7/16/2022 10:15 am

Dry AMD 3 Symposium

Assessment of the Inclusion of Racial/Ethnic Minorities in Retina Clinical Trials

- Vivienne Hau, MD, PhD
- Jennifer Pinal, BA
- Kin Li
- Monica Saavedra

Objective:
To what extent are racial and ethnic minorities underrepresented in retina clinical trials in the last 10 years?

Purpose:
The purpose of this study is to assess the inclusion of racial/ethnic minorities in retina clinical trials in the last 10 years as a starting point to further examine health inequities as it relates to clinical trials. People of racial/ethnic minority status and low socioeconomic status have consistently been shown to be associated with decreased utilization of eye examinations and decreased access to eye care. Considering these findings, we hypothesize that people of racial and ethnic minorities are underrepresented in retina clinical trials.

Methods:
This cross-sectional study examined data from completed US-based ophthalmology trials registered on ClinicalTrials.gov from 1/26/12-1/26/22. Results available for completed interventional phase II, III, and IV clinical trials for U.S. participants of all ages, sexes, with the term "retinal diseases" were searched. To be included, trials had to be categorized as completed and have available results. Trials that were completed but without results reported were excluded. Also excluded were studies with unknown status and those that were not yet recruiting, still recruiting, enrolling by invitation, active but not recruiting, suspended, terminated, or withdrawn. The numbers and percentages of racial/ethnic minorities were compared with US census data (https://data.census.gov/) from 2012-2020 were gathered.

Results:
A total of 157 studies were identified from the search, and a total of 96 US-based trials with 13016 participants were included in the study. 61 studies were excluded due to no results. 60[62.50%] were Phase II, 17[17.71%] were Phase III, 4[4.17%] were Phase II/III], and 15[15.63%] were Phase IV. 66[68.75%] trials were randomized, 10[10.42%] were not randomized, and 20[20.83%] of studies did not report or had unknown randomization status. All but 3[3.12%] studies reported sex, with 50.55% females, 48.76% males, and 0.69% having unknown sex; 38[39.58%] of studies had a mean age less than 65 and 43[44.79%] over 65, and 15[15.63%] was not reported. 63 [65.63%] studies reported race and 47 [48.96%] reported ethnicity. Compared to Census data, study participants, white individuals were overrepresented (65.2% ±.81%). Black individuals (6.26%±.41%), Latinx individuals (3.64% ±.32%), and American Indian or Alaska Native individuals (.35% ±.10%) were underrepresented compared with US Census data; enrollment of Asian individuals were (5.87%±.40%), which was closest to the US Census data.

Conclusion:
Racial and ethnic minorities of all categories were underrepresented in trials compared to U.S. census data. A notable finding is the lack of demographics reported in study results despite FDA guidance. Further initiatives are imperative to assess the barriers and facilitators to accessing clinical trials as a treatment option in ophthalmic care.

IRB APPROVAL No - no IRB or exemption

Percentage of Race Reported in Clinical Trials of Retinal Diseases

7/16/2022 10:21 am

Dry AMD 3 Symposium

Efficacy and Safety of Multiwavelength Photobiomodulation in Dry Age-Related Macular Degeneration Using the LumiThera Valeda System (LIGHTSITE III Interim Analysis)

- Richard Rosen, MD, DSc(Hon), FACS, FASRS, FARVO
- Marion Munk, MD, PhD
- David Boyer, MD
- Diana Do, MD, FASRS
- Samantha Xavier
- Allen Hu, MD
- David Warrow, MD
- Victor Gonzales, MD
- Eleanora Lad
- Todd Schneiderman, MD, FASRS
- Allen Ho, MD FASRS
- Glenn Jaffe, MD
- Stephanie Tedford, PhD
- Cindy Croissant
- Michael Walker, MD
- Rene Ruckert
- Clark Tedford

Objective:
To determine the efficacy and safety of multiwavelength photobiomodulation (PBM) treatment (Tx) in subjects with dry age-related macular degeneration (AMD).

