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Hypertension, Antihypertensive Medications Use and Risk of Age-Related Macular Degeneration in California Teachers Cohort

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Abstract

Sustained and inadequately controlled hypertension can promote the development of age-related macular degeneration (AMD) through multiple biologic pathways. Epidemiologic studies of high blood pressure, antihypertensive therapies, and the risk of AMD thus far have been inconclusive. However, few studies evaluated risks according to the use of different classes of antihypertensive drugs or took combinations of use into account. We performed a prospective cohort study by linking the California Teachers Study (CTS) cohort (N = 88 481) to statewide hospital discharge records up to Dec. 31, 2012. History of high blood pressure, regular use of antihypertensive medications, and comprehensive risk factor information was collected via self-administered questionnaires at baseline in 1995–1996, and information on specific classes of antihypertensive drugs was provided by a sub-sample of CTS participants who completed a follow-up questionnaire in 2000. We identified 1,762 female teachers with AMD during 14.8 years of follow-up on average. Applying Cox proportional hazard regression, we estimated increased risks of AMD among women treated for hypertension at baseline (HR = 1.15, 95% CI: 1.03, 1.30); the magnitude of the association increased with longer duration of antihypertensive treatment. In the subsample with more specific information on type of medication use, we estimated a 45% increased risk of AMD among women receiving diuretics as monotherapy compared to women with medications more potent than diuretics (HR = 1.45, 95% CI 1.10, 1.90) In women treated with a combination of antihypertensive drugs, we observed no increased risk of AMD for any individual class of drugs.

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Conflicts of interest: None of the authors

Introduction

Both age-related macular degeneration (AMD) and the prevalence of high blood pressure increase with advancing age. Hypertension is thought to increase the risk of AMD through damaging retinal vessels (1) or aggregate age-related vascular dysfunction (2). Narrowed retinal arteries resulting from chronic hypertension may result in reduced choroidal blood flow or a disturbed vascular homeostasis of the retina that causes geographic atrophy (GA) or stimulates choroidal neovascularization, a key feature of wet-AMD (3). Previous epidemiologic studies of elevated systemic blood pressure and its treatment and AMD reported inconsistent findings. The Framingham Study found increased risk of moderate to severe age-related maculopathy in 25 years of follow-up among participants who had hypertension at baseline and the strength of the associations increased with longer duration of chronic hypertension (4). This finding has been confirmed in some (5, 6) but not all population-based studies for AMD at any stage (7, 8).

Antihypertensive treatment effects on AMD have also been investigated. A case-control study that reported that a history of hypertension doubled the risk of neovascular AMD also found physician-reported antihypertensive medication treatment to increase the risk of neovascular AMD by 2.5 times (12). Increased risk of AMD for specific types of antihypertensive drugs was observed for calcium channel blockers (9, 13), beta blockers (11, 14), and thiazide diuretics (15) in some but not all studies (9, 11, 13, 14, 15). However, these studies have not supported a dose-dependent effect (9, 13) and it remains unclear whether these medications adversely affect the eye or are simply markers of the effects from the underlying hypertensive disorder. Moreover, previous studies targeting antihypertensive medications did not consider the combined use of blood pressure lowering drugs of different classes.

Given the high prevalence of hypertension and its treatment, even a modestly increased AMD risk would have considerable public health implications, and conversely any protective effect of antihypertensives on AMD risk would be of public health relevance. Thus, it is imperative to better understand the association between antihypertensive medication use and the risk of developing AMD. The purpose of this study is to investigate whether hypertension and regular use of specific antihypertensive medications is associated with the risk of AMD accounting for the duration of use.

Subjects and Methods

A detailed description of the California Teachers Study (CTS) and its data has been published (16, 17). Briefly, a prospective cohort of 133,479 female California teachers and school professionals who completed and returned a baseline self-administered questionnaire in 1995–1996 were followed both actively with questionnaires and passively through linkage to vital statistics, cancer registries, and hospitalization records. Comprehensive sociodemographic, life-style and health history information was collected at baseline and in 1997–1998, 2000–2001, 2005–2006, and 2011–2012. The CTS cohort was annually linked to the California Office of Statewide Health Planning and Development (OSHPD) hospital

discharge records and to the California Automated Mortality Linkage System (18), the Social Security Administration Death Master File and the National Death Index.

