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# Visual and Morphologic Outcomes in Eyes with Hard Exudate in the Comparison of Age-Related Macular Degeneration Treatments Trials

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***Purpose:*** To compare baseline characteristics, visual acuity (VA), and morphologic outcomes between eyes with hard exudate (HE) at baseline and all other eyes among patients with neovascular age-related macular degeneration (NVAMD) treated with anti−vascular endothelial growth factors (VEGFs).

***Design:*** Prospective cohort study within the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT).

***Participants:*** Patients with NVAMD.

***Methods:*** Readers evaluated baseline and follow-up morphology on digital color images, fluorescein angiography (FA), and optical coherence tomography (OCT) in eyes with NVAMD that were randomly assigned to treatment with ranibizumab or bevacizumab. Ophthalmologists identified HE on color images in the study eye.

***Main Outcome Measures:*** Visual acuity, scar, geographic atrophy, retinal thickness, retinal fluid, and number of anti-VEGF injections.

***Results:*** HE was present in 128 of 1185 study eyes (11%) at baseline, 77% within 1 disc diameter of the foveal center. Patients with study eye HE were more likely to be female (81% vs. 60%; $P < 0.001$) and nonsmokers (53% vs. 42%; $P = 0.004$). Both groups had similar proportions of hypercholesterolemia and hypertriglyceridemia. At baseline, eyes with HE had worse VA (mean 57 vs. 61 letters; $P = 0.003$), larger total lesion size (3.3 vs. 2.4 disc areas; $P < 0.001$), greater total foveal thickness (522 vs. 452 μm; $P < 0.001$), and more retinal angiomatous proliferation (RAP) (18% vs. 10%; $P = 0.009$) and sub−retinal pigment epithelium fluid (65% vs. 47%; $P < 0.001$). At 1 year, VA was similar in both groups; more eyes with baseline HE had no fluid (45% vs. 29%; $P < 0.001$) and greater reduction in total foveal thickness (−266 vs. −158 μm; $P < 0.001$). The VA at year 2 was similar, but retinas of eyes with baseline HE were thinner (267 vs. 299 μm; $P = 0.03$) and fewer eyes had subretinal fluid (23% vs. 36%; $P = 0.008$). HE was present in 19% of eyes at 1 year and 5% of eyes at 2 years. Hepatic lipase promoter single nucleotide polymorphism rs10468017 was not associated with NVAMD HE.

***Conclusions:*** Eyes with HE have larger choroidal neovascularization lesions and more RAP. Their initially thicker retina rapidly becomes thinner with anti-VEGF treatment. HE is not significantly associated with hyperlipidemia. HE at baseline does not significantly influence VA, scar, and geographic atrophy outcomes in eyes with NVAMD treated with anti-VEGF. Few eyes have HE at year 2. *Ophthalmology Retina 2017;1:25-33 © 2016 by the American Academy of Ophthalmology*

Retinal hard exudate (HE) occurs in eyes with macular edema caused by neovascular age-related macular degeneration (NVAMD). Patients who develop NVAMD are typically elderly, and many have coexisting chronic systemic diseases, such as hyperlipidemia, hypercholesterolemia, diabetes mellitus, and hypertension. These diseases by themselves have been associated with retinal HE and are risk factors for developing more severe macular edema in diabetes.[1−5]

Unlike in diabetic macular edema (DME), HE occurring in eyes with NVAMD has not been investigated as a biomarker for more severe macular fluid. It also is not clear whether the presence of HE is associated with any of the systemic diseases that coexist in elderly patients with NVAMD. Furthermore, little is known about the relationship between baseline HE and subsequent visual acuity (VA) in these eyes, other retinal morphologic features in eyes with NVAMD, and HE changes over time. We investigated whether systemic disease associations with the presence of HE reported in DME are present in eyes with NVAMD enrolled in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT). In addition, we investigated whether eyes with HE at baseline had different functional and morphologic outcomes after 2 years of treatment with anti−vascular endothelial growth factor (VEGF).

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## Methods

The methods used in CATT have been described.[6–8] Patients were recruited from 43 clinical centers in the United States between February 2008 and December 2009. Patients needed to be aged more than 50 years, and the study eye (1 per patient) needed to have treatment-naïve NVAMD. Study eye VA needed to be between 20/25 and 20/320. The neovascularization in the study eye could be subfoveal or extrafoveal, but if located in an extrafoveal area, a sequelae of neovascularization, such as fluid, serous pigment epithelial detachment (SPED), blocked fluorescence, or hemorrhage had to be under the foveal center. The presence of leakage on fluorescein angiography (FA) and any fluid on optical coherence tomography (OCT) defined active neovascularization. A history of systemic diseases, such as hypertension, hypercholesterolemia, diabetes mellitus, and hypertriglyceridemia, was obtained from patient interview. Eyes were randomly assigned to treatment with ranibizumab or bevacizumab on a monthly or an as-needed basis. Institutional review boards associated with each center approved the clinical trial protocol. All patients provided written informed consent. The study was compliant with Health Insurance Portability and Accountability Act regulations and adhered to the tenets of the Declaration of Helsinki. The CATT was registered with ClinicalTrials.gov (NCT00593450).

The CATT Fundus Photograph Reading Center at the University of Pennsylvania graded color and FA images at baseline and years 1 and 2. Two trained certified readers independently assessed the images, and discrepant results were adjudicated. Morphologic features identified on these images included active leakage of fluorescein on FA, fibrotic scar, nonfibrotic scar, type of neovascularization (classic, occult, and retinal angiomatous proliferation [RAP]), area of total choroidal neovascularization (CNV) lesion (consisting of CNV and contiguous sequelae other than fluid), hemorrhage, blocked fluorescence contiguous with the CNV, SPED, geographic atrophy (GA), non-GA, retinal pigment epithelium (RPE) tear, and the presence or absence of any of these pathologies in the foveal center. Two independent certified readers at the CATT OCT Reading Center at Duke University graded OCT scans. Discrepant data were arbitrated by an independent senior reader. Readers assessed the following parameters on OCT images: intraretinal fluid, subretinal fluid, sub-RPE fluid, vitreomacular adhesions, and subretinal hyperreflective material. In addition, the center point retinal thickness, subretinal fluid thickness, and subretinal tissue complex thickness were measured.[8] Retinal thickness was the width between the internal limiting membrane and the outer border of the photoreceptors at the foveal center, whereas total foveal thickness at the foveal center in addition to retinal thickness also included the subretinal fluid, subretinal lesion, RPE, and material or fluid below the RPE, and was the width between the internal limiting membrane and the Bruch's membrane at the foveal center irrespective of the RPE location.[8]

