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MD Research News

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Drug treatment

Invest Ophthalmol Vis Sci. 2014 Mar 7. pii: iovs.13-13769v1. doi: 10.1167/iovs.13-13769. [Epub ahead of print]

Change of Retinal Nerve Fiber Layer Thickness in Various Retinal Diseases Treated with Multiple Intravitreal Anti-vascular Endothelial Growth Factor.

Shin HJ, Shin KC, Chung H, Kim HC.

Purpose: To investigate the effect of multiple intravitreal injection of anti-vascular endothelial growth factor (VEGF) on the retinal nerve fiber layer (RNFL) in age-related macular degeneration (AMD), diabetes mellitus retinopathy (DMR), and retinal vein occlusion (RVO)

Methods: In this retrospective controlled case series, we reviewed the AMD, DMR, and RVO patients who received more than three anti-VEGF injections (injection group 148 eyes). Patients without treatment were included as control group (non-injection group 183 eyes). RNFL thickness was measured by SD-OCT. Also, correlation between RNFL change and associated factors including intraocular pressure (IOP), injection times, and severity of retinal ischemia were analyzed using multivariate logistic regression

Results: RNFL thickness (μm) had not changed in AMD, but it decreased from 100.0 to 97.1, and from 101.1 to 98.0 in injection groups of DMR and RVO, respectively, as well as the non-injection group. However, decreased RNFL thickness of the injection groups were not significantly different from those of the non-injection groups. Severity of retinal ischemia was associated with decreased RNFL thickness (odds ratio 4.667). However, number of injections and IOP-related variables had no association with RNFL change

Conclusions: Multiple intravitreal injection of anti-VEGF did not lead to significant change in RNFL thickness in wet AMD, DMR, and RVO patients. Furthermore IOP fluctuations and number of injection did not appear to adversely affect RNFL thickness. Decreased RNFL thickness associated with severity of retinal ischemia in the DMR and RVO patients suggests that inner retinal ischemia itself could be a cause of RNFL loss rather than anti-VEGF effect.

PMID: 24609624 [PubMed - as supplied by publisher]

Appl Health Econ Health Policy. 2014 Mar 8. [Epub ahead of print]

Modelling Cost Effectiveness in Neovascular Age-Related Macular Degeneration: The Impact of Using Contrast Sensitivity vs. Visual Acuity.

Butt T, Patel PJ, Tufail A, Rubin GS.

BACKGROUND: The cost utility of treatments of age-related macular degeneration (AMD) is commonly assessed using health state transition models defined by levels of visual acuity. However, there is evidence that another measure of visual function, contrast sensitivity, may be better associated with utility than visual acuity. This paper investigates the difference in cost effectiveness resulting from models based on visual acuity and contrast sensitivity using the example of bevacizumab (Avastin) for neovascular AMD. The implications of the choice of outcome on structural uncertainty in the model are investigated.

METHOD: Health state transition Markov models based on levels of visual acuity and contrast sensitivity are used to represent the costs, health utilities and outcomes of the Avastin for choroidal neovascular age-related macular degeneration (ABC) trial. Health states are associated with costs and utilities based on literature values. Treatment outcomes from the ABC trial are used to predict transitions between states in both models. Total costs and quality-adjusted life-years (QALYs) are calculated for a cohort of patients treated over a defined number of model cycles.

RESULTS: Over a 5-year time horizon, a contrast sensitivity model predicts a statistically significant ($p < 0.05$) 25 % greater QALY gain than the visual acuity model based on 10,000 Monte Carlo simulations. Bevacizumab is more effective and less costly than the comparator in the contrast sensitivity model and the visual acuity model.

CONCLUSION: There is considerable structural uncertainty associated with the choice of outcome for modelling the cost effectiveness of AMD treatments. Bevacizumab has a higher incremental QALY gain and more favourable incremental cost-effectiveness ratio when cost effectiveness is assessed using contrast sensitivity outcomes compared with using visual acuity outcomes. Previous cost-effectiveness analyses may have underestimated the cost effectiveness of anti-vascular endothelial growth factor (anti-VEGF) therapy.

