Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Stephen D. McLeod, MD

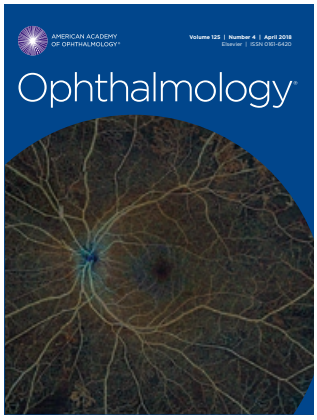
Mortality and Age-Related Eye Disease: AREDS2, Report 13

April 2018

Papudesu et al., of the Age-Related Eye Disease Study 2 (AREDS2) Research Group, looked at mortality in relation to visual impairment, age-related macular degeneration (AMD), and cataract surgery. They found that mortality correlated strongly with late AMD, bilateral cataract surgery, and best-corrected visual acuity (BCVA) worse than 20/40.

The authors' study included patients with intermediate and late AMD enrolled in the AREDS2 randomized controlled trial of lutein plus zeaxanthin and/or omega-3 fatty acids for treatment of AMD and cataract. Baseline and annual eye exams included BCVA assessment, slit-lamp exam, and stereoscopic fundus photographs that were graded for development of late AMD (central geographic atrophy or neovascular AMD) or pseudophakia. Cause-specific mortality was determined from ICD codes. Risk of all-cause and cause-specific mortality was measured from Cox proportional hazards models that were adjusted for age, sex, BCVA, severity of AMD, history of cataract surgery, and the assigned AREDS2 treatment. Analyses included the baseline variables of race, education, smoking status, diabetes, and cardiovascular disease.

Of the 4,203 AREDS2 participants, 368 (~ 9%) died during follow-up (median, 5 years). Risk of death was much higher for patients with neovascular AMD in 1 eye at baseline than for patients with no or few drusen. After adjusting for age, sex, and significant covariates, shorter survival rates showed a stronger correlation with pre-enrollment bilateral cataract surgery than with baseline bilateral unoperated crystalline lens and a stronger correlation with BCVA < 20/40.



Patients who received anti-VEGF therapy for neovascular AMD had a lower mortality risk than those who did not. No significant correlations were found between all-cause mortality and the assigned oral supplementation regimen (overall or individually).

The effect of ocular disorders on mortality may relate to factors that increase the risk of both eye disease and death, suggesting a systemic component, the authors said. Early detection of age-related eye disease may prevent deterioration of BCVA and improve quality of life.

Link Between Serious Sensory Deficit and Cognitive/Functional Difficulty

April 2018

Fuller et al. estimated the nationwide prevalence of self-reported serious vision impairment, serious hearing impairment, and serious dual sensory impairment (serious vision plus serious hearing impairment) and examined their association with self-reported difficulties in cognition, independent living, self-care, and ambulation. They found that any sensory impairment portends greater cognitive and functional decline and that self-reported sensory impairments increase with age.

Study data were derived from the 2011-2015 sample of the American Community Survey of the U.S. Census Bureau (7,210,535 individuals ≥ 45 years of age). Main outcome measures were self-reported difficulties with cognition, independent living, self-care, and ambulation. Using a weighted sample, the authors calculated descriptive statistics for each of the 4 mutually exclusive sensory impairment categories: no sensory impairment, serious vision impairment, serious hearing impairment, and serious dual sensory impairment. Adjusted odds ratios of the unweighted sample were used to measure the magnitude of associations between sensory impairment status and related difficulties.

Findings showed that, among individuals aged ≥ 45 years, the estimated nationwide prevalence of self-reported serious vision impairment alone, serious hearing impairment alone, and serious

dual sensory impairment was 2.8%, 6.0%, and 1.6%, respectively. The prevalence of each sensory impairment increased substantially with age. For example, the prevalence of serious dual sensory impairment increased from 0.7% for ages 45-64 to 1.8% for ages 65-79 to 7.6% for ages ≥ 80.

With respect to race and ethnicity, the incidence of impairment was highest among Native Americans, including those in Alaska (serious vision impairment, 4.8%; serious hearing impairment, 8.5%; and serious dual sensory impairment, 3.7%) and lowest among Asians (1.7%, 3.47%, and 1.04%, respectively, for the same categories).

