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The Association of Statin Use with Age-Related Macular Degeneration Progression The Age-Related Eye Disease Study 2 Report Number 9

Shaza N. Al-Holou, MD[1], **William R. Tucker, MBBS, BSc**[2], **Elvira Agrón, MA**[1], **Traci E. Clemons, PhD**[3], **Catherine Cukras, MD, PhD**[1], **Frederick L. Ferris III, MD**[1], and **Emily Y. Chew, MD**[1] **For The Age-Related Eye Disease Study 2 Research Group**

[1]Clinical Trials Branch, Division of Epidemiology and Clinical Applications, National Eye Institute/National Institutes of Health, Bethesda, Maryland [2]Laboratory of Immunology, National Eye Institute/National Institutes of Health, Bethesda, Maryland [3]The EMMES Corporation, Rockville, Maryland

Abstract

Objective/purpose—To evaluate the association of statin use with progression of age-related macular degeneration (AMD).

Design—Preplanned, prospective cohort study within a controlled clinical trial of oral supplementation for age-related eye diseases.

Subjects—Age-Related Eye Disease Study 2 participants, aged 50 to 85 years.

Methods—Factors, including age, gender, smoking status, aspirin use, and history of diabetes, hypertension, heart disease, angina, and stroke, all known to be associated with statin use, were included in a logistic regression model to estimate propensity scores for each participant. Age-adjusted proportional hazards regression models, with and without propensity score matching, were performed to evaluate the association of statin use with progression to late AMD. Analyses were also performed adjusting for the competing risk of death.

Main Outcome Measures—Baseline and annual stereoscopic fundus photographs were assessed centrally by masked graders for the development of late AMD, either neovascular AMD or geographic atrophy (GA).

Results—Of the 3791 participants (2462 with bilateral large drusen and 1329 with unilateral late AMD at baseline), 1659 (43.8%) were statin users. The overall analysis, with no matching of

Correspondence: Emily Y. Chew, MD, National Eye Institute, National Institutes of Health, Building 10, CRC Room 3-2531, 10 Center Drive, MSC 1204, Bethesda, MD 20892-1204, echew@nei.nih.gov.

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propensity scores and no adjustment for death as a competing risk, showed that statin use was not associated with progression to late AMD (hazard ratios [HR] of 1.08, 95% confidence intervals [CI] of 0.83–1.41, P=0.56). When matched for propensity scores and adjusted for death as a competing risk, the result was not statistically significant with HR: 0.81, 95% CI: 0.55–1.20, P=0.29. Further subgroup analyses of persons with or without late AMD at baseline to the various components of late AMD (neovascular, central geographic atrophy, or any geographic atrophy) also showed no statistically significant association of statin use with progression to AMD.

Conclusions—Statin use was not statistically significantly associated with the progression to late AMD in the AREDS2 participants, and these findings are consistent with the findings in the majority of previous studies. Statins have been demonstrated to reduce the risks of cardiovascular disease, but our data do not provide evidence of a beneficial effect on slowing AMD progression.

Introduction

Age-related macular degeneration (AMD), a progressive disease that results in central vision loss, is the leading cause of blindness in persons over the age of 60 years in the United States.[1] The pathogenesis of AMD is unknown. Associated risk factors include increasing age, cigarette smoking, hypertension, increased body mass index, lower educational level, presence of lens opacities, and others[2–5]. The use of antioxidant vitamins and minerals, known as the Age-Related Eye Disease Study (AREDS) supplement, reduces the risk of progression to late AMD, suggesting that oxidative stress may play a role in AMD.[6] The association of genetic polymorphism in the complement pathway involving *complement factor H* and many other complement factors suggest that local or systemic inflammatory pathways may also be important in the pathogenesis of AMD.[7–11] This potential inflammatory pathway is further supported by the statistically significant association of elevated serum C-Reactive Protein (CRP) with AMD in the Women's Health Study, Rotterdam Study, and AREDS.[4,7,8,12,13]

Statins, or 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, currently the most commonly prescribed lipid-lowering class of drugs,[14] are proven to lower serum lipids and reduce cardiovascular morbidity and mortality.[15] The main role of statins is to inhibit 3-hydroxy-3-methyl-glutaryl-CoA reductase in the liver, down-regulating lipid metabolism.[16] However, this class of drugs has exhibited unexpected anti-inflammatory, antioxidative, and anti-angiogenic effects.[17–20] Pathological studies in AMD have also demonstrated the accumulation of lipids in Bruch's membrane similar to the atherosclerotic changes of cardiovascular disease[21–23], suggesting that statins might have an effect on AMD. Previous observational studies demonstrated that statin use was associated with a protective effect on AMD[24–33]; however, other studies were not confirmatory.[34–37] Lipid lowering with 40 mg of simvastatin in a small proof of concept study, was associated with a possible beneficial effect especially for those persons with bilateral intermediate AMD and those with genotype of the risk alleles for *Complement Factor H (CFH)* for progression to late AMD.[38]

The Age-Related Eye Disease Study 2 (AREDS2) was a prospective, multi-centered clinical trial that tested oral supplements of omega-3 fatty acids and lutein/zeaxanthin for the treatment of AMD and cataract.[39] These participants were followed for a median of 5 years

and the observational data from this study provided the opportunity to investigate the effect of statins on progression to late AMD.

Methods

Study population

The study design for AREDS2 is detailed in a previous report but briefly summarized here.[39] Between 2006 and 2008, 4203 participants ranging from 50 to 85 years of age were enrolled at 82 retinal specialty clinics in the United States. At enrollment, participants were included if they had either bilateral large drusen or unilateral late AMD in one eye and large drusen in the fellow eye. Institutional review board approval was obtained at each clinical site, and written informed consents for the research were obtained from all study participants.

The AREDS2 participants were randomly assigned to placebo, lutein/zeaxanthin, docosahexaenoic acid (DHA) plus eicosapentaenoic acid (EPA) or the combination. At the baseline and each annual study visits, comprehensive eye exams were performed, including stereoscopic fundus photographs by certified photographers. These images were assessed by trained graders using a standardized protocol at the University of Wisconsin Fundus Photograph Reading Center. The main study outcome is the development of late AMD as graded from annual fundus photographs.

In AREDS2, late AMD was defined as having at least 2 features of neovascularization including serous detachment of the sensory retina, hemorrhage, retinal pigment epithelial detachment, fibrous tissue, or hard exudates; or geographic atrophy of an area of 360 μm or greater in diameter, involving the center of the macula; or a history of treatment for neovascular AMD. In this study we used the recently recommended and more inclusive definition of “late AMD”, which includes any definite GA in the definition, not just central GA.[12]

Questionnaires administered at the baseline and annual study visits were used to collect information on nutrition, medications, adverse events, and treatment compliance, among others. Telephone calls were performed twice in the first year of randomization and annually thereafter to collect information about adverse events as well as treatment for AMD and incidence of cataract surgery between the study visits.

Statistical methods

We included only participants who had no missing values to evaluate the effect of statins on eyes with intermediate AMD on the progression to late AMD. Baseline patient characteristics were compared between statin users and non-users using the t-test for continuous variables (age) and χ^2 test for categorical variables including gender, race, education level, smoking status, diabetes, non-steroidal anti-inflammatory drug (NSAID) use, acetaminophen use, hypertension (defined as >140 mmHg systolic and/or >90 mmHg diastolic blood pressures), congestive heart failure, coronary heart disease, angina, history of myocardial infarction (MI), and history of stroke.

Propensity score approach can be used to reduce or eliminate the effects of confounding when using observational data (e.g., statin use) to estimate treatment effects.[40] In order to reduce the effects of confounding for statin use, we used logistic regression to estimate propensity scores, which range from zero to one and indicate the probability that a participant is a statin user, based upon the risk factors listed above. Values closer to one indicate a higher likelihood of a participant using statins. After developing the propensity score for statin users and non-users, we matched statin users to non-users using the propensity scores in order to mimic characteristics of a controlled clinical trial.[41] Applied in the context of statin usage in AREDS2, propensity matching approach consisted of forming match sets of statin user and non-statin users who share a similar value for the propensity score. Baseline characteristics were included in the matching model which excluded data that could not be matched.

This propensity score matching is a second method to attempt to control for the confounding from the variables in the propensity score that are both associated with statin use and with progression of AMD. The matching was done using a Greedy Matching Technique (Parsons LS. Reducing Bias in a Propensity Score Matched-Pair Sample Using Greedy Matching Techniques. Paper presented at: Proceedings of the Twenty-Sixth Annual SAS Users Group International Conference, 2001; Long Beach, CA).

Age-adjusted proportional hazards regression models were used to evaluate the effect of statin use on progression to any late AMD, including neovascular AMD and GA, in the entire cohort. Additional analyses were conducted separately for the development of neovascular AMD and GA. The competing risk of death was taken into account using the macro of Kohl and Heinze to fit a proportional sub-distribution hazards model.[42,43] Hazard ratios (HRs) were calculated with 95% confidence intervals (CIs) with $P < 0.05$ being considered significant for all analyses.

Analyses were performed both matching and not matching statin users and non-users by the propensity scores, in addition to adjusting for death as a competing risk. Analyses were also performed separately for the two groups: participants with bilateral large drusen and participants with unilateral late AMD. No adjustments were made for multiplicity of analyses. All analyses were conducted using SAS version 9.3 (SAS Institute Inc).

Results

Of the 3791 participants included in this analysis, progression to late AMD by the end of the study occurred in 1650 (869 any geographic atrophy, 479 central geographic atrophy, and 998 neovascular AMD). Each participant could have any combination of the late forms of AMD. Associations of possible confounders with statin use are shown in Table 1. The result from proportional hazards regression model on the entire cohort, adjusting for the propensity scores, age, baseline AMD status, showed no association of statin use with the development of late AMD (hazard ratios [HR]: 1.08, 95% confidence interval [CI] of 0.83–1.41, P=0.56) (Table 2). Similar models were developed separately for the association of statin use with the components of late AMD: any GA, central GA and neovascular AMD. Statin use was

not statistically significantly associated with the development of any of these outcomes, with or without accounting for the competing risk of death (Table 2).