PMID: 24610632 [PubMed - as supplied by publisher]

PLoS One. 2014 Mar 11;9(3):e91227. doi: 10.1371/journal.pone.0091227. eCollection 2014.

Foveal morphology affects self-perceived visual function and treatment response in neovascular age-related macular degeneration: a cohort study.

Subhi Y, Henningsen GØ, Larsen CT, Sørensen MS, Sørensen TL.

OBJECTIVES: To investigate the relationship between foveal morphology and self-perceived visual function in patients with neovascular age-related macular degeneration (AMD) and whether foveal characteristics are associated with Ranibizumab treatment response on the self-perceived visual function.

METHODS: This prospective cohort study included patients with newly diagnosed neovascular AMD found eligible for treatment with Ranibizumab. Foveal morphology of both eyes was assessed using spectral-domain optical coherence tomography and all patients were interviewed using the 39-item National Eye Institute Visual Function Questionnaire (VFQ). Patients were re-interviewed 3 and 12 months after initiation of treatment with Ranibizumab. We evaluated foveal morphology at baseline in relation to VFQ scores at baseline and clinically meaningful changes in VFQ after 3 and 12 months.

RESULTS: VFQ scores correlated with central foveal thickness, central foveal thickness of neuroretina (CFN), foveal RPE elevation, foveal integrity of the photoreceptor inner segment/outer segment junction (IS/OS), and external limiting membrane. In a multiple linear regression model, only best-corrected visual acuity of the better eye ($p<0.001$) and the IS/OS status in the better eye ($p=0.012$) remained significant (Adjusted $R2=0.418$). Lower baseline VFQ and a baseline CFN within 170-270 µm in the better eye were both associated with a clinically meaningful increase in the VFQ scores after 3 and 12 months. An absent foveal IS/OS band in the better eye was associated with a clinically meaningful decrease in the VFQ scores

at 12 months.

CONCLUSIONS: Foveal morphology in the better eye influences the self-perceived visual function in patients with neovascular AMD and possesses a predictive value for change in the self-perceived visual function at 3 and 12 months after initiation of treatment. These findings may help clinicians provide patients more individualized information of their disease and treatment prognosis from a patient-perceived point-of-view.

PMID: 24618706 [PubMed - in process] PMCID: PMC3949984

Br J Clin Pharmacol. 2014 Mar 6. doi: 10.1111/bcp.12371. [Epub ahead of print]

Anti Vascular Endothelial Growth Factor therapies in Ophthalmology: Current Use, Controversies and the Future.

Kwong TQ, Mohamed M.

Abstract: Use of anti-Vascular endothelial growth factor (VEGF) therapies was restricted to systemic administration for certain cancers until 2005 when localised intra-ocular administration was introduced for the treatment of ocular disorders. In the UK, the current licenced and NICE approved indications are for the treatment of neovascular age-related macular degeneration (nAMD), diabetic macular oedema (DMO), macular oedema secondary to a retinal vein occlusion (RVO) and choroidal neovascularisation in Pathological Myopia. These diagnoses alone account for two thirds of the main causes of legally registrable visual impairment and blindness. Some idea of the magnitude of impact of these landmark therapies can be gauged from reports of blindness registration, which have halved between 2000 and 2010 in Denmark, the bulk of which are attributable to these agents.

PMID: 24602183 [PubMed - as supplied by publisher]

Ophthalmology. 2014 Jan;121(1):e4. doi: 10.1016/j.ophtha.2013.09.020. Epub 2013 Nov 20.

Is there risk of stroke with aflibercept?

Beaumont PE, Petocz P, Kang HK.

Comment on Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. [Ophthalmology. 2012]

PMID: 24268853 [PubMed - indexed for MEDLINE]

Ophthalmology. 2014 Jan;121(1):e5. doi: 10.1016/j.ophtha.2013.09.019. Epub 2013 Nov 18.

Safety in Aflibercept versus Ranibizumab.

Ueta T.

Comment on Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. [Ophthalmology. 2012]

PMID: 24256894 [PubMed - indexed for MEDLINE]

Ophthalmology. 2014 Jan;121(1):e5-e6.

Author reply

Heier JS, Brown DM, Chong V, Korobelnik JF, Kaiser PK, Nguyen QD, Kirchhof B, Ho A, Ogura Y, Schmidt

-Erfurth U.

