Effect of retinal thickness variability on visual outcomes and fluid persistence in neovascular age-related macular degeneration: a post hoc analysis of the HAWK and HARRIER studies

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EFFECT OF RETINAL THICKNESS VARIABILITY ON VISUAL OUTCOMES AND FLUID PERSISTENCE IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION

A Post Hoc Analysis of the HAWK and HARRIER Studies

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Purpose: To determine the association between central subfield thickness (CST) variability and visual outcomes in eyes with neovascular age-related macular degeneration treated with anti–vascular endothelial growth factor therapies.

Methods: In this post hoc, treatment-agnostic analysis, patients (N = 1,752) were grouped into quartiles of increasing CST variation. The association between CST variability and best-corrected visual acuity was measured from baseline, or from the end of the loading phase, until the end of the study using a multilevel modeling for repeated-measures model. The association between CST variability and the presence of retinal fluid was also assessed.

Results: Increased CST variability was associated with worse best-corrected visual acuity outcomes at the end of study, with a least-square mean difference in best-corrected visual acuity of 8.9 Early Treatment Diabetic Retinopathy Study letters between the quartiles with the lowest and highest CST variability at the final visit. Increased variability was also associated with a higher mean fraction of visits with the presence of fluid.

Conclusion: More stable CST was associated with better visual outcomes at the end of treatment suggesting that CST variability may provide a more reliable prognostic marker of visual outcomes than the presence of fluid alone, with the potential to enhance the clinical care of neovascular age-related macular degeneration patients.

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Neovascular age-related macular degeneration (nAMD) is a leading cause of vision loss in the developed world, predominantly affecting people older than 60 years. With an estimated global prevalence of 8.7%, it is predicted that 288 million people worldwide will be affected by the year 2040.[1] Neovascular age-related macular degeneration is characterized by the presence of exudative manifestations in the macula, including intraretinal, subretinal, and sub-retinal pigment epithelium fluid as indicators of active disease for which anti–vascular endothelial growth factor (VEGF) treatment may be warranted.[2–5]

Optical coherence tomography (OCT) is an important diagnostic imaging tool for the management of nAMD by supporting diagnosis and monitoring of anti-VEGF treatment outcomes and facilitating retreatment decisions through the accurate assessment of retinal thickness and morphology over time.[3,4] However, real-world patient outcomes with anti-VEGF treatment continue to fall short of those in prospective clinical studies, and definitive conclusions on the prognostic value of morphologic parameters are lacking.[6,7] Although studies have shown that the absence of fluid on OCT, if not associated with atrophy or fibrosis development, is associated with

favorable best-corrected visual acuity (BCVA) outcomes, the relationship between morphological change and visual outcomes remains unclear and may vary depending on fluid localization, extent, and individual patient factors.[8–14] Therefore, there is a need for additional parameters that can predict visual outcomes to allow for more tailored treatment regimens for individual patients.

Recently, a post hoc analysis of OCT data from the CATT and IVAN studies investigated the association between fluctuations in retinal thickness and visual function in eyes with nAMD undergoing anti-VEGF treatment with ranibizumab or bevacizumab. Using a treatment-agnostic approach, this analysis showed that participants with higher levels of variation in retinal thickness over time had worse BCVA outcomes than those with lower levels; higher levels of variability were also associated with an increased likelihood of fibrosis at the end of the study.[15]

The Phase-3 HAWK and HARRIER studies demonstrated that brolucizumab, a novel single-chain antibody fragment anti-VEGF therapy, is noninferior to aflibercept in BCVA outcomes in patients with nAMD.[16,17] The aim of this post hoc treatment-agnostic analysis of data from the HAWK and HARRIER studies was to assess the association between variability in retinal thickness and BCVA in patients with nAMD receiving anti-VEGF treatment of brolucizumab or aflibercept; the relationship between retinal thickness fluctuations and the likelihood of fluid presence after the loading phase was also examined. In addition to confirming the outcomes of the CATT and IVAN analysis, which evaluated retinal thickness fluctuations from baseline until the end of the study, this analysis of HAWK and HARRIER data examined retinal thickness fluctuations after the loading phase from Week 12.

