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Use of olmesartan and enteropathy outcomes: a multi-database study

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Summary

Background: Multiple case reports suggest that olmesartan may be linked to sprue-like enteropathy; however, few epidemiological studies have examined this association and results have been mixed.

Aim: To assess whether olmesartan is associated with a higher rate of enteropathy vs other angiotensin II receptor blockers (ARBs).

Methods: We conducted a cohort study among ARB initiators in 5 US claims databases representing different health insurance programmes. Cox regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for enteropathy-related outcomes, including coeliac disease, malabsorption, concomitant diagnoses of diarrhoea and weight loss, and non-infectious enteropathy, comparing olmesartan initiators to initiators of other ARBs after propensity score (PS) matching.

Results: We identified 1 928 469 eligible patients. The unadjusted incidence rates were 0.82, 1.41, 1.66 and 29.20 per 1000 person-years for coeliac disease, malabsorption, concomitant diagnoses of diarrhoea and weight loss, and non-infectious enteropathy respectively. HRs after PS matching comparing olmesartan to other ARBs were 1.21 (95% CI, 1.05-1.40), 1.00 (95% CI, 0.88-1.13), 1.22 (95% CI, 1.10-1.36) and 1.04 (95% CI, 1.01-1.07) for each outcome. HRs were larger for patients aged 65 years and older (eg for coeliac disease, 1.57 [95% CI, 1.20-2.05]), for patients receiving treatment for more than 1 year (1.62 [95% CI, 1.24-2.12]), and for patients receiving higher cumulative olmesartan doses (1.78 [95% CI, 1.33-2.37]).

Conclusions: This large-scale, multi-database study found a higher rate of enteropathy in olmesartan initiators as compared to initiators of other ARBs, although the absolute incidence rate was low in both groups.

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1 | INTRODUCTION

Angiotensin II receptor blockers (ARBs) are commonly used in the management of hypertension.[1,2] Approved for marketing in the US in 2002, olmesartan is a widely used ARB. Through 2011, approximately 45.3 million olmesartan prescriptions were dispensed to 4.5 million patients in the US.[3] While existing evidence has shown that olmesartan has a good tolerability profile and treatment-related adverse events are generally transient and mild,[4] severe sprue-like enteropathy associated with olmesartan has been reported.

Rubio-Tapia et al observed that, in a cohort of patients with chronic diarrhoea, weight loss or unexplained sprue-like enteropathy, one-fourth of them used olmesartan.[5] A subsequent case series published in 2012 described 22 patients who took olmesartan for at least several months and experienced chronic diarrhoea, weight loss, and duodenal villous atrophy and inflammatory changes with clinical and histological improvement after discontinuation of olmesartan treatment.[6] The symptoms and biopsy characteristics were similar to those of coeliac disease, an autoimmune gluten-intolerance disorder.[7-9] However, the negative coeliac serology findings and the absence of response to a gluten-free diet raised concerns about a distinct form of enteropathy associated with olmesartan.[10] Subsequent case reports, case series and systematic reviews also noted common clinical and pathophysiological manifestations.[11-17] In 2013, the US Food and Drug Administration (FDA) issued a warning and approved changes to the drug's label to include sprue-like enteropathy.[18-20] This warning, however, did not extend to other ARBs[18-20] and has not yet been widely adopted by regulatory agencies in other countries.

Several case reports have suggested that other ARBs, including irbesartan, telmisartan and valsartan, may also be associated with sprue-like adverse events, raising the concern that, if olmesartan does increase risk of enteropathy, it could be a class effect.[11,21-23] However, limited epidemiological studies compared enteropathy outcomes between olmesartan and other antihypertensive medications, including other ARBs and angiotensin-converting enzyme (ACE) inhibitors, and results have been mixed.[24-28] We conducted a large cohort study using multiple administrative claims databases to investigate whether olmesartan is associated with a higher rate of enteropathy than other ARBs.