HE at baseline, 1 year, and 2 years was graded from stereo color and red-free digital images by an ophthalmologist (E.D.). HE was identified as white or yellowish white waxy deposits with sharp margins on color retinal images, arranged as individual dots, confluent patches, and partial or complete rings surrounding zones of retinal edema and fluid (Fig 1). The red-free image enhanced the discrete nature of the HE and corroborated the assessment from color images. Quantification of HE was based on the total area of retinal HE in relation to the disc area (DA); area was categorized as mild (<0.25 DA), intermediate (≥0.25−<1.00 DA), and severe (≥1.00 DA). The location of HE within 1 disc diameter (DD) of the foveal center was recorded. HE categorized as "suspect" by the ophthalmologist was reviewed by 2 retina specialists (B.J.K. and J.E.G.) to reach a final consensus. A random sample of images containing definite HE, suspect HE, and no HE was graded independently by 1 of the retinal specialists (B.J.K.) and the ophthalmologist (E.D.) to assess agreement on definitive HE.

### Statistical Methods

Baseline characteristics and outcomes at year 1 and year 2 between eyes with and without baseline HE were statistically compared. The 2-group independent *t* test was used to compare means of continuous variables, and the Fisher exact test was used to compare categoric variables. Because of the exploratory nature of our analyses, no adjustment for multiple testing was performed, and a $P$ value <0.05 was considered to be statistically significant. All the statistical analyses were performed using SAS version 9.2 (SAS Institute, Inc., Cary, NC).

## Results

### Baseline Characteristics

Baseline characteristics are listed in Table 1. HE was present in 128 of 1185 CATT patients (11%) at enrollment. The amount of HE at baseline was mild in 63.5% of eyes, intermediate in 25.5% of eyes, and severe in 11% of eyes. The distributions at baseline of age and presence of systemic hypertension, hypercholesterolemia, diabetes, and hypertriglyceridemia in patients with HE were similar to those without HE. A smaller proportion of patients with HE reported a history of myocardial infarction at baseline (6% vs. 13%; $P = 0.02$) than those without HE. A higher proportion of patients with HE were female (81% vs. 60%; $P < 0.001$) and nonsmokers (53% vs. 42%; $P = 0.004$). Eyes with baseline HE had worse baseline mean VA (57 vs. 61 letters; $P = 0.003$), larger CNV area (2.2 vs. 1.7 DAs; $P = 0.009$), and total CNV lesion area (3.3 vs. 2.4 DAs; $P < 0.001$) than eyes without baseline HE. Eyes with HE were more likely to have RAP (18% vs. 10%; $P = 0.009$) and SPED on FA (13% vs. 4%; $P < 0.001$). Although mean retinal thickness was similar between the 2 groups (220 vs. 219 μ; $P = 0.92$), the mean total thickness at the fovea was greater in eyes with HE (522 vs. 452 μm; $P < 0.001$). More eyes with HE had sub-RPE fluid than eyes without HE (65% vs. 45%; $P < 0.001$), whereas cystoid spaces within the retina[8] (80% vs. 74%; $P = 0.20$) and subretinal fluid (83% vs. 82%; $P = 0.90$) were similar in both groups. Cystoid macular edema detected on FA as a petaloid pattern was not significantly associated with HE. The hepatic lipase (LIPC) promoter single nucleotide polymorphism (SNP) rs10468017 was not associated with the presence of HE at baseline.

### Year 1 Outcomes

Mean VA was similar in both groups at 1 year (66 vs. 68 letters; $P = 0.21$). Although the retinal thickness was similar (152 vs. 158 μm; $P = 0.33$), the total thickness at the foveal center was less in eyes that had HE at baseline (263 vs. 295 μm; $P = 0.01$), and there was a larger change in total thickness at the foveal center from baseline (−266 vs. −158 μm; $P < 0.001$). More eyes with HE at baseline had no retinal fluid at 1 year (45% vs. 29%; $P < 0.001$). These eyes also had less subretinal fluid (13% vs. 32%; $P < 0.001$) and sub-RPE fluid (19% vs. 33%; $P = 0.003$) when compared with eyes with no baseline HE. Intraretinal fluid (46% vs. 47%; $P = 0.85$) was not different between the 2 groups at 1 year. Although there were more RPE tears in eyes that had HE at baseline (3.5% vs. 1.5%; $P = 0.11$), this difference was not statistically significant. Among eyes assigned to pro re nata treatment, both groups required the same mean number of injections (7 vs. 7; $P = 0.89$) (Table 2).

