Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

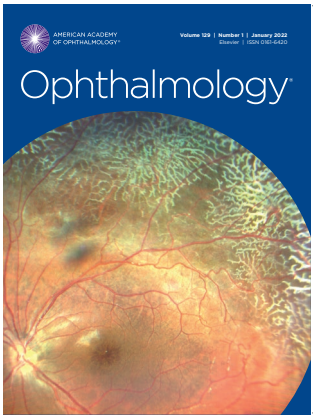
Ophthalmology

Selected by Stephen D. McLeod, MD

Rates and Predictors of PVD in Comprehensive Ophthalmic Practice

January 2022

In an effort to aid comprehensive eye care clinicians who are presented with cases of acute posterior vitreous detachment (PVD), **Seider et al.** explored rates and risk factors for complicated PVD in a large comprehensive care practice. The researchers included an examinaton of the relationship between refractive error and the risk of retinal tear or rhegmatogenous retinal detachment (RRD) in patients with symptoms of acute PVD. They found that rate of retinal tear or RRD linked to PVD was lower than that previously reported in retina subspecialty settings, although it remains clinically significant. The strongest predictor of retinal tear and detachment was the presence of vitreous pigment.



For this research, the authors compiled data for adult patients in the Kaiser Permanente Northern California Healthcare System who were seen in 2018 by an ophthalmologist or optometrist and were diagnosed as having PVD, vitreous degeneration, vitreous floaters, vitreous flashes, vitreous hemorrhage, retinal tear, or RRD.

The patients' medical records were reviewed to capture acute symptomatic PVD events, to document patient history and eye exam findings, and to confirm diagnoses. The main outcome measure was the presence of retinal tear or detachment at initial presentation or subsequently within one year of presentation.

Altogether, 8,305 patients met the study criteria. The diagnosis was retinal tear in 448 (5.4%) and RRD in 335 (4.0%). Preexisting factors associated with heightened risk of retinal tear or detachment were blurred vision (odds ratio [OR], 2.7), male sex (OR, 2.1), younger age (<60 years; OR, 1.8), and previous keratorefractive or cataract surgery (OR, 1.6 and 1.4, respectively). Flashes were found to be mildly protective (OR, 0.8).

Exam variables that raised the risk of retinal tear and RRD included vitreous pigment (OR, 57.0), vitreous hemorrhage (OR, 5.9), lattice degeneration (OR, 6.0), and visual acuity worse than 20/40 (OR, 3.0).

Late retinal tear or detachment occurred in 12.4% of patients who had vitreous hemorrhage, lattice degeneration, or a history of retinal tear/RRD in the fellow eye at initial presentation; only 0.7% of patients had none of these three risk factors.

Endophthalmitis Risk of Sequential Bilateral Cataract Surgery

January 2022

Friling et al. compared postoperative endophthalmitis rates for unilateral cataract surgery and immediate sequential bilateral cataract surgery (ISBCS) and found that the risk of infection was lower with ISBCS.

The investigators began by gathering data for endophthalmitis cases reported to the Swedish National Cataract Register during a 16-year period (2002-2017). They compared incidence and other details of postoperative endophthalmitis for IBSCS versus unilateral surgery (control group). They also assessed patient characteristics, surgical techniques, and capsular complications.

Of the 1,457,172 cataract extractions, endophthalmitis occurred in 422, representing an overall incidence of 0.029%. The rate of post-op endophthalmitis was 0.0299% (408 of 1,364,934 operations) for unilateral procedures and 0.0152% for ISBCS (14 of 92,238 operations; p = .01).

According to logistic regression analysis of all cataract extractions, risk factors independently linked to postoperative endophthalmitis included capsular complications, older patient age (≥85 years), male gender, ocular comorbidity, and no use of intracameral antibiotics. All of these factors were present in both cohorts, but each was less common in the ISBCS group. In the same multivariate analysis, ISBCS carried a significantly lower risk of endophthalmitis.

