

# Potential Public Health Impact of Age-Related Eye Disease Study Results

## AREDS Report No. 11

Age-Related Eye Disease Study Research Group\*

**Objective:** To estimate the potential public health impact of the findings of the Age-Related Eye Disease Study (AREDS) on reducing the number of persons developing advanced age-related macular degeneration (AMD) during the next 5 years in the United States.

**Methods:** The AREDS clinical trial provides estimates of AMD progression rates and of reduction in risk of developing advanced AMD when a high-dose nutritional supplement of antioxidants and zinc is used. These results are applied to estimates of the US population at risk, to estimate the number of people who would potentially avoid advanced AMD during 5 years if those at risk were to take a supplement such as that used in AREDS.

**Results:** An estimated 8 million persons at least 55 years old in the United States have monocular or binocular

intermediate AMD or monocular advanced AMD. They are considered to be at high risk for advanced AMD and are those for whom the AREDS formulation should be considered. Of these people, 1.3 million would develop advanced AMD if no treatment were given to reduce their risk. If all of these people at risk received supplements such as those used in AREDS, more than 300 000 (95% confidence interval, 158 000-487 000) of them would avoid advanced AMD and any associated vision loss during the next 5 years.

**Conclusion:** If people at high risk for advanced AMD received supplements such as those suggested by AREDS results, the potential impact on public health in the United States would be considerable during the next 5 years.

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**I**N 2001, the Age-Related Eye Disease Study (AREDS) Research Group reported a reduced risk of advanced age-related macular degeneration (AMD) (choroidal neovascularization or central geographic atrophy) and its associated vision loss for study participants with monocular intermediate AMD, binocular intermediate

AMD, monocular vision loss from AMD, or monocular advanced AMD who were assigned to high-dose supplementation with antioxidants (vitamin C, vitamin E, and beta carotene) plus zinc as zinc oxide or zinc alone.<sup>1</sup> From an individual's point of view, on the basis of these findings, the AREDS Research Group<sup>1</sup> and others<sup>2</sup> recommend that persons with these features, and without contraindications, should consider taking supplements such as those used in AREDS. From a public health point of view, the potential impact of these results can be assessed by estimating the number of people at least 55 years old for whom supplement treatment has been recommended. On the basis of information from the AREDS database, we can apply progression rates to advanced AMD for this population and estimate the numbers of persons who would have developed advanced AMD with or without treatment. The purpose of this article is to report that potential impact.

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AMD, monocular vision loss from AMD, or monocular advanced AMD who were assigned to high-dose supplementation with antioxidants (vitamin C, vitamin E, and beta carotene) plus zinc as zinc oxide or zinc alone.<sup>1</sup> From an individual's point of view, on the basis of these findings, the AREDS Research Group<sup>1</sup> and others<sup>2</sup> recommend that persons with these features, and without contraindications, should consider taking supplements such as those used in AREDS. From a public health point of view, the potential impact of these results can be assessed by estimating the number of people at least 55 years old for whom supplement treatment has been recommended. On the basis of information from the AREDS database, we can apply progression rates to advanced AMD for this population and estimate the numbers of persons who would have developed advanced AMD with or without treatment. The purpose of this article is to report that potential impact.

### METHODS

#### ESTIMATING NUMBER AT RISK FOR DEVELOPING ADVANCED AMD

On the basis of AREDS data, persons with intermediate AMD in either eye or those with vision loss from AMD or advanced AMD in only one eye were at relatively higher risk of developing advanced AMD (compared with those

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with few or no drusen, the risk of advanced AMD was 18 and 43 times higher for these 2

**Table 1. Estimated Prevalence of AMD by Stage in Individuals at Least 55 Years Old in the United States From 2000 Census and Eye Disease Prevalence Study\***

AMD Stage	Whites	Blacks	Hispanics	Others†	Total
Neovascular	900 000	63 000	35 000	25 000	<b>1 023 000</b>
Geographic atrophy	762 000	21 000	24 000	17 000	<b>824 000</b>
Binocular intermediate	1 877 000	102 000	89 000	63 000	<b>2 131 000</b>
Monocular intermediate	3 858 000	315 000	216 000	153 000	<b>4 542 000</b>
<b>Total</b>	<b>7 397 000</b>	<b>501 000</b>	<b>364 000</b>	<b>258 000</b>	<b>8 520 000</b>

Abbreviation: AMD, age-related macular degeneration.