With institutional review board (IRB) approval, we generated a linked hospital, vital status, and baseline questionnaire dataset for each CTS participant. Eligibility was limited to women who were California residents at baseline and had at least one OSHPD record available (N = 89 877) (18). Participants who, according to OSHPD records, suffered from AMD prior to completing the baseline questionnaire (N = 22) and those who did not report their regular antihypertensive medication use (n = 1 347) at baseline were excluded, leaving 88,481 participants for analysis.

The earliest AMD event was identified (ICD-9-CM codes 362.50, 362.51, 362.52, and 362.57) from OSHPD hospital discharge data (available from 12/1990−−12/2012), which captured up to 25 diagnoses. According to the guideline for secondary diagnoses in hospitals (19), only co-existing conditions that affect current treatments should be recorded. Thus, we assume that the majority of AMD cases identified in this manner were intermediate to advanced and had impaired central vision, because these patients are more likely to require additional therapeutic procedures, and increased nursing care and have an extended length of stay (20). In contrast, patients with early stage AMD do not meet the criteria for a comorbid disorder relevant to current treatment and care during hospitalization; thus, we most likely did not capture early stage AMD with our passive linkage to hospital discharge records.

Follow-up started on the day the baseline questionnaire was completed by a participant and ended at the earliest occurrence of one of four events: 1) AMD diagnosis; 2) moving out of California; 3) death; or 4) date of the most recent linkage of the CTS to OSHPD records (Dec. 31st, 2012).

At baseline, participants reported their history of high blood pressure (ever or never), regular medication use, average frequency of use, and total years of use. Regular intake of reserpine, diuretics, and other high blood pressure medications was asked separately. More detailed antihypertensive medication use was recorded in a subsequent questionnaire mailed to cohort members in 2000–2001 assessing daily medication use for at least two months within 2 years prior to the survey: thiazide diuretics, loop diuretics, calcium blocker, angiotensin-converting enzyme (ACE) inhibitors, and other antihypertensive medications. According to hypertension treating guidelines, at least two drugs are recommended at the initiation of antihypertensive therapy when the hypertension is severe (21), when there are comorbidities such as chronic kidney diseases and cardiovascular diseases, or in the presence of asymptomatic organ damage. On the other hand, adding a new agent to an existing therapeutic combination or switching to another drug is required whenever the blood pressure control target is not achieved (22). Therefore, we used the number of different classes of antihypertensive agents initiated (using 1, 2 or 3 types vs. never used) as a proxy for the difficulty of achieving BP control and compared the AMD risk across categories of these severity indicators among women who reported having hypertension in 2000.

Potential confounder and effect modifier information was identified from questionnaire data (Supplement Table 1) or OSHPD hospital discharge records and selected based on the AMD

literature (15, 23). We included in our models age (continuous), race/ethnicity (Non-Latina white, African-American, Latina, Asian/Pacific Islander, Other), body mass index (Underweight: <18.5, Normal: 18.5 to 25, Overweight: 25 to <29, Obese: ≥30) (24), diabetes mellitus (ever/never), smoking (never, former, current, passive), alcohol use in the year prior to baseline (no use, less than 20 grams per day, greater than 20 grams per day), lifetime average moderate or strenuous recreational physical activity per week (<2, 2 to <4, 4 to <6, 6 hrs or more), acetaminophen and non-steroidal anti-inflammatory medication use; baseline history of a heart failure diagnosis or other circulatory system diseases were obtained from OSHPD hospital discharge data. We also assessed percent daily dietary calories from fat, and dietary antioxidant consumption but we ultimately decided to not include them in our analyses because they changed the point estimate by less than 10%.

In our analyses of medication data reported in 2000, all the above-mentioned risk factors were updated to reflect the most recently available data. We additionally adjusted for the type of cardiac disease diagnoses that may affect the choice of antihypertensive agents: cardiac failure, cardiac arrhythmia, coronary artery disease, and other circulatory system diseases. Cholesterol-lowering medication use was also accounted for in these analyses.

