

Issue 320

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This free weekly bulletin lists the latest published research articles on macular degeneration (MD) and some other macular diseases as indexed in the NCBI, PubMed (Medline) and Entrez (GenBank) databases.

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## Drug treatment

**Ophthalmic Res. 2017 Mar 17. [Epub ahead of print]**

### **Influence of Vitreomacular Adhesion on Anti-Vascular Endothelial Growth Factor Treatment for Neovascular Age-Related Macular Degeneration.**

Kanadani TC, Dos Reis Veloso CE, Dorairaj S, Nehemy MB.

**PURPOSE:** To investigate the effect of vitreomacular adhesion (VMA) on the outcome of antiangiogenic treatment for neovascular age-related macular degeneration (AMD).

**METHODS:** Ninety-nine eyes of 83 patients were used in our cohort study. We prospectively evaluated best corrected visual acuity (BCVA) and central retinal thickness (CRT) in patients with neovascular AMD at baseline and 1, 2, 3, 6, and 12 months after treatment with anti-vascular endothelial growth factor (anti-VEGF) agents. All patients were stratified by spectral domain optical coherence tomography into 2 groups (i.e., VMA[+] and VMA[-]) according to the presence or absence of VMA, and the response to treatment was evaluated.

**RESULTS:** Fifty-four eyes (54.5%) were included in the VMA(-) group and 45 eyes (45.5%) comprised the VMA(+) group. In paired comparisons of mean BCVA between baseline and each follow-up visit (1, 2, 3, 6, and 12 months), the VMA(-) group showed statistically significant improvement at 1, 2, and 3 months compared to baseline, and BCVA significantly improved only at 3 months in the VMA(+) group. For both groups, paired comparisons of CRT showed a statistically significant decrease when data obtained at 1, 2, 3, 6, and 12 months were compared to baseline values ( $p < 0.05$ ).

**CONCLUSIONS:** Posterior VMA is associated with a worse short-term outcome in patients with neovascular AMD treated with anti-VEGF agents.

PMID: 28301850

**Am J Ophthalmol. 2017 Mar 13. [Epub ahead of print]**

### **Experience of Anti-VEGF Treatment and Clinical Levels of Depression and Anxiety in Patients with Wet Age-Related Macular Degeneration.**

Senra H, Balaskas K, Mahmoodi N, Aslam T.

**PURPOSE:** To investigate detailed patient experiences specific to receiving vascular endothelial growth factor inhibitors (anti-VEGF) for wet Age-Related Macular Degeneration (wAMD), and to acquire a snapshot of the frequency of clinically significant levels of depression, anxiety and post-traumatic stress among patients and levels of burden in patients' carers.

**DESIGN:** Observational cross-sectional mixed-methods study **METHODS:** 300 patients with wAMD receiving anti-VEGF treatment and 100 patient carers were recruited. Qualitative data on patients' experience of treatment were collected using a structured survey. Standardised validated questionnaires were used to quantify clinically significant levels of anxiety, depression, post-traumatic stress, as well as cognitive function and carers' burden.

**RESULTS:** Qualitative data showed that 56% of patients (n =132) reported anxiety related to anti-VEGF treatment. The main sources of anxiety were fear of going blind due to intravitreal injections, and concerns about treatment effectiveness rather than around pain. From validated questionnaires, 17% of patients (n=52) showed clinical levels of anxiety, and 12% (n=36) showed clinical levels of depression. Depression levels, but not anxiety, were significantly higher in patients who received up to 3 injections compared to patients who received from 4 to 12 injections (ANOVA P=.027) and compared to patients who received more than 12 injections (ANOVA P=.001).

**CONCLUSIONS:** Anti-VEGF treatment is often experienced with some anxiety related to treatment regardless of the number of injections received. Clinical levels of depression seem to be more frequent in patients at early stages of anti-VEGF treatment. Strategies to improve patient experience of treatment and minimise morbidity are suggested.

PMID: 28302534

**JAMA Ophthalmol. 2017 Mar 16. [Epub ahead of print]**

### **Association of Repeated Intravitreal Bevacizumab Injections With Risk for Glaucoma Surgery.**

Eadie BD, Etminan M, Carleton BC, Maberley DA, Mikelberg FS.

**IMPORTANCE:** Intravitreal injections of anti-vascular endothelial growth factor (VEGF) agents are associated with a sustained increase in intraocular pressure. This sustained elevated intraocular pressure could lead to higher rates of glaucoma surgery to lower this pressure.

**OBJECTIVE:** To determine the risk of glaucoma surgery following repeated intravitreal bevacizumab injections.

**DESIGN, SETTING, PARTICIPANTS:** This nested, case-control study acquired and analyzed data from large, population-based, linked health databases supported by the British Columbia Ministry of Health in Canada. Study participants included all patients with ophthalmic issues in British Columbia, such as those of the Provincial Retinal Diseases Treatment Program, who had received intravitreal bevacizumab injections for exudative age-related macular degeneration between January 1, 2009, and December 31, 2013. Cases were identified using glaucoma surgical codes for trabeculectomy, complicated trabeculectomy, glaucoma drainage device, and cycloablative procedure. For each case, 10 controls were identified and matched for age, preexisting glaucoma, calendar time, and follow-up time. The number of intravitreal bevacizumab injections received per year-3 or fewer, 4 to 6, or 7 or more-was determined for both cases and controls. Data analysis was performed from February 23, 2016, to November 14, 2016.

**MAIN OUTCOMES AND MEASURES:** Risk of glaucoma surgery compared with the number of intravitreal bevacizumab injections per year in cases and controls. Rate ratios were adjusted for covariates (diabetes mellitus, myocardial infarction, stroke, and verteporfin use).

**RESULTS:** Seventy-four cases of glaucoma surgery and 740 controls were identified, with a mean (SD) age of 81.3 (8.4) years for cases and 81.4 (7.9) for controls. The case group had more males than the control group (38 [51.4%] vs 272 [36.8%]). The adjusted rate ratio of glaucoma surgery among those who received 7 or more injections per year was 2.48 (95% CI, 1.25-4.93). There was a 10.3% higher number of 7 or more injections among cases compared with controls. The adjusted rate ratio for those who received 4 to 6 injections per year compared with those who received 3 or fewer was 1.65% (95% CI, 0.84-3.23).

**CONCLUSIONS AND RELEVANCE:** Findings from this large, pharmacoepidemiologic study suggest that 7 or more intravitreal injections of bevacizumab annually is associated with a higher risk of glaucoma surgery and that 4 to 6 injections per year show a nonstatistically significant rate ratio in the same direction.

PMID: 28301639

**Ophthalmic Surg Lasers Imaging Retina. 2017 Mar 1;48(3):230-236.**

**Short-Term Effects of Early Switching to Ranibizumab or Aflibercept in Diabetic Macular Edema Cases With Non-Response to Bevacizumab.**

Ashraf M, Souka AA, ElKayal H.

