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The Association between Retinal Thickness Fluctuations and Visual Outcomes under Anti-Vascular Endothelial Growth Factor Therapy: A Systematic Review and Meta-Analysis

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Keywords
Retinal thickness fluctuation · Visual acuity · Anti-vascular endothelial growth factor · Age-related macular degeneration · Retinal vein occlusion · Diabetic macular edema

Abstract
Introduction: The objective of this study was to examine the association between retinal thickness (RT) fluctuations and best corrected visual acuity (BCVA) in eyes with neovascular AMD, macular edema secondary to RVO, and DME treated with anti-VEGF therapy. ***Methods:*** A systematic search of Ovid MEDLINE, EMBASE, and the Cochrane Library was performed from January 2006 to March 2024. Studies comparing visual or anatomic outcomes of patients treated with anti-VEGF therapy, stratified by magnitudes of RT fluctuation, were included. ROBINS-I and Cochrane RoB 2 tools were used to assess risk of bias, and certainty of evidence was evaluated with GRADE criteria. Meta-analysis was performed with a random-effects model. Primary outcomes were final BCVA and change in BCVA relative to baseline. ***Results:*** 15,725 articles were screened; 15 studies were identified in the systematic review and 5 studies were included in the meta-analysis. Final ETDRS VA was significantly worse in eyes with the highest level of RT fluctuation (weighted mean difference [WMD] = 7.86 letters; 95% CI, 4.97, 10.74; $p < 0.00001$; $I^2 = 81\%$; 3,136 eyes). RT at last observation was significantly greater in eyes with high RT fluctuations (WMD = −27.35 μm; 95% CI, −0.04, 54.75; $p = 0.05$; $I^2 = 88\%$; 962 eyes). ***Conclusions:*** Final visual outcome is associated with magnitude of RT fluctuation over the course of therapy. It is unclear whether minimizing RT fluctuations would help optimize visual outcomes in patients treated with anti-VEGF therapy. These findings are limited by a small set of studies, risk of bias, and considerable heterogeneity.

Introduction

Anti-vascular endothelial growth factor (anti-VEGF) therapy is indicated in several conditions, including neovascular age-related macular degeneration (nAMD), macular edema (ME) secondary to retinal vein occlusion

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(RVO), and diabetic macular edema (DME) secondary to diabetic retinopathy (DR) [1]. Adherence to therapy is crucially important as significant visual compromise may result due to inadequate treatment [2, 3].

Optical coherence tomography (OCT) imaging is crucial for monitoring disease activity and morphologic changes in the retina, and the presence of certain OCT patterns may be helpful in prognosticating visual outcomes [4]. Retinal thickness (RT) is a closely scrutinized metric that is followed in eyes with ME. Indeed, in the setting of DME, studies have demonstrated a correlation between elevated RT and worse visual outcomes [5]. In nAMD, elevated RT secondary to intraretinal fluid (IRF) is associated with worse best corrected visual acuity (BCVA) compared to elevated RT secondary to subretinal fluid (SRF) [6]. A growing body of literature has examined the association between RT fluctuations and VA in nAMD, RVO, and DME. For example, Evans and colleagues [7] conducted a post hoc analysis of the IVAN and CATT trials and found that greater variability in RT over the course of treatment was associated with poorer final VA and increased likelihood of developing macular atrophy and fibrosis. Similarly, Chakravarty et al. [8] observed worse visual outcomes in highly fluctuating nAMD eyes. Thus, large fluctuations in RT may reflect a suboptimal anti-VEGF treatment regimen and may be indicative of poor visual prognosis. Therefore, a rigorous analysis of the potential impact of RT fluctuations on visual outcomes is needed to further guide anti-VEGF treatment decisions. In this systematic review and meta-analysis, we consolidated findings from studies that have reported on the association between RT fluctuations and VA outcomes in patients treated with anti-VEGF therapy for nAMD, RVO, and DME.

Methods

Search Strategy and Eligibility Criteria

We performed a systematic literature search on Ovid MEDLINE, EMBASE, and Cochrane Library from January 2006 to April 2024. Our search strategy for Ovid MEDLINE can be found in Supplementary Table 1 (for all online suppl. material, see https://doi.org/10.1159/000539648). We included peer-reviewed studies comparing functional and anatomical outcomes of patients treated with anti-VEGF agents for retinal vascular diseases, stratified by categories of standard deviation (SD) of RT to quantify RT fluctuations. We included patient populations from the following settings: nAMD, DME, and ME secondary to RVO. We excluded (I) studies that did not use RT SD as a measure of RT fluctuations, (II) studies that did not present outcomes stratified by RT SD categories (e.g., tertiles or quartiles), (III) studies in which patients received intravitreal corticosteroids or laser therapy as part of their treatment regimen, and (IV) studies that did not provide the sample size, mean, or SD for at least one of our considered outcomes. Studies that stratified patients by categories of RT SD but did not provide sufficient data to perform meta-analysis (e.g., due to missing data) were included as part of the systematic review but were excluded from the meta-analysis. We also excluded studies with no published results, no English full-text, literature reviews, systematic reviews, meta-analyses, conference proceedings, letters to editors, and theses. Our study adhered to the tenets of the Declaration of Helsinki, and we did not require institutional ethics approval. The protocol for our study was registered in the International Prospective Register of Systematic Reviews (PROSPERO; ID: CRD42022382400).

