person-years.\(^2\)–\(^4\) Most cases are classic TN, which lacks objective evidence of motor or sensory deficit and is not attributed to another disorder,\(^5\) while a minority of cases are symptomatic TN, which is related to underlying causes, such as multiple sclerosis\(^6\)–\(^8\) or nerve compression by a tumor.\(^9\),\(^10\) The exact pathophysiology of classic TN is unknown, but increasing evidence suggests that it may be related to compression of the trigeminal nerve entry zone close to the brainstem by a tortuous vessel, which leads to demyelination, resulting in ectopic excitation and ephaptic transmission.\(^10\)–\(^12\) Because cerebral vascular tortuosity has been associated with hypertension,\(^13\) it was of interest whether the occurrence of hypertension is associated with increased risk of developing TN. However, pilot studies have given inconsistent results on the relationship between hypertension and TN, with 2 supporting a positive association between TN and hypertension\(^3\),\(^14\) and 1 being unable to show a signifi-
cant association. This inconsistency may be partly due to insufficient statistical power, and partly due to the cross-sectional design adopted in the majority of studies which makes it impossible to identify a temporal relationship between hypertension and TN. The present population-based follow-up study aimed to investigate whether hypertension is associated with an increased risk of developing TN using a large population insurance-based database.

METHODS Data source. The data used in this study were from the complete National Health Insurance (NHI) claim database in Taiwan for the period 2000 to 2003. The NHI program has been implemented in Taiwan since 1995, and the coverage rate was 96% of the whole population in 2000 and 97% at the end of 2003, at which time more than 21.9 million inhabitants were enrolled. It should be noted that the rationale for using the NHI database after 2000 is that from January 1, 2000, according to the rules of the Bureau of NHI, NHI claim data were all encoded using the standardized International Classification of Diseases, ninth revision, Clinical Modification (ICD-9-CM). To determine the date and cause of death, the claim database was linked to the national mortality registry.

Standard protocol approvals, registrations, and patient consents. To keep individual information confidential in order to satisfy regulations on personal privacy in Taiwan, all personal identification numbers in the data were encrypted by converting the personal identification numbers into scrambled numbers before data processing. Because the database used in this study consists of deidentified secondary data released for research purposes, this principle meets the Personal Information Protection Act in Taiwan, and this study was exempt from full review by the Institutional Review Board.

Study subjects and design. We used a prospective age- and sex-matched cohort design to examine whether patients with hypertension are at increased risk for developing subsequent TN. The study cohort included a hypertension group and a nonhypertension group, both of which were selected from Taiwanese residents in the complete NHI claims database for 2001. Note that, in 2001, more than 21.6 million persons were registered in the NHI, accounting for approximately 97% of the total population in Taiwan. This large-scale population-based NHI database provides a unique opportunity for investigating the temporal relationship between hypertension and the occurrence of TN.

The hypertension group consisted of subjects who had received a principal diagnosis of hypertension (ICD-9-CM code 401) in ambulatory medical care visits between January 1, 2001, and December 31, 2001. To maximize case ascertainment, only patients with at least 2 ambulatory visits with the principal diagnosis of hypertension in this period were considered for inclusion in the hypertension group (n = 956,525). The index visit was defined as the first ambulatory visit during which the principal diagnosis of hypertension was made. The exclusion criteria for the recruitment of subjects into the hypertension group were as follows: 1) age less than 18 years (n = 41) or greater than 100 years (n = 493) to restrict the research sample to the general adult population; 2) a previous diagnosis of hypertension during 2000 (n = 816,437) to increase the likelihood of identifying only new incident hypertension cases in 2001; 3) a previous diagnosis of TN (ICD-9-CM codes 350.1) (n = 2,899) before the index visit; and 4) a diagnosis of multiple sclerosis (MS) (ICD-9-CM code 340, n = 363) or benign or malignant neoplasm of the nervous system (ICD-9-CM code 191, 192, 225, n = 6,097) before their index ambulatory visit or within 2 years after the index visit, in order to reduce the possibility of developing symptomatic TN. A total of 138,492 subjects were included in the final hypertension group.

