Antihypertensive medications associated with eczematous dermatitis in older adults: A longitudinal cohort study

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Abbreviations

ACE – Angiotensin-Converting Enzyme
ARB – Angiotensin II receptor antagonists/blocker
AD – Atopic Dermatitis
BPH – Benign Prostatic Hyperplasia
CCB – Calcium Channel Blockers
CI – Confidence Interval
HR – Hazard Ratio
IQR – Interquartile Range
NICE – National Institute for Health and Care Excellence
OR – Odds Ratio
SD – Standard Deviation
SRC – Scientific Review Committee
THIN – The Health Improvement Network
UK – United Kingdom

Key Points (100 words, currently 71)

Question: Is antihypertensive drug use associated with diagnoses of eczematous dermatitis among older adults?

Findings: In a population-based primary care cohort of 1.5 million older adults, antihypertensive drug use was associated with a 29% increase in the rate of eczematous dermatitis diagnoses. The hazard rate was highest for diuretics and calcium channel blockers and lowest for ACE-inhibitors.

Meaning: Physicians should consider antihypertensive treatments as part of the differential diagnosis for older patients presenting with eczematous dermatitis.

ABSTRACT (349, limit 350 words)

Importance: Rates of physician-diagnosed eczema have been increasing among older adults, but little is known about the pathophysiology and best treatments in this subgroup. Preliminary data suggest that medications, and antihypertensive medications in particular, may contribute to eczematous dermatitis, but there have been no population-based studies to quantify the proportion of eczematous diagnoses among older adults that could be attributed to antihypertensive drugs.

Objectives: To determine whether antihypertensive drug use is associated with eczematous dermatitis.

Design: Longitudinal cohort study

Setting: United Kingdom primary care practices participating in The Health Improvement Network

Participants: Population-based sample of individuals ages 60 years and older without a diagnosis of eczematous dermatitis at baseline

Exposure: Exposure date was based on the first prescription for an antihypertensive drug within each drug class.

Main outcome measures: Newly active eczematous dermatitis was based on the first date for one of the five most common eczema codes used in a previously validated algorithm.

Results: Among 1,561,358 older adults (54% female), the overall prevalence of atopic eczema was 6.7% during a mean of 6 years of follow-up (range 3-11 years). Eczematous dermatitis incidence was higher among participants receiving antihypertensive drugs than those did not (12 vs 9/1,000 person-years of follow-up). Using adjusted Cox proportional hazards models, we found that participants who received any antihypertensive drugs had a 29% increased hazard rate of any eczematous dermatitis (Hazard Ratio (HR) 1.29; 95% CI 1.26-1.31). When examining each antihypertensive drug classes individually, the largest effect size was seen for diuretics (HR 1.21; 95% CI 1.19-2.24) and calcium channel blockers (HR 1.16; 95% CI 1.14-1.18), and the smallest effect sizes were for angiotensin-converting enzyme inhibitors (HR 1.02; 95% CI 1.00-1.04) and beta-blockers (HR 1.04; 95% CI 1.02-1.06).

Conclusions and Relevance: Antihypertensive drugs were associated with a small increased rate of eczematous dermatitis. Effect sizes were largest for calcium channel blockers and diuretics, and smallest for angiotensin-converting enzyme inhibitors and beta-blockers. Although additional research is needed to understand the mechanisms underlying the association, these data could be helpful to clinicians to guide clinical management after a patient presents with eczematous dermatitis in older age.

INTRODUCTION

Rates of physician-diagnosed atopic eczema (also known as atopic dermatitis) have been increasing among older adults; a recent population-based study found that 8% of adults over age 60 had prevalent disease, and that this proportion had been increasing over time, especially among the oldest adults.[1] Because most eczema research has focused on children and younger adults, little is known about the pathophysiology and best treatments for the older adult subgroup.[2] Moreover, the clinical presentation among older adults can be non-specific, especially among those with late-onset disease. It has been hypothesized that drug-induced eczematous dermatitis may be a common cause of atopic eczema misdiagnosis among older adults.[3,4]

When making a diagnosis of atopic eczema, it is recommended that clinicians rule out adverse drug reactions as an exclusionary condition.[5-7] However, this is challenging to do in clinical practice because most older adults take multiple prescription drugs, skin reactions may take months to clear after drug discontinuation, and skin patch tests are rarely helpful in this context.[8] Therefore, it would be helpful for clinicians to have more data on potential candidate drugs to guide clinical decisions about drug discontinuation and quantify some of the heterogeneity in causes of eczematous dermatitis among older adults.