\*"Whites" and "blacks" are non-Hispanic whites and non-Hispanic blacks.

†"Others" includes American Indians, Alaskan natives, Asian Americans, Native Hawaiians, other Pacific Islanders, multiracial individuals, and all other individuals not otherwise described. Prevalence rates for Hispanics and others are assumed to be average prevalence of non-Hispanic whites plus non-Hispanic blacks.

groups, respectively).<sup>1</sup> To determine the number of people in these higher-risk groups from all individuals in the US 2000 census at least 55 years old,<sup>3</sup> the Eye Disease Prevalence Study (EDPS) performed a meta-analysis of 7 large population-based studies involving approximately 20 000 people inside and outside of the United States. On the basis of this analysis, the EDPS estimated the age-sex-race-specific prevalence of individuals with large drusen (greatest linear dimension,  $\geq 125 \mu\text{m}$ ) in one or both eyes but no advanced AMD in either eye (as a marker for monocular or binocular intermediate AMD), and of individuals with advanced AMD (from either choroidal neovascularization or geographic atrophy of the retinal pigment epithelium) in one or both eyes. For this report, the EDPS prevalence estimates for the total age group at least 55 years old were used, rather than age-specific estimates. Data with respect to race were directly estimated for non-Hispanic whites and non-Hispanic blacks. Data for all other races were estimated to be the average prevalence for non-Hispanic whites and non-Hispanic blacks, since the prevalence data on Hispanics were judged to be too sparse, and since there were no other US prevalence data on American Indians, Alaskan natives, Asian Americans, Native Hawaiians, other Pacific Islanders, multiracial individuals, and all others.

Because identification of individuals with advanced AMD in the EDPS did not differentiate those with monocular advanced AMD from those with binocular advanced AMD, the proportion with monocular and binocular advanced AMD was estimated on the basis of an approximation of the proportion of individuals with monocular or binocular advanced AMD from the Beaver Dam Eye Study<sup>4</sup> and the Baltimore Eye Survey.<sup>3</sup> From these studies, two thirds of persons reported to have advanced AMD were estimated to have monocular advanced AMD.

Identification of individuals with geographic atrophy in the EDPS did not differentiate those with central geographic atrophy from those with geographic atrophy not involving the center of the retina. These proportions were determined from the proportion of individuals with central vs noncentral geographic atrophy in AREDS. Grading of baseline AREDS photographs demonstrated that approximately 50% of participants with geographic atrophy at baseline had the center of the retina involved by the atrophy. On the basis of this observation, we assumed that approximately 50% of persons estimated to have geographic atrophy in the EDPS had the center involved.

#### PROGRESSION RATES TO ADVANCED AMD

Five-year progression rates to advanced AMD in the absence of supplementation of antioxidants plus zinc, such as that used in AREDS, for individuals at least 55 years old in the United States in 2000 with monocular intermediate AMD (6.3%), binocular intermediate AMD (26.4%), and monocular advanced

AMD (43.0%) were based on progression rates for individuals with these characteristics in AREDS assigned to a placebo.<sup>1</sup>

#### ESTIMATING RISK REDUCTION

The risk of progressing to advanced AMD, for individuals with monocular intermediate AMD, binocular intermediate AMD, or monocular advanced AMD, was presumed to be reduced by the same amount with use of a supplement of antioxidants plus zinc such as that used in AREDS. There may be some differences in these rates, but the AREDS data do not show any statistically significant differences in the treatment effect between these groups. Without clear evidence of a difference, assuming one treatment effect seems appropriate.

