Avastin Beneficial in Treating Pseudophakic CME

Intravitreal Bevacizumab for Refractory Pseudophakic Cystoid Macular Edema: The Pan-American Collaborative Retina Study Group Results.
Arevalo JF, Maia M, et al:

Ophthalmology 2009; 116 (August): 1481-1487

Intravitreal injection of bevacizumab appears to be a safe and effective treatment for management of refractory cystoid macular edema after cataract surgery.

Objective: To evaluate the safety and efficacy of intravitreal injection of bevacizumab (Avastin) for management of refractory cystoid macular edema (CME) after cataract surgery.

Design: Interventional, retrospective, non-comparative clinical case series.

Participants/Methods: 36 eyes of 31 patients treated for refractory CME after routine cataract surgery with intravitreal bevacizumab were included in the study. A review of medical records allowed determination of change in best-corrected visual acuity after intravitreal injection of 1.25 or 2.5 mg of bevacizumab. All patients had undergone uncomplicated cataract surgery but had developed CME that did not respond to routine therapy with topical, periocular, or systemic corticosteroids or NSAIDs. Patients were monitored at periodic intervals throughout 1 year of follow-up. Optical coherence tomography measurement of retinal thickness allowed for objective determination of the effect of treatment on retinal thickness.

Results: Best-corrected visual acuity improved in 72% of eyes by at least 2 lines on the Early Treatment Diabetic Retinopathy Study visual acuity chart. No eye experienced a reduction in best-corrected visual acuity. A significant reduction in macular thickness was also observed, with a reduction in mean macular thickness from 500 μm to 286 μm at 12 months' follow-up (P <0.0001). Multiple injections were required in 64% of patients in order to achieve these results.

Conclusions: Intravitreal injection of bevacizumab is effective in reducing macular thickness and improving visual acuity in patients with refractory CME following cataract surgery.

Reviewer's Comments: CME is a frustrating complication of cataract surgery, particularly when it fails to respond spontaneously or in response to topical NSAIDs. The study demonstrates the efficacy of the vascular endothelial growth factor inhibitor bevacizumab when injected intraocularly for management of refractory CME. Although the exact mechanism of action of this drug and its efficacy in this particular application remains uncertain, it is likely that a reduction in biologic activity of cytokines and vascular endothelial growth factor, which can lead to reduced vascular permeability in the retina, is responsible for its efficacy. (Reviewer-Scott D. Smith, MD, MPH).

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Keywords: Cystoid Macular Edema, Intravitreal Bevacizumab, Cataract Surgery

Print Tag: Refer to original journal article
Objective: To determine the incidence of cystoid macular edema (CME) after cataract surgery in patients with uveitis and to evaluate risk factors for development of this complication.

Design: Prospective, comparative clinical study.

Participants/Methods: Patients from a single-center academic center (41 eyes with uveitis, 52 eyes without uveitis) with visually significant cataracts undergoing cataract surgery were enrolled in this study. Preoperative measurement of retinal thickness by optical coherence tomography (OCT) was performed within 4 weeks before cataract surgery and was repeated 1 month and 3 months after surgery. All patients underwent clear corneal phacoemulsification with a foldable acrylic posterior chamber intraocular lens, performed by an experienced cataract surgeon. Control of uveitis was optimized prior to surgery, and surgery was performed only in the presence of active inflammation when complete control of inflammation was not possible. Uveitis patients were classified with regard to length of time of quiescence prior to cataract surgery. Statistical analysis allowed estimation of the incidence of CME in uveitis and control patients, amount of visual improvement, and risk factors associated with development of CME in uveitis patients.

Results: Mean improvement in visual acuity in both groups was approximately 3 lines. A significantly lower degree of improvement in visual acuity was seen in patients who developed persistent CME, which was seen only in the uveitis group. The overall incidence of CME at 1 month was 12% in uveitic eyes and 4% in control eyes. At 3 months, the proportion of patients with residual CME was 8% in uveitic eyes and 0% in control eyes. Use of oral corticosteroids reduced the risk of development of CME by 7-fold (relative risk [RR], 0.14; \( P = 0.05 \)). Presence of active inflammation within 3 months before surgery significantly increased the risk of CME compared to those eyes without inflammation (RR, 6.2; \( P = 0.04 \)).

Conclusions: Eyes with well-controlled uveitis can achieve a good outcome with cataract surgery, particularly with use of perioperative oral corticosteroids and adequate control of inflammation for at least 3 months prior to surgery.

Reviewer's Comments: Factors identified with improved visual outcomes in this study are extremely important to remember when managing patients with uveitis who are undergoing cataract surgery. Achievement of optimal control of inflammation is important, and quiescence for at least 3 months significantly improves the clinical outcome. In addition, perioperative oral steroids should be used to minimize the risk of CME. If these factors are kept in mind, then good clinical results can be achieved in spite of presence of uveitis. (Reviewer-Scott D. Smith, MD, MPH).

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Keywords: Uveitis, Cystoid Macular Edema, Cataract Surgery, Optical Coherence Tomography

Print Tag: Refer to original journal article
Telemedicine Improves Time Efficiency of ROP Dx

Speed of Telemedicine vs Ophthalmoscopy for Retinopathy of Prematurity Diagnosis.

Richter GM, Sun G, et al:


Telemedicine diagnosis of retinopathy of prematurity significantly reduces the time commitment required by the ophthalmologist for evaluation of the patient.

Objective: To compare the time requirement for diagnosis of retinopathy of prematurity (ROP) using standard bedside indirect ophthalmoscopy and telemedicine.

Design: Prospective, comparative clinical study.

Participants/Methods: 3 ophthalmologists conducted ROP diagnosis by standard indirect ophthalmoscopy at the bedside in the neonatal ICU, then again by telemedicine. Each examiner performed standard ophthalmoscopy on 72 to 150 consecutive infants at his institution, and conducted 125 consecutive telemedicine diagnostic sessions in which high-resolution digital images of the retina were examined at a remote location after being taken by ICU personnel. Time requirements for travel to and from the ICU and for performance of bedside examinations were calculated by averaging time spent during weekly sessions over a 4-month period. Time requirements for telemedicine sessions were recorded by internal software built into the telemedicine system, which included time required for documentation of findings.