Methods

Study Population and Treatment

The HAWK (NCT02307682) and HARRIER (NCT02434328) studies were two prospective, 96-week, randomized, double-masked, multicenter, Phase-3 clinical trials conducted at 408 sites in North, Central, and South America; Europe; Asia; Australia; and Japan.[16] The studies were conducted in accordance with the principles of the Declaration of Helsinki, International Conference on Harmonization E6 Good Clinical Practice Consolidated Guidelines, and other regulations as applicable and were compliant with the Health Insurance Portability and Accountability Act of 1996. The protocol was approved by an Independent Ethics Committee/Institutional Review Board at each study site, and all study participants provided written informed consent. The trial protocols and statistical analysis plans have been previously published.[16]

Eligible patients were aged ≥50 years and had untreated, active, choroidal neovascularization lesions

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secondary to AMD affecting the central subfield; intraretinal fluid (IRF) and/or subretinal fluid (SRF) affecting the central subfield as assessed on spectral-domain OCT (SD-OCT); and BCVA between 78 and 23 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (Snellen equivalent approximately 20/32–20/400). Full inclusion and exclusion criteria have been reported previously.[16]

Eyes were randomized 1:1:1 to brolucizumab 3 mg, brolucizumab 6 mg, or aflibercept 2 mg (HAWK) or 1:1 to brolucizumab 6 mg or aflibercept 2 mg (HARRIER). After injections at Weeks 0, 4, and 8 (loading phase), brolucizumab was injected every 12 weeks unless disease activity was identified, whereby treatment was adjusted to every 8 weeks for the remainder of the study; aflibercept was injected every 8 weeks, as per label at study initiation.[16,17]

Clinical Assessments

In both studies, visual and anatomical assessments were conducted at baseline and every four weeks thereafter by masked investigators. Best-corrected visual acuity was measured using ETDRS charts. Central subfield thickness (CST) and the presence of IRF and/or SRF were assessed using SD-OCT. A Central Reading Center (Duke Reading Center, NC for HAWK and Vienna Reading Center, Vienna, Austria for HARRIER) was used to assess SD-OCT images. Standardized procedures for the collection of images were provided by the Central Reading Center to the study centers. Before study images were obtained, study center personnel, test images, systems, and software were certified and validated by the Central Reading Center.

Statistical Analyses

For this post hoc analysis of the HAWK and HARRIER studies, pooled data were analyzed using a treatment-agnostic approach. The standard deviation (SD) of a patient's CST measurements (SD [CST]) for either the entire study (baseline to Week 96) or postloading phase (Week 12–96) was used as a metric of individual CST variability/stability. Patients were grouped into quartiles of increasing SD (CST), designated as Q1 (lowest variability) to Q4 (highest variability). Only patients with at least three observations of CST postloading phase were included in the analysis.

To evaluate the association between SD (CST) and BCVA outcomes, data from all treatment arms of both studies were pooled. Least-squares mean difference in BCVA at Week 96 and adjusted mean BCVA change for the entire study or postloading phase for each quartile were calculated using a multilevel modeling for repeated measures model. Best-corrected visual acuity (at baseline or Week 12), SD (CST) quartile, clinical study, and age ($<$75 years old, $\geq$75 years old) were fixed effects.

