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Original article

Number of daily antihypertensive drugs and the risk of osteoporotic fractures in older hypertensive adults: National health insurance service – Senior cohort

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ABSTRACT

Background: Antihypertensive medication represents one of the most common prescriptions for senior individuals. Numerous studies have assessed the influence of antihypertensive treatment on the risk for osteoporotic fracture, yet much controversy remains. We analyzed the relationship between the incidence of osteoporotic fracture and the average number of daily antihypertensive drugs (NDAD) included in the prescription of elderly hypertensive patients.

Methods: The study population was derived from the National Health Insurance Service–Senior Cohort (2002–2013), and consisted of elderly patients (≥ 60 years) diagnosed with hypertension in 2009, who did not have osteoporotic fractures in 2008, and underwent at least one national health check-up between 2009 and 2013, and had complete records after 2010. The outcome measured was the incidence of osteoporotic fractures between 2010 and 2013. The study population was stratified into the three groups (low, moderate, and high), in terms of NDAD.

Results: A total of 137,304 hypertensive patients were included. A multivariate model corrected by age, gender, body mass index, systolic blood pressure, underlying disease, smoking status, and use of medicines showed that the groups with moderate and high NDAD exhibited, respectively, 12% and 16% lower risk of osteoporotic fracture compared to that in the group with low NDAD. In terms of the risk of osteoporotic fracture associated with the number of daily thiazide diuretics (NDTD), the adjusted odds ratios (aOR; 95%CI) were 0.89 (0.84–0.94) and 0.93 (0.84–1.02) in the groups with moderate and high NDTD, respectively compared to low NDTD as reference. As to NDADnotTD, the aOR (95%CI) were 0.90 (95%CI, 0.86–0.94) and 0.89 (95%CI, 0.84–0.95) in the groups with moderate and high NDADnotTD, respectively compared to low NDADnotTD as reference.

Conclusion: In elderly hypertensive patients, the incidence of osteoporotic fracture decreased as the NDAD increased. The incidence rate of osteoporotic fracture also decreased with the increase in the number of daily non-thiazide antihypertensive drugs.

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Introduction

Hypertension and osteoporosis are among the most common chronic diseases, and the number of patients having both diseases

concomitantly is increasing as the population is aging [1]. According to Wade et al., the prevalence of osteoporosis increases with age and is higher in female than in male patients, with an overall incidence of 2–8% and 9–38%, respectively, in men and women of developed nations [2]. Furthermore, the prevalence of hypertension in individuals in their 60s is >60%, with over half of the patients undergoing lifelong treatment with antihypertensive medication [3]. Both osteoporosis and hypertension are known to be related to low calcium uptake, lack of vitamins D and K, and high consumption of sodium salts [4]. Specifically, hypercalciuria is a

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common change that can be observed in women with hypertension, and is related to a decrease in bone density, which is more common in women with osteoporosis and hypertension [5]. Among commonly used antihypertensive medications, thiazide diuretics (TDs) decrease the elimination of calcium by urination, thus reducing the risk of fracture [6].

Considering this interconnection of pathologies, it has been suggested that the treatment for hypertension may decrease the risk of osteoporosis, which led to numerous studies exploring the potential therapeutic effects of antihypertensive medications. However, only TDs were proven to increase bone density, while the relationship between other antihypertensive medications and bone density or osteoporotic fracture remains controversial [4]. Several studies have reported that taking antihypertensive medication increases the risk of falls or fracture [7–9], while others have indicated that the blood-pressure lowering effect indirectly increases bone density, which may decrease the risk of fracture [6,10–12]. Rejnmark et al. found that the use of beta-blockers, angiotensin-converting-enzyme inhibitors, and calcium-channel blockers can decrease the risk of fracture, and this effect increases with the dose of antihypertensive medication used. However, the report fell short on correcting for key factors such as blood pressure, body mass index (BMI), and lifestyle aspects such as smoking status [6]. Meanwhile, according to Callisaya, the risk of fall in seniors increases with the daily dose of antihypertensive medication prescribed [13]. Similarly, Tinetti et al. reported that, compared to individuals not undergoing antihypertensive treatment, hypertensive patients have a significantly higher risk of serious fall injury if receiving moderate-intensity (adjusted hazard ratio, aHR: 1.40; 95% confidence interval, 95%CI: 1.03–1.90) or high-intensity antihypertensive treatment (aHR: 1.28; 95%CI: 0.91–1.80), and this effect increases with the daily dose of antihypertensive medication prescribed [14]. However, Callisaya confirmed only the relationship between antihypertensive medication and fall injury, while Tinetti et al. considered all fall-related injuries (i.e. not just osteoporosis-induced), such as traumatic brain injury or joint dislocation.