2 | METHODS

2.1 | Data sources

We identified eligible patients from 5 US databases covering the years 2002 (olmesartan was approved in the US on 25 April, 2002) to 2015. Specifically, we used a commercial health insurance database, Clinformatics Data Mart (OptumInsight, Eden Prairie, MN; Optum; 1 July 2004 to 30 September 2015), a Medicaid database, the Medicaid Analytic eXtract (MAX, 25 April 2002 to 31 December 2010) and 3 Medicare databases: (1) pharmacy claims data from the Pharmaceutical Assistance Contract for the Elderly programme linked to Medicare claims data for beneficiaries in Pennsylvania (PACE, 25 April 2002 to 31 December 2005); (2) pharmacy claims data from the Pharmaceutical Assistance for the Aged and Disabled programme linked to Medicare claims data for beneficiaries in New Jersey (PAAD, 25 April 2002 to 31 December 2005); and (3) pharmacy claims data from stand-alone Medicare Part D plans or retiree drug plans administered by CVS CareMark linked to Medicare claims data (CareMark, 1 July 2005 to 31 December 2008).

The commercial plan provides primarily employer-based insurance benefits for working individuals; Medicaid provides insurance benefits for those with low income; and Medicare provides insurance benefits for those aged 65 years or older as well as those with certain disabilities. Combined, these databases cover around 100 million individuals and represent each of the 3 main insured segments of the population in the US. These databases include information on demographic and enrolment records, in-patient and out-patient diagnoses and procedures, and out-patient pharmacy dispensings (Data S1). This study was approved by the Institutional Review Board of the Brigham and Women's Hospital.

2.2 | Study population and study drugs

From each database, we identified patients who initiated ARB treatment with either olmesartan or other ARBs (candesartan, eprosartan, irbesartan, losartan, telmisartan, valsartan, azilsartan, including single and combination products). ARB initiation was defined as a first ARB prescription dispensing during the study period with no dispensings for any ARBs in the preceding 180 days during which patients were required to have continuous health plan enrolment. The index date was defined as the date of the first ARB prescription. We excluded those with age less than 20 years in Optum and MAX or less than 65 years in the Medicare databases (PACE, PAAD and CareMark) on the index date, those with missing age or ambiguous sex information, and those who initiated both olmesartan and other ARBs on the same date.

2.3 | Outcomes and follow-up

Given that no specific diagnosis code is available for ARB-associated sprue-like enteropathy, which had not been described prior to the first published case series,[6] and given the similarity in presentation, we used coeliac disease as a primary surrogate outcome, as was done in the analyses performed by the FDA.[19,20] To identify potential diagnoses or symptoms related to enteropathy that were not coded as coeliac disease, our study team, with expertise in gastroenterology, pharmacy and epidemiology, reviewed available case series or reports and observational studies[6,11-17,26-28] and included malabsorption, concomitant diagnoses of diarrhoea and weight loss occurring within 1 month, and non-infectious enteropathy as secondary outcomes. We assessed any diagnosis codes based on in-patient and out-patient diagnosis files. International Classification of Diseases, 9th Revision, Clinical modification (ICD-9-CM) codes for the outcomes, which have been used by the FDA's Sentinel

system[19,20] and 2 epidemiological studies,[26,28] are provided in Table S1.

Patients were followed from the index date to the earliest of the following: outcome occurrence, ARB treatment discontinuation or change, death, disenrollment from the health insurance programme, or the end of data in the respective database. ARB treatment discontinuation was defined using a grace period of 30 days between the end of one prescription and the date of the next prescription, if any. ARB treatment change (switch or addition) was defined as a dispensing of another ARB for olmesartan initiators and a dispensing of olmesartan for other ARB initiators.

2.4 | Covariate assessment

We measured a large number of potential baseline confounders including age on the index date, sex and calendar year of the index date, as well as prior resource utilisation, comorbidities and other medication use within 180 days preceding the index date. We also calculated a combined comorbidity score, which comprises 20 clinical conditions derived from the Charlson Index and the Elixhauser Index.[29] Measures of resource utilisation included numbers of hospital admissions, out-patient visits and nursing home admission. Comorbidities were ascertained based on in-patient and out-patient diagnosis files and medication use was derived from out-patient pharmacy dispensing claims. Table S2 provides detailed covariate information.

2.5 | Statistical analyses

Using the covariates mentioned above, we estimated baseline propensity scores (PS) using logistic regression models to predict the probability of initiating olmesartan vs other ARBs. Because we had many more patients who initiated other ARBs, we matched up to 10 patients who initiated other ARBs to each patient who initiated olmesartan using a nearest-neighbour algorithm without replacement and with a maximum matching calliper of 0.025 on the PS scale.[30] We used Cox proportional hazard models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) in the 1:10 variable-ratio matched cohort. To account for the variable-ratio matching, the Cox model was stratified on matching ratio.[30] Variable-ratio matching produces covariate balance within matched set but not marginally in the overall matched population.[30] We therefore randomly selected 1 initiator of other ARBs from each set of patients matched to each olmesartan initiator and examined whether adequate balance in covariates was achieved between treatment groups using standard differences[31] among this sample.