PMID: 24536092 [PubMed - indexed for MEDLINE]

Ophthalmology. 2014 Mar 7. pii: S0161-6420(14)00066-9. doi: 10.1016/j.ophtha.2013.12.043. [Epub ahead of print]

RE: Risk of Geographic Atrophy in the Comparison of Age-related Macular Degeneration Treatments Trials.

Sophie R, Wang J, Campochiaro PA.

PMID: 24613823 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Ophthalmology. 2014 Mar 7. pii: S0161-6420(13)01256-6. doi: 10.1016/j.ophtha.2013.12.035. [Epub ahead of print]

Visual Acuity after Cataract Surgery in Patients with Age-Related Macular Degeneration: Age-Related Eye Disease Study 2 Report Number 5.

Age-Related Eye Disease Study 2 Research Group; Writing Committee, Huynh N, Nicholson BP, Agrón E, Clemons TE, Bressler SB, Rosenfeld PJ, Chew EY.

OBJECTIVE: To evaluate visual acuity outcomes after cataract surgery in persons with varying degrees of severity of age-related macular degeneration (AMD).

DESIGN: Cohort study.

PARTICIPANTS: A total of 1232 eyes of 793 participants who underwent cataract surgery during the Age-Related Eye Disease Study 2, a prospective, multicenter, randomized controlled trial of nutritional supplements for treatment of AMD.

METHODS: Preoperative and postoperative characteristics of participants who underwent cataract extraction during the 5-year trial were analyzed. Both clinical data and standardized red-reflex lens and fundus photographs were obtained at baseline and annually. Photographs were graded by a centralized reading center for cortical and posterior subcapsular lens opacities and for AMD severity. Cataract surgery was documented at annual study visits or by history during the 6-month telephone calls. Analyses were conducted using multivariate repeated-measures regression.

MAIN OUTCOME MEASURES: Change in best-corrected visual acuity (BCVA) after cataract surgery compared with preoperative BCVA.

RESULTS: Adjusting for age at time of surgery, gender, interval between preoperative and postoperative visits, and type and severity of cataract, the mean changes in visual acuity were as follows: eyes with mild AMD (n = 30) gained 11.2 letters (95% confidence interval [CI], 6.9-15.5), eyes with moderate AMD (n = 346) gained 11.1 letters (95% CI, 9.1-13.2), eyes with severe AMD (n = 462) gained 8.7 letters (95% CI, 6.7 -10.7), eyes with noncentral geographic atrophy (n = 70) gained 8.9 letters (95% CI, 5.8-12.1), and eyes with advanced AMD (central geographic atrophy, neovascular disease, or both; n = 324) gained 6.8 letters (95% CI, 4.9-8.8). The visual acuity gain across all AMD severity groups was statistically significant from preoperative values ($P < 0.0001$).

CONCLUSIONS: Mean visual acuities improved significantly after cataract surgery across varying degrees of AMD severity.

PMID: 24613825 [PubMed - as supplied by publisher]

Pathogenesis

Eye (Lond). 2014 Mar 7. doi: 10.1038/eye.2014.50. [Epub ahead of print]

Melatonin and amfenac modulate calcium entry, apoptosis, and oxidative stress in ARPE-19 cell culture exposed to blue light irradiation (405 nm).

Argun M, Tök L, Uğuz AC, Celik O, Tök OY, Naziroğlu M.

Purpose: Under conditions of oxidative stress, cell apoptosis is triggered through the mitochondrial intrinsic pathway. Increased levels of reactive oxygen species (ROS) are linked to excess cell loss and mediate the initiation of apoptosis in a diverse range of cell types. The aims of this study were to assess intracellular Ca2+ release, ROS production, and caspase-3, and -9 activation in ARPE-19 cells during the blue light-mediated cell death, and to examine a potential protective effect of melatonin and amfenac, in the apoptotic cascade.

Methods: ARPE-19 cells were cultured in their medium. First, MTT tests were performed to determine the protective effects of amfenac and melatonin. Cells were then exposed to blue light irradiation in an incubator. Intracellular Ca2+ release experiments, mitochondrial membrane depolarization, apoptosis assay, glutathione (GSH), glutathione peroxidase (GSH-Px), and ROS experiments were done according to the method stated in the Materials and methods section.