Study Selection and Data Collection

At least two independent authors (B.P., A.M., A.H., and J.G.) performed title and abstract screening for all articles followed by full-text screening on Covidence (Veritas Health Innovation, Melbourne, VIC, Australia). Two independent authors collected data (B.P. and A.M.) on Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA). When necessary, an impartial author (M.M.P.) was consulted for conflict resolution. The following baseline characteristics were collected: study name, country, year of publication, retinal vascular disease, number of males, total eyes, right eyes, phakic eyes, pseudophakic/aphakic eyes, anti-VEGF agent, treatment regimen, BCVA, RT, type of RT reported, and the SD of RT fluctuation in study groups. In studies stratifying patients by quartiles of fluctuation, quartiles 1 (Q1) and 4 (Q4) represented the least and greatest RT fluctuation, respectively.

Our primary outcomes were final BCVA and change in BCVA from baseline. Our secondary outcomes were final RT and incidence of IRF and SRF per quartile of RT fluctuation. A subgroup analysis was also conducted to evaluate primary and secondary endpoints in eyes with nAMD.

Risk of Bias and Certainty of Evidence Assessment

The risk of bias (ROB) of included studies was assessed by two independent authors (A.H. and J.G.). The certainty of evidence associated with each study outcome was also evaluated by two independent authors (A.M. and B.P.). We used the risk of bias tool 2 (ROB2) for RCTs [9] and the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool for observational studies [10]. We evaluated the certainty of evidence of each outcome in our meta-analysis with the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) tool [11].

Statistical Analysis

We performed our meta-analysis using a random-effects model on Review Manager 5.4 (RevMan 5.4; The Nordic Cochrane Centre, Cochrane, Copenhagen, Denmark) and weighted every outcome by number of eyes. Weighted mean difference (WMD) and SD was reported for continuous outcomes. The inverse variance method was applied to continuous outcomes. Outcomes with I^2 >50% were associated with substantial heterogeneity and >75% were associated with considerable heterogeneity [12]. We used methods outlined in Beck et al. [13] (2003) to calculate Snellen fractions and methods outlined in Khoshnood et al. [14] (2010) to convert logMAR values to ETDRS letters. To evaluate the robustness of our results, a subgroup analysis was restricted to nAMD patients only, and a leave-one-out sensitivity analysis was