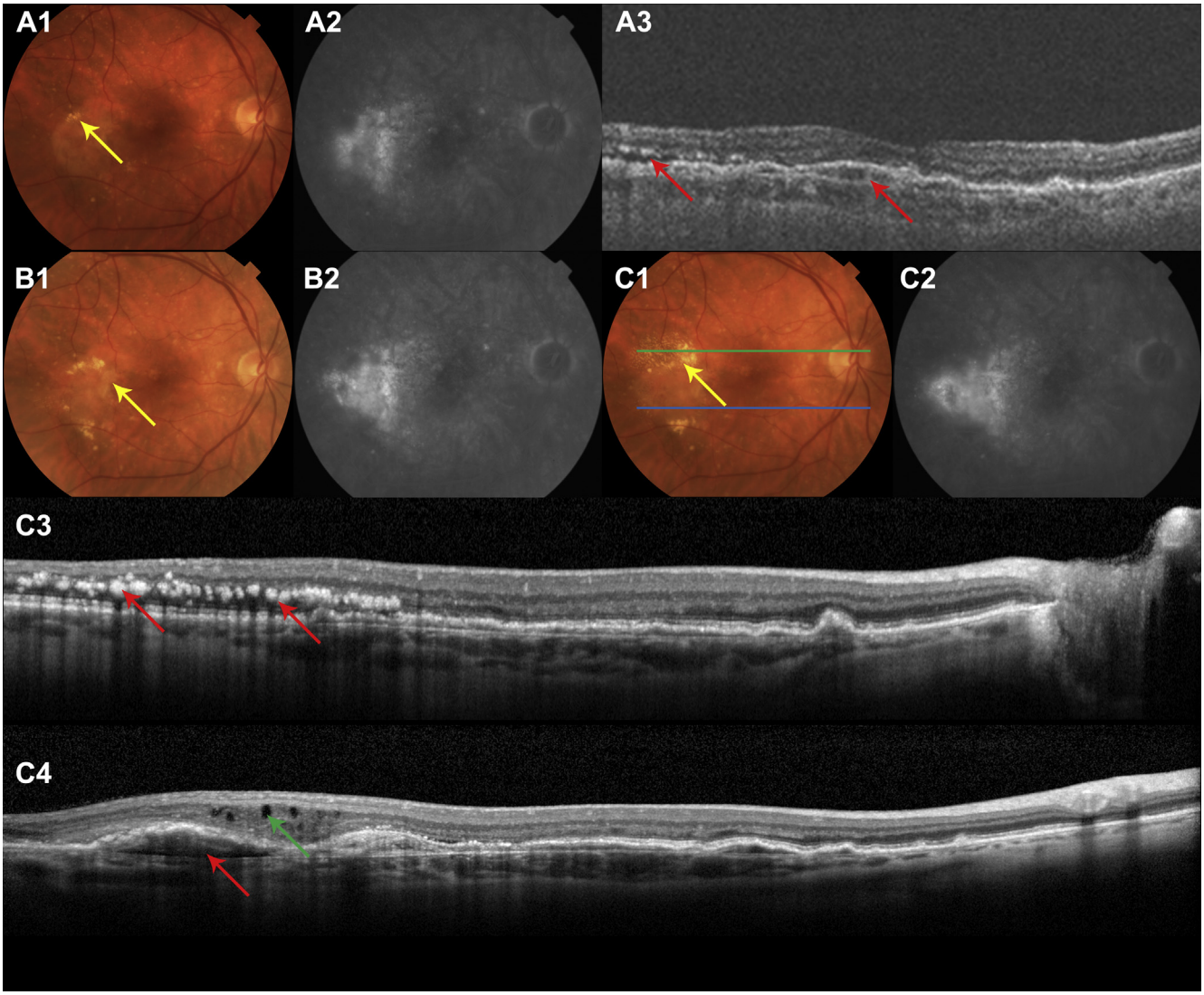


**Figure 1.** **A**, Baseline images: **A1**, color image with a small amount of hard exudate (HE) (*yellow arrow*), **A2**, fluorescein angiogram showing leakage, and **A3** = time-domain optical coherence tomography (OCT) with subretinal and sub−retinal pigment epithelium (RPE) fluid (*red arrows*). **B**, Year 1 images: **B1**, color image with increased amounts of HE, **B2**, fluorescein angiogram showing leakage. **C**, Year 2 images: **C1**, color image showing increased amounts of HE, **C2**, fluorescein angiogram showing leakage. *Top green line* in **C1** corresponds to the Spectralis (Heidelberg Engineering, Carlsbad, CA) OCT scan in **C3** showing HE on OCT (*red arrows*) occupying the lower portion of the inner retina and some HE in the subretinal space. *Bottom blue line* in **C1** corresponds to **C4**, where the Spectralis OCT shows a sub-RPE lesion and fluid (fibrovascular pigment epithelial detachment) (*red arrow*) and intraretinal cystoid spaces (*green arrow*).

## Year 2 Outcomes

Mean VA was similar in both groups at 2 years (65 vs. 68 letters; $P = 0.20$). Although the retinal thickness remained similar (156 vs. 160 μm; $P = 0.56$), the total foveal thickness at the foveal center was less in eyes that had HE at baseline (267 vs. 299 μm; $P = 0.03$), and there was a larger change in total foveal thickness from baseline (−265 vs. −151 μm; $P < 0.001$). Absence of any fluid on OCT was similar in both groups at 2 years (29% vs. 25%; $P = 0.35$), and there was no significant difference in the percentages with intraretinal fluid (60% vs. 50%; $P = 0.09$) or sub-RPE fluid (35% vs. 36%; $P = 0.92$). However, subretinal fluid at 2 years was seen less frequently in eyes that had baseline HE (23% vs. 36%; $P = 0.008$). The RPE tears were similar in both groups (1.8% vs. 1.5%; $P = 0.69$). Both groups required the same number of pro re nata injections in year 2 (6.4 vs. 6.4; $P = 0.86$). At 2 years, HE was present in 6 of 112 eyes (5%) that had HE at baseline (Table 3).

The mean total thickness at the foveal center of eyes with and without HE from baseline through 2 years is shown in Figure 2. Eyes with HE start with greater retinal thickness than eyes without HE but at 4 weeks become slightly thinner, are thinner still at 1 year, and remain thinner through 2 years.

## Hard Exudate within 1 Disc Diameter of Foveal Center versus Hard Exudate Outside 1 Disc Diameter of Foveal Center at Baseline

Among eyes that had HE at baseline, 99 (77%) had HE within 1 DD of the foveal center, and the remaining 29 (23%) had HE