**BACKGROUND AND OBJECTIVES:** To study the effect of early switching to ranibizumab (Lucentis; Genentech, South San Francisco, CA) or aflibercept (Eylea; Regeneron, Tarrytown, NY) in cases of diabetic macular edema (DME) that have shown no response to bevacizumab (Avastin; Genentech, South San Francisco, CA).

**PATIENTS AND METHODS:** A retrospective study involving 59 eyes of 45 patients with DME previously treated with bevacizumab. Patients were switched either to ranibizumab or aflibercept. Detailed ophthalmological examination, best-corrected visual acuity (BCVA), and optical coherence tomography (Spectralis; Heidelberg Engineering, Heidelberg, Germany) were performed prior to and 1 month post-switch.

**RESULTS:** Fifty-nine eyes of 45 patients were included in the study, of whom 14 patients (17 eyes) were switched to aflibercept and 31 patients (42 eyes) were switched to ranibizumab. Post-switch, there was a statistically significant improvement in the BCVA in the combined group (aflibercept and ranibizumab), as well as in the ranibizumab group alone. In addition, there was a statistically significant decrease in the central subfield thickness (CST) in the combined group, as well as in the ranibizumab and aflibercept groups individually. There was no significant difference with regard to the change in macular thickness or BCVA between the aflibercept and ranibizumab groups. In addition, neither the pre-switch central macular thickness, previous number of injections, nor the pre-switch visual acuity affected the response to switching.

**CONCLUSION:** Aflibercept and ranibizumab both appear to be effective for patients showing no initial response to bevacizumab. [Ophthalmic Surg Lasers Imaging Retina. 2017;48:230-236.].

PMID: 28297035

**BMC Ophthalmol. 2017 Mar 14;17(1):28.**

**Short-term effects of intravitreal ranibizumab therapy on diabetic macular edema.**

Minami Y, Nagaoka T, Ishibazawa A, Yoshida A.

**BACKGROUND:** The short-term effects of intravitreal ranibizumab (IVR) on diabetic macular edema (DME) remains unclear. We assessed the short-term effects of IVR on DME.

**METHODS:** Eighteen eyes of 14 patients with DME were enrolled in this prospective interventional case series. After intravitreal ranibizumab was injected into treatment-naïve eyes with DME, we measured the foveal thickness (FT) before and 2 h, 1 day, 1 week, and 1 month later and the best-corrected visual acuity (BCVA) at all times except 2 h and compared the changes to baseline ( $\Delta$ FT and  $\Delta$ VA).

**RESULTS:** The mean FT decreased significantly ( $p < 0.0001$ ) from  $452 \pm 77$  to  $429 \pm 65$  microns after 2 h. The mean logarithm of the minimum angle of resolution BCVA improved significantly ( $p = 0.032$ ) after 1

month from  $0.41 \pm 0.24$  to  $0.32 \pm 0.21$  (20/51 to 20/42, Snellen equivalent). The  $\Delta$ FT after 2 h was significantly ( $r = 0.53$ ,  $p = 0.025$ ) correlated with the  $\Delta$ FT after 1 month. The  $\Delta$ VA after 1 day was significantly ( $r = 0.59$ ,  $p = 0.01$ ) correlated with the  $\Delta$ VA after 1 month.

**CONCLUSIONS:** The structural effects of IVR for DME occurred within 2 h, whereas the functional effects occurred after 1 month. The short-term effects (within 1 day) of IVR may predict the therapeutic outcome 1 month after IVR in patients with DME.

PMID: 28292270 PMCID: PMC5351159

**Vestn Oftalmol. 2017;133(1):11-18.**

**[Clinical associations between photoreceptor status and visual outcomes in diabetic macular edema]. [Article in Russian]**

Fursova AZ, Chubar' NV, Tarasov MS, Saifullina IF, Pustovaya GG.

**AIM:** To investigate morphological changes and visual acuity response to ranibizumab therapy in patients with different OCT-types of diabetic macular edema (DME) as well as different state of the inner and outer photoreceptor segments (IS and OS) and the outer limiting membrane (OLM); to study relationships between functional and morphological parameters before and after the treatment; to study the effect of glycated hemoglobin levels on morphological parameters and ME duration.

**MATERIAL AND METHODS:** The study included 113 patients (113 eyes) with DME, who underwent 3 once-monthly intravitreal injections of ranibizumab (the mean patient age,  $63.5 \pm 2.2$  years; men, 51.3%; type 2 diabetes, 81.4%). Basing on the results of OCT, 3 groups were formed: group 1 (40 patients) - intact IS and OS; group 2 (32 patients) - disturbed photoreceptor segments integrity, but intact OLM; group 3 (41 patients) - destruction of both layers.

**RESULTS:** Visual acuity at baseline and after the treatment was the highest in group 1 ( $p < 0.05$ ). In all groups, most parameters that indicated the state of photoreceptor segments and the OLM improved. Correlation analysis revealed a statistically significant negative correlation between visual acuity at baseline and after the treatment and morphological parameters ( $p < 0.05$ ). There was also a direct correlation between the morphometric parameters at baseline and after the treatment ( $p < 0.05$ ). The most favorable type of DME in terms of preserving the integrity of photoreceptor segments and the OLM was sponge-like edema, while DME with neuroepithelial detachment and mixed-type DME were prognostically unfavorable. Moreover, the state of photoreceptors and the OLM depended on the duration of ME and the level of glycated hemoglobin. Thus, the integrity of the inner and outer photoreceptor segments as well as the outer limiting membrane can contribute to prognosis for functional outcomes in DME patients that receive antiangiogenic therapy.

PMID: 28291194

**Int J Retina Vitreous. 2017 Feb 13;3:5. eCollection 2017.**

**The comparative effectiveness and cost-effectiveness of ranibizumab for neovascular macular degeneration revisited.**

Brown GC, Brown MM, Lieske HB, Turpcu A, Rajput Y.

**BACKGROUND:** To compare a near decade of follow-up, newer control cohort data, use of both the societal and third party insurer cost perspectives, and integration of unilateral/bilateral therapy on the comparative effectiveness and cost-effectiveness of intravitreal ranibizumab therapy for neovascular, age-related macular degeneration (AMD).

**METHODS:** Value-Based Medicine®, 12-year, combined-eye model, cost-utility analysis employing MARINA and HORIZON clinical trial data. Preference-based comparative effectiveness outcomes were quantified in (1) QALY (quality-adjusted life-year) gain, and (2) percent improvement in quality-of-life, while cost-effectiveness outcomes were quantified in (3) the cost-utility ratio (CUR) and financial return-on-investment (ROI) to society.

