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Vasodilators and Blood Pressure Lowering Medications and Age-Related Macular Degeneration: The Beaver Dam Eye Study

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Abstract

Objective—To examine the association of vasodilator and antihypertensive medication use to the incidence of age-related macular degeneration (AMD).

Design—A longitudinal population-based study.

Participants—Persons 43–86 years of age living in Beaver Dam, Wisconsin in 1988–1990.

Methods—Examinations were performed every 5 years over a 20-year period. There were 9676 total person-visits over the course of the study. Status of AMD was determined from grading retinal photographs.

Main Outcome Measures—Incidence of AMD.

Results—The 5-year incidence of early AMD over the 20-year period was 8.4%, for late AMD it was 1.4%, for pure geographic atrophy (GA) it was 0.6%, for exudative AMD it was 0.9%, and for progression of AMD it was 24.9%. While adjusting for age, sex, and other factors, using a vasodilator (hazard ratio [HR]=1.72; 95% confidence interval [CI] 1.25 – 2.38), particularly oral nitroglycerin (1.81, 1.14 – 2.90) was associated with an increased risk of early AMD. Using an oral beta blocker was associated with an increased hazard of incident exudative AMD (1.71, 1.04 – 2.82) but not pure GA (0.51, 0.20 – 1.29) or progression (0.92, 0.67 – 1.28) of AMD over the 20-year period.

Conclusions—Use of vasodilators is associated with a 72% increase in the hazard of incidence of early AMD and use of oral beta blockers is associated with a 71% increase in the hazard of

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This article contains additional online only material. The following should appear online only: Tables 1 and 5.

incident exudative AMD. If these findings are replicated it may have implications for care of older adults as vasodilators and oral beta blockers are commonly used drugs by older persons.

Vasodilator medications are commonly used for treatment of angina pectoris and erectile dysfunction and blood pressure lowering drugs for the treatment of hypertension.¹⁻⁴ These drugs have been hypothesized to cause subretinal new vessels through their effect on the choroidal perfusion pressure.^{5,6} Epidemiologic data, however, have shown inconsistent relationships of vasodilator and blood pressure lowering medication use to the incidence of exudative age-related macular degeneration (AMD) and geographic atrophy (GA).⁷⁻¹¹ The Beaver Dam Eye Study, a longitudinal study of age-related eye diseases, has followed an adult population at 5-year intervals over a 20-year period. This study provides an opportunity to investigate the association between history of vasodilator and blood pressure lowering drug use and the incidence and progression of early and late AMD in a population.

Methods

Participants

A private census of Beaver Dam, Wisconsin was performed in 1987–1988 to identify all residents eligible for the study.¹² Of the 5924 eligible, 4926 (83%) persons aged 43–86 years participated in the baseline examination in 1988–1990. Ninety-nine percent of the population was white and 56% was female. The cohort was re-examined at 5- (n=3722), 10- (n=2962), 15- (n=2375) and 20-year (n=1913) follow-up examinations. There was greater than 80% participation among survivors at each examination.¹²⁻¹⁶ Differences between participants and nonparticipants have been presented elsewhere.¹²⁻¹⁶ Participants included in these analyses differed little from the total population at baseline (data not shown). All data were collected with Institutional Review Board approval from the University of Wisconsin-Madison in conformity with all federal and state laws, the work was Health Insurance Portability and Accountability Act compliant, and the study adhered to the tenets of the Declaration of Helsinki.

Participants were examined at the study suite, a nursing home, or their homes. The same protocols for measurements relevant to this investigation were used at each examination.^{17,18} Height, weight, blood pressure, and intraocular pressure (IOP) were measured. Date of birth was recorded. Smoking, drinking, and education histories were obtained using a standard questionnaire. Participants were asked to bring all medications they were regularly using during the 3 months prior to the examination. In addition, they were asked if they regularly used medications for treatment of hypertension, glaucoma, and angina pectoris and, if so, the name of the specific drug used. Information concerning use of medications for erectile dysfunction was ascertained if the subject brought the medication to the examination.