Results: Mean time required for diagnosis was significantly less with telemedicine than with bedside examination. For each of the 3 physicians, the mean ophthalmoscopic diagnosis time ranged from 4.2 minutes to 6.6 minutes per infant. For telemedicine diagnosis, the mean time required for each of the 3 ophthalmologists ranged from 1.0 minute to 1.8 minutes per infant. When including travel time to and from the neonatal ICU, as well as communication with families and hospital staff, the time requirement per infant was even greater for bedside examination, ranging from 10.1 to 14.4 minutes per infant.

Conclusions: Time requirements for ophthalmologists conducting ROP diagnoses are significantly reduced by telemedicine in comparison with standard ophthalmoscopic diagnosis.

Reviewer’s Comments: This study is important in that it illustrates how telemedicine for ROP diagnosis can considerably improve the efficiency of health care delivery. Other studies have already demonstrated that ROP diagnosis is accurate using this telemedicine methodology. The cost of delivering health care is increasing and is coming under greater and greater scrutiny by government and health insurance companies. This study is an example of how technology can improve the efficiency of health care delivery. (Reviewer-Scott D. Smith, MD, MPH).

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Keywords: Retinopathy of Prematurity, Telemedicine, Diagnosis, Speed

Print Tag: Refer to original journal article
Objective: To determine the effective age on retinal nerve fiber layer (RNFL) and retinal thickness in healthy subjects using optical coherent tomography (OCT).

Design: Prospective, cross-sectional observational study.

Participants/Methods: 124 healthy subjects were recruited for this study. Data from a total of 226 eyes were used in the analysis. Eligible subjects underwent a complete ophthalmic examination including optic nerve examination and visual field testing and were free from any ophthalmic pathology. For OCT, RNFL thickness and retinal thickness measurements were made using the Fast RNFL, Fast Macular, and Fast Optic Disc scan patterns of the Stratus OCT (Carl Zeiss Meditec). Global and sectoral RNFL and macular thickness measurements were calculated and stratified by age into 5 categories.

Results: A statistically significant decrease in global and sectoral RNFL thickness measurements was seen with increasing age. This was true of all sectors except the temporal quadrant and corresponding clock hours, where no statistically significant decrease with age was seen. An overall slope of -0.26 μm per year was seen in mean fiber layer thickness. This corresponds to an approximate 2.5-μm decrease in mean RNFL thickness per decade of increasing age. A similar decrease in macular thickness was also seen.

Conclusions: Age-related decreases in RNFL thickness and macular thickness are expected with serial measurements, even in the absence of glaucoma.

Reviewer's Comments: This age-related decline should be kept in mind when evaluating RNFL thickness measurements for change in patients with glaucoma. A rate of change greater than that seen in this study is suggestive of glaucoma progression, but should be confirmed with follow-up measurements given the variability in RNFL thickness measurements within an individual. (Reviewer-Scott D. Smith, MD, MPH).

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Keywords: Glaucoma, Retinal Nerve Fiber Layer, Optical Coherence Tomography, Age

Print Tag: Refer to original journal article
Uveitic patients with a steroid-induced mechanism, as opposed to an inflammatory mechanism, of intraocular pressure elevation are more easily controlled with topical glaucoma medications.

**Objective:** To evaluate the outcome of raised intraocular pressure (IOP) in uveitis patients with a uveitic or a steroid-induced mechanism for IOP elevation.

**Design:** Retrospective, observational clinical case series.

**Methods:** Medical records were reviewed of a consecutive series of patients who presented for treatment at a tertiary care uveitis clinic during a 3-month period. Medical records were reviewed to determine the cause of IOP elevation (defined as IOP >21 mm Hg). Patients were classified as having either a steroid-induced or inflammatory mechanism of IOP elevation according to the time course of IOP elevation relative to initiation of corticosteroid therapy.

**Results:** A total of 891 subjects were included in the study; IOP elevation occurred in 21.4%. Those eyes with a steroid-induced mechanism of IOP elevation were more easily controlled with glaucoma medications. These patients required fewer glaucoma medications (2.06 vs 2.52; \( P = 0.009 \)) and were less likely to need glaucoma filtering surgery (8.9% vs 22.4%; \( P = 0.002 \)). Recurrence of intraocular inflammation in association with use of prostaglandin analogs for treatment of IOP elevation was not seen in any patients in this study.

**Conclusions:** In patients with uveitis, IOP elevation due to corticosteroid medication use is usually more easily controlled than when it is caused by complications of the inflammatory process.

**Reviewer's Comments:** This study demonstrates that structural changes to the trabecular meshwork caused by the inflammatory process, such as accumulation of inflammatory debris within the trabecular meshwork or development of anterior synechia, result in IOP elevation that is more chronic, more severe, and more difficult to control medically. Steroid-induced IOP elevation can usually be managed medically, and careful observation with use of glaucoma medications can often get patients through the period of steroid-induced ocular hypertension without the need for surgical intervention. In addition, in spite of the theoretical possibility of prostaglandin use exacerbating uveitis, this appears to be an uncommon phenomenon, which was not observed in this study. When patients require supplemental glaucoma medication after other classes of drugs have been used, prostaglandins can be a good alternative to invasive procedures for IOP control, with a low risk of exacerbating the course of uveitis. (Reviewer-Scott D. Smith, MD, MPH)

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Keywords: Glaucoma, Uveitis, Steroid Therapy, Intraocular Pressure

Print Tag: Refer to original journal article
Latanoprost reduces intraocular pressure variability more effectively than does timolol.

**Objective:** To compare the efficacy of latanoprost and timolol with regard to changes in intraocular pressure (IOP) variability, as assessed by the intervisit IOP range.