Statistical Analysis

Multivariable Cox proportional hazards regression was used to assess the association between hypertension, antihypertensive medication use and AMD, using calendar time at start and end of follow-up (in days) to define person-time. Women with no history of high blood pressure were used as the reference in comparison with women with treated or untreated hypertension. We examined baseline antihypertensive medications by duration of use categories and tested for trend using category midpoints. The longest duration of use of reserpine, diuretics, or other high blood pressure medications was considered the duration of any antihypertensive medication use. Since reserpine was taken by a very small number of participants and is rarely prescribed nowadays, it was used to co-adjusted analyses of other classes of drugs but not analyzed as a separate category. The proportional hazards assumption was checked using Kaplan-Meier survival curves and graphing the log(-log(survival)) versus log of survival time; parallel lines indicate proportionality of hazards (25).

To evaluate the strength of associations between hypertension and AMD according to severity and to assess whether treatment with a specific class of antihypertensive was inferior or superior to another with regard to AMD, subsample analyses were conducted relying on the year 2000 questionnaire information. Severity of hypertension was treated as a categorical variable. Each major class of antihypertensive medication was evaluated separately. After excluding women who developed AMD, moved out of California, died before 2000, or who did not return a questionnaire in the year 2000 or did not answer questions on medication use, 56 628 subjects were eligible for subsample analyses.

Code Availability: All of the data associated with this publication and in the California Teachers Study are available for research use. The California Teachers Study welcomes all

such inquiries and encourages individuals to visit https://www.calteachersstudy.org/for-researchers.

Results

Among 88,481 female teachers enrolled in the CTS, we identified 1,762 with AMD. During an average of 14.8 years of follow-up, 6,598 (7.5%) women moved out of California and 16,444 (18.6%) died, leaving 63,677 (72%) subjects who were right censored at the end of follow-up. The median time to first AMD diagnosis was 13.5 years (interquartile range: 10.2, 15.5). The distributions of demographic and life-style factors among women who did or did not use antihypertensive medications at baseline are presented in Table 1. The self-reported rate of regular antihypertensive medication use in 1995 was 21.6%. The frequency of antihypertensive medication use increased with age and was higher among overweight or obese women (BMI ≥ 30 kg/m^2), women who exercised little (<2 hr/week moderate and strenuous physical activity), and women with a self-reported history of medical conditions at baseline that are strongly related to high blood pressure (heart attack, stroke and diabetes). The current smoking rates in this cohort were low but slightly higher among antihypertensive drug users, and the total pack-years of smoking were higher among women who regularly took antihypertensive medication due to a higher proportion of former smokers amongst them. A slightly lower proportion of women drank alcohol among antihypertensive drug users, but heavier drinkers (≥20 g/day) were more common among users.

In those with a history of high blood pressure at baseline 85% reported taking at least one antihypertensive drug with 37% taking them for more than 10 years (Table 2). Compared with teachers without high blood pressure, the risk of AMD was slightly increased in women with treated hypertension (HR = 1.15, 95% CI: 1.03, 1.30), but not in women with untreated hypertension. A positive trend was suggested with increasing duration of antihypertensive medication use (P-trend=0.08). No difference was seen between diuretic use and other antihypertensive drug use reported at baseline.

For women in the year 2000 subsample, the median time to diagnosis of AMD was 9.6 years (interquartile range: 7.0, 11.2). Compared with baseline, a higher proportion of women reported using at least one type of antihypertensive drug (27.5% vs. 21.3%). When stratifying by our indicator for severity of hypertension (number of anti-hypertensives reported), we estimated a 70% increased risk among women who reported two types of anti-hypertensives, and the risk of AMD doubled in women who used three types or more (Table 3).

Restricting to all women with hypertension only, for those who were treated with combination therapy, we saw no increased risk of AMD for any individual class of drugs. In contrast, among antihypertensive women reporting monotherapy, using diuretics only increased AMD risk (HR=1.45, 95% CI: 1.10, 1.90) (Table 4). There was however no increased risk of AMD with monotherapy of ACE inhibitors, calcium channel blockers, or other antihypertensive medications.

In sensitivity analyses, we excluded women who had their first AMD diagnosis within the first five years of follow-up assuming they were prevalent cases. Excluding the first five years of AMD diagnoses after the years 1995 or 2000, however, did not change our results more than minimally (Supplement Table 2). Another sensitivity analysis incorporated the antihypertensive medications as time-varying variables and used censoring due to death or moving out of California. The risk for AMD in women who reported antihypertensive medication use remained increased (Supplement Table 3). Finally, we restricted to women with two or more hospitalization records.