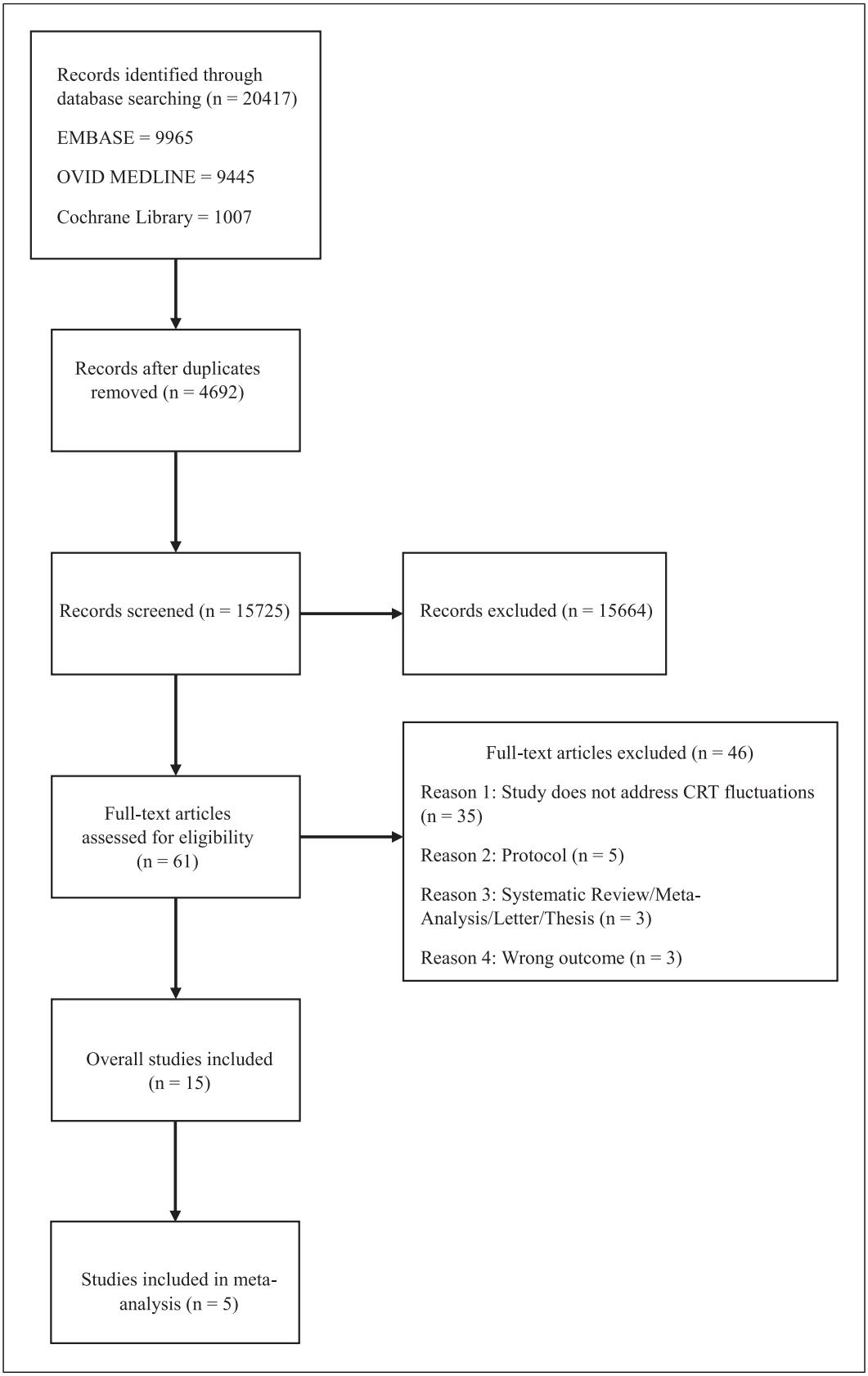

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchartoutlining study exclusion criteria.

Table 1. General study information, including country, study design, condition, and anti-VEGF agent used

Reference	Country	Study design	Condition	Anti-VEGF agent	Baseline treatment status	Treatment regimen	Examination frequency
Chakravarthy et al. [8] (2021)	UK	Retrospective observational	nAMD	Any licensed agent	N/A	N/A	Minimum of 2 OCT scans during maintenance phase
Chen et al. [15] (2022)	USA	Retrospective observational	nAMD	BEV/ RAN/AFL	Treatment-naïve	N/A	Every 3 months
Cheong et al. [16] (2021)	Singapore	Prospective observational	nAMD	BEV/ RAN/AFL	Treatment-naïve	PRN or treat-and-extend	N/A
Ciucci et al. [17] (2022)	Italy	Retrospective observational	nAMD	AFL	N/A	Loading phase followed by bimonthly; PRN after 1 year	N/A
Dugel et al. [18] (2022) (Hawk and Harrier)	USA	Post hoc RCT	nAMD	AFL/BRO	Treatment-Naïve	Loading phase followed by BRO every 12 weeks and then 8 weeks, and AFL every 8 weeks	Every 4 weeks
Evans et al. [7] (2020) (IVAN and CATT)	USA	Post hoc RCT	nAMD	BEV/RAN	Treatment-naïve	Monthly or PRN	Every 3 months
Guo et al. [27] (2023)	China	Retrospective observational	nAMD	RAN	Treatment-naïve	Loading dose for 3 months followed by PRN or treat-and-extend	N/A
Lai and Lai, [19] (2021)	Hong Kong	Retrospective observational	nAMD	BEV/ RAN/AFL	Treatment-naïve	3 loading doses followed by PRN	Minimum of 3 OCT scans in 24-month follow-up period
Sheth et al. [20] (2022) (Harbor)	USA	Post hoc RCT	nAMD	RAN	Treatment-naïve	Monthly or PRN	Every month
Chen et al. [21] (2020)	USA	Retrospective observational	CRVO/ BRVO	BEV/ RAN/AFL	Treatment-naïve	N/A	Every 3 months
Nagasato et al. [22] (2022)	Japan	Retrospective observational	BRVO	AFL/RAN	Treatment-naïve	PRN	Every 3 months for 12 months followed by every 12 months
Nagasato et al. [26] (2024)	Japan	Retrospective observational	CRVO	AFL/RAN	Treatment-naïve	PRN	Every 3 months or earlier
Scott et al. [23] (2022) (SCORE2)	USA	Post hoc RCT	CRVO/ HRVO	BEV/AFL	Treatment-naïve and pretreated	Monthly or treat-and-extend	Every 4 weeks for 6 months
Starr et al. [24] (2021) (Protocol T)	USA	Post hoc RCT	DME	BEV/ RAN/AFL	Treatment-naïve within last 12 months	Modified PRN	Every 1 month for 12 months followed by every 2 months and then every 4 months
Wang et al. [25] (2022)	USA	Retrospective observational	DME	BEV/ RAN/AFL	Treatment-naïve	PRN	Every 3 months

BEV, bevacizumab; RAN, ranibizumab; AFL, aflibercept; BRO, brolucizumab; PRN, pro re nata; OCT, optical coherence tomography.

performed for all included studies. All p values were two-sided, and we considered p values ≤0.05 as statistically significant. For the primary analysis, Q1/Q2 and Q3/Q4 eyes were pooled, and for the sensitivity analysis, Q1 eyes were compared against Q4.

Results

Study Screening and Baseline Demographics

Title and abstract screening was performed on 15,725 articles. Overall, 61 articles underwent full-text screening, and 15 studies met inclusion criteria (Fig. 1) [7, 8, 15–27]. There were 10 observational studies [8, 15–17, 19, 21, 22, 25–27] and 5 post hoc analyses of RCTs (Table 1) [7, 18, 20, 23, 24]. Various measures of RT were employed, including central subfield thickness (CST) [8, 15, 16, 18, 19, 21, 23–25], central retinal thickness (CRT) [17, 27], central foveal thickness [20], foveal thickness [22, 26], and foveal center point thickness [7]. A variety of treatment regimens were employed across studies, including pro re nata (PRN), treat-and-extend, and fixed-dosing intervals (Table 1). Moreover, 11 studies included treatment-naïve patients only; 1 study included both treatment-naïve and pretreated patients; 1 study included patients who were treatment-naïve for at least 12 months; and 2 studies did not report on the treatment status of patients (Table 1). The patient examination frequency at which OCT scans were taken was also varied across studies; however, 6 of 12 studies (50%) examined patients at least every 3 months (Table 1). Of all included studies, 5 were included in the meta-analysis as these were the only studies that provided BCVA data stratified by categories of RT SD [7, 8, 22, 24, 26]. Overall, 7,563 eyes were included at baseline [7, 8, 15–27]. Moreover, 40.0% of patients were male, and the mean patient age was 75.1 ± 10.7 years. The mean number of anti-VEGF injections was 8.83 ± 5.0 (N = 1,933 eyes) [8, 15–17, 21, 22, 25–27], and the mean follow-up period was 24.2 months. A summary of baseline characteristics is provided in Table 2.

