

# MDFA Research update

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## FEATURED ARTICLE

### **Incidence, Risk Factors and Outcomes of Rhegmatogenous Retinal Detachment after Intravitreal Injections of Anti-Vascular Endothelial Growth Factor for Retinal Diseases: Data from the Fight Retinal Blindness! Registry.**

Ophthalmology Retina 2022 May 16.

Gabrielle PH, Nguyen V, Arnould L, Viola F, Zarranz-Ventura J, Barthelmes D, Creuzot-Garcher C, Gillies M; Fight Retinal Blindness! Study Group.

**Purpose:** To report the estimated incidence, probability, risk factors and one-year outcomes of rhegmatogenous retinal detachment (RRD) in eyes receiving intravitreal injections (IVT) of vascular endothelial growth factor (VEGF) inhibitors for various retinal conditions in routine clinical practice.

**Design:** Retrospective analysis of data from a prospectively designed observational outcomes registry: the Fight Retinal Blindness!

**Participants:** Eyes starting IVT with VEGF inhibitors (ranibizumab, aflibercept or bevacizumab) for neovascular age-related macular degeneration (nAMD), diabetic macular edema (DME) or retinal vein occlusion (RVO) from 1 January 2006 to 31 December 2020. All eyes that developed RRD within 90 days of an intravitreal injection were defined as RRD cases and were matched with control eyes.

**Methods:** Estimated incidence, probability, and hazard ratios (HR) of RRD were measured using Poisson regression, Kaplan-Meier survival curve and Cox-proportional hazards models. Locally weighted scatterplot smoothing curves were used to compare visual acuity (VA) between cases and matched controls.

**Main Outcome Measures:** Estimated incidence of RRD.

**Results:** We identified 16915 eyes of 13792 patients who collectively received 265781 IVT over 14 years. Thirty-six eyes were reported to develop RRD over the study period. The estimated incidence (95% confidence interval [95%CI]) per year per 1000 patients and per 10000 injections was 0.77 (0.54, 1.07) and 1.36 (0.95, 1.89), respectively. The probability of RRD did not increase significantly at each successive injection ( $P = 0.95$ ) with the time of follow-up. Older patients (hazard ratio [HR] [95%CI] = 1.81 [1.21, 3.62] for every decade increase in age,  $P < 0.01$ ) were at higher

risk of RRD, while patients with good presenting VA (HR = 0.85 [0.70, 0.98] for every 10-letter increase in VA,  $P = 0.02$ ) were at a lower risk. Neither the type of retinal disease ( $P = 0.52$ ) nor the VEGF inhibitor ( $P = 0.09$ ) were significantly associated with RRD risk. RRD cases lost three lines of vision on average compared to the prior-RRD VA and had significantly fewer injections than matched controls over the year following the RRD.

**Conclusions:** RRD is a rare complication of VEGF inhibitor IVT in routine clinical practice with poor visual outcomes at one year.

DOI: [10.1016/j.oret.2022.05.008](https://doi.org/10.1016/j.oret.2022.05.008)

## EPIDEMIOLOGY

### Thirty-Year Time Trends in Diabetic Retinopathy and Macular Edema in Youth With Type 1 Diabetes.

Diabetes Care. 2022 May 20.

Allen DW(1), Liew G, Cho YH, Pryke A, Cusumano J, Hing S, Chan AK, Craig ME, Donaghue KC.

**Objective:** To examine trends in diabetic retinopathy (DR) and diabetic macular edema (DME) in adolescents with type 1 diabetes between 1990 and 2019.

**Research Design and Methods:** We analyzed 5,487 complication assessments for 2,404 adolescents (52.7% female, aged 12-20 years, diabetes duration >5 years), stratified by three decades (1990-1999, 2000-2009, 2010-2019). DR and DME were graded according to the modified Airlie House classification from seven-field stereoscopic fundal photography.

