AREDS Investigators Distort Findings

In my opinion, the Age-Related Eye Disease Study (AREDS) investigators promoted a nonsignificant result into a conclusive recommendation. Here is how they did it.

The primary study outcomes for AREDS are explicitly stated in the “Participants and Methods” section of the article: (1) progression to advanced age-related macular degeneration (AMD) and (2) a 15-letter decrease in visual acuity. These outcomes were to be evaluated in all patients by independent tests of significance of the 2 primary treatments. This carefully specified primary analysis led to 4 tests, none of which was statistically significant. One, testing the effect of zinc on progression to advanced AMD, achieved a level of significance defined by the investigators as suggestive.

Despite these negative results, the investigators recommend combined treatment with antioxidants and zinc based on their secondary analysis. Two analytic approaches provided them with significant results. First, the authors restricted the analysis to a subgroup. The mainstream practice of clinical trials warns that unless the main overall comparison is significant, investigators should be conservative in their interpretation of significant subgroup results. Second, they featured the combined treatment group, which in secondary analysis broke the boundary of statistical significance, thereby disregarding the primary analysis in which neither treatment was significant.

In its discussion of relevant literature, the “Comment” section is as selective as the analysis. At a planning meeting, the AREDS chairman recounted his efforts to review retinal photographs from the first published meeting, the AREDS chairman recounted his efforts to review retinal photographs from the first published meeting. The authors restricted the analysis to a subgroup. The mainstream practice of clinical trials warns that unless the main overall comparison is significant, investigators should be conservative in their interpretation of significant subgroup results. Second, they featured the combined treatment group, which in secondary analysis broke the boundary of statistical significance, thereby disregarding the primary analysis in which neither treatment was significant.

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Analyses in clinical trials are complex endeavors. Austin Bradford Hill observed that the inferences we draw turn on our personalities. In an article in the New York Times, Gina Kolata spoke to public frustration at reports of clinical research that convert suggestive results to conclusive ones. A public that is concerned with AMD, physicians who need to advise and treat, and industry representatives who wish to provide us with products that are effective all depend on us to get it right in clinical research. In my opinion, the message that should have emerged from AREDS is that these treatments failed to demonstrate efficacy in preventing AMD and are not recommended for that use.

Daniel Seigel, ScD
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In reply

We thank Dr Seigel for his interest in AREDS Report No. 8 but disagree that the trial failed to demonstrate efficacy in reducing progression to advanced AMD.

Dr Seigel appears to base his conclusion on 2 assertions. The first is that there is no statistically significant effect of treatment in the total group studied and the second, which follows from the first, is that in the absence of an overall statistical effect of treatment, we should be conservative in interpreting subgroup results. Subgroup analyses of non-prespecified groups should be cautiously interpreted. However, we are looking at prespecified groups of participants, and we believe we have adequate evidence that the results are statistically significant.

One of our 3 prespecified stratification variables represents a population that essentially did not develop the primary outcome of interest. We found that the 1063 AMD Category 2 participants experienced only 15 advanced AMD events over 5 years, contrary to the 50 events expected. Because of the few events in these participants, it is appropriate to analyze and to base the study’s recommendations on the group at risk of developing advanced AMD (Categories 3 and 4). In addition to the analyses presented in the article, another way to address whether the treatment effects are statistically significant overall is to look at the main effects adjusting for the prespecified AMD category risk groups. This analysis also...
finds a significant treatment effect. The 3 degrees of freedom test for differential treatment effect is significant (P = .006), as is the zinc main effect (P = .009). This is the same conclusion reached by the analysis restricted to AMD Category 3 and 4 participants that is presented in the article. Finally, the consistency of the prespecified assessments of the antioxidant plus zinc treatment effect across multiple outcomes (advanced AMD, neovascular AMD, geographic atrophy, and loss of visual acuity) and across many different analytic approaches and methods provides additional evidence of treatment effect in the population at risk for developing advanced AMD and helps further rule out chance.

We limited the comparison of our findings to those from randomized trials because of the well-known difficulty in interpreting observational studies of nutrition and disease and because they rarely assessed high-dose supplementation.

Our data show, for those at risk, that the use of the combination of antioxidants and zinc slows the development of advanced AMD and its associated vision loss. Based on these results, persons at high risk of developing advanced AMD and without contraindications should consider taking high-dose supplements such as those used in AREDS. None of the AREDS investigators nor the data and safety monitoring committee has a financial interest in any of the supplements studied.

