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Association between alpha blocker use and the risk of fractures in patients with chronic kidney disease: a cohort study

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Abstract

Background Alpha blockers (ABs) are frequently prescribed to patients with chronic kidney disease (CKD), which is often complicated by refractory hypertension (HT). Although there have been several reports on the association between AB use and the risk of fractures, their conclusions have not yet been drawn. Therefore, this study aimed to investigate the association between AB use and the risk of fractures in patients with CKD.

Method This population-based cohort study used patient data obtained between April 2008 and August 2021 from a large-scale Japanese medical claims database. Consecutive patients with CKD who were newly prescribed ABs or non-AB antihypertensive drugs were included; males and females were analysed separately. The AB group was then divided into AB for HT and voiding dysfunction (VD) groups according to the drug approval in Japan. The primary outcome was the first hospitalisation due to fracture, and the variables were evaluated with weighted Cox proportional hazard model using overlap weights.

Results A total of 65,012, 4,723, and 10,958 males constituted the non-AB, AB for HT (doxazosin), and AB for VD (naftopidil, silodosin, tamsulosin, or urapidil) groups, respectively. A total of 31,887, 2,409, and 965 females constituted the non-AB, AB for HT (doxazosin or guanabenz), and AB for VD (urapidil) groups, respectively. In males, hazard ratio (HR) for primary outcome was not increased in the non-AB and AB for VD groups compared with the AB for HT group (HR, 0.70; 95% confidence interval [CI], 0.38–1.28 and HR, 1.33; 95% CI, 0.67–2.66, in the non-AB and AB for VD groups, respectively). Whereas, in females, although HR for the primary outcome was not increased in the non-AB group (HR, 1.06; 95% CI, 0.56–1.99), it was significantly increased in the AB for VD group (HR, 2.28; 95% CI, 1.01–5.16) compared with the AB for HT group.

Conclusion AB use in patients with CKD did not increase the risk of fractures when used for the treatment of HT; however, it increased the risk of fractures when used for the treatment of VD in females. These results suggest that ABs should be used with caution in these patients.

Keywords Alpha blocker, Hypertension, Chronic kidney disease, Fracture, Voiding dysfunction

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Background

The prevalence of chronic kidney disease (CKD) is >10% in the general population, and CKD is associated with an increased risk of death and cardiovascular disease [1–4]. Hypertension (HT) affects >80% of patients with CKD [5] and is a strong risk factor for death, cardiovascular disease, and aggravation of renal function [6].

Alpha blockers (ABs) exert antihypertensive effect by competitive inhibition of the $\alpha_1$adrenoreceptors of vascular smooth muscles, leading to relaxing peripheral blood vessels and decreasing vascular resistance [7]. Several guidelines, including Japanese guidelines, recommend ABs as an add-on therapy for resistant or refractory HT owing to efficacy concerns about preventing cardiovascular disease and safety concerns about complications related to orthostatic hypotension [8–11]. However, the prevalence of resistant HT is reportedly 20–40% in hypertensive patients with CKD [12–14], suggesting that ABs are frequently prescribed to patients with CKD. Additionally, ABs have been used for voiding dysfunction (VD) caused by benign prostatic hyperplasia (BPH) [15–17], and some agents have shown efficacy in treating female VD [18, 19].

Some studies have reported an association between AB use and the risk of fractures [20–22], while others have not [23–27]. A recent report on patients with HT indicated that AB use did not increase the risk of fractures and reduced the risk of death and cardiovascular events compared with non-AB antihypertensive drugs, although this study excluded patients with BPH [26].

Therefore, our study aimed to examine the safety of ABs for the treatment of HT or VD in patients with CKD by investigating the risk of fractures associated with the use of ABs and non-AB antihypertensive drugs, using a Japanese medical claims database.

Methods

Study design

We conducted a non-interventional, population-based cohort study using the Japanese Medical Claims Database acquired from Medical Data Vision Co., Ltd. Data were obtained from 36,690,000 patients in 449 hospitals between April 2008 and August 2021. The database included individual records of prescriptions, procedures, surgeries, hospitalisations, and laboratory data. Database evaluation was approved by the Ethics Committee of the International Review Board of Nagoya University Hospital (approval number: 2021–0350). The requirement for informed consent was waived because the claims database was anonymised.