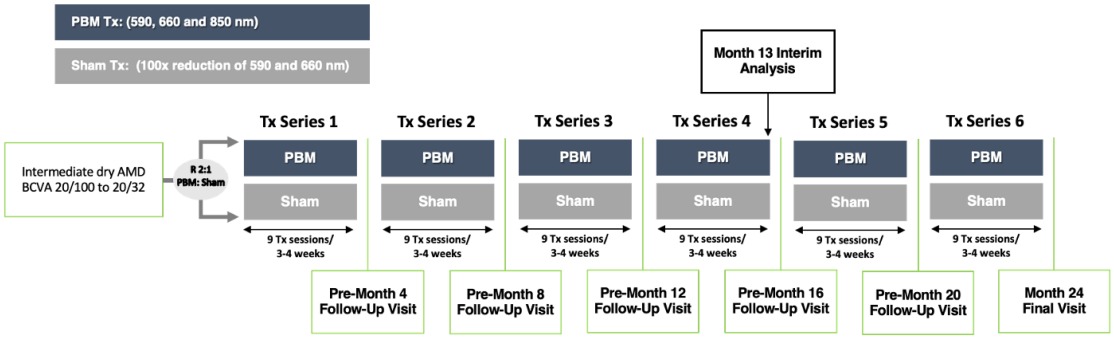
Purpose:
Dry age-related macular degeneration (AMD) is a leading cause of visual impairment across the globe. There is no cure and current Tx strategies available outside of vitamin supplementation and lifestyle changes. LIGHTSITE III is evaluating multiwavelength photobiomodulation (PBM) Tx using the LumiThera Valeda® Light Delivery System in dry AMD.

Methods:
LIGHTSITE III (NCT04065490) is a prospective, double-masked, randomized, sham-controlled, parallel group, multi-center study to assess the safety and efficacy of PBM in subjects with dry AMD. Target enrollment was approximately 96 subjects and 144 eyes. Subjects are treated with six series of PBM/Sham treatments (3x per week/3 weeks) delivered over a 24-month period with a 13-month interim analysis. PBM consists of low-level light exposure to selected tissues resulting in positive effects on mitochondrial output and improvement in cellular activity. Valeda is used to deliver multiwavelength PBM treatment consisting of 590, 660 and 850 nm of light. Subjects are assessed for clinical and safety outcomes (i.e., best-corrected visual acuity (BCVA), low-luminance BCVA, contrast sensitivity, reading speed, color vision, VFQ-25 and perimetry). Independent OCT, FAF and color fundus imaging outcomes at selected timepoints are analyzed by a masked imaging center.

Results:
A total of 148 eyes from 100 subjects with dry AMD have been enrolled and randomized in a 2:1 design (PBM:Sham). The majority of subjects are female (n = 68; 68.0%) compared to male (n = 32; 32.0%). Most subjects are Caucasian (n = 99, 99.0%). The average age at enrollment is 75 years and mean time since dry AMD diagnosis is 4.9 years. COVID-19 interference has been minimal and has not significantly impacted subject enrollment or retention to date. Clinical and anatomical outcome data from the interim analysis conducted at Month 13 (following 4 series of Tx) will be presented. LIGHTSITE III provides the largest randomized controlled trial dataset to date evaluating the effects of PBM in dry AMD. All patients have completed the 13-month time point for initial efficacy. Results from the 21-month time point are expected Q4 of 2022.

Conclusion:
PBM therapy may offer a novel treatment strategy with a unique mechanism and modality for patients with dry AMD.

IRB APPROVAL Yes



LIGHTSITE III Study Design. Intermediate dry AMD subjects were randomized in a 2:1 fashion (PBM: Sham). The 24-month study included six series of treatment (Tx) delivered every four months. An interim analysis was conducted at Month 13 after four series of treatment.

LIGHTSITE III Study Design

7/16/2022 10:27 am

Dry AMD 3 Symposium

Preliminary Results from a Phase I/II Gene Therapy (FOCUS) of Subretinally Delivered GT005 in Patients With Geographic Atrophy Secondary to Age-Related Macular Degenerationatients with Geographic Atrophy Secondary to Age-related Macular Degeneration

- Szilárd Kiss, MD
- Robert MacLaren, FRCS, FRCOph
- Jeffrey Heier, MD
- David Steel, MBBS, FRCOphth, MD(Res)
- Paulo Stanga, MD
- Tsveta Ivanova
- Jared Nielsen, MD, MBA
- Sobha Sivaprasad, FRCOphth
- Clare Bailey, BM BCh MD FRCP FRCOphth
- Peter Issa
- Luisa Mendonca
- James Francis, PhD
- Darin Curtiss
- Jane Hughes
- Nadia Waheed

Objective:
The safety and dose response of a subretinally delivered AAV2 Vector encoding Complement Factor I, GT005, in patients with geographic atrophy secondary to age-related macular degeneration was evaluated in this first in human clinical trial.