Visual Acuity

Mean initial BCVA across all studies was 59.8 ± 15.1 Early Treatment of Diabetic Retinopathy Study (ETDRS) letters (N = 7,125) [7, 8, 15–22, 24–26], and mean final BCVA was 67.6 ± 18.7 letters (N = 4,141) [7, 8, 15–17, 21, 22, 24–26]. The overall change in BCVA was 6.3 ± 16.7 letters (N = 3,515) (Table 3) [7, 8, 15, 21, 24, 25]. Patients stratified in quartile 1 (i.e., least RT fluctuation) had a mean initial BCVA of 66.3 ± 11.3 letters (N = 1,112) [7, 8, 18, 24] and a mean final BCVA of 74.6 ± 15.0 letters (N = 785) [7, 8, 22, 24, 26], resulting in a mean improvement of 7.0 ± 13.4 letters (N = 671) (Table 4) [7, 8, 24]. Patients stratified in quartile 4 (i.e., greatest RT fluctuation) had a mean initial BCVA of 55.5 ± 14.2 letters (N = 1,111) [7, 8, 18, 24] and a mean final BCVA of 61.5 ± 21.2 letters (N = 784) [7, 8, 22, 24, 26], leading to a mean change of 5.6 ± 19.5 letters (N = 672) (Fig. 2) [7, 8, 24].

Retinal Thickness

Mean initial RT across all studies was 440.8 ± 163.8 μm (N = 7,201) [7, 8, 15–22, 24–27], and mean final RT was 290.3 ± 106.0 μm (N = 2,492) [8, 15–17, 21, 22, 24–27], resulting in a mean change of −109.3 ± 144.2 μm (N = 1,598) (Table 5) [15, 16, 21, 24, 25, 27]. In quartile 1, the mean initial and final RTs were 323.1 ± 64.5 μm (N = 1,089) [7, 8, 18, 24] and 264.1 ± 68.2 μm (N = 241), respectively (Table 2) [8, 24]. In quartile 4, the mean initial and final RTs were 605.1 ± 187.9 μm (N = 1,108) [7, 8, 18, 24] and 301.0 ± 117.3 μm (N = 241), respectively (Fig. 3) [8, 24].

GRADE and Risk of Bias Assessment

Of three outcomes in the primary analysis, our GRADE assessment found that BCVA at last study observation was associated with a moderate certainty of evidence. The change in BCVA from baseline and RT at last study observation were associated with a low certainty of evidence (online suppl. Table 2).

The Cochrane risk of bias tool 2 was used to conduct ROB assessment for five post hoc analyses of RCTs. A low ROB across the five domains of bias was generally observed. There were some concerns around author conflict(s) of interest and industry sponsorship. Our ROB assessment of 10 observational studies via the ROBINS-I tool found that 52 (74.3%) domains had a low ROB, and 18 (25.7%) domains had a moderate risk of bias. The following represents the proportion of observational studies with a low ROB across ROBINS-I domains: bias in classification of interventions (100%), bias due to deviations from intended interventions (90.0%), bias in measurement of outcomes (90.0%), bias due to confounding (70.0%), bias in selection of participants into study (60.0%), bias due to missing data (60.0%), and bias due to selection of the reported results (50.0%) (online suppl. Tables 3, 4).

Meta-Analysis

Comparison of Final VA, VA Change, and Final RT by Quartile

Two post hoc analyses [7, 24] and 3 retrospective studies [8, 22, 26] reported final BCVA data in patients stratified by quartiles of RT fluctuations. Overall, the final visual outcome in Q1/Q2 eyes (N = 1,569) was significantly better at final follow-up compared to Q3/Q4 eyes (N = 1,567) (WMD = 7.86 letters; 95% CI, 4.97, 10.74; $p < 0.00001$; I^2 = 81%;

