Published in final edited form as:

Mayo Clin Proc. 2015 June ; 90(6): 730–737. doi:10.1016/j.mayocp.2015.04.002.

Blockers of Angiotensin Other Than Olmesartan in Patients with Villous Atrophy: A Nationwide Case-Control Study

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Abstract

Objective—To examine the association between previous use of non-olmesartan angiotensin receptor blockers (ARBs) or any angiotensin-converting enzyme inhibitors (ACEIs) in patients with small-intestinal villous atrophy (VA) as compared with general population matched controls.

Patients and methods—A case-control study was used to link nationwide histopathology data on 2933 individuals with VA (Marsh grade 3) to the Swedish Prescribed Drug Register to examine the association between use of ACEIs as well as the specific use of ARBs other than olmesartan and subsequent VA. Olmesartan is not available in Sweden and so this exposure was not examined. All individuals with VA were biopsied between July 1st 2005 and January 29th 2008

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Conflict of interest: The authors have no conflict of interest.

Author contributions: ICMJE criteria for authorship read and met: KM; BL; PG; JAM; JFL.

Agree with the manuscript's results and conclusions: KM; BL; PG; JAM; JFL.

Designed the experiments/the study: KM, JFL.

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Responsible for data integrity: KM, JFL.

Supervised the project including data analyses: JFL.

Obtained funding: JFL.

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and matched on age, sex, calendar period of birth and county of residence to 14,571 controls from the general population.

Results—Use of non-olmesartan ARBs was not associated with VA (Odds ratio (OR) = 0.84; 95 % confidence interval [CI] = 0.64-1.09; $P=.19$). Neither was VA associated with a prior medication of any ACEIs (OR = 1.08; 95% CI = 0.90-1.30; $P=.41$). Restricting the analysis to individuals with repeated prescriptions for ACEIs or ARBs revealed only marginally changed risk estimates for VA.

Conclusion—The lack of association between use of ACEIs and non-olmesartan ARBs and subsequent VA suggests that, in the general population, these medications are not a major risk factor for VA development.

Keywords

angiotensin receptor blocker; inflammation; pharmaceutical preparations; population-based; case-control study

Introduction

A duodenal biopsy showing villous atrophy (VA) has long been considered a diagnostic hallmark of celiac disease (also known as celiac sprue).¹ In celiac disease, dietary gluten causes small-intestinal VA and inflammation. Celiac disease is prevalent in 1-2% of the Western population.^{2,3} Although celiac disease is by some margin the most common cause of VA, several additional causes of VA exist, e.g. tropical sprue, infective gastroenteritis and immunodeficiency states.⁴

In 2012, Rubio-Tapia *et al.*⁵ first described 22 patients taking olmesartan medoxomil, an angiotensin receptor blocker (ARB) used for the treatment of hypertension, who developed sprue-like enteropathy. These patients, suffering from chronic diarrhea and weight loss accompanied with small-intestinal VA or inflammation, showed all a marked clinical improvement after discontinuing of olmesartan. While these patients' intestinal histology resembled that of celiac disease, none of these patients had characteristics entirely consistent with celiac disease, i.e. positive celiac disease serology and/or a symptomatic improvement on a gluten free diet. Although questioned by some,^{6,7} a number of case series^{8,9} and one national case finding study¹⁰ have since then reported additional cases of olmesartan-associated sprue-like enteropathy. Some data have also suggested that other ARBs, besides olmesartan, may induce similar outcomes.¹⁰ Drug-induced enteropathy is a challenging, often overlooked, differential diagnosis towards celiac disease. Despite this, there are few general population-based data on the previous use of angiotensin-converting enzyme inhibitors (ACEIs) and ARB use other than olmesartan prior to development of VA.

The main objective of this study was to examine the association between previous use of non-olmesartan ARBs as well as any ACEIs, in patients with small-intestinal VA as compared with general population matched controls. In order to contrast the use of these drugs in patients with VA we also examined their usage in VA-patients as compared with individuals with milder small-intestinal histopathology: small-intestinal inflammation without VA or normal small-intestinal mucosa but positive celiac disease serology.³

Methods

In this case-control study we linked nationwide histopathology data on individuals undergoing small-intestinal biopsy to the Swedish Prescribed Drug Register in order to examine the association between use of non-olmesartan ARBs or any ACEIs and subsequent VA.