We identified study cohorts, extracted information on variables, fit PS models, and performed PS matching separately within each database. We fit separate Cox proportional hazards regression models in each database to obtain database-specific estimates. We computed standardised differences across the databases for each variable using pooled means and standard deviations (SD). We pooled the 1:10 variable-ratio matched cohorts from the 5 databases and used Cox models, stratified on matching ratios, to estimate summary HRs and 95% CIs.[32]

2.6 | Sensitivity analyses

To evaluate outcomes over a longer period of exposure, we applied a "first exposure carried forward" follow-up scheme in which we continued to follow patients regardless of ARB treatment discontinuation or change, censoring at the first of outcome occurrence, death, disenrollment from the health insurance programme or the end of data. As there is no diagnosis code specific to ARB-associated sprue-like enteropathy, we varied the outcome definition in several sensitivity analyses. First, we focused on severe cases of enteropathy-related symptoms[6,11-17] by restricting to diagnosis codes from in-patient settings. Second, patients may experience chronic symptoms of enteropathy and may undergo upper or lower gastrointestinal endoscopic examination for diagnosis confirmation.[6,11-17] We thus restricted to cases with at least 2 enteropathy-related diagnosis codes (coeliac disease, malabsoroption, diarrhoea, weight loss, or non-infectious enteropathy) from separate encounters or with an endoscopic examination within 3 months before or after the first diagnosis of coeliac disease. Table S3 provides detailed information on procedure codes for gastrointestinal endoscopic examination. Finally, some patients who experience severe diarrhoea and weight loss may have accompanying dehydration leading to acute kidney injury (AKI).[6,11,12,14] To assess whether olmesartan is associated with a higher rate of enteropathy-related AKI, we examined those cases involving a hospitalised AKI diagnosis (ICD-9-CM code: 584) within 3 months before or after the first diagnosis of coeliac disease.

To focus on incident cases of enteropathy, we conducted an analysis by excluding patients with any diagnosis of coeliac disease, malabsorption, concomitant diagnoses of diarrhoea and weight loss, or non-infectious enteropathy within 180 days before the index date. Given that diabetes may be associated with bacterial overgrowth, diabetic diarrhoea or coeliac disease,[33] we also conducted another analysis by excluding those with any diabetes diagnosis at baseline.

2.7 | Subgroup analyses

Because older patients are often more vulnerable to adverse drug reactions and coeliac disease is more common in women,[7] we conducted subgroup analyses to examine potential effect measure modification by age (≥ 65 and < 65 years) and sex. Based on case reports, enteropathy-related symptoms often occur months or even years after olmesartan initiation.[6,11,12,14,16,17] To assess for a duration-response relation between olmesartan and enteropathy, we separately examined HRs from the index date to 364 days for all eligible patients and HRs from 365 days to the end of follow-up for patients treated for at least 365 days. For patients treated for at least 365 days, we further examined if incidence rates varied by cumulative olmesartan dose within the first year of treatment. We used 365 cumulative defined daily doses (DDDs) as a cut-point and

separately calculated HRs comparing high cumulative doses of olmesartan (> 365 DDDs) vs other ARBs and low cumulative doses of olmesartan (≤ 365 DDDs) vs other ARBs. Finally, we also estimated HRs comparing olmesartan vs other individual ARBs. We re-estimated the PS and re-matched patients within each subgroup.[34]

3 | RESULTS

3.1 | Baseline characteristics

A total of 1 928 469 eligible patients were identified across the 5 databases; 350 790 initiated olmesartan (18%) and 1 577 679 initiated other ARBs (82%) (Figure S1 and Table S4). Most patients were enrolled in Optum (47%), followed by MAX (42%). Among patients who initiated other ARBs, valsartan (n = 679 039) was the most common, followed by losartan (n = 543 797), irbesartan (n = 171 239) and telmisartan (n = 123 089). The mean (SD) age of the cohort was 55 (14) years and 58% were female. Most patients had hypertension (77%); 39% had dyslipidemia and 28% had diabetes.

