# Enteropathy and intestinal malabsorption in patients treated with antihypertensive drugs. *A retrospective cohort study*

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## ABSTRACT

**Objectives:** To investigate differences in the incidence of enteropathy or intestinal malabsorption in patients taking angiotensin II receptor blockers (ARBs), angiotensin-converting enzyme inhibitor (ACEI), calcium channel blocker (CCB), and beta blockers (BBs) at a single center in Korea.

**Methods:** In this retrospective study, we utilized data from the Yangsan electronic medical records to identify 129,169 patients. These individuals were prescribed olmesartan, other ARBs, ACEI, CCB, and BBs between November 2008 and February 2021.

**Results:** Of the 44,775 patients, 51 (0.11%) were observed to have enteropathy or intestinal malabsorption. Compared with the ACEI group, the adjusted odds ratios (ORs) for enteropathy and intestinal malabsorption were OR=1.313 (95% confidence interval [CI]: [0.188-6.798], $p$=0.893) for olmesartan, OR=0.915 (95% CI: [0.525-1.595], $p$=0.754) for the other ARBs, OR=0.928 (95% CI: [0.200-4.307]; $p$=0.924) for the CCB, and OR=0.663 (95% CI: [0.151-2.906]; $p$=0.586) for the BBs group. These findings were adjusted for factors such as age, gender, duration of antihypertensive medication, and comorbidities.

**Conclusion:** In a retrospective cohort study of patients on antihypertensive medications, no significant difference was found in the incidence of enteropathy or intestinal malabsorption when ACEI was compared to olmesartan, other ARBs, CCB, and BBs.

**Keywords:** antihypertensive drugs, diarrhea, enteropathy, intestinal malabsorption

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Olmesartan is an angiotensin II receptor blocker (ARB), acting as a competitive antagonist of angiotensin II receptors, which reduces blood pressure.[1] Rubio-Tapia et al[2] reported the unexpected occurrence of chronic diarrhea and weight loss in patients taking olmesartan (olmesartan-related sprue-like enteropathy [SLE] and seronegative villous atrophy). Furthermore, enteropathies such as severe diarrhea and resembling SLE have been noted in patients taking angiotensin-converting enzyme inhibitors (ACEIs), other ARBs, calcium channel blockers (CCBs), and even beta-blockers (BBs).[3-7]

In clinical practice, when a definitive cause for villous atrophy is elusive and with limited case reports on celiac disease, clinicians tend to lean towards a generic and nonspecific diagnosis code.[8] Comparative studies have analyzed the differences in the frequency of enteropathy or intestinal malabsorption using primarily diagnosis codes, but the results have been inconsistent.[4,8,9] Thus, we investigated the incidence of enteropathy or intestinal malabsorption among hypertensive patients taking ARBs, ACEI, CCB, and BBs.

**Methods.** This retrospective cohort study was carried out from November 2021 to May 2022. The Yangsan electrical medical records system, YES 2.0, at the Pusan National University Yangsan Hospital (PNUYH) facilitated the analysis of prescription data through the Clinical Data Warehouse (CDW). This database encompasses health insurance electronic records of medical and prescription drug claims, detailing demographics, clinical diagnoses, hospital discharge diagnoses, and provided medical treatments. Prescription data included the brand name, quantity, and duration. For our study, we leveraged sociodemographic characteristics such as age, gender, comorbidities, hospital discharge diagnoses, and prescription details of antihypertensive medications. We extracted retrospective data on patients prescribed olmesartan, other ARBs, ACEI, CCB, or BBs, starting from the initial day of medical care for each patient (N=129,169). This extraction was carried out using the PNUYH YES 2.0 CDW database, spanning from November 2008 to February 2021. Current exposure to antihypertensive drugs was defined as prescription duration plus an additional 30-day grace period. Diagnoses within the database employed the Korean

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Classification of Disease 6 (KCD-6) system, which aligns with the International Classification of Diseases, 10th Revision (ICD-10). This study was approved by the institutional review board of PNUYH (IRB No.: 05-2021-284). The procedures were in accordance with the institutional review board at PNUYH and the principles of the Helsinki Declaration.