**RESULTS:** Using MARINA and HORIZON trial data and a meta-analysis control cohort after 24 months, ranibizumab therapy conferred a combined-eye patient value (quality-of-life) gain of 16.3%, versus 10.4% found in 2006. The two-year direct ophthalmic medical cost for ranibizumab therapy was \$46,450, a 33.8% real dollar decrease from 2006. The societal cost perspective CUR was -\$242,920/QALY, indicating a \$282,517 financial return-on-investment (ROI), or 12.3%/year to society for direct ophthalmic medical costs expended. The 3rd party insurer CUR ranged from \$21,199/QALY utilizing all direct, medical costs, to \$69,591/QALY using direct ophthalmic medical costs.

**CONCLUSIONS:** Ranibizumab therapy for neovascular AMD in 2015, considering treatment of both eyes, conferred greater patient value gain (comparative effectiveness) and improved cost-effectiveness than in 2006, as well as a large monetary return-on-investment to the Gross Domestic Product and nation's wealth. The model herein integrates important novel features for neovascular age-related macular degeneration, vitreoretinal cost effectiveness analyses, including: (1) treatment of both eyes, (2) a long-term, untreated control cohort, and (3) the use of societal costs.

PMID: 28289548 PMCID: PMC5304393

**Int Ophthalmol. 2017 Mar 11. [Epub ahead of print]**

**Treatment satisfaction of patients with neovascular age-related macular degeneration treated with anti-vascular endothelial growth factor agents.**

Marakis TP, Koutsandrea C, Chatzistefanou KI, Tountas Y.

**PURPOSE:** To assess the psychometric properties of the Greek Macular Disease Treatment Satisfaction Questionnaire (MacTSQ) and evaluate the factors that influence treatment satisfaction of patients with neovascular age-related macular degeneration (nAMD).

**METHODS:** The MacTSQ was translated into Greek and administered to 176 patients. All patients completed the SF-12 Health Survey and the Macular disease Dependent Quality of Life Questionnaire (MacDQoL) and underwent vision measurements. For test-retest reliability, a subset of 19 participants completed the MacTSQ twice, two weeks apart. Stepwise multiple linear regression analyses were performed to identify predictors of treatment satisfaction. Change in MacTSQ scores over time was assessed on 83 patients who completed the MacTSQ at a follow-up visit, one year later.

**RESULTS:** The intraclass correlation coefficients between the first and second test-retest administration ranged from 0.88 to 0.98 for the items and total score. Internal reliability of the total score was adequate (Cronbach's  $\alpha = 0.837$ ). Principal component analysis revealed three subscales (effectiveness, information provision and convenience, impact). The MacTSQ score showed significant correlations with SF-12 summary scales and MacDQoL scores ( $p = 0.16-0.27$ ). The most important factor that determined the satisfaction was mental health. Distance visual acuity (VA) in better eye was the best predictor of the effectiveness subscale, and the total number of injections was a negative predictor for the convenience subscale. Treatment satisfaction increased at one-year follow-up, despite the deterioration in distance VA.

**CONCLUSIONS:** The Greek MacTSQ is a reliable and valid instrument for assessing nAMD patients' perceptions of treatment satisfaction, especially using its three new subscales. Treatment satisfaction is multifactorial and was primarily determined by patients' mental health status.

PMID: 28285389



**Graefes Arch Clin Exp Ophthalmol. 2017 Mar 11. [Epub ahead of print]**

**Novel therapeutics for Stargardt disease.**

Lu LJ, Liu J, Adelman RA.

**DESCRIPTION OF SITUATION:** Stargardt disease, an inherited macular dystrophy caused by mutations in the ABCA4 gene encoding a retinal transporter protein, is the most prevalent form of macular degeneration in children. Patients with Stargardt disease develop severe vision loss within their first or second decades of life, which progresses to irreversible decreased visual acuity in almost all cases. Presently, there are no standard treatments for Stargardt disease. However, encouraging progress has been made in the development of innovative approaches to preventing vision loss in Stargardt patients.

**OBJECTIVE OF STUDY:** Among the promising treatment candidates include ALK-001, fenretinide, and A1120 as pharmacological agents to modulate the visual cycle, StarGen™ as a vector for supplementation of a functional ABCA4 gene, and stem-cell transplantation of hESC-RPE cells for regeneration of the retinal pigment epithelium. This study aims to systematically review and summarize evidence concerning the most up-to-date developments in pharmacologic, gene, and stem-cell therapies as novel therapeutic strategies to improve vision for patients with Stargardt disease.

PMID: 28285324

**Am J Ophthalmol. 2017 Mar 13. [Epub ahead of print]**

**Outcomes With As-Needed Aflibercept and Macular Laser Following the Phase III VISTA DME Trial: ENDURANCE 12-Month Extension Study.**

Wykoff CC, Le RT, Khurana RN, Brown DM, Ou WC, Wang R, Clark WL, Boyer DS; ENDURANCE Study Group.

PMID: 28302270

**Am J Ophthalmol. 2017 Mar 10. [Epub ahead of print]**

**Outcomes With As-Needed Aflibercept and Macular Laser Following the Phase III VISTA DME Trial: ENDURANCE 12-Month Extension Study.**

Călugăru D, Călugăru M1.

PMID: 28285714

## Other treatment & diagnosis

**Transl Vis Sci Technol. 2017 Mar 1;6(2):1. eCollection 2017.**

**Variability of Retinal Thickness Measurements in Tilted or Stretched Optical Coherence Tomography Images.**

Uji A, Abdelfattah NS, Boyer DS, Balasubramanian S, Lei J, Sadda SR.

**PURPOSE:** To investigate the level of inaccuracy of retinal thickness measurements in tilted and axially stretched optical coherence tomography (OCT) images.

**METHODS:** A consecutive series of 50 eyes of 50 patients with age-related macular degeneration were included in this study, and Cirrus HD-OCT images through the foveal center were used for the analysis.

The foveal thickness was measured in three ways: (1) parallel to the orientation of the A-scan (Tx), (2) perpendicular to the retinal pigment epithelium (RPE) surface in the instrument-displayed aspect ratio image (Ty), and (3) thickness measured perpendicular to the RPE surface in a native aspect ratio image (Tz). Mathematical modeling was performed to estimate the measurement error.

**RESULTS:** The measurement error was larger in tilted images with a greater angle of tilt. In the simulation, with axial stretching by a factor of 2, Ty/Tz ratio was  $> 1.05$  at a tilt angle between  $13^\circ$  to  $18^\circ$  and  $72^\circ$  to  $77^\circ$ ,  $> 1.10$  at a tilt angle between  $19^\circ$  to  $31^\circ$  and  $59^\circ$  to  $71^\circ$ , and  $> 1.20$  at an angle ranging from  $32^\circ$  to  $58^\circ$ . Of note with even more axial stretching, the Ty/Tz ratio is even larger. Tx/Tz ratio was smaller than the Ty/Tz ratio at angles ranging from  $0^\circ$  to  $54^\circ$ . The actual patient data showed good agreement with the simulation.