To evaluate the association between SD (CST) and the presence of fluid post-loading phase, categorized as the mean fraction of visits with the presence of IRF and/or SRF, pooled data from all treatment arms are presented separately for each study. Statistical analysis was performed using R software (Version 3.4.3).[18]

Results

Post hoc Analysis Population

In the HAWK and HARRIER studies, 1,825 patients were randomized to treatment (1,082 in HAWK and 743 in HARRIER).[16] Of 1,817 patients in the full analysis set (all enrolled patients who received $\geq$1 injection), 1,752 patients with $\geq$3 CST observations post loading phase were included in this post hoc analysis. Baseline demographics and patient characteristics were generally well balanced across studies (see **Table**, **Supplemental Digital Content 1**, http://links.lww.com/IAE/B561).[16] Mean BCVA at baseline was 60.6 ETDRS letters in HAWK and 61.2 letters in HARRIER, and mean CST at baseline was 462.5 μm in HAWK and 469.5 μm in HARRIER.[16]

Patients included in the post hoc analysis were categorized into quartiles (n = 438 each) of increasing CST variability (Q1 [lowest] to Q4 [highest]), from both baseline to Week 96 and from Week12 to Week 96. The quartiles ranged from minimal variability in CST post-loading phase in Q1 to marked variability in CST post-loading phase in Q4. The range of SD (CST) for each quartile for the entire study and for the post-loading phase is shown in Table 1, baseline ocular characteristics for each quartile in the two analyses are shown in **Supplemental Digital Content 2** (see **Table**, http://links.lww.com/IAE/B562) and **Supplemental Digital Content 3** (see **Table**, http://links.lww.com/IAE/B563).

Relationship Between Central Subfield Thickness Variability and Best-Corrected Visual Acuity Outcomes

An analysis of BCVA outcomes for each SD (CST) quartile showed a least-squares mean difference between Q1 and Q4 of 8.9 ETDRS letters for the entire study and 6.5 letters for the post-loading phase (Figure 1, A and B). With Q1 as the reference quartile, there was evidence of a gradation of worsening BCVA with increasing magnitude in CST fluctuation. A similar pattern was seen within each

Table 1. Central Subfield Thickness Variability Quartiles: Range of CST Variation for Each Quartile

Quartile	Patients (n)	Baseline to Week 96 Analysis SD (CST) Range (μm)	Week 12 (Postloading) to Week 96 Analysis SD (CST) Range (μm)
Q1	438	<26	<8
Q2	438	26–43	8–18
Q3	438	43–67	18–39
Q4	438	>67	>39

Q, quartile.

trial (see **Figure**, **Supplemental Digital Content 4**, http://links.lww.com/IAE/B564). A further analysis of BCVA over time showed that patients with lower CST variability had a higher mean increase in BCVA from baseline until Week 96 (Figure 2A), with a difference of approximately 8 ETDRS letters between Q1 and Q4 by the end of the study (least-squares mean [standard error] change in BCVA: Q1, 10.1 [0.59]; Q2, 8.5 [0.58]; Q3, 6.8 [0.58]; Q4, 1. 2 [0.59]).

In addition to analyzing the impact of CST variability over the entire study, patients were also grouped into quartiles based on SD (CST) between Week 12 and Week 96. Once initial variability in CST during the loading phase is excluded, there is a notable change in the trajectory of BCVA between quartiles with Q1 (lowest variability) showing a sustained increase in BCVA to a mean gain of approximately 3 letters at the end of the study, whereas Q4 (highest variability) steadily worsens to a mean loss of approximately 3.5 letters over the maintenance phase; Q2 and Q3 display a similar pattern with a mean gain of approximately 1 letter (Figure 2B).