Discussion

In the prospective California Teachers Study, severe, longer term, and possibly badly controlled hypertension was associated with an increased risk of developing intermediate- or late-stage AMD. While those treated for hypertension were at a slightly increased risk of AMD (HR = 1.15, 95% CI: 1.03, 1.30), we observed an increasing trend with presumed severity of the newly reported hypertension in 2000. In our subcohort of women who responded to the 2000 questionnaire, we were able to assess major subclasses of antihypertensive agents. There was a 45% increase in risk of AMD in women who reported daily diuretic use alone compared with women who used other antihypertensive agents as monotherapy, but no risk increase in women who received combination therapy. At the time of active data collection in the CTS (1995 and 2000), Congress had not yet passed the Medicare prescription drug benefit, and medication coverage was not extended to retired teachers until 2003, thus, some CTS participants may have opted for the most affordable antihypertensive, which at the time was diuretics.

According to the third National Health and Nutrition Examination Survey (NHANES III), less than half of all women treated with antihypertensive medication are able to adequately control their blood pressure (SBP <140 mm Hg and DBP <90 mm Hg) (26). We are not able to disentangle any potential association between antihypertensive medications and AMD from the adverse effect of residual high blood pressure, a phenomenon commonly referred to as confounding by indication. Thus, the observed associations between treated high blood pressure and AMD risk may reflect either pharmacologic effects of the antihypertensive drugs or the chronic pathophysiologic effects of badly controlled high blood pressure. However, this could not be fully assessed without time-varying BP measures.

Previous studies evaluating the association between high blood pressure and AMD risk have been inconclusive (3, 4, 6, 7). A large prospective cohort study reported that a 10 mmHg systolic blood pressure increase at baseline exam was associated with a 20% increased risk of wet-AMD after 10 years (6). Another similar study estimated a 10% increase in risk and associations strengthened with increasing severity of hypertension (5). The increased risk of AMD among hypertensive women in our study was consistent with a pooled estimate for any antihypertensive drug use in three population-based prospective cohorts that covered almost all Northern European populations (HR = 1.20, 95% CI 1.0–1.5) (14). Similar strength and direction of association were also seen in two other studies for wet-AMD but not for early AMD (11, 13). A history of mild or temporarily elevated blood pressure, found in 13% of hypertensives (22), that requires only life-style modification and not therapeutic

drug use was not associated with AMD among women with “untreated hypertension” in our study.

Apart from the effects that hypertension in general has on the an organ’s vascular system including the retina, one biological mechanism linking hypertension and AMD involves the increased activity of the renin-angiotensin system (RAS) and specifically its major component angiotensin II (Ang II), which is affected by high plasma renin activity that occurs in about 70% of all hypertensives (27). The systemic activation of the RAS in hypertension interacts with the local RAS in the retina and contributes to inflammation and neovascularization, both key components of AMD pathogenesis. Specifically, through the activation of angiotensin II type 1 receptors expressed in the retina, Ang II exerts its vasoconstriction effect on the retinal capillary network and induces endothelial cell apoptosis, which may contribute to neovascularization as a consequence of disturbed retinal circulation (3, 29). Moreover, Ang II can potentiate neovascularization through upregulations of the vascular endothelial growth factor (3)(29).

Few studies for risk factors of AMD investigated more than one subtype of antihypertensive agents. In our study, only diuretics but not more potent agents were associated with an increased risk of AMD when compared with other classes of medications used by women as monotherapy. The Age-Related Eye Disease Study Research Group (AREDS) also reported finding an increased frequency of intermediate- or large Drusen in people who used hydrochlorothiazide diuretics (OR =1.51) (15), but this was not reported in other studies that assessed diuretics separately, although elevated hazard ratios were estimated among diuretics users in a prospective cohort study with 20 years follow-up (10–12). The discrepancy between existing studies may reflect different degrees of residual confounding, the various lengths and cumulative dose of drug use, and the lack of consideration of the concurrent use of other types of drug use while assessing each class individually in previous studies. Although some studies accounted for measured blood pressure, a one-time measure may not sufficiently reflect the degree of blood pressure control in the long term. Furthermore, indications and contraindications such as heart failure, chronic kidney disease, cardiac arrhythmia or coronary artery disease which may affect the selection of therapeutic agents were not taken into account (30).