The Ty/Tz ratio was greater than 1.05 (5% error) at angles ranging from  $13^\circ$  to  $18^\circ$  and  $72^\circ$  to  $77^\circ$ , greater than 1.10 (10% error) angles ranging from  $19^\circ$  to  $31^\circ$  and  $59^\circ$  to  $71^\circ$ , and greater than 1.20 (20% error) angles ranging from  $32^\circ$  to  $58^\circ$  in the images axially stretched by a factor of 2 ( $b/a = 2$ ), which is typical of most OCT instrument displays.

**CONCLUSIONS:** Retinal thickness measurements obtained perpendicular to the RPE surface were overestimated when using tilted and axially stretched OCT images.

**TRANSLATIONAL RELEVANCE:**

If accurate measurements are to be obtained, images with a native aspect ratio similar to microscopy must be used.

PMID: 28299239 PMCID: PMC5347660

## **Ophthalmic Surg Lasers Imaging Retina. 2017 Mar 1;48(3):223-229.**

### **The Role of Posterior Vitreous Detachment and Vitreomacular Adhesion in Patients With Age-Related Macular Degeneration.**

Ilim O, Akkin C, Oztas Z, Nalcaci S, Afrashi F, Degirmenci C, Montes J.

**BACKGROUND AND OBJECTIVE:** The aim of this study was to assess the prevalence of posterior vitreous detachment (PVD) and vitreoretinal interface in patients with age-related macular degeneration (AMD).

**PATIENTS AND METHODS:** This clinical trial included 206 eyes of 138 patients who presented to the authors' clinic between January 2012 and November 2014. Patients were divided into three groups: 98 eyes of 67 patients with exudative AMD, 55 eyes of 36 patients with nonexudative AMD, and 53 eyes of 35 patients having no vitreoretinal disease. All patients underwent complete ocular examination, including best-corrected visual acuity, Goldmann applanation tonometry, fundus photography, spectral-domain optical coherence tomography, and B-mode ultrasonography at 6 months and 12 months after the initial examination.

**RESULTS:** Total and partial PVD rates were significantly higher at baseline, 6 months, and 12 months in both exudative and nonexudative AMD groups when compared to the control group (Chi-square test,  $P = .006$ ,  $P = .001$ , and  $P = .009$ , respectively). The prevalence of total PVD was significantly higher in nonexudative AMD, whereas partial PVD was higher in exudative AMD. The exudative AMD group reported significantly more VMA than the other two groups at baseline, 6 months, and 12 months (Chi-square test,  $P = .005$ ,  $P = .003$ , and  $P = .019$ , respectively).

**CONCLUSION:** This study indicates that the incidence of vitreoretinal interface abnormalities such as partial PVD and vitreomacular adhesion were higher in the exudative AMD group. It can be concluded that abnormal adhesive and tractional forces due to PVD may play a role in the progression of AMD.

PMID: 28297034

**Retina. 2017 Mar 13. [Epub ahead of print]**

# **ASSESSMENT OF DRUSEN AND OTHER RETINAL DEGENERATIVE CHANGES IN PATIENTS WITH HEREDITARY HEMOCHROMATOSIS.**

Menghini M, Prunte C, Krayenbuehl PA, Nowak A.

**PURPOSE:** Iron can exert oxidative damage, and increased accumulation is believed to play a role in age-related macular degeneration. Hereditary hemochromatosis leads to an increase in total body iron. Patients with HH were assessed for drusen and other retinal changes.

**METHODS:** Descriptive uncontrolled study of spectral-domain optical coherence tomography, short-wavelength autofluorescence, and color fundus images from patients with HH were used. Diagnosis of HH was established by measuring ferritin and transferrin saturation, and confirmed by genetic testing. Classification of the patients according to initial ferritin level was: Group A >1,032 µg/L; Group B below.

**RESULTS:** Twenty-five percent of the invited participants were enrolled. Mean age at diagnosis was  $46 \pm 15$  years in Group A, and  $38 \pm 13$  years in Group B,  $P = 0.07$ , whereas mean age at imaging was  $60 \pm 13$  years in Group A, and  $48 \pm 15$  years in Group B ( $P = 0.003$ ). The median of the initial ferritin level was 1,869 (1,262-3,256) ng/mL in Group A, and 534 (439-679) ng/mL in Group B. No subject in either group revealed multiple drusen, unambiguous changes of the retinal pigment epithelium, or increased lipofuscin in any of the images.

**CONCLUSION:** The study results did not show an increased prevalence of drusen or other retinal degenerative changes in patients with HH. Thus, it was concluded that increased intestinal iron absorption as well as increased blood iron concentration are not risk factors for the early development of retinal degenerative changes in this study population.

PMID: 28291154

**Invest Ophthalmol Vis Sci. 2017 Feb 1;58(2):1001-1007.**

# **Differential Disease Progression in Atrophic Age-Related Macular Degeneration and Late-Onset Stargardt Disease.**

Lindner M, Lambertus S, Mauschitz MM, Bax NM, Kersten E, Lüning A, Nadal J, Schmitz-Valckenberg S, Schmid M, Holz FG, Hoyng CB, Fleckenstein M; Foveal sparing Atrophy Study Team (FAST).

**PURPOSE:** To compare the disease course of retinal pigment epithelium (RPE) atrophy secondary to age-related macula degeneration (AMD) and late-onset Stargardt disease (STGD1).

**METHODS:** Patients were examined longitudinally by fundus autofluorescence, near-infrared reflectance imaging, and best-corrected visual acuity (BCVA). Areas of RPE atrophy were quantified using semi-automated software, and the status of the fovea was evaluated based on autofluorescence and near-infrared reflectance images. Mixed-effects models were used to compare atrophy progression rates. BCVA loss and loss of foveal integrity were analyzed using Turnbull's estimator.

**RESULTS:** A total of 151 patients (226 eyes) with RPE atrophy secondary to AMD and 38 patients (66 eyes) with RPE atrophy secondary to late-onset STGD1 were examined for a median time of 2.3 years (interquartile range, 2.7). Mean baseline age was 74.2 years (SD, 7.6) in AMD and 63.4 (SD, 9.9) in late-onset STGD1 ( $P = 1.1 \times 10^{-7}$ ). Square root atrophy progression was significantly faster in AMD when compared with late-onset STGD1 (0.28 mm/year [SE, 0.01] vs. 0.23 [SE, 0.03];  $P = 0.030$ ). In late-onset STGD1, the median survival of the fovea was significantly longer when compared with eyes with AMD (8.60 vs. 3.35 years;  $P = 0.005$ ) with a trend to a later BCVA loss of  $\geq 3$  lines (5.97 vs. 4.37 years;  $P = 0.382$ ).