**Results:** Over three decades, the prevalence of DR was 40, 21, and 20% ( $P < 0.001$ ) and DME 1.4, 0.5, and 0.9% ( $P = 0.13$ ), respectively, for 1990-1999, 2000-2009, and 2010-2019. Continuous subcutaneous insulin infusion (CSII) use increased (0, 12, and 55%;  $P < 0.001$ ); mean HbA1c was bimodal (8.7, 8.5, and 8.7%;  $P < 0.001$ ), and the proportion of adolescents meeting target HbA1c <7% did not change significantly (8.3, 7.7, and 7.1%;  $P = 0.63$ ). In multivariable generalized estimating equation analysis, DR was associated with 1-2 daily injections (odds ratio 1.88, 95% CI 1.42-2.48) and multiple injections in comparison with CSII (1.38, 1.09-1.74); older age (1.11, 1.07-1.15), higher HbA1c (1.19, 1.05-1.15), longer diabetes duration (1.15, 1.12-1.18), overweight/obesity (1.27, 1.08-1.49) and higher diastolic blood pressure SDS (1.11, 1.01-1.21). DME was associated with 1-2 daily injections (3.26, 1.72-6.19), longer diabetes duration (1.26, 1.12-1.41), higher diastolic blood pressure SDS (1.66, 1.22-2.27), higher HbA1c (1.28, 1.03-1.59), and elevated cholesterol (3.78, 1.84-7.76).

**Conclusions:** One in five adolescents with type 1 diabetes had DR in the last decade. These findings support contemporary guidelines for lower glycemic targets, increasing CSII use, and targeting modifiable risk factors including blood pressure, cholesterol, and overweight/obesity.

DOI: [10.2337/dc21-1652](https://doi.org/10.2337/dc21-1652)

## DRUG INTERACTIONS

### Association of Diabetes Medication With Open-Angle Glaucoma, Age-Related Macular Degeneration, and Cataract in the Rotterdam Study.

**Importance:** Recent studies suggest that the diabetes drug metformin has a protective effect on open-angle glaucoma (OAG) and age-related macular degeneration (AMD). However, studies have not addressed the critical issue of confounding by indication, and associations have not been evaluated in a large prospective cohort.

**Objective:** To determine the association between diabetes medication and the common eye diseases OAG, AMD, and cataract and to evaluate their cumulative lifetime risks in a large cohort study.

**Design, Setting, and Participants:** This cohort study included participants from 3 independent cohorts from the prospective, population-based Rotterdam Study between April 23, 1990, and June 25, 2014. Participants were monitored for incident eye diseases (OAG, AMD, cataract) and had baseline measurements of serum glucose. Data on diabetes medication use and data from ophthalmologic examinations were gathered.

**Exposures:** Type 2 diabetes (T2D) and the diabetes medications metformin, insulin, and sulfonylurea derivatives.

**Main Outcomes and Measures:** Diagnosis and cumulative lifetime risk of OAG, AMD, and cataract.

**Results:** This study included 11 260 participants (mean [SD] age, 65.1 [9.8]; 6610 women [58.7%]). T2D was diagnosed in 2406 participants (28.4%), OAG was diagnosed in 324 of 7394 participants (4.4%), AMD was diagnosed in 1935 of 10 993 participants (17.6%), and cataract was diagnosed in 4203 of 11 260 participants (37.3%). Untreated T2D was associated with a higher risk of OAG (odds ratio [OR], 1.50; 95% CI, 1.06-2.13;  $P = .02$ ), AMD (OR, 1.35; 95% CI, 1.11-1.64;  $P = .003$ ), and cataract (OR, 1.63; 95% CI, 1.39-1.92;  $P < .001$ ). T2D treated with metformin was associated with a lower risk of OAG (OR, 0.18; 95% CI, 0.08-0.41;  $P < .001$ ). Other diabetes medication (ie, insulin, sulfonylurea derivatives) was associated with a lower risk of AMD (combined OR, 0.32; 95% CI, 0.18 to 0.55;  $P < .001$ ). The cumulative lifetime risk of OAG was lower for individuals taking metformin (1.5%; 95% CI, 0.01%-3.1%) than for individuals without T2D (7.2%; 95% CI, 5.7%-8.7%); the lifetime risk of AMD was lower for individuals taking other diabetes medication (17.0%; 95% CI, 5.8%-26.8% vs 33.1%; 95% CI, 30.6%-35.6%).

