Risk of Stroke in Patients Hospitalized for Isolated Vertigo
A Four-Year Follow-Up Study

Ching-Chih Lee, MD; Yu-Chieh Su, MD; Hsu-Chieh Ho, MD; Shih-Kai Hung, MD; Moon-Sing Lee, MD; Pesus Chou, PhD; Yung-Sung Huang, MD

Background and Purpose—Vertigo is a common presenting symptom in ambulatory care settings, and stroke is its leading and most challenging concern. This study aimed to determine the risk of stroke in vertigo patients in a 4-year follow-up after hospitalization for acute isolated vertigo.

Methods—The study cohorts consisted of all patients hospitalized with a principal diagnosis of vertigo (n=3021), whereas patients hospitalized for an appendectomy in 2004 (n=3021) comprised the control group and surrogate for the general population. Cox proportional hazard model was performed as a means of comparing the 4-year stroke-free survival rate between the 2 cohorts after adjusting for possible confounding and risk factors. Among vertigo patients, there was further stratification for risk factors to identify the group at high risk for stroke.

Results—Of the 243 stroke patients, 185 (6.1%) were from the study cohort and 58 (1.9%) were from the control group. Comparing the 2 groups, patients with vertigo symptoms had a 3.01-times (95% CI, 2.20–4.11; P<0.001) higher risk for stroke after adjusting for patient characteristics, comorbidities, geographic region, urbanization level of residence, and socioeconomic status. Vertigo patients with ≥3 risk factors had a 5.51-fold higher risk for stroke (95% CI, 3.10–9.79; P<0.001) than those without risk factors.

Conclusions—Vertigo patients are at higher risk for stroke than the general population. They should have a comprehensive neurological examination, vascular risk factors survey, and regular follow-up for several years after hospital discharge after treatment of isolated vertigo. (Stroke. 2011;42:48-52.)

Key Words: cerebrovascular accident ■ cumulative risk ■ hazard ratio ■ stroke ■ vertigo

Vertigo or dizziness is a common symptom among patients examined by primary care physicians, otolaryngologists, and neurologists. Up to 7.5 million patients with vertigo and dizziness are seen in ambulatory care settings in the United States. The most common causes are peripheral vestibular disease, although central nervous system disorders like cerebrovascular disorders, multiple sclerosis, tumor over the posterior cranial fossa, and neurodegenerative disorders should be excluded. Kerber et al reported that stroke is diagnosed in 3.2% of all patients presenting to the emergency department with vertigo or dizziness in a population-based study and conclude that vertigo alone is not predictive of stroke. Estol et al reasoned that recurrent isolated episodes of vertigo without neurological signs and symptoms is an uncommon manifestation of vertebrobasilar insufficiency. However, recent case reports and small series studies reveal that vertigo may be a principal or sole manifestation of stroke patients. In vertebrobasilar insufficiency, it may not be possible to determine if vertigo is a symptom of a peripheral or central vestibular syndrome. Although most patients with vertigo or dizziness will receive treatment in ambulatory settings, those with severe cases may visit the emergency room or be admitted for further detailed survey and treatment. Hospitalized patients with a definite diagnosis of peripheral vertigo will encounter problems whether the incapacitating vertigo is benign or if they confer a higher risk of stroke in the future. Nevertheless, there has been no longitudinal study on the risk of stroke after hospitalization and discharge for isolated vertigo.

This study aimed to determine the subsequent risk of stroke in hospitalized patients with isolated vertigo identified through the National Health Insurance Research Database in Taiwan. This nationwide population-based dataset allows the investigation of isolated vertigo and subsequent risks for stroke after adjustments for demographic and clinical factors.
Materials and Methods

Database
This study used the 2004 to 2007 National Health Insurance Research Database published by Taiwan’s National Health Research Institutes. The National Health Insurance Research Database covered medical benefit claims for ~97% of the population and contained a registry of board-certified physicians and contracted medical facilities. Because the data consisted of de-identified secondary data released to the public for research, this study was exempt from full review by the Institutional Review Board.

The study design featured a study cohort and a comparison cohort. The study cohort consisted of all patients who were hospitalized with a principal diagnosis of vertigo (ICD-9-CM codes 386.0–386.9, excluding 386.2, which is central vertigo). The control cohort included all patients hospitalized for an appendectomy in 2004 with an ICD-OP code of 47.0 as the primary operative procedure.