Antihypertensive drugs are among the most prescribed medications for older adults and two small single-institution case-control studies have found associations between antihypertensive drugs and eczematous dermatitis: a study of 102 patients found that calcium channel blockers were associated with an odds ratio (OR) of 2.5 (95% CI 1.3-4.6) for eczematous dermatitis,[9] and a study of 94 cases found an increased odds of eczematous rashes among individuals receiving calcium channel blockers (CCB) and thiazides (OR 4.21, 95%CI 1.77-9.97 and OR 2.07, 95%CI, 1.08-3.96 respectively).[10] To date, there have been no population-based studies to quantify the proportion of eczema diagnoses among older adults that could be attributed to antihypertensive drugs and to examine the relative rate of eczematous rashes among different

antihypertensive drug classes. The objective of this study was to evaluate the association between antihypertensive drug prescriptions and diagnoses of eczematous dermatitis among older adults in a large nationally representative cohort.

METHODS

Participants. We used routinely collected primary care electronic health record data from The Health Improvement Network (THIN) cohort from 1994 to 2015, SRC Approval #14-083. The study was exempt from UCSF IRB approval because we received fully de-identified data. We chose the THIN cohort for this analysis because it contains population-based longitudinal data enabling valid assessment of physician-diagnosed atopic dermatitis, prescriptions, and relevant covariates.[11-15] THIN contains the records of over 17 million patients (3.1 million of which are actively registered and followed) collected from 562 general practices, covering approximately 7% of the UK population.[16] Patients in participating practices are automatically enrolled until the practice opts out from the study, and all data are fully de-identified, processed, and validated by a central organization. Because of more equitable access to health care services through universal healthcare and key role of the general practitioner as the gatekeeper for all care in the UK, THIN is generally considered to be reliable for the study of pharmacoepidemiology and chronic conditions.[13,17] THIN used the Read medical classicization system through 2016 before switching to the ICD coding system; code lists used to define variables for our analysis are listed in the supplementary material.

Cohort Selection. Start of follow-up began at the latest of the following dates: start of follow-up, one year after a patient's registration date, the date the patient turned 60 years of age, or the date their practice met THIN quality control standards (based on computerized prescriptions and acceptable mortality reporting). Patients that met the definition of eczematous dermatitis or received a prescription for an antihypertensive drug before their start of follow-up were excluded from analysis (Figure 1 and Figure 2). This resulted in

a unique sample size for each drug group analysis. The follow-up period ended at the first occurrence of the following events: the outcome of interest (eczema diagnosis), a death date recorded in THIN, end of registration with practice, or end of available follow-up data.

Exposure. The exposure date was based on the first prescription for an antihypertensive drug within each drug class. Participants contributed follow-up time in the unexposed category until they received a prescription for the drug class of interest and, for the primary analysis, remained in the exposed group until the end of follow-up. In a sensitivity analysis described below, we allowed patients to return to the unexposed group 3 months after their last prescription; if they received a subsequent prescription after >3 months, they were censored at that time because of the limitations of the THIN database for studying detailed windows of drug exposure.

Outcome. The primary outcome, newly active eczematous dermatitis, was defined based on medical codes. We previously validated an algorithm among older adults which includes at least one eczema medical code and at least two eczema treatments on different dates,[11] but this algorithm was designed to detect prevalent eczema rather than newly active eczema. Therefore, we used the first time a participant receives a code for one of the five most common eczema codes used in the validated algorithm. We examined alternate definitions using other sets of codes in sensitivity analyses as described in the sensitivity analysis section below.

Covariates. Covariates included patient sex, general practice, age at start of follow-up, an area-level measure of socioeconomic status (Townsend score), and time-updated exposure to other antihypertensive classes. To address potential ascertainment bias, we also included the number of general practice (aka primary care) visits one year prior to start of follow-up, and influenza vaccination one year prior to start of follow-up. To address possible confounding by indication, we also included codes for a history of chronic kidney disease (modeled as a time-varying variable), which is both associated with eczema and

can influence antihypertensive choice.[18,19] We performed an eValue analysis to evaluate the potential magnitude of unmeasured confounders.[20,21]

Statistical Analysis. The primary analysis examined the rate of eczematous dermatitis diagnosis by antihypertensive drug exposure status. We used Kaplan Meier curves to illustrate eczematous dermatitis diagnosis rates among status groups, calculated the incidence rate and absolute rate difference for eczematous dermatitis diagnosis among those with and without drug exposures, and developed Cox proportional hazard models that controlled for covariates.