Grading AMD

Photographs of the retina were taken using film after pupil dilation according to protocol and graded in masked fashion by experienced graders.^{17,19} The Wisconsin Age-Related Maculopathy Grading System was used to assess the presence and severity of lesions

associated with AMD from the fundus photographs.^{17–22} Grading procedures, lesion descriptions, and detailed definitions of presence and severity have appeared elsewhere.²³

The severity of AMD was determined using the 5-step 3-continent consortium AMD Severity Scale.²⁴ The definitions of each level are as follows:

10 (No AMD): Hard drusen or small soft drusen (<125 μm in diameter only) regardless of area of involvement and no pigmentary abnormalities (defined as increased retinal pigment or retinal pigment epithelial [RPE] depigmentation present); or no definite drusen with any pigmentary abnormality.

20 (Minimally severe early AMD): Hard drusen or small soft drusen (<125 μm in diameter), regardless of area of involvement, with any pigmentary abnormality; or soft drusen (>125 μm in diameter) with drusen area <331,820 μm^2 (equivalent to O_2 , a circle with a diameter of 650 μm) and no pigmentary abnormalities.

30 (Moderately severe early AMD): Soft drusen (>125 μm in diameter) with drusen area <331,820 μm^2 (equivalent to O_2) and any pigmentary abnormality; or soft drusen (>125 μm in diameter) with drusen area $\geq 331,820 \mu\text{m}^2$ (equivalent to O_2) with or without increased retinal pigment but no RPE depigmentation.

40 (Severe early AMD): Soft drusen (>125 μm in diameter) with drusen area $\geq 331,820 \mu\text{m}^2$ (equivalent to O_2) and RPE depigmentation present with or without increased retinal pigment.

50 (Late AMD): Pure GA in the absence of exudative macular degeneration; or exudative macular degeneration with or without GA present.

Presence of AMD was analyzed by person using the worse eye. When data for one eye was missing (this occurred in less than 10% of participants at any exam) that eye was assumed to have the same AMD severity level as the fellow eye. Incidence of early AMD in the worse eye was defined by developing Level 20, 30, or 40 in at least 1 eye when both eyes were Level 10 at all previous examinations. Similarly, incidence of late AMD was defined as developing Level 50 in at least 1 eye when no signs of late AMD were observed at any previous visit. To be at risk for incidence of pure GA, an individual must have been free of any late AMD lesion at all previous examinations; however, individuals with pure GA were considered at risk for exudative AMD as long as no exudative lesions were present at any previous exam. Progression of AMD was defined as transitioning by one or more steps to a more severe AMD level in at least one eye in persons with level 20–40 at baseline. Quality assurance procedures were employed throughout the study.

Participants were asked to bring all current medications to the examination. If a participant was not taking any medications, this was recorded. Examiners followed-up with participants by phone to verify the name of any medication reported but not brought to the examination. All medication names were recorded by trained examiners and American Hospital Formulary Service (AHFS) coding was used to classify all medications. Vasodilators were defined as medications containing an active ingredient with AHFS code 2412 or containing

an active ingredient that was a direct vasodilator (Table 1, available at www.aaojournal.org). These medications were classified as sublingual nitroglycerin, topical nitroglycerin, isosorbide or “other vasodilators,” a class which contained phosphodiesterase type 5 inhibitor drugs. Medications were also classified as having blood pressure lowering and diuretic properties using the AFHS (Table 1, available at www.aaojournal.org). Participants were classified as using a medication with a specific property (e.g., vasodilating property, blood pressure lowering property) regardless of the other types of medications they were taking. For example, an individual who was concurrently taking both a vasodilator and an anti-hypertensive medication would have been classified as using a vasodilator and as using an anti-hypertensive medication.