**Design:** Analysis of three 6-month multicenter, randomized, double-masked clinical trials comparing latanoprost and timolol.

**Methods:** Data for this analysis came from 3 clinical trials evaluating the efficacy of latanoprost and timolol in clinical centers in the United States, United Kingdom, and Scandinavia. Patients underwent baseline and eligibility visits that allowed measurement of IOP both before and after initiation of glaucoma therapy on multiple visits. After initiating treatment, follow-up visits were conducted at 2 and 6 weeks, as well as 3, 4 and 6 months following treatment. The pretreatment intervisit IOP range was defined by the difference between maximum and minimum IOP at the screening and baseline visits, while posttreatment intervisit IOP range was defined by the difference between the maximum and minimum IOP measurements at the 3- and 4-month follow-up visits. A high intervisit IOP range was considered to be one where the difference exceeded 6 mm Hg.

**Results:** Treatment with both latanoprost and timolol significantly reduced the intervisit IOP range. Pretreatment intervisit IOP range was high in 22% of latanoprost-treated patients and 23% of timolol-treated patients prior to initiation of therapy. After treatment, a high intervisit IOP range was seen in only 6% of latanoprost patients and 11% of timolol-treated patients. Although the intervisit IOP range was significantly reduced in both treatment groups, more effective reduction in this parameter was seen in association with latanoprost therapy (P = 0.03). Other clinical factors associated with persistence of high intervisit IOP range included high pretreatment intervisit IOP range, black race, longer time since glaucoma diagnosis, and higher mean pretreatment IOP.

**Conclusions:** Latanoprost results in a significantly greater reduction in intervisit IOP range than does timolol.

**Reviewer's Comments:** The question of whether IOP fluctuation contributes independently to glaucoma progression is a question that has received greater and greater attention in recent years. There is increasing evidence that not only mean IOP but also IOP fluctuation plays an important role in the progression of this disease. Although further study is needed to better define the role that IOP fluctuation plays in glaucoma progression, it is likely that the future evaluation of glaucoma patients will include a measure of IOP fluctuation such as that described in this study. It is evident that the prostaglandin analog latanoprost, probably due to its mechanism of action of reducing aqueous outflow resistance, leads to better buffering of IOP levels and reduced IOP variability, which may be a very desirable characteristic as a glaucoma medication. (Reviewer-Scott D. Smith, MD, MPH).

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Keywords: Glaucoma, Medical Therapy, Latanoprost, Timolol

Print Tag: Refer to original journal article
Use of a blue-filtering intraocular lens reduces glare disability in patients following cataract surgery.

**Objective:** To evaluate the effect of a blue-filtering intraocular lens (IOL) on glare disability and photostress recovery following cataract surgery.

**Design:** Case-control study.

**Participants/Methods:** A total of 58 subjects were recruited for this study. Seventeen patients had undergone previous cataract extraction with implantation of a blue-filtering yellow IOL (AcrySof Natural, SN60WF, Alcon Laboratories). An additional 20 patients were recruited who had previous implantation of a clear IOL at the time of cataract surgery. Twenty-one phakic control subjects were also recruited, who were in the same age category as the pseudophakic subjects. Each subject underwent glare sensitivity and photostress recovery testing using a customized optical device, which presented targets with varying glare conditions for glare sensitivity testing and bleach of the retina with a bright light stimulus. Statistical analysis allowed a comparison of the results of this type of testing among the 3 groups.

**Results:** Subjects with the AcrySof Natural lens had significantly less glare sensitivity than did phakic controls and subjects with clear IOLs. Those with clear IOLs had an intermediate level of glare sensitivity, which was significantly less than that of phakic control subjects. Photostress recovery was significantly longer for subjects with clear IOLs compared with phakic controls. Those with AcrySof Natural Lenses had an intermediate level of photostress recovery.

**Conclusions:** The AcrySof Natural Lens is associated with reduced glare disability in comparison to clear IOLs and may also offer improved photostress recovery.

**Reviewer’s Comments:** Blue-filtering IOLs reduce the total quantity of light entering the eye, and this appears to be associated with improved glare disability and photostress recovery. Previous studies have also demonstrated improved contrast sensitivity and color vision in association with use of this type of IOL. What remains uncertain is whether filtration of the higher-energy spectrum of visible light reduces phototoxicity to the retina and thereby reduces the risk of development of macular degeneration. Although this subject has been discussed at length, no clinical studies have demonstrated this type of benefit. (Reviewer-Scott D. Smith, MD, MPH).

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Keywords: AcrySof Natural Lens, Glare Disability, Photostress

Print Tag: Refer to original journal article
Managing Infantile Esotropia -- Is One Method Better Than the Other?

A Randomised Comparison of Bilateral Recession Versus Unilateral Recession - Resection as Surgery for Infantile Esotropia.

Polling J-R, Eijkemans MJC, et al:

Br J Ophthalmol 2009; 93 (July): 954-957

Objective: To compare the clinical outcome of bilateral recession versus unilateral recession-resection for surgical management of infantile esotropia.

Design: Randomized, controlled clinical trial.

Participants/Methods: 124 children aged 3 to 8 years with infantile esotropia (onset at age <1 year) were enrolled in this study. Children with an angle of strabismus $>24^\circ$ or $<10^\circ$, those having any binocular vision, and those having $>1$ line of difference in visual acuity between eyes were excluded. In addition, children with extreme hyperopia, myopia, extreme A- or V-pattern strabismus, or vertical strabismus were excluded. A standardized protocol for orthoptic evaluation and performance of strabismus surgery was used across all 12 centers participating in the study. Children were randomly assigned to undergo either bilateral medial rectus recession or unilateral medial rectus recession and lateral rectus resection, using a predetermined algorithm for the amount of movement of the muscle insertion. Residual angle of esotropia 3 months after surgery and development of binocular vision were the primary and secondary outcomes of this study.