For all age groups, those who noted serious dual sensory impairment were more likely than those with no sensory impairment to report problems with cognition, independent living, self-care, and ambulation. Cognitive and functional difficulties were greatest in those with serious dual sensory impairment. Serious vision impairment alone was associated with more cognitive and functional difficulties than serious hearing impairment alone.

Thus, the national prevalence of self-reported serious sensory impairment grows with age and has disparate distribution among racial and ethnic groups. According to the Census Bureau, the subpopulation ≥ 65 years of age is expected to continue growing, from 43.1 million in 2012 to 83.7 million by 2050. Targeting visual impairment in a preventive manner may reduce the burden of functional limitations and improve the ability to live independently.

Generating Personalized Target IOPs for Patients With OAG

April 2018

In secondary analyses of longitudinal data from 2 randomized controlled trials, **Kazemian et al.** forecasted the progression of open-angle glaucoma (OAG) at different levels of intraocular pressure (IOP) to help establish personalized IOP goals for patients. The tool they derived from real-world experience may improve clinical decision making.

For their study, the authors developed and validated Kalman filter (KF) models for fast-, slow-, and nonprogressing disease among participants with moderate or advanced OAG in the Collaborative Initial Glaucoma Treatment Study (CIGTS) or the Advanced Glaucoma Intervention Study (AGIS). The KF can generate personalized and dynamically updated forecasts of OAG progression for different IOP targets. For each participant, the authors determined the expected change in mean deviation (MD) if the patient were to maintain IOP at 1 of 7 levels (6, 9, 12, 15, 18, 21, or 24 mm Hg) for 5 years. In addition, the authors modeled and predicted MD changes for the same time frame if IOP were increased or decreased by 3, 6, and 9 mm Hg from the level attained in the trials. Main outcomes were personalized estimates of the change in MD under the various target IOP levels.

Among the 571 participants (mean age, 64.2 years; mean follow-up, 6.5 years), the model predicted that, on average, fast disease progression would result in an MD loss of 2.1, 6.7, and 11.2 dB under IOP targets of 6, 15, and 24 mm Hg (respectively) over 5 years. Using the same time frame and IOP targets, the MD loss for slow disease progression would be 0.8, 2.1, and 4.1 dB (respectively). When the tool was used to quantify OAG progression dynamics for all 571 patients, there were no significant differences in progression during the 5-year period between blacks and whites, males and females, or CIGTS and AGIS participants for the IOP levels studied.

To the authors' knowledge, this is the first clinical decision-making tool that generates personalized forecasts of the trajectory of OAG progression for different IOP targets. Thus, it may help clinicians determine appropriate IOP targets for patients with OAG. The authors reported that they are expanding their approach into a user-friendly method that enables uploading of patients' tonometric and perimetric data, which will generate a personalized real-time forecast of the trajectory of change in MD for different target IOP levels.

—Summaries by Lynda Seminara

Ophthalmology Retina

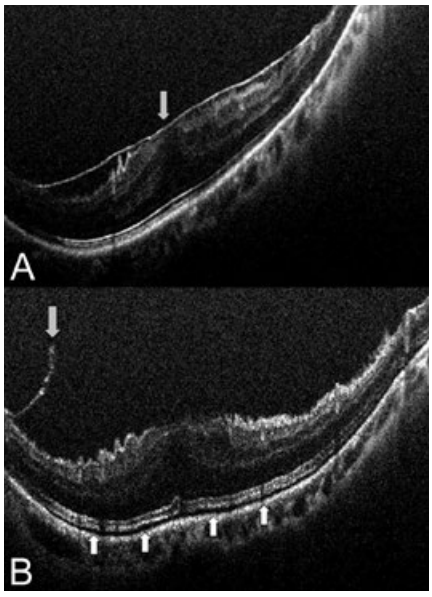
Selected by Andrew P. Schachat, MD

Intraoperative OCT for Epiretinal Membrane Surgery

April 2018

The PIONEER study examined the feasibility and utility of intraoperative optical coherence tomography (iOCT) imaging during ophthalmic surgery. In this analysis, **Ehlers et al.** evaluated eyes that were treated via iOCT-guided epiretinal membrane (ERM) surgery during PIONEER. They found that iOCT-assisted ERM peeling resulted in improved visual acuity (VA), reduction in macular thickness, and low recurrence rates. They also found that iOCT guidance minimized unnecessary surgical maneuvers and allowed for assessment of retinal architectural details.