**Conclusions and Relevance:** Results of this cohort study suggest that, although diabetes was clearly associated with cataract, diabetes medication was not. Treatment with metformin was associated with a lower risk of OAG, and other diabetes medication was associated with a lower risk of AMD. Proof of benefit would require interventional clinical trials.

DOI: [10.1001/jamaophthalmol.2022.1435](https://doi.org/10.1001/jamaophthalmol.2022.1435)

## CASE STUDY

### Nocturnal normobaric hyperoxia treatment in a case of chronic diabetic macular edema.

Song S, Lemire CA, Seto B, Arroyo JG.

**Purpose:** To study the long-term anatomic and physiologic effects of nocturnal normobaric hyperoxia (NNBH) in a patient with treatment-resistant diabetic macular edema (DME).

**Methods:** A 64-year-old diabetic man with bilateral DME requiring regular anti-VEGF treatments in both eyes was started on 5 LPM (40% FiO<sub>2</sub>) NNBH treatment 6-h per night. Visual acuity, OCT measurements of retinal thickness and volume, as well as the number of injections given in each eye were retrospectively examined one year prior and prospectively after initiation of NNBH, as well as before and after a planned 1-month discontinuation of NNBH.

**Results:** The patient received 12 anti-VEGF injections in the year prior to beginning NNBH treatment (4 OD; 8 OS) and did not require any injections after commencing NNBH treatment. Visual acuity improved and stabilized to 20/20 and macular edema rapidly resolved in both eyes following initiation of NNBH. After a planned 1-month NNBH vacation, DME recurred but quickly resolved once NNBH treatment was restarted.

**Conclusion:** This model case demonstrates that a 6-h NNBH regimen can be successful in treating DME and improving vision, without the need for intravitreal injections. NNBH is a more acceptable treatment regimen compared to 24-h continuous oxygen delivery and may provide a less invasive alternate method for treating DME in patients with diabetes. Further study is warranted.

DOI: [10.1177/11206721221101365](https://doi.org/10.1177/11206721221101365)

## Long-term outcomes of anti-vascular endothelial growth factor treatment in peripapillary choroidal neovascularisation due to age-related macular degeneration.

Eye (London). 2022 May 17.

Stanescu N, Friehmann A, Nemet A, Keshet Y, Ohayon A, Greenbaum E, Rabina G, Nemet AY, Geffen N, Segal O.

**Objective:** To report the long-term outcomes of anti-vascular endothelial growth factor (VEGF) treatment in eyes with peripapillary choroidal neovascularisation (PPCNV) associated with age-related macular degeneration (AMD).

**Methods:** A retrospective cohort study included patients with AMD-related PPCNV. Eyes were treated with anti-VEGF according to pro re nata regimen. Inactivation index was calculated as the proportion of disease inactivity from the total follow up time.

**Results:** Sixty-seven eyes of 66 consecutive patients were included in the study; mean follow-up time was 53.2 months. Best corrected visual acuity (BCVA) remained stable for the first four years of follow up, with a significant deterioration in BCVA thereafter. Baseline BCVA was a significant predictor of final BCVA ( $p < 0.001$ ). The mean inactivation index was  $0.38 \pm 0.23$ . Subretinal fluid (SRF) at presentation was significantly associated with decreased inactivation index ( $p < 0.05$ ). Worse baseline BCVA, SRF and pigment epithelium detachment (PED), male sex, and younger patient age were associated with increased risk for recurrence after first inactivation ( $p < 0.05$ ).

**Conclusion:** The use of anti-VEGF agents in the treatment of AMD-related PPCNV managed to preserve BCVA in the first four years of follow-up. Male sex, SRF and PED at presentation and baseline BCVA are associated with increased risk for PPCNV recurrence after the first inactivation, and should prompt careful follow-up in these patients.