Study population

From the claims in the database, we identified patients with CKD codes, aged ≥ 20 years (n = 924, 238). We identified patients who were newly prescribed ABs or non-AB antihypertensive drugs. ABs were selected based on the Anatomical Therapeutic Chemical (ATC) classification (ATC codes: C02A2 and G04C2). Non-AB antihypertensive drugs included beta blockers (BBs); calcium channel blockers (CCBs); and renin–angiotensin–aldosterone system inhibitors (RAASis), including angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and angiotensin receptor neprilysin inhibitors. To accurately assess the effect of drugs on fractures, inclusion was limited to patients with no history of treatment for fractures, and those who were prescribed medications for osteoporosis (bisphosphonates, denosumab, romosozumab, or teriparatide) at baseline were excluded. Patients with a history of fractures were excluded because they were more likely to be treated for osteoporosis. Furthermore, we excluded patients with no data on smoking history or body mass index (BMI), which are important risk factors for fractures [28, 29]. In our data, BMI was manually entered, which may lead to data errors, and we excluded patients whose BMI is considered to be uncommon (BMI < 5 or > 75). In addition, we excluded patients who were prescribed other drugs for the treatment of BPH (phosphodiesterase-5 inhibitors, 5-alpha-reductase, or anti-androgen drugs) to eliminate their possible influence on fractures [30, 31].

Exposure

Because some ABs are approved only for BPH, the ABs prescribed for males and females differ substantially. Therefore, we evaluated males and females separately. Drugs extracted as ABs based on the ATC code included budralazine, bunazosin, doxazosin, guanabenz, hydralazine, prazosin, terazosin, urapidil, naftopidil, silodosin, and tamsulosin. To restrict the analysis to clinically important drugs, we excluded drugs prescribed to < 1% of all AB prescriptions in both males and females. In Japan, budralazine, bunazosin, doxazosin, guanabenz, and hydralazine are approved only for HT; prazosin and terazosin are approved for HT and BPH; urapidil is approved for HT, BPH, and VD due to neurogenic bladder; and naftopidil, silodosin, and tamsulosin are approved only for BPH. We classified drugs approved only for HT (budralazine, bunazosin, doxazosin, guanabenz, and hydralazine) as AB for HT and drugs approved for BPH or VD (prazosin, terazosin, urapidil, naftopidil, silodosin, and tamsulosin) as AB for VD.

Study exposure was defined as a new prescription of non-AB antihypertensive drugs and ABs for HT or VD

within the database period, with the date of prescription defined as baseline. Patients who were prescribed new non-AB antihypertensive drugs and ABs at the same time were included in the AB group and patients who were prescribed ABs for HT and VD at the same time were excluded. The follow-up period began at the initiation of the prescription of these drugs and lasted for 2 years. Follow-up was censored at the occurrence of an outcome event, discontinuation of the prescription, last medical visit, or death.

Outcome

Our primary outcome was the first hospitalisation due to femoral or vertebral fractures (ICD10 codes: S7200, S7201, S7210, S7211, S7220, S7221, S3200, S3201, S3270, S2200, S2201, S2210, and S2211). As secondary outcomes, we evaluated femoral and vertebral fractures alone.

Statistical analysis

Baseline characteristics were summarised as percentages for categorical variables and medians (25th and 75th percentiles) for continuous variables. The number of categories of antihypertensive drugs prescribed at baseline was evaluated.

For the primary outcome, we generated cumulative incidence curves and performed log-rank tests to compare the cumulative incidence. To reduce the differences in confounders between each group, we applied propensity score weighting using overlap weights [32]. Differences between variables in the weighted analysis were evaluated by calculating the maximum of pairwise absolute standardized differences, and values ≥ 0.1 were defined imbalanced. Moreover, we assessed weighted estimation of hazard ratios (HRs) and 95% confidence intervals (CI) using Cox proportional hazard model for primary and secondary outcomes. We used Bonferroni method for multiple comparisons. HRs were adjusted for the following covariations: age, BMI, renal replacement therapy (RRT), smoking history, comorbid conditions (diabetes, cardio-cerebrovascular disease, osteoporosis, arthritis including rheumatoid arthritis, cancer, dementia, and epilepsy), medications (loop diuretics, thiazide diuretics, oral active vitamin D_3, proton pomp inhibitors, glucocorticoids, warfarin, antidepressants, and antipsychotics). We used the AB for HT group as a reference and compared with the non-AB or AB for VD group. ICD10 codes of the diseases in the study are shown in Supplementary Table (see Additional file1). All data were statistically analysed using R software version 4.3.0 (R group for statistical computing) and EZR version 1.66 (Saitama Medical Center, Jichi Medical University, Saitama, Japan). Analysis using overlap weights was performed by PSweights package version 1.2.0 (Yale University, Connecticut, U.S.).