The authors identified 100 eyes that had undergone iOCT-guided ERM peeling with 3-port small-gauge pars plana vitrectomy. Of these, 24 eyes were excluded because of insufficient iOCT image quality. In the remaining 76 cases, the mean preoperative VA was 20/63 (range, 20/25-20/2000). Postoperatively, mean VA was 20/41 (range, 20/20-



OCT GUIDANCE. *(A) Before peeling surgery, ERM is evident on iOCT (arrow). (B) After, iOCT shows occult residual membrane (down arrow) and increased subretinal hyporeflectance (up arrows).*

20/400) at 3 months, 20/37 (range, 20/15-20/500) at 6 months, and 20/34 (range, 20/15-20/200) at 12 months. Similarly, mean central subfield thickness (CST) was 434 µm preoperatively (range, 283-649) and improved postoperatively to 377 µm (range, 209-559) at 3 months, 367 µm (range, 211-592) at 6 months, and 359 µm (range, 215-531) at 12 months.

In 12% of the cases, iOCT revealed residual membranes that required additional peeling. In addition, in 9% of cases, iOCT images confirmed peel completion, directly contradicting the surgeons' clinical impressions. Significant recurrent ERM was noted in 2 eyes, and reoperation was performed in 1 eye.

Finally, iOCT allowed for assessment of retinal microarchitecture during ERM procedures. Further research is needed to better understand the correlation between architectural alterations and long-term visual outcomes, the authors said.

—Summary by Jean Shaw

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Is NSAID Use Linked to AMD?

April 2018

Inflammation has been implicated in the pathogenesis of age-related macular degeneration (AMD), which suggests that nonsteroidal anti-inflammatory drugs (NSAIDs) may modulate disease activity. To date, most research on the link between NSAIDs and AMD has focused on aspirin, and results have been conflicting. **Modjtahedi et al.** looked at the relationship between AMD and multiple types of NSAIDs. They found that, overall, NSAID use was not associated with a higher incidence of AMD—and that longer-term use was linked to a lower risk of wet AMD.

For this prospective cohort study, the researchers included participants of the California Men's Health Study who completed surveys during 2002-2003 and 2006. NSAID use was defined as taking aspirin, ibuprofen, naproxen, celecoxib, rofecoxib, and/or valdecoxib at least 3 days a week. Patients were categorized as nonusers, former users, new users, or longer-term users. NSAIDs were classified as aspirin, non-aspirin NSAIDs, and any NSAID.

Of the 51,371 study participants, 292 (0.6%) had wet AMD, and 1,536 (3%) had the dry form of the disease. The average follow-up time was 7.4 years. Longer-term use of any NSAID was associated with lower risk of exudative AMD. New users of aspirin or any NSAID had a lower risk of nonexudative AMD, but this trend was not observed for longer-term users. No other meaningful relationships were noted.

Although longer-term use of any NSAID appears to carry a lower risk of exudative AMD, the authors emphasized that more research is needed to determine whether this finding can be applied clinically to modify disease risk.

Improving Follow-Up Attendance Rates in the SToP Glaucoma Study

April 2018

Eye exam schedules can be challenging for underserved populations. **Zhao et al.** aimed to determine the factors associated with attaining follow-up care among patients with positive findings on initial screenings. They found that follow-up attendance rates can be improved by combining standard strategies with less-traditional ones.

SToP Glaucoma is an ongoing project from the U.S. Centers for Disease Control and Prevention to implement an effective program for detecting glaucoma and other eye diseases in high-risk individuals. It focuses on African Americans aged 50 and older who live in urban areas of Baltimore. A goal of the project is to screen 9,000 individuals during a 5-year period.