Study population

Between 2006 and 2008, we searched the computerized register of Sweden's 28 pathology departments to identify individuals with small-intestinal VA (Marsh grade 3).^{11,12} The biopsies were performed between July 1969 and January 2008.¹³ A detailed account of the data collection process has been described elsewhere.^{11,14} In an earlier validation study on a randomly selected sample of patients in our cohort, 95% (108/114) of the patients with VA had later received a clinical diagnosis of celiac disease.¹¹

In the current study we used the same dataset described in our previous study of mortality identifying 29,096 patients with VA.¹⁵ The government agency Statistics Sweden then matched each individual with VA with up to five controls from the general population for age, sex, calendar period of birth and county of residence. The number of controls was decided after consultations with the government agency Statistics Sweden. After exclusion of individuals with data irregularities (see our previous report¹⁵) we identified 144,522 controls.

Patients with VA and their matched controls were then linked to the Swedish Prescribed Drug Register (established on July 1st 2005).¹⁶ Through this linkage, we identified 2933 patients with VA biopsied between July 1st 2005 (the start of the Prescribed Drug Register) and January 29th 2008 (end of the study period) and 14,571 matched controls.

Using Swedish computerized pathology data we identified a secondary control group constituting of individuals with small-intestinal inflammation (Marsh grade 1-2) but without VA and individuals with normal small-intestinal mucosa (Marsh grade 0) but positive celiac disease serology.¹⁴ Data on individuals with normal mucosa and positive celiac disease serology were regional and obtained from the ascertainment areas of eight Swedish university hospitals covering approximately half of the Swedish population.¹⁴ Positive celiac disease serology was defined as a positive IgA or IgG antigliadin (AGA), endomysial (EMA) or tissue transglutaminase (TTG) test less than 180 days before or no later than 30 days after a normal biopsy (and with no prior or subsequent biopsy showing villous atrophy or inflammation).¹⁴ In total, this secondary control group included 2738 individuals (2118 individuals with inflammation and 620 individuals with normal mucosa but positive celiac disease serology).

Use of ARBs and ACEIs

The Swedish Prescribed Drug Register contains prospectively recorded individual data on more than 99% of all dispensed prescribed drugs in Sweden.¹⁶

We collected data on use of any ACEIs (anatomical therapeutic chemical, ATC code: C09) as well as specific use of ARBs other than olmesartan (ATC code: C09C and C09D) from July 1st 2005 (launch of the Prescribed Drug Register) through January 29th 2008 (end of the study period), and up to the date of the biopsy (and the corresponding date in matched controls). Olmesartan is not available in Sweden and so this exposure was not studied in this population-based investigation.

Statistical analyses

We used conditional logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs). Each stratum (one individual undergoing biopsy and up to five matched controls) was analyzed separately before a summary OR was calculated.¹⁷ This statistical approach therefore eliminates the effect of sex, age, county and calendar year on our ORs.

In the analyses on specific use of non-olmesartan ARBs and subsequent VA other types of ACEIs were not considered. For the usage of both ARBs and any ACEI we performed stratified analyses by sex and by age at time of biopsy showing VA (0-19 years, 20-39 years, 40-59 years and 60 years). In this study we choose to include also children, as national prescription data indicate that more than 1000 Swedish children per year are treated with any ACEIs.¹⁸ To evaluate potential causality we estimated the dose- and time-dependent association between ARB/ACEI medication and VA in two separate analyses: (1) when individuals had received at least 2 prescriptions of any ARB/ACEI and (2) when an ARB/ACEI had been prescribed one year (>365 days) before biopsy. Education level has been associated with overall drug utilization¹⁹ and health care utilization (and ascertainment of small-intestinal VA).²⁰ In a sub-analysis we therefore adjusted for education using seven predefined education categories determined by Statistics Sweden.

In order to contrast the use of ARBs/ACEIs in patients with VA we also examined its usage as compared with individuals with small-intestinal inflammation without villous atrophy (Marsh grade 1-2) and individuals with normal small-intestinal mucosa (Marsh grade 0) but positive celiac disease serology. In this subanalysis we used logistic regression adjusted for age at time of biopsy (showing VA, inflammation or normal mucosa), sex and calendar year of study entry to estimate ORs and 95% CIs.