Results

Patient characteristics

Patient flow in this study is shown in Fig. 1. The baseline characteristics of the patients are summarised in Tables 1A and B. In both sexes, AB for HT group patients were slightly younger and AB for VD group patients were older than the non-AB group patients. There were more patients on RRT in the AB for HT group and fewer in the AB for VD group. In both sexes, the AB for VD group had lower percentages of HT and cardio-cerebrovascular diseases. Moreover, the AB for VD group had a higher percentage of cancer and dementia.

Fewer patients of both sexes were prescribed antihypertensive drugs in the AB for VD group. In the AB for HT group, patients who were not prescribed antihypertensive drugs (BB, CCB, or RAASi) were only approximately 5% (5.5% and 5.2% in males and females, respectively), and patients who were prescribed two or more categories of antihypertensive drugs were > 70% (71.9% and 71.5% in males and females, respectively); in the AB for VD group, more than half of the patients were not prescribed antihypertensive drugs (54.0% and 59.9% in males and females, respectively). Supplementary Figure (see Additional file 2) shows the number of categories of prescribed antihypertensive drugs (BB, CCB, or RAASi) at baseline for each group.

Outcome

Tables 2A and B show the number of first episodes of hospitalisation due to fractures and the occurrences of each fracture type, number of deaths, and the follow-up period.

The cumulative incidence curves for the primary outcomes are shown in Fig. 2. In both sexes, the log-rank test showed a significant difference between the three groups ($p = 0.0102$ and $p = 0.00257$ for males and females, respectively). Moreover, in multiple comparisons using the Bonferroni method, there was no significant difference between the non-AB and AB for HT groups ($p = 1$ and $p = 0.471$ in males and females, respectively). The AB for HT and AB for VD groups were not significantly different in males ($p = 0.16$) but were significantly different in females ($p = 0.0026$).

The HRs and 95% CIs using the weighted Cox proportional hazards model are shown in Tables 3A and B. In males, HRs for the primary outcome were 0.70 (95% CI, 0.38–1.28; $p = 0.242$) in the non-AB group and 1.33 (95% CI, 0.67–2.66; $p = 0.418$) in the AB for VD group compared with the AB for HT group, showing no significant increase. In females, HR for the primary outcome