### RESULTS

#### ESTIMATING NUMBER AT RISK FOR DEVELOPING ADVANCED AMD

The US Census Bureau indicates that there were 59 266 437 individuals at least 55 years old in the United States in 2000. On the basis of race-specific prevalence of neovascular AMD (**Table 1**) from the EDPS (assuming the prevalence for Hispanics and races other than non-Hispanic whites and non-Hispanic blacks was the average of the prevalence for non-Hispanic whites and non-Hispanic blacks), a total of 1 023 000 individuals at least 55 years old in the United States were estimated to have neovascular AMD, of whom approximately two thirds, or 685 000, were estimated to have monocular neovascular AMD and have a fellow eye at high risk of developing advanced AMD (**Table 2**). In addition, 824 000 were estimated to have geographic atrophy (Table 1), of whom one half, or 412 000, had cases involving the center. Of these 412 000, approximately two thirds, or 275 000, had only one eye involved with geographic atrophy (Table 2) and thus had a fellow eye at high risk of developing advanced AMD. Thus, we estimated that approximately 1 million (960 000) individuals had monocular advanced AMD (Table 2).

The remaining 412 000 individuals with geographic atrophy not involving the foveal center are at high risk for developing advanced AMD in either eye, including two thirds (275 000) who were estimated to have this noncentral atrophy in one eye and one third (137 000) who were estimated to have this noncentral atrophy in both eyes. In addition to the 137 000 with binocular

**Table 2. Estimated Number of Individuals in the United States at Least 55 Years Old Considered to Be at High Risk for Advanced AMD in 2000**

AMD Stage for Individual	No. of Individuals
Monocular advanced AMD	
Monocular neovascular AMD*	685 000
Monocular central geographic atrophy†	275 000
Binocular high risk for advanced AMD	
Binocular intermediate AMD	2 131 000
Binocular noncentral geographic atrophy‡	137 000
Monocular high risk for advanced AMD with no advanced AMD in either eye	
Monocular intermediate AMD	4 542 000
Monocular noncentral geographic atrophy‡	275 000
<b>Total</b>	<b>8 045 000</b>

Abbreviation: AMD, age-related macular degeneration.

\*Assumes that two thirds of individuals with neovascular AMD described in Table 1 have monocular AMD.

†Assumes that two thirds of individuals with geographic atrophy described in Table 1 have monocular AMD and that the geographic atrophy in one half of these monocular cases extends under the center of the retina.

‡Assumes that one third of individuals with geographic atrophy described in Table 1 have binocular AMD and that the geographic atrophy in one half of these binocular cases does not extend under the center of the retina.

noncentral geographic atrophy, 2 131 000 were estimated to have binocular intermediate AMD (Table 1), for a total of 2 268 000 with binocular intermediate AMD or binocular noncentral geographic atrophy at high risk for developing advanced AMD (Table 2). Furthermore, in addition to the 275 000 with monocular noncentral geographic atrophy, 4 542 000 individuals were estimated to have monocular intermediate AMD (Table 1), for a total of 4 817 000 with monocular intermediate AMD or monocular noncentral geographic atrophy at high risk for advanced AMD (Table 2). Thus, on the basis of the US census for 2000 and the EDPS, 960 000 individuals with monocular advanced AMD, 2 268 000 with binocular intermediate AMD or binocular noncentral geographic atrophy, and 4 817 000 with monocular intermediate AMD or monocular noncentral geographic atrophy, for a total of 8 045 000 individuals at least 55 years old, were estimated to be at high risk for developing advanced AMD in the United States (Table 2).

#### NUMBER EXPECTED TO PROGRESS TO ADVANCED AMD FROM 2000 TO 2005

In AREDS, 43% of individuals with monocular advanced AMD developed advanced AMD in the second eye within 5 years. With the use of this estimate, of the 960 000 individuals with monocular advanced AMD, a total of 413 000 will develop advanced AMD within 5 years. In addition, of the 2 266 000 individuals with binocular intermediate AMD or binocular noncentral geographic atrophy, an estimated 26.4% will develop advanced AMD within 5 years, for a total of 598 000. Finally, of the 4 818 000 individuals with monocular intermediate AMD or monocular noncentral geographic atrophy, an estimated 6.3% will develop advanced AMD within 5 years, for a total of 304 000. Thus, an estimated total of 1 315 000