Sensitivity analyses. We performed multiple pre-planned sensitivity analyses to confirm the stability of our results to different assumptions (Supplemental Table 3). First, to examine whether there was potential confounding by indication, we repeated the analysis but stratified by whether participants received a diagnostic code for hypertension at any time point. We also repeated the main analysis additionally adjusting for time-updated hypertension. Second, to address potential severity bias by comparison to untreated patients, we restricted the sample to patients receiving only one drug subclass and compared between treatments (as opposed to unexposed time/participants). Third, to explore the attribution of exposure time, we allowed participants to accrue unexposed patient time if they did not receive a subsequent prescription for the drug of interest within 3 months. Fourth, to explore whether there were temporal differences in the association, we censored patients after 3 months, 9 months, and 12 months of treatment. Fifth, we examined the impact of using different definitions of the outcome based on a longer list of non-specific eczema codes, and codes specifically referring to drug-induced dermatitis. Sixth, we substituted the outcome with seborrheic keratoses – an alternative skin condition not hypothesized to have an association with antihypertensive drugs and meant to serve as a negative control. Post-hoc sensitivity analyses were added to examine the possibility for temporal (calendar year) trends, to account for the competing risk of death using a Fine-Gray model, to adjust for congestive heart failure, and to exclude patients with diagnoses of asteatotic eczema and varicose veins that could have been misdiagnosed as

eczematous dermatitis.[22] Finally, we examined whether there were differences among specific medications within subclasses of antihypertensives.

RESULTS

Participants. Among 1,561,358 participants, 105,007 (6.7%) were diagnosed with eczematous dermatitis over 8,378,067-10,569,959 person-years of follow-up depending on the antihypertensive class. The mean age at start of follow-up was 67 years (SD 9 years), and the median duration of follow-up was 6 years (IQR 3-11 years). Participants were predominantly female (54%), and 45% ever had a diagnosis of hypertension (Table 1).

The incidence of eczematous rashes ranged from 11-12/1000 patient-years among those receiving antihypertensive drugs, as compared to approximately 9/1000 patient-years among those not (Table 2). Assuming a population of 14.5 million older adults in the UK,[23] this absolute rate difference of 3 cases per 1,000 patient-years could mean that antihypertensives are associated with 43,500 new cases of eczematous dermatitis among older adults in the United Kingdom annually.

Overall, we found that participants who received any antihypertensive drug had a 33% increased rate of eczematous dermatitis (hazard ratio (HR) 1.33; 95% CI 1.31-1.35) in unadjusted analyses and a 29% increased rate of eczematous dermatitis (HR 1.29; 95% CI 1.26-1.31) after adjusting for potential confounders including age at start of follow-up, sex, practice, socioeconomic status, number of general practice visits one year prior to the start of follow-up, influenza vaccination one-year prior to start of follow-up, and chronic kidney disease in a Cox proportional hazard model (Table 2). When examining each antihypertensive drug classes individually, the largest effect size was seen for diuretics (HR 1.21; 95% CI 1.19-2.24) and calcium channel blockers (HR 1.16; 95% CI 1.14-1.18), and the smallest effect sizes were for angiotensin-converting enzyme (ACE) inhibitors (HR 1.02; 95% CI 1.00-1.04) and beta-

blockers (HR 1.04; 95% CI 1.02-1.06). Analysis of the most used drugs within the diuretics class showed larger effect sizes for loop diuretics and potassium-sparing diuretics than for thiazide diuretics, and results were similar by calcium channel blocker sub-type (Supp Table 12).