Results: There was no difference in the mean preoperative angle of strabismus between groups or in any other demographic or clinical factors. The mean residual angle of esotropia was equal at the 3-month postoperative visit in the 2 groups ($2.3^\circ$ for bimedial recession and $2.9^\circ$ for recession-resection; $P = 0.5$). An equivalent proportion of children (39%) developed some degree of binocular vision following surgery.

Conclusions: No clinically or statistically significant difference in clinical outcome was seen between bimedial recession and unilateral recession-resection in the management of infantile esotropia.

Reviewer's Comments: This is the first randomized, controlled clinical trial directly comparing these 2 alternative surgical techniques for management of infantile esotropia. The study was carefully designed and conducted, and it demonstrates that the strabismus surgeon should feel confident in using his/her own preferred technique for management of these patients without concern of differing clinical outcomes with one surgical procedure compared to the other. (Reviewer-Scott D. Smith, MD, MPH).

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Keywords: Infantile Esotropia, Strabismus Surgery, Recession, Resection

Print Tag: Refer to original journal article
The peripapillary retinal nerve fiber layer is not thinner among moderately amblyopic eyes.

**Background:** Patients with amblyopia cannot see well from a clinically normal appearing eye. The authors postulated that, subclinically, the retinal nerve fiber layer (RNFL) is thinner in an amblyopic eye.

**Objective:** To measure peripapillary RNFL in amblyopic eyes and to compare the results with those of fellow eyes.

**Design:** Prospective, observational case series.

**Participants:** 37 children with unilateral amblyopia from 12 centers in the U.S.

**Methods:** Eligibility criteria included amblyopia in 1 eye from either strabismus, anisometropia, or both; refractive error in each eye was between 0.25 and 5.00 diopters. Each eye underwent fast RNFL scanning using Stratus OCT. Scans were excluded for signal strength <5 or decentered ring.

**Results:** 48 patients had an OCT, but 11 were excluded for poor-quality scans. Of the remaining 37 patients, mean age was 9 years. Approximately half were female, 40% were white, and 50% were Hispanic. The cause of amblyopia was strabismus in one fourth of cases, anisometropia in half, and both in one fourth. The acuity in the amblyopic eye was 20/40 to 20/80 in 90% and 20/100 to 20/250 in the rest. Mean RNFL for amblyopic eyes measured 111 μm and was not significantly different from that of fellow eyes, which measured 110 μm. In one fourth of patients, the amblyopic eye was thicker by ≥8 μm, in 5% the fellow eye was thicker by ≥8 μm, and within 7 μm in 70%. There was no difference between eyes among any of the 4 quadrants. The RNFL was not affected by anisometropia.

**Conclusions:** The peripapillary RNFL is not significantly different in moderately amblyopic eyes compared to fellow eyes.

**Reviewer’s Comments:** Almost all patients had acuities in the 20/40 to 20/80 range, so this does not apply to severely amblyopic eyes. Although this study included only children, there is no reason to believe that amblyopia should induce a difference as an adult. So a substantial thinning of the RNFL in an amblyopic eye should raise suspicion for another cause. (Reviewer-Michael S. Lee, MD).

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Keywords: Retinal Nerve Fiber Layer, Optical Coherence Tomography, Amblyopia
Is Sham Tx Necessary When Measuring Visual Acuity?

*Visual Acuity Outcomes Among Sham vs No-Treatment Controls From Randomized Trials.*

Hawkins BS, Bressler NM, Reynolds SM:

Arch Ophthalmol 2009; 127 (June): 725-731

When visual acuity is the main outcome measure, sham treatment may be unnecessary.

**Background:** It is common for randomized controlled trials (RCTs) to include a placebo or sham therapy to reduce bias and promote similar compliance between groups. Occasionally, sham therapy may be invasive, which poses some risk, and it may deter patients from participating. Sham therapies increase costs and inconvenience.

**Objective:** To compare visual outcomes in RCTs between patients involved in trials that included a placebo arm or a no-treatment arm.

**Design:** There are no trials that include a treatment arm, a sham treatment arm, and a no-treatment arm.

**Participants:** Control patients in RCTs of age-related macular degeneration.

**Methods:** The authors obtained permission to use the control arms of 5 RCTs for treatment of choroidal neovascularization (CNV). Three trials had a simple observation or no-treatment control arm. The other 2 trials used a sham treatment. Treatment consisted of IV injection of placebo followed by a laser. Each sham patient was matched with a no-treatment patient for the following characteristics: age, gender, acuity, CNV size, fellow eye CNV, and previous therapy. Acuities had to be within 7 letters of each other. Of no-treatment control arms, 1 used a masked examiner to measure acuity and 1 did not. The main outcome measure was visual acuity at 2-year follow-up.

**Results:** There were 321 sham controls for which a full match was available for 72 (22%). A partial match of at least 4 characteristics was available for 93 (29%) sham-treated controls. Baseline visual acuity was better in sham-treated control groups by about 2.0 to 2.5 letters for fully matched and partially matched groups. Lack of 2-year data occurred in both fully matched and partially matched groups, leaving 56 and 72 patients, respectively. There was no difference in final visual acuity between sham and no-treatment controls in the fully matched group. In the partially matched group, sham controls lost 1.5 acuity lines more than did no-treatment controls. No-treatment controls using masked examiners lost 1.3 acuity lines less than did no-treatment controls with unmasked examiners.

**Conclusions:** This study legitimately raises the question of whether a sham treatment control is necessary in a RCT where visual acuity is the main outcome measure.

**Reviewer's Comments:** These results are surprising. I would have expected that the placebo group would have better acuity than the no-treatment group. Instead, the sham group lost more acuity. It wasn't a huge amount, but the partially matched sham group still had worse acuities. (Reviewer-Michael S. Lee, MD).

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Keywords: Visual Acuity, Outcome Measure, Sham, Control, Randomized Trial

Print Tag: Refer to original journal article
The inner retinal layer is thinned among patients with Parkinson disease.