Overall, even though the endophthalmitis rate seems to be lower with ISBCS than with unilateral extraction, it is not negligible. Thus, the authors said, it is crucial to exercise caution. Of note, during follow-up, visual acuity for five of the 14 patients with ISBCS-related endophthalmitis was 20/200 or worse. One such patient, a 93-year-old, had endophthalmitis postoperatively in both eyes.

In addition, the authors hypothesized that if the surgeons would have routinely used intracameral antibiotic prophylaxis with ISBCS and had refrained from offering the bilateral procedure to patients over 84 years of age, the incidence of post-op endophthalmitis could have been as low as 0.0073% (six of 81,226 eyes). They suggested that these data will be useful for decision-making for patients for whom ISBCS may be an option.

Achieving Target IOP Slows VF Decline

January 2022

In a longitudinal study, **Villasana et al.** looked at the effect of achieving clinician-established IOP targets on visual field (VF) status. They found that failure to attain IOP goals coincides with VF worsening and that eyes with moderate glaucoma have the greatest rate of VF decline.

This retrospective study included 1,688 patients (2,852 eyes) with suspected or confirmed glaucoma who were treated in a tertiary care practice. For all eyes, data were available for at least five reliable VF tests and five IOP measures. Each eye had a target IOP, established by the clinician in the patient's first or second visit for glaucoma care. In general, the clinicians followed published guidelines for target IOPs: values in the low teens for eyes with advanced disease, the mid-teens for moderate disease, and the high teens for mild disease.

The primary dependent variable was the slope of mean deviation (MD) over time (dB/year), and the main independent variable was mean difference between actual and target IOP values. Linear regression models and mixed-effects linear models were used to explore the relationship between MD slope and mean difference from target for each eye. The mixed models included an interaction term to account for disease severity (mild/suspect, moderate, advanced) and a spline term to account for difference between success and failure to attain the IOP goal. The main outcome measure was the rate of change in MD slope for each 1-mm Hg difference from the target IOP.

In the overall analysis, a difference (increase) of 1 mm Hg from the goal IOP corresponded to a –.018 dB/year effect on MD slope ($p < .05$). In eyes with moderate glaucoma, each 1-mm Hg increase from the target value was associated with an MD slope of .119 dB/year ($p < .05$). The effect of missed IOP on VF decline was more profound than the effect of absolute IOP on VF decline, for which each 1-mm Hg increase in IOP had an effect of –.004 dB/year on the MD slope ($p > .05$). Achieving target IOP led to a lower likelihood of VF loss in comparison to achieving any arbitrarily defined target not set by the clinician, as long as the goal IOP was <21 mm Hg for mild or suspected glaucoma and <18 mm Hg for moderate glaucoma.

In light of these findings, the difference between actual and target IOP may be a predictor of VF decline, said the authors.

—Summaries by Lynda Seminara

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

Retinal Atrophy After Luxturna Injections for LCA

January 2022

Gange et al. report the observation of perifoveal chorioretinal atrophy in eyes that underwent subretinal injection of the gene therapy voretigene neparvovec (VN; Luxturna) for *RPE65*-mediated Leber congenital amaurosis (LCA). They recommend further study to isolate the factors that may predispose patients to this previously undescribed complication.

For this study, the authors performed a retrospective chart review on all patients who received a subretinal VN injection at four of the 10 clinical sites currently treating patients with the gene therapy. Patients were identified as having perifoveal chorioretinal atrophy if 1) the areas of atrophy were not directly related to the touchdown site of the subretinal cannula, and 2) the area of atrophy grew larger over time. Main outcome measures included change in visual acuity (VA), visual fields, and location of atrophy relative to subretinal bleb position.

All told, 10 patients (18 eyes) at the four sites participating in this study were found to have developed atrophy, and the atrophy was bilateral in eight of the 10 patients. The patients' mean age was 11.6 years (range, 5-20 years), and six were male.

The atrophy was first noticeable from one week to one year following surgery (mean, 4.7 months post-op), and it progressively enlarged in all cases up to the last follow-up examination (mean follow-up, 11.3 months; range, 4-18 months).