Appendectomy patients were selected as the control because their difference with the general population was not discernible. Furthermore, procedures related to appendectomy were not associated with increased risk of stroke and vertigo. Patients with any type of stroke (ICD-9-CM 430–438) diagnosed before or during the index admission or appendectomy were excluded.

In 2004, 21,567 patients who underwent appendectomy and 3,021 patients with vertigo were identified. Because there was a significant difference in mean age between the 2 groups, the control cohort criteria were further refined by randomly selecting 3,666 age-matched appendectomy patients (ie, younger than 45, 45–64, 65–74, and older than 75 years). Each patient was tracked from the first hospitalization in 2004 until the end of 2007 using administrative data to identify all patients who had any type of stroke (ICD-9-CM codes 430–438). These patients were then linked to the death data covering the period 2004 to 2007 to calculate for stroke-free survival time, with cases censored if the patients died from nonstroke causes. The independent variables were gender, comorbid disorders, geographic area of residence and urbanization level, and socioeconomic status.

Details on medical comorbidities, including hypertension, diabetes, coronary artery disease, and hyperlipidemia, were extracted from the claims data at the time of index discharge. These conditions were then associated with stroke. Enrollee category (EC) was used as a proxy measure of socioeconomic status, which was an important risk factor for stroke. These patients were then classified into 4 subgroups: EC1 (highest socioeconomic status), EC2, EC3, and EC4 (lowest socioeconomic status).

Previous studies reported the association of stroke and geographic region and urbanization. Thus, these 2 variables were included. The urbanization levels were divided as urban, suburban, and rural.

Statistical Analysis
The SAS statistical package (version 9.2; SAS Institute) and SPSS (version 15; SPSS) were used for data analysis. The cumulative risk of stroke was estimated as a function of time from initial treatment. Pearson χ² test was used for categorical variables in the 2 cohorts, whereas the 4-year stroke-free survival rate was estimated using the Kaplan-Meier method. Cox proportional hazard regression model was used to calculate the risk of vertigo patients vs that of controls after adjustments for variables. P<0.05 was considered statistically significant in the regression models.

To find the high-risk group, stroke incidence among vertigo patients with different numbers of risk factors were analyzed.
Multivariate analysis with Cox proportional regression model further estimated the hazard ratio of different risk groups after adjusting for other factors.

Results

The distribution of demographic characteristics and selected comorbidities for the 2 cohorts is shown in Table 1. Patients with vertigo were more likely to be female, had hypertension, diabetes, coronary artery disease, and hyperlipidemia, resided in a rural area or central Taiwan, and had lower socioeconomic status (EC3) than the controls.

At the end of follow-up, 243 patients had strokes, including 185 (6.1%) from the vertigo group and 58 (1.9%) from the control group. The median duration of stroke event in the vertigo patients was 17.6 months and 114 (61.6%) stroke events developed within 24 months after the index admission (Figure 1). Vertigo patients also had a higher cumulative risk of stroke than controls (Figure 2; \( P < 0.001 \)).

Stroke subtypes between the 2 cohorts were further analyzed. There were 182 (98.4%), 2 (1.1%), and 1 (0.5%) patients with ischemic stroke, hemorrhagic stroke, and subarachnoid hemorrhage, respectively, among the vertigo patients, and 53 (91.4%), 4 (6.8%), and 1 (1.7%) patients, respectively, with ischemic stroke, hemorrhagic stroke, and subarachnoid hemorrhage in the controls. Vertigo patients had more ischemic strokes than the controls \((P=0.009)\).

Unadjusted and adjusted hazard ratios for stroke between vertigo and appendectomy patients are shown in Table 2. After adjustments for gender, age, comorbidities, geographic region, urbanization level, and socioeconomic status, stroke hazard during the 4-year follow-up period among vertigo patients was 3.01-times (95% CI, 2.20–4.11; \( P < 0.001 \)) higher than in the controls.

Six risk factors, which included age older than 55 years, male gender, hypertension, diabetes, coronary artery disease, and hyperlipidemia, were used to stratify the vertigo patients. They were divided into 3 groups: 941 patients in the low-risk group (no risk factor), 1654 in the intermediate-risk group (1–2 risk factors), and 426 in the high-risk group (≥3 risk factors). The 4-year cumulative risks for stroke for the 3 different risk groups were 1.9 (95% CI, 1.1%–2.7%), 7.7 (95% CI, 6.1%–9.3%), and 14 (95% CI, 10.5%–17.5%), respectively \((P<0.001; \text{Figure 3})\). Table 3 shows that the risk of stroke was greater for vertigo patients with ≥3 risk factors (HR, 5.51; 95% CI, 3.10–9.79) than for patients with 1 to 2 risk factors (HR, 3.20; 95% CI, 1.90–5.37) or those without any.