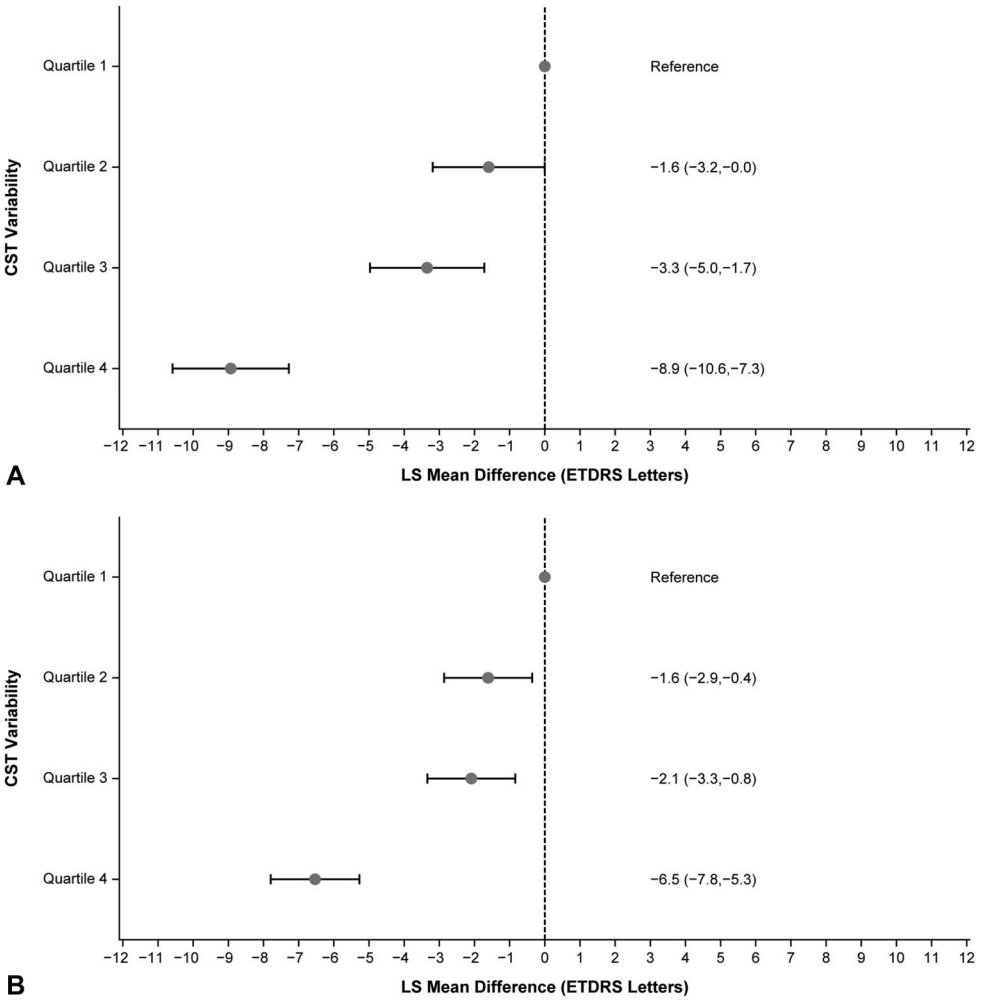

Fig. 1. Association between CST variability and BCVA from baseline to Week 96 (**A**) and Week 12 to Week 96 (**B**). Pooled data from the brolucizumab and aflibercept treatment arms from the HAWK and HARRIER studies were used. LS mean and SE estimates were calculated using a MMRM model with baseline BCVA, SD (CST) quartile, study, and age (<75, ≥75) as fixed effects. Error bars represent 95% confidence intervals. LS, least squares; MMRM, multilevel modeling for repeated measures; Q, quartile; SD, standard deviation; SE, standard error.