Before matching, patients who initiated olmesartan were younger and had lower medical resource utilisation as compared to patients who initiated other ARBs. Patients who initiated olmesartan were also less likely to have had a diagnosis of ischaemic heart disease, heart failure, diabetes and chronic kidney disease, and have used β blockers, nitrates, antiplatelet drugs and antidiabetic drugs (Table 1 and Table S5a-f). After PS matching, a total of 1 854 992 patients (350 430 olmesartan initiators and 1 504 562 other ARB initiators; 96% of the total study cohort) were included in the analysis (Figure S1 and Table S4). PS matching resulted in good balance in baseline characteristics between treatment groups (Table 1 and Table S5a-f).

3.2 | Follow-up and outcomes

The follow-up duration did not vary materially across databases (300 days for Optum, PACE, and CareMark; 288 days for PAAD; 258 days for MAX). During a mean follow-up of 282 days of ARB exposure, we observed 1227 cases of coeliac disease, 2102 cases of malabsorption, 2467 cases of concomitant diagnoses of diarrhoea and weight loss, and 42 440 cases of non-infectious enteropathy (based on in-patient and out-patient diagnoses). The crude incidence rates were 0.82, 1.41, 1.66 and 29.20 per 1000 person-years for each outcome respectively. Incidence rates of each outcome for each treatment group after PS matching are presented in Table 2 (across databases) and Table S6a-b (in individual databases).

In the primary analyses, the crude HRs comparing olmesartan to other ARBs were 1.21 (95% CI, 1.05-1.39) for coeliac disease, 0.90 (95% CI, 0.80-1.01) for malabsorption, 1.09 (95% CI, 0.98-1.20) for concomitant diagnoses of diarrhoea and weight loss, and 0.92 (95% CI, 0.61-0.95) for non-infectious enteropathy. After PS matching, use of olmesartan was associated with significantly increased rates of coeliac disease, concomitant diagnoses of diarrhoea and weight loss, and non-infectious enteropathy, with HRs of 1.21 (95% CI, 1.05-1.40), 1.22 (95% CI, 1.10-1.36) and 1.04 (95% CI, 1.01-1.07) respectively (Table 3). Use of olmesartan was consistently associated with higher rates of each outcome in individual databases, although estimates tended to be less precise (Table S7).

3.3 | Sensitivity analyses

In the "first exposure carried forward" approach, the mean follow-up duration was 857 days and the adjusted HR for coeliac disease was 1.21 (95% CI, 1.10-1.37). Among patients with enteropathy outcomes, 1%-10% required hospitalisation (124 cases for coeliac disease, 110 cases for malabsorption, 34 cases for concomitant diagnoses of diarrhoea and weight loss, and 4106 cases for non-infectious enteropathy). When we restricted outcomes to only in-patient cases, the adjusted HRs were consistently higher, with significant findings for concomitant diagnoses of diarrhoea and weight loss (2.84; 95% CI, 1.35-5.99) and for non-infectious enteropathy (1.17; 95% CI, 1.07-1.28) (Table 3). Among 1227 patients with a coeliac disease diagnosis during follow-up, 620 (51%) had at least another one enteropathy-related diagnosis code, 549 (45%) received gastrointestinal endoscopic examination and 17 (1.4%) were hospitalised with AKI. When we restricted outcomes to those cases, the adjusted HRs for coeliac disease were 1.49 (95% CI, 1.23-1.80), 1.45 (95% CI, 1.18-1.79), and 7.40 (95% CI, 3.63-15.11) respectively (Table S8).

Of eligible cohort members, 2% (n = 36 196) had diagnoses of coeliac disease, malabsorption, concomitant diagnoses of diarrhoea and weight loss, or non-infectious enteropathy and 28% (n = 544 676) had a diabetes diagnosis before the index date. Excluding these patients led to adjusted HRs for coeliac disease that was materially similar to those from the primary analyses (Table S8).

