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Adverse cardiovascular effects of nitrogen-containing bisphosphonates in patients with osteoporosis: A nationwide population-based retrospective study☆

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ABSTRACT

Background: Bisphosphonates (BPs) are a class of medications used for the treatment of osteoporosis. Nitrogen-containing BPs (N-BPs) are more potent than non-nitrogenous BPs in terms of their effects on osteoporosis. We examined the effects of N-BPs on osteoporosis in patients included in a large population-based cohort study.
Methods: Based on the National Health Insurance Research Database of Taiwan, we identified 1258 patients with osteoporosis who had received N-BP treatment from 2005 through 2010.
Results: During the retrospective observation period, N-BP users had significantly higher incidence rates of hypertension, acute ischemic stroke, atrial fibrillation (Af), and congestive heart failure (CHF), and lower rates of hyperlipidemia than patients who did not use N-BPs. Overall, N-BP users had a higher incidence of cardiovascular events at the end of the follow-up period. After adjustment for age, sex, and comorbidities, the risk of developing cardiovascular events was significantly high for patients using N-BPs. Patients who received N-BP therapy also had a higher risk of Af and CHF than those who did not during the five-year follow-up period.
Conclusion: We provide evidence that patients with osteoporosis using N-BP therapy have an increased risk of CHF and Af. This potential risk should be weighed against the reduction in the risk of osteoporotic fractures.

1. Introduction

Bisphosphonates (BPs) are a class of medications used for the treatment of osteoporosis, malignant osteolytic bone diseases, and hypercalcemia. Nitrogen containing BPs (N-BPs) are more potent than non-nitrogenous BPs in terms of their effects on osteoporosis. N-BPs can act to inhibit the farnesyl pyrophosphate synthase (FPPS) enzyme in the mevalonate pathway and interfere with the functions of small G proteins [1,2]. N-BPs have been shown to have anti-atherogenesis, anti-neovascularization, lipid-modifying, and immunomodulatory effects and may be associated with adverse cardiovascular effects [3–6]. N-BPs may also have an effect on changes in brachial-ankle pulse wave velocity and have a significant negative correlation with changes in lumbar spine bone mineral density [19].

Interestingly, animal studies, clinical observational studies, and meta-analyses yielded contradictory results regarding the effects of N-BPs on cardiovascular therapy. Some animal studies and clinical observations have shown that treatment with N-BPs could have favorable effects by inhibiting the progression of neointimal formation, atherosclerotic plaques, abdominal aortic aneurysms, and atherosclerotic cardiovascular diseases [7–12]. However, other studies have shown an increased incidence of atrial fibrillation (Af), acute ischemic stroke (AIS), congestive heart failure (CHF), and acute myocardial infarction (AMI) upon N-BP use [13–18].

Because of conflicting evidence, the cardiovascular effects of N-BPs remain widely debated. We therefore aimed to investigate, based on results from a nationwide population-based study, whether the use of N-BPs was associated with the development of cardiovascular diseases. As such, this study includes the use of a large national insurance population-based study sample that is representative of the national

☆ The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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population. The database includes complete data available on the medical services provided to and medications of patients across a wide range of demographic characteristics. This will facilitate the generation of highly reliable results. The compulsory centralized government-run, single-payer health insurance system that covers treatment for all major surgical or medical interventions either in the homeland or overseas also reduces the rate of loss of follow-up patients. This provides a more accurate estimation of disease incidence further contributing to the reliability and relevance of this retrospective study.

2. Material and methods

2.1. Data source

This retrospective cohort study used data extracted from the Taiwan National Health Insurance (NHI) Claims database. The NHI program has provided compulsory universal health insurance in Taiwan since 1995. It covers more than 99% of Taiwan's population of more than 22 million people. Patient identification numbers, gender, birthdays, dates of admission and discharge, medical institutions providing the services, the ICD-9-CM (International Classification of Diseases, 9th Revision, Clinical Modification) diagnostic and procedure codes (up to five each), and outcomes are encrypted. Researchers seeking to use the National Health Insurance Research Database (NHIRD) and its data subsets are required to sign a written agreement declaring that they do not intend to obtain information that could potentially violate the privacy of patients or care providers. The data for the nationwide population-based cohort study described here were obtained from the Longitudinal Health Insurance Database 2005 (LHID 2005), which is a subset database of the Taiwan NHIRD. The LHID 2005 contains information on medical services utilization from 2000 for a randomly selected sample of approximately one million beneficiaries. This representing approximately 5% of Taiwan's population. The information was extracted from NHIRD and registered in 2005. The accuracy of diagnoses in the NHIRD for major diseases such as stroke and acute coronary syndrome has been validated [20,21]. The LHID 2005 consists of "de-identified" secondary data released to the public for research purposes and this study was in accordance with the Declaration of Helsinki and relevant guidelines. All experimental protocols were approved. The requirement for informed consent from each patient was waived by the Institutional Review Board of Tri-Service General Hospital, Taipei, Taiwan.