Mean arterial blood pressure (MABP) was defined as systolic blood pressure + (2 × diastolic blood pressure) ÷ 3. Pulse pressure was defined as the systolic minus the diastolic blood pressure. Ocular perfusion pressure (OPP) in each eye was defined by the following formula: $OPP = (D + [S - D]/3) - IOP$, where S = systolic blood pressure and D = diastolic blood pressure and IOP = intraocular pressure.²⁵ OPP and IOP were summarized within a person using data from the right eye only. Diabetes status was defined as self-report of physician diagnosis with or without use of hypoglycemic medications or elevated (≥ 6.5%) glycosylated hemoglobin level. Body mass index (BMI) was calculated by dividing a participant's weight in kilograms by their height in meters squared. Obesity was defined as a BMI of >30 kg/m². Current smokers were identified as persons having smoked ≥ 100 cigarettes in their lifetime and were smoking at the time of the examination. Current heavy drinking was defined as consuming 4 or more servings of alcoholic beverages daily. Participants were considered physically active if they engaged in a regular activity long enough to work up a sweat at least once a week.

Statistical Analysis

We examined the relationship between self-reported vasodilator and antihypertensive medication use and the hazard of incidence of early and late AMD, exudative AMD, pure GA, and the progression of AMD over a 20-year period in the presence of other known risk variables. When analyzing the relationship of each class of medication to AMD, no assumptions were made about other medications an individual may have been taking concurrently. Incidence was modeled conditional on being free of disease at all previous examinations. Relationships were analyzed with discrete-time hazard models using the complementary log-log link function. Models first adjusted only for age and sex. Maximally adjusted models also included BMI, history of current smoking, MABP, physical activity, diabetes status, and history of heavy drinking. History of use of vasodilator and antihypertensive medications and other risk variables were updated in the model at each examination. We examined interactions for each of the 18 medication types × 4 blood pressure/IOP measures (MABP, PP, OPP and IOP) × 5 outcomes of interest for a total of 360 combinations, which would require a p-value of <0.0001 to attain statistical significance after Bonferroni correction for multiple comparisons. SAS software version 9.2 (SAS Institute, Cary, NC) was used for all analyses.

To be included in analyses, a participant must have had information on AMD level, medication use, and other covariates available at baseline and at every follow-up exam until the individual developed AMD or was censored. Of the 4926 participants seen at BDES 1, 3400 had met these criteria. Of these, 2714 (7012), 3386 (9133), 3366 (9049), 3400 (9171), and 671 (1295) individuals (person-visits) were included in analyses for the incidence of early AMD, late AMD, pure GA, and exudative AMD and progression of AMD, respectively.

Results

Baseline characteristics of those included and excluded from analyses are presented in Table 2. Of the 1526 individuals not included in analyses, 1401 were lost to follow-up (N=684 did not participate in the second exam, N=558 died before the second exam, and N=159 did not have gradable fundus photograph at the second exam), 26 had exudative AMD at baseline, 24 had photos that were not gradable for AMD at baseline, and 75 were missing data on covariates at baseline. Individuals who were excluded were more likely to be taking any of the medications analyzed except oral beta blockers. They were also older and, after adjusting for age and sex, more likely to be sedentary, have diabetes, have hypertension, have a history of stroke, have had myocardial infarction and angina, and have higher pulse pressure at baseline.

The use of specific medications and other covariates such as age, sex, MABP, perfusion pressure, OPP, IOP, BMI, smoking status, history of heavy drinking, angina, myocardial infarction, and stroke, and frequency of early AMD, pure GA, and exudative AMD at the beginning of each of the four study intervals are presented in Table 3. The cohort was older, and, after adjusting for age, had higher BMI and pulse pressure and lower MABP, IOP and OPP, was more likely to have diabetes, to have a history of myocardial infarction, and less likely to have a history of being a current smoker and of having a history of angina at more recent examinations.

Use of vasodilators, anti-hypertensive medications and diuretics increased with age. Use of vasodilators decreased over the exam phases while use of blood pressure medications and diuretics increased. Adjusting for age, use of vasodilators and anti-hypertensive medications was more frequent in men than in women and use of diuretics was more frequent in women than in men (Figure 1–3).