**Background:** Parkinson disease (PD) is a common neurodegenerative disease. Previous studies have shown that pattern electroretinographic and peripapillary retinal nerve fiber layer (RNFL) measurements using time-domain optical coherence tomography (OCT) are abnormal among patients with PD.

**Objective:** To study the thickness of the inner retinal layer (IRL) and the outer retinal layer (ORL) in PD patients using Fourier-domain OCT.

**Design:** Prospective, observational case series.

**Participants:** 24 PD patients and 17 normal controls from several centers in New York State.

**Methods:** Patients fulfilling UK Brain Bank criteria for diagnosis of PD were included. Patients with coincident posterior-pole disease, such as macular degeneration, or any optic neuropathy due to glaucoma or ischemic optic neuropathy were excluded. Each participant underwent Fourier-domain OCT (RTvue) of a 6-mm macular area and nerve (Macula Map and Nerve Head Map protocols). The IRL was defined as the nerve fiber layer, ganglion cell layer, and inner plexiform layer. The ORL was defined as the rest of the retina from the inner nuclear layer up to and including the retinal pigment epithelium.

**Results:** There were 23 PD patients (mean age, 63 years) and 17 controls (mean age, 64 years). PD patients received a diagnosis 3 years earlier. Half the PD patients were receiving treatment, and half had not yet begun. The mean IRL of 89 μm among PD patients was significantly thinner compared to 104 μm among controls \((P=0.01)\). These findings did not differ after separating out the superior and inferior macula. ORL thickness was not significantly different between healthy eyes and PD eyes, measuring approximately 170 μm. There was a strong correlation between the 2 eyes of a given individual \((r=0.82)\). There was no significant difference in IRL or ORL thickness between treated and untreated eyes.

**Conclusions:** Even relatively early in the disease, PD patients have a thinner IRL than do normal controls.

**Reviewer's Comments:** As more and more ophthalmologists order OCTs, it is important to realize that abnormal thinning in the macula or RNFL may result from PD instead of an intraocular process. (Reviewer-Michael S. Lee, MD).

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**Keywords:** Parkinson Disease, Retinal Thinning, Optical Coherence Tomography

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The incidence of seropositive myasthenia gravis is 7 per million.

**Background:** There are very few data on the incidence and prevalence of myasthenia gravis. Only one laboratory provides acetylcholine receptor antibody testing in the country of Norway. If acetylcholine receptor antibodies are elevated in a patient with symptoms, it is almost 100% that that patient has myasthenia gravis.

**Objective:** To look at antibody testing from this laboratory to determine the incidence, prevalence, and demographic data in seropositive myasthenia gravis.

**Design:** Retrospective, observational case series.

**Participants:** Patients who underwent acetylcholine receptor antibody testing in Norway.

**Methods:** The authors chose January 1, 2008, as their prevalence day (total population, 4,737,171). Any result >0.4 nmol/L was considered positive. The study population from 1983 to 2008 was used to calculate prevalence. The authors contacted a government authority to determine whether positive cases were alive on the prevalence day. After June 1994, the laboratory record system became automated and the data from 1995 to 2008 were used to calculate incidence. Incidence was calculated as the number of new positive tests on January 1 of every year from 1995 to 2008. The prevalence was calculated as the number of seropositive patients alive on the prevalence day.

**Results:** 8628 patients were tested from 1983 to 2008. Of those, 889 tests were positive. Almost 60% occurred after age 50 years. The yearly incidence was calculated as 7 per 1 million. The prevalence was calculated as 126 per million. Assuming that 15% of myasthenics are seronegative, the overall prevalence is approximately 143 per 1 million.

**Conclusions:** The incidence and prevalence of seropositive myasthenia gravis is 7 per 1 million and 126 per 1 million, respectively.

**Reviewer's Comments:** These are pretty robust numbers since all the data came from a single source over a 14-year period based on a population of almost 5 million people. This study also highlights the low incidence of myasthenia. For some comparison purposes, optic neuritis and ischemic optic neuropathy occur in about 2 to 5 per 100,000 cases. (Reviewer-Michael S. Lee, MD).
Diabetes appears to be associated with neovascular age-related macular degeneration, but not with other forms of the disease, including geographic atrophy or drusen.

**Objective:** To investigate the relationship between diabetes mellitus and having early or late-stage age-related macular degeneration (AMD).

**Design:** Cross-sectional population-based cohort study.

**Participants/Methods:** Random sampling of a population of elderly Europeans aged ≥65 years was performed. Subjects underwent a medical evaluation that included a medical history, and measurement of blood pressure, height, and weight. In addition, fundus photography was performed after pupillary dilation, which allowed the identification of cases of early and late AMD by a masked grader using standard accepted criteria for these conditions. Statistical analysis was performed to determine the association between diabetes and the presence of AMD.

**Results:** Data were analyzed from 2182 subjects with early AMD, 49 subjects with geographic atrophy of the retinal pigment epithelium, and 101 subjects with neovascular AMD. A random sample of 2117 control subjects was also analyzed. After adjustment for potential confounding factors, individuals with neovascular AMD were found to be significantly more likely to be diabetic (odds ratio, 1.81; \( P = 0.02 \)). No association between early AMD or geographic atrophy was found with diabetes.

**Conclusions:** Diabetes appears to be associated with neovascular AMD, but not with geographic atrophy or early AMD.

**Reviewer's Comments:** This study suggests that diabetes is associated with late-stage AMD, which is a new finding not previously described. Further investigation is needed into this issue to try to identify possible mechanisms that could explain the relationship between these 2 conditions. However, this association should be kept in mind when evaluating patients who have these 2 common conditions that affect the retina. (Reviewer-Scott D. Smith, MD, MPH).

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Keywords: Macular Degeneration, Diabetes

Print Tag: Refer to original journal article
Oral famciclovir may be a reasonable alternative to IV acyclovir for treatment of acute retinal necrosis caused by herpes viruses.