Table 2. Baseline data by study

Reference	Injections, mean (SD)	Eyes (initial), *N*	Eyes (final), *N*	Follow-up duration	Male, *n* (%)	Age, mean (SD), years	Eye laterality (right), *n* (%)
Chakravarthy et al. [8] (2021)	8.9 (4.0)	403	403	24 months	141 (37)	77.8 (6.8)	N/A
Chen et al. [15] (2022)	14.1 (4.9)	422	422	24 months	154 (36.5)	83.6 (8.3)	232 (55)
Cheong et al. [16] (2021)	7.6 (3.4)	141	141	12 months	56 (39.7)	70.5 (9.2)	N/A
Ciucci et al. [17] (2022)	9.07 (2.6)	41	41	24.93 months	15 (36.6)	78.56 (7.51)	N/A
Dugel et al. [18] (2022) (Harrier)	N/A	739	739	22.09 months	317 (42.9)	75.1 (8.24)	N/A
Dugel et al. [18] (2022) (Hawk)	N/A	1,078	1,078	22.09 months	469 (43.5)	76.5 (8.68)	N/A
Evans et al. [7] (2020)	N/A	1,731	1,731	24 months	673 (38.9)	78.6 (7.4)	N/A
Guo et al. [27] (2023)	4.5 (2.5)	76	76	120 months	19 (25.0)	N/A	N/A
Lai and Lai, [19] (2021)	Median: 7 (IQR 4–10)	64	64	24 months	38 (61.3)	75.3 (9.4)	N/A
Sheth et al. [20] (2022)	N/A	1,097	1,097	24 months	446 (40.7)	78.7 (8.4)	N/A
Chen et al. [21] (2020)	7.4 (2.2)	134	134	12 months	58 (43.3)	73.4 (10.7)	69 (51.5)
Nagasato et al. [22] (2022)	5.8 (4.6)	309	309	50.6 months	118 (38.2)	67.5 (10)	N/A
Nagasato et al. [26] (2024)	5.6 (3.6)	141	141	24 months	88 (62.4)	69.3 (12.4)	N/A
Scott et al. [23] (2022)	6	362	362	12 months	N/A	N/A	N/A
Starr et al. [24] (2021)	N/A	559	559	24 months	289 (51.7)	59.9 (10.4)	N/A
Wang et al. [25] (2022)	8.2 (2.4)	266	266	12 months	141 (53.0)	61.0 (11.3)	141 (53.0)
Overall	8.83 (4.96) (*N* = 1,933)	7,563 (*n* = 15)	7,563 (*n* = 15)	24.16 months	3,022 (40.0)	75.11 (10.67) (*n* = 13)	442 (53.8) (*n* = 3)

n, number of studies; *N*, number of eyes; SD, standard deviation.

GRADE = moderate; Fig. 4) [7, 8, 22, 24, 26]. No significant differences were observed with respect to the change in BCVA between Q1/Q2 (N = 1,343) and Q3/Q4 (N = 1,343) (WMD = 0.12 letters; 95% CI, −1.87, 2.12; p = 0.90; I^2 = 60%; GRADE = low; Fig. 5) [7, 8, 24]. The RT was significantly lower by final follow-up in Q1/Q2 eyes (N = 481) relative to Q3/Q4 eyes (N = 481) (WMD = −27.35 μm; 95% CI, −0.04, 54.75; p = 0.05; I^2 = 88%; GRADE = low; Fig. 6) [8, 24].

Sensitivity Analysis

Leave-one-out sensitivity analysis was performed for the following outcomes: BCVA at last study observation and change in BCVA from baseline (online suppl. Fig. 1, 2). The results from the leave-one-out analysis were consistent with the findings from the overall analysis of both outcomes.

Analysis of Q1 versus Q4 eyes was significant for final BCVA (p < 0.00001) and final RT (p = 0.02) (online suppl. Fig. 3). This was consistent with the results from the pooled analysis of Q1/Q2 versus Q3/Q4.

Subgroup Analysis – nAMD

Subgroup analysis of two nAMD studies [7, 8] revealed significantly better final visual outcomes in Q1/Q2 eyes (N = 1,065) when compared to Q3/Q4 eyes (N = 1,063), with considerable heterogeneity (WMD = 5.57 letters; 95% CI, 2.13, 9.01; p = 0.002; I^2 = 62%; online suppl. Fig. 4).

Subgroup Analysis – RVO

A subgroup analysis of two RVO studies [22, 26] demonstrated significantly better visual outcomes in Q1/Q2 eyes (N = 225) when compared to Q3/Q4 eyes (N = 224), with considerable heterogeneity (WMD = 14.45 letters; 95% CI, 5.51, 23.38; p = 0.002; I^2 = 74%; online suppl. Fig. 5).

Incidence of IRF and SRF

A meta-analysis of this outcome could not be performed due to insufficient data.