Atrophy developed within and outside the area of the subretinal bleb in 10 eyes, exclusively within the area of the bleb in seven eyes, and exclusively outside the bleb in one eye. VA improved in 12 eyes, held steady in three, and worsened in three. Overall, however, there was no significant change in mean VA before and after treatment ($p = .45$); the authors noted that this was likely due to the atrophy sparing the fovea.

In their discussion, the authors cited several potential factors that may have contributed to the atrophy, including direct toxicity of the vector to the photoreceptors and retinal pigment epithelium, an inflammatory or immune response to the vector, and surgical technique. It also is possible that the atrophy described in this study is consistent with preexisting ocular factors, such as myopia, or with the natural history of the disease, independent of the treatment, they said.

Given these uncertainties, further study is needed. This is particularly critical not only for LCA but also for the growing number of retinal gene therapy trials and their expansion to

such conditions as age-related macular degeneration and diabetic retinopathy, the authors noted.

—Summary by Jean Shaw

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Sequential Versus Simultaneous Patching for Unilateral Amblyopia

January 2022

Which patching regimen is best for children with unilateral amblyopia? The Academy recommends spectacle wear as the first step, followed by part-time occlusion of the nonamblyopic fellow eye if glasses alone aren't effective. In the approach known as simultaneous treatment, the child wears glasses full-time and uses occlusion on a part-time basis. **Chinn et al.** compared visual outcomes for the two regimens and found little difference between them.

For this retrospective study, the researchers assessed children (ages 3-12 years) with unilateral amblyopia diagnosed at Boston Children's Hospital during a five-year period. Other requirements were visual acuity (VA) of 20/40 to 20/200 (with interocular difference ≥3 lines) and a follow-up visit that occurred three to nine months after therapy was begun. Criteria for exclusion were deprivation amblyopia, any previous amblyopia treatment, and surgery for strabismus or cataract.

Patients were grouped by type of regimen: "simultaneous treatment" (concurrent glasses/patching initially) or "sequential treatment" (glasses at first visit plus patching at second visit). Median age was similar for the two cohorts (5.26 and 5.10 years, respectively). Outcome measures were VA and stereopsis at the most recent follow-up visit.

Of 2,311 patients in the Boston Amblyopia Study database, 98 met the inclusion criteria for this study; therapy was simultaneous for 36 and sequential for 62. VA improvement in amblyopic eyes was similar: The median change was +0.40 logMAR with each regimen (interquartile range [IQR]: 0.56-0.30 for simultaneous, 0.52-0.27 for sequential). For patients without stereopsis when therapy was initiated, outcomes for this parameter were better with sequential therapy (5.12 log stereopsis [IQR, 4.00-7.51]) than with simultaneous therapy (8.01 log stereopsis [IQR, 5.65-9.21]) (p = .046).

In this study, both regimens were found to improve VA by approximately 4 lines. For patients whose stereopsis is not problematic when treatment is begun, sequential patching may be the better choice, said the authors. They affirmed that additional studies are needed to validate these findings. Of note, the Pediatric Eye Disease Investigator Group is recruiting participants for a randomized controlled study of the two regimens.

Relationship of Vision to Retinal Fluid in Ranibizumab-Treated Neovascular AMD

January 2022

Evidence from recent studies has raised questions about using subretinal fluid (SRF) and/or intraretinal fluid (IRF) as biomarkers of disease activity in neovascular age-related macular degeneration (AMD), as well as the goal of achieving fluid-free retinas with anti-VEGF therapy. In a post hoc analysis of HARBOR data, **Holekamp et al.** explored the relationship between vision and retinal fluid in patients with neovascular disease treated by ranibizumab. They found that eyes with residual SRF alone had the highest mean best-corrected visual acuity (BCVA) and the greatest change in BCVA by 12 and 24 months of as-needed or monthly ranibizumab treatment. Eyes with residual IRF alone had the poorest visual outcomes.

For this analysis, the authors reviewed data for 917 participants of the phase 3, multicenter, randomized, controlled HARBOR trial. Patients were at least 50 years old, had subfoveal neovascular AMD associated with SRF and/or IRF (at baseline, screening, or week 1), and were treated with intravitreal ranibizumab .5 or 2.0 mg. Data for treatment arms were pooled. Mean BCVA and the change from baseline to months 12 and 24 were determined by fluid outcomes (e.g., the presence or absence of SRF and/or IRF).