Results: Cell death was clearly associated with increased levels of ROS production, as measured by 2',7'-dichlorofluorescein fluorescence, and associated increase in Ca2+ levels, as measured by Fura-2-AM. Blue light-induced cell death was associated with an increased level of caspase-3 and 9, suggesting mediation via the apoptotic pathway. Cell death was also associated with mitochondrial depolarization. Melatonin was shown to delay these three steps.

Conclusion: Melatonin, amfenac, and their combination protect ARPE-19 cells against blue light-triggered ROS accumulation and caspase-3 and -9 activation. The antiapoptotic effect of melatonin and amfenac at doses inhibiting caspase synthesis modified Ca2+ release and prevented excessive ROS production, suggesting a new therapeutic approach to age-related macular degeneration.Eye advance online publication, 7 March 2014; doi:10.1038/eye.2014.50.

PMID: 24603419 [PubMed - as supplied by publisher]

Mol Biol Rep. 2014 Mar 13. [Epub ahead of print]

Long non-coding RNAs: new players in ocular neovascularization.

Xu XD, Li KR, Li XM, Yao J, Qin J, Yan B.

Abstract: Pathological neovascularization are the most prevalent causes of moderate or severe vision loss. Long non-coding RNAs (lncRNAs) have emerged as a novel class of regulatory molecules involved in numerous biological processes and complicated diseases. However, the role of lncRNAs in ocular neovascularization is still unclear. Here, we constructed a murine model of ocular neovascularization, and determined lncRNA expression profiles using microarray analysis. We identified 326 or 51 lncRNAs that were significantly either up-regulated or down-regulated in the vaso-obliteration or neovascularization phase, respectively. Based on Pearson correlation analysis, lncRNAs/mRNAs co-expression networks were constructed. GO enrichment analysis of lncRNAs-co-expressed mRNAs indicated that the biological modules were correlated with chromosome organization, extracellular region and guanylate cyclase activator activity in the vaso-obliteration phase, and correlated with cell proliferation, extracellular region and guanylate cyclase regulator activity in the neovascularization phase. KEGG pathway analysis indicated that MAPK signaling was the most significantly enriched pathway in both phases. Importantly, Vax2os1 and Vax2os2 were not only dynamically expressed in the vaso-obliteration and neovascularization phases, but

also significantly altered in the aqueous humor of patients with neovascular age-related macular degeneration (AMD), suggesting a potential role of lncRNAs in the regulation of ocular neovascularization. Taken together, this study provided novel insights into the molecular pathogenesis of ocular neovascularization. The intervention of dysregulated lncRNA could become a potential target for the prevention and treatment of ocular vascular diseases.

PMID: 24623407 [PubMed - as supplied by publisher]

Dtsch Arztebl Int. 2014 Feb 21;111(8):133-8. doi: 10.3238/arztebl.2014.0133.

The role of the complement system in age-related macular degeneration.

Weber BH, Charbel Issa P, Pauly D, Herrmann P, Grassmann F, Holz FG.

BACKGROUND: Age-related macular degeneration (AMD) is a common retinal disease in older people. In Europe, about 1.6% of persons over age 65 and more than 13% of persons over age 85 have late-stage AMD, which can severely impair vision. The development of AMD is influenced both by environmental factors and by a strong hereditary component.

METHOD: We selectively searched the PubMed database for articles published between April 2001 and November 2013 with the key words "age-related macular degeneration," "risk factor," "complement," and "therapy." The website www.clinicaltrials.gov was also used to search for relevant clinical trials.

RESULTS: Old age and smoking are confirmed risk factors for AMD. Moreover, genetic association studies have pointed to signaling pathways in which the complement system, a part of the individual's innate immune system, takes on a central role in the pathogenesis of the disease. Several clinical trials designed to interfere specifically with these pathomechanisms have yielded rather disappointing results, although a phase II study of the monoclonal antibody lampalizumab showed that blocking complement factor D lessened the progression of geographic atrophy. A risk model based on 13 genetic markers was found to have positive predictive values in predisposed individuals that ranged from 5.1% (in persons aged 65 to 69) to 91.7% (in persons aged 85 or older). It should be borne in mind that 50% of patients with AMD are not carriers of risk-associated markers.