3.4 | Subgroup analyses

The adjusted HRs were higher in older patients but did not differ between female and male patients (Table 4). Of eligible cohort members, 23% were treated with ARBs (72 121 for olmesartan and 364 972 for other ARBs) for longer than 1 year. The duration-response analysis showed treatment with olmesartan for longer than 1 year yielded higher adjusted HRs (Table 5). Patients treated with high cumulative doses of olmesartan (> 365 DDDs, n = 48 316) also had a higher rate of coeliac disease (adjusted HR, 1.78; 95% CI, 1.33-2.37). We did not observe an increased rate of coeliac disease (adjusted HR, 1.06; 95% CI, 0.62-1.79) for those treated with low cumulative doses of olmesartan (≤ 365 DDDs, n = 23 805) vs those treated with other ARBs. Comparing olmesartan vs other individual ARBs yielded adjusted HRs of 1.19 (95% CI, 0.99-1.44) vs valsartan, 1.34 (95% CI, 1.12-1.61) vs losartan, 1.11 (95% CI, 0.88-1.41) vs irbesartan, and 1.47 (95% CI, 1.10-1.97) vs telmisartan for the coeliac disease outcome. We could not compare olmesartan to candesartan, eprosartan and azilsartan separately given that few patients took these medications.

TABLE 1 Selected baseline characteristics by ARB group[a] in the entire cohort

Variable	Before matching			After matching		
	Olmesartan n = 350 790	Other ARBs n = 1 577 679	Standardised difference	Olmesartan n = 350 430 n = 350 430[b]	Other ARBs n = 1 504 562 n = 350 430[b]	Standardised difference
Age, mean (SD)	53.31 (13.22)	55.23 (13.75)	−0.14	53.32 (13.22)	53.31 (13.49)	0.00
Female, n (%)	195 450 (55.72)	931 264 (59.03)	−0.07	195 351 (55.75)	195 008 (55.65)	0.00
Resource utilisation, mean (SD)						
Number of out-patient visits	5.60 (7.28)	6.50 (10.65)	−0.10	5.60 (7.26)	5.61 (8.35)	0.00
Number of hospitalisations	0.11 (0.44)	0.19 (0.64)	−0.15	0.11 (0.44)	0.11 (0.43)	0.00
Number of hospital days	0.63 (3.36)	1.24 (5.39)	−0.13	0.63 (3.36)	0.65 (3.34)	0.00
Comorbidities, n (%)						
Hypertension	284 226 (81.02)	1 208 989 (76.63)	0.11	283 867 (81.01)	284 034 (81.05)	0.00
Ischaemic heart disease	33 231 (9.47)	210 042 (13.31)	−0.12	33 229 (9.48)	33 185 (9.47)	0.00
Heart failure	13 381 (3.81)	112 717 (7.14)	−0.15	13 380 (3.82)	13 544 (3.86)	0.00
Cereborvascular disease	16 043 (4.57)	91 237 (5.78)	−0.05	16 031 (4.57)	15 992 (4.56)	0.00
Dyslipidemia	140 370 (40.02)	602 828 (38.21)	0.04	140 218 (40.01)	139 969 (39.94)	0.00
Diabetes	78 988 (22.52)	465 688 (29.52)	−0.16	78 981 (22.54)	79 126 (22.58)	0.00
Chronic kidney disease or ESRD	10 253 (2.92)	81 720 (5.18)	−0.11	10 252 (2.93)	10 399 (2.97)	0.00
Medications n (%)						
ACEIs	99 367 (28.33)	509 963 (32.32)	−0.09	99 336 (28.35)	98 571 (28.13)	0.00
Renin inhibitors	1 372 (0.39)	6 285 (0.40)	0.00	1 364 (0.39)	1 310 (0.37)	0.00
β blockers	84 781 (24.17)	450 191 (28.54)	−0.10	84 724 (24.18)	84 855 (24.21)	0.00
CCBs	98 192 (27.99)	421 215 (26.70)	0.03	97 846 (27.92)	98 042 (27.98)	0.00
Diuretics	191 803 (54.68)	874 874 (55.45)	−0.02	191 633 (54.69)	192 735 (55.00)	−0.01
Other antihypertensives	19 140 (5.46)	99 661 (6.32)	−0.04	19 110 (5.45)	19 215 (5.48)	0.00
Nitrates	11 101 (3.16)	85 244 (5.40)	−0.11	11 101 (3.17)	11 281 (3.22)	0.00
Antiplatelet drugs	23 333 (6.65)	171 297 (10.86)	−0.15	23 333 (6.66)	23 311 (6.65)	0.00
Anticoagulants	8 455 (2.41)	59 377 (3.76)	−0.08	8 455 (2.41)	8 564 (2.44)	0.00
Statins or fibrates	109 741 (31.28)	553 766 (35.10)	−0.08	109 671 (31.30)	109 658 (31.29)	0.00
Antidiabetic drugs	65 870 (18.78)	404 574 (25.64)	−0.17	65 865 (18.80)	65 745 (18.76)	0.00

ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; CCBs, calcium channel blockers; ESRD, end-stage renal disease; SD, standard deviation.