Participants were often taking more than one medication concurrently. At baseline, of the 3400 participants, 2223 were not taking a vasodilator, an anti-hypertensive medication, or a diuretic, 36 were taking a vasodilator only, 305 were taking an anti-hypertensive medication only, 7 were taking a diuretic only, 685 were taking an anti-hypertensive medication and a diuretic, 54 were taking a vasodilator and an anti-hypertensive medication, and 90 were taking all three types of medication.

The 5-year incidence of early AMD over the 20-year period was 8.4% (592 events in 7012 person-visits), of late AMD it was 1.4% (128 events in 9133 person-visits [0.6% for pure GA, 50 events in 9049 person-visits; 0.9% for exudative AMD, 83 events in 9171 person-

visits]), and of progression of AMD it was 24.9% (322 events in 1295 person-visits). All incident AMD outcomes increased with age and, while adjusting for age, sex was not associated with any of the AMD outcomes (data not shown).

While adjusting for age and sex, using a vasodilator and particularly oral nitroglycerin was associated with an increased risk of early AMD (Table 4, Model 1). These relationships remained after further adjustment for MABP, physical activity, BMI, diabetes, history of heavy drinking and smoking status. Using an oral beta blocker was associated with an increased hazard of 5-year incidence of exudative AMD over the 20-year period, adjusting for age, sex and other factors. While the hazard of incident exudative AMD was higher in those using diuretics or calcium channel blockers, these relationships were not statistically significant. There were no significant associations of using vasodilators or antihypertensive medications with late AMD, pure GA, or the progression of AMD (Table 4 and Table 5 (latter available at www.aaojournal.org)). These relationships were similar when adjusting for pulse pressure, OPP, and IOP in the multivariate models instead of MABP (data not shown).

There were no statistically significant interactions between use of any of the medications and MABP, PP, OPP or IOP for any of the AMD outcomes (data not shown).

Discussion

While adjusting for age, sex, and other factors, a history of vasodilator use (in particular oral nitroglycerin) was associated with greater hazard of incident early AMD. The incidence of exudative AMD was higher in persons taking oral beta blockers. There were too few persons reporting the use of medications specifically taken for erectile dysfunction to examine whether there was an association with AMD. Vasodilator use was not associated with 5-year incidence of pure GA or the progression of AMD.

The reasons for the association of vasodilators with incident AMD in the BDES are not understood. In the past, systemic vasodilators were used in the treatment of AMD.^{26–28} Vasoconstriction of the retinal and choroidal vessels were hypothesized to be involved in the pathogenesis of AMD and vasodilators were thought to reverse this vasoconstriction. The vasodilators were not recommended by some in the treatment of exudative AMD because they were thought to increase the risk of hemorrhage.²⁹

Increases in generalized stiffening of the sclera, Bruch's membrane, and choroidal and cerebral circulations are thought to occur with aging. This stiffening has been hypothesized by Friedman et al^{5,6} to cause increases in choroidal vascular and cerebrovascular resistance and, depending on which is higher, result in either a decrease or increase in the choroidal perfusion. According to this hypothesis, the former results in an increase in the osmotic gradient against which the RPE must pump and is thought to result in the deposition of metabolic waste in the RPE and the development of drusen. A higher choroidal perfusion pressure is hypothesized to result in the development of subretinal neovascular membrane.⁶ However, studies^{30–34} have shown inconsistent relationships of use of vasodilators taken for

erectile dysfunction with changes in either retinal blood flow and perfusion pressure in eyes with AMD.

There are few population-based studies and, to our knowledge, no randomized controlled clinical trials which have examined the relationship of coronary vasodilators with the incidence and progression of AMD. It is possible that the positive association of use of coronary vasodilators with incident early AMD in the BDES is due to bias by indication. That is, it is not due to the use of the vasodilator drugs themselves but due to the condition for which the drugs were used, e.g., angina pectoris. The lack of an association of myocardial infarction with the incidence of AMD provides some support against a bias by indication being present. When individuals who have had a myocardial infarction are excluded from the analyses the use of any vasodilator remained significantly associated with early AMD ($p=0.02$, Klein R et al., unpublished data) providing additional support against bias by indications as a reason for this finding.