The initial ophthalmic screening occurs in a local community venue, where trained personnel administer a questionnaire, measure visual acuity (VA) and intraocular pressure (IOP), and conduct visual field testing and imaging studies. Individuals with positive findings are referred for subsequent examination at the Wilmer Eye Institute. Patients receive the screenings at no cost.

In the first phase of the study, standard methods of follow-up—such as personal reminders via telephone and email—were used. Free transportation was offered to those who needed it. Additional contact efforts were made when a patient did not attend his or her follow-up appointment.

The second phase of the study included supplemental strategies to encourage follow-up: providing patients with vouchers stating the value of the exam, prescheduling follow-up visits within 4 weeks of initial screening, and showing educational videos to reinforce the importance of continuing care. Multivariable logistic regression was used to detect associations between follow-up attendance and demographic, general medical, and ocular factors.

The attendance rate for referred patients in the first phase of the study was 55.0%, which increased to 63.8% in the second phase. Fully adjusted models yielded the following odds ratios: 1.82 for screening in phase 2 versus phase 1; 0.62 for screening sites that were 3 to < 5 miles versus < 1 mile from the hospital; 1.70 for body mass index ≥ 30 kg/m^2 versus < 25 kg/m^2; 2.03 for presenting VA < 20/40 versus ≥ 20/40; 2.32 for abnormal versus normal macula; and 2.19 for IOP ≥ 23 mm Hg versus < 23 mm Hg. *—Summaries by Lynda Seminara*

JAMA Ophthalmology

Selected by Neil M. Bressler, MD, and Deputy Editors

Costs of Preoperative Testing for Patients With Cataract

March 2018

The 30-day window preceding cataract surgery is commonly used to study costs of preoperative testing. **Chen et al.** sought to estimate the full cost of preoperative testing by including all tests conducted after a cataract surgery is scheduled. They found that many tests are performed before the 30-day preoperative window, resulting in overall testing costs that are higher than previously reported.

For their cross-sectional study, the authors utilized a 50% sample of Medicare beneficiaries (> 66 years of age)

who underwent ambulatory cataract surgery in 2011. The surgery date was defined as the first day that a claim for routine cataract surgery was submitted by an ophthalmologist. Only the cataract surgery on the first eye (index surgery) was included. Tests that occurred between the first biometry claim and the index surgery were considered routine. Testing rates were determined for the interval between ocular biometry and cataract surgery and for the 6 months preceding biometry.

Of the 440,857 patients who underwent cataract surgery in 2011, those with a claim for ocular biometry before index surgery (n = 423,710) constituted the study population. Of these, 6.3% had a biometry claim submitted on the day of surgery, 25.4% underwent surgery more than 30 days after biometry, and 5.1% had surgery more than 90 days after biometry.

The mean number of tests per patient per month increased from 1.1 in the baseline period (≤ 6 months before biometry) to 1.7 in the interval between biometry and cataract surgery. Although the frequency of preoperative testing peaked for all patients in the 30-day preoperative window (1.8 tests/patient/month), the subset of patients with no time overlap between the postbiometry and presurgery periods had a higher testing rate during the 30 days after biometry (1.8 tests/patient/month), regardless of the amount of time between biometry and surgery.

The total estimated cost of routine preoperative testing in this study was $22.7 million, for an estimated annual cost burden for Medicare of up to $45.4 million. As a cost-cutting measure, the authors suggested avoiding routine tests between biometry and surgery. *(Also see related commentary by Farhan I. Merali, MD, MBA, and Oliver D. Schein, MD, MPH, MBA, in the same issue.)*

Infant Aphakia Contact Lens Wear and Cataract Surgery

March 2018

Although contact lenses have been used for decades to correct vision in children after cataract surgery, prospective data on adherence to lens wear are limited. In a secondary analysis of the Infant Aphakia Treatment Study, **Cromelin et al.** documented adherence to contact lens use and examined its association with visual outcomes. Overall, the adherence level was high, and consistent lens use resulted in improved visual acuity (VA).

In the authors' study, 57 children (32 girls, 25 boys) received follow-up through 5 years of age. As infants, they had undergone unilateral cataract extraction and had been assigned randomly to receive a contact lens to correct aphakia. (The other study arm received intraocular lens implantation.) The contact lens was provided at no cost, and 2 lenses were dispensed for each prescription fill so that a spare would be available if needed.