Table 1. Baseline Characteristics by Presence of Hard Exudate

| Characteristic | Value | Hard Exudate at Baseline | | P Value |
|---|---|---|---|---|
| | | *Present (n = 128)* | *Absent (n = 1057)* | |
| Age (yrs) | Mean (SD) | 78.2 (8.4) | 79.4 (7.4) | 0.09 |
| Sex | Female | 103 (80.5%) | 629 (59.5%) | <0.001 |
| Myocardial infarction | Yes | 7 (5.5%) | 133 (12.6%) | 0.02 |
| Congestive heart failure | Yes | 4 (3.1%) | 69 (6.5%) | 0.17 |
| Hypertension | Yes | 87 (68.0%) | 736 (69.6%) | 0.69 |
| Diabetes mellitus | Yes | 16 (12.5%) | 191 (18.1%) | 0.14 |
| Hypercholesterolemia | Yes | 64 (50.0%) | 612 (57.9%) | 0.09 |
| Hypertriglyceridemia | Yes | 10 (7.8%) | 146 (13.8%) | 0.07 |
| Cigarette smoking | Never | 68 (53.1%) | 439 (41.5%) | 0.004 |
| | Current | 15 (11.7%) | 86 (8.1%) | |
| | Former | 45 (35.2%) | 532 (50.3%) | |
| Drug | Ranibizumab | 70 (54.7%) | 529 (50.0%) | 0.35 |
| | Bevacizumab | 58 (45.3%) | 528 (50.0%) | |
| Regimen | Monthly for 2 yrs | 36 (28.1%) | 282 (26.7%) | 0.88 |
| | Monthly yr 1, PRN yr 2 | 27 (21.1%) | 242 (22.9%) | |
| | PRN for 2 yrs | 65 (50.8%) | 533 (50.4%) | |
| VA in study eye | <20/320 | 18 (14.1%) | 85 (8.0%) | 0.02 |
| | 20/200–20/320 | 36 (28.1%) | 220 (20.8%) | |
| | 20/100–20/160 | 43 (33.6%) | 424 (40.1%) | |
| | 20/50–20/80 | 31 (24.2%) | 328 (31.0%) | |
| | Mean (SD) | 57.2 (14.8) | 60.9 (13.3) | 0.003 |
| Type of CNV | Classic | 21 (16.4%) | 241 (23.4%) | 0.09 |
| | Occult | 88 (68.8%) | 608 (58.9%) | |
| | Mixed | 19 (14.8%) | 183 (17.7%) | |
| CNV area | Mean (SD) | 2.2 (2.0) | 1.7 (1.7) | 0.009 |
| Total CNV area* | Mean (SD) | 3.3 (3.3) | 2.4 (2.4) | <0.001 |
| RAP | Yes | 23 (18.1%) | 103 (9.8%) | 0.009 |
| Hemorrhage (associated with the lesion) | <1 DA | 73 (57.0%) | 538 (51.9%) | 0.22 |
| | <2 DA | 9 (7.0%) | 50 (4.8%) | |
| | >2 DA | 7 (5.5%) | 47 (4.5%) | |
| GA | Yes | 6 (4.7%) | 76 (7.2%) | 0.36 |
| Scar | Yes | 4 (3.1%) | 42 (4.0%) | 0.81 |
| Pathology in fovea center | No pathology | 1 (0.8%) | 0 (0.0%) | 0.09 |
| | Fluid only | 32 (25.0%) | 283 (26.8%) | |
| | CNV | 75 (58.6%) | 613 (58.0%) | |
| | Scar | 0 (0.0%) | 7 (0.7%) | |
| | GA | 1 (0.8%) | 0 (0.0%) | |
| | Hemorrhage | 12 (9.4%) | 81 (7.7%) | |
| | Other | 7 (5.5%) | 73 (6.9%) | |
| Angiographic CME (petaloid pattern) | CME | 15 (11.8%) | 77 (7.7%) | 0.21 |
| | IRF without CME | 86 (67.7%) | 680 (67.7%) | |
| | No IRF | 26 (20.5%) | 247 (24.6%) | |
| Serous pigment epithelial detachment | Yes | 16 (12.5%) | 46 (4.4%) | <0.001 |
| Retinal thickness (μm) | Mean (SD) | 220.3 (107.7) | 219.3 (107.7) | 0.92 |
| Total foveal thickness (μm)† | Mean (SD) | 521.6 (224.1) | 452.3 (180.5) | <0.001 |
| IRF | Yes | 102 (79.7%) | 785 (74.3%) | 0.20 |
| Subretinal fluid | Yes | 106 (82.8%) | 864 (81.8%) | 0.90 |
| Sub-RPE fluid | Yes | 82 (65.1%) | 491 (47.3%) | <0.001 |
| Vitreomacular adhesion/traction | Yes | 17 (13.7%) | 126 (12.7%) | 0.78 |
| Subretinal hyperreflective material | Yes | 102 (81.0%) | 806 (77.4%) | 0.43 |
| LIPC genotype | CC | 52 (61.9%) | 388 (51.9%) | 0.22 |
| | CT | 29 (34.5%) | 315 (42.1%) | |
| | TT | 3 (3.6%) | 45 (6.0%) | |

CME = cystoid macular edema; CNV = choroidal neovascularization; DA = disc area; GA = geographic atrophy; IRF = intraretinal fluid; LIPC = hepatic lipase; PRN = pro re nata; RAP = retinal angiomatous proliferation; RPE = retinal pigment epithelium; SD = standard deviation; VA = visual acuity.

*Total CNV area includes CNV and its sequelae, such as hemorrhage, blocked fluorescence, and serous pigment epithelial detachment.

†Total foveal thickness = (retina + subretinal fluid + subretinal hyperreflective material + RPE + sub-RPE fluid and material).

Table 2. Year 1 Outcomes by Presence of Hard Exudate

| Year 1 Outcomes | Value | Hard Exudate at Baseline | | P Value |
|---|---|---|---|---|
| | | *Present (n = 120)* | *Absent (n = 986)* | |
| VA, letters | Mean (SD) | 66.3 (19.2) | 68.2 (17.6) | 0.27 |
| VA change from baseline, letters | Mean (SD) | 9.1 (14.6) | 7.1 (14.7) | 0.15 |
| Hemorrhage contiguous with lesion | Yes | 4 (3.5%) | 17 (1.8%) | 0.27 |
| Serous pigment epithelial detachment | Yes | 1 (0.8%) | 21 (2.1%) | 0.72 |
| Total area of CNV lesion, DA | Mean (SD) | 3.11 (3.12) | 2.65 (2.64) | 0.14 |
| Change of total area of CNV lesion from baseline, DA | Mean (SD) | −0.17 (2.11) | 0.26 (2.30) | 0.07 |
| Retinal thickness (μm) | Mean (SD) | 152.2 (69.8) | 157.8 (58.5) | 0.33 |
| Total foveal thickness (μm)* | Mean (SD) | 262.6 (139.9) | 295.4 (135.2) | 0.01 |
| Change in total foveal thickness from baseline (μm) | Mean (SD) | −265.7 (235.4) | −158.2 (169.2) | <0.001 |
| IRF | Yes | 55 (46.2%) | 461 (47.4%) | 0.85 |
| Subretinal fluid | Yes | 16 (13.4%) | 308 (31.7%) | <0.001 |
| Sub-RPE fluid | Yes | 23 (19.3%) | 311 (32.5%) | 0.003 |
| No fluid on OCT | Yes | 53 (44.5%) | 275 (28.5%) | <0.001 |
| Leakage on FA | Yes | 50 (45.0%) | 429 (46.0%) | 0.92 |
| Pathology in fovea center | No pathology | 31 (25.8%) | 182 (18.5%) | 0.28 |
| | Fluid only | 8 (6.7%) | 78 (7.9%) | |
| | CNV | 22 (18.3%) | 237 (24.0%) | |
| | Scar | 16 (13.3%) | 186 (18.9%) | |
| | GA | 2 (1.7%) | 20 (2.0%) | |
| | Non-GA | 21 (17.5%) | 130 (13.2%) | |
| | Hemorrhage | 0 (0.0%) | 3 (0.3%) | |
| | RPE tear | 2 (1.7%) | 8 (0.8%) | |
| | Other | 18 (15.0%) | 142 (14.4%) | |
| RPE tear | Yes | 4 (3.5%) | 14 (1.5%) | 0.11 |
| GA | Yes | 21 (18.6%) | 153 (16.1%) | 0.50 |
| Scar | Yes | 37 (32.7%) | 342 (35.7%) | 0.60 |
| Subretinal hyperreflective material | Yes | 55 (46.2%) | 460 (47.8%) | 0.77 |
| Mean no. of injections, PRN only | Mean (SD) | 7.2 (3.1) | 7.3 (3.3) | 0.89 |

CNV = choroidal neovascularization; DA = disc area; FA = fluorescein angiogram; GA = geographic atrophy; IRF = intraretinal fluid; OCT = optical coherence tomography; PRN = pro re nata; RPE = retinal pigment epithelium; SD = standard deviation; VA = visual acuity.
*Total foveal thickness = (retina + subretinal fluid + subretinal hyperreflective material + RPE + sub-RPE fluid and material).

located only outside this area. Baseline characteristics and year 1 outcomes were similar between the 2 groups. Year 2 outcomes were similar except that eyes having HE located within 1 DD of the foveal center gained fewer letters (5.6 vs. 13.8 letters; $P = 0.04$).