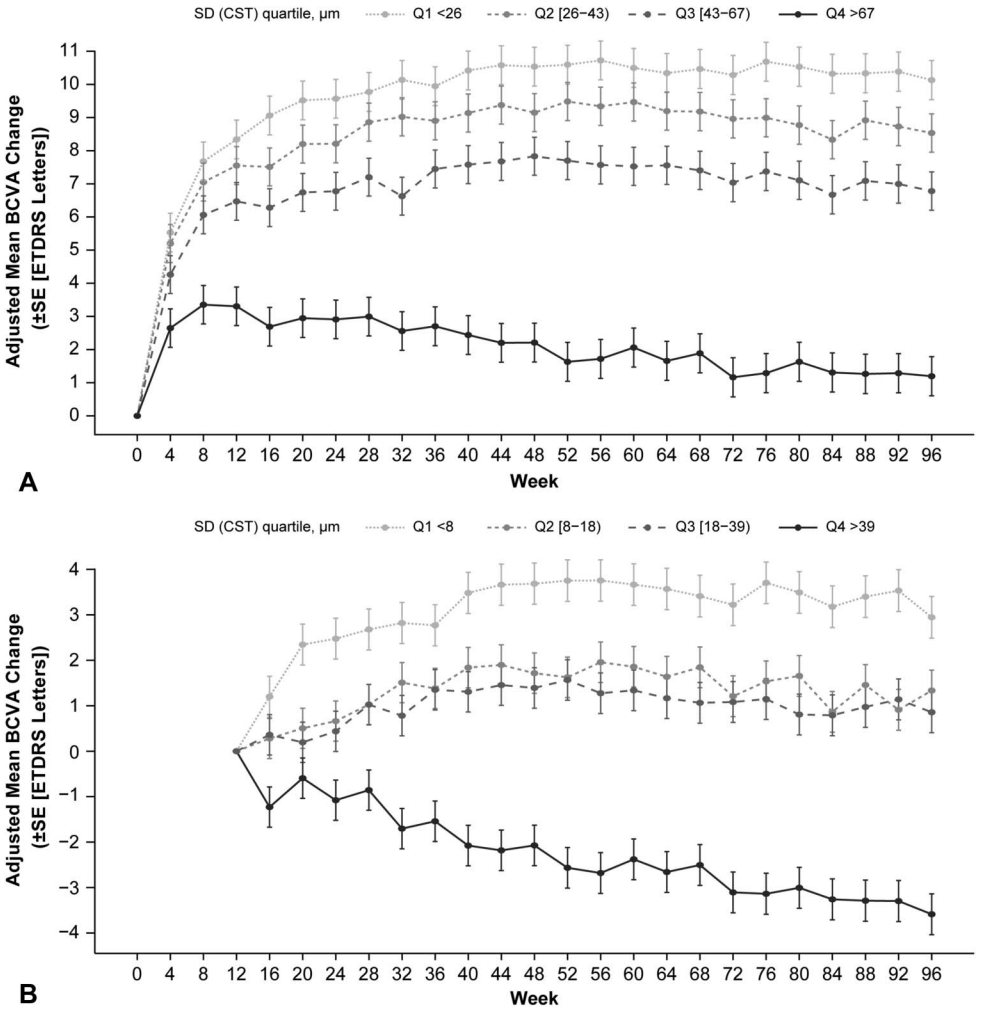

Fig. 2. Association between CST variability and BCVA change from baseline to Week 96 (**A**) and Week 12 to Week 96 (**B**). Pooled data from the brolucizumab and aflibercept treatment arms from the HAWK and HARRIER studies were used. LS mean and SE estimates were calculated using a MMRM model with baseline BCVA, SD (CST) quartile, study, and age (<75, ≥75 years) as fixed effects. LS, least squares; MMRM, multilevel modeling for repeated measures; Q, quartile; SE, standard error.

Relationship Between Central Subfield Thickness Variability and Presence of Fluid Post-loading Phase

The relationship between CST variability and the presence of fluid was also analyzed over the course of the maintenance phase, following initial fluid resolution during the loading phase. Pooled data from all treatment arms were assessed separately for each study. Patients with lower CST variability had fewer visits with the presence of IRF and/or SRF in both the HAWK and HARRIER studies and compared with Q1 (lowest variability), there was an almost monotonic relationship between the mean fraction of visits with the presence of IRF and/or SRF and increasing CST variability quartile (Figure 3).