Patients diagnosed with enteropathy or intestinal malabsorption were identified with at least one major primary diagnostic code or the first 4 minor diagnostic codes, based on physician-assigned diagnostic codes from inpatient and outpatient diagnosis files. Enteropathy or intestinal malabsorption was classified by the following KCD-6 codes: functional diarrhea (K591), chronic diarrhea (K529), allergic and dietetics gastroenteritis and colitis (K522), indeterminate colitis (K523), and intestinal malabsorption (K90x). To prevent left censoring, we excluded patients who initiated or were on antihypertensive drugs between November 2008 and October 2009 (n=8,340). We also excluded patients younger than 18 years (n=3,286). To eliminate overlapping exposure to different antihypertensive drugs, we excluded cases of simultaneous prescription of other antihypertensive drugs (n=55,327) and prescriptions combining multiple antihypertensive drugs (n=17,315). Additionally, patients diagnosed with enteropathy or intestinal malabsorption before starting antihypertensive drugs (n=44), or within 30 days of intake (n=82), were excluded from the analysis. Finally, data from 44,775 patients were included in our study. We categorized the study data into 5 groups: olmesartan, other ARBs, ACEI, CCB, and BBs.

***Statistical analysis.*** All data were represented as frequency (with percentage), mean with standard deviation (SD), or median with quartile 1, quartile 3 (Q1, Q3). Continuous variables were analyzed using one-way analysis of variance (ANOVA) and Duncan's post hoc test or Kruskall-Wallis H test and Duncan's post hoc test, while categorical variables were analyzed using the Chi-square test and Bonferrini's post hoc test or Fisher's exact test. A Poisson regression model was used to assess the incidence rate of antihypertensive drug-related enteropathy or intestinal malabsorption, adjusting for potential confounders. These included age, gender, duration of antihypertensive medication, and specific comorbidities identified from previous studies: immune-mediated diseases, heart failure, dementia, diabetes mellitus, cancer, chronic kidney disease (CKD), and organ transplantation.[8,10] All statistical analyses were carried out using the Statistical Package for the Social Sciences, version 22.0 (IBM Corp., Armonk, NY, USA), with significance set at a $p$-value of <0.05.

**Results.** The most commonly prescribed antihypertensive drugs were ARBs (48.7%), followed by BBs (33.2%), CCB (15.2%), and ACEI (2.9%) (Table 1). Among patients taking ARBs, the majority were on candesartan (30.5%), followed by losartan (15.1%), fimasartan (13.8%), valsartan (12.9%), irbesartan (9.3%), telmisartan (9.3%), and olmesartan (9.1%) (Table 2). The BBs group was the youngest (mean age 54.3 years), while the CCB group was the oldest (64.8 years). The proportion of males was highest in the ACEI group and lowest in the BBs groups. The total prescription days were longer for the ARB (77 days) and ACEI (67 days) groups compared to the CCB (22 days) and BB (23 days) groups. Concerning comorbidities, heart failure was notably prevalent in the ACEI group; diabetes was frequently observed in both the ARB and ACEI groups; cancer was prevalent in the CCB group, and CKD was commonly seen in the ARB group (Table 1). Among comparable antihypertensive drugs, the propranolol group was the youngest, while the amlodipine group was the oldest. The candesartan, fimasartan, and ramipril groups had the highest proportion of men, with the lowest proportion observed in the propranolol group. The total prescription days were the longest for the candesartan, fimasartan, and irbesartan groups, while the shortest for the propranolol group. Concerning comorbidities, heart failure was notably prevalent in the ramipril group, whereas diabetes, cancer, and CKD were especially infrequent in the propranolol group (Table 2).

No statistically significant difference was observed between the olmesartan and other antihypertensive drug groups concerning diagnoses of enteropathy or intestinal malabsorption (Table 2). For patients treated for less than one year, the incidences of enteropathy or intestinal malabsorption were 1.91 for the olmesartan group, 0.93 for the ARBs group, 0.00 for the ACEI group, 0.72 for the CCB group, and 0.49 for the BBs group per 1,000 persons. For those treated for more than one year, the incidence rates were 0.00 for the olmesartan group, 1.56 for the ARBs group, 5.32 for the ACEI group, 4.13 for the CCB group, and 3.46 for the BBs group per 1,000 persons.