Matching occurred with both participants in the bilateral large drusen group (n=1546), both in the unilateral AMD group (n=944), and one in the bilateral large drusen group and one in the other group (n=22). The baseline characteristics of these participants are displayed in Table 3. The previously statistically significant differences in the covariates, comparing statin users and the statin non-users, are no longer statistically significant, indicating the propensity matching has controlled for confounders. One problem with the propensity score matching is that although the age between statin users and non-users was similar as a whole, there was a large range in the age difference for individual pairs of propensity-matched participants, ranging from 0–30 years. Because older age is highly associated with an increased risk of development of AMD ($P < 0.0001$ for any AMD, any GA, central GA, and neovascular AMD), we adjusted the propensity score matched proportional hazards regression models for age.

Results of the propensity score matched proportional hazards regression models are shown in Table 4. The only statistically significant association found was for the outcome of any late AMD in the subgroup of patients with large drusen in both eyes in the model accounting for the competing risk of death: HR: 0.53, 95% CI 0.31–0.89, P=0.02.

Discussion

The results from the observational data from AREDS2 showed no statistically significant effect of statin use on progression to late AMD in persons at risk. The results for the endpoints of neovascular AMD or geographic atrophy were also very similar. Compared with previous studies evaluating this association, the AREDS2 had one of the largest numbers of persons with late AMD, and greater than 40% of the AREDS2 participants were statin users.

Following the initial report of the inverse association of statins with AMD by Hall et al,[26] many of the subsequent reports suggested no statistically significant beneficial or harmful effect of statin use on the progression of AMD (Table 5). Some of the previous reports included large retrospective studies, but they were limited by the lack of validated methods to determine the diagnosis of late AMD because the diagnosis was based upon medical record reviews instead of the fundus photographs that were obtained in AREDS2.[25,31,34,44] Another prospective study that had fundus photographs for detecting AMD lacked sufficient sample size because of small numbers of late AMD outcomes and participants taking statin.[32]

The Complications of AMD Prevention Trial, the Rotterdam Study, and a study pooling three different prospective studies all found no effects of statins on AMD progression.[35,37,45] These prospective studies also had fundus photographs that were graded with standardized protocol. However, these studies were again limited by the lack of large numbers of either statin users or participants with late AMD. The use of statins expanded considerably after the publication of the Scandinavian Simvastatin Survival Study (1994),

which demonstrated the safety and efficacy of simvastatin. Subsequently, the use of statins increased markedly, as reflected in the high proportion of AREDS2 participants taking statins two decades later.[15,46]

This current AREDS2 study has limitations. We lacked information on former statin use, dosages of statins, and exact duration of treatment, although our annual questionnaire results suggested that perhaps 85% of these participants were on a statin for the average 5 year follow-up in this study. While the AREDS2 participants were part of a controlled randomized clinical trial, the data used for analyses were observational and subject to confounding. In order to control for confounding variables, common in observational studies, we used propensity scores and subsequent matching, although it was difficult to match for age by the propensity score. Because the risk factors for AMD are similar to risk factors for cardiovascular disease and statin use, it is difficult to tease out the effects of confounding entirely. We also lacked the power to evaluate the potential of statin therapy to reduce the progression to early AMD as we did not have persons with no AMD in this study population. Such a study would require an extremely large number of participants.

Ideally, the best way to evaluate the effects of statins on the progression to late AMD would be a randomized controlled clinical trial. However, randomizing people to statin use is not possible, at least for those with elevated lipids, because statin use has been demonstrated to be effective in this group. Although randomly assigning persons with normal lipid levels to statins would be feasible, there are both ethical issues and concern related to compliance for persons developing cardiovascular risk factors during the study that make this problematic. For now, the totality of evidence would suggest that statins have little influence on progression to late AMD. Because of the beneficial effects of statins in reducing the risk of cardiovascular disease and mortality, persons with AMD should be encouraged to take statins when medically indicated and to be monitored regularly for progression of AMD regardless of statin use.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix 1 The Age-Related Eye Disease Study 2 (AREDS2) Research Group

(NEI) National Eye Institute

Emily Y. Chew, MD, Study Chair

Frederick L. Ferris III, MD, NEI Clinical Director

John Paul SanGiovanni, ScD, Project Officer

Elvira Agrón, MA, Statistician

Coordinating Center, The EMMES Corporation

Traci Clemons, PhD, Principal Investigator

Anne Lindblad, PhD, Co-Investigator

Robert Lindblad, MD, Chief Medical Officer

Nilay Shah, MD, Medical Monitor

Robert Sperduto, MD, Consultant

Wendy McBee, MA, AREDS2 Project Director

Gary Gensler, MS, Statistician

Molly Harrington, MS, Statistician

Alice Henning, MS, Genetics Project Director

Katrina Jones Data Manager

Kumar Thotapally Programmer

Diana Tull, MA, CPS, Administrative Coordinator

Valerie Watson Systems Coordinator

Kayla Williams Data Manager

Christina Gentry, Cognitive Function Specialist

Francine Kaufman Cog. Function/Data Mgr

Chris Morrison, Cognitive Function Specialist

Elizabeth Saverino Protocol Monitor

Sherrie Schenning Protocol Monitor

Fundus Photograph Reading Center

Barbara Blodi, MD, Co-PI

Ronald P. Danis, MD, Principal Investigator

Matthew Davis, MD, Co-PI

Amitha Domalpally Co-Director

Kathy Glander Research Project Mgr

Gregory Guilfoil Research Project Mgr

Larry D. Hubbard, MA, Assoc. Dir. Grading

Kristine Johnson Inventory Assistant

Ronald Klein, MD, Co-PI

Barbara Nardi Asst. to Ron Danis

Michael Neider Assoc. Dir. Photography

Nancy Robinson Assoc. Dir Operations

Eileen Rosensteel Inventory Assistant

Hugh Wabers Photographer

Grace Zhang AREDS2 Data Manager

(001) Vision Research Foundation

Alan J. Ruby, MD, (Site PI)

Antonio Capone, Jr., MD, (Ophthalmologist)

Bawa Dass, MD, (Ophthalmologist)

Kimberly Drenser, MD, PhD, (Ophthalmologist)

Bruce R. Garretson, MD, (Ophthalmologist)

Tarek S. Hassan, MD, (Ophthalmologist)

Michael Trese, MD, (Ophthalmologist)

George A. Williams, MD, (Ophthalmologist)

Jeremy Wolfe, MD, (Ophthalmologist)

Tina Bell (Clinic Coordinator)

Mary Zajechowski (Clinic Coordinator)

Dennis Bezaire (Photographer)

Fran McIver (Photographer)

Anthony Medina, CRA, (Photographer)

Jackie Pagett (Photographer)

Stephanie Hatch Smith (Photographer)

Lynn Swartz (Photographer)

Tom Treuter (Photographer)

(002) Charlotte Eye Ear Nose and Throat Associates

Andrew Antoszyk, MD, (Site PI)

Justin Brown, MD, (Ophthalmologist)

David J. Browning, MD, PhD, (Ophthalmologist)

Walter Holland, MD, (Ophthalmologist)

Angella Karow (Clinic Coordinator)

Kelly Stalford (Clinic Coordinator)

Angela Price, MPH, CCRC, Dir. Of Research

Sarah Ennis (Ophthalmic Technician)

Sherry Fredenberg (Ophthalmic Technician)

Jenna Herby (Ophthalmic Technician)

Uma Balasubramaniam (Photographer)

Loraine Clark (Photographer)

Donna McClain (Photographer)

Michael McOwen, CRA, (Photographer)

Lynn Watson (Photographer)

(003) Devers Eye Institute

Michael Klein, MD, (Site PI)

Steven T. Bailey, MD, (Ophthalmologist)

Thomas J. Hwang, MD, (Ophthalmologist)

Andreas Lauer, MD, (Ophthalmologist)

J. Timothy Stout, MD, PhD, FACS, (Ophthalmologist)

Patty McCollum (Clinic Coordinator)

Milt Johnson (Photographer)

Patrick B. Rice CRA (Photographer)

(004) Massachusetts Eye and Ear Infirmary

Ivana Kim, MD, (Site PI)

John Loewenstein, MD, (Ophthalmologist)

Joan Miller, MD, (Ophthalmologist)

Lucia Sobrin, MD, (Ophthalmologist)

Lucy Young, MD, PhD, (Ophthalmologist)

Jacqueline Sullivan (Clinic Coordinator)

Patricia Houlihan (Assistant Coordinator)

Linda Merry, RN, (Assistant Coordinator)

Ann Marie Lane (Office Manager)

Ursula Lord Bator, OD, (Ophthalmic Technician)

Claudia Evans, OD, (Ophthalmic Technician)

Sarah Brett (Photographer)

Charleen Callahan (Photographer)

Marcia Grillo (Photographer)

David Walsh (Photographer)

Kamella Lau Zimmerman (Photographer)

(005) Texas Retina Associates

Gary Edd Fish, MD, JD, (Site PI)

Rajiv Anand, MD, (Ophthalmologist)

Lori E. Coors, MD, (Ophthalmologist)

Dwain G. Fuller, MD, (Ophthalmologist)

Rand Spencer, MD, (Ophthalmologist)

Robert C. Wang, MD, (Ophthalmologist)

Karen Duignan (Clinic Coordinator)

Sally Arceneaux, COA, (Assistant Coordinator)

Hank Aguado, CRA, (Photographer)

Nicholas Hesse (Photographer)

Michael Mackens (Photographer)

Brian Swan (Photographer)

(006) National Eye Institute

Wai T. Wong, MD, PhD, (Site PI)

Catherine Cukras, MD, (Ophthalmologist)

Monica Dalal, MD, (Ophthalmologist)

Naima Jacobs-El, MD, (Ophthalmologist)

Catherine Meyerle, MD, (Ophthalmologist)

Benjamin Nicholson, MD, (Ophthalmologist)

Henry Wiley, MD, (Ophthalmologist)

Katherine Hall Shimel, RN, COT, MSN, (Clinic Coordinator)

Angel Garced, RN, (Assistant Coordinator)

Janice Oparah, RN, (Assistant Coordinator)