The increased risk of AMD associated with diuretics use was only observed in women receiving monotherapy but not with more extensive combination therapy indicating a lack of an adequate treatment strategy (31) and the resulting potential failure of high blood pressure control plays a role in the pathogenesis of AMD. Moreover, treatment with the most inexpensive medication alone may be an indicator of lower socioeconomic status and inadequate access to medical care. However, a potentially harmful effect attributable to the drug aside from the underlying high blood pressure cannot not be ruled out. There is no generally accepted biologic mechanism to explain a harmful effect of diuretics, but hyperlipidemia, one of the well-acknowledged side effects of diuretics therapy (32), may play a role (33). Moreover, thiazide diuretic use is associated with decreased serum zinc level (34), which plays an essential role in the function of antioxidant enzymes that can suppress AMD progression (35). Additionally, side effects of diuretics include the long-term activation of RAS that can contribute to AMD pathogenesis (36). However, when diuretics

were given as a component of combination therapy, no increased AMD risk was observed for diuretics compared to other treatment options.

Our study has several strengths. This prospective study with routine passive follow-up via administrative hospital records provides us with a long average follow-up time and precludes self-selection out of this cohort. The large number of AMD cases observed enabled us to investigate individual medications by duration, account for concurrent use of other types of medication, and evaluate both antihypertensive monotherapy and combination therapy. Furthermore, the use of OSHPD records allowed us to examine a comprehensive set of potential confounding factors, including indications and contraindications for the selection of different antihypertensive drugs. However, there are also several limitations, most notably, we had to rely on secondary diagnoses found in hospitalization records to identify AMD; thus, the onset of early AMD could not be captured with this passive follow-up method. On the other hand, we did not have to rely on self-reported diagnoses and any outcome misclassification would be expected to be non-differential and, thus, would be expected to most likely bias our estimates towards the null. In sensitivity analysis restricting to women with two or more hospital discharge records, the positive association between diuretics use and AMD remained. Moreover, we were not able to disentangle potential effects of medications on incident AMD from their effect on progression from early- to late-stage AMD. However, in sensitivity analyses that excluded AMD cases within the first five years of follow-up effect estimates did not change more than minimally. Also, we were not able to separate geographic atrophy and neovascular AMD, which may have different pathophysiologies (37). Third, the prevalence of high blood pressure was likely under-reported in our study. NHANES III estimated the prevalence of hypertension to be more than 50% among female non-Hispanic Whites who were greater than 60 years old in 1988–1991, (26) higher than the self-reported rate (34%) in our study. However, this non-differential misclassification of exposure would again likely bias the effect estimates towards the null. Fourth, two major subclasses of antihypertensive drugs, beta-blockers and angiotensin II receptor blockers were not queried separately. Fifth, for the assessment of combination medication use, we were not able to distinguish sequential use or concurrent use of different types of antihypertensive medications. Lastly, only women were included in this study, thus associations of intermediate- or late-stage AMD with high blood pressure that would be male specific could not be assessed.

In summary, hypertension and antihypertensive treatments were associated with an increased risk of intermediate- or late-stage AMD. However, increased risk of AMD was mainly due to possible inadequate blood pressure control in diuretics only users, but not those treated with other monotherapies. Nor did we observe increased AMD risk in any type of antihypertensive medication use when received as a part of the combination treatments for high blood pressure. Future prospective studies of AMD and antihypertensive medications should examine the level of blood pressure control by incorporating blood pressure measurements during follow up and evaluate the dosage and type and timing of use.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Summary Table

What is known about the topic?

- Sustained and inadequately controlled hypertension can promote the development of age-related macular degeneration (AMD) through multiple biologic pathways.
- Epidemiologic studies of high blood pressure, antihypertensive therapies, and the risk of AMD thus far have been inconclusive.

What this study adds?

- We estimated a 15% increased risk of AMD among women treated for hypertension at baseline, the magnitude of the association increased with longer duration of any antihypertensive treatment.
- Women who received diuretics as monotherapy had a 45% increased risk of AMD. While those treated with a combination of antihypertensive drugs or with medications more potent than diuretics to control blood pressure did not have an increased risk of AMD.

Table 1

Demographic characteristics and lifestyle factors in the California Teachers Cohort at baseline, followed from 1995–2012 (N=88 481).