CONCLUSION: There is no rationale at present for genetic testing to estimate the individual risk of developing AMD. Several recent clinical trials have incorpo - rated current pathophysiological knowledge, but nearly all of these trials have yielded negative findings, with only one exception.

PMID: 24622760 [PubMed - in process]

Cell Adh Migr. 2014 Feb 10;8(2). [Epub ahead of print]

Regulation of vascular endothelial junction stability and remodeling through Rap1-Rasip1 signaling.

Wilson CW, Ye W.

Abstract: The ability of blood vessels to sense and respond to stimuli such as fluid flow, shear stress, and trafficking of immune cells is critical to the proper function of the vascular system. Endothelial cells constantly remodel their cell-cell junctions and the underlying cytoskeletal network in response to these exogenous signals. This remodeling, which depends on regulation of the linkage between actin and integral junction proteins, is controlled by a complex signaling network consisting of small G proteins and their various downstream effectors. In this commentary, we summarize recent developments in understanding the small G protein RAP1 and its effector RASIP1 as critical mediators of endothelial junction stabilization, and the relationship between RAP1 effectors and modulation of different subsets of endothelial junctions. The vasculature is a dynamic organ that is constantly exposed to a variety of signaling stimuli and

mechanical stresses. In embryogenesis, nascent blood vessels form via a process termed vasculogenesis, wherein mesodermally derived endothelial precursor cells aggregate into cords, which subsequently form a lumen that permits trafficking of plasma and erythrocytes. 1, 2 Angiogenesis occurs after establishment of this primitive vascular network, where new vessels sprout from existing vessels, migrate into newly expanded tissues, and anastomose to form a functional and complex circulatory network. 1, 2 In the mouse, this process occurs through the second half of embryogenesis and into postnatal development in some tissues, such as the developing retinal vasculature. 3 Further, angiogenesis occurs in a variety of pathological conditions, such as diabetic retinopathy, age-related macular degeneration, inflammatory diseases such as rheumatoid arthritis, wound healing, and tumor growth. 1, 2, 4 Both vasculogenesis and angiogenesis are driven through signaling by vascular endothelial growth factor (VEGF), and therapeutic agents targeting this pathway have shown efficacy in a number of diseases. 5- 9 Blood vessels must have a sufficient degree of integrity so as to not allow indiscriminate leak of plasma proteins and blood cells into the underlying tissue. However, vessels must be able to sense their environment, respond to local conditions, and mediate the regulated passage of protein, fluid, and cells. For example, endothelial cells are the primary point of attachment for immune cells leaving the blood stream and entering tissue, and leukocytes subsequently migrate either through the endothelial cell body itself (the transcellular route), or through transient disassembly of cell-cell junctions (the paracellular route). 10 Precise regulation of endothelial junctions is critical to the proper maintenance of vascular integrity and related processes, and disruption of vascular cell-cell contacts is an underlying cause or contributor to numerous pathologies such as cerebral cavernous malformations (CCM) and hereditary hemorrhagic telangiectasia (HHT). 11- 13 Understanding the basic mechanisms of endothelial junction formation and maintenance will therefore lead to a greater chance of success of therapeutic intervention in these pathologic conditions, especially in instances where targeting of VEGF signaling is insufficient to resolve vascular abnormalities.

PMID: 24622510 [PubMed - as supplied by publisher]

Redox Biol. 2014 Feb 21;2:485-94. doi: 10.1016/j.redox.2014.01.023. eCollection 2014.

Inhibition of APE1/Ref-1 redox activity rescues human retinal pigment epithelial cells from oxidative stress and reduces choroidal neovascularization.

Li Y, Liu X, Zhou T, Kelley MR, Edwards P, Gao H, Qiao X.