Purpose:
To investigate safety and dose response of subretinally delivered GT005, an investigational recombinant adeno-associated viral (AAV2) vector encoding Complement Factor I (CFI), for treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

Methods:
FOCUS (NCT03846193) is an open-label multicenter study consisting of 4 parts: dose-escalation of GT005 delivered via transvitreal subretinal injection (TVSI), dose-expansion with TVSI, dose-escalation of GT005 delivered using the Orbit subretinal delivery system (Orbit SDS), dose-expansion with the Orbit SDS. All patients had bilateral GA at baseline and received a single subretinal administration of GT005 in the study eye. Primary endpoint is safety of GT005 over 48 weeks, with secondary endpoints including anatomical/functional outcomes and changes in complement protein expression in the vitreous humor. Part 1 explored 3 GT005 dose levels (2E10, 5E10 and 2E11 vector genomes [vg]) delivered via TVSI, Part 2 further explored dose-levels that were shown to be safe and tolerable in Part 1. Interim data from the TVSI cohorts are presented herein.

Results:
On December 2021, enrolment was complete for Parts 1 and 2 and 31 patients had received GT005 via TVSI, 11 in Part 1 and 20 in Part 2, with a mean follow-up of 51.8 weeks (range: 2.3 to 144.3). At baseline, the mean age was 80.3 years (68 to 93), 71.0% (22/31) were women, and 96.8% (30/31) were white. All 3 dose levels of GT005 delivered via TVSI were well-tolerated, with no dose-related trends in the frequency and type of reported adverse events (AEs) to date. Of the 48 treatment-emergent ocular AEs in 21 patients, 29 occurred in the study eye only and 10 were bilateral. From the AEs affecting the study eye, majority were mild (30/39) and considered unrelated to GT005 (37/39). From the moderate AEs affecting the study eye (9/39), 5 were related to worsening of cataracts, and 1 described the conversion to choroidal neovascularization. No severe or serious ocular AEs were reported. There were no signs of GT005-related inflammation. Biomarker analysis of vitreous including complement factors at baseline and follow-up will be presented.

Conclusion:
GT005 had a positive safety profile at 2E10 to 2E11vg with no signs of GT005-related inflammation.

IRB APPROVAL Yes

7/16/2022 10:33 am

Dry AMD 3 Symposium

Multicenter Randomized Sham-Controlled Double-Masked Phase 2b Clinical Trial of Multi-Characteristic Opsin in Patients With Advanced Retinitis Pigmentosa

- Peter Kaiser, MD FASRS
- Subrata Batabyal, PhD
- Sanghoon Kim, PhD
- Michael Carlson, Bachelor's in BioMedical Engineering
- Ananta Ayyagari, PhD
- Kissaou Tchedre, PhD, MBA
- Sai Chavala, MD
- Samarendra Mohanty, PhD

Objective:
To evaluate the safety and efficacy of a multi-characeristic opsin (MCO) that is activated at ambient light levels delivered by intravitreal AAV2 gene therapy in advanced retinitis pigmentosa patients.

Purpose:
Retinitis pigmentosa leads to progressive photoreceptor degeneration with profound loss of vision in advanced stage. By photosensitizing higher order neurons, optogenetic therapy offers the potential for vision restoration in these patients. Since this approach focuses on disease phenotype versus a specific genotype deficit, it is applicable to a wide patient population. Existing optogenetic tools utilize opsins that do not generate adequate electrical current in ambient light requiring an external device for stimulation. Further, evaluation of efficacy in such advanced RP patients require development and validation of novel endpoints.