Characteristics	All participants	Exposure to antihypertensive medications at baseline
Total	88481 (100%)	18812 (100%)
Age		
Mean (SD)	54.4 (15.3)	64.3 (12.4)
Median (Q1, Q3)	53.0 (43.0, 66.0)	65.0 (55.0, 74.0)
<50	35500 (40.1%)	2411 (12.8%)
51–60	19916 (22.5%)	4230 (22.5%)
61–70	16571 (18.7%)	5277 (28.1%)
71–80	11825 (13.4%)	4797 (25.5%)
>80	4669 (5.3%)	2097 (11.1%)
Race/Ethnicity		
Non-Latina white	77079 (87.9%)	16482 (88.5%)
African American	2260 (2.6%)	829 (4.5%)
Native American	3709 (4.2%)	379 (2%)
Latina	829 (0.9%)	234 (1.3%)
Asian/Pacific Islander	2796 (3.2%)	554 (3%)
Other	1048 (1.2%)	150 (0.8%)
Missing	760	184
BMI		
Underweight	2276 (2.7%)	310 (1.8%)
Normal	47374 (56.1%)	7132 (40.6%)
Overweight	21831 (25.8%)	5540 (29.4%)
Obese	13012 (15.4%)	4589 (24.4%)
Unknown	3988	1241
History of high blood pressure at baseline		
No	70874 (80.1%)	3799 (20.2%)
Yes	17607 (19.9%)	15013 (79.8%)
History of heart attack/MI		
No	87035 (98.4%)	17955 (95.4%)
Yes	1446 (1.6%)	857 (4.6%)
History of stroke		
No	87189 (98.5%)	18148 (96.5%)
Yes	1292 (1.5%)	664 (3.5%)
History of diabetes		
No	85492 (96.6%)	17251 (91.7%)
Yes	2989 (3.4%)	1561 (8.3%)
Smoking		
Never	16782 (19.2%)	2641 (14.2%)
Passive	40368 (46.1%)	8517 (45.8%)

Characteristics	All participants	Exposure to antihypertensive medications at baseline
Former	25751 (29.4%)	6388 (34.3%)
Current	4590 (5.2%)	1053 (5.7%)
Missing	990	213
No. of smoking pack-years		
Never or passive smoker	57150 (67.4%)	11158 (62.1%)
≤ 10	14052 (16.6%)	2763 (15.4%)
11–20	5187 (6.1%)	1338 (7.4%)
≥ 20	8464 (10%)	2722 (15.1%)
Missing	3628	831
Daily alcohol intake (g)		
None	29086 (34.9%)	6914 (39.1%)
<20	47340 (56.7%)	9038 (51.1%)
≥20	7015 (8.4%)	1735 (9.8%)
Unknown	5040	1125
Lifetime moderate and strenuous recreational physical activity (h/week)		
<2	29272 (33.3%)	6914 (39.1%)
2 to 4	21822 (24.8%)	9038 (51.1%)
4 to <6	14426 (16.4%)	1735 (9.8%)
≥ 6	22319 (25.4%)	3761 (20%)
Unknown	642	192

Table 2.

Hypertension, antihypertensive medications use at baseline and age-related macular degeneration in California Teachers Cohort, followed from 1995 through 2012 (N=88 481).

Regular medication use at baseline	No. of participants	Age-adjusted HR	Multivariable adjusted-HR[†]	P-trend
Self-reported high blood pressure				
None	70874 (80.1%)	1.00 (ref.)	1.00 (ref.)	
Treated hypertension	15013 (17.0%)	1.26 (1.13, 1.39)	1.15 (1.03, 1.30)	
Untreated hypertension	2594 (2.9%)	1.14 (0.89, 1.45)	0.97 (0.73, 1.30)	
Regular use of any antihypertensive medications				
No	69669 (78.7%)	1.00 (ref.)	1.00 (ref.)	
Yes	18812 (21.3%)	1.23 (1.12, 1.36)	1.09 (0.98, 1.22)	
Duration of any antihypertensive medications use				0.08
No regular use	70162 (79.3%)	1.00 (ref.)	1.00 (ref.)	
Less than 1 year	2022 (2.3%)	1.13 (0.85, 1.51)	0.92 (0.66, 1.29)	
1–4 years	5606 (6.3%)	1.20 (1.02, 1.41)	1.05 (0.88, 1.26)	
5–9 years	3801 (4.3%)	1.21 (1.00, 1.45)	1.08 (0.88, 1.33)	
More than 10 years	6884 (7.8%)	1.28 (1.12, 1.45)	1.13 (0.98, 1.31)	
Regular use of diuretics				
No	77706 (87.8%)	1.00 (ref.)	1.00 (ref.)	
Yes	10775 (12.2%)	1.18 (1.06, 1.33)	1.05 (0.91, 1.20)	
Duration of diuretic use				0.25
No regular use	77706 (88.1%)	1.00 (ref.)	1.00 (ref.)	
Less than 1 year	1331 (1.5%)	1.02 (0.72, 1.44)	0.86 (0.59, 1.27)	
1–4 years	3196 (3.6%)	1.11 (0.90, 1.36)	1.01 (0.80, 1.27)	
5–9 years	1972 (2.2%)	1.21 (0.95, 1.55)	1.12 (0.86, 1.47)	
More than 10 years	4026 (4.6%)	1.27 (1.09, 1.49)	1.09 (0.90, 1.30)	
Regular use of other antihypertensive drugs				
No	74652 (84.4%)	1.00 (ref.)	1.00 (ref.)	
Yes	13829 (15.6%)	1.20 (1.08, 1.33)	1.05 (0.92, 1.19)	
Duration of other antihypertensive drugs use				0.16
No regular use	74652 (84.8%)	1.00 (ref.)	1.00 (ref.)	