Post-hoc analyses

While most studies implicating drug-induced sprue-like enteropathy implicate olmesartan, two studies have reported cases of VA associated with non-olmesartan ARBs; irbesartan and valsartan, respectively.^{10,21} We therefore collected data on the specific use of irbesartan (ATC-code: C09CA04) and valsartan (ATC-code C09CA03).

In a post-hoc analysis we specifically examined the association between previous use of ARBs/ACEIs among 2118 individual with small-intestinal inflammation without VA (Marsh grade 1-2) as compared with matched controls from the general population (n=10,442) (see matching procedure described above for patients with VA).

We have previously shown that celiac patients with small-intestinal VA have a more favorable cardiac risk profile, including decreased risk of hypertension, as compared with

the general population.²² Therefore, to examine the susceptibility to confounding by indication we contrasted the use of ARBs/ACEIs by examining the association between VA and previous antihypertensive therapy with calcium channel blockers. Data on use of any calcium channel blocker (ATC code: C08) were collected from the Prescribed Drug Register between July 1st 2005 and January 29th 2008 and up to the date of biopsy showing VA (and the corresponding date in matched controls).

For the analyses on previous use of ARBs/ACEIs in individuals with VA we examined for interactions between sex and exposure via the inclusion of multiplicative interaction terms in an unconditional logistic regression model adjusted for age, sex and calendar year.

Statistical significance was defined as 95% CIs for risk estimates not including 1.0 and *P* values <.05. SPSS version 22.0 was used for all statistical analyses.

Ethics

This study was conducted in accordance with national and institutional standards and was approved by the Regional Ethical Vetting Board in Stockholm.

Results

Out of the 2933 individuals with VA some 60% were females. The median age at biopsy was 28 years (58.5% of those with VA were biopsied in adulthood) (Table 1).

Use of ARBs

66 individuals with VA (2.3%) and 387 controls (2.7%) had an earlier record of medication with a non-olmesartan ARB, equivalent to an OR of 0.84 for subsequent VA (95% CI = 0.64-1.09). None of the children with VA had a previous treatment with an ARB. Among adults with VA, ORs did not differ appreciably according to age at time of biopsy (Supplemental table 1). Adjustment for education level revealed an unchanged OR (adjusted OR = 0.84; 95% CI = 0.64-1.11; *P* = .22). As compared with sex-matched controls we found a significantly decreased risk estimate for VA in females with previous treatment with an ARB (OR = 0.61; 95% CI = 0.40-0.92), that was not found in men (OR = 1.09; 95% CI = 0.77-1.55). *P* value for interaction (sex*ARB) in an unconditional logistic regression model was .04. We found no association between VA and repeated prescriptions of ARBs or treatment initiated at least one year (>365 days) before biopsy (Table 2).

ORs for previous use of ARBs did not differ appreciably according to calendar year at the time of biopsy (Supplemental table 2).

Use of any ACEIs

Of the 2933 individuals with VA, 165 (5.6%) had received at least one prescription of any ACEI before biopsy showing VA as compared with 5.2% among the general population-based controls, corresponding to an OR for subsequent VA of 1.08 (95% CI = 0.90-1.30) (Table 3). Restricting our analysis to individuals with VA biopsied in adulthood we found largely unchanged risk estimates (OR = 1.08; 95% CI = 0.89-1.30; *P* = .44). Adjustment for education level revealed largely unchanged OR: adjusted OR = 1.12; 95% CI = 0.93-1.35;

$P=.25$. The association between use of any ACEI and subsequent VA was similar in males and females (Males: OR = 1.22, 95% CI = 0.95-1.56; Females: OR = 0.94; 95% CI = 0.71-1.25), as compared with sex-matched controls. P value for interaction (sex*ACEI) in an unconditional logistic regression model was .21.

We found no indication of a dose-response effect for individuals with repeated prescriptions of ACEIs (OR = 1.06, 95% CI = 0.88 - 1.28). As expected, treatment with ACEIs was very rare among children and was increasingly more common according to age at the time of biopsy. Among those aged 20-39 years at the time of biopsy, 6 individuals with VA (1.1%), as compared with 7 controls (0.2%) had previously been treated with any ACEI (OR = 3.82; 95% CI = 1.41-10.38). In none of the remaining age bands, nor in stratified analyses by calendar year at time of biopsy, did we find an association between prior use of ACEIs and subsequent VA (Supplemental table 3 and Supplemental table 4, respectively).