The use of anti-hypertensive medications has been inconsistently associated with AMD^{7–11} and, when associations were reported, they were not independent of the effect of hypertension.⁸ In a pooled analysis that included data from the Beaver Dam Eye Study, van Leeuwen et al.⁹ showed that users of antihypertensive medications in general, and beta blockers in particular, had a borderline statistically significant increased risk of incident early AMD (OR for beta blockers 1.3; 95% CI 1.0–1.6) over a 5-year period when adjusted for systolic (or diastolic) blood pressure and other confounders. This effect of beta blockers was consistent with data from an in vitro study by Ellis et al. (abstract by Ellis SJ, Balasubramaniam B, Davies S, Boulton. Specific antihypertensive drugs induce lipofuscin-like pigment within cultured retinal pigment epithelial cells. *Invest Ophthalmol Vis Sci* 40 [suppl]:224, 1999) which showed that the beta blocker propranolol and the calcium channel blockers verapamil and diltiazem rapidly induced lipofuscin-like pigmentation in cultured human RPE cells.

In the BDES, after adjusting for other risk factors, there was a 44% higher hazard of developing exudative AMD in those using calcium channel blockers compared to those who were not. This relationship did not reach statistical significance. In the Women's Health Initiative Sight Exam, a statistically significant association of use of calcium channel blockers with prevalent pigmentary abnormalities and pure GA and a borderline relationship with increased retinal pigment was observed.¹⁰ In an earlier examination of medication use and the 5-year incidence of early AMD in the Beaver Dam Eye Study, there was a borderline association with use of calcium channel blockers and early AMD (age-sex adjusted OR 1.70; 95% CI 0.93 to 3.12; $P=0.08$) but not with beta blockers and early AMD.¹¹

While there are many strengths of our study, including long follow-up in which standardized protocols were used to detect AMD from fundus photographs, care must be taken due to some limitations. First, there is a lack of detailed information on dosage and duration of antihypertensive, vasodilator, or other medication use. Second, there may be uncontrolled confounding. Third, the large number of analyses may have resulted in finding the reported relationships by chance. Fourth, limited power due to infrequency of use of some vasodilator

or antihypertensive agents or infrequency of some of the outcomes (e.g., GA) may have resulted in limited power to find an association. Fifth, we cannot rule out the possibility that the diseases for which beta blockers were taken (e.g., hypertension) were unrelated to the incidence of AMD. Finding an association of higher odds, although not statistically significant, of other antihypertensive drugs (e.g., calcium channel blockers and diuretics) with exudative AMD suggests that hypertension itself may have an effect on the relationship. In the BDES, untreated hypertension was not associated with an increased hazard of any AMD outcome compared to normotension (Klein R., unpublished data). However, unsuccessfully treated hypertension had a statistically significant association with the incidence of exudative AMD providing some support for the hypothesis that medications may be responsible. Sixth, the findings are limited to whites.

In summary, we found a modest association of history of vasodilator use with the incidence of early AMD and use of beta blocker with the incidence of exudative AMD. Exudative AMD is a potentially blinding condition, and there is an increasing number of people with this condition due to longer survival of the general population. With increasing use of vasodilators in an aging population, it is important to further examine this potential association. The findings from our study need additional replication to be confirmed. If they are confirmed, understanding the mechanisms underlying the associations will be important in developing methods to prevent or reduce the risk of development of neovascular AMD in persons who use beta blockers to treat hypertension and to reduce the incidence of early AMD in persons who use vasodilators to treat angina.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Distribution by age and sex of the use of vasodilator medications (includes oral and topical nitroglycerin and isosorbide) by age and sex in the Beaver Dam Eye Study.

Figure 2.

Distribution by age and sex of the use of anti-hypertensive medications (includes calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and oral beta blockers) by age and sex in the Beaver Dam Eye Study.

Figure 3.
Distribution by age and sex of the use of diuretics by age and sex in the Beaver Dam Eye Study.

Table 2

Baseline Characteristics of Individuals Included and Excluded from Analyses.