**Objective:** To investigate the vitreous penetration of the antiviral drug famciclovir when administered orally.

**Design:** Prospective, interventional clinical case series.

**Participants/Methods:** 10 patients scheduled for pars plana vitrectomy were enrolled in this study. Patients with a history of prior vitrectomy, rhegmatogenous retinal detachment, uveitis, or endophthalmitis were excluded, as these conditions may alter the normal blood-retina barrier and influence the penetration of orally administered drugs into the eye. Patients were instructed to take three 500-mg doses of famciclovir 8 hours apart beginning 24 hours prior to surgery. At the time of surgery, a vitreous sample was obtained prior to infusion of any fluid into the eye. A blood sample was also obtained at the time of surgery. Vitreous and serum specimens were sent to the laboratory for measurement of drug concentrations.

**Results:** Patient age ranged from 26 to 82 years. All patients had normal hepatic and renal function as determined by laboratory testing. The mean serum drug concentration was 4.45 ± 1.31 μg (range, 2.51 to 6.34 μg). The mean vitreous drug concentration was 1.21 ± 0.38 μg (range, 0.39 to 1.88 μg). Vitreous concentrations were within the inhibitory range for herpes simples 1, herpes simplex 2, and varicella zoster virus.

**Conclusions:** Oral administration of famciclovir may be a reasonable alternative to IV acyclovir for treatment of acute retinal necrosis caused by herpes viruses.

**Reviewer’s Comments:** Herpetic infections causing acute retinal necrosis have been managed to date with IV administration of acyclovir. The observation in this study that orally administered famciclovir results in vitreous concentrations that are within therapeutic ranges indicates that this drug and route of administration may be a reasonable alternative to IV acyclovir. (Reviewer-Scott D. Smith, MD, MPH).

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Keywords: Acute Retinal Necrosis, Viral Retinitis

Print Tag: Refer to original journal article
Diabetic patients with higher blood sugar and/or high blood pressure have an increased risk of developing macular edema.

**Objective:** To determine the 25-year incidence of diabetic macular edema (ME) in patients with type I diabetes, and to identify clinical factors associated with the development of this condition.

**Design:** Population-based cohort study.

**Participants/Methods:** A population of 911 insulin-dependent diabetics who were diagnosed before age 30 years was identified in an 11-county region in Wisconsin. Participants underwent a baseline examination between 1980 and 1982, and underwent follow-up examination 4 years, 10 years, 14 years, and/or 25 years after initial evaluation. Stereo fundus photographs were taken at study visits and were used to classify the severity of diabetic retinopathy in each subject. Standardized criteria were used to determine presence of ME and clinically significant macular edema (CSME).

**Results:** The 25-year cumulative incidence of ME and CSME was 29% and 17%, respectively. Multivariate statistical analysis demonstrated that higher baseline glycosylated hemoglobin and higher systolic blood pressure were each independently associated with a higher risk of developing ME. For each 1% increase in glycosylated hemoglobin level, there was a 17% increase in risk of developing ME ($P < 0.001$). For each 10-mm Hg increase in systolic blood pressure, there was a 15% increase in the risk of developing ME ($P = 0.004$).

**Conclusions:** The 25-year incidence of ME and CSME is high in type I diabetics. Control of systemic hypertension and blood sugar level appears to be important in reducing this risk.

**Reviewer's Comments:** This study illustrates the importance of systemic factors in the development of diabetic retinopathy, and highlights the importance of communication between ophthalmologists and primary care physicians in managing these patients optimally. Greater awareness on the part of primary care physicians as well as in individual patients of the status of the retina can help physicians to provide better overall diabetes care. (Reviewer-Scott D. Smith, MD, MPH).

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Keywords: Diabetic Retinopathy, Macular Edema, Clinical Factors

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Another Effective Option for Tx of Exudative Macular Degeneration

Systemic Bevacizumab (Avastin) Therapy for Exudative Neovascular Age-Related Macular Degeneration. The BEAT-AMD-Study.

Schmid-Kubista KE, Krebs I, et al:

Br J Ophthalmol 2009; 93 (July): 914-919

Systemic Avastin may be considered in treating patients with bilateral exudative macular degeneration or in those who refuse intravitreal injections, barring medical contraindications.

Objective: To investigate the safety and efficacy of systemic therapy with the vascular endothelial growth factor (VEGF) inhibitor bevacizumab (Avastin) for treatment of exudative age-related macular degeneration (AMD).

Design: Double-blind, randomized clinical trial.

Participants/Methods: 8 patients with bilateral exudative AMD were enrolled in this study. All patients had subfoveal choroidal neovascularization with an increase in macular thickness to >300 μm in both eyes. Patients with a history of proteinuria or renal impairment, hepatic disease, or a history of arterial thrombotic disease were excluded. Patients were monitored by an internist throughout the treatment period. Randomization was performed for each subject and patients were given either intravenous Avastin injection at a dose of 5 mg/kg body weight 3 times every 2 weeks, or a placebo saline injection with the same dosing schedule. Follow-up evaluation with fluorescein angiography and optical coherence tomography retinal imaging allowed analysis of the efficacy of therapy.

Results: Lesion size and macular thickness decreased significantly in patients in the Avastin group in comparison to the placebo group. Visual acuity remained stable throughout the 24-week study period in the placebo group, but showed a small, but statistically significant, improvement in the Avastin group. A significant increase in systolic blood pressure was seen in Avastin-treated patients.

Conclusions: Systemic Avastin is effective in inducing regression of subfoveal choroidal neovascularization. Reviewer's Comments: This study indicates that systemic Avastin is effective in treating exudative macular degeneration without the need for intravitreal injections. If a patient has need for bilateral therapy, or if he or she refuses intravitreal injections, systemic therapy may be an option to consider. However, systemic VEGF inhibitors have important potential adverse effects, which must also be considered. This therapy is contraindicated in patients with uncontrolled blood pressure or a history of systemic thrombosis. (Reviewer-Scott D. Smith, MD, MPH).