Discussion

This study adds several novel points to existing knowledge on stroke incidence in vertigo patients. The use of a population-based dataset has enabled the tracing of all stroke events within a 4-year follow-up. Appendectomy patients who comprised the control group are a surrogate or representative of the general population because their difference with the general population is not discernible.10,11 In vertigo patients with stroke, 35% has occurred in the first year after vertigo onset, and ∼62% occurred within 2 years. This suggests that efforts to prevent stroke development should last for several years after the onset of vertigo. Stratifying for risk factors is

Table 2. Crude and Adjusted Hazard Ratios for Stroke in the 4-Year Follow-Up Period (n=6042)

<table>
<thead>
<tr>
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<td>58 (1.9)</td>
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<td>&lt;0.001</td>
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<td>Vertigo group (n=3021)</td>
<td>185 (6.1)</td>
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</tbody>
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*Adjusted for gender, age, hypertension, diabetes, coronary heart disease, hyperlipidemia, geographic region, urbanization level, and enrollment category.
also useful in decision-making for individual patients and in designing surveillance.

Vertigo patients and clinicians will usually encounter 2 important questions. Is the vertigo a sign of verteobasilar insufficiency or of stroke? Will vertigo patients be at higher risk for stroke in the future? Because circulation to the inner ear arises from the verteobasilar system, usually from the anterior inferior cerebellar artery, vertigo from cerebrovascular disease can be of peripheral or central origin. Previous studies emphasize that isolated vertigo, when present longer than several weeks, is rarely attributable to vascular events.\(^{17,18}\) However, recent studies report contradictory findings. Of 29 patients with verteobasilar insufficiency, 21% have episodic vertigo for at least 4 weeks as the only presenting symptom.\(^{19,20}\) Moreover, patients with anterior inferior cerebellar artery infarction, anterior vestibular artery infarction, or cerebellar infarction may present with symptoms or signs similar to Meniere disease, benign paroxysmal positional vertigo, and vestibular neuritis, respectively.\(^{5,21–23}\) To prevent misdiagnosis of stroke in vertigo patients, verteobasilar insufficiency or posterior circulation infarction should be recognized as possible causes of acute-onset isolated vertigo.

Another important issue is whether vertigo patients will be at higher risk for stroke in the future. Aside from the current study, no previous study has explored stroke incidence in patients after hospital discharge for treatment of isolated vertigo. This study reveals that patients with isolated vertigo diagnosed confer a 3.01-times higher risk for stroke after discharge from index admission compared to the control group. During follow-up, 62% (114 of 185) of strokes are within the first 24 months. Isolated vertigo on a vascular basis is best explained by transient ischemia to the vestibular labyrinthine. The internal auditory artery is a small end-artery with minimal collaterals, which makes the labyrinthine vulnerable to ischemia.\(^{24–26}\) The current study posits a hypothesis that ischemic labyrinthine can be viewed as a systemic small vessel vasculopathy, which partially explains the increased incidence of stroke during follow-up and the nonposterior circulation infarction.

This study shows that vertigo patients without any risk factors (31% of all patients in the series) have a low 4-year stroke incidence of 1.9%. Patients at intermediate risk, with 1 to 2 risk factors, account for 55% of all patients and have a 4-year stroke probability of 6.8%, whereas patients at high risk with ≥3 risk factors account for 14% of all patients and a much higher 4-year incidence of 12.7%. After symptomatic treatment for the vertigo, more attention should be made to prevent stroke in the first 24 months after discharge. Therefore, interventions aimed at stroke prevention are extremely important. Complete survey of modifiable risk factors and intensive lifestyle modification are indicated in elderly vertigo patients (age older than 55 years). Brain CT and carotid duplex and transcranial Doppler are suggested for high-risk vertigo patients. Further studies are recommended for the role of aspirin in primary ischemic stroke prevention.