At 12 months, BCVA was better in patients with residual SRF than in those with resolved SRF (mean, 58.8 vs. 53.5 letters, respectively). Results at 24 months were similar (mean, 59.3 vs. 53.5 letters, respectively). The adjusted mean change in BCVA by month 12 was greater with residual SRF than with resolved SRF (mean difference of +2.4 letters), but it was lower with residual IRF versus resolved IRF (–3.5 letters). The assessment of BCVA changes by fluid group at 12 and 24 months showed that eyes with residual SRF alone had the greatest gains in acuity (+14.1 letters at 12 months and +13.2 letters at 24 months). The respective gains were +10.6 and +10.0 letters for patients with dry retina; +7.2 and +8.5 letters for patients with SRF/IRF; and +5.5 and +3.6 letters for those with IRF only.

The odds ratio of attaining visual acuity of 20/40 or better was similar for patients with residual and resolved SRF but was significantly worse with residual versus resolved IRF.

These findings indicate that visual outcomes are affected by the presence/absence and type of residual retinal fluid observed during ranibizumab treatment. Eyes with only residual SRF fared better than eyes with only residual IRF. Intraretinal fluid may not always be harmful to patients with neovascular AMD, said the authors, as long as anti-VEGF treatment is given regularly. They acknowledged that more studies are needed to assess the long-term effects of intraretinal fluid and to refine strategies for managing neovascular disease.

—Summaries by Lynda Seminara

JAMA Ophthalmology

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

Lapses in Care for PDR After Anti-VEGF Tx

December 2021

Maguire et al. set out to assess whether examinations of patients assigned to intravitreal injections of ranibizumab

for proliferative diabetic retinopathy (PDR) in a randomized controlled trial were completed as scheduled. They found that, over a five-year period, approximately half of the participants had long lapses in care, and nearly a third dropped out of the study, despite efforts of the DRCR Retina Network to ensure that all examinations were completed on time.

For this post hoc analysis, the researchers evaluated data from the DRCR Network's Protocol S, which was completed in 2015. Main outcomes were a long lapse in care of eight or more weeks past a scheduled examination, dropout from follow-up, and visual acuity (VA) at five years.

Of 191 participants with an eye assigned to ranibizumab, 21 died during the follow-up period. Of the remaining 170 participants, the median age at baseline was 51 (44-59 years), and 76 (44.7%) were female. During the five years of follow-up, 26 participants (15.3%) were fully compliant, with no lapses in care. For the remainder, the median number of episodes of any lapse in care was three (range, 0-16), and 63 patients (37.1%) had four or more lapses in care.

For 14 patients (9.7%), the first lapse in care resulted in dropping out entirely from the study. By the five-year mark, 50 participants (29.4%) had dropped out. Among the remaining 120 participants, the median change from baseline in VA was a loss of 2 letters for those who had one or more long lapses in care. In contrast, those without a long lapse in care gained a median of 5 letters ($p = .02$). However, the researchers noted, it is unclear whether the patients' poor outcomes in VA resulted from missed visits or were related to patient and/or eye characteristics that were more prevalent among those who missed visits.

In their discussion, the authors noted that most (90%) of participants returned for at least one appointment after their first lapse in care. Given that finding, they said, clinicians may have opportunities to counsel returning patients on why regular follow-up is essential to maximizing visual outcomes.

Residency Applications and Implicit Bias

December 2021

For ophthalmology residency applicants, does the redaction of identifiers that might trigger reviewers' bias have an impact on application scores? **Pershing et al.** compared redacted and unredacted application reviews at their academic institution. They found that the distribution of application scores was similar for redacted versus unredacted applications, with no differences based on an applicant's sex, race/ethnicity, or country of origin.