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Epithelial Origin of “Stromal” Corneal Dystrophies

We read with great interest the editorial by Dunaief et al in the January 2001 issue of the Archives, which discussed the epithelial genesis of most of the classical “stromal dystrophies” of the cornea, their ensuing reclassification, and new therapeutic approaches.1 We were, however, astonished to find that our early paper dealing with the same question2 is cited by the authors as supporting a fibroblastic origin of the stromal deposits. As a matter of fact, we were among the first, if not the first, who, after light-microscopic and electron-microscopic studies of early recurrent granular dystrophy, postulated an epithelial origin of the deposits in granular and also in lattice dystrophy. The last sentence of our summary reads, “The clinical pictures and microscopic findings strongly suggest that granular dystrophy may primarily be an epithelial not a stromal disease.” This suggestion was at that time strongly opposed by most experts but was adopted by Johnson et al in their 1981 paper.3 We were able to further support our hypothesis with additional morphological and immunohistochemical findings.4,5 But because the responsible gene and its product were not yet identified, an involvement of the keratocytes, at least in the late stages of the disease, could not be completely excluded. We found, however, the results indicating an epithelial origin convincing enough to start a surgical pilot study as early as 1995. We used the then recently developed variant of limbuskeratoplasty to prevent dystrophy recurrences by transplanting donor stem cells together with a clear donor cornea.6 The initial results of this study, which will have to go on for many more years to yield valid results, are correctly but incompletely cited in the editorial. The credit for the final proof of the epithelial genesis certainly goes to those who revealed the molecular genetic basis and thus definitively opened the way to new therapeutic options. Nevertheless, the older work should also be cited correctly.

In reply

We agree that Drs Witschel and Sundmacher provided important evidence of the epithelial genesis of granular corneal dystrophy in their 1979 article, and we appreciate their letter calling our attention to this fact. Their article also provided a useful review of older literature on the histopathology of granular dystrophy, which had led some authors to the reasonable but incorrect conclusion that the stromal deposits were produced by the keratinocytes rather than by the epithelial cells.

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Corneal Thickness Factors and Intraocular Pressure

The article1 and editorial2 concerning the correlation of intraocular pressure with other clinical factors neglect the influence of corneal thickness on pressure measurements. In this study, the patients with low-pressure glaucoma may include some with abnormally thin corneas,3 whereas others in the primary open-
angle glaucoma group may have thick corneas and only seem to have elevated pressures. Reduction in apparent tonometry values after refractive surgery is recognized. It appears that any surgical manipulation of the cornea, even without a reduction in thickness, affects subsequent measurements. Patients with progressive neuroretinal rim loss despite surgical reduction in intraocular pressure may actually have less rigid corneas. Thinning of the peripheral cornea and disruption of stromal fibers, which are inevitable consequences of filtering procedures, may contribute to an apparent normalization of intraocular pressure. Therefore, the contributions of this potentially important article are diminished by the failure to include corneal thickness factors in the assessment of intraocular pressures and glaucoma management.

Philip Lempert, MD
Ithaca, NY

In reply

We thank Dr Lempert for his interest and comments concerning our article. We agree with him that central corneal thickness may influence the results of applanation tonometry. However, although refractive surgery can alter central corneal thickness and affect subsequent intraocular pressure (IOP) measurements, such evidence is not present for filtration surgery in which there is no actual manipulation of the cornea. In contrast, no significant relationship was found between trabeculectomy and central corneal thickness in patients with glaucoma.

Since differentiation between primary open-angle glaucoma and normal-pressure glaucoma mostly depends on a simple IOP cutoff point of 21 to 23 mm Hg, the influence of central corneal thickness on IOP measurements may affect the classification of borderline cases. However, adjustment of tonometric readings for corneal thickness is not critical to improving the clinical definitions and does not seem to be a concern for our study, in which we essentially evaluated all eyes with glaucoma in a single group. In addition, our inclusion criteria substantiate the power of our observations. First, the patients with primary open-angle glaucoma were included in the study only if their treated IOP readings were less than 21 mm Hg. In fact, during the study period, most of our patients had lower IOP readings than this cutoff point. Second, we included patients with normal-pressure glaucoma only if their IOP readings were reduced by at least 20% from the untreated levels measured at the time of initial diagnosis. Therefore, even if there is an influence of central corneal thickness on IOP measurements in these patients, a 20% decrease of IOP was achieved by treatment. Lastly, and most importantly, IOP levels specified as inclusion criteria had to be achieved prior to the study period and maintained during a follow-up period of 5 years. Thus, during the study period, any impact of central corneal thickness on IOP measurements should be relatively constant, and the baseline IOP measurements are indeed an internal control for each eye in this longitudinal cohort.

Elevated IOP is an important risk factor for development and progression of glaucomatous neurodegeneration. Although it is possible that a greater reduction of IOP might have been beneficial in our cohort, analyses of our data did not reveal any evidence to support such a conclusion. Alternatively, however, there is accumulating evidence that multiple noxious events, either associated with elevated IOP or independent, potentially contribute to primary and/or secondary degeneration of retinal ganglion cells, which results in disease progression. More importantly, susceptibility for pressure-dependent injury and the significance of pressure-dependent vs pressure-independent pathogenic factors vary among patients.