Discussion

As all currently used intravitreal anti-VEGFs deliver a significant level of efficacy, brolucizumab and aflibercept data from the HAWK and HARRIER studies used here, or ranibizumab and bevacizumab data as per the post-hoc analysis of the CATT and IVAN studies, can be combined for treatment-agnostic analyses to understand a class therapeutic effect.[15,16,19] In this treatment-agnostic post hoc analysis of HAWK and HARRIER data, increased variability in CST over the course of the study was associated with less improvement in visual acuity and a higher likelihood of fluid persistence in the maintenance phase.

Findings on the relationship between CST variability and BCVA from baseline to the end of study are consistent with those from a post hoc analysis of the CATT and IVAN studies, which showed that variability in retinal thickness was negatively associated with BCVA.[15] Worse visual outcomes for eyes with higher CST variability could be associated with uncontrolled disease in a subset of patients with greater treatment need. The effect of repeated cycles of lesion quiescence and activity resulting in increases and decreases in macular thickness could also be

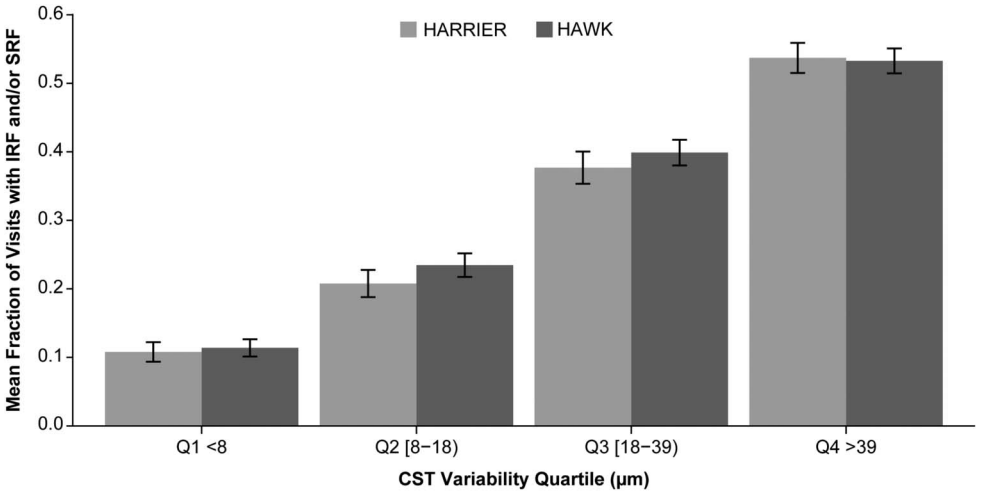

Fig. 3. Association between CST variability and the presence of IRF and/or SRF in the maintenance phase. Pooled data from the brolucizumab and aflibercept treatment arms were analyzed separately for the HAWK and HARRIER studies. Error bars are ± SE. SE, standard error.

detrimental long term; indeed, the CATT and IVAN post hoc analysis also showed a relationship between increased retinal thickness variability and the presence of fibrosis at the end of the study.[15] Regardless of the pathophysiological mechanisms underlying this relationship, both analyses revealed a closer correlation between an anatomical OCT parameter and visual outcomes than previous studies.

In addition to analyzing the association between CST variability and functional outcomes over the entirety of the study, as per the post hoc analysis of the CATT and IVAN studies,[15] the association between CST variability and BCVA postloading phase was also assessed. Most of the CST variability in treatment-naive patients occurs in the loading phase, which is likely due to an initial rapid fluid resolution in some eyes but not in others and is strongly associated with anti-VEGF treatment. Therefore, this additional post-loading phase analysis provides a more accurate reflection of a patient's inherent CST variability.[15] This approach also reduces the impact of differences in baseline characteristics between the quartiles when CST variability was measured over the entire study, reflected in the distinct profiles of BCVA change during the loading phase. Interestingly, rather than minimizing the differences in BCVA profile between quartiles, the analysis shows a sustained increase in BCVA for the quartile with the lowest variability and decrease for the quartile with the highest variability. Similarly, the association between CST variability and the presence of fluid was assessed after loading after initial drying of the retina. As expected, increased variability was associated with more study visits with the presence of fluid.