There were no significant associations in the crude and adjusted odds ratios (ORs) for enteropathy or intestinal malabsorption when comparing ACEI with other antihypertensive drugs. For example, compared to the ACEI group, the crude and adjusted ORs for enteropathy and intestinal malabsorption in various medication groups were as follows: for olmesartan, the ORs were 0.975 (95% CI: [0.162-5.836], $p$=0.978) and 1.313 (95% CI: [0.188-6.798], $p$=0.893); for other

**Table 1 -** Baseline characteristics and comorbidities according to antihypertensive drug.

| Total | Age (years) | Male, n (%) | Prescription days, median (Q1, Q3) | Comorbidities, n (%) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Auto immune | Heart failure | Dementia | Diabetes | Cancer | CKD |
| ***ARBs*** (n=21,820) | 63.1 ± 13.6[a] | 12,465 (57.1) | 77 (14, 497)[a] | 168 (0.8)[a] | 1,542 (7.8) | 727 (3.3)[a] | 5,271 (24.2)[a] | 1,469 (6.7)[a] | 2,657 (12.2) |
| Olmesartan (n=1,995) | 63.6 ± 13.3[a,b] | 1,122 (56.2)[b,c,d] | 35 (7, 271)[d] | 10 (0.5)[a,b] | 118 (5.9)[a,b] | 70 (3.5)[a,b,c,d] | 375 (18.8)[b,c] | 174 (8.7)[g] | 207 (10.4)[d,e,f] |
| Candesartan (n=6,650) | 63.2 ± 13.4[a,b] | 4,036 (60.7)[a] | 94 (14, 713)[b] | 32 (0.5)[b] | 83 (12.5)[c] | 199 (3.0)[a,b,c,d] | 1,723 (25.9)[a] | 357 (5.4)[e,f,h] | 797 (12.0)[f] |
| Fimasartan (n=3,005) | 63.7 ± 12.8[a,b] | 1,803 (60.0)[a,d] | 82 (15, 403)[a,b] | 16 (0.5)[a,b] | 86 (2.9)[d] | 128 (4.3)[c,d] | 570 (19.0)[b,c] | 127 (4.2)[h] | 153 (5.1)[c] |
| Irbesartan (n=2,021) | 63.4 ± 12.7[a,b] | 1,062 (52.5)[b,c] | 99 (21, 573)[b] | 10 (0.5)[a,b] | 72 (3.6)[d] | 88 (4.4)[b,d] | 575 (28.5)[a] | 117 (5.8)[c,d,f,h] | 169 (8.4)[b,d] |
| Losartan (n=3,300) | 62.6 ± 15.6[a,b] | 1,750 (53.0)[b,c] | 56 (9, 405)[a,c] | 71 (2.2) | 145 (4.4)[b,d] | 106 (3.2)[a,b,c,d] | 662 (20.1)[c] | 293 (8.9)[b,g] | 551 (16.7)[g,h] |
| Telmisartan (n=2,030) | 61.8 ± 13.4[a] | 1,118 (55.1)[b,c] | 49 (8, 407)[a,c] | 16 (0.8)[a,b] | 73 (3.6)[d] | 45 (2.2)[a,e] | 544 (26.8)[a] | 170 (8.4)[b,d,g] | 266 (13.1)[e,f,h] |
| Valsartan (n=2,819) | 63.4 ± 13.7[a,b] | 1,574 (55.8)[b,c,d] | 54 (10, 357)[a,c] | 23 (0.8)[a,b] | 332 (11.8)[c] | 91 (3.2)[a,b,c,d] | 822 (29.2)[a] | 231 (8.2)[b,d,g] | 514 (18.2)[g] |
| ***ACEI*** (n = 1,297) | 62.7 ± 14.5[a] | 843 (65.0) | 67 (9, 470)[a] | 8 (0.6)[a] | 289 (22.3) | 34 (2.6)[a,b] | 325 (25.1)[a] | 95 (7.3)[a] | 98 (7.6) |
| Ramipril (n = 1,297) | 62.7 ± 14.5[a] | 843 (65.0)[a] | 67 (9, 470)[a] | 8 (0.6)[a,b] | 289 (22.3) | 34 (2.6)[a,b,c,d] | 325 (25.1)[a] | 95 (7.3)[a,b,c,d,e,f,g] | 98 (7.6)[a,b,c,d] |
| ***CCB*** (n=6,769) | 64.8 ± 13.2 | 3,523 (52.0) | 22 (3, 175) | 35 (0.5)[a] | 79 (1.2) | 219 (3.2)[a] | 855 (12.6) | 699 (10.3) | 381 (5.6) |
| Amlodipine (n=6,769) | 64.8 ± 13.2 | 3,523 (52.0)[c] | 22 (3, 175) | 35 (0.5)[a,b] | 79 (1.2) | 219 (3.2)[a,b,c,d] | 855 (12.6) | 699 (10.3)[b,g] | 381 (5.6)[a,c] |
| ***BBs*** (n=4,889) | 54.3 ± 16.1 | 7,452 (50.1) | 23 (1, 149) | 115 (0.8)[a] | 359 (2.4) | 252 (1.7)[b] | 1,488 (10.0) | 541 (3.6) | 350 (2.4) |
| Bisoprolol (n=4,284) | 62.9 ± 14.4[a,b] | 2,424 (56.6)[b,d] | 31 (8, 306)[d] | 18 (0.4)[b] | 308 (7.2)[a] | 92 (2.1)[a] | 691 (16.1)[b] | 249 (5.8)[a,c,e,f,h] | 228 (5.3)[a,c] |
| Propranolol (n=10,605) | 50.8 ± 15.4 | 5,028 (47.4) | 15 (1, 103) | 97 (0.9)[a] | 51 (0.5) | 160 (1.5)[c] | 797 (7.5) | 292 (2.8) | 122 (1.2) |
| Total (N= 44,775) | 60.4 ± 15.1 | 24,283 (54.2) | 35 (7, 312) | 336 (0.8) | 2,387 (5.3) | 1,232 (2.8) | 7,939 (17.7) | 2,804 (6.3) | 3,486 (7.8) |