This study has several limitations. First, the diagnoses of vertigo, appendectomy, stroke, and any other comorbid conditions are completely dependent on ICD codes. Nonetheless, the National Health Insurance Bureau of Taiwan has randomly reviewed the charts and interviewed patients to verify the accuracy of diagnosis. Hospitals with outlier chargers or practice may undergo an audit, with subsequent heavy penalties for malpractice or discrepancies. Second, hospitalized patients with a principal diagnosis of peripheral vertigo have been chosen to reduce misdiagnosis. Neurology or otology specialists do not examine most vertigo patients in ambulatory or emergency settings. As such, subtle neurological findings indicative of central nervous system dysfunction may be missed in some patients. However, the selection bias prevents the generalization of the results to all vertigo patients. Third, the severity and territory of strokes cannot be exactly extracted from ICD codes, which prevent further subgroup analysis. Fourth, the database does not contain information on tobacco use, dietary habits, and body mass index, which also may be risk factors for stroke. Further study linking administrative data and primary hospitalization information like stroke location, stroke severity, and detailed risk factors is worthy of future investigation. Nonetheless, given the magnitude and statistical significance of the observed effects in this study, these limitations are unlikely to compromise the results.

### Conclusion

In summary, this study is the first to our knowledge to attempt to investigate the risk of stroke in patients after hospitalization for isolated vertigo. It reveals that hospitalized patients with isolated vertigo have increased risk for subsequent stroke and that their likelihood of stroke developing within 4 years is 3.01-times higher than that of the general population. There is a significant difference in the distribution of stroke subtypes between vertigo patients and the control patients.
with more cases of ischemic stroke in the former. Stratification for risk factors in predicting the cumulative risk of stroke may help identify high-risk (with ≥ 3 risk factors) and intermediate-risk (with 1–2 risk factors) vertigo patients who require regular monitoring to prevent the development of stroke.

Disclosures
This study is based partly on data from the National Health Insurance Research Database provided by the Bureau of National Health Insurance, Department of Health, and managed by the National Health Research Institutes (serial no. 99198). The interpretation and conclusions contained here do not represent those of the Bureau of National Health Insurance, Department of Health, or National Health Research Institutes.

References
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Data Supplement (unedited) at:
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현기증 단독으로 입원한 환자의 뇌졸중 위험
4년 추적 관찰 연구

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배경과 목적
현기증(vertigo)은 환자들이 외래 진료 시 가장 많이 호소하는 증상이며, 뇌졸중은 가장 종요하고 진단하기 어려운 현기증의 원인이다. 본 연구는 급성 현기증 단독 증상으로 입원한 환자를 4년간 추적 관찰하여, 이들에서 뇌졸중의 위험을 평가하기 위하여 수행되었다.

방법
본 연구 코호트는 현기증을 주 진단으로 하여 입원한 모든 환자로 구성되었으며(n=3,021), 2004년에 명확 계거 수술로 입원한 환자를 대조군으로 하여 일반 인구 집단을 대표하도록 하였다(n=3,021). 콕스 비례 위험 모델을 이용하여, 여러 임계적 인 교란변수 및 위험인자를 포함한 후, 두 코호트 사이에서 4년간 뇌졸중이 발생하지 않는 생존율을 측정하였다. 현기증 환자들에서 뇌졸중의 교환 집단을 찾아내기 위하여 여러 위험 인자를 기존으로 추가적인 증화 분석을 시행하였다.

결과
뇌졸중 환자 243명 중 185명(6.1%)은 현기증 환자군에 속하였으며, 58명(1.9%)은 대조군에 속하였다. 두 환자군을 비교할 때, 현기증 환자군은 환자 특성, 동반 질환, 치료기분포, 거주지의 도시화 정도 및 사회 경제적 상태를 보정한 후에도 3.01배 높은 뇌졸중 위험도를 보였다(95% CI, 2.20~4.11; P <0.001). 3개 이상의 위험인자를 가지고 있는 뇌졸중 환자들은 위험인자를 가지고 있지 않은 환자에 비하여 5.51배 높은 뇌졸중 위험도를 보였다(95% CI, 3.10~9.79; P<0.001).

결론
현기증 환자들은 일반 인구 집단에 비하여 뇌졸중의 위험이 높았다. 이들은 자세한 신경학적 검진, 혈관 위험인자 추적 및 급성 현기증 치료 및 퇴원 후 수년에 걸친 정기적 추적 관찰을 필 요로 한다.
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*Adjusted for gender, age, hypertension, diabetes, coronary heart disease, hyperlipidemia, geographic region, urbanization level, and enrollee category.

Figure 3. Cumulative risk of stroke by stratification for risk factors (n=3021).