### Presence or Absence of Hard Exudate at 1 Year

Among 128 eyes that had HE at baseline, 23 (18%) had HE at year 1. Baseline characteristics were similar among eyes with or without HE at year 1, except that eyes with HE at 1 year had a reduced total foveal thickness at the foveal center at baseline (178 vs. 230 μm; $P = 0.04$). At year 1, eyes with HE had a greater retinal thickness (181 vs. 145 μm; $P = 0.03$), a greater proportion with sub-RPE fluid (39% vs. 15%; $P = 0.02$), and a greater proportion with fluorescein leakage (70% vs. 39%; $P = 0.01$). At year 2, eyes with HE at 1 year continued to have greater retinal thickness than eyes without HE at 1 year (208 vs. 145 μm; $P = 0.007$), and a greater proportion had intraretinal fluid (84% vs. 54%; $P = 0.02$), sub-RPE fluid (58% vs. 30%; $P = 0.03$), and fluorescein leakage (50% vs. 18%; $P = 0.01$). Eyes with HE at 1 year had more anti-VEGF intravitreal injections (7.8 vs. 5.6; $P = 0.04$) during year 2.

## Discussion

Our findings demonstrate that the presence of HE in eyes with treatment-naïve NVAMD is associated with greater total foveal thickness (retina + subretinal fluid + subretinal hyperreflective material + RPE + sub-RPE material and fluid) but is not associated with sensory retinal thickness. HE within 1 DD of the foveal center is used as a surrogate marker for clinically significant macular edema (CSME) in diabetic retinopathy screening projects.[1,2] In diabetic maculopathy, HE within 1 DD of the macular center detects CSME with 94% sensitivity, and HE anywhere in the macular region predicted CSME with 89% sensitivity.[3] Although our study was not designed to evaluate the prediction of HE for CSME, the presence of HE anywhere in the macular area of eyes with treatment-naïve NVAMD correlated well with pronounced sub-RPE thickening but not with thickening of the sensory retina, making it useful for detecting fluid and material under the RPE in NVAMD. The appearance of HE in the fundus of patients with early or intermediate age-related macular degeneration (AMD) being followed up by a primary physician using only a handheld direct ophthalmoscope should dictate a quick referral to a retina specialist for a more extensive examination with indirect ophthalmoscopy and OCT, leading up to appropriate treatments.

The macular edema in CATT study eyes with HE at enrollment was composed predominantly of both intraretinal and subretinal fluid, even though the primary source of the fluid was likely from CNV, with only approximately 11% of

Table 3. Year 2 Outcomes by Presence of Hard Exudate

| Year 2 Outcomes | Value | Hard Exudate at Baseline | | P Value |
|---|---|---|---|---|
| | | *Present (n = 112)* | *Absent (n = 922)* | |
| VA, letters | Mean (SD) | 65.2 (20.3) | 67.5 (18.1) | 0.20 |
| VA change from baseline, letters | Mean (SD) | 7.6 (17.8) | 6.2 (16.4) | 0.40 |
| Hemorrhage contiguous with lesion | Yes | 1 (0.9%) | 29 (3.2%) | 0.36 |
| Serous pigment epithelial detachment | Yes | 3 (2.7%) | 22 (2.4%) | 0.74 |
| Total area of CNV lesion, DA | Mean (SD) | 3.70 (3.49) | 3.19 (3.08) | 0.16 |
| Change of total area of CNV lesion from baseline, DA | Mean (SD) | 0.27 (1.98) | 0.82 (2.68) | 0.01 |
| Retinal thickness (μm) | Mean (SD) | 156.0 (92.0) | 160.5 (73.7) | 0.56 |
| Total foveal thickness (μm)* | Mean (SD) | 267.3 (141.9) | 299.2 (142.7) | 0.03 |
| Change in total foveal thickness from baseline (μm) | Mean (SD) | −265.3 (243.2) | −151.4 (180.0) | <0.001 |
| IRF | Yes | 66 (59.5%) | 460 (50.4%) | 0.09 |
| Subretinal fluid | Yes | 26 (23.4%) | 328 (36.0%) | 0.008 |
| Sub-RPE fluid | Yes | 39 (35.1%) | 325 (36.1%) | 0.92 |
| No fluid on OCT | Yes | 32 (28.8%) | 225 (24.7%) | 0.35 |
| Leakage on FA | Yes | 25 (23.6%) | 255 (28.8%) | 0.30 |
| Pathology in fovea center | No pathology | 26 (23.2%) | 178 (19.3%) | 0.39 |
| | Fluid only | 5 (4.5%) | 28 (3.0%) | |
| | CNV | 12 (10.7%) | 165 (17.9%) | |
| | Scar | 22 (19.6%) | 207 (22.5%) | |
| | GA | 6 (5.4%) | 57 (6.2%) | |
| | Non-GA | 24 (21.4%) | 165 (17.9%) | |
| | Other | 17 (15.2%) | 122 (13.2%) | |
| RPE tear | Yes | 2 (1.8%) | 14 (1.5%) | 0.69 |
| GA | Yes | 29 (26.6%) | 187 (20.7%) | 0.17 |
| Scar | Yes | 45 (41.3%) | 394 (43.3%) | 0.76 |
| Subretinal hyperreflective material | Yes | 55 (49.5%) | 412 (46.1%) | 0.55 |
| Mean No. of injections, PRN only | Mean (SD) | 6.4 (3.6) | 6.4 (3.8) | 0.86 |

CNV = choroidal neovascularization; DA = disc area; FA = fluorescein angiogram; GA = geographic atrophy; IRF = intraretinal fluid; OCT = optical coherence tomography; PRN = pro re nata; RPE = retinal pigment epithelium; SD = standard deviation; VA = visual acuity.
*Total foveal thickness = (retina + subretinal fluid + subretinal hyperreflective material + RPE + sub-RPE fluid and material).

the CATT cohort having RAP lesions.[9] However, unlike these 2 types of fluid, sub-RPE fluid was not distributed similarly between the 2 groups (with and without HE), with more eyes that had HE having sub-RPE fluid, suggesting that leakage from occult lesions was the primary source of fluid in eyes with HE. Unlike CSME in diabetes, which is usually associated with large cystic accumulations of intraretinal fluid, presumably because the vascular pathology is located within the sensory retina, the CATT cohort study eyes with HE were not associated with petaloid patterns on FA (angiographic cystoid macular edema).[10] HE related to DME is derived from retinal vasculature and located in the inner layers of the retina down to the outer plexiform layer at its deepest level. This is in contrast to exudates from AMD that arise from subretinal or sub-RPE lesions or RAP and thus may develop preferentially in different locations compared with DME.