DOI: [10.1038/s41433-022-02089-0](https://doi.org/10.1038/s41433-022-02089-0)

## REVIEW

### **Systemic Complement Activation Profiles in Nonexudative Age-Related Macular Degeneration: A Meta-Analysis.**

Journal Clinical Medicine. 2022 Apr 23.

Lin JB, Serghiou S, Miller JW, Vavvas DG.

Although complement inhibition has emerged as a possible therapeutic strategy for age-related macular degeneration (AMD), there is not a clear consensus regarding what aspects of the complement pathway are dysregulated in AMD and when this occurs relative to disease stage. We recently published a systematic review describing systemic complement activation profiles in patients with early/intermediate AMD or geographic atrophy (GA) compared to non-AMD controls. Here, we sought to meta-analyze these results to estimate the magnitude of complement dysregulation in AMD using restricted maximum likelihood estimation. The seven meta-analyzed studies included 710 independent participants with 23 effect sizes. Compared with non-AMD controls, patients with early/intermediate nonexudative AMD (N = 246) had significantly higher systemic complement activation, as quantified by the levels of complement proteins generated by common final pathway activation, and significantly lower systemic complement inhibition. In contrast, there were no statistically significant differences in the systemic levels of complement common final pathway activation products or complement inhibition in patients with GA (N = 178) versus non-AMD controls. We provide evidence that systemic complement over-activation is a feature of early/intermediate nonexudative AMD; no such evidence was identified for patients with GA. These findings provide mechanistic insights and inform future clinical trials.

DOI: [10.3390/jcm11092371](https://doi.org/10.3390/jcm11092371) PMID: [PMC9105289](https://pubmed.ncbi.nlm.nih.gov/39105289/)

### **Association between Cataract Surgery and Age-Related Macular Degeneration: A Systematic Review and Meta-Analysis.**

Journal of Ophthalmology. 2022 May 5

Yang L, Li H, Zhao X, Pan Y.

**Purpose:** We performed a systematic review and meta-analysis to evaluate the association between cataract surgery and the development and progression of AMD.

**Methods:** This meta-analysis was registered at PROSPERO (CRD42017077962). We conducted a systematic literature search in August 2020 in Embase and PubMed and included cohort studies, case-control studies, or randomized controlled trials (RCTs) if they examined the association between cataract surgery and AMD. Odds

ratio (OR) was used as a measure of the association with a random effect model. The analysis was further stratified by factors that could affect the outcomes.

**Results:** 15 studies were included in this study. In the overall analysis, cataract surgery was significantly associated with the incidence of late AMD (OR, 1.80; 95% CI, 1.26-2.56;  $P = 0.001$ ), particularly geographic atrophy (OR, 3.20; 95% CI, 1.90-5.39;  $P \leq 0.001$ ). No significant associations were observed between cataract surgery and the incidence of early AMD. Subgroup analysis showed that the OR for incidence of early and late AMD was significantly higher for cataract surgery performed more than 5 years compared with less than 5 years. We also found an increased risk of progression of AMD after cataract surgery performed more than 5 years (OR, 1.97; 95% CI, 1.29-3.01;  $P = 0.002$ ).

**Conclusions:** Our results suggest that cataract surgery may be associated with an increased risk of late AMD development and AMD progression. In addition, increasing the follow-up time since cataract surgery may further increase the risk for the development and progression of AMD. In the future, prospective multicenter studies with well-designed RCTs are required to confirm our findings.

DOI: [10.1155/2022/6780901](https://doi.org/10.1155/2022/6780901)

## BIOMARKERS

### Baseline Sattler Layer-Choriocapillaris complex Thickness cutoffs associated with age-related macular degeneration progression.

Retina. 2022 May 12.

Amato A, Arrigo A, Borghesan F, Aragona E, 'Vigano' C, Saladino A, Bandello F, Parodi MB.

**Purpose:** This study aims to assess the relationship between choroidal overall and sublayer thickness and AMD stage progression.