Variable	Level/units	Excluded (N=1526)			Included (N=3400)			P-value
		N	Mean	SD	N	Mean	SD	
Any vasodilator medication *	% Taking	182	11.9		180	5.3		<.0001
Oral nitroglycerin	% Taking	80	5.2		64	1.9		<.0001
Topical nitroglycerin	% Taking	34	2.2		19	0.6		<.0001
Isosorbide	% Taking	29	1.9		22	0.6		0.0001
Other vasodilator	% Taking	77	5.0		98	2.9		0.0002
Any blood pressure medication *	% Taking	704	46.1		1134	33.4		<.0001
Calcium channel blocker	% Taking	107	7.0		116	3.4		<.0001
ACE inhibitor	% Taking	117	7.7		205	6.0		0.0319
Any beta blocker	% Taking	205	13.4		376	11.1		0.017
Beta blocker - eye	% Taking	40	2.6		44	1.3		0.0011
Beta blocker - oral	% Taking	168	11.0		336	9.9		0.2278
Any diuretic *	% Taking	525	34.4		782	23.0		<.0001
Age (yrs)	Years	1526	66.9	11.7	3400	59.8	10.2	<.0001
Sex	Male	675	44.2		1489	43.8		0.7739
Body mass index	kg/m ²	1481	28.7	5.4	3400	28.8	5.4	0.4098
Physical activity	% Sedentary	1256	82.4		2519	74.1		<.0001
Multivitamin supplement	% Taking	525	34.40		1168	34.35		0.9723
Diabetes status	% Present	193	12.9		248	7.3		<.0001
Smoking status	Current	846	55.6		1871	55.0		0.6997
History of heavy drinking	Current	290	19.2		551	16.2		0.0098
Hypertension	% Present	878	57.9		1611	47.4		<.0001
Mean arterial blood pressure (mmHg)	mmHg	1523	96.0	13.3	3400	95.4	11.7	0.1508
Pulse pressure (mmHg)	mmHg	1523	59.9	19.9	3400	52.5	16.4	<.0001
Ocular perfusion pressure right eye (mmHg)	mmHg	1491	48.5	9.0	3390	48.2	7.8	0.0969
Intraocular pressure right eye (mmHg)	mmHg	1357	15.5	3.4	3291	15.3	3.2	0.8354
History of angina	% Present	229	15.4		283	8.4		<.0001

Variable	Level/units	Excluded (N=1526)			Included (N=3400)			P-value
		N	Mean	SD	N	Mean	SD	
History of myocardial infarction	% Present	173	11.4		161	4.7		<.0001
History of stroke	% Present	113	7.4		72	2.1		<.0001
Early AMD	% Present	263	20.2		671	19.8		0.7591
Late AMD	% Present	63	4.6		14	0.4		<.0001
Pure geographic atrophy	% Present	8	0.6		14	0.4		0.372
Exudative AMD	% Present	55	4.0		0	0.0		0.9405

ACE, angiotensin-converting enzyme; AMD, age-related macular degeneration; SD, standard deviation.

No participant had a history of taking a phosphodiesterase type 5 inhibitor or angiotensin receptor blocker at BDES 1.

* See Table 1 for list of medications in each class, available at <http://aaojournal.org>

Table 3

Characteristics of Participants Included in Analyses at each Beaver Dam Eye Study Visit.