Abstract: The effectiveness of current treatment for age related macular degeneration (AMD) by targeting one molecule is limited due to its multifactorial nature and heterogeneous pathologies. Treatment strategy to target multiple signaling pathways or pathological components in AMD pathogenesis is under investigation for better clinical outcome. Inhibition of the redox function of apurinic endonuclease 1/redox factor-1 (APE1) was found to suppress endothelial angiogenesis and promote neuronal cell recovery, thereby may serve as a potential treatment for AMD. In the current study, we for the first time have found that a specific inhibitor of APE1 redox function by a small molecule compound E3330 regulates retinal pigment epithelium (RPEs) cell response to oxidative stress. E3330 significantly blocked sub-lethal doses of oxidized low density lipoprotein (oxLDL) induced proliferation decline and senescence advancement of RPEs. At the same time, E3330 remarkably decreased the accumulation of intracellular reactive oxygen species (ROS) and down-regulated the productions of monocyte chemoattractant protein-1 (MCP-1) and vascular endothelial growth factor (VEGF), as well as attenuated the level of nuclear factor-κB (NF-κB) p65 in RPEs. A panel of stress and toxicity responsive transcription factors that were significantly upregulated by oxLDL was restored by E3330, including Nrf2/Nrf1, p53, NF-κB, HIF1, CBF/NF-Y/YY1, and MTF-1. Further, a single intravitreal injection of E3330 effectively reduced the progression of laser-induced choroidal neovascularization (CNV) in mouse eyes. These data revealed that E3330 effectively rescued RPEs from oxidative stress induced senescence and dysfunctions in multiple aspects in vitro, and attenuated laser-induced damages to RPE-Bruch′s membrane complex in vivo. Together with its previously established anti-angiogenic and neuroprotection benefits, E3330 is implicated for potential use for AMD treatment.

PMID: 24624338 [PubMed]

Epidemiology

Acta Ophthalmol. 2014 Feb 25. doi: 10.1111/aos.12370. [Epub ahead of print]

Ocular diseases and 10-year mortality: The Beijing Eye Study 2001/2011.

Wang YX, Zhang JS, You QS, Xu L, Jonas JB.

PURPOSE: To examine the relationship between major ocular diseases and mortality.

METHODS: The population-based longitudinal study Beijing Eye Study was performed in 2001 and repeated in 2011. The participants underwent a detailed ophthalmic examination at baseline in 2001.

RESULTS: Of 4439 subjects examined in 2001, 2695 (60.7%) subjects returned for the follow-up examination in 2011, while 379 (8.5%) subjects were dead and 1365 (30.8%) subjects were alive, however, did not agree to be re-examined. In multivariate regression analysis, mortality was significantly associated with the systemic parameters of older age ($p < 0.001$; Odds ratio (OR): 1.07; 95% confidence interval (CI): 1.05, 1.09), male gender ($p < 0.001$; OR: 0.56; 95% CI: 0.40, 0.78), lower level of education ($p < 0.001$; OR: 0.66; 95% CI: 0.59, 0.74) and smoking ($p < 0.001$; OR: 1.84; 95% CI: 1.36, 2.49) and with the ocular parameters of presence of diabetic retinopathy ($p = 0.002$; OR: 2.26; 95% CI: 1.34, 3.81), non-glaucomatous optic nerve damage ($p = 0.001$; OR: 4.90; 95% CI: 1.90, 12.7) and higher degree of nuclear cataract ($p = 0.002$; OR: 1.29; 95% CI: 1.10, 1.52). In that model, mortality was not significantly (all $p > 0.05$) associated with refractive error, cortical or subcapsular posterior cataract, intraocular pressure, best corrected visual acuity, visual field defects, prevalence of age-related macular degeneration, retinal vein occlusions, open-angle glaucoma and angle-closure glaucoma.

CONCLUSIONS: After adjustment for age, gender, level of education and smoking, mortality was significantly higher in subjects with diabetic retinopathy, non-glaucomatous optic nerve damage and nuclear cataract. Other major ophthalmic parameters and disorders such as hyperopia, myopia, high myopia, pterygium, age-related macular degeneration, retinal vein occlusion, glaucoma and cortical or nuclear cataract were not significantly associated with mortality in the multivariate analysis.

PMID: 24612916 [PubMed - as supplied by publisher]

PLoS One. 2014 Mar 6;9(3):e90897. doi: 10.1371/journal.pone.0090897. eCollection 2014.