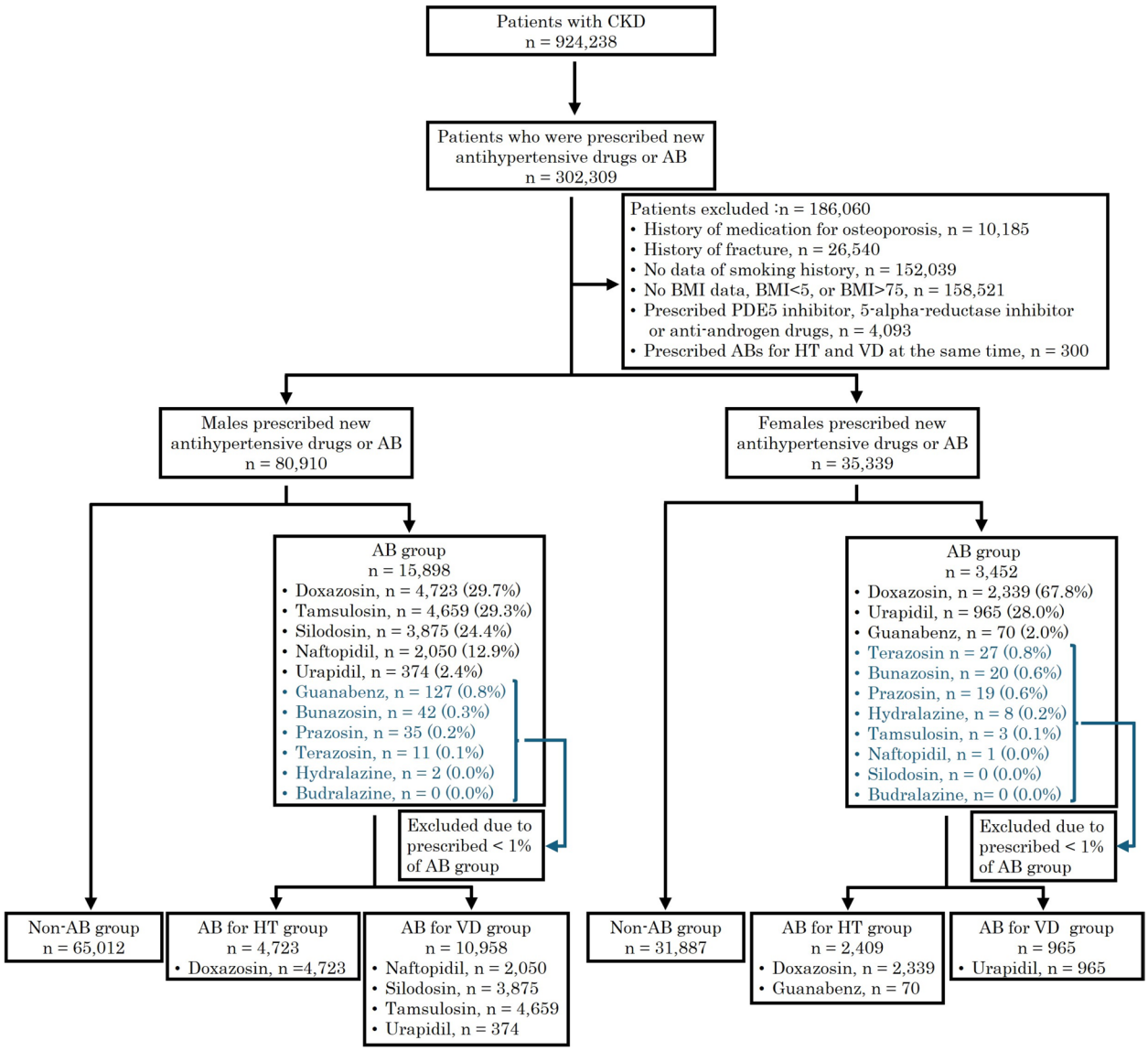

Fig. 1 Flow chart showing the inclusion and exclusion of patients. Abbreviations: AB, alpha blocker; BMI, body mass index; CKD, chronic kidney disease; HT, hypertension; PDE-5, phosphodiesterase-5; VD, voiding dysfunction

compared with the AB for HT group was 1.06 (95% CI, 0.56–1.99; $p = 0.854$) in the non-AB group, showing no significant increase as in males; however, HR was 2.28 (95% CI, 1.01–5.16; $p = 0.048$) in the AB for VD group, showing a significant increase. For each fracture, there was also no increase in the HRs between the AB for HT and non-AB or AB for VD group in males. Similarly, in females, there was no increase in HR for femoral or vertebral fractures in either the non-AB or AB for VD group compared with the AB for HT group.

Discussion

In this study, we evaluated the safety of ABs in patients with CKD, including those used for the treatment of HT, BPH, and VD, separately for males and females. We compared the non-AB group with the AB for HT group to assess the differences in fracture risks between the antihypertensive drugs; the AB for VD group was also compared with the AB for HT group to assess the differences in ABs for prescription purpose. In the unadjusted analysis, the incidence of fractures was not significantly