Visual acuity and morphologic outcomes did not differ with the location of HE at baseline, other than VA gain at year 2 was less in eyes that had HE located within 1 DD of the foveal center when compared with HE being present external to this area.

Our study results show that many of the associations of HE with serum lipids, comorbidities, and outcomes after treatment observed in patients with DME do not hold for patients with NVAMD. Observational studies, but not interventional studies, reported that patients whose eyes have HE and DME have high levels of serum cholesterol and low-density lipoproteins, and a high total cholesterol—to—high-density lipoprotein ratio, and high triglycerides, and low levels of high-density lipoprotein, when compared with those with DME without HE.[11–17] In contrast to these observations, we found no association between hypercholesterolemia or hypertriglyceridemia and HE in the eyes of patients enrolled in the CATT.

Other researchers have suggested that the causal pathways for cardiovascular disease and AMD could share similar risk factors.[18,19] Both diabetes and hypertension have been reported to be strong risk factors for NVAMD.[20–23] Although the presence of HE might indicate a severe form of diabetic and hypertensive retinopathy, the proportion of patients with diabetes or hypertension in the group with HE was similar to the proportion without HE. However, the CATT study eligibility criteria excluded patients who had any concurrent intraocular condition such as diabetic retinopathy that might require medical or surgical intervention during the 2 years of the study or that could likely contribute to loss of vision over the 2-year follow-up period. Therefore, patients with other signs of nonproliferative retinopathy who might be more likely to have HE generally were not enrolled, which could obscure any true association of these diseases with HE. However, we did find that the presence of HE was significantly associated with not having a history of myocardial infarction. A large retrospective cohort study reported that subjects with NVAMD have lower rates of myocardial infarction,[24] and another study[25] reported that the history of coronary artery disease was a risk

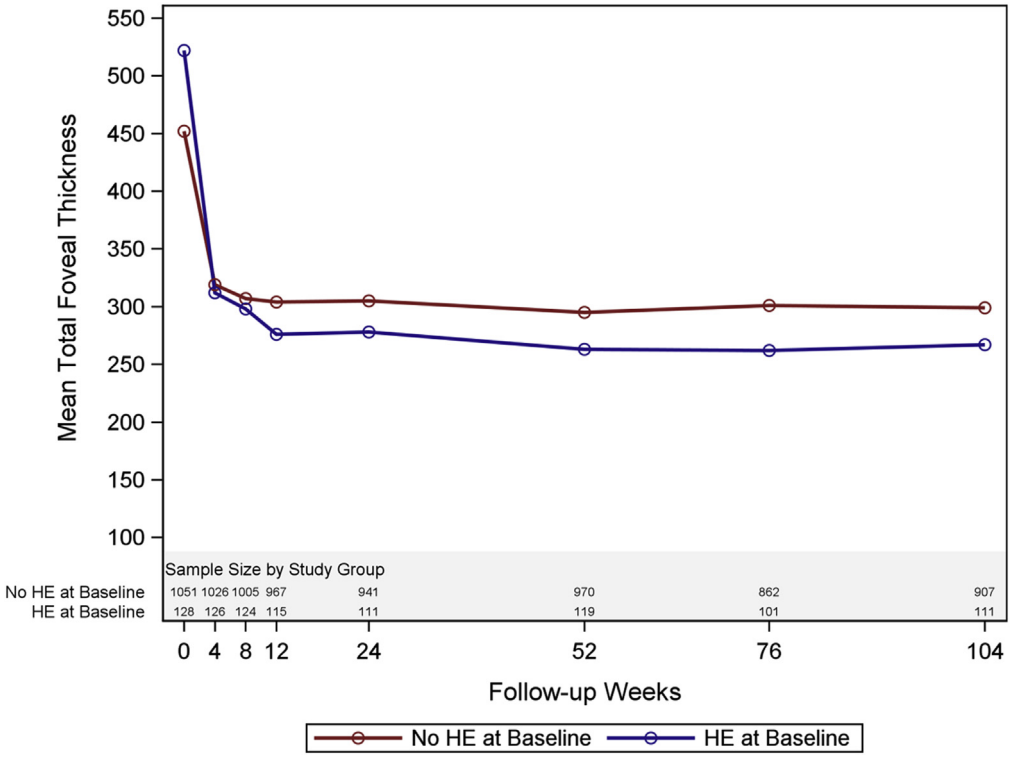


**Figure 2.** Mean total foveal thickness in micrometers (retinal thickness plus subretinal fluid and lesion plus retinal pigment epithelium [RPE] and sub-RPE fluid and lesion thickness) on optical coherence tomography through 2 years between the 2 groups. HE = hard exudate.

factor for polypoidal choroidal vasculopathy but was a protective factor against NVAMD. However, the presence of HE was not assessed in these 2 studies.[24,25]

Our study shows that fluid resolved more quickly with a larger reduction in retinal thickness after anti-VEGF therapy in the eyes that had baseline HE compared with eyes that did not have baseline HE. These findings are consistent with the results of a randomized interventional ranibizumab DME trial in which eyes with macular HE at baseline had a 31-μm (95% confidence interval, 8−53) greater reduction in thickness than eyes without any HE.[26] Diabetic macular edema develops when macromolecules such as lipoproteins and ions leak from retinal capillaries into the extravascular space of the retina, causing an oncotic influx of water into this space, resulting in retinal edema. As this edematous fluid is resorbed by relatively normal capillaries, the concentration of lipoproteins increases, leading to their precipitation and the formation of HE. These HE are often deposited at the border between abnormal and more normal retinal capillaries.[27,28] In NVAMD, in eyes without early RAP, fluid leakage would be derived mostly from CNV, and HE-associated NVAMD eyes, apart from having large amounts of intraretinal and subretinal fluid, also are observed to have more sub-RPE fluid when compared with eyes without HE. It is also possible that the process of fluid absorption had already begun in the eyes that had baseline HE and that the treatment with anti-VEGF drugs accelerated this process, resulting in a larger proportion of these eyes having complete resolution of all fluid and a more rapid decrease in retinal thickness.