Methods:
Multi-Characteristic Opsin (MCO) is an engineered opsin that is activated at ambient light levels, thereby avoiding phototoxicity. Targeting bipolar cells with MCO allows potential for greater spatial resolution. AAV2 was used to deliver *MCO* in advanced retinitis pigmentosa subjects. Subjects received prophylactic oral steroids prior to a single intravitreal injection of AAV2-*MCO* (vMCO). Safety of different intravitreal vMCO doses is evaluated using OCT, slit lamp and indirect ophthalmoscopy. Novel end points such as Y-Mobility Test (YMT) and Low-Vision Multi-Parameter Test (LVMPT) utilizing multiple luminance levels are deployed to evaluate efficacy.

Results:
The eyes with better pretreatment visual acuity could perform YMT at lower light intensity levels without hitting obstacles placed along the course. Approximately 50% low-vision subjects at multiple centers passed the screening criterion requiring failing of the YMT at 1 lux. The three-dimensional shape recognition by LVMPT allowed measurement of accuracy in shape recognition at different light intensities for each eye, which was found to be dependent on vision level. The two different vMCO doses were well tolerated with no reported serious adverse events. Ocular adverse events include minimal inflammation and slight intraocular pressure rise in few subjects, controlled via topical medication without requiring any surgery.

Conclusion:
All the vMCO doses were well tolerated with no serious adverse events. The novel endpoint measurements in low-vision subjects in a randomized and masked manner provide opportunity to evaluate the efficacy of the optogenetic vMCO monotherapy in improving functional vision in advanced RP patients.

IRB APPROVAL Yes

7/16/2022 10:49 am

Dry AMD 3 Symposium

Baseline Characteristics in the Phase 2 GOLDEN Study of IONIS-FB-LRx, an Investigational Antisense Oligonucleotide Designed to Treat AMD-Associated Geographic Atrophy

- Glenn Jaffe, MD
- Qingqing Yang
- Terry Barrett
- Sascha Fauser
- David Kent
- Corinna Wentzel
- April Flora
- Richard Geary
- Eugene Schneider
- Mark Lomax
- Michael McCaleb

Objective:
To determine the baseline characteristics in the Phase 2 GOLDEN study of IONIS-FB-L_{Rx}, an investigational antisense oligonucleotide designed to treat AMD-associated GA and whether they are comparable to other GA trials

Purpose:
IONIS-FB-L_{Rx} is a novel investigational antisense oligonucleotide that is designed to target liver factor B in the complement cascade. In a phase 1 study, it was well-tolerated, reduced systemic factor B levels and selectively lowered the alternative complement pathway. The pre-clinical and phase 1 data supported further development. A phase 2 study, Golden, has been initiated, and is designed to determine if IONIS-FB-L_{Rx} reduces the GA growth rate in eyes with AMD. Herein, the baseline study characteristics are described.

Methods:
Subjects $\geq$ 50 years old with study eye AMD-associated GA, BCVA > 35 letters, and GA area GA area $\geq$1.9 mm^2 to $\leq$17 mm^2 without macular neovascularization have been enrolled. Two screening visits were performed 3 months apart to assess initial growth rate for randomization stratification.

Results:
Based on analysis of the first 100 subjects, the median participant age is 76 and approximately 58% are female. Approximately 67% of GA lesions are subfoveal, 65% are multifocal, 95% are bilateral, and the mean baseline GA area is 7.6mm^2. The mean annualized GA area change is approximately 2.0 mm^2during the screening period. The growth rate was fastest for non-foveal centered multifocal lesions and slowest for unifocal non-foveal centered lesions. The baseline BCVA was more than 2 lines better for multifocal lesions than unifocal lesions, and, as expected, was worse for foveal centered lesions on average.

Conclusion:
The IONIS-FB-L_{Rx} phase 1 study informed the phase 2 trial design and supports the proposed mechanism of action to suppress complement activation by

inhibiting factor B. The baseline characteristics and annualized growth rates were generally similar to previously reported studies including Chroma/Spectri, GATHER 1, Proxima A, and Derby/Oaks. The GOLDEN study is currently ongoing.