For this quality improvement study, 46 faculty members reviewed randomized sets of 462 redacted and unredacted applications during the 2019-2020 ophthalmology residency application cycle. Redacted identifiers included name, sex or gender, race and ethnicity, and race- or gender-associated groups or activities (e.g., student associations). Each application was reviewed in redacted form by one reviewer and in unredacted form by another. All reviewers received implicit bias training, and each faculty member reviewed a mix of redacted and unredacted applications. Applications were assigned a score from 1 (best) to 9 (worst). Linear regression was used to evaluate the adjusted association of redaction, self-reported applicant characteristics, and reviewer characteristics with application scores.

Of the 462 applicants, 185 (40%) were female, 277 (60%) were male, 71 (15.4%) self-identified as underrepresented in medicine (URiM) individuals, and 47 (10.2%) were international medical graduates (IMGs). Of the 46 faculty members, 14 (30.4%) were female, 32 (69.6%) were male, and two (.4%) were URiM individuals.

The mean application review score was 4.83. The distribution of scores was similar for redacted versus unredacted applications, with no difference based on sex, URiM status, or IMG status. Applicants were more likely to receive better scores if they had attended a top 20 medical school (as ranked by *U.S. News & World Report*), held an additional advanced degree, and had higher United States Medical Licensing Examination (USMLE) Step 1 and Step 2 scores.

Overall, the authors said, they believe that these results are encouraging. However, they noted that metrics such as medical school rankings and USMLE scores may be subject to confounding and bias. They recommended other initiatives to improve diversity, such as pipeline programs, implicit bias training for faculty, and targeted outreach to underrepresented applicants. *(Also see related commentary by O'Rese J. Knight, MD, Elise V. Mike, MD, PhD, and Angela R. Elam, MD, in the same issue.)*

IOP-Related Events After IVIs for Macular Edema in SCORE2

December 2021

In a secondary analysis of the SCORE2 study, **Aref et al.** investigated IOP-related events in patients who received intravitreal injections (IVIs) of anti-VEGF medications for macular edema secondary to central retinal vein occlusion (CRVO) or hemiretinal vein occlusion (HRVO). They found that the risk of an IOP-related event in these patients warrants ongoing monitoring of IOP for up to 60 months.

For this study, the researchers assessed 312 patients with macular edema secondary to CRVO or HRVO who were not taking an IOP-lowering medication at baseline in SCORE2. Main outcomes were a rise in IOP more than 10 mm Hg from baseline, a rise in IOP to a level higher than 35 mm Hg, and the need for IOP-lowering incisional or laser surgery.

During SCORE2, patients were randomized to IVIs of aflibercept or bevacizumab. At the six-month mark, good responders were re-randomized to either continued monthly injections or a treat-and-extend protocol with their original drug. Poor responders were switched to the alternative anti-VEGF medication. After month 12, participants were treated at investigator discretion using any commercially available anti-VEGF drug, and follow-up visits were conducted through month 60.

For this analysis, the mean age of the 312 participants was 67.8 years (standard deviation [SD], 12.1 years), and 138 (44.2%) were female. Through 60 months of follow-up, 25 eyes (8%) experienced a rise in IOP more than 10 mm Hg over baseline, and five (1.6%) had an IOP higher than 35 mm Hg. The 60-month Kaplan-Meier cumulative incidences of IOP elevation greater than 10 mm Hg over baseline and IOP higher than 35 mm Hg were .13 and .02, respectively. No definitive differences were noted in the number of IOP-related events between recipients according to initial randomization to aflibercept or bevacizumab injections.

Finally, three participants (1%) underwent IOP-lowering incisional surgery, and an additional three (1%) had IOP-lowering laser surgery.

In summary, the authors said, the proportion of eyes with IOP-related events in SCORE2 participants supports monitoring IOP in eyes treated with IVIs of anti-VEGF drugs for macular edema associated with CRVO or HRVO. *—Summaries by Jean Shaw*

OTHER JOURNALS

Selected by Prem S. Subramanian, MD, PhD

Phaco-ECP for POAG: Results at Three Years

Eye (London)
Published online Sept. 15, 2021

Endoscopic cyclophotocoagulation (ECP) is often considered for surgically naive patients with cataract and inadequately controlled primary open-angle glaucoma (POAG). **Yap et al.** looked at the long-term safety and efficacy of phacoemulsification plus ECP (phaco-ECP) for such patients. They found that the safety of phaco-ECP was sustained through three years, although the effectiveness decreased somewhat.