Values are mean ± SD (age), median (Q1, Q3) (prescription days), or number (%). The analysis was conducted separately for antihypertensive drug classes and individual antihypertensive drugs. The same superscript lowercase letters indicate no statistical significance between the groups being compared: ANOVA and Duncan's post hoc test or Kruskall-Wallis H test and Duncan's post hoc test for continuous variables and Chi-square test and Bonferrini's post hoc test for categorical variables. ACEI: angiotensin-converting enzyme inhibitor, ARBs: angiotensin receptor blockers, CCB: calcium channel blocker, BBs: beta-blockers, CKD: chronic kidney disease

ARBs, the ORs were 0.743 (95% CI: [0.176-3.137], *p*=0.686) and 0.915 (95% CI: [0.525-1.595], *p*=0.754); for CCBs, the ORs were 0.862 (95% CI: [0.186-3.991], *p*=0.850) and 0.928 (95% CI: [0.200-4.307], *p*=0.924); and for BBs, the ORs were 0.653 (95% CI: [0.149-2.857], *p*=0.572) and 0.663 (95% CI: [0.151-2.906], *p*=0.586). This trend persisted for other drugs, with no significant differences noted (Table 3).

**Discussion.** In our study, we observed no differences in the incidence of enteropathy or intestinal malabsorption among patients on ARBs, CCB, and BBs compared to those on ACEI. This result remained consistent even after adjusting for factors such as age, gender, duration of prescription, and comorbidities.

Rubio-Tapia et al[2] reported SLE symptoms, such as chronic diarrhea and weight loss, in 22 patients taking olmesartan. In a previous case report, villous atrophy of the duodenal region was confirmed by histologic examination during gastroscopy; however, the IgA serology test was negative. Furthermore, enteropathy symptoms, such as severe diarrhea and conditions resembling SLE have also been reported in patients taking other ARBs, ACEIs, CCBs, and BBs.[3-7] However, biopsy confirmation was absent in the majority of these cases. Given the challenges of carrying out histology and serology in large-scale comparative studies, we relied on diagnostic codes pertinent to enteropathy and intestinal malabsorption.