Greg Short, COMT, (Assistant Coordinator)

Alana Temple, RN, (Assistant Coordinator)

Babilonia Ayukawa, RN, (Phlebotomist)

Guy Foster, COT, (Ophthalmic Technician)

Darryl Hayes, COA, (Ophthalmic Technician)

Dessie Koutsandreas (Ophthalmic Technician)

Roula Nashwinter (Ophthalmic Technician)

John Rowan (Ophthalmic Technician)

Emily Y. Chew, MD, Study Chair (Project Sponsor Staff (NEI))

Michael Bono (Photographer)

Denise Cunningham (Photographer)

Marilois Palmer (Photographer)

Alicia Zetina (Photographer)

(007) Ingalls Memorial Hospital

David H. Orth, MD, (Site PI)

Kourous Rezaei, MD, Co-PI (Site Co-PI)

Joseph Civantos, MD, (Ophthalmologist)

Sohail Hasan, MD, PhD, (Ophthalmologist)

Kirk Packo, MD, (Ophthalmologist)

Celeste Figliulo (Clinic Coordinator)

Pam Stanberry (Phlebotomist)

Tara Farmer (Photographer)

Kiersten Nelson (Photographer)

Shannya Townsend-Patrick (Photographer)

(008) Bascom Palmer Eye Institute

Philip Rosenfeld, MD, PhD, (Site PI)

Royce Chen, MD, (Ophthalmologist)

Rishi Doshi, MD, (Ophthalmologist)

Sander Dubovy, MD, (Ophthalmologist)

Brian T. Kim, MD, (Ophthalmologist)

Matthew Lowrance, DO, (Ophthalmologist)

Andrew Moshfeghi, MD, (Ophthalmologist)

Zayna Nahas, MD, (Ophthalmologist)

Gary Schienbaum, MD, (Ophthalmologist)

John Vishak, MD, (Ophthalmologist)

Christina Weng, MD, (Ophthalmologist)

Zohar Yehoshua, MD, (Ophthalmologist)

Belen Rodriguez (Clinic Coordinator)

Jose Rebimbas (Assistant Coordinator)

Jane Gleichauf, RN, (Phlebotomist)

Mike Kicak (Ophthalmic Technician)

Jason Mena (Ophthalmic Technician)

Tim Odem (Ophthalmic Technician)

Elizabeth Sferza-Camp (Ophthalmic Technician)

Alicia Disgdiertt (Photographer)

Jim Oramas (Photographer)

Isabel Rams (Photographer)

Stephanie Thatcher (Photographer)

(009) The Retina Division at the Wilmer Eye Institute

Susan B. Bressler, MD, (Site PI)

Neil M. Bressler, MD, (Ophthalmologist)

Daniel Finkelstein, MD, (Ophthalmologist)

Steven H Sherman, MD, (Ophthalmologist)

Sharon Solomon, MD, (Ophthalmologist)

Howard S. Ying, MD, (Ophthalmologist)

Rita Denbow (Clinic Coordinator)

Deborah Phillips (Assistant Coordinator)

Elizabeth Radcliffe (Phlebotomist)

Judy Belt (Photographer)

Dennis Cain (Photographer)

David Emmert (Photographer)

Mark Herring (Photographer)

Jacquelyn McDonald (Photographer)

(010) Emory University Eye Center

G. Baker Hubbard, MD, (Site PI)

Chris S Bergstrom, MD, (Ophthalmologist)

Blaine Cribbs, MD, (Ophthalmologist)

Andrew Hendrick, MD, (Ophthalmologist)

Brandon Johnson, MD, (Ophthalmologist)

Philip Laird, MD, (Ophthalmologist)

Sonia Mehta, MD, (Ophthalmologist)

Timothy Olsen, MD, (Ophthalmologist)

Justin Townsend, MD, (Ophthalmologist)

Jion Yan, MD, (Ophthalmologist)

Steven Yeh, MD, (Ophthalmologist)

Linda Curtis, BSM, (Clinic Coordinator)

Judy Brower (Assistant Coordinator)

Hannah Yi (Assistant Coordinator)

Jannah Rutter Dobbs (Photographer)

Debbie Jordan (Photographer)

(011) Elman Retina Group, PA

Michael J. Elman, MD, (Site PI)

Robert A Liss, MD, (Ophthalmologist)

JoAnn Starr (Clinic Coordinator)

Jennifer Belz (Assistant Coordinator)

Charlene Putzulo (Assistant Coordinator)

Teresa Coffey (Ophthalmic Technician)

Ashley Davis (Ophthalmic Technician)

Pamela Singletary (Ophthalmic Technician)

Giorya Shabi Andreani (Photographer)

Theresa Cain (Photographer)

Daniel Ketner (Photographer)

Peter Sotirakos (Photographer)

(012) University of Wisconsin

Suresh Chandra, MD, (Site PI)

Barbara A. Blodi, MD, (Site Co-PI)

Michael M. Altaweel, MD, (Ophthalmologist)

Ronald P. Danis, MD, (Ophthalmologist)

Justin L. Gottlieb, MD, (Ophthalmologist)

Michael Ip, MD, (Ophthalmologist)

Ronald Klein, MD, (Ophthalmologist)

T. Michael Nork, MD, (Ophthalmologist)

Thomas S. Stevens, MD, (Ophthalmologist)

Kathryn Burke (Clinic Coordinator)

Shelly Olson (Clinic Coordinator)

Kristine Dietzman (Assistant Coordinator)

Barbara Soderling (Assistant Coordinator)

Guy Somers, RN, (Assistant Coordinator)

Angie Wealti (Assistant Coordinator)

Denise Krolnik (Photographer)

John Peterson (Photographer)

Sandra Reed (Photographer)

(013) UPMC Eye Center

Thomas Friberg, MD, (Site PI)

Andrew Eller, MD, (Ophthalmologist)

Denise Gallagher, MD, (Ophthalmologist)

Leanne Labriola, DO, (Ophthalmologist)

Melissa Pokrifka (Clinic Coordinator)

Aron Gedansky (Assistant Coordinator)

Natalie Anthony (Photographer)

Cassandra Grzybowski (Photographer)

Dawn Matthews (Photographer)

Sharon Murajda-Jumba (Photographer)

Jessica Toro (Photographer)

(014) Texas Retina Associates

Gary Edd Fish, MD, JD, (Site PI)

David G. Callanan, MD, (Ophthalmologist)

Wayne A. Solley, MD, (Ophthalmologist)

Patrick Williams, MD, (Ophthalmologist)

Sandy Lash (Clinic Coordinator)

Bob Boleman (Photographer)

Chris Dock (Photographer)

(015) Texas Retina Associates

Gary Edd Fish, MD, JD, (Site PI)

Michel Shami, MD, (Ophthalmologist)

Brenda Arrington (Clinic Coordinator)

Ashaki Meeks (Ophthalmic Technician)

(017) Vision Research Foundation

Alan J. Ruby, MD, (Site PI)

Alan R Margherio, MD, (Ophthalmologist)

Paul Raphaelian, MD, (Ophthalmologist)

Debra Markus (Clinic Coordinator)

Justin Langdon (Ophthalmic Technician)

Elizabeth Truax (Ophthalmic Technician)

Sandy Lewis (Photographer)

Brad Terry (Photographer)

(018) Vision Research Foundation

Alan J. Ruby, MD, (Site PI)

Amy Noffke, MD, (Ophthalmologist)

Kean Oh, MD, (Ophthalmologist)

Ramin Sarrafizadeh, MD, PhD, (Ophthalmologist)

Scott Sneed, MD, (Ophthalmologist)

Julie Hammersley, RN, (Clinic Coordinator)

Serena Neal (Assistant Coordinator)

Mary Doran (Ophthalmic Technician)

Nan Jones (Ophthalmic Technician)

Lisa Preston (Ophthalmic Technician)

Heather Jessick (Photographer)

Tanya Tracy Marsh (Photographer)

(020) Center for Retina and Macular Disease

Michael Tolentino, MD, (Site PI)

Adam Berger, MD, (Ophthalmologist)

Richard Hamilton, MD, (Ophthalmologist)

David Misch, MD, (Ophthalmologist)

Suk Jin Moon, MD, (Ophthalmologist)

Dawn Sutherland (Clinic Coordinator)

Vera Dilts (Assistant Coordinator)

Sara Henderson (Assistant Coordinator)

Esmeralda Medina (Assistant Coordinator)

Donald Trueman (Assistant Coordinator)

Laura Holm, LPN, (Ophthalmic Technician)

Jason Strickland (Photographer)

(021) Delaware Valley Retina Associates

Darmakusuma Ie, MD, (Site PI)

Jeffrey L. Lipkowitz MD(Ophthalmologist)

Kekul B. Shah, MD, (Ophthalmologist)

Susan Geraghty (Clinic Coordinator)

Beverly Sannazzaro (Clinic Coordinator)

Morgan Harper (Ophthalmic Technician)

Krista Bayer (Photographer)

(022) Eldorado Retina Associates, PC

Mary B. Lansing, MD, (Site PI)

Lauren B. Fox (Clinic Coordinator)

Rebecca Lee (Photographer)

(023) Georgia Retina, PC

Jay B. Stallman, MD, FACS, (Site PI)

Michael Jacobson, MD, (Ophthalmologist)

Sean Koh, MD, (Ophthalmologist)

Scott Lampert, MD, (Ophthalmologist)

John Miller, MD, (Ophthalmologist)

Mark Rivellese, MD, (Ophthalmologist)

Atul Sharma, MD, (Ophthalmologist)

Robert A. Stoltz, MD, (Ophthalmologist)

Stephanie Vanderveldt, MD, (Ophthalmologist)

Leslie Marcus (Clinic Coordinator)

Starr Hendricks (Assistant Coordinator)

Ryan Hollman (Assistant Coordinator)

Grethel Betanzos (Ophthalmic Technician)

Leslie Ellorin (Ophthalmic Technician)

Shelly Fulbright (Ophthalmic Technician)

Debbie McCormick (Photographer)

(024) Henry Ford Health System - Eye Care Services

Paul A. Edwards, MD, (Site PI)