In this retrospective single-center series, the authors analyzed data for adults with POAG of any severity who underwent phaco-ECP from 2007 to 2017. The primary outcome measure was change in IOP of the first treated eye in each patient. Secondary outcomes included visual acuity, visual field indexes, medication burden, and surgical complications. Failure of the procedure was defined as IOP greater than 21 mm Hg or less than 20% reduction at two consecutive visits, IOP lower than 5 mm Hg, or the need for additional IOP-lowering surgery.

Altogether, 83 patients (83 eyes) were included in the study. Their mean IOP decreased significantly after surgery and remained low throughout follow-up. By one year, mean IOP had declined from 18.4 mm Hg (pre-op) to 14.3 mm Hg. Additional reductions were noted at year 2 (to 14.1 mm Hg) and year 3 (to 13.6 mm Hg). Considering the criteria for failure, the procedure was deemed successful for 70% of patients at one year, 54% at two years, and 45% at three years. The mean burden of topical ocular hypotensive drugs was reduced significantly, from 2.7 medications at baseline to 1.3 at one year, which remained fairly steady thereafter (1.7 at two years and 1.8 at three years). Significant improvement in visual acuity from baseline was observed at all post-op visits. However, visual field indexes remained similar to those at baseline. The most common complication was uveitis, which affected 6% of the study population. No patient had hypotony or retinal detachment, and only one patient required a second IOP-lowering surgery within the three years.

These findings may be relevant for patients who could benefit from reducing topical medications, said the authors, even though failure rates appear to increase over time. Given the advantages of phaco-ECP, including minimal disruption to tissue, the authors recommend considering it as an alternative to minimally invasive procedures for glaucoma.

Cost-Utility Comparison of RRD Interventions

Retina
Published online Aug. 30, 2021

Belin et al. performed a cost-utility comparison of three procedures commonly used to repair rhegmatogenous retinal detachments (RRDs): scleral buckle (SB), pars plana vitrectomy (PPV), and the combination procedure (SB-PPV). They found that SB was modestly better than PPV or SB-PPV in terms of cost-effectiveness. In addition, they found that the expenses associated with any of these procedures were far below the maximum willingness-to-pay standard, indicating that all three have a favorable cost-utility profile.

This study was a secondary analysis of patient data from the Primary Retinal Detachment Outcomes Study and fee data from CMS. Mathematical modeling was used to estimate specific costs, lifetime utility (quality-adjusted life years [QALYs] afforded), and lifetime cost per QALY for phakic patients with moderately complex RRD who received SB, PPV, or SB-PPV. Costs were estimated for hospital ORs and ambulatory surgery centers. It was assumed that costs for the initial and subsequent follow-up office exams were the same for all three procedures; therefore, these costs were not included in the analyses.

Results were as follows:

- The estimated costs and QALYs gained were $5,975 and 5.4 (respectively) with SB, $8,125 and 4.7 with PPV, and $7,551 and 4.7 with SB-PPV. This corresponds to costs per QALY of $1,106 for SB, $1,729 for PPV, and $1,607 for the combined procedure.
- The estimated cost of ambulatory surgery centers was $3,774 for SB, $5,082 for PPV, and $4,713 for SB-PPV.
- The overall costs associated with any of these procedures were found to be well below the willingness-to-pay ceiling of $100,000 to $150,000 per QALY.
- At $1,106 per QALY, SB was marginally superior to PPV and SB-PPV, but the authors acknowledged that the SB group was younger, which may have contributed to the lower cost per QALY.

These findings suggest that SB, PPV, and SB-PPV are highly and similarly cost-effective for managing moderately complex RRD. In particular, the researchers said, these findings "should encourage retinal surgeons to utilize whichever method they believe will be most successful given the patient's RRD characteristics, and give payers the confidence that repair of RRD is a highly cost-effective therapy."

—Summaries by Lynda Seminara