We found that among eyes that had HE at baseline, only a small percentage of eyes have HE at the end of the 2-year anti-VEGF treatment period. In contrast, in a short-term study with a 6-month follow-up, there were increasing amounts of HE in eyes with DME that were treated with anti-VEGF therapy, suggesting that the nonlipid fluid components resolve first, followed by resolution of the HE.[29] However, a longer follow-up study found that after 6 months, the percentage of eyes without HE increased from approximately 20% to 60% at the end of 2 years.[30]

A retrospective study done before the era of anti-VEGF treatment for NVAMD that specifically compared eyes with and without HE in NVAMD reported that ill-defined neovascular lesions were significantly associated with the presence of HE.[31] This association, although not statistically significant, was also observed in another study that suggested that the presence of HE in NVAMD was related to large lesion size and occult leakage.[32] In the CATT, CNV and the total CNV lesion areas (comprising the CNV and confluent hemorrhage, blocked fluorescence, SPED) were larger in eyes that had HE. The occult type of CNV also was more common in eyes with HE, although this was not statistically significant. Eyes with HE had more angiographically observed SPED, a finding corroborated by the other study. Retinal angiomatous proliferation is known to be a risk factor in the development of GA, and although eyes with HE had more RAP lesions and more SPED, the development of GA was similar in eyes with and without HE. This is probably because a RAP lesion as a whole seems to be a risk factor for the development of

GA, whereas individual components of RAP, such as HE or SPED, do not seem to carry that risk.

Categorization of eyes with and without HE at year 1 from among those eyes that had HE at baseline did not show any significant difference in visual outcomes at 2 years. In our study, VA outcomes in eyes that had HE at baseline were similar to a DME ranibizumab-treated study that did not find the presence of baseline HE to be a prognostic indicator of a poor VA outcome.[30] Although eyes with HE had thicker retinas, more fluid, and larger CNV lesions than eyes that did not have HE, the VA outcome after anti-VEGF treatment was not much different between the 2 groups. The Early Treatment Diabetic Retinopathy Study reported that severe HE is the strongest risk factor for the development of subretinal fibrosis.[33] HE in NVAMD did not seem to influence the outcome of scar or GA.

Several studies have reported that lipids may play an important role in AMD.[34,35] A genome-wide association study found a significant association between advanced AMD and *LIPC*, the gene encoding hepatic triglyceride lipase.[36,37] A meta-analysis showed that LIPC rs10468017 variant is associated with a reduced risk of advanced AMD.[38] Because HE is composed primarily of lipid material, we investigated whether there could be an association between the LIPC promoter SNP rs10468017 and HE in eyes with NVAMD; our results show that there was no significant association. There are no comparable studies in the current literature investigating SNPs and HE in diabetes.

### Study Limitations

A limitation of our study is that we performed many statistical comparisons between eyes with and without HE for various outcomes without considering multiple testing and other possible confounders. The findings from these exploratory secondary data analyses need to be validated in future studies. The sample size in the HE group also may limit our statistical power to detect small differences between eyes with and without HE.

## Conclusions

The presence of retinal HE in eyes with treatment-naïve NVAMD is a sign of retinal thickening and sub-RPE macular fluid. Anti-VEGF treatment resolves subretinal and sub-RPE fluid better and faster in eyes that had HE at baseline when compared with eyes that did not have HE at baseline. Only a small number of eyes have HE at the end of 2 years. HE is not significantly associated with VA outcomes nor the development of scar or GA. Unlike HE in DME, HE does not seem to be significantly associated with hypercholesterolemia or hypertriglyceridemia. There is no significant association between HE and LIPC promoter SNP rs10468017.

### References


1. Miljanovic B, Glynn RJ, Nathan DM, et al. A prospective study of serum lipids and risk of diabetic macular edema in type 1 diabetes. *Diabetes*. 2004;53:2883–2892.
2. Klein BE, Moss SE, Klein R, Surawicz TS. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. XIII. Relationship of serum cholesterol to retinopathy and hard exudate. *Ophthalmology*. 1991;98:1261–1265.
3. Varma R, Bressler NM, Doan QV, et al. Prevalence of and risk factors for diabetic macular edema in the United States. *JAMA Ophthalmol*. 2014;132:1334–1340.
4. King P, Peacock I, Donnelly R. The UK prospective diabetes study (UKPDS): clinical and therapeutic implications for type 2 diabetes. *Br J Clin Pharmacol*. 1999;48:643–648.
5. Panagiotoglou TD, Ganotakis ES, Kymionis GD, et al. Atorvastatin for diabetic macular edema in patients with diabetes mellitus and elevated serum cholesterol. *Ophthalmic Surg Lasers Imaging*. 2010;41:316–322.
6. CATT Research Group, Martin DF, Maguire MG, Ying GS, et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2011;364:1897–1908.
7. Grunwald JE, Daniel E, Ying GS, et al. Photographic assessment of baseline fundus morphologic features in the Comparison of Age-Related Macular Degeneration Treatments Trials. *Ophthalmology*. 2012;119:1634–1641.
8. DeCroos FC, Toth CA, Stinnett SS, et al. Optical coherence tomography grading reproducibility during the Comparison of Age-related Macular Degeneration Treatments Trials. *Ophthalmology*. 2012;119:2549–2557.
9. Daniel E, Shaffer J, Ying GS, et al. Outcomes in eyes with retinal angiomatous proliferation in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT). *Ophthalmology*. 2016;123:609–616.
10. Shah N, Maguire MG, Martin DF, et al, Comparison of Age-related Macular Degeneration Treatments Trials Research Group. Angiographic cystoid macular edema and outcomes in the Comparison of Age-Related Macular Degeneration Treatments Trials. *Ophthalmology*. 2016;123:858–864.
11. Deák GG, Bolz M, Ritter M, et al, Diabetic Retinopathy Research Group Vienna. A systematic correlation between morphology and functional alterations in diabetic macular edema. *Invest Ophthalmol Vis Sci*. 2010;51:6710–6714.
12. Chew EY, Klein ML, Ferris 3rd FL, et al. Association of elevated serum lipid levels with retinal hard exudate in diabetic retinopathy. Early Treatment Diabetic Retinopathy Study (ETDRS) Report 22. *Arch Ophthalmol*. 1996;114:1079–1084.
13. Sachdev N, Sahni A. Association of systemic risk factors with the severity of retinal hard exudates in a north Indian population with type 2 diabetes. *J Postgrad Med*. 2010;56:3–6.
14. Roy MS, Klein R. Macular edema and retinal hard exudates in African Americans with type 1 diabetes: the New Jersey 725. *Arch Ophthalmol*. 2001;119:251–259.
15. Chang YC, Wu WC. Dyslipidemia and diabetic retinopathy. *Rev Diabet Stud*. 2013;10:121–132.
16. Uçgun NI, Yildirim Z, Kiliç N, Gürsel E. The importance of serum lipids in exudative diabetic macular edema in type 2 diabetic patients. *Ann N Y Acad Sci*. 2007;1100:213–217.
17. Nowak M, Swietochowska E, Marek B, et al. Changes in lipid metabolism in women with age-related macular degeneration. *Clin Exp Med*. 2005;4:183–187.
18. Snow KK, Seddon JM. Do age-related macular degeneration and cardiovascular disease share common antecedents? *Ophthalmic Epidemiol*. 1999;6:125–143.
19. Vassilev ZP, Ruigómez A, Soriano-Gabarró M, García Rodríguez LA. Diabetes, cardiovascular morbidity, and risk of age-related macular degeneration in a primary care population. *Invest Ophthalmol Vis Sci*. 2015;56:1585–1592.
20. Olea JL, Tuñón J. Patients with neovascular age-related macular degeneration in Spain display a high cardiovascular risk. *Eur J Ophthalmol*. 2012;22:404–411.
21. Hyman L, Schachat AP, He Q, Leske MC. Hypertension, cardiovascular disease, and age-related macular degeneration.