Sensitivity analyses showed that the results were robust to the variable definitions. When we additionally adjusted for time-updated hypertension, the results were similar (Supp Table 3a), and in a stratified analysis, we found higher effect sizes among those without a hypertension diagnosis than among those with a hypertension diagnosis (Supp Table 3b). When comparing the rate among participants who received only one drug class, we found an elevated rate of all eczema/dermatitis outcomes among those receiving alpha blockers and diuretics, and a lower rate among those receiving angiotensin-converting enzyme inhibitors as compared to those receiving calcium channel blockers (Supp Table 3c). Sensitivity analyses exploring the attribution of participant time revealed similar results to the main analysis (Supp Table 3d), and we did not find consistent evidence of changing effect sizes when censoring after 3, 9, or 12 months of antihypertensive use (Supp Table 3e). We evaluated the impact of using different combinations of medical codes to define eczematous dermatitis. When we used a larger list of non-specific eczema codes (Supp Table 4), 278,487 or 18.9% met the new definition of the outcome and we found similar but slightly attenuated associations with each of the drug classes (range 1.06-1.19, Supp Table 5). When we used a narrower set of codes specifically for drug-induced dermatitis, 2,013 or 0.1% of the population met the new definition of the outcome and we found larger hazard ratios, ranging from 1.18-1.50 for each of the drug classes (Supp Table 5). When we substituted the outcome with a negative control, we did not find associations for most drug classes, with the exception of angiotensin receptor blockers (Supp Table 6). The eValue analysis found that an unmeasured confounder would need to have a hazard ratio of 1.9 with both antihypertensive drug use and eczematous dermatitis to fully explain the associations (Supp Table 7). Adding a covariate for calendar year, using a Fine-Gray approach accounting for the competing risk of death (Supp Tables 8-9), adjusting for congestive heart failure, and excluding

patients with diagnoses of asteatotic eczema and varicose veins also showed similar results (Supp Tables 10-11).

DISCUSSION

Using a well-characterized primary care database with physician diagnoses and comprehensive prescription information on over 1,500,000 older adults, we found a small increased rate of eczematous dermatitis after prescriptions of antihypertensive drugs. The association was largest for diuretics and calcium channel blockers (16-21% increased rate), and the smallest for ACE inhibitors and beta-blockers (2-4% increased rate). Within antihypertensive drug classes, loop and potassium-sparing diuretics appear to account for more of the effect than thiazide diuretics, and there do not appear to be large clinically meaningful differences between calcium channel blockers. Given the size of our database, we had good statistical power to detect small effect sizes; it is unclear whether this small increase in rate is clinically meaningful. Nonetheless, these results may be useful to guide management decisions among the large population of older adults that present with hypertension and eczematous dermatitis.

Two smaller case-control studies from clinic populations also found associations between antihypertensive drugs and eczematous dermatitis: a French study found an OR of 2.50 (95% CI: 1.30-4.60) for eczematous dermatitis after CCB use among patients over age 60,[9] and a US study found ORs of 4.21 (95% CI, 1.77-9.97) and 2.07 (95% CI, 1.08-3.96), respectively, after CCB and thiazide diuretic use among patients over age 50.[10] The difference in the 2 to 4-fold increase in risk in these studies and the 16%-21% increase in rate in our study could be because the studies were conducted in dermatology clinics, which may have led to a selection of more severe forms of eczematous dermatitis cases, and/or lack of adjustment for potential confounders like chronic kidney disease and socioeconomic status, which we adjusted for in our study. Neither of these studies found an association with ACE inhibitors, angiotensin II receptor antagonists/blockers (ARBs), beta blockers, and alpha blockers, whereas we found

evidence of a small increase in rate for all of these drug classes. Our database was much larger, therefore we had greater statistical power to detect small effect sizes which may not be clinically relevant. Because they were single-institution studies, they were limited in sample size, and many of these drug classes had small numbers of users, potentially decreasing their power to detect any significant associations. A limitation of our study is lack of detailed data on dermatitis severity and resolution. In the French study, resolution of symptoms occurred in 68% of the cases three weeks after stopping CCB use and recurrence of symptoms half a week after restarting treatment.[9] A case series of 23 patients aged 66 to 87 years found that eczematous rashes resolved within three to four months in all cases after ACE inhibitors and ARBs withdrawal and recurred in seven out of 11 patients with re-challenge of the drugs.[4] Case reports of one to two patients showed similar findings with treatment with amlodipine, ARBs, and ACE inhibitors.[24,25]

The drug labels for most antihypertensives mention rash or dermatitis, but most report it as an adverse effect in <1% of patients. Exceptions include pruritus or rash in <3% of patients for nifedipine which is a calcium channel blocker, 1-10% of patients for metoprolol which is a beta blocker, 1-10% rash for candesartan, irbesartan, and telmisartan which are ARBs, and >10% rash with captopril which is an ACE inhibitor.