Subanalyses

In a number of pre-planned subanalyses we also examined the use of ARBs/ACEIs in patients with VA as compared with individuals with small-intestinal inflammation without VA and individuals with normal small-intestinal mucosa but positive celiac disease serology. Overall, we identified 2738 individuals with these potentially prodromal stages of VA. In this secondary control group 63% were females and the median age at time of biopsy was 41 years.

Using logistic regression analysis adjusting for sex, age and calendar year of study entry we found only marginally changed ORs for previous use of any ACEIs in individuals with VA as compared with individuals with mucosal inflammation or with normal biopsy but positive celiac disease serology (adjusted OR = 1.08; 95% CI = 0.87-1.35) (Supplemental table 5). Neither did we find a statistically significant association between VA and repeated use of any ACEI medication as compared with individuals with mucosal inflammation or normal mucosa but positive celiac disease serology (adjusted OR = 1.07; 95% CI = 0.85-1.34).

Overall, use of ARBs was not related with subsequent VA as compared with individuals with small-intestinal inflammation or normal mucosa but positive celiac disease serology (Supplemental table 6).

Post-hoc analyses

In a post-hoc analysis 7 individuals with VA (0.2%) and 37 controls (0.3%) had an earlier record of irbesartan (ATC-code: C09CA04), equivalent to an OR of 0.93 for subsequent VA (95% CI = 0.42-2.09; $P=.87$). Looking specifically at the earlier use of valsartan (VA: 4/2933 [0.1%]; controls: 38/14,571 [0.3%]), revealed a slightly lower OR for subsequent VA (OR = 0.52; 95% CI = 0.19-1.44; $P=.21$).

Out of the 2118 individuals with small-intestinal inflammation without VA, 111 (5.2%) had an earlier record of medication with a non-olmesartan ARB, as compared with 341/10,442 (3.3%) controls from the general population (OR = 1.63; 95% CI = 1.31-2.03; $P<.001$). We found largely similarly increased ORs for subsequent smallintestinal inflammation without VA after repeated prescriptions of ARBs (OR = 1.62; 95% CI = 1.30-2.02; $P<.001$),

however no increased risk after ARB treatment initiated at least one year (>365 days) before biopsy (OR = 1.09; 95% CI = 0.73-1.64; $P=.66$). In individuals with intestinal inflammation without VA ORs for previous ACEI treatment was 1.57 (95% CI = 1.33-1.86; $P<.001$) (repeated use of ACEIs: OR = 1.57; 95% CI = 1.32-1.86; $P<.001$; ACEI treatment initiated at least one year before biopsy: OR = 1.17; 95% CI = 0.88-1.58; $P=.28$).

Finally, to contrast the use of ARBs/ACEIs we examined the previous use of calcium channel blockers in individuals with VA (86/2933 [2.9%]) as compared with general population-based controls (502/14,571 [3.4%]) (OR = 0.83; 95% CI = 0.66-1.06; $P=.13$)

Discussion

In this study we examined the association between blockers of the angiotensin pathway and VA. Our study involved almost 3,000 individuals with VA and we found overall no positive association with prior use of ARBs or ACEIs as compared with the general population; nor did we find a relationship between these drugs and VA when restricting our definition of exposure to multiple prescriptions. Neither did we find an association between previous use of ARBs/ACEIs in individuals with VA as compared with individuals with milder small-intestinal histopathology.

Olmесartan is not used in Sweden, but a large number of individuals are treated with non-olmesartan ARBs and a positive finding here would have larger health implications than an effect restricted to olmesartan. While the bulk of recent case reports and series implicating drug-induced sprue-like enteropathy implicate olmesartan, a recent French study¹⁰ included one case of non-olmesartan (irbesartan) associated VA, and there is also case reports of valsartan- and telmisartan-associated VA.²¹²³ Subtle histologic abnormalities short of VA have been reported with olmesartan use, but not with other ARBs.²⁴ It therefore has been a pressing concern whether this recently-described sprue-like enteropathy is a class effect or is unique to (or more closely associated with) olmesartan. Our study, which includes 2933 patients with VA and 14,571 matched controls who were exposed to ACEIs and non-olmesartan ARBs found no association between these drugs and VA.

