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Association between orthostatic hypotension, mortality, and cardiovascular disease in Asians

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ABSTRACT

Background: Orthostatic hypotension (OH) is a common condition encountered in the elderly. The present study aimed to examine the relationship between OH and adverse events in Asians.
Methods: We used the "National Health Insurance Research Database" in Taiwan. A total of 1226 patients with OH and without previous history of ischemic stroke and myocardial infarction were identified as the study group. For each study patient, ten age-, sex- and comorbidity-matched subjects without OH were selected to constitute the control group (n = 12,260). The clinical endpoints were ischemic stroke, myocardial infarction and all-cause mortality.
Results: The mean age of the study population was 54.8 ± 19.0 years and males accounted for 47% of the patients. During the follow-up of 4.5 ± 2.9 years, 704 (5.2%) patients developed ischemic stroke, 190 (1.4%) patients developed myocardial infarction, and 733 (5.4%) patients died. In the multivariable Cox regression analyses which were adjusted for age, gender and differences in medication usages, OH was significantly associated with an increased risk of ischemic stroke (hazard ratio [HR] = 1.40, 95% confidence interval (CI) = 1.09–1.81, p = 0.009), all-cause mortality (HR = 1.35; 95% CI = 1.05–1.73, p = 0.018) and adverse events (ischemic stroke, myocardial infarction or mortality) (HR = 1.41; 95% CI = 1.18–1.68, p < 0.001).
Conclusion: OH is an independent factor associated with ischemic stroke and mortality in Asians. Whether aggressive managements for stroke prevention could improve the outcome for OH patients deserves further study.

1. Introduction

Orthostatic hypotension (OH), with prevalence from 5 to 20% in different populations, is a common symptom in the elderly. When autonomic reflexes are impaired, a significant reduction in blood pressure occurs upon standing. OH is defined as a decrease in systolic blood pressure of more than 20 mm Hg, or a decrease in diastolic of more than 10 mm Hg within 3 min of standing [1]. It was found to be associated with dizziness, syncope, falls, fractures, and potential morbidity. In addition to the neurologic symptoms, more and more investigators found that OH is related to cardiovascular diseases, such as coronary artery disease, ischemic stroke, heart failure, and cardiac death [2,3]. However, most available data came from clinical trials performed on Caucasians [2–4], who may have different etiologies and mechanisms of cardiovascular events compared to Asians. The aim of the present study is to investigate whether OH increases the risk of ischemic stroke, myocardial infarction and all-cause mortality in Asians using the National Health Insurance Research Database (NHIRD) in Taiwan.

2. Methods

2.1. Database

This study used the NHIRD released by the Taiwan National Health Research Institutes (NHRI). The National Health Insurance (NHI) system is a mandatory universal health insurance program that offers comprehensive medical care coverage to all Taiwanese residents. The NHIRD is a cohort dataset that contains all medical claim data for 1,000,000 beneficiaries, who were randomly sampled from the 25.68 million enrollees under the NHI program. These random samples have been confirmed by

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the NHRI to be representative of the Taiwanese population. In this cohort dataset, the patients' original identification numbers were encrypted to protect their privacy. The encrypting procedure was consistent, so that linking claims belonging to the same patient was feasible within the NHI database and could be followed continuously. The database has a large sample size and provides a good opportunity to study the risk of ischemic stroke, myocardial infarction and mortality among patients with or without orthostatic hypotension.

Information about important comorbid conditions of each individual was retrieved from the medical claims based on the International Classification of Diseases (ICD), Ninth Revision, Clinical Modification (ICD-9-CM) codes. We defined patients with a certain disease only when it was a discharge diagnosis or confirmed more than twice in the outpatient department. The diagnostic accuracies of important comorbidities in NHIRD, such as hypertension, diabetes mellitus, heart failure, myocardial infarction, hyperlipidemia and chronic obstructive pulmonary disease, have been validated before [5,6].

2.2. Study population

From January 1, 2000 to December 31, 2011, the medical claim data of 1,000,000 beneficiaries were analyzed. Patients with history of stroke and myocardial infarction younger than 18 years were excluded. Thereafter, a total of 1226 patients having the diagnosis of orthostatic hypotension (ICD-9-CM code = 458.00) were identified as the study group. To ensure the accuracy of diagnosis, only those patients whose OH was confirmed more than twice in the outpatient department or diagnosed at discharge were included in the study. On the same date of enrollment of one study patient, we randomly selected ten age-, sex- and comorbidity-matched subjects without OH for each included study patient to constitute the control group (n = 12,260). Data about concomitant medication usages, including aspirin, warfarin, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta-blockers, and statins were also retrieved from the NHIRD. A flowchart of the enrollment of the study population is shown in Fig. 1.