**Methods:** A prospective, observational case series was performed. 262 eyes of 262 patients with different stages of AMD were imaged by Optical Coherence Tomography (OCT). AMD stage, choroidal thickness (CT), Sattler layer-choriocapillaris complex thickness (SLCCT) and Haller layer thickness (HLT) were determined at the baseline visit, at a 1-year follow-up visit, at a 2-year follow up visit and at a final visit (performed after a mean of  $5 \pm 1$  years from the baseline visit).

**Results:** Baseline AMD stages were distributed as follows: early AMD (30 eyes; 12%), intermediate AMD (97 eyes; 39%) and late AMD (126 eyes; 49%). At the final follow-up, AMD stages were so distributed: early AMD (14 eyes; 6%), intermediate AMD (83 eyes; 33%) and late AMD (156 eyes; 61%). Each group showed a statistically significant decrease in CT values over the entire follow-up ( $p < 0.001$ ) and SLCCT reduction was associated with AMD progression ( $p < 0.001$ ). Moreover, SLCCT quantitative cutoffs  $< 20.50 \mu\text{m}$  and  $< 10.5 \mu\text{m}$  were associated with a moderate and high probability of AMD progression, respectively, and SLCCT quantitative cutoffs  $< 18.50 \mu\text{m}$  and  $< 8.50 \mu\text{m}$  implied a moderate and high probability of macular neovascularization (MNV) onset, respectively.

**Conclusions:** Progressive choroidal impairment contributes to AMD progression. Among choroidal layers, a reduced SLCCT is a promising biomarker of disease worsening and its quantitative evaluation could help to identify patients at higher risk of stage advancement.

DOI: [10.1097/IAE.0000000000003530](https://doi.org/10.1097/IAE.0000000000003530)



# DIAGNOSIS AND IMAGING

## Rapid Macular Thinning is an Early Indicator of Hydroxychloroquine Retinal Toxicity.

Ophthalmology. 2022 May 11.

Melles RB, Marmor MF.

**Purpose:** To demonstrate rapid macular thinning as an early and objective sign of hydroxychloroquine (HCQ) retinopathy. DESIGN: Retrospective case cohort.

**Subjects:** Cohort of 301 long-term HCQ therapy patients at Kaiser Permanente Northern California who had a minimum of four optical coherence tomography (OCT) studies which included Early Treatment Diabetic Retinopathy Study (ETDRS) retinal thickness values over a minimum interval of four years.

**Methods:** Creation of sequential retinal thickness plots to show the rate of change in macular thickness within ETDRS regions.

**Main Outcome Measures:** 1) Identification of rapid macular thinning, 2) Comparison of patients with rapid thinning to those with stable macular thickness, and 3) Comparison of rapid thinning patients with and without conventional OCT or 10-2 visual field signs of HCQ toxicity.

**Results:** Retina thinning in 219 stable patients on long-term HCQ therapy averaged  $0.62 \pm 0.45$  (mean  $\pm$  standard deviation) microns per year, while 82 patients showed a period of relatively linear rapid thinning with a loss of  $3.75 \pm 1.34$  microns per year. Of the patients with rapid thinning, 38 eventually developed conventional OCT or 10-2 visual field signs of HCQ retinal toxicity. The cumulative retinal thinning in these patients was  $25.1 \pm 6.2$  microns compared to  $15.7 \pm 4.0$  microns in those without conventional toxicity ( $p < 0.01$ ).

**Conclusions:** Retinal thickness remains stable for many years in most patients on long-term HCQ therapy, but after a critical point the retina may begin to thin rapidly. Sequential plots of inner and outer ETDRS ring macular thickness provide objective evidence of this early structural change several years before conventional signs appear. This approach can alert patients and prescribing physicians to potential retinal damage and uses readily available OCT measurements that could be automated by manufacturers for use in comprehensive eyecare settings.

DOI: [10.1016/j.ophtha.2022.05.002](https://doi.org/10.1016/j.ophtha.2022.05.002)