The nonhypertension group was taken from the remaining subjects without a diagnosis of hypertension in the same 2001 NHI claim database. The first ambulatory medical care visit during 2001 was assigned as the index visit. The exclusion criteria for recruiting subjects into the nonhypertension group were 1) a previous diagnosis of hypertension before the index visit; 2) a previous diagnosis of TN before the index visit; and 3) a diagnosis of MS or benign or malignant neoplasm of the nervous system before the index visit or within 2 years after the index visit. We randomly selected 2 age- and sex-matched subjects for each subject in the hypertension group. A total of 276,984 subjects was included in the nonhypertension group.

Outcome and follow-up. All the medical care records for each subject in the above 2 groups were tracked from their index visit until the end of 2003 and the mortality data for the subjects who died during the follow-up were obtained from the mortality registry. The date of the first principal diagnosis of TN (ICD-9-CM codes 350.1) within the follow-up period was defined as the primary endpoint. The case ascertainment for TN required at least 2 ambulatory medical care visits with the principal diagnosis of TN. All subjects were followed from the index visit to the first occurrence of TN, death, or end of follow-up. We analyzed the influence of hypertension on TN-free survival, adjusting for demographic factors, including age, sex, and comorbid chronic diseases, including diabetes mellitus (ICD-9-CM code 250) and hyperlipidemia (ICD-9-CM code 272). The data for these preexisting comorbid medical disorders were acquired by tracking all the ambulatory medical care and inpatient records in the NHI database in the year before the index visit.

Statistical analysis. The χ² test and Student t test were used to examine differences in demographic variables and comorbid medical disorders between the hypertension and nonhypertension groups. Incidence rates of TN during the follow-up period by hypertension status were calculated by number of incident cases divided by the person-years of TN-free. We used the Poisson test to examine the difference of risk of developing TN between the hypertension and nonhypertension groups. The TN-free survival curves for the 2 groups were estimated using the Kaplan-Meier method. The cumulative incidence was then calculated as 1 minus the TN-free survival probability, and the differences in cumulative incidence rates between the 2 groups were tested with the log-rank test. We used the Cox proportional hazards regression analysis to estimate the effect of hypertension on TN-free survival after adjusting for the above demographic and clinical variables. Univariate analysis was performed for each variable, and then the best subsets selection method was used to develop the final multiple regression model. Age and sex were considered as basic elements and were always included in the multiple regression analysis. An α level of 0.05 was considered statistically significant. The analyses were performed using SAS 9.2 software (SAS Institute, Cary, NC).
RESULTS Descriptive findings. Table 1 shows the distribution of demographic characteristics and comorbid chronic diseases for the hypertension and nonhypertension groups. The mean age and gender proportion were identical in the 2 groups. The hypertension group had a higher prevalence of hyperlipidemia (p < 0.0001) than the nonhypertension group. There was no difference (p = 0.7976) in the prevalence of diabetes between the 2 groups.

Cumulative incidence of trigeminal neuralgia. The median follow-up time was 31.8 months (interquartile range [IQR] = 7.1 months). In the total study cohort, the risk of developing incident TN cases during the follow-up period was 0.07% (288/415,476) and the corresponding risks for the hypertension group and nonhypertension group were 0.09% (121/138,492) and 0.06% (167/276,984), respectively. The hypertension group had a higher incidence rate of TN than the nonhypertension group (35.2 vs 23.2 per 100,000 person-years, p = 0.0005). The cumulative incidence rate of TN over time was higher in the hypertension group than the nonhypertension group (figure, p = 0.0005).

Results of Cox regression analysis. The results of the Cox proportional hazards regression analysis are listed in table 2. The left panel shows the unadjusted hazard ratio for each variable based on univariate analysis. The covariates with a p value less than 0.05 were hypertension and age. Compared to the nonhypertension group, the unadjusted hazard ratio (HR) for the hypertension group was 1.52 (95% CI 1.20–1.92; p = 0.0005). The middle panel shows the full multivariate model including all variables from the univariate analysis. The significant prognostic factors were hypertension and age. Using the best subsets selection method, the final multiple regression model was developed, as shown in the right panel of table 2. Age and sex were considered as basic elements and were always included in the analysis. The variables included in final model were hypertension, age, and sex. The adjusted hazard ratio (aHR) for developing incident TN cases during the 3-year follow-up was 1.51 (95% CI 1.19–1.90; p = 0.0006) for the hypertension group compared to the nonhypertension group. Older subjects were at greater risk of developing TN, with an increased risk of 3% (aHR = 1.03; 95% CI 1.02–1.04, p < 0.0001) per year of age.