We did not anticipate finding an association across all antihypertensive drug classes. Multiple studies have reported an association between eczema and hypertension,[26] and therefore it is possible that there is confounding by indication (i.e., participants with hypertension are also more likely to be diagnosed with eczema). However, in stratified analyses, the effect sizes were larger among those without hypertension diagnoses (Supp Table 3b) and confounding by indication is unlikely to explain the differential effect across antihypertensive classes. Notably, the HR was most increased among those without hypertension receiving alpha blockers, many of whom are likely to have a diagnosis of benign prostatic hyperplasia (BPH) and those without hypertension receiving diuretics who are likely to have a diagnosis of heart failure. These results could suggest that sicker patients with more comorbidities are most likely to develop

eczematous rashes. They could also explain why the HR is the larger for the 'any antihypertensive' group as compared to any individual antihypertensive class; only the first antihypertensive is used in the 'any' group, therefore there may be an apparent relative increase in the effect size because of depletion of susceptible patients that are receiving multiple antihypertensives and who are likely to be sicker or have more treatment-resistant disease.

There also exists the potential for ascertainment bias, wherein patients who are more likely to go to the doctor and receive antihypertensive drugs are also more likely to receive eczema diagnoses, though the true rate of eczema may be the same. We attempted to address this by adjusting for the number of times participants had seen their physician and whether they had received standard immunizations recommended for their age group, and our analyses did not suggest ascertainment bias was likely. An eValue analysis showed that a confounder would require a relative strong association (a relative rate of at least 1.9) with both the exposure and outcome to explain the results; future research should examine the impact of confounders we were unable to measure in this study, including dietary salt intake, which is strongly associated with hypertension and possibly linked to eczema.[27,28] Though additional research is needed to confirm our results and understand the potential underlying mechanisms, the results of these sensitivity analyses, including those using a negative control, suggest a real effect unlikely to be due to confounding.

Limitations of the study: The presentation and severity of dermatitis is quite heterogeneous, especially among older adults, and we lacked detailed data on dermatitis severity and resolution. Also, there was no data on what happens to patients when they change antihypertensive medications. Clinicians should consider the trade-offs of changing antihypertensive medications versus treating the eczematous dermatitis, which could potentially be managed with relatively low-risk therapies like topical steroids or phototherapy. Moreover, while THIN is representative of the UK general population, the extent to which the results generalize to other contexts is unclear. In particular, the UK is predominantly European and

THIN only includes data on the ethnic makeup of 23.1% of participants.[29] Future research should address the impact of race and ethnicity because hypertension treatment guidelines often differentiate based on race/ethnicity.

In summary, we found that in a large, population-based study, antihypertensive drugs were associated with a small increased rate of eczematous dermatitis. The association was largest for diuretics and calcium channel blockers (16-21% increased rate), and the smallest for ACE inhibitors and beta-blockers (2-4% increased rate). Current National Institute for Clinical Effectiveness hypertension treatment guidelines recommend starting a CCB for adults over age 55.[30] Based on the currently available evidence, if a clinical workup does not identify another cause for the dermatitis,[31] and it is bothersome and does not respond to treatment, clinicians could consider switching patients to a different class of antihypertensive like an ACE inhibitor. Although additional research is needed to understand the mechanisms underlying the association and this observational study was unable to assess causality or study the effect of antihypertensive discontinuation on dermatitis remission, these data could be helpful to clinicians to guide clinical management after a patient presents with eczematous dermatitis in older age.

Data Sharing Statement: Data were accessed through a vendor (https://www.the-health-improvement-network.com/) and are protected from direct sharing through a data access agreement. Code lists are available on LSHTM Data Compass (https://datacompass.lshtm.ac.uk/), and analytic code is available on request from the corresponding author.