**CONCLUSIONS:** These natural history data indicate differential disease progression in AMD versus late-



onset STGD1. The results underline the relevance of refined phenotyping in elderly patients presenting with RPE atrophy in regard to prognosis and design of interventional trials.

PMID: 28288486

## **Ophthalmology. 2017 Mar 8. [Epub ahead of print]**

### **The Clinical Importance of Changes in Diabetic Retinopathy Severity Score.**

Ip MS, Zhang J, Ehrlich JS.

**PURPOSE:** To investigate the clinical importance of changes in diabetic retinopathy severity score (DRSS) in patients with diabetic macular edema (DME) treated with intravitreal ranibizumab.

**DESIGN:** Post hoc analysis of the phase III RIDE and RISE studies of ranibizumab for treatment of DME.

**PARTICIPANTS:** Four hundred sixty-eight eyes treated with ranibizumab from randomization with gradable DRSS on baseline fundus photographs.

**METHODS:** Visual and anatomic outcomes were examined in eyes grouped according to DRSS change from baseline to month 24.

**MAIN OUTCOME MEASURES:** Mean best-corrected visual acuity (BCVA) letter score change, proportion of patients with 15 or more Early Treatment Diabetic Retinopathy Study (ETDRS) letter score change, mean contrast sensitivity change, proportion of patients with resolved macular edema, and leakage on fluorescein angiography.

**RESULTS:** Most (56.8%) patients treated with ranibizumab experienced 1-step or more improvement in DRSS from baseline to month 24; 40.0% had no change, and 3.2% experienced DRSS worsening. Patients with DRSS stability or improvement had greater mean BCVA letter score changes (+15.1, +14.2, +11.3, and +11.2 letters for  $\geq 3$ -step improvement,  $\geq 2$ -step improvement, 1-step improvement, and no DRSS change, respectively) compared with +5.0 letters in patients who had any DRSS worsening. Best-corrected visual acuity letter score gain of 15 letters or more was more common in patients with 2-step or 3-step or more DRSS improvement (51.9% and 44.6%, respectively) compared with those with a 1-step DRSS improvement, no change, or worsening (37.9%, 39.6%, and 26.7%, respectively). A loss of 15 letters or more in BCVA was more common in patients with any DRSS worsening (13.3%) compared with patients who had stable or improved DRSS (0%-2.8%). Resolution of macular edema was more common in patients with DRSS improvement: 84.2%, 87.7%, and 92.3% of patients with 1-step, 2-step or more, and 3-step or more improvement in DRSS achieved central foveal thickness of 250  $\mu\text{m}$  or less, compared with 65.2% and 53.3% of patients who had no DRSS change or any DRSS worsening.

**CONCLUSIONS:** These findings provide further support that improvement in DRSS is a clinically important outcome that should be evaluated as a measure of treatment effectiveness in future studies of diabetic eye disease.

PMID: 28284785

## **Pathogenesis**

### **Diab Vasc Dis Res. 2017 Mar 1:1479164116683149. [Epub ahead of print]**

**Retinal pathology is associated with increased blood-retina barrier permeability in a diabetic and hypercholesterolaemic pig model: Beneficial effects of the LpPLA2 inhibitor Darapladib.**

Acharya NK, Qi X, Goldwaser EL, Godsey GA, Wu H, Kosciuk MC, Freeman TA, Macphee CH, Wilensky

RL, Venkataraman V, Nagele RG.

**Abstract:** Using a porcine model of diabetes mellitus and hypercholesterolaemia, we previously showed that diabetes mellitus and hypercholesterolaemia is associated with a chronic increase in blood-brain barrier permeability in the cerebral cortex, leading to selective binding of immunoglobulin G and deposition of amyloid-beta1-42 peptide in pyramidal neurons. Treatment with Darapladib (GlaxoSmithKline, SB480848), an inhibitor of lipoprotein-associated phospholipase-A2, alleviated these effects. Here, investigation of the effects of chronic diabetes mellitus and hypercholesterolaemia on the pig retina revealed a corresponding increased permeability of the blood-retina barrier coupled with a leak of plasma components into the retina, alterations in retinal architecture, selective IgG binding to neurons in the ganglion cell layer, thinning of retinal layers due to cell loss and increased glial fibrillary acidic protein expression in Müller cells, all of which were curtailed by treatment with Darapladib. These findings suggest that chronic diabetes mellitus and hypercholesterolaemia induces increased blood-retina barrier permeability that may be linked to altered expression of blood-retina barrier-associated tight junction proteins, claudin and occludin, leading to structural changes in the retina consistent with diabetic retinopathy. Additionally, results suggest that drugs with vascular anti-inflammatory properties, such as Darapladib, may have beneficial effects on eye diseases strongly linked to vascular abnormalities such as diabetic retinopathy and age-related macular degeneration.

PMID: 28301218

**Front Aging Neurosci. 2017 Mar 1;9:43. eCollection 2017.**

**Bis-Retinoid A2E Induces an Increase of Basic Fibroblast Growth Factor via Inhibition of Extracellular Signal-Regulated Kinases 1/2 Pathway in Retinal Pigment Epithelium Cells and Facilitates Phagocytosis.**

Balmer D, Bapst-Wicht L, Pyakurel A, Emery M, Nanchen N, Bochet CG, Roduit R.

**Abstract:** Age-related macular degeneration (ARMD) is the leading cause of vision loss in developed countries. Hallmarks of the disease are well known; indeed, this pathology is characterized by lipofuscin accumulation, is principally composed of lipid-containing residues of lysosomal digestion. The N-retinyl-N-retinylidene ethanolamine (A2E) retinoid which is thought to be a cytotoxic component for RPE is the best-characterized component of lipofuscin so far. Even if no direct correlation between A2E spatial distribution and lipofuscin fluorescence has been established in aged human RPE, modified forms or metabolites of A2E could be involved in ARMD pathology. Mitogen-activated protein kinase (MAPK) pathways have been involved in many pathologies, but not in ARMD. Therefore, we wanted to analyze the effects of A2E on MAPKs in polarized ARPE19 and isolated mouse RPE cells. We showed that long-term exposure of polarized ARPE19 cells to low A2E dose induces a strong decrease of the extracellular signal-regulated kinases' (ERK1/2) activity. In addition, we showed that A2E, via ERK1/2 decrease, induces a significant decrease of the retinal pigment epithelium-specific protein 65 kDa (RPE65) expression in ARPE19 cells and isolated mouse RPE. In the meantime, we showed that the decrease of ERK1/2 activity mediates an increase of basic fibroblast growth factor (bFGF) mRNA expression and secretion that induces an increase in phagocytosis via a paracrine effect. We suggest that the accumulation of deposits coming from outer segments (OS) could be explained by both an increase of bFGF-induced phagocytosis and by the decrease of clearance by A2E. The bFGF angiogenic protein may therefore be an attractive target to treat ARMD.