DISCUSSION This population insurance-based cohort study showed that occurrence of hypertension was associated with a higher risk of developing TN. The 3-year cumulative incidence of TN for the subjects with hypertension was significantly higher than that for the nonhypertension group.

In our longitudinal study, we followed patients with hypertension from the time of the diagnosis of hypertension for 3 years to examine the temporal relationship between hypertension and the development of subsequent TN and found that the adjusted HR for the hypertension group relative to the nonhypertension group was 1.51 (95% CI 1.19–1.90). These findings are compatible with the results of a previous population-based study of TN in Rochester, MN,3 which showed that 25% (19 out of 75) of patients with TN had a history of hypertension and that the OR for hypertension in patients with TN was 1.96 (95% CI 1.2–3.1).3

It has been suggested that TN is usually caused by vascular compression of the trigeminal nerve root at the brainstem by a tortuous vessel.10 This compression results in demyelination of the nerve root entry zone, leading to ectopic impulse generation, ephaptic transmission of impulses, and the symptoms of TN.10,16 Similarly, neurovascular compression of the facial and glossopharyngeal nerves is thought to be responsible for most cases of hemifacial spasm (HFS).
and glossopharyngeal neuralgia, respectively. Previous case-control studies have suggested that hypertension was associated with HFS, and hypertension was related to vascular tortuosity in the cerebello-pontine angle. These findings suggest that hypertension may accelerate the development of arterial tortuosity, which leads to compression and demyelination of the facial nerve, resulting in ectopic excitation and ephaptic transmission in the facial nerve. Hypertension has been suggested to be a predisposing factor for arterial tortuosity, which may increase the chance of developing neurovascular compression at the brainstem. From this perspective, a possible mechanism underpinning the temporal relationship between hypertension and TN seen in our study is that hypertension may exacerbate the arterial tortuosity at the brainstem and increase the chance of developing neurovascular compression, which, in turn, contributes to a higher risk for TN.

Conversely, some studies have suggested that vascular compression of the ventrolateral medulla is associated with a subgroup of patients with essential hypertension. It raises a possibility that the link between hypertension and TN seen in our study may be attributed to a common etiology, namely, neurovascular compression at the brainstem. However, various epidemiologic, neuroimaging, and histopathologic studies have provided evidence against a major role of neurovascular compression at the brainstem in the pathogenesis for most cases with essential hypertension. These conflicting findings suggest that the association between neurovascular compression at the brainstem and essential hypertension is still uncertain, and neurovascular compression appears to be a rare cause for essential hypertension, which is thought to have a multifactorial etiology involving interactions between various environmental and genetic factors. Therefore, it would be more plausible that the primary pathophysiologic mechanism underlying the association between hypertension and TN is hypertension-related arterial tortuosity, which in turn predisposes the development of neurovascular compression of the brainstem, resulting in an increased risk of TN.

In the present study, the estimated incidence rate of TN for the nonhypertension group was 23.2 (95% CI 19.8–27.0) per 100,000 person-years, and carbamazepine was prescribed as the initial therapy in 54.2% (156 out of 288) of the patients with TN. These findings are consistent with the results from a large-scale observational study of neuropathic pain in the United Kingdom which used the diagnostic information collected routinely from UK primary care records (the General Practice Research Database) from January 1992 to April 2002. In that study, the estimated incidence rate of TN was 27 per 100,000 person-years and carbamazepine was prescribed as the initial therapy to 58% of patients with TN.

Since the present study is a large population insurance-based cohort study and the temporal sequence between hypertension and TN is ordered, the observed significant association seems unlikely to be due to artificial phenomenon, such as selection bias and information bias (e.g., patients with hypertension would be more likely to be diagnosed with TN than those without hypertension). In addition, the temporal sequence, i.e., hypertension preceding TN, in our prospective study might also eliminate the possible differential misclassification of hypertension that might occur in a retrospective study. Our findings therefore provide evidence for a temporal association between hypertension and TN. Such a temporal relationship is essential for establishing a causal connection.