**Table 2 -** Incidence of enteropathy and intestinal malabsorption according to antihypertension drug class and antihypertension drugs.

| Antihypertensive drug classes | | | Antihypertension drugs | | |
|---|---|---|---|---|---|
| **Classes** | **Incidence, n (%)** | ***P*-value*** | **Drugs** | **Incidence, n (%)** | ***P*-value*** |
| Olmesartan (n=1,995) | 3 (0.2) | | Olmesartan (n=1,995) | 3 (0.2) | |
| Other ARBs (n=19,825) | 22 (0.1) | 0.620 | Candesartan (n=6,650) | 7 (0.1) | 0.604 |
| | | | Fimasartan (n=3,005) | 4 (0.1) | 0.873 |
| | | | Irbesartan (n=2,021) | 3 (0.2) | 0.987 |
| | | | Losartan (n=3,300) | 5 (0.2) | 0.992 |
| | | | Telmisartan (n=2,030) | 1 (0.1) | 0.309 |
| | | | Valsartan (n=2,819) | 2 (0.1) | 0.400 |
| ACEI (n=1,297) | 2 (0.2) | 0.978 | Ramipril (n=1,297) | 2 (0.2) | 0.978 |
| CCB (n=6,769) | 9 (0.1) | 0.854 | Amlodipine (n=6,769) | 9 (0.1) | 0.854 |
| Beta-blockers (n=14,889) | 15 (0.1) | 0.524 | Bisoprolol (n=4,284) | 3 (0.1) | 0.338 |
| | | | Propranolol (n=10,605) | 12 (0.1) | 0.679 |
| Total (N=44,775) | 51 (0.1) | | Total (N=44,775) | 51 (0.1) | |

Values are presented as number (%). ACEI: angiotensin-converting enzyme inhibitor, ARBs: angiotensin receptor blockers, CCB: calcium channel blocker, *Fisher exact test

**Table 3 -** Risk over time (descriptive data) and odds ratios of enteropathy or intestinal malabsorption over time according to antihypertensive drugs.

| **Drugs** | **PY** | **Number of events** | **Crude incidient rate (per 100,000 PY)** | **Crude ORs** | | **Adjusted ORs*** | |
|---|---|---|---|---|---|---|---|
| | | | | **Value (95% CI)** | ***P*-value** | **Value (95% CI)** | ***P*-value** |
| ACEI | 523,850 | 2 | 0.38 | Reference | | Reference | |
| ***ARBs*** | 9,216,302 | 25 | 0.27 | 0.743 (0.176-3.137) | 0.686 | 0.915 (0.525-1.595) | 0.754 |
| Olmesartan | 527,739 | 3 | 0.57 | 0.975 (0.162-5.836) | 0.978 | 1.131 (0.188-6.798) | 0.893 |
| Candesartan | 3,559,887 | 7 | 0.20 | 0.683 (0.142-3.286) | 0.634 | 0.621 (0.129-2.995) | 0.553 |
| Fimasartan | 1,027,994 | 4 | 0.39 | 0.863 (0.158-4.713) | 0.865 | 0.929 (0.170-5.079) | 0.932 |
| Irbesartan | 992,926 | 3 | 0.30 | 0.963 (0.161-5.761) | 0.967 | 0.910 (0.152-5.457) | 0.918 |
| Losartan | 1,273,802 | 5 | 0.39 | 0.983 (0.191-5.064) | 0.983 | 1.055 (0.204-5.443) | 0.949 |
| Telmisartan | 880,282 | 1 | 0.11 | 0.319 (0.029-3.523) | 0.351 | 0.326 (0.030-3.600) | 0.360 |
| Valsartan | 953,672 | 2 | 0.21 | 0.460 (0.065-3.266) | 0.438 | 0.493 (0.069-3.503) | 0.479 |
| Amlodipine | 1,798,591 | 9 | 0.50 | 0.862 (0.186-3.991) | 0.850 | 0.928 (0.200-4.307) | 0.924 |
| ***Beta-blokers*** | 3,638,386 | 15 | 0.41 | 0.653 (0.149-2.857) | 0.572 | 0.663 (0.151-2.906) | 0.586 |
| Propranolol | 1,320,971 | 12 | 0.91 | 0.454 (0.076-2.718) | 0.387 | 0.492 (0.082-2.948) | 0.438 |
| Bisoprolol | 2,317,415 | 3 | 0.13 | 0.734 (0.164-3.279) | 0.685 | 1.301 (0.285-5.949) | 0.734 |