Julianne Hall (Clinic Coordinator)

Mary Monk (Clinic Coordinator)

Melanie Gutkowski (Assistant Coordinator)

Melina Mazurek (Assistant Coordinator)

Janet Murphy (Assistant Coordinator)

Katherine Gusas (Office Manager)

Crystal Moffett (Office Manager)

David Burley (Photographer)

Nicole Chesney (Photographer)

Katie Kilgo (Photographer)

Brian Rusinek (Photographer)

Bradley Stern (Photographer)

Tracy Troszak (Photographer)

Rhonda Baker-Levingston (Pharmacist)

(025) Paducah Retinal Center

Carl W. Baker, MD, (Site PI)

Tracey Caldwell (Clinic Coordinator)

Tammy Walker (Assistant Coordinator)

Lynnette F. Lambert (Ophthalmic Technician)

Tracey Martin (Ophthalmic Technician)

Mary Jill Palmer (Ophthalmic Technician)

Tana Williams (Photographer)

(026) Retina Associates of Cleveland

Michael A Novak, MD, (Site PI)

Joseph Coney, MD, (Ophthalmologist)

David G. Miller, MD, (Ophthalmologist)

Scott Pendergast, MD, (Ophthalmologist)

Lawrence Singerman, MD, (Ophthalmologist)

Nicholas Zakov, MD, (Ophthalmologist)

Hernando Zegarra, MD, (Ophthalmologist)

Kim DuBois (Clinic Coordinator)

Susan Rath (Clinic Coordinator)

Lori Revella (Clinic Coordinator)

Tammy Brink (Ophthalmic Technician)

Kim Drury (Ophthalmic Technician)

Lisa Hogue (Ophthalmic Technician)

Mary Ilc (Ophthalmic Technician)

Connie Keller (Ophthalmic Technician)

Elizabeth McNamara (Ophthalmic Technician)

Vivian Tanner (Ophthalmic Technician)

Tamara Cunningham (Photographer)

John DuBois (Photographer)

Gregg Greanoff (Photographer)

Trina Nitzsche (Photographer)

Sheila Smith-Brewer (Photographer)

(027) Retina Associates of Kentucky

Ricky D. Isernhagen, MD, (Site PI)

John W. Kitchens, MD, (Ophthalmologist)

Thomas W. Stone, MD, (Ophthalmologist)

William J. Wood, MD, (Ophthalmologist)

Diana Holcomb (Clinic Coordinator)

Virginia Therrien (Office Manager)

Michelle Buck, COT, (Ophthalmic Technician)

Jeanne Van Arsdall (Ophthalmic Technician)

Edward Slade, CRA, COA, (Photographer)

(029) Retina Center Northwest

Todd E. Schneiderman, MD, (Site PI)

David J. Spinak, MD, (Ophthalmologist)

Jackie Gaedke (Clinic Coordinator)

Heather Davis Brown (Assistant Coordinator)

Dan Helgren (Assistant Coordinator)

Jenifer Garrison Pangelinan (Photographer)

(030) Retina Group of Florida

Lawrence Halperin, MD, (Site PI)

Scott Anagnoste, MD, (Ophthalmologist)

Mandeep Dhalla, MD, (Ophthalmologist)

Krista Rosenberg, MD, (Ophthalmologist)

Barry Taney, MD, (Ophthalmologist)

W. Scott Thompson, MD, (Ophthalmologist)

Jaclyn Lopez (Clinic Coordinator)

Monica Hamlin (Assistant Coordinator)

Monica Lopez (Assistant Coordinator)

Jamie Mariano, COA, (Ophthalmic Technician)

Evelyn Quinchia (Ophthalmic Technician)

Patricia Aramayo (Photographer)

Rita Veksler (Photographer)

(031) Retina Northwest, PC

Michael Lee, MD, (Site PI)

Richard Dreyer, MD, (Ophthalmologist)

Irvin Handelman, MD, (Ophthalmologist)

Colin Ma, MD, (Ophthalmologist)

Mark Peters, MD, (Ophthalmologist)

Stephen Hobbs III (Clinic Coordinator)

Amanda Milliron (Assistant Coordinator)

Marcia Kopfer (Ophthalmic Technician)

Michele Connaughton (Photographer)

A. Christine Hoerner (Photographer)

R. Joseph Logan (Photographer)

Harry J. Wohlsein (Photographer)

(032) Retina-Vitreous Associates Medical Group

David Boyer, MD, (Site PI)

Thomas G. Chu, MD, PhD, (Ophthalmologist)

Pouya Dayani, MD, (Ophthalmologist)

David Liao, MD, (Ophthalmologist)

Roger L. Novack, MD, PhD, (Ophthalmologist)

Firas M. Rahhal, MD, (Ophthalmologist)

Richard Roe, MD, (Ophthalmologist)

Homayoun Tabandeh, MD, (Ophthalmologist)

Janet Bayramyan (Clinic Coordinator)

Tammy Gasparyan (Assistant Coordinator)

Connie Hoang (Assistant Coordinator)

Janet Kurokouchi (Assistant Coordinator)

Tammy Eileen Lo (Assistant Coordinator)

Richard Ngo (Assistant Coordinator)

Mary Ann Nguyen (Assistant Coordinator)

Michael Peyton (Assistant Coordinator)

Charles Yoon (Assistant Coordinator)

Julio Sierra (Ophthalmic Technician)

Adam Zamboni (Ophthalmic Technician)

Jeff Kessinger (Photographer)

Eric Protacio (Photographer)

Adam Smucker (Photographer)

(033) Retina Vitreous Consultants

Pamela Rath, MD, (Site PI)

Robert Bergren, MD, (Ophthalmologist)

Bernard Doft, MD, (Ophthalmologist)

Judy Liu, MD, (Ophthalmologist)

Karl Olsen, MD, (Ophthalmologist)

Lori Merlotti (Clinic Coordinator)

Willia Ingram (Assistant Coordinator)

Kellianne Marfisi (Ophthalmic Technician)

Kimberly Yeckel (Ophthalmic Technician)

Heather Schultz Carmelo (Photographer)

Amanda Fec (Photographer)

Keith McBroom (Photographer)

David Steinberg (Photographer)

(034) Sarasota Retina Institute

Marc Levy, MD, (Site PI)

Jody Abrams, MD, (Ophthalmologist)

Melvin Chen, MD, (Ophthalmologist)

Waldemar Torres, MD, (Ophthalmologist)

Peggy Jelemensky (Clinic Coordinator)

Mark Prybylski (Ophthalmic Technician)

Tara Raphael (Ophthalmic Technician)

Diana Appleby (Photographer)

Charlotte Rodman (Photographer)

Mark Sneath, COA, (Photographer)

(035) Scott and White Memorial Hospital

Robert H. Rosa, Jr., MD, (Site PI)

Vanessa Hoelscher (Clinic Coordinator)

Adelia Castano (Ophthalmic Technician)

Jocelyn Parker (Photographer)

(036) Southeastern Retina Associates, PC

John Hoskins, MD, (Site PI)

Nicholas Anderson, MD, (Ophthalmologist)

Joseph Googe, Jr., MD, (Ophthalmologist)

Tod A McMillan, MD, (Ophthalmologist)

James Miller Jr., MD, (Ophthalmologist)

Stephen Perkins, MD, (Ophthalmologist)

Kristina Oliver (Clinic Coordinator)

Jennifer Beerbower (Ophthalmic Technician)

Bruce Gilliland, OD, (Ophthalmic Technician)

Cecile Hunt (Ophthalmic Technician)

Mike Jacobus (Photographer)

Raul Lince (Photographer)

Christopher Morris (Photographer)

Sarah Oelrich (Photographer)

Jerry Whetstone (Photographer)

(037) Southern California Desert Retina Consultants, MC

Clement K. Chan, MD, (Site PI)

Steven Lin, MD, (Ophthalmologist)

Kim Walther (Clinic Coordinator)

Tiana Gonzales (Assistant Coordinator)

Lenise Myers (Ophthalmic Technician)

Kenneth Huff, COA, (Photographer)

(038) Retina Consultants of Houston

David M. Brown, MD, (Site PI)

Eric Chen, MD (Ophthalmologist)

Matthew S. Benz, MD, (Ophthalmologist)

Richard H. Fish, MD, FACS, (Ophthalmologist)

Rosa Y. Kim, MD, (Ophthalmologist)

James Major Jr, MD, (Ophthalmologist)

Tien Pei Wong, MD, (Ophthalmologist)

Charles Wycoff, MD, PhD, (Ophthalmologist)

Cassandra Cone (Clinic Coordinator)

Debbie Goates Gilaspia (Assistant Coordinator)

Nubia Landaverde (Assistant Coordinator)

Robert Smith (Assistant Coordinator)

Deneva Zamora (Assistant Coordinator)

Veronica Sneed (Ophthalmic Technician)

Melina Vela (Ophthalmic Technician)

Eric Kegley (Photographer)

(039) Wake Forest University Eye Center

Craig Greven, MD, (Site PI)

Shree Kurup, MD, (Ophthalmologist)

Charles Richards, MD, (Ophthalmologist)

Madison Slusher, MD, (Ophthalmologist)

Cara Everhart (Clinic Coordinator)

Joan Fish, RN, CCRC, (Assistant Coordinator)

Mark Clark (Photographer)

David Miller (Photographer)

Marshall Tyler, CRA, FOPS, (Photographer)

(040) West Coast Retina Medical Group, Inc

J. Michael Jumper, MD, (Site PI)

Arthur D. Fu, MD, (Ophthalmologist)

Robert N. Johnson, MD, (Ophthalmologist)

Brandon Lujan, MD, (Ophthalmologist)

H. Richard McDonald, MD, (Ophthalmologist)

Rosa Rodriguez (Clinic Coordinator)

Nina Ansari (Ophthalmic Technician)

Jeanifer Joaquin (Ophthalmic Technician)

Silvia Linares (Ophthalmic Technician)

Lizette Lopez (Ophthalmic Technician)

Jessica Sabio (Ophthalmic Technician)

Sean Grout (Photographer)

Chad Indermill (Photographer)

Yesmin Urias (Photographer)

