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Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers reduced dementia risk in patients with diabetes mellitus and hypertension

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ABSTRACT

Objective: The effects of angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) on dementia risk in patients with type 2 diabetes mellitus (DM) and hypertension remain unknown. We investigated the effects of ACEIs and ARBs on dementia risk in patients with type 2 DM and hypertension.
Methods: We conducted a cohort study by using the Taiwan National Health Insurance Research Database. We included 2377 patients receiving ACEIs and 1780 patients receiving ARBs in the ACEI and ARB cohorts, respectively. We included a comparable number of patients not receiving ACEIs and ARBs as controls in the non-ACEI and non-ARB cohorts through propensity score matching. The effect of ACEIs and ARBs on dementia risk was estimated through multivariate Cox proportional hazard regression after adjustment for several confounding factors.
Results: During the 12-year follow-up period, compared with the non-ACEI cohort, all-cause dementia risk decreased by 26% in the ACEI cohort [hazard ratio (HR) = 0.74, 95% confidence interval (CI) = 0.56–0.96]. The all-cause dementia risk was nearly 40% lower in the ARB cohort than in the non-ARB cohort (HR = 0.60, 95% CI = 0.37–0.97). These drugs prevented the occurrence of vascular dementia (VD), however, this effect was non-significant for Alzheimer's dementia (AD). Treatment duration- and dosage-related protection effects on dementia occurrence were observed.
Conclusions: ACEIs and ARBs may effectively prevent all-cause dementia, particularly VD, in patients with type 2 DM and hypertension. Moreover, compared with ACEIs, ARBs appear to be more advantageous in dementia prevention.

1. Introduction

Dementia is a disorder characterized by progressive decline in cognition involving one or more cognitive domains such as memory, learning, orientation, language, comprehension, and judgment [1]. Dementia is a major public health problem with substantial economic impact [2]. Moreover, dementia is often distressing for caregivers and families of patients with dementia and causes serious disabilities in dementia patients. According to the World Health Organization report [3], the number of patients with dementia worldwide was estimated to be 35.6 million in 2011 and is estimated to double to 65.7 million by 2030 and triple to 115.4 million by 2050. Although the key risk factor for most dementia types is advanced age, cardiovascular risk factors, such as diabetes mellitus (DM), hypertension, and hyperlipidemia, in midlife also increase the dementia risk [4,5].

The increasing prevalence of type 2 DM is also a major public health concern. Type 2 DM has been associated with several cardiovascular risk factors, including obesity, insulin resistance, dyslipidemia, hypertension, and proinflammatory states. Increasing epidemiological evidence

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suggests that both type 2 DM and hypertension independently increase dementia risk [6,7]. Therefore, patients with type 2 DM and hypertension may have a higher dementia risk, and early primary prevention may be the most effective treatment strategy for these patients. Some antihypertensive drugs have been reported to be beneficial in preventing dementia [8,9]. The renin–angiotensin system (RAS) is a hormone system that regulates the blood volume and systemic vascular resistance and mediates several physiological and pathological brain functions [10]. In a recent study, Zhuang et al. reported that RAS-targeting antihypertensive drugs [angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB)] may have remarkable efficacy in reducing the incidence of vascular dementia (VD) [11]. To date, few studies have reported about the efficacy of RAS-targeting antihypertensive drugs in the prevention of dementia in patients with type 2 DM and hypertension. Therefore, we conducted a large population-based cohort study to investigate the dementia risk in patients with type 2 DM and hypertension with and without ACEI or ARB treatment.

2. Methods

2.1. Database

The Taiwan National Health Insurance Research Database (NHIRD) is a large medical claims database and contains the data of beneficiaries enrolled in the Taiwan National Health Insurance (NHI) program. The Taiwan NHI program covers 99% of the residents of Taiwan (23 million).

The data source of this study was the Longitudinal Health Insurance Database 2000 (LHID2000). The LHID2000 was established by the National Health Research Institutes (NHRI) and contains 1996–2000 medical claims data, including data on registry for beneficiaries, ambulatory care, hospital care, prescription files, and other medical expenditure files, of 1 million randomly selected insurants. In the Taiwan NHI database, disease history is recorded using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. To protect the privacy of patients and care providers, the NHRI encrypts the information of each individual in the database. This study was approved by the Ethics Review Board of China Medical University (CMUH104-REC2-115).

2.2. Study population

To investigate the dementia risk in patients with type 2 DM with and without ACEI or ARB treatment, we designed a population-based cohort study. From the LHID2000, we identified patients aged ≥50 years diagnosed with type 2 DM (ICD-9-CM code 250) between January 1, 2000, and December 31, 2011, with a history of hypertension (ICD-9-CM codes 401–405) before their type 2 DM diagnosis. We classified these patients into four cohorts: ACEI, non-ACEI, ARB, and non-ARB. The patients with type 2 DM who received ACEI but not ARB for at least 180 days were included in the ACEI cohort. The patients with type 2 DM who did not receive both ACEI and ARB were matched in a 1:1 ratio with the ACEI cohort according to age, sex, type 2 DM diagnosis year, comorbidities, and medications through propensity score matching [12] and included in the non-ACEI cohort. The patients with type 2 DM who received ARB but not ACEI for at least 180 days were included in the ARB cohort. The patients with type 2 DM who did not receive both ACEI and ARB were matched in a 1:1 ratio with the ARB cohort according to age, sex, type 2 DM diagnosis year, comorbidities, and medications through propensity score matching and included in the non-ARB cohort. We excluded patients with a history of dementia diagnosis before the study period. All patients in the four cohorts were followed until withdrawal from the Taiwan NHI program, dementia diagnosis, or December 31, 2011.