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**Med Hypothesis Discov Innov Ophthalmol. 2016 Summer;5(2):47-52.**

**Schwann Cell-Mediated Preservation of Vision in Retinal Degenerative Diseases via the Reduction of Oxidative Stress: A Possible Mechanism.**

Mahmoudzadeh R, Heidari-Keshel S, Lashay A.

**Abstract:** After injury to the central nervous system (CNS), regeneration is often inadequate, except in the case of remyelination. This remyelination capacity of the CNS is a good example of a stem/precursor cell-mediated renewal process. Schwann cells have been found to act as remyelinating agents in the peripheral nervous system (PNS), but several studies have highlighted their potential role in remyelination in the CNS too. Schwann cells are able to protect and support retinal cells by secreting growth factors such as brain-derived neurotrophic factor, glial cell line-derived neurotrophic factor, and basic fibroblast growth factor. Retinal degenerative diseases can be highly debilitating, and they are a major concern in countries with an ageing populations. One of the leading causes of permanent loss of vision in the West is a retinal degenerative disease known as age-related macular degeneration (AMD). In the United States, nearly 1.75 million people over the age of 40 have advanced AMD, and it is estimated that this number will increase to approximately 3 million people by 2020. One of the most common pathways involved in the initiation and development of retinal diseases is the oxidative stress pathway. In patients with diabetes, Schwann cells have been shown to be able to secrete large amounts of antioxidant enzymes that protect the PNS from the oxidative stress that results from fluctuations in blood glucose levels. This antioxidant ability may be involved in the mechanism by which Schwann cells are able to promote reconstruction in the CNS, especially in individuals with retinal injuries and degenerative diseases.

PMID: 28293647 PMCID: PMC5347187

**J Exp Med. 2017 Mar 13. [Epub ahead of print]**

**VEGF165-induced vascular permeability requires NRP1 for ABL-mediated SRC family kinase activation.**

Fantin A, Lampropoulou A, Senatore V, Brash JT, Prahst C, Lange CA, Liyanage SE, Raimondi C, Bainbridge JW, Augustin HG, Ruhrberg C.

**Abstract:** The vascular endothelial growth factor (VEGF) isoform VEGF165 stimulates vascular growth and hyperpermeability. Whereas blood vessel growth is essential to sustain organ health, chronic hyperpermeability causes damaging tissue edema. By combining in vivo and tissue culture models, we show here that VEGF165-induced vascular leakage requires both VEGFR2 and NRP1, including the VEGF164-binding site of NRP1 and the NRP1 cytoplasmic domain (NCD), but not the known NCD interactor GIPC1. In the VEGF165-bound receptor complex, the NCD promotes ABL kinase activation, which in turn is required to activate VEGFR2-recruited SRC family kinases (SFKs). These results elucidate the receptor complex and signaling hierarchy of downstream kinases that transduce the permeability response to VEGF165. In a mouse model with choroidal neovascularisation akin to age-related macular degeneration, NCD loss attenuated vessel leakage without affecting neovascularisation. These findings raise the possibility that targeting NRP1 or its NCD interactors may be a useful therapeutic strategy in neovascular disease to reduce VEGF165-induced edema without compromising vessel growth.

PMID: 28289053

## Epidemiology

**Medicine (Baltimore). 2017 Mar;96(11):e6405.**

**Association between macular degeneration and mild to moderate chronic kidney disease: A nationwide population-based study.**

Chen CY, Dai CS, Lee CC, Shyu YC, Huang TS, Yeung L, Sun CC, Yang HY, Wu IW.

**Abstract:** Chronic kidney disease (CKD) and macular degeneration (MD) are 2 grave diseases leading to

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significant disability secondary to renal failure and blindness. The 2 diseases share not only common risk factors but also similar pathogenic mechanisms to renal and retinal injuries. Previous epidemiological studies indicated association between these 2 diseases. However, this concept is challenged by recent investigations. Patients with mild to moderate CKD ( $n=30,696$ ) between January 1, 1995 and December 31, 2005 were selected from the Taiwan National Health Insurance Database. Controls ( $n=122,784$ ) were matched by age, gender, diabetes mellitus type 2, and hypertension status (1:4 ratios). The risk of MD was compared between the 2 groups. The mean age of patients was  $54.9 \pm 15.7$  years. The proportion of MD was 2.7% in mild to moderate CKD patients and 1.9% in normal controls ( $P<0.001$ ); and, 0.39% and 0.26% ( $P<0.001$ ) in advanced MD. Mild to moderate CKD patients had higher risk for MD [adjusted odds ratio (OR), 1.301; 95% confidence interval (CI), 1.200-1.411;  $P<0.001$ ] than normal renal function subjects. The association was more pronounced for advanced MD. From all age strata (10 years increase), the presence of CKD in those patients aged less than 40 years had highest OR for all MD (OR=2.125, 95% CI: 1.417-3.186,  $P<0.001$ ). The results were consistent in interaction terms, highlighting the importance of CKD in young age patient for risk of MD. The high risk for MD in mild to moderate CKD patients remains significant after adjustment for personal habits (alcohol drinking and smoking, model 1; OR: 1.371; 95% CI: 1.265-1.486;  $P<0.001$ ), comorbidities (dyslipidemia, cerebrovascular disease, and peripheral vascular disease, model 2; OR: 1.369; 95% CI: 1.264-1.484;  $P<0.001$ ) and all these factors (model 3; OR: 1.320, 95% CI: 1.218-1.431,  $P<0.001$ ). This association was consistent in the subanalysis, excluding those patients with diabetic retinopathy. Proper diagnosis and timely intervention should be warranted to retard visual loss of these patients.

PMID: 28296786

## Genetics

**Invest Ophthalmol Vis Sci. 2017 Mar 1;58(3):1656-1664.**

### **Rearing Light Intensity Affects Inner Retinal Pathology in a Mouse Model of X-Linked Retinoschisis but Does Not Alter Gene Therapy Outcome.**

Marangoni D, Yong Z, Kjellström S, Vijayasarathy C, A Sieving P, Bush RA.

**PURPOSE:** To test the effects of rearing light intensity on retinal function and morphology in the retinoschisis knockout (Rs1-KO) mouse model of X-linked retinoschisis, and whether it affects functional outcome of RS1 gene replacement.

**METHODS:** Seventy-six Rs1-KO mice were reared in either cyclic low light (LL, 20 lux) or moderate light (ML, 300 lux) and analyzed at 1 and 4 months. Retinal function was assessed by electroretinogram and cavity size by optical coherence tomography. Expression of inward-rectifier K<sup>+</sup> channel (Kir4.1), water channel aquaporin-4 (AQP4), and glial fibrillary acidic protein (GFAP) were analyzed by Western blotting. In a separate study, Rs1-KO mice reared in LL ( $n = 29$ ) or ML ( $n = 27$ ) received a unilateral intravitreal injection of scAAV8-hRs-IRBP at 21 days, and functional outcome was evaluated at 4 months by electroretinogram.