**Table 3. Summary of Potential Public Health Impact of AREDS**

Feature	Estimated No.
US 2000 census: No. of people $\geq 55$ y old	59 million
Individuals at risk for advanced AMD in 2000*	
Monocular advanced AMD	1.0 million
Binocular high risk for advanced AMD	2.3 million
Monocular high risk for advanced AMD with no advanced AMD in either eye	4.8 million
Individuals expected to progress to advanced AMD from 2000 to 2005 in absence of antioxidant plus zinc supplementation†	
Monocular advanced AMD	413 000
Binocular high risk for advanced AMD	598 000
Monocular high risk for advanced AMD with no advanced AMD in either eye	304 000
Individuals expected to <i>avoid</i> progression to advanced AMD from 2000 to 2005 using antioxidant plus zinc supplementation‡	
Point estimate	329 000
95% Confidence interval	158 000-487 000

Abbreviations: AMD, age-related macular degeneration; AREDS, Age-Related Eye Disease Study.

\*From Table 2.

†Assumes progression rates of 43% for monocular advanced AMD, 26.4% for binocular high risk for advanced AMD, and 6.3% for monocular high risk for advanced AMD with no advanced AMD in either eye.

‡Assumes that 25% of all individuals expected to develop advanced AMD will avoid advanced AMD (95% confidence interval, 12%-37%).

individuals at least 55 years old in the United States will develop advanced AMD within 5 years (**Table 3**).

#### INDIVIDUALS AVOIDING PROGRESSION TO ADVANCED AMD WITH USE OF SUPPLEMENT OF ANTIOXIDANTS PLUS ZINC

The AREDS results suggested that persons with intermediate AMD, or with advanced AMD in one eye, who used the AREDS combination formulation (antioxidants plus zinc), reduced their 5-year risk of developing advanced AMD by approximately 25% (95% confidence interval, 12%-37%). Therefore, 25% of the 1 315 000 individuals who were estimated to develop advanced AMD within 5 years, or 329 000 individuals (95% confidence interval, 158 000-487 000), will avoid developing advanced AMD if all 8 million individuals at least 55 years old who were estimated to be at high risk for developing advanced AMD in the United States take these supplements (Table 3). For the 413 000 individuals with monocular advanced AMD who will develop advanced AMD within 5 years in the second eye in the absence of an antioxidant plus zinc supplementation, approximately 103 000 (95% confidence interval, 50 000-153 000) would avoid developing advanced AMD within this period if they used the AREDS combination formulation, assuming a risk reduction of approximately 25% (95% confidence interval, 12%-37%).

#### COMMENT

While avoiding the development of advanced AMD—with its attendant likelihood of vision loss—in 329 000

persons during 5 years has major public health impact, this information must be considered to have major *potential* public health impact because of the numerous assumptions, large and small, used to derive these numbers. For example, it is unknown whether markedly different numbers would be obtained if age-specific prevalence and progression rates were used. Although age-specific prevalence is available from the EDPS, no precise information on age-specific progression rates can be obtained from AREDS. Second, it is unknown at this time if there are differential effects of reducing the risk of developing advanced AMD depending on whether an individual has monocular advanced AMD, binocular intermediate AMD or noncentral geographic atrophy, or monocular intermediate AMD or noncentral geographic atrophy, although there is no strong biological rationale at this time to suspect that there may be a differential effect. Third, it is unlikely that all individuals at high risk for advanced AMD would take the recommended supplement because of medical complications, intolerance, or noncompliance. Also, study participants may have been more compliant with medication use than one would expect in the general population. Finally, as shown by the use of confidence intervals around the treatment effect estimate, the real number people avoiding advanced AMD is highly dependent on the actual treatment effect, for which only a "best estimate" can be provided.

Avoiding the development of advanced AMD can have a major effect on the quality of life for an individual. Preventing this development in the first eye of an individual is important, since the second eye will also be at risk; preventing this development in the second eye of an individual will have a direct effect on that individual's visual function for central visual tasks and thus

on that individual's quality of life. Therefore, if even half of the individuals at high risk for advanced AMD were identified and compliant with the recommended supplement, it is likely that more than 150000 individuals would avoid vision loss for some time. These data suggest that the recommendation of such a supplement for those individuals should have a major impact on them as well as on the public health.

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