[a]presenting as summary estimates for mean, SD and standardised difference across databases.

[b]1 initiator of olmesartan: 1 randomly sampled initiator of other ARBs in each matched subset.

4 | DISCUSSION

In this large-scale, multi-database cohort study, we found an increased rate of enteropathy among patients treated with olmesartan as compared to those treated with other ARBs. Results were consistent across individual outcomes and across databases encompassing diverse populations from various health systems. Results were qualitatively similar with varying outcome definitions and when patients with potential intestine problems or diabetes at baseline were excluded from the analysis. The increased incidence rate associated with olmesartan was more pronounced for older patients, for patients receiving treatment more than 1 year, and for patients receiving cumulative doses more than 365 DDDs.

The mechanism by which olmesartan might increase risk of enteropathy is not well understood. Several explanations have been proposed. First, except for negative coeliac serology findings and the absence of response to a gluten-free diet, olmesartan-associated enteropathy and coeliac disease have similar features, including an increase in the numbers of CD8+ cells and overexpression of interleukin-15.[35] Because of an apparent increase in the numbers of CD8+ cells in duodenal biopsies and the long delay between start of olmesartan treatment and the onset of clinical symptoms, Rubio-Tapia et al suggested that cell-mediated immunity damage, rather than type 1 hyper-sensitivity, may play an important role.[6,36] Second, there are 2 types of angiotensin II receptors, AT1 and AT2. AT1 receptors are expressed throughout

TABLE 2 Follow-up and outcome event rates after propensity score matching, by ARB group

Outcome	Olmesartan (n = 350 430)			Other ARBs (n = 1 504 562)		
	Number of events	Person-days at risk	Incidence (per 1000 person-years)[a]	Number of events	Person-days at risk	Incidence (per 1000 person-years)[a]
In-patient or out-patient diagnoses						
Coeliac disease	246	92 773 140	1.017	935	429 740 467	0.765
Malabsorption	331	92 755 505	1.469	1606	429 599 574	1.392
Concomitant diagnoses of diarrhoea and weight loss	452	92 750 516	3.110	1889	429 590 864	2.395
Non-infectious enteropathy	6837	90 735 057	33.724	33 000	41 8932 975	32.699
In-patient diagnoses only						
Coeliac disease	25	92 843 945	0.143	88	430 051 812	0.084
Malabsorption	15	92 846 557	0.064	75	430 066 362	0.054
Concomitant diagnoses of diarrhoea and weight loss	11	92 847 703	0.061	22	430 077 683	0.030
Non-infectious enteropathy	584	92 709 706	3.956	3120	429 178 035	3.158

ARBs, angiotensin II receptor blockers.
[a]Data were weighted by matching ratio and were pooled across databases using random-effects meta-analysis.

TABLE 3 Hazard ratios and 95% confidence intervals comparing use of olmesartan vs other ARBs after propensity score matching

Outcome	In-patient or out-patient diagnoses	In-patient diagnoses only
Coeliac disease	1.21 (1.05-1.40)	1.56 (0.99-2.47)
Malabsorption	1.00 (0.88-1.13)	1.25 (0.71-2.21)
Concomitant diagnoses of diarrhoea and weight loss	1.22 (1.10-1.36)	2.84 (1.35-5.99)
Non-infectious enteropathy	1.04 (1.01-1.07)	1.17 (1.07-1.28)

ARBs, angiotensin II receptor blockers.

the alimentary tract and might be involved in angiotensin II-mediated transforming growth factor β (TGF-β) signalling,[37-42] which is necessary for the maintenance of gut immune homeostasis.[43,44] AT2 receptors are expressed in the duodenum and jejunum and may induce intestinal epithelial cell apoptosis.[37-39] The translocation of AT2 receptors from cytosol to external membranes has been observed in the presence of high concentrations of angiotensin II in rat smooth muscle cells.[45] As compared to other ARBs, olmesartan has a greater affinity for inhibiting AT1.[4,46] Thus, it is possible that olmesartan may cause greater disruption of gut immune homeostasis. In addition, if AT1 receptors become saturated by olmesartan, circulating angiotensin II may be more likely to bind to AT2 receptors and lead to pro-apoptotic effects and intestinal adverse reactions. More research exploring these complex biological pathways would be helpful to further distinguish olmesartan-induced enteropathy and coeliac disease.