**RESULTS:** At 1 month, no functional or structural differences were found between LL- or ML-reared Rs1-KO mice. At 4 months, ML-reared Rs1-KO mice showed significant reduction of b-wave amplitude and b/a-wave ratio with no changes in a-wave, and a significant increase in cavity size, compared to LL-reared animals. Moderate light rearing increased Kir4.1 expression in Rs1-KO mice by 4 months, but not AQP4 and GFAP levels. Administration of scAAV8-hRS1-IRBP to Rs1-KO mice showed similar improvement of inner retinal ERG function independent of LL or ML rearing.

**CONCLUSIONS:** Rearing light conditions affect the development of retinal cavities and post-photoreceptor function in Rs1-KO mice. However, the effect of rearing light intensity does not interact with the efficacy of RS1 gene replacement in Rs1-KO mice.

PMID: 28297725

**Front Cell Neurosci. 2017 Feb 27;11:20. eCollection 2017.**

### **Hypoxia-Inducible Factor-1 $\alpha$ Target Genes Contribute to Retinal Neuroprotection.**

Cheng L, Yu H, Yan N, Lai K, Xiang M.

**Abstract:** Hypoxia-inducible factor (HIF) is a transcription factor that facilitates cellular adaptation to hypoxia and ischemia. Long-standing evidence suggests that one isotype of HIF, HIF-1 $\alpha$ , is involved in the pathogenesis of various solid tumors and cardiac diseases. However, the role of HIF-1 $\alpha$  in retina remains poorly understood. HIF-1 $\alpha$  has been recognized as neuroprotective in cerebral ischemia in the past two decades. Additionally, an increasing number of studies has shown that HIF-1 $\alpha$  and its target genes contribute to retinal neuroprotection. This review will focus on recent advances in the studies of HIF-1 $\alpha$  and its target genes that contribute to retinal neuroprotection. A thorough understanding of the function of HIF-1 $\alpha$  and its target genes may lead to identification of novel therapeutic targets for treating degenerative retinal diseases including glaucoma, age-related macular degeneration, diabetic retinopathy, and retinal vein occlusions.

PMID: 28289375 PMCID: PMC5326762

## **Stem cells**

**N Engl J Med. 2017 Mar 16;376(11):1038-1046.**

### **Autologous Induced Stem-Cell-Derived Retinal Cells for Macular Degeneration.**

Mandai M1, Watanabe A1, Kurimoto Y1, Hirami Y1, Morinaga C1, Daimon T1, Fujihara M1, Akimaru H1, Sakai N1, Shibata Y1, Terada M1, Nomiya Y1, Tanishima S1, Nakamura M1, Kamao H1, Sugita S1, Onishi A1, Ito T1, Fujita K1, Kawamata S1, Go MJ1, Shinohara C1, Hata KI1, Sawada M1, Yamamoto M1, Ohta S1, Ohara Y1, Yoshida K1, Kuwahara J1, Kitano Y1, Amano N1, Umekage M1, Kitaoka F1, Tanaka A1, Okada C1, Takasu N1, Ogawa S1, Yamanaka S1, Takahashi M1.

**Abstract:** We assessed the feasibility of transplanting a sheet of retinal pigment epithelial (RPE) cells differentiated from induced pluripotent stem cells (iPSCs) in a patient with neovascular age-related macular degeneration. The iPSCs were generated from skin fibroblasts obtained from two patients with advanced neovascular age-related macular degeneration and were differentiated into RPE cells. The RPE cells and the iPSCs from which they were derived were subject to extensive testing. A surgery that included the removal of the neovascular membrane and transplantation of the autologous iPSC-derived RPE cell sheet under the retina was performed in one of the patients. At 1 year after surgery, the transplanted sheet remained intact, best corrected visual acuity had not improved or worsened, and cystoid macular edema was present. (Funded by Highway Program for Realization of Regenerative Medicine and others; University Hospital Medical Information Network Clinical Trials Registry [UMIN-CTR] number, UMIN000011929 .).

PMID: 28296613

**N Engl J Med. 2017 Mar 16;376(11):1047-1053.**

### **Vision Loss after Intravitreal Injection of Autologous "Stem Cells" for AMD.**

Kuriyan AE, Albin TA, Townsend JH, Rodriguez M, Pandya HK, Leonard RE 2nd, Parrott MB, Rosenfeld PJ, Flynn HW Jr, Goldberg JL.

**Abstract:** Adipose tissue-derived "stem cells" have been increasingly used by "stem-cell clinics" in the United States and elsewhere to treat a variety of disorders. We evaluated three patients in whom severe bilateral visual loss developed after they received intravitreal injections of autologous adipose tissue-



derived "stem cells" at one such clinic in the United States. In these three patients, the last documented visual acuity on the Snellen eye chart before the injection ranged from 20/30 to 20/200. The patients' severe visual loss after the injection was associated with ocular hypertension, hemorrhagic retinopathy, vitreous hemorrhage, combined traction and rhegmatogenous retinal detachment, or lens dislocation. After 1 year, the patients' visual acuity ranged from 20/200 to no light perception.

PMID: 28296617

**N Engl J Med. 2017 Mar 16;376(11):1007-1009. Epub 2016 Nov 30.**

### **Clarifying Stem-Cell Therapy's Benefits and Risks.**

Marks PW, Witten CM, Califf RM.

PMID: 27959704

## **Diet, lifestyle & low vision**

**Br J Ophthalmol. 2017 Mar 14. [Epub ahead of print]**

### **A nationwide cohort study of cigarette smoking and risk of neovascular age-related macular degeneration in East Asian men.**

Rim TH, Cheng CY, Kim DW, Kim SS, Wong TY.

**BACKGROUND:** Few longitudinal studies have evaluated the relationship between cigarette smoking and risk of neovascular age-related macular degeneration (AMD) among Asian populations. This study aimed to prospectively evaluate the association between cigarette smoking and risk of neovascular AMD among Korean men.

**METHODS:** Men between the ages of 45 and 79 years included in the Korea National Health Insurance Service database from 2002 through 2013. We compared hazard ratios (HR) for neovascular AMD between 64 560 past/current and 64 560 never smokers by 1:1 propensity-matched analysis and 85 267 past/current and 72 347 never smokers by unmatched cohort and propensity-adjusted analysis.