IRB APPROVAL Yes

Caricature of antisense oligonucleotide hybridized to mRNA

7/16/2022 10:55 am

Dry AMD 3 Symposium

Early Progression of Atrophy in AMD: Post Hoc Analysis From the GATHER1 Study

- David Lally, MD
- Jeffrey Heier, MD
- SriniVas Sadda, MD
- David Eichenbaum, MD, FASRS
- Carl Danzig, MD

Objective:
This post hoc analysis of GATHER1 examined features of early atrophy progression in patients with geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

Purpose:
Identification of predictors of early atrophy in individuals with GA is important for the development of early interventions for AMD.

Methods:
The GATHER1 study was a prospective, randomized, double-masked, phase 2/3 trial that evaluated avacincaptad pegol compared with sham in 286 patients with nonfoveal-centered GA secondary to AMD. The study protocol was approved by the ethics committee or institutional review board of each site. Patients with choroidal neovascularization in either eye were excluded. GA progression was evaluated based on the change in GA lesion area over 6, 12 and 18 months. A post hoc analysis was conducted to evaluate predictors of progression from iRORA to cRORA (i.e., incomplete to complete retinal pigment epithelium and outer retinal atrophy) and progression from drusen to iRORA and/or cRORA. The post hoc analysis examined optical coherence tomography (OCT) regions >500 µm from the border of the GA lesion(s).

Results:
The least squares mean change from baseline to Month 18 in square-root GA lesion area was 0.599 mm in sham-treated patients vs 0.430 mm in avacincaptad pegol 2 mg–treated patients (28% reduction; P <.0014). In the avacincaptad pegol 2 mg group, compared with the sham group over 18 months, a smaller proportion of patients progressed from iRORA to cRORA (20% vs 42%, respectively) and from drusen to iRORA or cRORA (8% vs 27%, respectively). Additional analyses on predictors of early atrophy progression in patients with GA secondary to AMD are being evaluated to determine features potentially associated with disease progression. The most frequently reported ocular adverse events with avacincaptad pegol were related to the injection procedure and there were no reports of avacincaptad pegol-related inflammation or discontinuation after 18 months of administration.

Conclusion:
In this post hoc analysis of the GATHER1 trial, avacincaptad pegol 2 mg was associated with a greater numerical reduction compared with sham in the progression of iRORA to cRORA, and in the progression of drusen to iRORA or cRORA over 18 months.

IRB APPROVAL Yes

7/16/2022 10:59 am

Dry AMD 3 Symposium

Relationship Between Number of Intermediate-Large Drusen and Geographic Atrophy Lesion Growth Rate in the Sham Groups of the DERBY, OAKS, and FILLY Trials

- Eleonora Lad, MD, PhD
- Nikolas London, MD, FACS, FASRS
- Daniel Jones
- Caleb Bliss, PhD
- Ramiro Ribeiro, PhD
- Larry Singerman

Objective:
To investigate the impact of the number of intermediate or large drusen at baseline on the rate of GA lesion growth in the sham arms of the Phase 3 OAKS (NCT03525613) and DERBY (NCT03525600), and Phase 2 FILLY (NCT02503332) trials of pegcetacoplan in patients with GA secondary to age-related macular degeneration.

Purpose:
As previously reported, the primary endpoint was met in OAKS and FILLY, and narrowly missed in DERBY. Imbalances in several baseline disease characteristics were identified that may have contributed to differences in observed treatment effects across studies. We report a post-hoc analysis of the impact of intermediate or large drusen number on GA lesion growth.

Methods:
The number of small (<63 µm), intermediate (63–125 µm), or large (≥125 µm) drusen in the study eye was quantified for patients in OAKS, DERBY, and FILLY based on color fundus pictures. Imbalances in the number of patients with >20 intermediate or large drusen at baseline were identified across study arms in the DERBY and FILLY studies. To understand the relationship between number of intermediate or large drusen and rate of GA progression, lesion growth was analyzed for sham patients with ≤20 intermediate or large drusen vs those with >20 intermediate or large drusen at baseline.