Further points of difference from the previous post hoc analysis of CATT and IVAN include a different study design (brolucizumab every 12 weeks/every 8 weeks and aflibercept every 8 weeks in HAWK and HARRIER vs. PRN/monthly treatment in CATT and IVAN) and analysis of the trajectory of visual change over time by quartile. In addition, the current analysis is based on CST, as measured by SD-OCT, whereas the CATT and IVAN analysis was based on foveal center point thickness, measured by either time-domain OCT or SD-OCT. Although CST and foveal center point thickness are often highly correlated, as they both reflect an aspect of macular lesion activity, CST can provide a better reflection of the extent and severity of disease activity because some lesions may be eccentric to the fovea and therefore have a minimal effect on changes in foveal center point thickness. The current analysis also provides information on the role that IRF plays in the intensity of fluctuation, which was not addressed in the CATT and IVAN analysis.

Owing to the study design in the HAWK and HARRIER trials, all aflibercept patients had a fixed dosing schedule of every 8 weeks and approximately half of the participants in the brolucizumab arm were on a every-8-week regimen at the end of the study. Therefore, with a majority of participants in the current work having an every-8-week treatment frequency, the potential for differences in treatment frequency between quartiles to impact on the analysis is likely to be low.

Patients with nAMD have individual treatment needs and the results of this analysis show that, for a subgroup of patients with persistent CST variability, anti-VEGF treatment at the treatment frequency used in the HAWK and HARRIER studies cannot adequately address these needs. Taken together, these data suggest that minimizing CST fluctuations in eyes receiving anti-VEGF treatment for nAMD may improve visual outcomes. The use of CST fluctuations as a marker of disease activity offers the potential to

identify optimal treatment regimens for patients. This can be achieved through more frequent injections with established anti-VEGF therapies or through newer therapies with longer duration that can stabilize fluid with fewer treatments.

Limitations of this study include the retrospective, post hoc design, lack of volumetric analyses, and the fact that the analysis did not account for factors that might impact on nAMD disease progression and response to anti-VEGF therapy, such as disease duration, lesion type, and lesion size. It is also not possible to demonstrate causality between CST variability and visual outcomes because it is not possible to match quartile membership for disease severity at every visit. A further limitation is the lack of data on the contribution of variability in individual fluid compartments (IRF, SRF, and sub-retinal pigment epithelium), and additional analyses of these parameters would be beneficial. There is also potential for the disease activity re-treatment criteria to influence variability, although it was not possible to extract its impact on the outcomes of this analysis. However, because the analysis was treatment agnostic and disease activity re-treatment criteria were applied uniformly across the HAWK and HARRIER studies based on investigators' assessment, the impact is likely to be low.

Although OCT images can be affected by artifacts or issues with reproducibility over time or between devices, assessment of OCT images by masked investigators in the HAWK and HARRIER studies was standardized, including validation of the images at Central Reading Centers. Additional strengths of this analysis are the large sample size and the treatment-agnostic approach, which allows for an unbiased assessment of the relationship between retinal thickness, visual outcomes, and the persistence of fluid.

This analysis confirms the findings of the post hoc analysis of CATT and IVAN in showing a relationship between increased CST variability and worse visual outcomes in patients with nAMD receiving anti-VEGF treatment. This study also found an association between CST variability and the proportion of visits with fluid after the loading phase. Although the amplitude of BCVA gain varied between patients, more stable CST was found to be associated with better visual outcomes, and individual variation in CST may provide a more reliable prognostic marker of visual outcomes than the presence of fluid alone, with the potential to enhance the clinical care of nAMD patients. Future research, potentially using emerging artificial intelligence tools and real-world data sets, may continue to clarify our understanding of the relationship between disease stability and functional outcomes in nAMD.

Key words: neovascular age-related macular degeneration, anti-vascular endothelial growth factor therapy, central subfield thickness, variability.

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