**RESULTS:** The risk of neovascular AMD among past/current smokers was 50% higher than that among never smokers (propensity-adjusted whole cohort analysis: HR, 1.48; 95% CI 1.22 to 1.79; propensity-matched analysis: HR, 1.50; 95% CI 1.22 to 1.84), with the risk more pronounced among current than past smokers (current vs past smokers: propensity-adjusted whole cohort analysis, HR, 1.66; 95% CI 1.35 to 2.04 vs HR, 1.15, 95% CI 0.87 to 1.52; propensity-matched analysis, HR, 1.65; 95% CI 1.32 to 2.05 vs HR, 1.21; 95% CI 0.90 to 1.63). Duration of smoking and daily cigarette consumption was associated with the incidence of neovascular AMD in a dose-dependent manner ( $p < 0.001$  for trend).

**CONCLUSIONS:** Cigarette smoking is associated with a strong risk of neovascular AMD among Korean men. These data highlight the public health impact of smoking on blindness in Asia.

PMID: 28292774

**Med Hypothesis Discov Innov Ophthalmol. 2016 Spring;5(1):32-38.**

### **Short-term Outcomes of Saffron Supplementation in Patients with Age-related Macular Degeneration: A Double-blind, Placebo-controlled, Randomized Trial.**

Lashay A, Sadough G, Ashrafi E, Lashay M, Movassat M, Akhondzadeh S.

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**Abstract:** In modern pharmacological medicine, saffron is used for various purposes due to its antioxidant effect. This study evaluated retinal function after treatment with saffron supplementation during a follow-up period of 6 months to provide further insight into the efficacy and safety considerations of this treatment. Sixty patients with wet or dry age-related macular degeneration (AMD) were randomly assigned to receive oral saffron 30 mg/d or placebo supplementation for 6 months. Optical coherence tomography (OCT), electroretinography (ERG), fluorescein angiography, and visual acuity testing were performed at baseline and 3 and 6 months after treatment. The main outcome measures were OCT, ERG amplitude, and implicit time. Six months after treatment, no statistically significant decrease in OCT results was observed between the groups with dry AMD ( $P = 0.282$ ). However, there was a statistically significant increase in ERG results between the groups at 3 months after treatment ( $P = 0.027$ ). In addition, there was a significant decrease in OCT results between groups with wet AMD at the follow-up ( $P = 0.05$ ). Finally, there was a significant increase in ERG findings between the groups with wet AMD at 3 months after treatment ( $P = 0.01$ ), but these changes decreased at 6 months after treatment ( $P = 0.213$ ). Daily supplementation with 30 mg of saffron for 6 months may result in a mid-term, significant improvement in retinal function in patients with AMD.

PMID: 28289690 PMCID: PMC5342880

### **Ophthalmic Epidemiol. 2017 Mar 13:1-10. [Epub ahead of print]**

#### **Survival Bias When Assessing Risk Factors for Age-Related Macular Degeneration: A Tutorial with Application to the Exposure of Smoking.**

McGuinness MB, Karahalios A, Kasza J, Guymer RH, Finger RP, Simpson JA.

**PURPOSE:** We illustrate the effect of survival bias when investigating risk factors for eye disease in elderly populations for whom death is a competing risk. Our investigation focuses on the relationship between smoking and late age-related macular degeneration (AMD) in an observational study impacted by censoring due to death.

**METHODS:** Statistical methodology to calculate the survivor average causal effect (SACE) as a sensitivity analysis is described, including example statistical computing code for Stata and R. To demonstrate this method, we examine the causal effect of smoking history at baseline (1990-1994) on the presence of late AMD at the third study wave (2003-2007) using data from the Melbourne Collaborative Cohort Study.

**RESULTS:** Of the 40,506 participants eligible for inclusion, 38,092 (94%) survived until the start of the third study wave, 20,752 (51%) were graded for AMD (60% female, aged 47-85 years, mean  $65 \pm 8.7$  years). Late AMD was detected in 122 participants. Logistic regression showed strong evidence of an increased risk of late AMD for current smokers compared to non-smokers (adjusted naïve odds ratio 2.99, 95% confidence interval, CI, 1.74-5.13). Among participants expected to be alive at the start of follow-up regardless of their smoking status, the estimated SACE odds ratio comparing current smokers to non-smokers was at least 3.42 (95% CI 1.57-5.15).

**CONCLUSIONS:** Survival bias can attenuate associations between harmful exposures and diseases of aging. Estimation of the SACE using a sensitivity analysis approach should be considered when conducting epidemiological research within elderly populations.

PMID: 28287849

### **Exp Eye Res. 2017 Mar 9. [Epub ahead of print]**

#### **Retinal accumulation of zeaxanthin, lutein, and $\beta$ -carotene in mice deficient in carotenoid cleavage enzymes.**

Li B, Vachali PP, Shen Z, Gorusupudi A, Nelson K, Besch BM, Bartschi A, Longo S, Mattinson T, Shihab S, Polyakov NE, Suntsova LP, Dushkin AV, Bernstein PS.

**Abstract:** Carotenoid supplementation can prevent and reduce the risk of age-related macular degeneration (AMD) and other ocular disease, but until now, there has been no validated and well-characterized mouse model which can be employed to investigate the protective mechanism and relevant metabolism of retinal carotenoids.  $\beta$ -Carotene oxygenases 1 and 2 (BCO1 and BCO2) are the only two carotenoid cleavage enzymes found in animals. Mutations of the *bco2* gene may cause accumulation of xanthophyll carotenoids in animal tissues, and BCO1 is involved in regulation of the intestinal absorption of carotenoids. To determine whether or not mice deficient in BCO1 and/or BCO2 can serve as a macular pigment mouse model, we investigated the retinal accumulation of carotenoids in these mice when fed with zeaxanthin, lutein, or  $\beta$ -carotene using an optimized carotenoid feeding method. HPLC analysis revealed that all three carotenoids were detected in sera, livers, retinal pigment epithelium (RPE)/choroids, and retinas of all of the mice, except that no carotenoid was detectable in the retinas of wild type (WT) mice. Significantly higher amounts of zeaxanthin and lutein accumulated in the retinas of BCO2 knockout (*bco2*<sup>-/-</sup>) mice and BCO1/BCO2 double knockout (*bco1*<sup>-/-</sup>/*bco2*<sup>-/-</sup>) mice relative to BCO1 knockout (*bco1*<sup>-/-</sup>) mice, while *bco1*<sup>-/-</sup> mice preferred to take up  $\beta$ -carotene. The levels of zeaxanthin and lutein were higher than  $\beta$ -carotene levels in the *bco1*<sup>-/-</sup>/*bco2*<sup>-/-</sup> retina, consistent with preferential uptake of xanthophyll carotenoids by retina. Oxidative metabolites were detected in mice fed with lutein or zeaxanthin but not in mice fed with  $\beta$ -carotene. These results indicate that *bco2*<sup>-/-</sup> and *bco1*<sup>-/-</sup>/*bco2*<sup>-/-</sup> mice could serve as reasonable non-primate models for macular pigment function in the vertebrate eye, while *bco1*<sup>-/-</sup> mice may be more useful for studies related to  $\beta$ -carotene.

PMID: 28286282

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