Our study and the FDA's Sentinel system[19,20] used coeliac disease as a primary surrogate outcome for ARB-associated enteropathy outcomes. In our ARB cohort with a mean age of 55 years, the incidence rates per 1000 person-years were 0.98 for females and 0.61 for males. Similarly, the FDA found incidence rates per 1000

TABLE 4 Hazard ratios and 95% confidence intervals comparing use of olmesartan vs other ARBs after propensity score matching, by age and sex

Outcome	Age		Sex	
	Age < 65	Age ≥ 65	Female	Male
In-patient or out-patient diagnoses				
Coeliac disease	1.13 (0.96-1.33)	1.57 (1.20-2.05)	1.27 (1.07-1.50)	1.11 (0.87-1.43)
Malabsorption	0.96 (0.84-1.09)	0.97 (0.75-1.24)	0.99 (0.86-1.15)	0.87 (0.70-1.07)
Concomitant diagnoses of diarrhoea and weight loss	1.12 (0.97-1.28)	1.30 (1.12-1.52)	1.14 (1.00-1.30)	1.11 (0.93-1.32)
Non-infectious enteropathy	0.93 (0.91-0.96)	1.04 (0.98-1.10)	0.94 (0.91-0.98)	0.99 (0.95-1.04)
In-patient diagnoses only				
Coeliac disease	1.17 (0.65-2.11)	1.77 (0.90-3.48)	1.62 (0.98-2.69)	0.71 (0.27-1.82)
Malabsorption	0.92 (0.49-1.71)	1.14 (0.33-3.94)	0.71 (0.34-1.48)	1.22 (0.52-2.82)
Concomitant diagnoses of diarrhoea and weight loss	1.96 (0.60-6.35)	3.17 (1.27-7.96)	1.64 (0.65-4.14)	7.10 (1.70-29.70)
Non-infectious enteropathy	0.81 (0.73-0.90)	1.09 (0.93-1.29)	0.89 (0.80-0.99)	0.84 (0.71-0.99)

ARBs, angiotensin II receptor blockers.

TABLE 5 Hazard ratios and 95% confidence intervals comparing use of olmesartan vs other ARBs after propensity score matching, by follow-up duration

Outcome	From the index date to the end of follow-up (Primary analysis)	From the index date to 364 days	From 365 days to the end of follow-up
In-patient or out-patient diagnoses			
Coeliac disease	1.21 (1.05-1.40)	1.08 (0.91-1.29)	1.62 (1.24-2.12)
Malabsorption	1.00 (0.88-1.13)	0.98 (0.85-1.13)	1.05 (0.82-1.33)
Concomitant diagnoses of diarrhoea and weight loss	1.22 (1.10-1.36)	1.18 (1.04-1.34)	1.29 (1.07-1.55)
Non-infectious enteropathy	1.04 (1.01-1.07)	1.04 (1.00-1.07)	1.05 (0.99-1.11)
In-patient diagnoses only			
Coeliac disease	1.56 (0.99-2.47)	0.99 (0.53-1.87)	2.68 (1.30-5.52)
Malabsorption	1.25 (0.71-2.21)	1.18 (0.61-2.28)	1.29 (0.41-4.04)
Concomitant diagnoses of diarrhoea and weight loss	2.84 (1.35-5.99)	2.67 (1.06-6.74)	3.97 (1.09-14.50)
Non-infectious enteropathy	1.17 (1.07-1.28)	1.19 (1.07-1.32)	1.08 (0.90-1.30)

ARBs, angiotensin II receptor blockers.

person-years were 0.91 for females and 0.51 for males who used ARBs.[20] Another US population-based study including patients with a median age of 38 years found incidence rates of 0.21 and 0.14 per 1000 person-years for female and male patients respectively.[47] While coeliac disease is more common among females than males, sex does not appear to modify the association between olmesartan and sprue-like enteropathy. We did not observe differences in HRs for olmesartan vs other ARBs by sex (Table 4). Another French nationwide cohort study also did not observe HRs of olmesartan vs ACE inhibitors differ apparently for individual enteropathy outcomes by sex.[28] Further research focusing on a sex-specific effect may be helpful to elucidate whether sex is an important effect modifier of this association.

