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# Association Between Cilioretinal Arteries and Advanced Age-Related Macular Degeneration

## Secondary Analysis of the Comparison of Age-Related Macular Degeneration Treatment Trials (CATT)

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**IMPORTANCE** Recent reports suggest that cilioretinal arteries (CRAs) confer protection against developing advanced age-related macular degeneration (AMD).

**OBJECTIVE** To further characterize the association between the presence of a CRA and incidence of geographic atrophy (GA) or choroidal neovascularization (CNV).

**DESIGN** This cohort study constituted an ad hoc secondary analysis of data from the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) and was performed at 44 clinical centers in the United States among participants in CATT with CNV in the study eye and without advanced AMD in the fellow eye at baseline. The presence of a CRA was determined by 2 graders, masked to clinical data, using color fundus photographs, red-free fundus photographs, and fluorescein angiography. The proportion with CRAs at baseline between the study eye with CNV and fellow eye without CNV was first compared. The association of a CRA with incidence of CNV or GA at 5 years among fellow eyes and with incidence of GA among study (treated) eyes was then assessed. In addition, the association of CRAs with the Age-Related Eye Disease Study severity scale among the fellow eyes at baseline was assessed. Data were collected from February 1, 2008, through April 30, 2015, and analyzed from July 1, 2018, through April 30, 2019.

**EXPOSURES** Presence of a CRA.

**MAIN OUTCOMES AND MEASURES** The association between the presence of a CRA and incidence of CNV or GA at 5 years of follow-up.

**RESULTS** A total of 350 patients (700 eyes) (230 [65.7% women; mean [SD] age, 77 [7.2] years) were included in the analysis. Cilioretinal arteries were present in 67 of 345 (19.4%) fellow eyes without baseline CNV and 73 of 349 (20.9%) study eyes with baseline CNV ($P$ = .60). Cilioretinal arteries in fellow eyes were not associated with incidence of CNV at 5 years (125 of 278 [45.0%] among eyes without CRAs and 30 of 67 [44.8%] among eyes with CRAs; $P$ = .99) or with incidence of GA at 5 years (110 of 278 [39.6%] among eyes without CRAs and 25 of 67 [37.3%] among eyes with CRAs; $P$ = .89). Cilioretinal arteries in study eyes were not associated with incidence of GA at 5 years (105 of 276 [38.0%] study eyes without CRAs and 26 of 73 [35.6%] study eyes with CRAs; $P$ = .72).

**CONCLUSIONS AND RELEVANCE** The analysis did not find a protective association between CRAs and incidence of CNV or GA among CATT participants who had unilateral exudative AMD. Why these findings were different from those of previous publications is unclear but may be partially explained by the different techniques used to detect CRAs or by the baseline advanced disease in CATT participants.

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Our understanding of the pathophysiology of age-related macular degeneration (AMD) and its risk factors is incomplete. Early AMD is characterized by drusen and is thought to be related to lipid leakage and accumulation, complement system factors, and choroidal factors involving hypoperfusion and reduced heat dissipation.[1-3] Geographic atrophy (GA) and choroidal neovascularization (CNV) define advanced AMD, although they are disparate conditions and likely have distinct pathophysiological features.

The primary insult leading to exudative AMD may be degeneration of the choriocapillaris.[4] Tissue hypoxia may result in production of vascular endothelial growth factor (VEGF) and the development of exudative AMD.[4] Recently, Snyder et al[5] used data and images from the Age-Related Eye Disease Study (AREDS) and found that cilioretinal arteries (CRAs) were protective against developing exudative AMD. Cilioretinal arteries are supplementary arteries, not present in all eyes, that arise from the choroidal vasculature and supply blood to the retina.[6] The retina is supplied by 2 arterial systems: the choroid supplies the outer retina, and the retinal arteries—along with CRAs, if present—deliver blood to the inner retina.

Studies using ophthalmoscopic examination and fundus photography have identified CRAs in 15% to 28% of eyes.[7-9] Fluorescein angiography has also been used to identify CRAs and is believed to be more accurate.[6]

Reports from additional smaller studies have noted that CRAs are protective against the development of AMD.[10] These findings are consistent with the hypothesis that the presence of CRAs could improve oxygen delivery to the macula, thus improving the hypoxic state thought to contribute to the development of CNV. We sought to study the association between CRAs and advanced AMD by using photographs from the Comparisons of Age-Related Macular Degeneration Treatments Trials (CATT).