2.3. Clinical endpoints

The clinical endpoint was defined as the occurrence of ischemic stroke, with concomitant imaging studies of the brain, including computed tomography or magnetic resonance imaging. The accuracy of diagnosis of ischemic stroke in Taiwan's NHIRD has been reported to be around 94% [5]. Another validation study also demonstrated that the diagnostic accuracy of ischemic stroke in NHIRD was high, with the positive predictive value and sensitivity of 88.4% and 97.3%, respectively [7]. The occurrences of myocardial infarction and all-cause mortality were also analyzed.

2.4. Statistical analysis

The data are presented as the mean value and standard deviation for normally distributed continuous variables and proportions for categorical variables. The differences between continuous values were assessed using an unpaired 2-tailed t test for normally distributed continuous variables, Mann–Whitney rank-sum test for skewed variables, and chi-square testing for nominal variables. The survival curves of ischemic stroke, myocardial infarction, death, and adverse events (ischemic stroke, myocardial infarction, or death) were plotted using the Kaplan–Meier method with statistical significance examined by the log-rank test. To assess the independent effects of OH on clinical events, we conducted Cox proportional hazard regression models simultaneously adjusting for age, gender, and variables which had significant differences between study and control groups. Adjusted variables included the use of aspirin, warfarin, ACEIs, ARBs, beta-blockers, and statins. All statistical significances were set at $p < 0.05$ and all statistical analyses were carried out by SPSS 18.0 (SPSS Inc., USA).

3. Results

3.1. Patient characteristics

A total of 13,486 patients were enrolled in this study, including 1226 subjects with OH and 12,260 controls without OH. The mean age of the study population was 54.8 ± 19.0 years and males accounted for 47% of the patients. The baseline characteristics of patients with and without OH are shown in Table 1. Since age, sex, and comorbidities between the study and control groups were matched, the usages of medications became the only statistically different factors between the two groups. Patients with OH were found to have a higher percentage of medication usages, including aspirin, warfarin, ACEIs, ARBs, beta-blockers, and statins.

3.2. Orthostatic hypotension and risk of clinical events

During the mean follow-up of 4.5 ± 2.9 years, 704 (5.2%) patients developed ischemic stroke, 190 (1.4%) patients developed myocardial infarction, and 733 (5.4%) patients died. There were a total of 1420

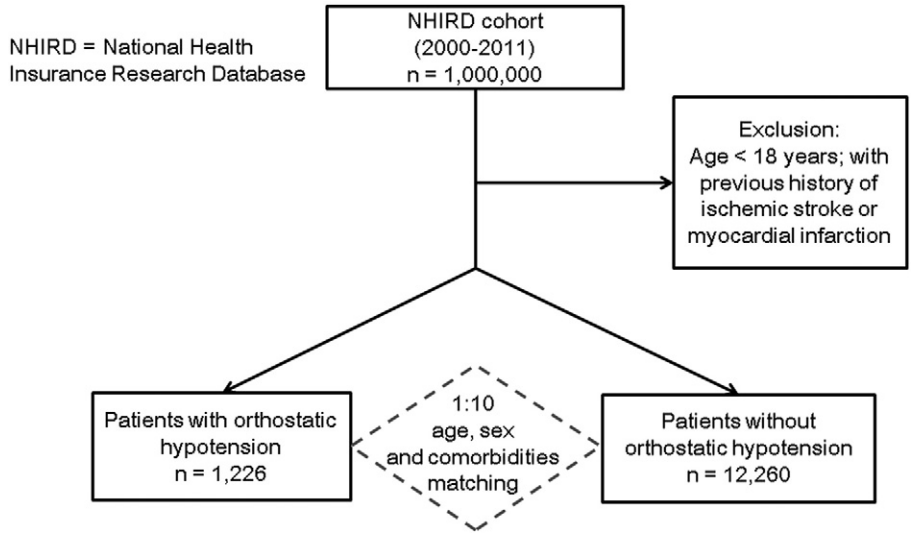

Fig. 1. A flowchart of the enrollment of study patients.