Table 3. Visual acuity data by study

Reference	Eyes (baseline), *N*	Eyes (final), *N*	Initial BCVA, mean (SD), ETDRS	BCVA at 3 months, mean (SD), ETDRS	BCVA at 12 months, mean (SD), ETDRS	BCVA at 24 months, mean (SD), ETDRS	Final BCVA, mean (SD), ETDRS	Change in BCVA, mean (SD), ETDRS
Chakravarty et al. [8] (2021)	403	403	58.2 (10.4)	63.3 (12.5)	N/A	61.6 (15.8)	61.6 (15.8)	3.4 (14.5)
Chen et al. [15] (2022)	422	422	58.8 (19.2)	N/A	64.3 (17.8)	62.4 (20.6)	62.4 (20.6)	3.7 (20.8)
Cheong et al. [16] (2021)	141	141	49.9 (17.8)	N/A	N/A	N/A	56 (16.1)	5.6
Ciucci et al. [17] (2021)	41	41	66.09 (32.6)	N/A	N/A	N/A	65.85 (29.5)	−0.24
Dugel et al. [18] (2022) (Harrier)	739	739	61.2 (12.76)	N/A	N/A	N/A	N/A	N/A
Dugel et al. [18] (2022) (Hawk)	1,078	1,078	60.6 (13.71)	N/A	N/A	N/A	N/A	N/A
Evans et al. [7] (2020)	1,731	1,731	61.0 (14.0)	N/A	N/A	N/A	66.5 (18.5) (*n* = 1,725)	5.5 (16.0)
Guo et al. [27] (2023)	76	76	Median: 60.5 (50.0, 70.0)	N/A	N/A	N/A	N/A	N/A
Lai and Lai, [19] (2021)	64	64	55.5 (20)	N/A	N/A	N/A	N/A	N/A
Sheth et al. [20] (2022)	1,097	1,097	53.9 (12.7)	N/A	N/A	N/A	N/A	N/A
Chen et al. [21] (2020)	134	134	52.8 (20.9)	N/A	65.9 (17.3)	N/A	65.9 (17.3)	13.1 (20.3)
Nagasato et al. [22] (2022)	309	309	70 (15)	N/A	N/A	N/A	80.5 (14)	10.5
Nagasato et al. [26] (2024)	141	141	52.5 (26)	N/A	N/A	59 (28.5)	59 (28.5)	6.5
Scott et al. [23] (2022)	362	362	N/A	N/A	N/A	N/A	N/A	N/A
Starr et al. [24] (2021)	559	559	65 (11)	N/A	77 (10)	77 (12)	77 (12)	12 (14)
Wang et al. [25] (2022)	266	266	63.5 (15.7)	N/A	69.0 (13.8)	N/A	69.0 (13.8)	5.1 (16.1)
Overall	7,563 (*n* = 15)	7,563 (*n* = 15)	59.81 (15.13) (*N* = 7,125)	N/A	70.5 (15.3) (*N* = 1,381)	67.23 (19.15) (*N* = 1,525)	67.59 (18.68) (*N* = 4,141)	6.34 (16.65) (*N* = 3,515)

n, number of studies; *N*, number of eyes; SD, standard deviation; BCVA, best corrected visual acuity; ETDRS, Early Treatment of Diabetic Retinopathy Study.

Table 4. Visual acuity and RT data stratified by quartiles

Quartile	Eyes, *N*	Age, mean (SD), years	Male (%)	Initial BCVA, mean (SD), ETDRS	Final BCVA, mean (SD), ETDRS	Overall change in BCVA, mean (SD), ETDRS	Initial RT, mean (SD), μm	Final RT, mean (SD), μm	Overall change in RT, mean (SD), μm
1	1,453 (*n* = 7)	74.44 (10.60) (*n* = 3)	238/572 (41.6; *n* = 2)	66.32 (11.30) (*N* = 1,112)	74.55 (15.04) (*N* = 785)	6.95 (13.37) (*N* = 671)	323.05 (64.53) (*N* = 1,089)	264.12 (68.22) (*N* = 241)	N/A
2	1,420 (*n* = 7)	74.67 (10.46) (*n* = 3)	253/573 (44.2; *n* = 2)	62.97 (11.77) (*N* = 1,111)	70.42 (16.85) (*N* = 784)	6.35 (14.40) (*N* = 672)	387.32 (74.60) (*N* = 1,103)	271.25 (68.99) (*N* = 240)	N/A
3	1,435 (*n* = 7)	74.90 (10.77) (*n* = 3)	247/573 (43.1; *n* = 2)	59.94 (13.11) (*N* = 1,111)	68.69 (17.88) (*N* = 783)	7.20 (14.84) (*N* = 671)	454.62 (105.79) (*N* = 1,100)	283.88 (84.62) (*N* = 240)	N/A
4	1,435 (*n* = 7)	74.41 (11.74) (*n* = 3)	234/572 (40.9; *n* = 2)	55.53 (14.22) (*N* = 1,111)	61.45 (21.20) (*N* = 784)	5.56 (19.45) (*N* = 672)	605.07 (187.88) (*N* = 1,108)	301.03 (117.34) (*N* = 241)	N/A

n, number of studies; *N*, number of eyes; SD, standard deviation; BCVA, best corrected visual acuity; ETDRS, Early Treatment of Diabetic Retinopathy Study; RT, retinal thickness.