Results:
Across OAKS, DERBY, and FILLY, GA lesions in sham patients with ≤20 intermediate or large drusen (N=102, 96, and 48, respectively) at baseline grew at a faster rate than those with >20 intermediate or large drusen (N=103, 98, and 31, respectively). The least squares mean change (95% confidence interval) in GA lesion size from baseline to Month 12 in patients with >20 intermediate or large drusen was less than for those with ≤20 intermediate or large drusen (1.77 [1.57, 1.96] mm^2 vs 2.21 [1.96, 2.46] mm^2 in OAKS, 1.65 [1.40, 1.90] mm^2 vs 2.36 [2.08, 2.63] mm^2 in DERBY, and 1.84 [1.34, 2.34] mm^2 vs 2.28 [1.86, 2.70] mm^2 in FILLY, respectively). Notably, the DERBY sham arm was enriched for patients with >20 intermediate or large drusen at baseline, potentially predisposing patients randomized to sham in the DERBY study to progress more slowly.

Conclusion:
The impact of the number of intermediate or large drusen on GA lesion growth is an important finding. Across all three large, well-controlled studies, a lower number of intermediate or large drusen at baseline was linked to a higher rate of GA lesion growth in patients randomized to sham treatment. These results are in agreement with prior findings of retinal pigment epithelium drusen complex thinning in a pre-atrophic stage and highlight the need for further research into disease mechanisms relating drusen to atrophic lesion progression.

IRB APPROVAL Yes

7/16/2022 11:03 am

Dry AMD 3 Symposium

Could We Save Lives With Retinal Imaging by Finding Undetected High-Risk Vascular Diseases?

- R THEODORE SMITH, MD PhD

Objective:
Find the connection between age-related macular degeneration, cardiovascular disease and stroke

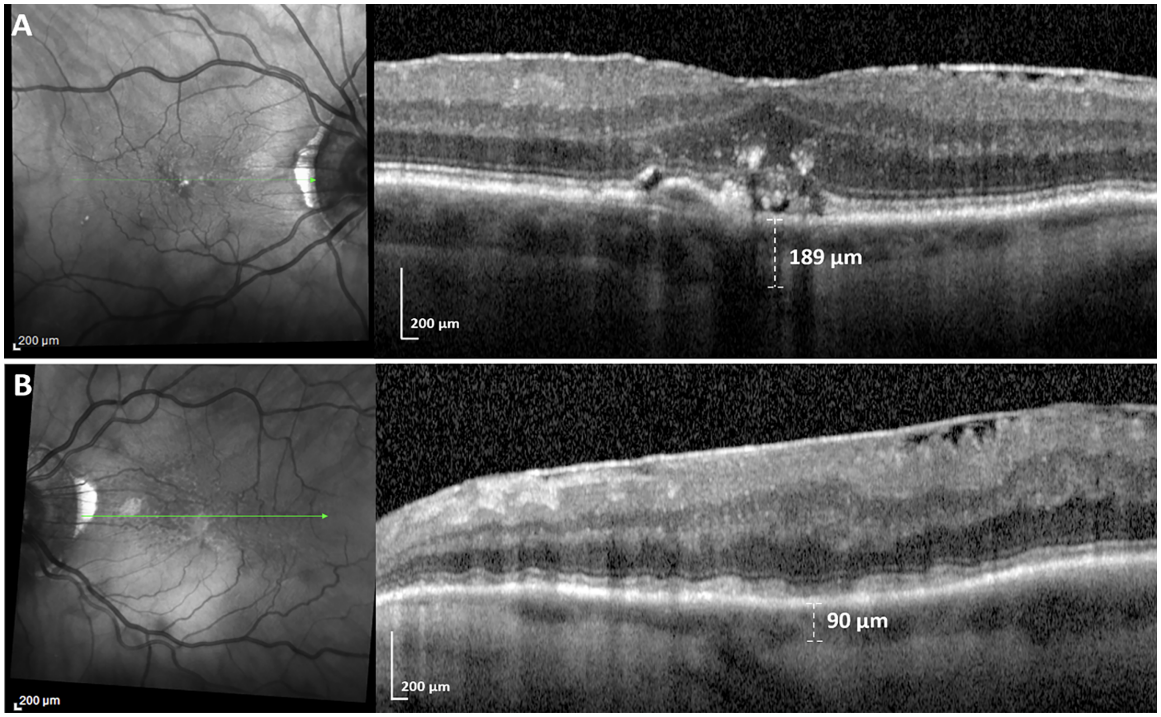
Purpose:
Undetected vascular diseases still claim unacceptably many lives, especially among women and underserved populations. We will demonstrate a new, specific strong association of certain common, high-risk vascular diseases (HRVDs) with the subretinal drusenoid deposit (SDD) phenotype of age-related macular degeneration (AMD), not with soft drusen (SD).