Age-Related Macular Degeneration Risk Factors Study Group. *Arch Ophthalmol*. 2000;118:351−358.
22. Hogg RE, Woodside JV, Gilchrist SE, et al. Cardiovascular disease and hypertension are strong risk factors for choroidal neovascularization. *Ophthalmology*. 2008;115:1046−1052.
23. Chen X, Rong SS, Xu Q, et al. Diabetes mellitus and risk of age-related macular degeneration: a systematic review and meta-analysis. *PLoS One*. 2014;9:e108196.
24. Nguyen-Khoa BA, Goehring Jr EL, Werther W, et al. Hospitalized cardiovascular diseases in neovascular age-related macular degeneration. *Arch Ophthalmol*. 2008;126:1280−1286.
25. Meng Q, Huang L, Sun Y, et al. Effect of high-density lipoprotein metabolic pathway gene variations and risk factors on neovascular age-related macular degeneration and polypoidal choroidal vasculopathy in China. *PLoS One*. 2015;10:e0143924.
26. Bressler SB, Qin H, Beck RW, et al, Diabetic Retinopathy Clinical Research Network. Factors associated with changes in visual acuity and central subfield thickness at 1 year after treatment for diabetic macular edema with ranibizumab. *Arch Ophthalmol*. 2012;130:1153−1161.
27. Ferris 3rd FL, Patz A. Macular edema. A complication of diabetic retinopathy. *Surv Ophthalmol*. 1984;28:452−461.
28. Sophie R, Lu N, Campochiaro PA. Predictors of functional and anatomic outcomes in patients with diabetic macular edema treated with ranibizumab. *Ophthalmology*. 2015;122:1395−1401.
29. Pemp B, Deák G, Prager S, et al, Diabetic Retinopathy Research Group Vienna. Distribution of intraretinal exudates in diabetic macular edema during anti-vascular endothelial growth factor therapy observed by spectral domain optical coherence tomography and fundus photography. *Retina*. 2014;34:2407−2415.
30. Domalpally A, Ip MS, Ehrlich JS. Effects of intravitreal ranibizumab on retinal hard exudate in diabetic macular edema: findings from the RIDE and RISE phase III clinical trials. *Ophthalmology*. 2015;122:779−786.
31. Lozano-Rechy D, Duker JS, Jalkh AE. Lipid exudation in age-related macular degeneration. *Am J Ophthalmol*. 1993;116:140−147.
32. Ali F, Chan WC, Stevenson MR, et al. Morphometric analysis of angiograms of exudative lesions in age-related macular degeneration. *Arch Ophthalmol*. 2004;122:710−715.
33. Early Treatment Diabetic Retinopathy Study Research Group. Subretinal fibrosis in diabetic macular edema. Early Treatment Diabetic Retinopathy Study Report Number 23. *Arch Ophthalmol*. 1997;115:873−877.
34. Seddon JM, Cote J, Rosner B. Progression of age-related macular degeneration: association with dietary fat, transunsaturated fat, nuts, and fish intake. *Arch Ophthalmol*. 2003;121:1728−1737.
35. SanGiovanni JP, Chew EY, Clemons TE, et al. The relationship of dietary lipid intake and age-related macular degeneration in a case-control study: AREDS report no. 20. *Arch Ophthalmol*. 2007;125:671−679.
36. Neale BM, Fagerness J, Reynolds R, et al. Genome-wide association study of advanced age-related macular degeneration identifies a role of the hepatic lipase gene (LIPC). *Proc Natl Acad Sci U S A*. 2010;107:7395−7400.
37. Reynolds R, Rosner B, Seddon JM. Serum lipid biomarkers and hepatic lipase gene associations with age-related macular degeneration. *Ophthalmology*. 2010;117:1989−1995.
38. Lou LX, Hu KM, Jin K, et al. The relationship between hepatic lipase gene variant and advanced age-related macular degeneration: a meta-analysis. *JAMA Ophthalmol*. 2014;132:1226−1231.

## Footnotes and Financial Disclosures

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Abbreviations and Acronyms:
**AMD** = age-related macular degeneration; **CATT** = Comparison of Age-Related Macular Degeneration Treatments Trials; **CNV** = choroidal neovascularization; **CSME** = clinically significant macular edema; **DA** = disc area; **DD** = disc diameter; **DME** = diabetic macular edema; **FA** = fluorescein angiography; **GA** = geographic atrophy; **HE** = hard exudate; **LIPC** = hepatic lipase; **NVAMD** = neovascular age-related macular degeneration; **OCT** = optical coherence tomography; **RAP** = retinal angiomatous proliferation; **RPE** = retinal pigment epithelium; **SNP** = single nucleotide polymorphism; **SPED** = serous pigment epithelial detachment; **VA** = visual acuity; **VEGF** = vascular endothelial growth factor.

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