Roberto Zimmerman (Photographer)

(041) Veterans Affairs - Northern California Health Care System

Linda Margulies, MD, (Site PI)

Sara J. Schmidt, PharmD, (Clinic Coordinator)

Joy L. Meier, PharmD, (Assistant Coordinator)

Sherry L. Hadley COT(Ophthalmic Technician)

(042) Mid-America Retina Consultants, PA

William Rosenthal, MD, (Site PI)

Barbara Johnson, RN, (Clinic Coordinator)

Lois Swafford (Office Manager)

Richard Shields, RN, (Ophthalmic Technician)

R. Scott Varner (Photographer)

(043) New York Eye and Ear Infirmary

Richard Rosen, MD, (Site PI)

Ronald Gentile, MD, (Ophthalmologist)

Melissa Rivas (Clinic Coordinator)

Katy W. Tai, CRC, (Assistant Coordinator)

Wanda Carrasquillo-Boyd (Photographer)

Robert Masini (Photographer)

(044) Ophthalmic Consultants of Long Island

Glenn Stoller, MD, (Site PI)

Ken Carnevale, MD, (Ophthalmologist)

Diane M. LaRosa, CRNO, (Clinic Coordinator)

Barbara Burger, RN, CCRC, (Assistant Coordinator)

Tereza Conway (Assistant Coordinator)

Carla Del Castillo (Assistant Coordinator)

Julissa Diaz (Assistant Coordinator)

Susan Jones (Assistant Coordinator)

Nina Mondoc (Assistant Coordinator)

Charlene Balfour (Ophthalmic Technician)

CH Vitha (Ophthalmic Technician)

Jennifer Lutz (Photographer)

Barbara McGinley (Photographer)

(045) The Research Foundation of SUNY/SB

Fadi El Baba, MD, (Site PI)

Ann Marie Lavorna (Clinic Coordinator)

Renee Jones (Assistant Coordinator)

Jean Lewis (Assistant Coordinator)

Ruth Tenzler, RN, BSN, (Assistant Coordinator)

Mary Salvas-Mladek, CRA, (Ophthalmic Technician)

Diane Van Kesteren, COA, (Ophthalmic Technician)

(046) Western Carolina Retinal Associates

W. Copley McLean, Jr., MD, (Site PI)

W. Zachery Bridges, Jr., MD, (Ophthalmologist)

Cameron Stone, MD, (Ophthalmologist)

Denise Ammons (Clinic Coordinator)

Mary Lamy (Assistant Coordinator)

Andrea Menzel (Assistant Coordinator)

Lea Doll Raymer (Assistant Coordinator)

Barbara Campbell (Ophthalmic Technician)

Lisa Hawkins (Ophthalmic Technician)

Leslie Rickman (Ophthalmic Technician)

Lorraine Sherlin (Ophthalmic Technician)

Paula Price (Photographer)

Albert Sinyai (Photographer)

(047) Dean McGee Eye Institute

Ronald Kingsley, MD, (Site PI)

Reagan H. Bradford, Jr., MD, (Ophthalmologist)

Robert E. Leonard II, MD, (Ophthalmologist)

Sonny Icks (Clinic Coordinator)

Vanessa Bergman (Ophthalmic Technician)

Brittany Ross (Ophthalmic Technician)

Russ Burris (Photographer)

Amanda Butt (Photographer)

Rob Richmond (Photographer)

(048) Northwestern University, Ophthalmology

Alice Lyon, MD, (Site PI)

Manjot Gill, MD, (Ophthalmologist)

Lee Jampol, MD, (Ophthalmologist)

Rukhsana Mizra, MD, (Ophthalmologist)

Zuzanna Rozenbajgier (Clinic Coordinator)

Jeremy Chapman (Assistant Coordinator)

Lori Kaminski (Assistant Coordinator)

Andrea Degillio (Photographer)

Evica Simjanoski, CRA, (Photographer)

(049) Ophthalmic Consultants of Boston

Jeffrey Heier, MD, (Site PI)

Hyung Cho, MD, (Ophthalmologist)

Tina Scheufele Cleary, MD, (Ophthalmologist)

Darin Goldman, MD, (Ophthalmologist)

Chirag Shah, MD, (Ophthalmologist)

Trexler Topping, MD, (Ophthalmologist)

Marissa Weber, MD, (Ophthalmologist)

Torsten Wiegand, MD, PhD, (Ophthalmologist)

Jeremy Schindelheim (Clinic Coordinator)

Joy Bankert (Assistant Coordinator)

Jennifer Stone (Assistant Coordinator)

Alison Nowak (Office Manager)

Sandy Chong (Ophthalmic Technician)

Lindsay Williams (Ophthalmic Technician)

Steven Bennett (Photographer)

Dennis Donovan (Photographer)

Margaret Graham (Photographer)

Cullen Jones (Photographer)

(050) Pacific Eye Associates

Anne Fung, MD, (Site PI)

Jan-Kristine Bayabo (Clinic Coordinator)

Razelda Bosch (Assistant Coordinator)

Esperanza Cruz (Assistant Coordinator)

Ashley Emerson (Assistant Coordinator)

Alycia Fleming (Ophthalmic Technician)

Denice Barsness (Photographer)

Jorge Rodriguez (Photographer)

Marina Soboleva (Photographer)

(051) Penn State M.S. Hershey Medical Center

Ingrid U. Scott, MD, MPH, (Site PI)

Esther Bowie, MD, (Ophthalmologist)

Kimberly A Neely, MD, PhD, (Ophthalmologist)

David A. Quillen, MD, (Ophthalmologist)

Laura Walter (Clinic Coordinator)

Timothy Bennett (Photographer)

James Strong (Photographer)

(052) Palmetto Retina Center

John Wells, III, MD, (Site PI)

Lloyd Clark, MD, (Ophthalmologist)

David Johnson, MD, (Ophthalmologist)

Peggy Miller (Clinic Coordinator)

Mallie Taylor (Assistant Coordinator)

Tiffany Swinford (Ophthalmic Technician)

Robbin Spivey (Photographer)

(053) Pennsylvania Retina Specialists, PC

Michael Banach, MD, (Site PI)

Lawrence Ho, MD, (Ophthalmologist)

Richard Lanning, MD, (Ophthalmologist)

Thomas R Pheasant, MD, (Ophthalmologist)

Jay G Prensky, MD, (Ophthalmologist)

Steven Truong, MD, (Ophthalmologist)

Julia Teatsworth, COT, (Clinic Coordinator)

Michelle Dietrich (Assistant Coordinator)

Ann Wasilus (Phlebotomist)

Ann Miller (Ophthalmic Technician)

Megan Rakes (Ophthalmic Technician)

Teresa Slagle (Ophthalmic Technician)

Michelle Richards (Photographer)

Patricia Schuessler (Photographer)

Lacy Stover (Photographer)

(054) Retina Consultants, PLLC

Paul Beer, MD, (Site PI)

Naomi S. Falk, MD, (Ophthalmologist)

Mary Beth Shannon (Clinic Coordinator)

Jeannie Olmeda (Ophthalmic Technician)

Don Berdeen (Photographer)

Joseph F. Fisher, Jr. (Photographer)

(055) University of Iowa

James Folk, MD, (Site PI)

Stephen Russell, MD, (Ophthalmologist)

Barbara Taylor (Clinic Coordinator)

Connie Hinz (Assistant Coordinator)

Jean Walshire (Assistant Coordinator)

Heather Stockman (Ophthalmic Technician)

Bruce Critser (Photographer)

Stefani Karakas (Photographer)

Cindy Montague (Photographer)

Randy Verdick (Photographer)

(056) Wills Eye Hospital/Mid Atlantic Retina

Omesh Gupta, MD, (Site PI)

Joseph Maguire, MD, (Site PI)

Christopher Brady, MD, (Ophthalmologist)

Francis Char DeCroos, MD, (Ophthalmologist)

Michael Dollin, MD, (Ophthalmologist)

Sunir Garg, MD, (Ophthalmologist)

Adam Gerstenblith, MD, (Ophthalmologist)

Julia Haller, MD, (Ophthalmologist)

Allen C. Ho, MD, (Ophthalmologist)

Jason Hsu, MD, (Ophthalmologist)

Richard Kaiser, MD, (Ophthalmologist)

John Pitcher, MD, (Ophthalmologist)

Carl Regillo, MD, (Ophthalmologist)

Rajiv Shah, MD, (Ophthalmologist)

Marc Spirn, MD, (Ophthalmologist)

William Tasman, MD, (Ophthalmologist)

James Vander, MD, (Ophthalmologist)

Noga Senderowitsch (Clinic Coordinator)

Michele Formoso (Assistant Coordinator)

Michelle Markun (Assistant Coordinator)

Cedric George

Christina Centinaro (Ophthalmic Technician)

Lisa Grande (Ophthalmic Technician)

Stefanie Carey (Photographer)

Elaine Liebenbaum (Photographer)

(057) Doheny Eye Institute USC

SriniVas Sadda, MD, (Site PI)

Mark Humayun, MD, PhD, (Ophthalmologist)

Rachel Sierra (Clinic Coordinator)

Elizabeth Corona (Assistant Coordinator)

Margaret Padilla (Assistant Coordinator)

Moonseok Nu (Office Manager)

Sylvia Ramos (Ophthalmic Technician)

Cullen Barnett (Photographer)

Glenn Currie (Photographer)

Cornelia Gottlieb (Photographer)

(058) The Retina Group of Washington

Richard Garfinkel, MD, (Site PI)

Daniel Berinstein, MD, (Ophthalmologist)

Marcus Colyer, MD, (Ophthalmologist)

William Deegan, III, MD, (Ophthalmologist)

Michael Min-Shyue Lai, MD, (Ophthalmologist)

Robert Murphy, MD, (Ophthalmologist)

Michael Osman, MD, (Ophthalmologist)

Michael Rivers, MD, (Ophthalmologist)

Reginald Sanders, MD, (Ophthalmologist)

Manfred A. von Fricken, MD, (Ophthalmologist)

Debbie Oliver (Clinic Coordinator)

Jeanne Kirshon (Assistant Coordinator)