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Keywords: Age-Related Macular Degeneration, Bevacizumab, Avastin, Subfoveal Choroidal Neovascularization

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A Change in Oxygen Supplementation Can Decrease the Incidence of Retinopathy of Prematurity.

Sears JE, Pietz J, et al:

Ophthalmology 2009; 116 (March): 513-518

Lower oxygen targets at early gestational age and higher oxygen targets at older gestational age can reduce the risk of development of retinopathy of prematurity.

Objective: To determine the incidence of retinopathy of prematurity (ROP) during a 2-year period before and after a change in oxygen saturation targets for preterm infants.

Design: Non-randomized, prospective, observational clinical study.

Methods: The gestational age, birth weight, stage, and zone of ROP were prospectively recorded in a consecutive series of preterm infants managed in a single neonatal ICU. During the first year, standard oxygen saturation targets were implemented according to a uniform protocol, with targets of 95% to 100% saturation. During the second year, lower oxygen saturation targets were implemented that varied by gestational age. Infants at <34 weeks' gestational age had strictly monitored target saturations of 85% to 92%, and those aged at ≥34 weeks had target saturations of 92% to 97%. Statistical comparison of the incidence and severity of ROP between infants before and after the change in oxygen saturation targets was performed.

Results: 114 children were managed in the year before the change in oxygen saturation targets, and 108 children were managed in the year after the change in oxygen saturation targets. ROP developed in 35% of infants managed with higher oxygen saturation targets, and in 13% of those managed with lower oxygen saturation targets (P=0.02). The frequency of development of stage 3 ROP decreased from 13% to 2% after the change in the protocol of oxygen management (P=0.001).

Conclusions: Lower oxygen saturation targets at early gestational age and higher targets at older gestational age can significantly reduce the risk of development of ROP.

Reviewer's Comments: This study demonstrates that altering the oxygen saturation targets according to gestational age, with reduced levels of oxygenation at earlier gestational age, significantly reduced the severity of ROP. While further randomized prospective clinical trials are needed to more clearly delineate the optimal management of oxygenation of preterm infants, this study demonstrates the need to consider gestational age, as well as documentation of zone and stage of ROP, in determining optimal oxygen saturation targets in these children. (Reviewer-Scott D. Smith, MD, MPH).

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Keywords: Retinopathy of Prematurity, Oxygen Supplementation

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Cutaneous Nevi, Iris Nevi Associated With Uveal Melanoma


Cutaneous nevi, cutaneous freckles, and iris nevi are all associated with an increased risk of having uveal melanoma.

Objective: To investigate the association between cutaneous nevi, cutaneous freckles, iris nevi, and choroidal melanoma.

Design: Meta-analysis of published studies investigating this association.

Methods: An exhaustive search of the medical literature was performed using the Ovid, PubMed, EMBASE, MD Consult, and Web of Science databases for studies published between 1966 and August 2007. Attempts were made to contact authors of published studies to see if unpublished data were available that could contribute to the analysis. Studies that did not use standardized epidemiologic methodology were excluded. Standard methods for meta-analysis were used to combine the data from the studies that met the criteria for inclusion. Odds ratios describing the association between uveal melanoma and cutaneous nevi, cutaneous freckles, and iris nevi were determined.

Results: The combined sample size in the meta-analysis of atypical cutaneous nevi with uveal melanoma was 850 cases. Sample sizes for evaluation of the association between uveal melanoma and typical cutaneous nevi, cutaneous freckles, and iris melanoma were 825 cases, 2122 cases, and 825 cases, respectively. A significant association was found, with an increased odds of having uveal melanoma of 2.82 (95% CI, 1.10 to 7.26; \( P = 0.03 \)). A similar association was found between uveal melanoma and typical cutaneous nevi (OR, 1.74; 95% CI, 1.27 to 2.39; \( P = 0.0001 \)) and cutaneous freckles (OR, 1.22; 95% CI, 1.03 to 2.27; \( P = 0.04 \)). Iris nevi were also associated with an increased odds of having uveal melanoma (OR, 1.53; 95% CI, 1.03 to 2.27; \( P = 0.03 \)).

Conclusions: Cutaneous nevi, cutaneous freckles, and iris nevi are all associated with an increased risk of having uveal melanoma.

Reviewer's Comments: The increased risk of development of uveal melanoma in individuals with cutaneous freckles and nevi, as well as those with iris nevi, probably relates to both an underlying genetic predisposition as well as exposure to environmental ultraviolet light. Host factors that appear to be important include light pigmentation of the eyes and skin and susceptibility to sunburn. (Reviewer-Scott D. Smith, MD, MPH).

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Keywords: Uveal Melanoma, Iris Nevi

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**Improve O$_2$ Flow to Optic Nerve With Dorzolamide**

*Dorzolamide-Timolol Combination and Retinal Vessel Oxygen Saturation in Patients With Glaucoma or Ocular Hypertension.*

Traustason S, Hardarson SH, et al:


Oxygen saturation in retinal vessels and increased blood flow both suggest that dorzolamide improves oxygen delivery to the optic nerve.

**Objective:** To determine whether the addition of dorzolamide to timolol monotherapy for glaucoma influences the oxygen saturation in retinal blood vessels.

**Design:** Prospective, comparative clinical study.

**Participants/Methods:** 20 patients with open-angle glaucoma or ocular hypertension were recruited to participate in this study. Patients were randomly assigned to receive either timolol monotherapy or combination therapy with dorzolamide-timolol in fixed combination for an 8-month period. Noninvasive measurements of retinal oxygen saturation were performed using spectrophotometric retinal oximetry at baseline and at 2-month intervals after initiation of therapy. After 8 months, patients were switched to the alternative glaucoma medication for another 8-month period, during which repeat retinal oxygen saturation measurements were made at 2-month intervals. Statistical analysis was performed to determine changes in retinal oxygen saturation using each of the 2 treatments.