Adherence to prescribed lens wear was assessed from 48-hour–recall telephone interviews with caregivers, which were administered every 3 months, starting 3 months after surgery and continuing until the child was 5 years old. A traveling examiner tested visual acuity when the children were 4.5 years of age. Adherence estimates were calculated from the mean percentage of waking hours of lens use reported during at least 2 interviews for each year of life.

Overall, 872 interviews were completed. The proportion of children who wore their lens for nearly all waking hours was 95% in the first year of life, 93% in years 2 through 4, and 89% in the fifth year. Subanalysis by several factors resulted in similar findings.

Linear regression showed that, in general, the children who wore their lens for more waking hours had better VA at 4.5 years of age, even when accounting for adherence to patching. Overall, the results demonstrate that good adherence to contact lens wear is possible for young children following cataract surgery. The fact that the lenses were provided at no cost may have contributed to the high rates of adherence.

Treating Persistent DME: Comparison of 3 Anti-VEGF Drugs

March 2018

Treatment of diabetic macular edema (DME) with anti–vascular endothelial growth factors has improved visual acuity and retinal thickness but not the persistent DME (pDME) or chronic persistent DME (cpDME) that some patients experience, thus raising questions about the benefits and long-term outcomes associated with these drugs. To provide answers, **Bressler et al.** analyzed data from a DRCR.net trial and found that pDME was more common with bevacizumab than aflibercept or ranibizumab at 24 weeks of treatment —and that cpDME was more likely to occur in eyes that received bevacizumab than in those that received aflibercept. They also noted that the risk of vision loss was minimal regardless of the agent used or whether there was chronic persistence of DME.

The authors' post hoc analysis was based on data for 546 eyes in the DRCR.net Protocol T trial. All treated eyes had central-involved DME and a best-corrected visual acuity letter score of 24 to 78. They were assigned randomly to receive up to 6 injections monthly, initially, of aflibercept, bevacizumab, or ranibizumab. Additional injections or focal/grid laser sessions were administered to achieve stability.

Through week 24, the rate of pDME was higher with 1.25-mg bevacizumab (118 of 180 eyes; 65.6%) than with 2-mg aflibercept (60 of 190 eyes; 31.6%) or 0.3-mg ranibizumab (73 of 176 eyes; 41.5%). At 1 year, 98 eyes treated with bevacizumab had cpDME, versus 59 of those treated with ranibizumab and 47 treated with aflibercept. At 2 years, the number of eyes with cpDME were as follows: 70 bevacizumab eyes, 38 ranibizumab eyes, and 29 aflibercept eyes.

Among eyes with pDME at 24 weeks, the proportion with gains of 10 or more letters from baseline to 2 years did not differ significantly by the presence or absence of cpDME: 51%, 62%, and 44% of eyes with cpDME that received bevacizumab, aflibercept, and ranibizumab (respectively) gained 10 or more letters, as did 54.8%, 63.3%, and 65.5% (respectively) of those without cpDME. Only 3 eyes with cpDME lost ≥ 10 letters.

This research indicates that aflibercept and ranibizumab are better than bevacizumab at preventing pDME

through 24 weeks and that aflibercept is superior to bevacizumab for resolving cpDME by 2 years. The authors cautioned against switching agents after just a few injections because the edema may resolve by continuing treatment with the same agent. *(Also see related commentary by Rajendra S. Apte, MD, PhD, in the same issue.)*

—Summaries by Lynda Seminara

OTHER JOURNALS

Selected by Deepak P. Edward, MD

MIGS Surgery: Safety and Efficacy of the XEN45 Gel Stent

Graefe's Archive for Clinical and Experimental Ophthalmology
Published online Jan. 22, 2018

The XEN45 Gel Stent (Allergan) is a flexible hydrophilic tube used for minimally invasive glaucoma surgery (MIGS). The stent is placed in the subconjunctival space, and its flexibility and small diameter pose minimal stress to surrounding tissue, thus decreasing the possibility of erosion or migration. The stent also is designed to avoid hypotony, obviating a valve system. **Widder et al.** studied the device's risk profile and ability to lower intraocular pressure (IOP) and observed favorable results for both endpoints.