Tanya Alexander Snowden (Assistant Coordinator)

Thomas Blondo (Ophthalmic Technician)

Alysia Cronise (Ophthalmic Technician)

Vanessa Denny (Ophthalmic Technician)

Kylie Mendez (Ophthalmic Technician)

Janine Newgen (Ophthalmic Technician)

Justin Davis (Photographer)

Mike Flory (Photographer)

Robert Frantz (Photographer)

Bryan Murphy (Photographer)

Steve Rauch (Photographer)

(060) The Medical College of Wisconsin

Judy E. Kim, MD, (Site PI)

Jane Bachman, OD, (Ophthalmologist)

Thomas B. Connor, Jr., MD, (Ophthalmologist)

Dennis P. Han, MD, (Ophthalmologist)

Kimberly Stepian, MD, (Ophthalmologist)

David V. Weinberg, MD, (Ophthalmologist)

William J. Wirostko, MD, (Ophthalmologist)

Krissa Packard (Clinic Coordinator)

Tracy Kaczanowski (Assistant Coordinator)

Vesper Williams (Assistant Coordinator)

Vicki Barwick (Ophthalmic Technician)

Judy Flanders (Ophthalmic Technician)

Dennis Backes (Photographer)

Joe Beringer (Photographer)

Kristy Keller (Photographer)

Kathy Selchert (Photographer)

(061) John Moran Eye Center

Paul Bernstein, MD, PhD, (Site PI)

Michael Teske, MD, (Ophthalmologist)

Albert Vitale, MD, (Ophthalmologist)

Susan Allman, COA, (Clinic Coordinator)

Bonnie Carlstrom COA (Assistant Coordinator)

Kimberley Wegner (Assistant Coordinator)

Anne Haroldsen (Office Manager)

Deborah Harrison, MS, (Office Manager)

Cyrie Fry (Photographer)

James Gilman, CRA, (Photographer)

Glen Jenkins (Photographer)

Paula Morris, CRA, (Photographer)

(063) Loma Linda University

Michael Rauser, MD, (Site PI)

Joseph Fan, MD, (Ophthalmologist)

Mukesh Suthar, MD, (Ophthalmologist)

Gisela Santiago (Clinic Coordinator)

Kara Rollins Halsey (Assistant Coordinator)

Christy Quesada (Assistant Coordinator)

William Kiernan, OD, (Ophthalmic Technician)

Jesse Knabb (Photographer)

(064) Baylor College of Medicine

Richard Alan Lewis, MD, MS, (Site PI)

Cindy Dorenbach, COT, (Clinic Coordinator)

Steven Spencer, COMT, (Ophthalmic Technician)

Dana Barnett (Photographer)

Joseph Morales, CRA, (Photographer)

(066) Carolina Retina Center

Barron C. Fishburne, MD, (Site PI)

Jeffrey G. Gross, MD, (Ophthalmologist)

Michael A. Magee, MD, (Ophthalmologist)

Amy Flowers (Clinic Coordinator)

Angie McDowell (Ophthalmic Technician)

Randall Price (Photographer)

(067) Case Western Reserve University

Suber Huang, MD, MBA, (Site PI)

Johnny Tang, MD, (Ophthalmologist)

Shawn Wilker, MD, (Ophthalmologist)

Cherie Hornsby (Clinic Coordinator)

Lisa Ferguson (Assistant Coordinator)

Kirk Krogstad (Assistant Coordinator)

Riva Adamovsky (Ophthalmic Technician)

Peggy Allchin (Ophthalmic Technician)

Kathleen Carlton (Ophthalmic Technician)

Claudia Clow (Ophthalmic Technician)

Kelly Sholtis (Ophthalmic Technician)

Stephanie Burke (Photographer)

Mark Harrod (Photographer)

Stacie Hrvatin (Photographer)

Geoffrey Pankhurst (Photographer)

(069) Eye Foundation of Kansas City

Nelson R. Sabates, MD, (Site PI)

Michael Cassell, MD, (Ophthalmologist)

Komal Desai, MD, (Ophthalmologist)

Abraham Poulose, MD, (Ophthalmologist)

Felix Sabates, MD, (Ophthalmologist)

Yin Chen (Clinic Coordinator)

Gary Gallimore, COMT, (Photographer)

Yolanda Konior (Photographer)

(070) Jones Eye Institute - UAMS

Nicola Kim, MD, (Site PI)

Sami Uwaydat (Ophthalmologist)

Deborah Troillett (Clinic Coordinator)

Karen Aletter (Photographer)

(071) Kresge Eye Institute

Robert N. Frank, MD, (Site PI)

Gary Abrams, MD, (Ophthalmologist)

James Puklin, MD, (Ophthalmologist)

Asheesh Tewari, MD, (Ophthalmologist)

Cheryl Milanovic (Clinic Coordinator)

Melanie Bailey (Photographer)

David Griffith (Photographer)

Dena McDonald (Photographer)

Kit Morehead (Photographer)

Zlatan Sadikovic (Photographer)

Lisa Schillace (Photographer)

Elizabeth Silvis (Photographer)

(072) Colorado Retina Associates PC

Brian Joondeph, MD, (Site PI)

Nancy Christmas, MD, (Ophthalmologist)

David Johnson, MD, (Ophthalmologist)

Alan Kimura, MD, (Ophthalmologist)

Mimi Liu, MD, (Ophthalmologist)

Stephen Petty, MD, (Ophthalmologist)

John Zilis, MD, (Ophthalmologist)

Jenny Benitez (Clinic Coordinator)

Cassandra Berryman Catlett (Assistant Coordinator)

Eric Fluegel, RN, (Assistant Coordinator)

Shane Mowry (Photographer)

Hoang Nguyen (Photographer)

David Reflow (Photographer)

(074) UNC Department of Ophthalmology

Odette M. Houghton, MD, (Site PI)

Seema Garg, MD, PhD, (Ophthalmologist)

Maurice B. Landers, MD, (Ophthalmologist)

Travis Meredith, MD, (Ophthalmologist)

Sandy Barnhart, MPH, (Clinic Coordinator)

Megha Karmalkar (Assistant Coordinator)

Debra Cantrell (Photographer)

Rona Lyn Esquejo-Leon (Photographer)

Linda Manor (Pharmacist)

Sue Pope (Pharmacist)

David Stines (Pharmacist)

Amelia Stokely (Pharmacist)

(075) University Health Care - Mason Eye Institute

Dean Hainsworth, MD, (Site PI)

Dyann Helming (Clinic Coordinator)

Debbie Eichelberger (Office Manager)

Mary Paige Leaton (Ophthalmic Technician)

Chuck Hamm (Photographer)

(076) University of Tennessee HSC

Edward Chaum, MD, PhD, (Site PI)

Alessandro Iannaccone, MD, (Ophthalmologist)

Barbara Jennings, MA, OD, (Clinic Coordinator)

Tracy Murray (Ophthalmic Technician)

Joe Mastellone (Photographer)

(077) Fletcher Allen Health Care

Robert Millay, MD, (Site PI)

Brian Kim, MD, (Ophthalmologist)

Theresa Goddard (Clinic Coordinator)

Liza Jarrett Beaudette (Ophthalmic Technician)

Nina Changelian-Aitken (Ophthalmic Technician)

Fernando Corrada (Photographer)

Jason Dubuque (Photographer)

(078) Mayo Clinic

Raymond Iezzi, MD, (Site PI)

Sophie J. Bakri, MD, (Ophthalmologist)

Jose S. Pulido, MD, (Ophthalmologist)

Diane Vogen (Clinic Coordinator)

Rebecca Nielsen, LPN, (Assistant Coordinator)

Karin Berg (Ophthalmic Technician)

Jean Burrington, COA, (Ophthalmic Technician)

Shannon Howard, COA, (Ophthalmic Technician)

Joan Overend (Ophthalmic Technician)

Zbigniew Krason (Photographer)

Denise Lewison (Photographer)

Thomas Link, CRA, (Photographer)

(079) The Retina Institute

Kevin J. Blinder, MD, (Site PI)

Nicholas E. Engelbrecht, MD, (Ophthalmologist)

M. Gilbert Grand, MD, (Ophthalmologist)

Daniel P. Joseph, MD, PhD, (Ophthalmologist)

Gaurav K. Shah, MD, (Ophthalmologist)

Bradley Smith, MD, (Ophthalmologist)

Matthew Thomas, MD, (Ophthalmologist)

Rhonda Weeks (Clinic Coordinator)

Lynda Boyd (Ophthalmic Technician)

Dana Gabel (Photographer)

(080) Yale University Eye Center

Ron Adelman, MD, (Site PI)

John Huang, MD, (Ophthalmologist)

James Kempton, MD, (Ophthalmologist)

Aaron Parnes, MD, (Ophthalmologist)

Jennifer Dupont (Clinic Coordinator)

Elizabeth Perotti (Assistant Coordinator)

Victoria Donaldson (Ophthalmic Technician)

Kenneth Fong (Photographer)

Pamela Ossorio (Photographer)

(081) Vanderbilt Eye Institute

Anita Agarwal, MD, (Site PI)

Paul Sternberg, MD, (Ophthalmologist)

Sandy Owings (Clinic Coordinator)

Tony Adkins (Photographer)

Elaine Lok (Photographer)

Garvin Munn (Photographer)

Buddy Skellie (Photographer)

(082) UMDNJ

Neelakshi Bhagat, MD, MPH, (Site PI)

Monique S. Roy, MD, (Ophthalmologist)

Marco Zarbin, MD, PhD, (Ophthalmologist)

Catherine Fay (Clinic Coordinator)

Michael Lazar (Photographer)

Beth Malpica (Photographer)

Tatiana Mikheyav (Photographer)

(084) The University of Illinois

Lawrence Ulanski II, MD, (Site PI)

Jennifer Lim, MD, (Ophthalmologist)

Marcia Niec, BS CCRP, (Clinic Coordinator)

Tametha Johnson (Ophthalmic Technician)

Yesenia Ovando (Ophthalmic Technician)

Catherine Nail Carroll (Photographer)

Mark Janowicz (Photographer)

(085) Jules Stein Eye Institute

Steven Schwartz, MD, (Site PI)