The results of this study should be interpreted in the context of prior epidemiological research. No association between olmesartan and intestinal adverse reactions was observed in the Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) trial[24,25] and in a US cohort study[26] that enrolled diabetic patients only. One possible explanation for the discrepancy in results between these studies and our study is that these studies assessed nonspecific gastrointestinal events, which are much more common than the outcomes that we studied, and which may have obscured an association with a more specific enteropathy outcome. Also, as enteropathy is a rare event, clinical trials or single-database studies may be underpowered to detect differences between treatment groups.

In the present study, we used data from 5 large databases that cover geographically, socioeconomically and clinically diverse populations. We identified all incident ARB users without restricting to diabetic patients as the eligible cohort, defined enteropathy-related outcomes in multiple ways,[6,11-17,19,20,24-28] and followed patients longitudinally. These approaches are relative strengths of our study because they facilitate the study of uncommon outcomes and promote the generalisability of the findings. As compared to the French cohort study that suggested that olmesartan was associated with higher rates of hospitalised coeliac disease and malabsorption as compared to ACE inhibitors,[28] our study provides further information on the comparative safety of olmesartan and other ARBs, as a whole group or individual medications (valsartan, losartan, irbesartan and telmisartan). Our duration-response and dose-response findings also bolster our findings.

There are important limitations of administrative healthcare data and of our study that must be considered when interpreting our results. First, pharmacy claims data provide accurate information about the prescriptions that patients fill, but they do not necessarily reflect whether patients consume the medications, which can lead to exposure misclassification. However, this misclassification is expected to be nondifferential between our exposure groups and would likely lead to a bias towards the null. Second, in our primary analysis, we stopped following patients once they discontinued or changed their index ARB treatment. This reduced the possibility of exposure misclassification but resulted in a short mean follow-up duration (only 282 days). Also, unlike the previous French cohort in which 60% of patients were treated for more than 1 year and 34% treated for more than 2 years,[28] only 23% of patients in our study were treated for more than 1 year and 9% treated for more than 2 years. This precluded precise rate estimation for patients receiving ARB treatment for more than 2 years. However, our study reflects the actual use patterns of ARBs in real-world clinical settings in the US. Third, although we used multiple approaches for defining outcomes based on multiple diagnoses and symptoms identified in the literature; restricted outcomes to in-patient cases; required additional enteropathy-related diagnoses, endoscopic examination or hospitalised AKI episodes; and excluded patients with potential underlying intestinal disorders or diabetes in sensitivity analyses, we acknowledge the possibility of outcome misclassification given that no validated diagnostic codes for ARB-induced enteropathy, no diet information, and no

histological and coeliac serology testing results were available. However, more than 90% of data included in our study covered the period before the first case series was published (June 2012). Therefore, physicians were unlikely to be biased by specific ARB treatment when they diagnosed enteropathy-related outcomes or symptoms. Thus, we expect any outcome misclassification to be nondifferential between exposure groups. Finally, we used an active comparison design, controlled for a number of confounders, including immunosuppressants, which have been found to be associated with the occurrence of enteropathy,[48-50] and conducted PS matching to mitigate potential confounding. Nevertheless, we cannot rule out the possibility of unmeasured confounding, which is an inherent limitation of all observational studies.

In conclusion, we found evidence of a higher rate of enteropathy outcomes among initiators of olmesartan vs initiators of other ARBs although the absolute rate was low. Considering the widespread, long-term use of olmesartan in clinical settings and more pronounced relative risk for older patients, those treated for longer periods and those treated with higher cumulative doses, the potential olmesartan-associated enteropathy deserves attention in clinical practice. Until more evidence is available, clinicians should consider olmesartan as a potential cause when evaluating patients with enteropathy and should consider alternative ARBs for these patients. Prospective studies with primary data on sprue-like enteropathy outcomes, including histology and serology results, are warranted to comprehensively assess this safety issue.

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AUTHORSHIP

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SUPPORTING INFORMATION

Additional Supporting Information will be found online in the supporting information tab for this article.

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