Risk factor	BDES 1 N=3400		BDES 2 N=2496		BDES 3 N=1968		BDES 4 N=1541		P- value*
	%/ Mean	SD	%/ Mean	SD	%/ Mean	SD	%/ Mean	SD	
Any vasodilator medication**	5.29		3.49		4.57		3.70		0.0009
Oral nitroglycerin	1.88		1.44		2.29		1.17		0.0301
Topical nitroglycerin	0.56		0.84		1.02		0.65		0.7531
Isosorbide	0.65		0.92		1.63		1.62		0.0048
Other vasodilator	2.88		1.08		0.66		0.71		<.0001
PDE5i	0.00		0.00		0.25		0.58		0.0006
Any blood pressure medication**	33.35		38.14		50.56		60.42		<.0001
Calcium channel blocker	3.41		10.30		14.08		15.18		<.0001
ACE inhibitor	6.03		10.82		16.72		23.95		<.0001
ARB	0.00		0.00		2.18		6.88		<.0001
Any beta blocker	11.06		10.94		18.24		26.41		<.0001
Beta blocker - eye	1.29		1.48		2.18		1.62		0.3403
Beta blocker - oral	9.88		9.62		16.21		25.18		<.0001
Any diuretic**	23.00		18.51		22.71		29.92		0.0062
Age (yrs)	59.85	10.23	63.00	9.59	66.47	8.58	69.17	7.52	0.0002
Sex	43.79		43.11		41.51		42.76		<.0001
Body mass index	28.78	5.39	29.60	5.46	30.18	5.86	30.71	5.92	<.0001
Physical activity	74.09		69.79		70.48		64.37		<.0001
Multivitamin supplement use	34.35		48.60		68.09		74.37		<.0001
Diabetes status	7.29		8.45		10.32		14.28		<.0001
Smoking status	55.03		52.68		53.10		51.65		0.0387
History of heavy drinking	16.21		16.63		14.74		13.24		0.705
Hypertension	47.38		46.53		55.18		62.40		<.0001
Mean arterial blood pressure (mmHg)	95.43	11.75	93.80	11.74	93.30	11.23	93.00	11.36	<.0001
Pulse pressure (mmHg)	52.54	16.36	51.46	15.38	56.00	16.13	56.01	14.24	<.0001

Risk factor	BDES 1 N=3400		BDES 2 N=2496		BDES 3 N=1968		BDES 4 N=1541		P- value*
	%/ Mean	SD	%/ Mean	SD	%/ Mean	SD	%/ Mean	SD	
Ocular perfusion pressure right eye (mmHg)	48.24	7.79	47.23	7.80	47.00	7.50	46.88	7.63	<.0001
Intraocular pressure right eye (mmHg)	15.31	3.24	15.24	3.09	15.14	2.96	15.09	3.24	<.0001
History of angina	8.42		7.44		8.54		7.21		0.0639
History of myocardial infarction	4.74		6.14		7.68		7.79		<.0001
History of stroke	2.12		1.88		2.64		2.40		0.8202
Early AMD	8.73		8.38		7.77		8.70		0.0008
Late AMD	0.83		1.09		1.97		2.57		0.0821
Pure geographic atrophy	0.30		0.45		0.97		0.80		0.4597
Exudative AMD	0.59		0.69		1.01		1.84		0.1801

ACE, angiotensin-converting enzyme; AMD, age-related macular degeneration; ARB, angiotensin receptor blocker; BDES, Beaver Dam Eye Study; PDE5i, phosphodiesterase type 5 inhibitor; SD, standard deviation.

* For trend over visits, adjusted for age.

** See Table 1 for list of medications in each class, available at <http://aaojournal.org>

Table 4
Relationship of Vasodilator and Anti-hypertensive Medication Use to the Incidence of Age-related Macular Degeneration.