David Cupp, MD, (Ophthalmologist)

Michael Gorin, MD, PhD, (Ophthalmologist)

Gad Heilweil, MD, (Ophthalmologist)

Hamid Hosseini, MD, (Ophthalmologist)

Jean-Pierre Hubschman, MD, (Ophthalmologist)

Allan Kreiger, MD, (Ophthalmologist)

Tara Young McCannel, MD, (Ophthalmologist)

Carolyn Pan, MD, (Ophthalmologist)

David Sarraf, MD, (Ophthalmologist)

Irena Tsui, MD, (Ophthalmologist)

Joshua Udoetek MD(Ophthalmologist)

Vinad Voleti, MD, (Ophthalmologist)

Logan Hitchcock (Clinic Coordinator)

Rosaleen Ostrick (Assistant Coordinator)

Melissa Chun, OD, (Ophthalmic Technician)

Jennie Kageyama, OD, (Ophthalmic Technician)

Nilo Davila (Photographer)

Kristin Lipka (Photographer)

Christina Shin (Pharmacist)

(086) Univ. of Alabama at Birmingham

Cynthia Owsley, PhD, (Site PI)

Michael Albert, Jr., MD, (Ophthalmologist)

Richard Feist, MD, (Ophthalmologist)

John Mason, MD, (Ophthalmologist)

Martin Thomley, MD, (Ophthalmologist)

Angelia Johnson (Clinic Coordinator)

Mark Clark (Assistant Coordinator)

Tracy Emond (Assistant Coordinator)

Joanna Hamela (Assistant Coordinator)

Angela Marsh (Office Manager)

Karen Searcey (Office Manager)

Kia Rookard (Ophthalmic Technician)

(087) UT Southwestern Medical Center

Yu-Guang He, MD, (Site PI)

Rafael L. Ufret-Vincenty, MD, (Ophthalmologist)

Mike Molai (Clinic Coordinator)

William Anderson (Photographer)

John Horna (Photographer)

(088) Ohio State University

Alan Letson, MD, (Site PI)

Colleen Cebulla, MD, PhD, (Ophthalmologist)

Susie Chang, MD, (Ophthalmologist)

Fred Davidorf, MD, (Ophthalmologist)

Jill Salerno (Clinic Coordinator)

Laura Sladoje (Office Manager)

Christina Stetson (Office Manager)

Jeri Perry (Ophthalmic Technician)

Scott Savage (Photographer)

(089) Duke University

Cynthia Toth, MD, (Site PI)

Glenn Jaffe, MD, (Ophthalmologist)

Stefanie Schuman, MD, (Ophthalmologist)

Neeru Sarin, MBBS, (Clinic Coordinator)

Jim Crowell (Photographer)

Tiffanie Keaton (Photographer)

Michael Kelly (Photographer)

Brian Lutman (Photographer)

Marriner Skelly (Photographer)

Lauren Welch (Photographer)

(090) University of California, Davis

Lawrence Morse, MD, PhD, (Site PI)

Allan Hunter, MD, (Ophthalmologist)

Susanna Soon-Chun Park MD, PhD (Ophthalmologist)

Cynthia Wallace (Clinic Coordinator)

Ember Dhillon (Assistant Coordinator)

Marisa Salvador (Assistant Coordinator)

Barbara Holderreed (Office Manager)

Karishma Chandra (Photographer)

Sashi Kaur (Photographer)

Ellen Redenbo (Photographer)

Smiley Hom (Pharmacist)

(091) Manhattan Eye, Ear and Throat Hospital

Michael Cooney, MD, (Site PI)

Irene Barbazetto, MD, (Ophthalmologist)

James M. Klancnik, Jr., MD, (Ophthalmologist)

John A. Sorenson, MD, (Ophthalmologist)

Lawrence Yannuzzi, MD, (Ophthalmologist)

Maria Scolaro (Clinic Coordinator)

Eugene Agresta (Photographer)

Nancy Gonzalez (Photographer)

(092) University of Florida

Sandeep Grover, MD, (Site PI)

K.V. Chalam, MD, PhD, (Ophthalmologist)

Shailesh Gupta, MD, (Ophthalmologist)

Christopher Lyons (Clinic Coordinator)

Wenhua Li (Assistant Coordinator)

Chirag Patel, MD, (Assistant Coordinator)

Jose Carrion (Photographer)

(093) Shiley Eye Center - UCSD

Henry Ferreyra, MD, (Site PI)

Amberly Rodriguez (Clinic Coordinator)

Iliana Molina (Assistant Coordinator)

Gabriel Balea (Photographer)

Pam Emory (Photographer)

Marlene Rico (Photographer)

Giorgio Siqueiros (Photographer)

(094) Scheie Eye Institute

Alexander J. Brucker, MD, (Site PI)

Joshua Dunaief, MD, (Ophthalmologist)

Juan Grunwald, MD, (Ophthalmologist)

Benjamin Kim, MD, (Ophthalmologist)

Albert M. Maguire, MD, (Ophthalmologist)

Brian VanderBeek, MD, (Ophthalmologist)

Sheri Drossner, MSW, (Clinic Coordinator)

Joan DuPont (Assistant Coordinator)

Rebecca Salvo (Assistant Coordinator)

Jim Berger (Photographer)

Cheryl Devine (Photographer)

Bill Nyberg (Photographer)

Laurel Weeney (Photographer)

(095) University of Rochester Eye Institute

David DiLoreto, MD, (Site PI)

Mina Chung, MD, (Ophthalmologist)

Valerie Davis (Clinic Coordinator)

Peter MacDowell (Assistant Coordinator)

George O Gara (Assistant Coordinator)

Daniel Castillo (Ophthalmic Technician)

Andrea Czubinski (Ophthalmic Technician)

Melissa Keim (Ophthalmic Technician)

Brandi Hardy (Photographer)

Rachel Grunhaus Hollar (Photographer)

Lynn Schueckler (Photographer)

(148) NorthShore University HealthSystems

Alice T. Lyon, MD, (Site PI)

Aaron Weinberg, MD, Site Co-PI

Mira Shiloach (Clinic Coordinator)

Nicole Pelkofer (Ophthalmic Technician)

Qin Zhou (Ophthalmic Technician)

Laura McPoland (Photographer)

(179) Washington University School of Medicine

Rajendra Apte, MD, PhD, (Site PI)

P. Kumar Rao, MD, (Ophthalmologist)

Sam Pistorius (Clinic Coordinator)

Jamie Kambarian (Assistant Coordinator)

Eve Adcock (Ophthalmic Technician)

Sarah Gould (Ophthalmic Technician)

Melanie Quinn (Ophthalmic Technician)

Rhonda Curtis (Photographer)

Amy Frost (Photographer)

Charla Meyer (Photographer)

Greg Rathert (Photographer)

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Table 1

Baseline Characteristics of the AREDS2 Participants included in the Unmatched Analyses.

	All participants (N = 3791)			Bilateral Large Drusen (N = 2462)			Unilateral Late AMD (N = 1329)		
	Statin use			Statin use			Statin use		
	No (N=2132) [N (%)]	Yes (N=1659) [N (%)]	P value	No (N=1436) [N (%)]	Yes (N=1026) [N (%)]	P value	No (N=696) [N (%)]	Yes (N=633) [N (%)]	P value
Age (mean ± SD)	72.3 ± 8.1	73.5 ± 7.3	<.0001	71.2 ± 8.3	72.5 ± 7.4	0.0001	74.5 ± 7.4	75.3 ± 6.7	0.0408
Female	1302 (61.1%)	847 (51.1.%)	<.0001	916 (63.8%)	524 (51.1%)	<.0001	386 (55.5%)	323 (51.0%)	0.1057
White race	2065 (96.9%)	1594 (96.1%)	0.1963	1389 (96.7%)	985 (96.0%)	0.3407	676 (97.1%)	609 (96.2%)	0.3503
Education			0.0678			0.1253			0.8312
High school or less	642 (30.1%)	557 (33.6%)		374 (26.0%)	304 (29.6%)		268 (38.5%)	253 (40.0%)	
At least some college	1019 (47.8%)	763 (46.0%)		709 (49.4%)	491 (47.9%)		310 (44.5%)	272 (43.0%)	
Post-graduate	471 (22.1%)	339 (20.4%)		353 (24.6%)	231 (22.5%)		118 (17.0%)	108 (17.1%)	
Smoking			0.0011			0.0043			0.3676
Never	986 (46.2%)	669 (40.3%)		705 (49.1%)	435 (42.4%)		281 (40.4%)	234 (37.0%)	
Former	1010 (47.4%)	880 (53.0%)		652 (45.4%)	530 (51.7%)		358 (51.4%)	350 (55.3%)	
Current	136 (6.4%)	110 (6.6%)		79 (5.5%)	61 (5.9%)		57 (8.2%)	49 (7.7%)	
Diabetes	146 (6.8%)	347 (20.9%)	<.0001	84 (5.8%)	198 (19.3%)	<.0001	62 (8.9%)	149 (23.5%)	<.0001
NSAID use	241 (11.3%)	168 (10.1%)	0.2464	157 (10.9%)	116 (11.3%)	0.7714	84 (12.1%)	52 (8.2%)	0.0206
Acetaminophen use	178 (8.3%)	172 (10.4%)	0.0332	118 (8.2%)	100 (9.7%)	0.1879	60 (8.6%)	72 (11.4%)	0.0937
Aspirin use	837 (39.3%)	1000 (60.3%)	<.0001	580 (40.4%)	646 (63.0%)	<.0001	257 (36.9%)	354 (55.9%)	<.0001
Hypertension	1018 (47.7%)	1164 (70.2%)	<.0001	632 (44.0%)	694 (67.6%)	<.0001	386 (55.5%)	470 (74.2%)	<.0001
Congestive heart failure	45 (2.1%)	70 (4.2%)	0.0002	27 (1.9%)	41 (4.0%)	<.0001	18 (2.6%)	29 (4.6%)	0.0492
Coronary heart disease	73 (3.4%)	277 (16.7%)	<.0001	43 (3.0%)	173 (16.9%)	<.0001	30 (4.3%)	104 (16.4%)	<.0001
Angina	44 (2.1%)	129 (7.8%)	<.0001	18 (1.3%)	73 (7.1%)	<.0001	26 (3.7%)	56 (8.8%)	0.0001
History of myocardial infarction	55 (2.6%)	187 (11.3%)	<.0001	25 (1.7%)	113 (11.0%)	<.0001	30 (4.3%)	74 (11.7%)	0.0001
History of stroke	66 (3.1%)	117 (7.1%)	<.0001	40 (2.8%)	74 (7.2%)	<.0001	26 (3.7%)	43 (6.8%)	0.0121

SD = standard deviation; NSAID = non-steroidal anti-inflammatory drug; Hypertension defined as >140 systolic and/or >90 diastolic blood pressures.