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Table 1. Participant characteristics

Characteristic	Total N=1,561,358	Antihypertensives N = 1,001,025 (64.11%)	No Antihypertensives N = 560,333 (35.89%)
Sex			
Female	845,913 (54.18)	555,443 (55.49)	290,470 (51.84)
Male	715,445 (45.82)	445,582 (44.51)	269,863 (48.16)
Townsend score			
1 (least deprived)	410,156 (26.27)	250,753 (25.05)	159,403 (28.45)
2	371,759 (23.81)	233,830 (23.36)	137,929 (24.62)
3	323,279 (20.70)	210,046 (20.98)	113,233 (20.21)
4	273,194 (17.50)	183,016 (18.28)	90,178 (16.09)
5 (most deprived)	182,970 (11.72)	123,380 (12.33)	59,590 (10.63)
Hypertension			
Yes	707,500 (45.31)	671,013 (67.03)	36,487 (6.51)
No	853,858 (54.69)	330,012 (32.97)	523,846 (93.49)
Chronic kidney disease			
Yes	224,243 (14.36)	204,184 (20.40)	20,059 (3.58)
No	1,337,115 (85.64)	796,841 (79.60)	540,274 (96.42)
Flu vaccination			
Yes	52,575 (3.37)	40,804 (4.08)	11,771 (2.10)
No	1,508,783 (96.63)	960,221 (95.92)	548,562 (97.90)
General practice visits			
0	290,538 (18.61)	151,557 (15.14)	138,981 (24.80)
1-5	644,392 (41.27)	396,555 (39.61)	247,837 (44.23)
6+	626,428 (40.12)	452,913 (45.24)	173,515 (30.97)
Age at start-of-follow-up (years)			
Mean (SD)	67.36 (8.91)	68.39 (9.11)	65.51 (8.24)
Median (IQR)	63.50 (12.78)	65.50 (14.51)	60.50 (8.50)
Duration of follow-up (years)			
Mean (SD)	6.92 (5.12)	7.70 (5.26)	5.52 (4.54)
Median (IQR)	5.81 (8.00)	6.90 (8.45)	4.52 (6.43)

Table 2. Absolute and relative rate of eczematous dermatitis by antihypertensive drug class

	N	Person-years	Eczema events	Eczema incidence rate/1000 person-years	Unadjusted HR (95%CI)	Adjusted HR (95%CI)
Any antihypertensive[a]						
Non-users	560,333	4729294	37968	8.0 (7.9- 8.1)	Ref	Ref
Users	352,972	2091302	23149	11.1 (10.9-11.2)	1.33 (1.31, 1.35)	1.29 (1.26, 1.31)
By antihypertensive class[b]						
Alpha Blockers						
Non-users	1,423,640	10021799	95347	9.5 (9.5-9.6)	Ref	Ref
Users	88,579	501728	6384	12.7 (12.4-13.0)	1.28 (1.24, 1.31)	1.08 (1.05, 1.11)
Angiotensin-Converting Enzyme Inhibitors						
Non-users	1,038,474	8049494	73907	9.2 (9.1-9.3)	Ref	Ref
Users	302,887	1595028	18394	11.5 (11.4-11.7)	1.20 (1.18, 1.22)	1.02 (1.00, 1.04)
Angiotensin Receptor Blockers						
Non-users	1,392,306	9977804	94738	9.5 (9.4-9.6)	Ref	Ref
Users	114,634	592155	7489	12.7 (12.4-12.9)	1.28 (1.25, 1.31)	1.12 (1.09, 1.15)
Beta Blockers						
Non-users	1,063,338	7631412	70345	9.2 (9.2-9.3)	Ref	Ref
Users	196,576	1195140	13339	11.2 (11.0-11.4)	1.16 (1.14, 1.18)	1.04 (1.02, 1.06)
Calcium Channel Blockers						
Non-users	1,071,954	8016190	72114	9.0 (8.9-9.1)	Ref	Ref
Users	256,706	1400926	16872	12.0 (11.9-12.2)	1.29 (1.26, 1.31)	1.16 (1.14, 1.18)
Diuretics						
Non-users	848,622	6601397	56808	8.6 (8.5-8.7)	Ref	Ref
Users	311,631	1776671	20782	11.7 (11.5-11.9)	1.30 (1.28, 1.33)	1.21 (1.19, 1.24)

[a]Exclusion criteria was implemented for all drugs at the same time and adjusted for age at start of follow-up, sex, general practice, socioeconomic status, number of general practice visits one year prior to start of follow-up, influenza vaccination one year prior to start of follow-up, and chronic kidney disease.

[b]Additionally adjusted for remaining five antihypertensive drug classes