Outcome (N individuals at risk)	Medication**	% Events in those taking medication	% Events in those not taking medication	Model 1		Model 2	
				HR (95% CI)	P- value	HR (95%CI)	P- value
Early AMD (N=2714)	Any vasodilator medication	19.08	8.21	1.70(1.23–2.34)	0.0011	1.72(1.25–2.38)	0.0010
	Oral nitroglycerin	16.67	8.59	1.81 (1.13–2.88)	0.0129	1.81 (1.14–2.90)	0.0127
	Topical nitroglycerin	14.29	8.70	1.54(0.81–2.90)	0.1849	1.58(0.83–3.00)	0.1666
	Non-nitroglycerin vasodilator	19.48	8.21	1.46(0.90–2.37)	0.1205	1.48(0.92–2.40)	0.1085
	Isosorbide	26.67	8.63	1.36(0.72–2.60)	0.3452	1.37(0.72–2.61)	0.3392
	PDE5i	0.00	8.73	1.30(0.17–10.1)	0.8047	1.30(0.16–10.4)	0.8036
	Other vasodilator	17.14	8.51	1.58(0.90–2.77)	0.1104	1.60(0.92–2.81)	0.0981
	Any blood pressure medication	11.16	7.61	1.04(0.88–1.24)	0.6147	1.05(0.88–1.25)	0.5792
	Calcium channel blocker	15.38	8.50	1.11 (0.85–1.44)	0.4441	1.11 (0.85–1.44)	0.4457
	ACE inhibitor	11.90	8.52	0.86(0.67–1.11)	0.2529	0.86(0.66–1.11)	0.2440
	ARB	0.00	8.73	1.07(0.60–1.91)	0.8103	1.07(0.60–1.90)	0.8212
	Any beta blocker	12.54	8.30	1.09(0.88–1.36)	0.4331	1.09(0.87–1.36)	0.4474
	Beta blocker - eye	23.33	8.57	1.28(0.74–2.22)	0.3821	1.27(0.73–2.21)	0.3899
	Beta blocker - oral	11.55	8.45	1.07(0.85–1.34)	0.5863	1.06(0.85–1.34)	0.5960
	Any diuretic	11.21	8.05	1.00(0.82–1.21)	0.9834	1.01 (0.83–1.22)	0.9335
Exudative AMD (N=3400)	Any vasodilator medication	2.22	0.50	1.69(0.91–3.17)	0.0991	1.62(0.83–3.13)	0.1550
	Oral nitroglycerin	3.13	0.54	1.92(0.82–4.51)	0.1341	1.94(0.78–4.81)	0.1550
	Topical nitroglycerin	0.00	0.59	0.72(0.10–5.37)	0.7501	0.70(0.09–5.29)	0.7279
	Non-nitroglycerin vasodilator	1.89	0.50	2.02 (0.86–4.72)	0.1047	1.83(0.75–4.45)	0.1856
	Isosorbide	0.00	0.59	1.41 (0.43–4.65)	0.5722	1.33(0.38–4.70)	0.6583
	PDE5i	3.06	0.52	*	*	*	*
	Other vasodilator	0.00	0.59	2.77(1.13–6.81)	0.0266	2.50 (0.97–6.39)	0.0566
	Any blood pressure medication	0.98	0.40	1.29(0.80–2.07)	0.2977	1.21 (0.74–1.96)	0.4509
	Calcium channel blocker	0.00	0.61	1.49(0.84–2.65)	0.1717	1.43(0.80–2.53)	0.2264

Outcome (N individuals at risk)	Medication**	% Events in those taking medication	% Events in those not taking medication	Model 1		Model 2	
				HR (95% CI)	P- value	HR(95%CI)	P- value
	ACE inhibitor	0.00	0.63	0.81 (0.42–1.56)	0.5251	0.79(0.41–1.51)	0.4716
	ARB	0.00	0.59	1.00(0.25–3.98)	0.9999	0.89(0.21–3.86)	0.8764
	Any beta blocker	1.07	0.53	1.40(0.85–2.31)	0.1924	1.37(0.83–2.27)	0.2175
	Beta blocker - eye	0.00	0.60	0.31 (0.04–2.30)	0.2499	0.31 (0.04–2.38)	0.2618
	Beta blocker - oral	1.20	0.52	1.74(1.06–2.84)	0.0286	1.71 (1.04–2.82)	0.0355
	Any diuretic	1.16	0.42	1.39(0.88–2.20)	0.1580	1.28(0.79–2.07)	0.3088

ACE, angiotensin-converting enzyme; AMD, age-related macular degeneration; ARB, angiotensin receptor blocker; CI, confidence interval; HR, hazard ratio; PDE5i, phosphodiesterase type 5 inhibitor

* Too few individuals taking this medication to draw reliable conclusions.

** See Table 1 for list of medications in each class, available at <http://aaojournal.org>

Model 1 adjusts for age and sex.

Model 2 adjusts for age, sex, body mass index, history of current smoking, mean arterial blood pressure, physical activity, diabetes status, and history of heavy drinking.