## Key Points

**Question** Is the presence of cilioretinal arteries, supplemental retinal arteries, associated with the incidence of advanced age-related macular degeneration?

**Findings** In this cohort study, among 350 patients who did not have advanced age-related macular degeneration in the nonstudy eye at baseline and were followed up for 5 years, no association between the presence of cilioretinal arteries and choroidal neovascularization or geographic atrophy was found.

**Meaning** The pathophysiological features of age-related macular degeneration may be secondary to tissue hypoxia and impaired heat dissipation, although no association between cilioretinal arteries and the incidence of advanced age-related macular degeneration was found.

## Methods

CATT is a multicenter randomized clinical trial of treatment with anti-VEGF agents for exudative AMD.[11,12] Patients with exudative AMD were randomized to ranibizumab or bevacizumab for monthly intravitreal injections or as needed. CATT participants who completed 5 years of follow-up and who had exudative AMD in the study eye, no exudative AMD in the fellow eye, and no GA in either eye at baseline were included in this ad hoc substudy performed at 44 clinical centers in the United States. This study was approved by the institutional review board of each participating clinical site, and participants provided written informed consent. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Data were collected from February 1, 2008, through April 30, 2015. Two ophthalmologists (J.C.B. and E.D.) who were masked to clinical data graded the presence of CRAs in each eye using color fundus photography, red-free photography, and fluorescein angiography. We defined a CRA as a retinal vessel arising from the border of the optic disc with a curved path extending into the macular region, with no clear association with any branches arising from the central retinal artery.

The incidence of CNV in the CATT fellow eyes was indicated by treatment with anti-VEGF injection during follow-up.[13] Incidence of GA was defined by a color photographic finding of atrophy of the retinal pigment epithelium of at least 250 µm with at least 2 of the following 3 features: visible choroidal vessels, sharp edges, and a circular shape.[14]

### Statistical Analysis

Data were analyzed from July 1, 2018, through April 30, 2019. We used $\chi^2$ tests to compare the 5-year incidence rates of GA and CNV between fellow eyes with vs without CRAs. We calculated the odds ratios and their 95% CI for their associations using multivariable logistic regression models with adjustment of age, sex, and smoking status at baseline. Similar analysis was performed among study eyes for the association between CRAs and incidence of GA. We evaluated the difference in the proportion with CRAs between the study eye and fellow eye without CNV at baseline using the McNemar test. In addition, we assessed the association of CRAs with the AREDS simplified severity scale (range, 0-2, with higher scores indicating greater severity) among the fellow eyes at baseline. Two-sided $P < .05$ indicated significance.

## Results

The study included 700 eyes from 350 participants. At baseline, the mean (SD) age was 77 (7.2) years, 230 (65.7%) were women, 120 (34.3%) were men, 176 (50.3%) were former smokers, and 23 (6.6%) were current smokers. Five fellow eyes and 1 study eye had indeterminate findings for CRAs and were excluded from the analysis. We found no significant difference in the presence of CRAs in fellow eyes and study eyes at baseline. CRAs were present in 67 of 345 (19.4%) fellow eyes without baseline CNV and 73 of 349 (20.6%) study eyes with baseline CNV ($P = .60$); CRAs were present in both eyes in 25 of 344 participants (7.3%). Cilioretinal arteries in fellow eyes were not associated with incidence of CNV at 5 years (125 of 278 [45.0%] in eyes without CRAs and 30 of 67 [44.8%] in eyes with CRAs; $P = .99$) or with incidence of GA at 5 years (110 of 278 [39.6%] in eyes without CRAs and 25 of 67 [37.3%] in eyes with CRAs; $P = .89$) (**Table**). Cilioretinal arteries in study eyes treated with anti-VEGF agents for neovascular AMD were not associated with incidence of GA at 5 years (105 of 276