Table 2

Results of the Age-Adjusted Proportional Hazards Regression of the Effect of Statin Use on AMD progression based on AMD Subtype: Hazard Ratios and 95% Confidence Limits for Unmatched for Statin Use Propensity Scores.

	All participants N=3791		Bilateral Large Drusen N = 2462		Unilateral Late AMD N = 1329	
	Hazard Ratio	**95% CI**	**Hazard Ratio**	**95% CI**	**Hazard Ratio**	**95% CI**
Any late age-related macular degeneration						
Without accounting for the competing risk of death	1.08	0.83–1.41	1.00	0.72–1.41	1.20	0.79–1.83
Accounting for the competing risk of death	0.94	0.72–1.22	0.84	0.60–1.18	1.08	0.71–1.65
Any geographic atrophy						
Without accounting for the competing risk of death	1.21	0.85–1.73	1.13	0.74–1.73	1.42	0.74–2.73
Accounting for the competing risk of death	1.06	0.74–1.51	0.96	0.62–1.48	1.29	0.66–2.49
Central geographic atrophy						
Without accounting for the competing risk of death	1.08	0.67–1.74	1.03	0.59–1.80	1.24	0.49–3.16
Accounting for the competing risk of death	0.92	0.57–1.48	0.85	0.48–1.49	1.14	0.45–2.87
Neovascular age-related macular degeneration						
Without accounting for the competing risk of death	1.24	0.89–1.73	1.34	0.86–2.09	1.11	0.66–1.86
Accounting for the competing risk of death	1.07	0.80–1.50	1.12	0.73–1.74	1.00	0.60–1.67

CI = confidence interval.

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Table 3

Baseline Characteristics of Propensity Score-Matched Participants for Statin Use in the Entire Cohort and also in the Groups Stratified by the Baseline AMD Status.

	All participants (N = 2512)*			Bilateral Large Drusen (N = 1546)			Unilateral Late AMD (N = 944)		
	Statin use			Statin use			Statin use		
	No (N=1256) [N (%)]	Yes (N=1256) [N (%)]	P value	No (N=773) [N (%)]	Yes (N=773) [N (%)]	P value	No (N=472) [N (%)]	Yes (N=472) [N (%)]	P value
Age (mean ± SD)	73.3 ± 7.8	73.2 ± 7.4	0.8016	72.1 ± 8.2	72.0 ± 7.4	0.7559	75.2 ± 6.8	75.2 ± 6.8	0.9493
Female	727 (57.9%)	697 (55.5%)	0.2271	453 (58.6%)	433 (56.0%)	0.3038	264 (55.9%)	262 (55.5%)	0.8957
White race	1215 (96.7%)	1213 (96.6%)	0.8016	750 (97.0%)	744 (96.2%)	0.3973	460 (97.5%)	462 (97.9%)	0.6661
Education			0.9848			0.8919			0.8659
High school or less	412 (32.8%)	416 (33.1%)		220 (28.5%)	228 (29.5%)		185 (39.2%)	187 (39.6%)	
At least some college	593 (47.2%)	591 (47.1%)		382 (49.4%)	379 (49.0%)		211 (44.7%)	204 (43.2%)	
Post-graduate	251 (20.0%)	249 (19.8%)		171 (22.1%)	166 (21.5%)		76 (16.1%)	81 (17.2%)	
Smoking			0.7388			0.8257			0.7291
Never	564 (44.9%)	545 (43.4%)		359 (46.4%)	351 (45.4%)		192 (40.7%)	183 (38.8%)	
Former	613 (48.8%)	628 (50.0%)		372 (48.1%)	375 (48.5%)		243 (51.5%)	255 (54.0%)	
Current	79 (6.3%)	83 (6.6%)		42 (5.4%)	47 (6.1%)		37 (7.8%)	34 (7.2%)	
Diabetes	143 (11.4%)	137 (10.9%)	0.7037	77 (10.0%)	67 (8.7%)	0.3815	62 (13.1%)	67 (14.2%)	0.6357
NSAID use	126 (10.0%)	136 (10.8%)	0.5139	78 (10.1%)	81 (10.5%)	0.8017	46 (9.7%)	49 (10.4%)	0.7455
Acetaminophen use	130 (10.4%)	115 (9.2%)	0.3131	74 (9.6%)	68 (8.8%)	0.5973	55 (11.7%)	52 (11.0%)	0.7581
Aspirin use	685 (54.5%)	668 (53.2%)	0.4962	441 (57.1%)	431 (55.8%)	0.6080	232 (49.2%)	288 (48.3%)	0.7945
Hypertension	818 (65.1%)	811 (64.6%)	0.7699	481 (62.2%)	483 (62.5%)	0.9164	331 (70.1%)	322 (68.2%)	0.5259
Congestive heart failure	34 (2.7%)	40 (3.2%)	0.4790	21 (2.7%)	22 (2.8%)	0.8771	15 (3.2%)	16 (3.4%)	0.8551
Coronary heart disease	72 (5.7%)	84 (6.7%)	0.3212	42 (5.4%)	47 (6.1%)	0.5851	30 (6.4%)	29 (6.1%)	0.8930
Angina	42 (3.3%)	45 (3.6%)	0.7434	17 (2.2%)	16 (2.1%)	0.8603	25 (5.3%)	25 (5.3%)	1.0000
History of myocardial infarction	54 (4.3%)	58 (4.6%)	0.6990	25 (3.2%)	31 (4.0%)	0.4141	30 (6.4%)	29 (6.1%)	0.8930
History of stroke	60 (4.8%)	68 (5.4%)	0.4679	36 (4.7%)	37 (4.8%)	0.9046	25 (5.3%)	33 (7.0%)	0.2782

SD = standard deviation; NSAID = non-steroidal anti-inflammatory drug; Hypertension defined as >140 systolic and/or >90 diastolic blood pressures.

* includes 22 participants who were matched based on propensity score with one of the pair from the bilateral large drusen group and the other from the unilateral AMD group.

Table 4

Results of the Age-Adjusted Proportional Hazards Regression of the Effect of Statin Use on AMD Progression Based on AMD Subtype: Hazard Ratios and 95% Confidence Limits for Matched Statin Use Propensity Scores.

	All participants N = 2512*		Bilateral Large Drusen N = 1546		Unilateral Late AMD N = 944	
	Hazard Ratio	**95% CI**	**Hazard Ratio**	**95% CI**	**Hazard Ratio**	**95% CI**
Any late age-related macular degeneration						
Without accounting for the competing risk of death	0.92	0.62–1.36	0.63	0.37–1.05	1.22	0.67–2.20
Accounting for the competing risk of death	0.81	0.55–1.20	0.53	0.31–0.89	1.12	0.62–2.01
Any geographic atrophy						
Without accounting for the competing risk of death	1.07	0.63–1.82	0.74	0.38–1.43	1.86	0.76–4.56
Accounting for the competing risk of death	0.94	0.55–1.62	0.64	0.32–1.26	1.75	0.72–4.24
Central geographic atrophy						
Without accounting for the competing risk of death	0.88	0.43–1.82	0.90	0.38–2.15	1.18	0.32–4.41
Accounting for the competing risk of death	0.76	0.37–1.56	0.76	0.32–1.83	1.14	0.32–4.09
Neovascular age-related macular degeneration						
Without accounting for the competing risk of death	1.07	0.65–1.76	0.86	0.44–1.69	1.36	0.66–2.82
Accounting for the competing risk of death	0.92	0.57–1.52	0.73	0.38–1.42	1.25	0.06–2.59

CI = confidence interval.

* includes 22 participants who were matched based on propensity score with one of the pair from the bilateral large drusen group and the other from the unilateral AMD group.

Table 5

Summary of Previous Study Findings of Studies Evaluating the Association of Statin Use with Age-Related Macular Degeneration (AMD)

Paper	Year	Total participants (N)	OR/HR	95% CI	Odds Ratio/Hazard Ratio Plot Protective Harmful
Hall et al [26]*	2001	379	OR: 0.09	0.01-0.73	
van Leeuwen et al [37]**	2003	4822	HR: 1.1	0.7-1.9	
Klein et al [27]**	2003	2204	OR: 0.41	0.12-1.45	
McGwin et al [28]‡	2003	6050	OR: 0.30	0.21-0.45	
Wilson et al [33] †	2004	326	HR: 0.54	0.33-0.87	
van Leeuwen et al [42]**	2004	8649	OR: 1.0	0.6-1.6	
Smeeth et al [31]***	2005	104176	OR: 0.93	0.81-1.07	
McGwin et al [29]***	2005	12588	OR: 0.83	0.64-1.06	
McGwin et al [36]***	2006	2755	OR: 1.40	0.99-1.98	
Tan et al [32]**	2007	2178	HR: 0.52	0.26-1.04	
Kaiserman et al [44]***	2009	139894	OR: 1.0	0.8-1.3	
Maguire et al [35]**	2009	744	RR: 1.15	0.87-1.52	
Fong et al [25]***	2010	86635	OR: 0.89	0.77-1.03	
Barbosa et al [24]*	2014	5604	OR: 0.69	0.51-0.94	

*Cross-sectional study; **Cohort study; ***Case control study; †Retrospective consecutive case series study; ‡ Nested case control study.

0.001 0.01 0.1 1 10

*Cross-sectional study;

**Cohort study;

***Case control study;

†Retrospective consecutive case series study;

‡Nested case control study.