Olmесartan appears to cause a sprue-like enteropathy, but has not been shown to trigger celiac disease *per se*. In a chart validation of a randomly selected sample of patients from our cohort, 95% of those with VA later received a clinical diagnosis of celiac disease.¹¹ However, it is likely that prior to the first report of this clinical entity in June 2012,⁵ patients with this condition would be misdiagnosed with celiac disease. Indeed, the initial case series describing olmesartan-associated enteropathy arose from referral centers for celiac disease, as many of these patients were initially thought to have non-responsive or refractory celiac disease.^{5,25} Therefore, we believe that a sprue-like enteropathy would be detectable in an analysis of patients with VA biopsied prior to 2012. The fact that we found no association between ARB/ACEI use and VA suggests that sprue-like enteropathy is not commonly triggered by these drugs.

Instead, the findings of our study are more consistent with the randomised clinical trial by Menne *et al* who were unable to detect an increased risk of enteropathy in patients

prescribed olmesartan.⁷ That study included a median follow-up of 3.2 years and olmesartan-associated enteropathy can develop after even 10 years of drug exposure.¹⁰ It is possible that non-olmesartan ARBs may trigger an enteropathy that we were unable to detect due to the relatively short drug exposure time in our study.

Our null findings in regard of subsequent VA can be interpreted in several ways. First, the available non-olmesartan drugs used in Sweden may not be associated with VA. The mechanism underlying olmesartan-induced enteropathy is unknown but it has been hypothesized to be the result of a pro-apoptotic effect of angiotensin II on intestinal epithelial cells.⁸ Speculatively this apoptotic effect may hence be limited to olmesartan. Second, several papers have linked olmesartan to serology-negative villous atrophy.²⁵ Our data collection was based on mucosal abnormalities and not primarily serology, but an earlier validation of a subset of patients with VA from our cohort found that 88% had a positive celiac serology at time of biopsy (here defined as TTG/EMA but also positive antigliadin since our cohort stretches back to 1969).¹¹ On interviewing 180 gastroenterologists and 68 pediatricians at the time of data collection (year 2008), 86 and 100% respectively reported that a positive serology was part of their diagnostic algorithm in at least 8/10 patients.¹¹ Hence the proportion of serology-negative individuals in our study is low potentially adding to our null findings. Third, as noted above, if ARBs only induce VA after long period of use, we may have missed a positive association. The Swedish Prescribed Drug Register that was used to ascertain ARB medication has only been in use since mid-2005 and hence we had a short follow-up of patients.

Because celiac patients with small-intestinal VA may have a reduced risk of hypertension,^{22,26} we carried out a sensitivity analysis revealing no statistically significant association between VA and previous treatment with calcium channel blockers. These results argue against confounding by indication as a sole cause of our null-findings.

In post-hoc analyses we found positive associations between subsequent small-intestinal inflammation without VA and previous treatment with ARBs/ACEIs. However, these statistically significant increased risk estimates were confined to treatment initiated within one year before biopsy and one explanation for these findings could be that some individuals with multiple preexisting morbidity (including cardiovascular disease) undergo small-intestinal biopsy as part of a general investigation.

This study has some strengths and limitations. Among the strengths are the large numbers of patients with VA, and that ARB use was collected from an independent source (the Swedish Prescribed Drug Registry). While we cannot rule out that a small proportion of individuals with villous atrophy in this study were false-positive (an earlier blinded validation study found that Swedish pathologists correctly identify 90% of all villous atrophy),¹¹ a misclassification rate of 10% should not drive the risk estimate down to 1.08 (95% CI=0.90-1.30) and 0.84 (95% CI=0.64-1.09) for previous use of ACEIs and ARBs, respectively.

While olmesartan has often been linked to clinically severe celiac like enteropathy,⁵ we lacked individual-based information on symptom severity in our participants. However,

when examining the patient charts of 118 random individuals with VA, some 79% had gastrointestinal symptoms. Hence it is unlikely that our null findings are due to lack of classical symptoms³ in our cohort. If non-olmesartan ARBs cause enteropathy as a very rare, long-term adverse effect, our study is unlikely to have the statistical power or follow-up time to detect this effect.