Table 1 Baseline characteristics

A. Males					
Characteristics	**Non-AB**	**AB for HT**	**AB for VD**	**Unweighted ASD**	**Weighted ASD**
Number of patients	65,012	4723	10,958	-	-
Age (years)	73 [64, 80]	71 [61, 78]	79 [73, 84]	0.758	0.085
BMI, kg/m^2	23.4 [21.1, 26.0]	24.3 [22.0, 27.2]	23.0 [20.7, 25.3]	0.411	0.059
RRT	5045 (7.8%)	587 (12.4%)	355 (3.2%)	0.348	0.027
Smoking history	32,406 (49.8%)	2413 (50.7%)	4913 (44.8%)	0.125	0.015
Comorbid conditions					
Hypertension	62,489 (96.1%)	4718 (99.9%)	8922 (81.4%)	-	-
Diabetes	39,927 (61.4%)	3182 (67.4%)	5854 (53.4%)	0.283	0.015
CVD	48,357 (74.4%)	3348 (70.9%)	7289 (66.5%)	0.173	0.033
Osteoporosis	7256 (11.2%)	538 (11.4%)	1478 (13.5%)	0.072	0.021
Arthritis	2687 (4.1%)	158 (3.3%)	550 (5.0%)	0.083	0.010
Cancer	16,701 (25.7%)	980 (20.7%)	4461 (40.7%)	0.447	0.010
Dementia	1405 (2.2%)	72 (1.5%)	413 (3.8%)	0.146	0.011
Epilepsy	1985 (3.1%)	164 (3.5%)	427 (3.9%)	0.046	0.017
Medications					
Alpha-blocker					
Doxazosin	-	4723 (100.0%)	-	-	-
Naftopidil	-	-	2050 (18.7%)	-	-
Silodosin	-	-	3875 (35.4%)	-	-
Tamsulosin	-	-	4659 (42.5%)	-	-
Urapidil	-	-	374 (3.4%)	-	-
RAAS inhibitor	37,997 (58.4%)	3164 (67.0%)	3008 (27.5%)	-	-
Calcium channel blocker	38,647 (59.4%)	4066 (86.1%)	3139 (28.6%)	-	-
Beta blocker	28,476 (43.8%)	1719 (36.4%)	2082 (19.0%)	-	-
Loop diuretic	24,806 (38.2%)	2154 (45.6%)	3069 (28.0%)	0.371	0.045
Thiazide diuretic	3201 (4.9%)	581 (12.3%)	386 (3.5%)	0.351	0.026
Oral active vitamin D_3	4297 (6.6%)	494 (10.5%)	532 (4.9%)	0.221	0.028
PPI	31,343 (48.2%)	2081 (44.1%)	4213 (38.4%)	0.198	0.064
Glucocorticoid	4582 (7.0%)	231 (4.9%)	845 (7.7%)	0.111	0.033
Warfarin	7568 (11.6%)	328 (6.9%)	861 (7.9%)	0.166	0.026
Antidepressant	1095 (1.7%)	64 (1.4%)	245 (2.2%)	0.068	0.026
Antipsychotics	856 (1.3%)	50 (1.1%)	197 (1.8%)	0.065	0.025
B. Females					
Characteristics	**Non-AB**	**AB for HT**	**AB for VD**	**Unweighted ASD**	**Weighted ASD**
Number of patients	31,887	2409	965	-	-
Age (years)	78 [68, 84]	76 [66, 83]	80 [72, 86]	0.339	0.018
BMI, kg/m^2	22.7 [20.0, 25.9]	24.0 [21.2, 27.4]	22.6 [19.6, 25.7]	0.341	0.044
RRT	2344 (7.4%)	243 (10.1%)	21 (2.2%)	0.324	0.015
Smoking history	3757 (11.8%)	317 (13.2%)	99 (10.3%)	0.085	0.011
Comorbid conditions					
Hypertension	30,742 (96.4%)	2405 (99.8%)	799 (82.8%)	-	-
Diabetes	17,279 (54.2%)	1524 (63.2%)	512 (53.1%)	0.200	0.030
CVD	22,938 (71.9%)	1765 (73.3%)	611 (63.3%)	0.222	0.005
Osteoporosis	7527 (23.6%)	494 (20.5%)	269 (27.9%)	0.166	0.045
Arthritis	2483 (7.8%)	155 (6.4%)	88 (9.1%)	0.094	0.013
Cancer	6317 (19.8%)	401 (16.6%)	249 (25.8%)	0.227	0.010
Dementia	1205 (3.8%)	88 (3.7%)	74 (7.7%)	0.184	0.013
Epilepsy	968 (3.0%)	69 (2.9%)	56 (5.8%)	0.151	0.003

Table 1 (continued)

Medications					
Alpha blocker					
Doxazosin	-	2339 (97.1%)	-	-	-
Guanabenz	-	70 (2.9%)	-	-	-
Urapidil	-	-	965 (100.0%)	-	-
RAAS inhibitor	18,189 (57.0%)	1577 (65.5%)	218 (22.6%)	-	-
Calcium channel blocker	19,925 (62.5%)	2099 (87.1%)	254 (26.3%)	-	-
Beta blocker	12,384 (38.8%)	883 (36.6%)	144 (14.9%)	-	-
Loop diuretic	14,152 (44.4%)	1323 (54.9%)	286 (29.6%)	0.520	0.016
Thiazide diuretic	1829 (5.7%)	344 (14.3%)	45 (4.7%)	0.353	0.027
Oral vitamin D	3750 (11.8%)	316 (13.1%)	83 (8.6%)	0.141	0.007
PPI	15,825 (49.6%)	1089 (45.2%)	368 (38.1%)	0.237	0.073
Glucocorticoid	3136 (9.8%)	190 (7.9%)	79 (8.2%)	0.072	0.032
Warfarin	3781 (11.9%)	171 (7.1%)	73 (7.6%)	0.169	0.035
Antidepressant	908 (2.8%)	49 (2.0%)	44 (4.6%)	0.138	0.009
Antipsychotics	509 (1.6%)	27 (1.1%)	33 (3.4%)	0.161	0.016