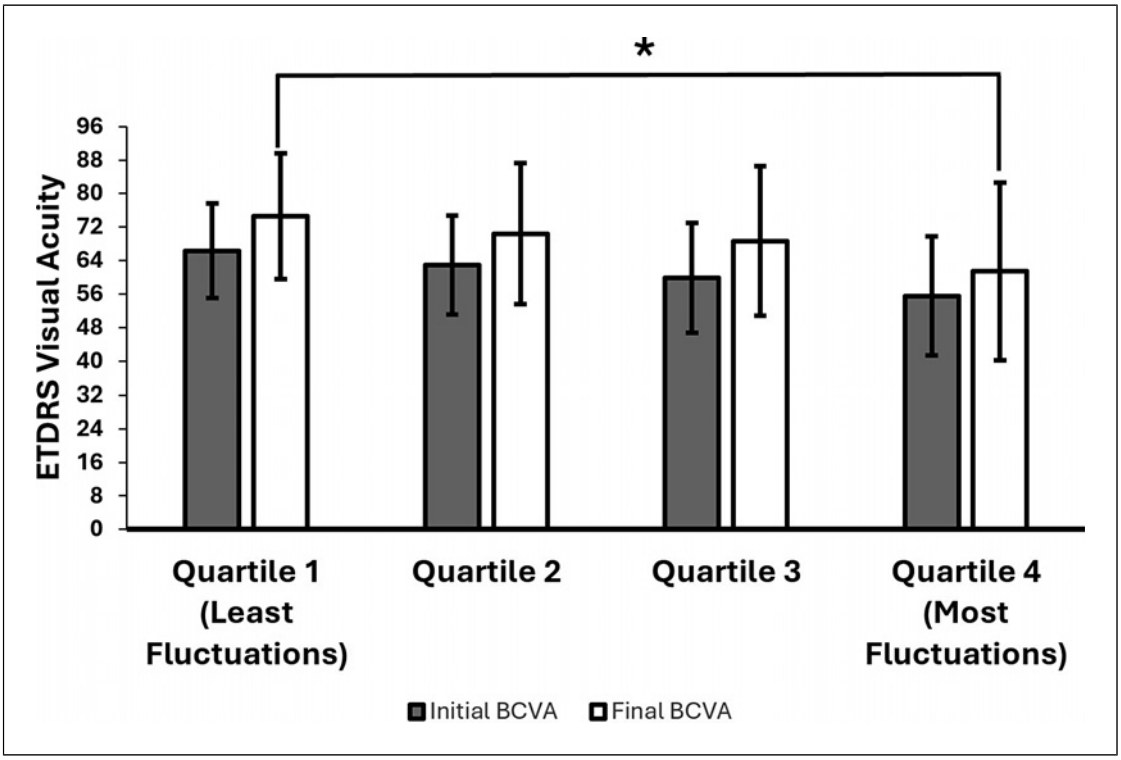

Fig. 2. Bar plot comparison of initial and final best corrected visual acuity (BCVA) by quartiles. The final BCVA trends downwards with increasing quartiles of RT fluctuation. Bars represent mean BCVA, and error bars represent SD. ETDRS, Early Treatment of Diabetic Retinopathy Study. *$p \leq 0.05$.

Table 5. Retinal thickness data by study

Reference	Eyes (baseline), *N*	Eyes (final), *N*	Initial RT, mean (SD), μm	RT at 3 months, mean (SD), μm	RT at 12 months, mean (SD), μm	RT at 24 months, mean (SD), μm	Final RT, mean (SD), μm	Change in RT, mean (SD), μm
Chakravarty et al. [8] (2021)	403	403	350.1 (109.7)	248.0 (66.7)	N/A	239.2 (64.9)	239.2 (64.9)	N/A
Chen et al. [15] (2022)	422	422	331.2 (97.6)	N/A	259.9 (53.7)	253.4 (53.6)	253.4 (53.6)	−77.8 (104.7)
Cheong et al. [16] (2021)	141	141	495.2 (223.3)	N/A	343 (162.9)	N/A	343 (162.9)	−150.7 (176)
Ciucci et al. [17] (2021)	41	41	348.5 (164.4)	N/A	N/A	N/A	235.6 (163.8)	−112.9
Dugel et al. [18] (2022) (Harrier)	739	739	469.5 (161.57)	N/A	N/A	N/A	N/A	N/A
Dugel et al. [18] (2022) (Hawk)	1,078	1,078	462.5 (160.31)	N/A	N/A	N/A	N/A	N/A
Evans et al. [7] (2020)	1,731	1,731	440.1 (167.4)	N/A	N/A	N/A	N/A	N/A
Guo et al. [27] (2023)	76	76	293.6 (89.1)	N/A	252.5 (68.6)	N/A	252.5 (68.6)	−41.3 (104.1)
Lai and Lai, [19] (2021)	64	64	364 (113)	N/A	N/A	N/A	N/A	N/A
Sheth et al. [20] (2022)	1,097	1,097	440.7 (151.2)	N/A	N/A	N/A	N/A	N/A
Chen et al. [21] (2020)	134	134	488.6 (165)	N/A	334.3 (131.9)	N/A	334.3 (131.9)	−154.3 (210.2)
Nagasato et al. [22] (2022)	309	309	503.1 (162.4)	N/A	N/A	N/A	287.1 (103.3)	−216
Nagasato et al. [26] (2024)	141	141	661.1 (257.4)	N/A	N/A	328.9 (157.8)	328.9 (157.8)	−332.2
Scott et al. [23] (2022)	362	362	N/A	N/A	N/A	N/A	N/A	N/A
Starr et al. [24] (2021)	559	559	453 (127)	N/A	318 (96)	310 (91)	310 (91)	−145 (143)
Wang et al. [25] (2022)	266	266	396.9 (109.7)	N/A	337.7 (100.7)	N/A	337.7 (100.7)	−59.2 (114.8)
Overall	7,563 (*n* = 15)	7,563 (*n* = 15)	440.82 (163.82) (*N* = 7,201)	N/A	306.39 (103.74) (*N* = 1,598)	277.38 (91.68) (*N* = 1,525)	290.35 (105.98) (*N* = 2,492)	−109.32 (144.20) (*N* = 1,598)

n, number of studies; *N*, number of eyes; SD, standard deviation; RT, retinal thickness.