In conclusion, we found no increased risk of VA in Swedish individuals with a prior record of non-olmesartan ARB use or ACEI use. Future studies should elucidate the distinct features by which olmesartan, more so than other members of this drug class, induces VA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Grant Support (Funding): KM: Karolinska Institutet, The Swedish Society of Medicine; BL: The National Center for Advancing Translational Sciences, National Institutes of Health (UL1 TR000040); JFL: The Swedish Society of Medicine, the Swedish Research Council, the Karolinska Institutet, and the Swedish Celiac Society.

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Abbreviations

ACEI	angiotensin-converting-enzyme inhibitor
ARB	angiotensin receptor blocker
ATC	anatomical therapeutic chemical (pharmaceutical classification)
AGA	antigliadin antibody
CI	confidence interval
EMA	endomysial antibody
OR	odds ratio

TTG tissue transglutaminase antibody
VA villous atrophy

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Table 1

Descriptive characteristics of individuals with small-intestinal villous atrophy.

	Villous atrophy
Total	2933
Females (%)	1796 (61.2)
Males (%)	1137 (38.8)
Median age at study entry, years (range)	28; 0-94
Age 0-19 (%)	1218 (41.5)
Age 20-39 (%)	566 (19.3)
Age 40-59 (%)	583 (19.9)
Age 60+ (%)	566 (19.3)
2005 ^a (%)	819 (27.9)
2006 (%)	1828 (62.3)
2007 ^b (%)	274 (9.3)
2008 ^c (%)	12 (0.4)

^a Beginning of study period: July 1st 2005.

^b The majority of the pathology departments delivered data on individuals with small-intestinal pathology undergoing biopsy up to the beginning of year 2007. The remaining pathology departments reported histopathology data to the end of 2007 or very early 2008. For this reason, our data included fewer individuals with villous atrophy biopsied in 2007 compared with 2006.

^c End of study period: January 29th 2008.

Reference individuals have not been included in the table because their age, sex and entry year distributions were identical to those of the individuals with villous atrophy (due to matching).

Table 2

Odds ratios ^a for prior use of angiotensin receptor blockers (ARBs) in individuals with villous atrophy as compared with general population matched controls.

	Villous atrophy (%)	Controls (%)	Odds ratio	95% CI	P value
ARBs ^b	66/2933 (2.3)	387/14,571 (2.7)	0.84	0.64-1.09	.19
Sex					
Males	41/1137 (3.6)	187/5645 (3.3)	1.09	0.77-1.55	.62
Females	25/1796 (1.4)	200/8926 (2.2)	0.61	0.40-0.92	.02
Repeated prescriptions of ARBs	64/2931 (2.2)	378/14,562 (2.6)	0.83	0.63-1.09	.18
Use of ARBs >1 year before biopsy	22/2889 (0.8)	119/14,303 (0.8)	0.93	0.59-1.49	.78

ARBs, angiotensin receptor blockers; CI, confidence interval.

^a Odds ratios estimated through conditional logistic regression. Through this statistical approach all analyses were carried out stratumwise and thereby conditioned on age at time of biopsy (and corresponding date in controls), calendar period, sex and county of residence.

^b Use of ARBs (ATC-code: C09C) used between July 1st 2005 and January 29th 2008.

Table 3

Odds ratios ^a for prior use of any angiotensin-converting enzyme inhibitors (ACEIs) in individuals with villous atrophy as compared with general population matched controls.

	Villous atrophy (%)	Controls (%)	Odds ratio	95% CI	P value
Any ACEI ^b	165/2933 (5.6)	762/14,571 (5.2)	1.08	0.90-1.30	.41
Sex					
Males	99/1137 (8.7)	418/5645 (7.4)	1.22	0.95-1.56	.12
Females	66/1796 (3.7)	344/8926 (3.9)	0.94	0.71-1.25	.66
Repeated prescriptions of any ACEI	160/2928 (5.5)	751/14,560 (5.2)	1.06	0.88-1.28	.52
Use of ACEI > 1 year before biopsy	47/2815 (1.7)	238/14,047 (1.7)	1.01	0.72-1.41	.98

ACEIs, angiotensin-converting enzyme inhibitors; CI, confidence interval.

^a Odds ratios estimated through conditional logistic regression. Through this statistical approach all analyses were carried out stratumwise and thereby conditioned on age at time of biopsy (and corresponding date in controls), calendar period, sex and county of residence.

^b Any ACEI (ATC-code: C09) used between July 1st 2005 and January 29th 2008.