Abbreviations AB Alpha blocker, *ASD* Absolute standardized difference, *BMI* Body mass index, *CVD* Cardio-cerebrovascular disease, *HT* Hypertension, *PPI* Proton pump inhibitor, *RAAS* Renin–angiotensin–aldosterone system, *RRT* Renal replacement therapy, *VD* Voiding dysfunction

Table 2 Number of primary and secondary outcome events and the follow-up period

A. Males

	All	Non-AB	AB for HT	AB for VD
Primary outcome	298 (0.4%)	232 (0.4%)	14 (0.3%)	52 (0.5%)
Femoral fracture	186 (0.2%)	143 (0.2%)	11 (0.2%)	32 (0.3%)
Vertebral fracture	112 (0.1%)	89 (0.1%)	3 (0.1%)	20 (0.2%)
Number of Deaths	3377 (4.2%)	2663 (4.1%)	121 (2.6%)	593 (5.4%)
Follow-up period (days)	154 [49, 441]	161 [49, 464]	154 [53, 392]	114 [39, 347]

B. Females

	All	Non-AB	AB for HT	AB for VD
Primary outcome	382 (1.1%)	347 (1.1%)	17 (0.7%)	18 (1.9%)
Femoral fracture	252 (0.7%)	229 (0.7%)	13 (0.5%)	10 (1.0%)
Vertebral fracture	130 (0.4%)	118 (0.4%)	4 (0.2%)	8 (0.8%)
Death	1385 (3.9%)	1249 (3.9%)	96 (4.0%)	40 (4.1%)
Follow-up period (days)	147 [48, 429]	151 [49, 441]	140 [49, 364]	98 [37, 329]

Abbreviations AB Alpha blocker; *HT* Hypertension, *VD* Voiding dysfunction

different in the non-AB and AB for VD groups compared with the AB for HT group in males. In females, the incidence of fractures was not different in the non-AB group compared with the AB for HT group; however, it was significantly increased in the AB for VD group compared with the AB for HT group. The HRs estimated by weighted COX proportional hazard model showed similar results in both sexes. Several studies have evaluated the association between AB use and the risk of fractures. Some case–control studies have indicated an increased risk of fractures [20], while others have not [23, 24]. Welk et al. analysed the use of prostate-specific ABs (tamsulosin, alfuzosin, or silodosin) in males aged > 66 years using propensity score matching and reported an increased risk of fractures. [21] In addition, Seo et al. investigated the use of ABs (alfuzosin, doxazosin, prazosin, terazosin, or tamsulosin) for the treatment of VD in females aged ≥ 50 years with a self-controlled case series design and found an increased risk of fractures. [22] Hiremath et al. compared the use of ABs (doxazosin, prazosin, or tamsulosin) with other hypertensive drugs in female patients with hypertension, aged ≥ 66 years, using propensity score matching and showed an increase in the composite of hypotension, syncope, falls, and fractures, but not fractures alone. [25] Furthermore, Hundemer et al. also compared the use of ABs (doxazosin, prazosin,

