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Vasodilators, Blood Pressure-Lowering Medications, and Age-Related Macular Degeneration

The Beaver Dam Eye Study

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

Design: Longitudinal population-based study.

Participants: Persons 43 to 86 years of age living in Beaver Dam, Wisconsin, from 1988 through 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, gender, and other factors, using a vasodilator (hazard ratio [HR], 1.72; 95% confidence interval [CI], 1.25−2.38), particularly oral nitroglycerin (HR, 1.81; 95% CI, 1.14−2.90), was associated with an increased risk of early AMD. Using an oral β-blocker was associated with an increased hazard of incident exudative AMD (HR, 1.71; 95% CI, 1.04−2.82), but not pure GA (HR, 0.51; 95% CI, 0.20−1.29) or progression of AMD (HR, 0.92; 95% CI, 0.67−1.28) 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 β-blockers is associated with a 71% increase in the hazard of incident exudative AMD. If these findings are replicated, it may have implications for care of older adults because vasodilators and oral β-blockers are drugs that are used commonly by older persons. *Ophthalmology 2014;121:1604-1611 © 2014 by the American Academy of Ophthalmology.*

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Vasodilator medications are used commonly for treatment of angina pectoris and erectile dysfunction and as 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 (BDES), a longitudinal study of age-related eye diseases, has followed up 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 from 1987 through 1988 to identify all residents eligible for the study.[12] Of the 5924 eligible, 4926 (83%) persons 43 to 86 years of age participated in the baseline examination from 1988 through 1990. Ninety-nine percent of the population was white and 56% was female. The cohort was re-examined at 5-year (n = 3722), 10-year (n = 2962), 15-year (n = 2375), and 20-year (n = 1913) follow-up examinations. There was more 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 complied with the Health Insurance

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Portability and Accountability Act, and the study adhered to the tenets of the Declaration of Helsinki.

Participants were examined at the study site, 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 using regularly during the 3 months before 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(s) used. Information concerning use of medications for erectile dysfunction was ascertained if the subject brought the medication to the examination.

Grading Age-related Macular Degeneration

Photographs of the retina were obtained using film after pupil dilation according to protocol and were 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 less than 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 less than 331,820 μm^2 (equivalent to O_2) and any pigmentary abnormality; or soft drusen (≥125 μm in diameter) with drusen area 331,820 μm^2 or larger (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 331,820 μm^2 or larger (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 participants using the worse eye. When data for one eye were missing (this occurred in less than 10% of participants at any examination), 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 severity in at least 1 eye when both eyes demonstrated level 10 severity at all previous examinations. Similarly, incidence of late AMD was defined as developing late level 50 severity, defined by the presence of exudative AMD or GA, 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 examination. Progression of AMD was defined as transitioning by 1 or more steps to a more severe AMD level in at least 1 eye in persons with a severity level of 20 through 40 at baseline. Quality assurance procedures were used 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 coding was used to classify all medications. Vasodilators were defined as medications containing an active ingredient with American Hospital Formulary Service 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 that contained phosphodiesterase type 5 inhibitor drugs. Medications also were classified as having blood pressure-lowering and diuretic properties using the American Hospital Formulary Service (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 concurrently was taking both a vasodilator and an antihypertensive medication would have been classified as using a vasodilator and as using an antihypertensive medication.

Mean arterial blood pressure (MABP) was defined as follows: 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 is systolic blood pressure, D is diastolic blood pressure, and IOP is intraocular pressure.[25] The 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 square meters. Obesity was defined as a BMI of more than 30 kg/m^2. Current smokers were identified as persons having smoked 100 cigarettes or more 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 weekly.

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 conditionally 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 gender. 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/OPP/IOP measures (MABP, PP, OPP and IOP)×5 outcomes of interest, for a total of 360 combinations, which would require a