Therefore, to clarify how the use of antihypertensive medication, which is common in senior citizens, affects the risk for osteoporotic fracture, we analyzed the influence of the number of daily antihypertensive drugs (NDAD) on the prevalence of osteoporotic fractures in a cohort of elderly individuals. We wanted to know whether higher daily total number of antihypertensive drugs is associated with reduced osteoporotic fractures in terms of daily clinical practice.

Methods

Study design

The present study utilized dataset from the National Health Insurance Service – Senior Cohort (NHIS-SC; 2002–2013). The NHIS-SC is a population-based cohort established by the National Health Insurance Service (NHIS) in South Korea. The NHIS-SC was built by randomly selecting a representative sample of 558,147 seniors, comprising about 10% of the total eligible Korean 60+ population (5,500,000 persons) in 2002, and followed for 11 years until 2013 unless participants' eligibility was disqualified due to death or emigration. Therefore, the subjects are aged 67 or more because the baseline year of this study is 2009.

The NHIS-SC contains information on insurance membership, income, history of use of medical services, health check-up results, and long-term care. NHIS provides medical check-ups every 2 years for all the elderly insurance-beneficiaries, and the data collected during such check-ups include diagnosis code (KCD-6), blood pressure levels, lifestyle behavior (smoking status, alcohol

consumption), past medical history, medical prescriptions (name of drug, dose, and duration of treatment), etc. [15].

We reviewed the records of 251,667 elderly insurance-beneficiaries diagnosed with hypertension in 2009 (from January 1st to December 31st), who were prescribed antihypertensive medication. The following exclusion criteria were applied: osteoporotic fracture recorded in 2008 ($n = 21,641$); did not participate in any national health check-up between January 1st 2009 and December 31st 2013 ($n = 92,339$); incomplete medical record for the study period, so that it was not possible to confirm the osteoporotic fracture ($n = 383$). Therefore, 137,304 participants were included in our analysis. This study was approved by the Kyung Hee University Hospital Research Ethics Committee organization's Institutional Review Board (KMC IRB 1607-05).

Exposure: Number of daily antihypertensive drugs

The following classes of antihypertensive drugs were considered, as suggested by the National Health Insurance Corporations: angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), beta blockers, calcium channel blockers (CCB), and diuretics. Patients were stratified into groups based on the number of daily drugs, which was obtained by dividing the total number of antihypertensive drugs by 365 days. Three groups were defined in terms of NDAD as “low” ($0 < NDAD \leq 0.5$), “moderate” ($0.5 < NDAD \leq 2$), and “high” ($2 < NDAD$). Similarly, three groups were defined in terms of the number of daily thiazide diuretics (NDTD), as “low” ($0 < NDTD \leq 0.5$), “moderate” ($0.5 < NDTD \leq 1$), and “high” ($1 < NDTD$). An additional descriptor was defined as the number of daily antihypertensive drugs that are not thiazide diuretics (NDADnotTD), and the patients were stratified in terms of NDADnotTD in a similar manner as that applied for NDAD. Complex prescriptions comprising two types of antihypertensive medicines were considered equivalent to 2 uses per one medicine.

Outcome: major osteoporotic fractures

While our study population included individuals undergoing antihypertensive treatment after being diagnosed with hypertension (diagnostic codes I10, I11, I12, I13, and I15) in 2009, the outcome measured in our study was the incidence of major osteoporotic fracture during the 4-year period from January 1st 2010 to December 31st 2013. Major osteoporotic fracture was identified in the patient records based on the diagnosis codes for fracture of the hip, vertebra, lower end of the radius, lower end of both the ulna and the radius, upper end of the humerus, and shaft of the humerus [3,16]. Pathologic and traumatic fractures were detected based on the diagnosis code, and subsequently excluded from the analysis.

Covariates

In our assessment of the relationship between use of antihypertensive medication and osteoporotic fracture, we corrected for factors that are expected to affect the risk for osteoporotic fracture (confounding variables). For this purpose, the 5-year records (from January 1st 2009 to December 31st 2013) were reviewed in order to confirm the patients' age, sex, underlying diseases (osteoporosis, diabetes mellitus, dementia, Parkinson's disease, and convulsive disorder), and history of medication (oral steroids, selective serotonin reuptake inhibitor, proton pump inhibitor, hormone replacement therapy, and anticoagulants). The database containing the results of the regular national health check-ups for the same period was also reviewed in order to confirm the patients' height, body weight, blood pressure

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