**Results:** During each 8-month treatment period, retinal oxygen saturation levels remained stable. Patients who initially used dorzolamide-timolol fixed combination therapy showed a significant reduction in retinal arteriolar oxygen saturation levels after switching to monotherapy with timolol (98% vs 95%; $P = 0.01$). These patients also demonstrated a reduction in retinal venous oxygen saturation levels after switching to timolol monotherapy (69% vs 66%; $P = 0.05$).

**Conclusions:** Differences in retinal oxygen saturation when switching from dorzolamide-timolol fixed combination therapy to timolol monotherapy suggest that dorzolamide increases oxygen delivery to the retina and optic nerve.

**Reviewer’s Comments:** This study lends support to the concept that topically applied carbonic anhydrase inhibitors increase oxygen delivery to the optic nerve. While the role that ischemia plays in the pathogenesis of glaucoma is uncertain, it has been hypothesized that some patients with glaucoma that develops or progresses at low levels of intraocular pressure may have optic nerve ischemia as a contributing factor. (Reviewer-Scott D. Smith, MD, MPH).

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Keywords: Glaucoma Medication, Carbonic Anhydrase Inhibitor, Oxygen Saturation, Timolol, Dorzolamide

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New Technology Improves Reproducibility of RNFL Measurements

Retinal Nerve Fibre Layer Thickness Measurement Reproducibility Improved With Spectral Domain Optical Coherence Tomography.

Kim JS, Ishikawa H, et al:


Improvements in resolution with the newer spectral-domain optical coherence tomography (OCT) technology result in improved retinal nerve fiber layer measurement reproducibility, as compared to time-domain OCT.

**Objective:** To compare the reproducibility of measurements of retinal nerve fiber layer (RNFL) thickness using spectral-domain optical coherence tomography (SD-OCT) and time-domain optical coherence tomography (TD-OCT).

**Design:** Prospective, comparative clinical study.

**Participants/Methods:** 27 eyes of 14 healthy subjects underwent repeated measurements of peripapillary RNFL thickness using SD-OCT (Cirrus OCT, Carl Zeiss Meditec) and TD-OCT (Stratus OCT, Carl Zeiss Meditec). TD-OCT measurements were performed 3 times in each eye, using a 3.4-mm circular circumpapillary scan pattern. SD-OCT measurements were performed using 3 raster scans surrounding the optic nerve head. After defining the location of the optic nerve head, thickness values in a 3.4-mm circle surrounding the optic nerve were determined in a location corresponding to the TD-OCT measurements.

**Results:** The variance component of a linear mixed-effects model was used to define reproducibility for each instrument. Using this technique, reproducibility of RNFL thickness measurements was superior using SD-OCT in all but 1 parameter measured (RNFL thickness in the 11-o'clock sector), where reproducibility was similar between instruments.

**Conclusions:** Reproducibility is improved with SD-OCT in comparison to TD-OCT.

**Reviewer’s Comments:** Measurement of change in retinal thickness and RNFL thickness is a useful method of monitoring patients with retinal disease or glaucoma. Improvement in the reproducibility of these measurements is an important way of increasing the diagnostic utility of retinal imaging. The newer technology of SD-OCT is now clinically available, and will improve the utility of these instruments in the diagnosis and management of a wide range of ophthalmic conditions. (Reviewer-Scott D. Smith, MD, MPH).

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Keywords: Ocular Imaging, Retinal Nerve Fiber Layer Thickness, Reproducibility

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The rarer euthyroid and hypothyroid forms of Graves' ophthalmopathy tend to be milder and more asymmetric than the more common hyperthyroid form of the disease.

**Objective:** To compare clinical findings of patients with Graves' ophthalmopathy (GO) who are clinically hyperthyroid, euthyroid, or hypothyroid.

**Design:** Retrospective, comparative, observational clinical case series.

**Participants/Methods:** A consecutive series of patients diagnosed with GO were included in this retrospective study. A review of medical records allowed the classification of patients according to their thyroid status, based on the results of measurement of thyroid function tests at the time of diagnosis. Patients eligible for inclusion presented within 6 months of onset of symptoms, had no prior anti-inflammatory therapy, were followed for at least 1 year, and had positive results on thyroid antibody testing. Patients were seen every 6 to 12 weeks during the 1 year of follow-up, at which time assessment of proptosis, eyelid position and function, ocular motility, and presence of periocular inflammation were assessed. Previously described methods of quantifying the severity of disease were used, including the clinical activity score (CAS) and the modified NOSPECS classification system.

**Results:** The study included 143 primarily hyperthyroid, 28 euthyroid, and 11 hypothyroid patients. Patients who were euthyroid or hypothyroid had significantly lower NOSPECS severity scores (4.4 vs 5.7; \( P = 0.03 \)). These patients also had lower activity scores than hyperthyroid patients (CAS score, 3.9 vs 5.2; \( P = 0.002 \)). More asymmetric proptosis was seen in euthyroid and hypothyroid patients (mean asymmetry of 1.9 mm vs 1.0 mm; \( P = 0.01 \)). The level of thyroid-specific autoantibodies was lower in hypothyroid and euthyroid patients than in hyperthyroid patients.

**Conclusions:** Euthyroid and hypothyroid patients with GO have milder and more asymmetric disease than do those who are primarily hyperthyroid.

**Reviewer’s Comments:** Graves’ ophthalmopathy usually occurs in patients with hyperthyroidism. However, a small percentage of patients with autoimmune thyroid disease that leads to proptosis and restrictive strabismus typical of Graves’ ophthalmopathy are euthyroid or hypothyroid. This study indicates that orbital and ophthalmic findings differ in patients who do not have hyperthyroidism compared to the more common category of patients who present with this condition. (Reviewer-Scott D. Smith, MD, MPH).

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Keywords: Asymmetrical Disease, Euthyroid, Hypothyroid

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