Refractive error and risk of early or late age-related macular degeneration: a systematic review and meta-analysis.

Li Y, Wang J, Zhong X, Tian Z, Wu P, Zhao W, Jin C.

OBJECTIVE: To summarize relevant evidence investigating the associations between refractive error and age-related macular degeneration (AMD).

DESIGN: Systematic review and meta-analysis.

METHODS: We searched Medline, Web of Science, and Cochrane databases as well as the reference lists of retrieved articles to identify studies that met the inclusion criteria. Extracted data were combined using a random-effects meta-analysis. Studies that were pertinent to our topic but did not meet the criteria for quantitative analysis were reported in a systematic review instead.

MAIN OUTCOME MEASURES: Pooled odds ratios (ORs) and 95% confidence intervals (CIs) for the associations between refractive error (hyperopia, myopia, per-diopter increase in spherical equivalent [SE] toward hyperopia, per-millimeter increase in axial length [AL]) and AMD (early and late, prevalent and incident).

RESULTS: Fourteen studies comprising over 5800 patients were eligible. Significant associations were

found between hyperopia, myopia, per-diopter increase in SE, per-millimeter increase in AL, and prevalent early AMD. The pooled ORs and 95% CIs were 1.13 (1.06-1.20), 0.75 (0.56-0.94), 1.10 (1.07-1.14), and 0.79 (0.73-0.85), respectively. The per-diopter increase in SE was also significantly associated with early AMD incidence (OR, 1.06; 95% CI, 1.02-1.10). However, no significant association was found between hyperopia or myopia and early AMD incidence. Furthermore, neither prevalent nor incident late AMD was associated with refractive error. Considerable heterogeneity was found among studies investigating the association between myopia and prevalent early AMD (P=0.001, I2=72.2%). Geographic location might play a role; the heterogeneity became non-significant after stratifying these studies into Asian and non-Asian subgroups.

CONCLUSION: Refractive error is associated with early AMD but not with late AMD. More large-scale longitudinal studies are needed to further investigate such associations.

PMID: 24603619 [PubMed - in process] PMCID: PMC3946285

Diet & lifestyle

Curr Opin Ophthalmol. 2014 Mar 8. [Epub ahead of print]

Age-related Eye Disease Study 2: perspectives, recommendations, and unanswered questions.

Aronow ME, Chew EY.

PURPOSE OF REVIEW: This review provides a perspective on the Age-related Eye Disease Study 2 (AREDS2) including a summary of the goals and rationale of the study, major findings, subsequent management recommendations, and questions that remain to be answered.

RECENT FINDINGS: The primary goal of the AREDS2 was to evaluate the efficacy and safety of lutein plus zeaxanthin and/or omega-3 long-chain polyunsaturated acid supplementation in reducing the risk of developing advanced age-related macular degeneration (AMD). AREDS2 also investigated the effects of omitting β-carotene and reducing the concentration of zinc from the original AREDS formulation. Although primary analysis from the AREDS2 did not reveal a benefit of daily supplementation with lutein/zeaxanthin on AMD progression, secondary exploratory analyses suggested that lutein/zeaxanthin were helpful in reducing this risk. Comparison of low-dose to higher-dose zinc showed no significant benefit.

SUMMARY: The overall evidence on the beneficial and adverse effects from AREDS2 and other studies suggests that lutein/zeaxanthin could be more appropriate than β-carotene in AREDS-type supplements. Questions remain regarding the AREDS2 study results such as: whether the findings are generalizable to the population as a whole, what is the long-term safety profile of lutein/zeaxanthin supplementation, should other carotenoids be included in AREDS-type supplements, and at what optimal doses?

PMID: 24614146 [PubMed - as supplied by publisher]

Ophthalmic Epidemiol. 2014 Apr;21(2):111-23. doi: 10.3109/09286586.2014.888085.

Central Retinal Enrichment Supplementation Trials (CREST): Design and Methodology of the CREST Randomized Controlled Trials.

Akuffo KO, Beatty S, Stack J, Dennison J, O'Regan S, Meagher KA, Peto T, Nolan J.