Methods:
Two hundred unselected AMD patients, ages 51 to 100, 121 females, 79 males, were prospectively recruited from 2 retinal centers. Other retinal disorders were excluded. Volume spectral-domain optical coherence tomography (SD-OCT), autofluorescence (AF) and Near-infrared reflectance (NIR) imaging, health history questionnaires, and lipid profiles were obtained. Patients were assigned by Health questionnaires into those with or without these HRVDs : severe cardiac valve defect (e.g., aortic stenosis), myocardial defect (myocardial infarction, congestive heart failure), and carotid stroke or transient ischemic attack (TIA) with severe carotid stenosis. Masked readers of retinal imaging assigned patient into two groups, SDD (with or without soft drusen) and SD (soft drusen only). Chi-square testing was used for categorical variables. We built a multivariate risk model to predict HRVD as a function of SDD status and other covariates.

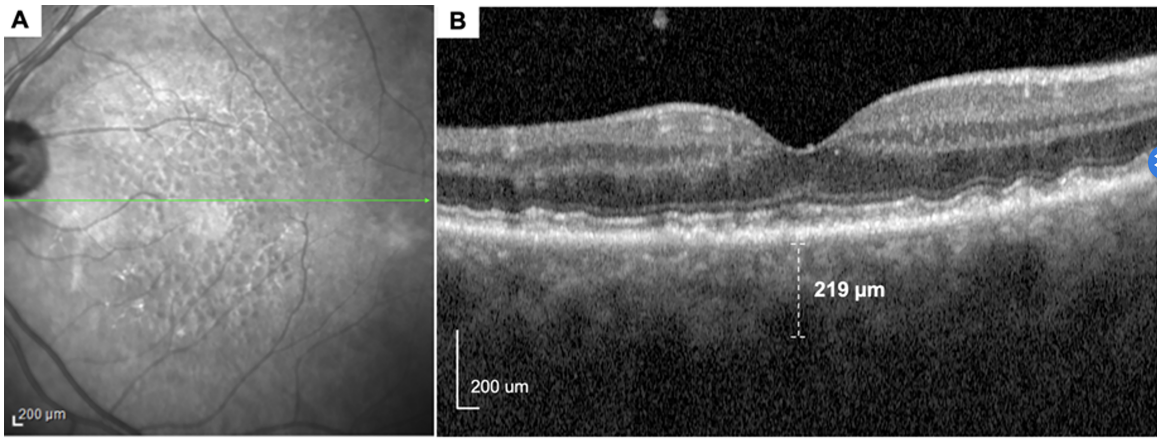
Results:
The prevalence of HRVD was 41.2% (40/97) and 6.8% (7/103) in the SDD and SD groups respectively (p =0.000000009), OR 9.62, 95% Confidence intervaI (CI), 4.04 – 22.9. Differences in the prevalence of HRVD sub-types in these groups were also significant: Valve defects 14/97 in SDD vs. 3/103 in SD (p = 0.0035), myocardial defects 16/97 vs. 3/103 (p = 0.0011), stroke/TIA 10/97 vs. 1/103 (p = 0.0038). Data modeling found a serum HDL < 62 mg/dL (Y/N) strongly predicted HRVD in our total AMD cohort (p = 0.0046). Risk modeling found that 85% of all subjects that had both SDDs and an HDL<62 suffered from some high-risk vascular disease (95% CI, 77.5 % - 90.7 %).

Conclusion:
HRVDs were significantly more prevalent in subjects with SDDs than those with SD only. This suggests that SDDs specifically are a biomarker of these life-threatening systemic vasculopathies Further, these disorders all share compromised ocular perfusion. A direct vascular mechanism for SDDs therefore seems likely and merits investigation. Most important, we might save lives by detecting occult HRVD with retinal imaging and serum risk factors.

IRB APPROVAL Yes



Left carotid stenosis A. OD few drusen. B. OS myriad SDD, thin choroid.



Aortic Valve Stenosis. No atherosclerosis. SDD OS, on InfraRed and SD-OCT