Nevertheless, several limitations in our study need to be addressed. First, the diagnosis of hypertension, TN, diabetes, and hyperlipidemia in our study was entirely determined by the ICD codes from the NHI claim database. One may be concerned over the diagnostic accuracy of the database. However, the Bureau

### Table 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted HR (95% CI)</th>
<th>p Value</th>
<th>Full multivariate model, adjusted HR (95% CI)</th>
<th>p Value</th>
<th>Best subset selected model, adjusted HR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (vs nonhypertension)</td>
<td>1.52 (1.20–1.92)</td>
<td>0.0005</td>
<td>1.50 (1.19–1.90)</td>
<td>0.0007</td>
<td>1.51 (1.19–1.90)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Age (year)</td>
<td>1.03 (1.02–1.04)</td>
<td>&lt;0.0001</td>
<td>1.03 (1.02–1.04)</td>
<td>&lt;0.0001</td>
<td>1.03 (1.02–1.04)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sex (female vs male)</td>
<td>1.09 (0.87–1.38)</td>
<td>0.4509</td>
<td>1.04 (0.82–1.31)</td>
<td>0.7517</td>
<td>1.04 (0.82–1.31)</td>
<td>0.7471</td>
</tr>
<tr>
<td>Diabetes mellitus (yes vs no)</td>
<td>1.06 (0.71–1.58)</td>
<td>0.7875</td>
<td>0.84 (0.50–1.40)</td>
<td>0.4975</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Hyperlipidemia (yes vs no)</td>
<td>1.27 (0.87–1.86)</td>
<td>0.2211</td>
<td>1.24 (0.70–2.19)</td>
<td>0.4695</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: CI = confidence interval; HR = hazard ratio; NA = not applicable.
* The variables of age and sex were always retained in the multiple regression analysis in the best subset selection procedure.
of NHI has formed different audit committees that make it a rule to randomly sample the claim data from every hospital and review charts on a regular basis to verify the diagnostic validity and quality of care. Accordingly, the NHI claim database is an established research database and has been applied to various biomedical research fields. In the NHI research database, each ambulatory visit has its own individual record which includes 3 ICD codes: 1 principal diagnosis code and 2 secondary diagnosis codes. The principal diagnosis is defined as the condition chiefly responsible for the visit. In addition, we further adopted a case ascertainment algorithm that required at least 2 ambulatory medical care visits with a principal diagnosis code of hypertension or trigeminal neuralgia to further validate the diagnosis; such case definition may be expected to provide adequate diagnostic accuracy. Moreover, the estimated incidence rate of TN and the pattern of the initial pharmacologic therapy are similar between our study and a large-scale study of neuropathic pain which used the routinely collected primary care records in the United Kingdom. Such consistency may also support an acceptable pattern of diagnosis or drug use for TN in our study.

Second, the NHI database lacks some information regarding the risk assessment of hypertension, such as smoking, alcohol use, body mass index, physical activity, or detailed blood pressure values, which may affect the interpretation of our results. Third, the follow-up time was only 3 years and the long-term effects of hypertension on the development of TN cannot therefore be evaluated. Fourth, most of the inhabitants in Taiwan are of Chinese ethnicity; it is uncertain whether our findings can be generalized to other ethnic groups.

This population insurance-based cohort study demonstrates that hypertension leads to a higher risk of TN. Further long-term follow-up study would be required to validate our findings and to investigate the underlying pathophysiologic mechanism for the positive association between hypertension and TN.

AUTHOR CONTRIBUTIONS
Dr. Pan: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, statistical analysis. Dr. Yen: drafting/revising the manuscript, analysis or interpretation of data. Dr. Chiu: study concept or design, analysis or interpretation of data, statistical analysis. Dr. L.-S. Chen: analysis or interpretation of data, acquisition of data. Dr. T.H.-H. Chen: drafting/revising the manuscript, study concept or design, analysis or interpretation of data.

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DISCLOSURE
Dr. Pan, Dr. Yen, Dr. Chiu, and Dr. L.-S. Chen report no disclosures. Dr. H.-H. Chen serves as an Associate Editor for Journal of Epidemiology and Community Health and on the editorial advisory board of the World Journal of Gastroenterology.

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