Diseases associated with dementia were considered as comorbidities. The baseline comorbidities were chronic kidney disease (ICD-9-CM code 585), hyperlipidemia (ICD-9-CM code 272), chronic obstructive pulmonary disease (ICD-9-CM codes 491, 492, and 496), asthma (ICD-9-CM code 493), stroke (ICD-9-CM codes 430–435), head injury (ICD-9-CM codes 310.2, 800, 801, 803, 804, 850–854, and 959.01), and coronary artery disease (ICD-9-CM codes 410–414). The medications considered were antihypertensive drugs used before type 2 DM diagnosis and included α-blockers, β-blockers, potassium-sparing diuretics, thiazides, loop diuretics, and calcium channel blockers (CCBs).

2.3. Main outcome measures

The primary outcome of this study was the diagnosis of dementia. The diagnosis of dementia was identified using ICD-9-CM codes 290.0–290.4, 294.1, 294.2, and 331.0–331.1. We investigated two dementia subtypes, Alzheimer's dementia (AD) and VD. The diagnosis of AD was defined as a diagnosis of ICD-9-CM code 331.0 or a patient with dementia receiving a combination of acetylcholinesterase inhibitors (AChEIs) and memantine. In the NHI program, only patients with AD without any comorbidity affecting cognitive function are reimbursed for AChEIs and memantine. Reimbursement claims for AChEI and memantine prescriptions for patients with AD undergo a special review process to assess the patient's medical records, biochemistry data, and neuroimages. The diagnosis of VD was identified using the ICD-9-CM code 290.4. We calculated the lifetime cumulative dose of ACEI and ARB and standardized the dose of ACEI and ARB as defined daily dose (DDD) according to the Anatomical Therapeutic Chemical classification system.

2.4. Statistical analysis

Age was presented as mean and standard deviation, and the difference in age among the cohorts was evaluated using 2-sample t test (ACEI cohort vs. non-ACEI cohort and ARB cohort vs. non-ARB cohort). Sex, comorbidities, and medications were presented as number and percentage, and their difference among cohorts was evaluated using the chi-square test. Crude and adjusted Cox proportional hazard models were used to calculate the incidence density of dementia in all cohorts, estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the dementia risk, and compare the dementia risk between the ACEI and non-ACEI cohorts and that between the ARB and non-ARB cohorts. In addition, sensitivity analysis was performed to evaluate the competing risks of death. Death was defined as patient death after hospital discharge or withdrawal from the NHI program. The Fine and Gray model [13], which extends the standard Cox proportional hazard regression model, was used to estimate the dementia risk, after accounting for the competing risks of death. We used SAS, Version 9.4 (SAS Institute, Cary, NC, USA) to perform all statistical analyses, and 2-tailed $P < 0.05$ was considered significant.

3. Results

3.1. Demographic characteristics

Table 1 presents the demographic data, baseline characteristics, and comorbidities of the four cohorts. After propensity score matching, age, sex, comorbidities, and medications did not differ between the ACEI and non-ACEI cohorts as well between the ARB and non-ARB cohorts.

3.2. Cumulative incidence of dementia

The cumulative incidence of dementia (Fig. 1) was significantly lower in the ACEI and ARB cohorts than in the non-ACEI and non-ARB cohorts during the long-term follow-up period (log-rank test: all $P < 0.05$). In the ACEI and non-ACEI cohorts, 219 patients developed dementia (Table 2). The incidence of all-cause dementia was 11.3 and 8.18 per 1000 person-years in the non-ACEI and ACEI cohorts, respectively. Compared with the non-ACEI cohort, the HR of all-cause dementia risk in the ACEI cohort was 0.74 (95% CI = 0.56–0.96) after adjustment for age, sex, comorbidities, and medications. Moreover, compared with the non-ACEI cohort, the HR of the VD risk in the ACEI cohort was 0.42 (95% CI = 0.21–0.85); however, the AD risk did not significantly differ between the ACEI and non-ACEI cohorts (HR = 1.43, 95% CI = 0.67–3.04). Table 2 presents the dementia risk in the ARB and non-ARB cohorts. The all-cause dementia risk was nearly 40% lower in the ARB cohort than in the non-ARB cohort (HR = 0.60, 95% CI = 0.37–0.97). In addition, the VD risk was significantly lower in the ARB cohort than in the non-ARB cohort (HR = 0.41, 95% CI = 0.19–0.89); however, the AD risk did not significantly differ between the ARB and non-ARB cohorts (HR = 0.80, 95% CI = 0.29–2.17).

3.3. Effect of treatment duration and cumulative dose on dementia

Table 3 presents the dementia risk among patients receiving different drug treatments (cumulative treatment day and cumulative treatment dose). The dementia risk was significantly lower only in the patients of the ACEI cohort who received a high DDD of ACEI than in those of the non-ACEI cohort (patients receiving ACEI for >1100 days: HR = 0.72, $P < 0.05$; patients receiving >1500 DDD of ACEI: HR = 0.66, $P < 0.05$). Similarly, the dementia risk was lower in the patients of the ARB cohort who received a high ARB DDD than in those of the non-ARB cohort (patients receiving ARB for >1500 days: HR = 0.53, 95% CI = 0.35–0.81; patients receiving >1500 DDD of ARB: HR = 0.52, 95% CI = 0.34–0.79).