Table. Association of Baseline CRAs With Study Findings

| Feature | Baseline CRA Present, No./Total No. (%) | | | Adjusted Analysis[a] | |
|---|---|---|---|---|---|
| | No | Yes | *P* Value | AOR (95% CI) | *P* Value |
| Fellow eyes[b] | 278/345 (80.6) | 67/345 (19.4) | NA | NA | NA |
| Incidence of CNV in fellow eye by 5 y | 125/278 (45.0) | 30/67 (44.8) | .98 | 0.99 (0.58-1.71) | .99 |
| Incidence of GA in fellow eye by 5 y | 110/278 (39.6) | 25/67 (37.3) | .75 | 0.96 (0.54-1.71) | .89 |
| AREDS simplified severity scale in fellow eye at baseline[c,d] | | | | | |
| 0 | 18/271 (6.6) | 3/65 (4.6) | | | |
| 1 | 51/271 (18.8) | 10/65 (15.4) | .82 | NA | NA |
| 2 | 202/271 (74.5) | 52/65 (80.0) | | | |
| Study eyes[e] | 276/349 (79.1) | 73/349 (20.9) | NA | NA | NA |
| Incidence of GA in study eye by 5 y | 105/276 (38.0) | 26/73 (35.6) | .71 | 0.90 (0.52-1.58) | .72 |

Abbreviations: AOR, adjusted odds ratio; AREDS, Age-Related Eye Disease Study; CNV, choroidal neovascularization; CRAs, cilioretinal arteries; GA, geographic atrophy; NA, not applicable.

[a] Calculated using those without CRAs as the reference group and adjusted by age, sex, and smoking status.

[b] Five fellow eyes had indeterminate findings for CRAs and were excluded from analysis.

[c] Seven fellow eyes without baseline CRAs and 2 fellow eyes with baseline CRAs had indeterminate findings in the AREDS simplified severity scale and were excluded from this analysis.

[d] Scores range from 0 to 2, with higher scores indicating greater severity.

[e] One study eye had indeterminate findings for CRAs and was excluded from analysis.

[38.0%] in study eyes without CRAs and 26 of 73 [35.6%] in eyes with CRAs; *P* = .72) (Table). Among fellow eyes, no association between presence of a CRA and the AREDS severity scale score at baseline was found (*P* = .82) (Table).

## Discussion

Although the pathogenesis of exudative AMD is incompletely understood, one proposed mechanism involves a primary vascular disease with degeneration of the choriocapillaris, which could lead to angiogenic signaling resulting in CNV.[4] The finding by Snyder et al[5] that CRAs were protective against development of CNV suggests that accessory blood supply to the retina alters the environmental factors, preventing development of CNV. Furthermore, CRAs have been associated with less subretinal fluid in eyes with exudative AMD,[15] again suggesting changes to the retinal environment associated with CRAs.

Our study, however, found no association between CRAs and exudative AMD. The reasons for these different findings are unclear. One possible contributing factor to the conflicting results is the different techniques used to detect CRAs. Our study included multiple imaging modalities, which may have allowed for more accurate evaluation than the color fundus photography used by Snyder et al,[5] although the prevalence of CRAs detected in the 2 studies was similar at approximately 20% of eyes. Also, AREDS followed up participants with early AMD at baseline, whereas CATT study participants already had exudative AMD in the study eye at baseline, and more than one-third of fellow eyes developed advanced AMD during the 5-year follow-up. Along with more advanced disease, the mean age of the CATT cohort (77 years) was older than the mean age of the AREDS cohort (69 years). It is possible that the protective effect of CRAs was not seen in CATT participants because their more advanced disease may have been resistant to minor protective environmental factors. In addition, our sample size was smaller, and, as reflected by 95% CIs, a small or moderate effect may exist.

The primary defect in GA, in contrast to the vascular etiology proposed for CNV, is thought to be degeneration of the retinal pigment epithelium, with possible contributions from oxidative stress, light toxicity, and genetic factors.[4] As such, how a CRA would protect against development of GA is unclear, and no association was found between CRAs and GA in this study or that of Snyder et al.[5]

### Limitations

A limitation of our study and that of Snyder et al[5] is imperfect identification of CRAs. The most definitive technique would require fluorescein angiography, although we found that capturing early CRA fluorescence is technically difficult, likely owing to the brief window of choroidal fluorescence before retinal arterial fluorescence. Describing the area supplied by the CRA is also challenging and would likely be an important variable.

## Conclusions

The proposed mechanisms for advanced AMD, especially CNV, suggest that variations in vascular supply, such as CRAs, could affect disease progression. However, such an association was not found in this study. Further research, with methods addressing our limitations, might help further characterize the mechanisms of progression to advanced AMD.

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