In their study, results were analyzed for 233 eyes that received stent placement in an effort to achieve IOP reduction without medication. Stent placement was used as a pseudophakic standalone procedure (139 eyes), as a phakic standalone procedure (45 eyes), or in combination with cataract surgery and lens implantation (49 eyes). The primary success rate was based on the number of eyes in which appropriate IOP was attained without medication or surgical revision. The overall success rate allowed for 1 surgical revision. The mean follow-up time was 8.5 months.

Mean IOP was lowered from 24.3 mm Hg to 16.8 mm Hg, and revision surgery was performed in 80 eyes (34%). After the initial revision, mean IOP was 14.0 mm Hg. The primary success rate was 66%, and the overall success rate was 90%. The primary success rate was higher for pseudophakic eyes (73%) than for phakic eyes (53%) or eyes with combination surgery (55%). Therefore, it may be prudent to combine cataract and angle-related surgery, recognizing that the XEN45 stent could be implanted later, with better outcomes expected in pseudophakic eyes. The most common side effects were intraoperative bleeding (9.4%) and postoperative hyphema (5.6%); the latter resolved spontaneously.

Visual Network Changes Due to Optic Neuritis

JAMA Neurology
Published online Jan. 2, 2018

Backner et al. looked at anatomic and functional visual networks of patients with a first attack of optic neuritis (ON) and compared them with the visual networks of patients with symptoms of demyelination in other functional systems. They found that local demyelinating damage of the optic nerve did not affect distant wiring—and that functional modification was possible even in the presence of an intact anatomic network.

This prospective study involved 39 adults, 18 of whom had clinically isolated syndrome (CIS) ON. The remaining 21 had CIS unrelated to ON. Patients were enrolled 1 to 28 months following their initial clinical event and were required to have a suggestive clinical or paraclinical diagnosis of CIS or multiple sclerosis.

Anatomic connectivity was assessed by diffusion tensor imaging, and functional connectivity was evaluated by resting-state functional magnetic resonance imaging. Visual pathways were delineated (including optic tracts, optic radiations, and splenial fibers), and the resting-state visual networks were detected. Connectivity changes were quantified and compared.

Diffusion tensor imaging showed reduced diffusivity along the optic tracts of patients with ON, suggesting local extension of the optic nerve damage, but neither the optic radiations nor the splenial fibers showed loss of integrity. However, among patients with an intact postgeniculate anatomic network, functional connectivity within the visual network was higher in those with ON. The functional connectivity observed in areas related to cortical motion correlated inversely with conduction velocity measured by visual evoked potential.

It has been suggested that clinical outcomes for patients with multiple sclerosis are driven by remyelination as well as adaptive reorganization. The functional network changes observed in this study may play a role in the visual recovery process, but further research is needed to fully understand the mechanisms involved.

—Summaries by Lynda Seminara

Comparing Ranibizumab Dosages for ROP

JAMA Pediatrics
2018;172(3):278-286.

Stahl et al. set out to compare 2 doses of ranibizumab for retinopathy of prematurity (ROP). They found that treatment with 0.12 mg of the drug was as effective as treatment with 0.20 mg.

This double-blind study, known as CARE-ROP, was conducted at 9 academic medical centers in Germany. Infants with bilateral ROP in zone I or posterior zone II ROP were eligible; the primary endpoint of the study was the number of infants who did not require rescue therapy at 24 weeks.

Initially, 19 infants were enrolled; of these, 10 infants (20 eyes) received 0.12 mg of ranibizumab, while the remaining 9 infants (18 eyes) received 0.20 mg. One infant in the lower-dose group and 2 in the higher-dose group died during the study. A causal relationship to the received treatment was not suspected in any of the 3 deaths; all occurred at least 14 weeks after treatment, and the 3 infants had not received more than the baseline injections.

Control of ROP without the need for rescue therapy was achieved in 14 of the 16 surviving infants. One eye in each study group showed insufficient response to ranibizumab and required rescue therapy with laser therapy. Four infants (2 in each dose group) showed recurrence of ROP and required retreatment with ranibizumab.

—Summary by Jean Shaw