Abstract Purpose: The Central Retinal Enrichment Supplementation Trials (CREST) aim to investigate the potential impact of macular pigment (MP) enrichment, following supplementation with a formulation containing 10 mg lutein (L), 2 mg zeaxanthin (Z) and 10 mg meso-zeaxanthin (MZ), on visual function in normal subjects (Trial 1) and in subjects with early age-related macular degeneration (AMD; Trial 2).

Methods: CREST is a single center, double-blind, randomized clinical trial. Trial 1 (12-month follow-up) subjects are randomly assigned to a formulation containing 10 mg L, 10 mg MZ and 2 mg Z (n = 60) or placebo (n = 60). Trial 2 (24-month follow-up) subjects are randomly assigned to a formulation containing 10 mg L, 10 mg MZ, 2 mg Z plus 500 mg vitamin C, 400 IU vitamin E, 25 mg zinc and 2 mg copper (Intervention A; n = 75) or 10 mg L and 2 mg Z plus 500 mg vitamin C, 400 IU vitamin E, 25 mg zinc and 2 mg copper (Intervention B; n = 75). Contrast sensitivity (CS) at 6 cycles per degree represents the primary outcome measure in each trial. Secondary outcomes include: CS at other spatial frequencies, MP, best-corrected visual acuity, glare disability, photostress recovery, light scatter, cognitive function, foveal architecture, serum carotenoid concentrations, and subjective visual function. For Trial 2, AMD morphology, reading speed and reading acuity are also being recorded.

Conclusions: CREST is the first study to investigate the impact of supplementation with all three macular carotenoids in the context of a large, double-blind, randomized clinical trial.

PMID: 24621122 [PubMed - in process]

PLoS One. 2014 Mar 7;9(3):e90973. doi: 10.1371/journal.pone.0090973. eCollection 2014.

Elevated high-density lipoprotein cholesterol and age-related macular degeneration: the alienor study.

Cougnard-Grégoire A, Delyfer MN, Korobelnik JF, Rougier MB, Le Goff M, Dartigues JF, Barberger-Gateau P, Delcourt C.

BACKGROUND: Lipid metabolism and particularly high-density lipoprotein (HDL) may be involved in the pathogenic mechanism of age-related macular degeneration (AMD). However, conflicting results have been reported in the associations of AMD with plasma HDL and other lipids, which may be confounded by the recently reported associations of AMD with HDL-related genes. We explored the association of AMD with plasma lipid levels and lipid-lowering medication use, taking into account most of HDL-related genes associated with AMD.

METHODS: The Alienor study is a population-based study on age-related eye diseases performed in 963 elderly residents of Bordeaux (France). AMD was graded from non mydriatic color retinal photographs in three exclusive stages: no AMD (n=430 subjects, 938 eyes); large soft distinct drusen and/or large soft indistinct drusen and/or reticular drusen and/or pigmentary abnormalities (early AMD, n=176, 247); late AMD (n=40, 61). Associations of AMD with plasma lipids (HDL, total cholesterol (TC), Low-density lipoprotein (LDL), and triglycerides (TG)) were estimated using Generalized Estimating Equation logistic regressions. Statistical analyses included 646 subjects with complete data.

RESULTS: After multivariate adjustment for age, sex, educational level, smoking, BMI, lipid-lowering medication use, cardiovascular disease and diabetes, and for all relevant genetic polymorphisms (ApoE2, ApoE4, CFH Y402H, ARMS2 A69S, LIPC rs10468017, LIPC rs493258, LPL rs12678919, ABCA1 rs1883025 and CETP rs3764261), higher HDL was significantly associated with an increased risk of early (OR=2.45, 95%CI: 1.54-3.90; P=0.0002) and any AMD (OR=2.29, 95%CI: 1.46-3.59; P=0.0003). Association with late AMD was far from statistical significance (OR=1.58, 95%CI: 0.48-5.17; p=0.45). No associations were found for any stage of AMD with TC, LDL and TG levels, statin or fibrate drug use.

CONCLUSIONS: This study suggests that elderly patients with high HDL concentration may be at increased risk for AMD and, further, that HDL dysfunction might be implicated in AMD pathogenesis.

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