Our study was retrospective and therefore has some limitations intrinsic to such a study. Nevertheless, our findings clearly indicate that conventional treatment of glaucoma to reduce IOP is not always sufficient to halt disease progression, particularly in patients with advanced optic nerve damage and patients with normal-pressure glaucoma. This may partly be related to insufficient reduction of IOP because of limited response or intolerance of patients to treatment, diurnal variability, or unreliable assessment of IOP by tonometry. However, all of these factors warrant that glaucoma progression should be carefully examined so that further reduction of IOP can be planned or, perhaps in future, neuroprotective treatments can be adjunctive to IOP-lowering treatment.

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Treating Subretinal Hemorrhage With Tissue Plasminogen Activator

Currently, the use of intravitreally injected tissue plasminogen activator (tPA) and expansile gas is an effective treatment to rapidly displace subretinal hemorrhage. I read with interest the recent ar-
ticle by Handwerger et al,1 who presented a retrospective series of 14 patients. However, I believe that some points in this study should be clarified.

First, I am surprised that the supplier of tPA was not mentioned in the article. Detailed information about the dilution volume and buffer used would be of great value because both can severely influence the enzymatic activity of tPA. The reader would also like to know what type of syringe was used that allows a differentiation between 18, 20, 24, and 30 µg of injected tPA? What was the rationale for injecting 5 different doses of tPA in a series of 14 patients?

In addition, I believe it is important to discriminate between liquefaction and displacement of subretinal hemorrhage. Liquefaction is an effect of the fibrinolytic enzyme, whereas displacement is caused by the gas bubble mechanically.3 Displacement of subretinal hemorrhage may result from the gas bubble even in patients without prior fibrinolysis.3 Figure 1C of the article shows a large subretinal fibrotic mass at the inferior temporal arcade. This photograph clearly demonstrates an incomplete liquefaction after tPA injection, indicating an insufficient low dose of tPA (20 µg). How often did the authors observe those remnants of a clot?

Although one can understand that the authors have some fear of using 100 µg of tPA, my group has reported an inadequate low dose of tPA, degenerative changes in the overlying retina induced by clot organization may succeed the toxic effects of tPA. So far, we have not found a reliable method to distinguish between the retinal toxic effects of tPA and retinal degeneration caused by subretinal hemorrhage or an underlying disease of age-related macular degeneration. Handwerger et al failed to mention the most likely explanation for the passage of tPA into the subretinal space. Retinal microlesions that develop after the retina stretches during acute bleeding allow the diffusion of the large tPA protein into the subretinal space. Such small rips in the retina may also be responsible for vitreous opacities and migration of subretinal blood into the vitreous cavity.4 This concept also explains why subretinal fibrinolysis failed in flat subretinal hemorrhage after tPA injection.5 Recently, microlesions were created in rats by stretching the retina after subretinal fluid injection.5

Despite the fact that the study of Handwerger et al raised some important issues, I feel there are still not enough data available to recommend an intravitreal tPA injection of less than 50 µg for the treatment of subretinal hemorrhage in humans. Lutz Hesse, MD Marburg, Germany


In reply

We thank Dr Hesse for his insightful comments. In our study, the supplier of tPA was Genentech Inc, San Francisco, Calif (the commercial name is Activase), and the tPA was diluted in sterile balanced salt solution (Alcon Laboratories, Ft Worth, Tex). A 30-gauge needle on a tuberculin syringe was used to inject a 0.1 to 0.2 mL dose of tPA. The concentration of tPA was either 20 µg/mL or 30 µg/mL, depending on the physician who ordered the tPA. The dose recorded in the table represents what the physician estimated to be the true dose injected into the vitreous.

Dr Hesse notes that in some of our cases, the submacular blood may have been displaced but not liquefied due to an insufficient dose of tPA. While it is difficult to assess the degree of liquefaction, all patients with partial or complete displacement of blood had a notable decrease in the height of the clot as well as a spreading out of the hemorrhage (at times the hemorrhage would form a thin rim in the superior macula because of the facedown position). These 2 features suggest some clot liquefaction in addition to clot displacement.

We share Dr Hesse’s concerns regarding the optimum dose of tPA. We did not see degenerative changes in the retinal pigment epithelium or retina due to chronic subretinal blood. Rather, the patients were left with fibrovascular pigment epithelial detachments (often quite large) as the cause of loss of visual acuity. We agree with Dr Hesse that “microlesions” in the retina may be responsible for the diffusion of tPA into the subretinal space. Such microlesions may be the reason that low-dose tPA is effective.

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