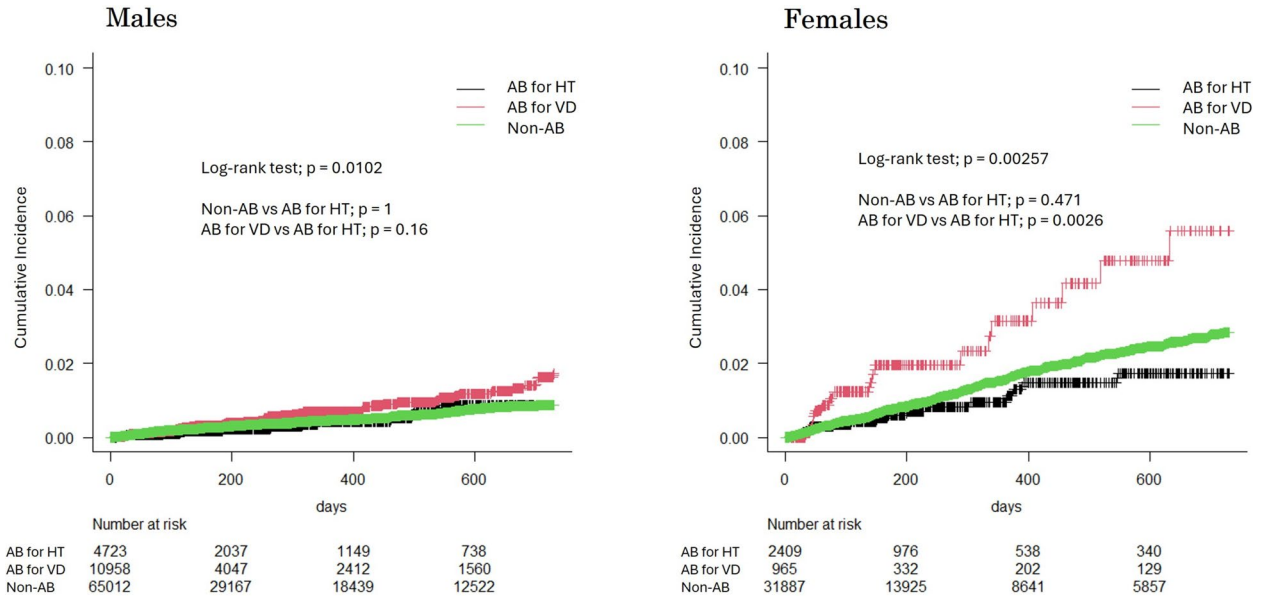

Fig. 2 Cumulative incidence curve of the primary outcome. Abbreviations: AB, alpha blocker; HT, hypertension; VD, voiding dysfunction

Table 3 Hazard ratios for outcomes estimated by weighted Cox proportional hazard model

A. Males		
Outcome name		**Hazard ratio (95% CI)**
First hospitalization due to all fractures	AB for HT	reference
	non-AB	0.70 (0.38–1.28); $p=0.242$
	AB for VD	1.33 (0.67–2.66); $p=0.418$
First hospitalization due to femur fractures	AB for HT	reference
	non-AB	0.65 (0.31–1.34); $p=0.242$
	AB for VD	1.43 (0.62–3.29); $p=0.398$
First hospitalization due to vertebral fractures	AB for HT	reference
	non-AB	0.80 (0.27–2.43); $p=0.700$
	AB for VD	1.13 (0.33–3.88): $p=0.842$
B. Females		
Outcome name		**Hazard ratio (95% CI)**
First hospitalization due to all fractures	AB for HT	reference
	non-AB	1.06 (0.56–1.99); $p=0.854$
	AB for VD	2.28 (1.01–5.16); $p=0.048$
First hospitalization due to femur fractures	AB for HT	reference
	non-AB	1.14 (0.52–2.51); $p=0.746$
	AB for VD	1.59 (0.57–4.42); $p=0.376$
First hospitalization due to vertebral fractures	AB for HT	reference
	non-AB	0.94 (0.32–2.74); $p=0.911$
	AB for VD	3.50 (0.93–13.17); $p=0.063$

Abbreviations AB Alpha blocker, *CI* Confidence interval, *HT* Hypertension, *VD* Voiding dysfunction

or tamsulosin) with other hypertensive drugs in patients with hypertension, aged ≥ 66 years, with propensity score matching and demonstrated no increased risk of fractures. [26] In addition, Iseri et al. examined the use of ABs (doxazosin, bunazosin, prazosin, or urapidil) and other antihypertensive drugs in Japanese patients undergoing haemodialysis and reported no increased risk of fractures [27].