2.2. Sampled patients

The study design featured a study and comparison cohort. Using the LHID 2005, we selected adult patients aged >18 years who had been newly diagnosed with osteoporosis (ICD-9-CM 733.0) and who were followed up between 2005 and 2010. We excluded patients who had been diagnosed with osteoporosis (ICD-9-CM 733.0) prior to the index date. All insurance claims were scrutinized by medical reimbursement specialists. Peer review was undertaken according to standard and clinical diagnosis criteria, such as dual-energy X-ray absorptiometry data, for osteoporosis. The diagnoses of osteoporosis in this study should therefore be highly reliable [22].

We then selected patients who had received N-BP therapy, including alendronate, zoledronic acid, pamidronate, and ibandronic acid, between 2005 and 2010. The date of initiation of N-BP therapy was used as the index date for the patient. Treatments with clodronate and etidronate were limited to malignancy-related bone disease; patients receiving these treatments were excluded from this study. The control cohort included patients with osteoporosis who did not receive BP therapy. Patients in the study and control cohorts were selected by 1:4 matching according to baseline variables including age, sex, and comorbidities including hypertension (ICD-9-CM 401–405), diabetes (ICD-9-CM 250), and hyperlipidemia (ICD-9-CM 272.0–272.4).

2.3. Outcome measurements

Outcome measurements were identified using the ICD-9 codes, and included aortic aneurysm (441.1–441.9), surgical repair for aortic aneurysm, acute myocardial infarction (410–411), angina (413), AIS (433–434), Af (427.31), CHF (428,402.01,402.11,402.91,404.01, 404.11,404.91), subarachnoid hemorrhage (430), intracerebral hemorrhage (431), and carotid stenosis (433.1).

2.4. Statistical analysis

The clinical characteristics of patients were expressed in numerical form. Categorical variables, presented as percentages, were compared using Chi-square/Fisher exact tests. Continuous variables, presented as means and standard deviations, were compared using a t-test. The primary goal of the study was to determine whether a patient's clinical characteristics were associated with predefined adverse outcomes (i.e., stroke, AMI and all-cause mortality). The association between those time-to-event-outcomes (prognoses) and clinical characteristics were investigated using Kaplan–Meier survival analysis and multivariate Cox regression analysis with forward stepwise selection. The results are presented as adjusted hazard ratios (HR) with corresponding 95% confidence intervals (CIs). The threshold for statistical significance was $p < 0.05$. All data analyses were conducted using SPSS software version 18 (SPSS Inc., Chicago, IL, USA).

3. Results

A total of 14,161 patients with osteoporosis were identified in the NHIRD, which contains a total of 956,785 patients. All study patients were adults and had been newly diagnosed with osteoporosis. After matching for gender, age group, hypertension, diabetes, and hyperlipidemia, there were no significant differences in the distributions of AMI, angina, stroke, Af, CHF, subarachnoid hemorrhage, intracerebral hemorrhage and carotid stenosis among the patients who received N-BP therapy and the comparison patients.

A flow diagram of the patient enrollment scheme is presented in Fig. 1. A total of 1258 patients who had received treatment with N-BPS was identified. Another 5032 age-, gender-, and comorbidity-matched patients were designated as controls. As shown in Table 1, there were no significant differences regarding the age, gender and comorbidities between these two cohorts. Table 2 shows the incidence of cardiovascular events during the five-year follow-up period. At the end of the follow-up period, 933 patients had received N-BPs, and 4290 patients had not. When compared with non-users over the respective observation period, N-BP users had a statistically significantly higher incidence of hypertension (28.51% vs. 25.15%, $p = 0.018$), AIS (8.04% vs. 5.64%, $p = 0.002$), Af (3.00% vs. 1.40%, $p < 0.001$), and CHF (14.04% vs. 6.36%, $p < 0.001$). Overall, N-BP users had a higher incidence of total cardiovascular events (32.48% vs. 20.70%, $p < 0.001$). On the other hand, N-BP-treated osteoporotic patients were at lower risk for developing hyperlipidemia than those without N-BP treatment (9.86% vs. 10.05%, $p = 0.022$). When compared with patients having osteoporosis who did not receive N-BP treatment, those treated with N-BPs had a statistically significantly higher cumulative risk of composed cardiovascular events (log rank test <0.001, Fig. 2A) and higher all-cause mortality rates (Kaplan–Meier curve, log rank test <0.001, Fig. 2B). Table 3 shows that, after adjusting for age, gender, and comorbidities, patients who received N-BP therapy were at a higher risk for cardiovascular events including Af (adjusted HR = 1.551, 95% CI = 1.037–2.394, $p = 0.033$) and CHF (adjusted HR = 1.652, 95% CI = 1.362–1.989,