Regular medication use at baseline	No. of participants	Age-adjusted HR	Multivariable adjusted-HR†	P-trend
Less than 1 year	1426 (1.6%)	1.20 (0.87, 1.85)	0.93 (0.64, 1.35)	
1–4 years	4476 (5.1%)	1.19 (0.98, 1.39)	1.01 (0.83, 1.23)	
5–9 years	2922 (3.3%)	1.17 (0.95, 1.45)	1.03 (0.81, 1.30)	
More than 10 years	4526 (5.1%)	1.26 (1.08, 1.46)	1.14 (0.95, 1.36)	

†Multivariate model adjusted for age, smoking, diabetes, race/ethnicity, BMI, physical activities, history of cardiovascular disease, acetaminophen use, NSAIDS use and mutually adjusted for other categories of antihypertensive drugs.

Number of participants may not add up to total due to unknown value.

Table 3.

Self-reported antihypertensive medication use and age-related macular degeneration among respondents of the 2000 follow-up survey stratified by treatment derived index of severity of underlying hypertension in the California Teachers Cohort, followed from 2000 through 2012 (N=46 734).

Combination of antihypertensive medication use in 2000	No. of participants	No. of AMD	HR (95% CI)
Never used	40206	565	1.00 (ref.)
Used for hypertension (reported in 2000)			
Single type	5162	158	1.16 (0.94, 1.43)
2 types	1137	47	1.70 (1.20, 2.40)
3 types or more	229	14	1.93 (1.02, 2.40)

Table 4.

Self-reported antihypertensive medications use and age-related macular degeneration among respondents to the follow-up survey with hypertension stratified by type of treatment in California Teachers Cohort, followed from 2000 through 2012 (N=15 562).

	Women with Monotherapy		Women with Combination Therapy	
	No. of participants	Adjusted-HR ǂ (95% CI)	No. of participants	Adjusted-HR ǂ (95% CI)
Any diuretic *				
No regular use	8154	1.00 (Ref.)	1258	1.00 (Ref.)
Regular use	2120	1.45 (1.10, 1.90)	4016	1.14 (0.79, 1.65)
Calcium channel blocker				
No regular use	9285	1.00 (Ref.)	3485	1.00 (Ref.)
Regular use	989	1.05 (0.70, 1.56)	1789	0.81 (0.59, 1.12)
ACE inhibitor				
No regular use	8816	1.00 (Ref.)	3012	1.00 (Ref.)
Regular use	1458	0.98 (0.68, 1.40)	2262	1.03 (0.76, 1.40)
Other antihypertensive medication €				
No regular use	4567	1.00 (Ref.)	1349	1.00 (Ref.)
Regular use	5707	0.75 (0.59, 0.96)	3925	1.27 (0.88, 1.84)

ǂFor specific types, multivariate models adjusted for age, smoking, diabetes, race/ethnicity, BMI, physical activities, history of cardiovascular disease, asthma, acetaminophen use, NSAIDS use, and cholesterol lowering drug use.

*The diuretics category includes both thiazide and loop diuretics.

€Other types of antihypertensive medications were not specified in the CTS questionnaire and may include beta-blockers, Ang II blockers etc..