Our results are consistent with these studies in that there was no increased risk of fractures in the non-AB antihypertensive drug group compared with the AB for HT group. These results suggest that ABs do not increase the risk of fractures when used for the treatment of HT but increase the risk of fractures when used for the treatment of VD in females. This may be because ABs are recommended as an add-on therapy for refractory hypertension [8–11], and it is speculated that complications due to hypotension are less likely to occur. In fact, in our study, >70% of patients in the AB for HT group were already prescribed two or more categories of antihypertensive drugs. Moreover, serious complications, such as fractures due to excessive hypotension may be prevented because blood pressure is checked while prescribing ABs as antihypertensive drugs. In contrast, patients in the AB for VD group had relatively fewer incidences of HT and cardio-cerebrovascular complications, and >50% of the patients were not prescribed antihypertensive drugs, which may have led to an increase in complications due to hypotension. The reason for the lack of an increased risk of fractures in the AB for VD group in males in our study is partly because most male patients in the AB for VD group in our study were prescribed prostate-specific ABs (naftopidil, silodosin, or tamsulosin). It has been suggested that prostate-specific ABs that are highly specific to α_{1A} or α_{1D} receptor may reduce the risk of cardiovascular complications compared with non-selective ABs because α_{1B}receptors are abundant in vascular smooth muscles [17, 33, 34].

Nevertheless, our study is quite important in that it is the first to examine the safety of ABs, taking into the purpose of use, in large number of patients with CKD who are often complicated by refractory HT. In a recent meta-analysis of ABs, the risk of fractures was analysed by integrating the reports of Welk et al., [21] Hiremath et al., [25] and Hundemer et al., [26] which demonstrated no increased risk of fractures [35]. However, this is difficult to interpret considering that the purpose of using ABs may be to treat HT or VD due to BPH. The results of our study suggest that while the risk of fractures does not seem to increase when ABs are used for the treatment of HT, we should always be careful about complications due to hypotension, especially fractures, when ABs are used for the treatment of VD.

The results of our study should be interpreted with consideration of several limitations. First, the study design was observational, and although it was possible to indicate an association between AB use and outcomes, we were unable to prove causation. Second, the study relies on data from a single country's health care system; therefore, it may be difficult to generalize our findings. Third, our data lacked information related to the risk of fractures such as amount of alcohol intake, frailty, admission to older adult care facilities, and actual blood pressure. Fourth, laboratory data were only available for a limited number of patients, making it impossible to determine the CKD stage. Laboratory data related to fractures, such as serum calcium and phosphate levels, were also unavailable. Fifth, our primary outcome was hospitalization for fractures, and we may have failed to capture fractures that did not result in hospitalization. Finally, our exclusion criteria may have introduced selection bias and affected the generalization of the results.

Conclusions

AB use in patients with CKD did not increase the risk of fracture when used for the treatment of HT; however, it increased the risk of fracture when used for the treatment of VD in females. ABs should be used with caution to prevent falls and fractures in these patients.

Abbreviations

AB	Alpha blocker
ATC	Anatomical therapeutic chemical
BB	Beta blocker
BMI	Body mass index
BPH	Benign prostatic hyperplasia
CCB	Calcium channel blocker
CI	Confidence interval
CKD	Chronic kidney disease
HR	Hazard ratio
HT	Hypertension
RAASi	Renin-angiotensin-aldosterone system inhibitor
RRT	Renal replacement therapy
VD	Voiding dysfunction

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12882-024-03892-5.

Additional file 1: Supplementary Table. ICD10 codes of diseases specified in the study. Description of data: List of ICD10 codes of diseases specified in the study.

Additional file 2: Supplementary Figure. Number of categories of prescribed antihypertensive drugs (BB, CCB, or RAASi) in each group at baseline. Description of data: In the AB for HT group, patients who were not prescribed antihypertensive drugs (BB, CCB, or RAASi) were only approximately 5%, and patients who were prescribed two or more categories of antihypertensive drugs were > 70%; in the AB for VD group, more than half of the patients were not prescribed antihypertensive drugs.

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Authors' Contributions

KS, CO, AT, KF, and SM developed the study concept and design. KS, CO, and AT drafted the manuscript. AT conducted the data acquisition. KS, CO, AT, KF, and SM performed the statistical analyses and interpreted the results. AT, KF, and SM supervised the study. All authors critically reviewed and revised the manuscript, and approved the final version for submission. All authors agreed to accept the reasonableness of all aspects of the study.

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Data availability
The data analysed in this study were obtained from Medical Data Vision Co., Ltd., with an agreement not to disclose them to outside parties. Please contact the corresponding author if you have any reasonable excuses or would like to review the data.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the Ethics Committee of the International Review Board of Nagoya University Hospital (approval number: 2021–0350). The requirement for informed consent was waived because the claims database was anonymised. Clinical trial number: not applicable.

Consent for publication
Need for consent for publication was waived because the claims database was anonymised.

Competing interests
The authors declare no competing interests.

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