*Adjusting with age, gender, comorbidities disease, duration of antihypertensive medication. PY: person year, ACEI: angiotensin-converting enzyme inhibitor, ARBs: angiotensin receptor blockers, CCB: Calcium channel blocker, ORs: odds ratio, CI: confidence interval

Comparative studies regarding ARBs-related enteropathy have yielded inconsistent results.[4,8,9] Basson et al[10] found a higher rate of intestinal malabsorption in the olmesartan group compared to the ACEIs group using the French National Claims database. However, other studies have shown different results. In a study carried out with Italian local healthcare units and an extensive German claims database, researchers utilized the intestinal malabsorption ICD code, given the lack of a specific diagnostic code defining SLE.

They found that unspecified intestinal malabsorption rates were higher in patients taking other ARBs than in those on olmesartan.[8] Moreover, You et al[9] observed no difference in the incidence of enteropathy among the ACEIs, olmesartan, and other ARBs groups in a sample of 108,687 Korean patients. These findings suggest that enteropathy might not be a symptom exclusive to olmesartan use but could be associated with the entire ARB class.

The mechanism of ARB-associated enteropathy has not been clearly elucidated. One study on ARB-induced SLE patients showed that the HLA-DQ2/DQ8 haplotype, commonly seen in celiac disease, was present at a high rate (70%).[11] However, the prevalence of the HLA-DQ2/DQ8 haplotype is lower in Koreans (5%) than in the West and India (more than 20%), suggesting that the likelihood of ARB-induced SLE in Koreans is very low.[12] Moreover, there was no increase in the incidence per 1,000 when comparing the use of olmesartan for less than one year and more than one year. The number needed to harm of ARB-associated intestinal malabsorption is extremely low, exceeding 31,000 patient-years; when it occurs, it is usually reported as a case.[4] Our study confirmed that enteropathy or intestinal malabsorption occurred at meager rates (25 cases, 0.1%) in patients taking antihypertensive drugs. The incidence of ARBs-related SLE was minimal, and there seemed to be no difference when compared to the ACEI, CCB, and BBs groups.

***Study limitations.*** Firstly, potential misclassification exists since the diagnosis of intestinal diseases, including SLE, was based on the diagnosis code of symptoms. Secondly, the retrospective nature of this study means we cannot establish a direct causal link between antihypertensive medications and gastrointestinal symptoms. Furthermore, we couldn't determine if the symptoms of enteropathy or diarrhea remitted after discontinuation of antihypertensive medication or if recurred after rechallenging. Finally, this study was carried out at a single medical center.

Despite the aforementioned limitations, this study offers notable strengths. Firstly, it was compare the incidence of enteropathy or malabsorption across various classes of antihypertensive medications, including olmesartan, ARBs, ACEI, CCB, and BBs, over more than a decade. Secondly, our study method enabled identification of intestinal malabsorption or enteropathy after antihypertensive medication in both inpatient and outpatient settings.

In conclusion, the incidence of enteropathy or intestinal malabsorption in hypertensive patients taking olmesartan was a mere 0.15%, which was not significantly different from that in those taking ACEI, other ARBs, CCB, and BBs. Although infrequent, unexplained symptoms, such as persistent abdominal discomfort, diarrhea, and weight loss, can manifest in patients taking any hypertensive drug. In such instances, hypertensive drug-associated enteropathy or intestinal malabsorption should be suspected, prompting consideration of a switch to a different drug class.

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