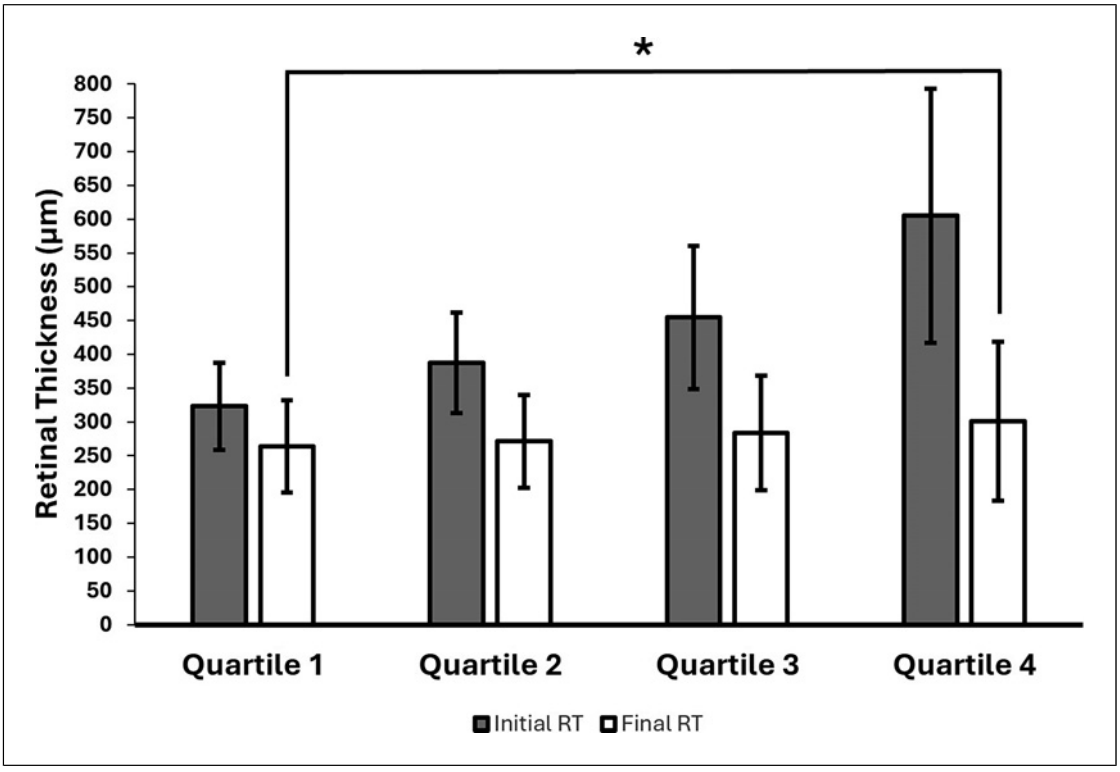

Fig. 3. Bar plot comparison of initial and final retinal thickness (RT) by quartiles. There is a modest increase in final RT with increasing quartiles of fluctuation. Bars represent mean BCVA, and error bars represent SD. *$p \leq 0.05$.

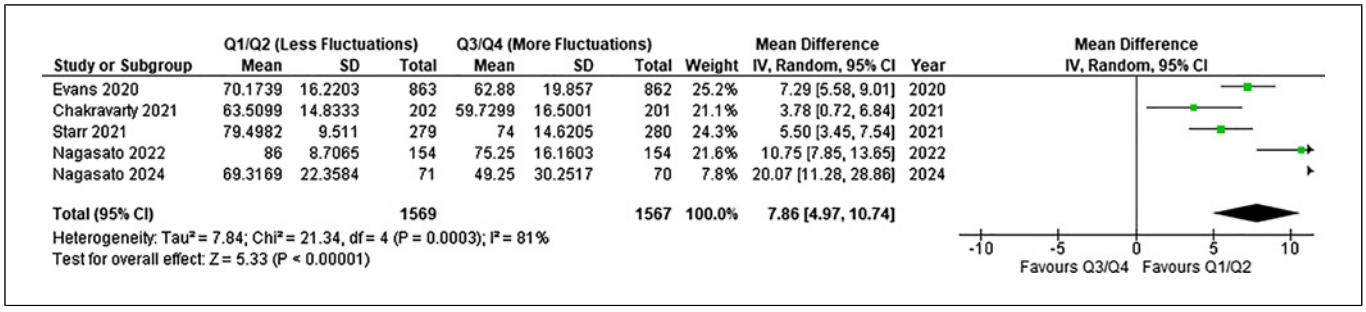

Fig. 4. Forest plot depicting final VA comparison between Q1/Q2 and Q3/Q4 eyes, demonstrating favorable BCVA outcomes in Q1/Q2 eyes with less RT fluctuations. Blocks represent point estimates; horizontal lines, 95% confidence intervals; diamond, overall effect estimate of meta-analysis. SD, standard deviation.

Systematic Review

Neovascular Age-Related Macular Degeneration Studies

This systematic review identified 10 studies that examined the association between RT fluctuations and visual outcomes in eyes with nAMD treated with anti-VEGF therapy. The majority of studies stratified patients by quartiles of fluctuation; however, one study stratified patients by tertiles [16]. In general, the visual outcome was significantly worse in eyes with high RT fluctuations compared to eyes with low fluctuations. Indeed, Ciucci et al. [17] found a significantly inverse association between CRT/SD and final BCVA (Pearson's $r = 0.43$; $p = 0.005$), indicating that greater CRT fluctuation was associated with poorer visual outcome. Similarly, Lai and colleagues [19] observed a significant correlation between final BCVA and CST fluctuation ($p < 0.0001$; Spearman's $\rho = 0.54$). Extent of

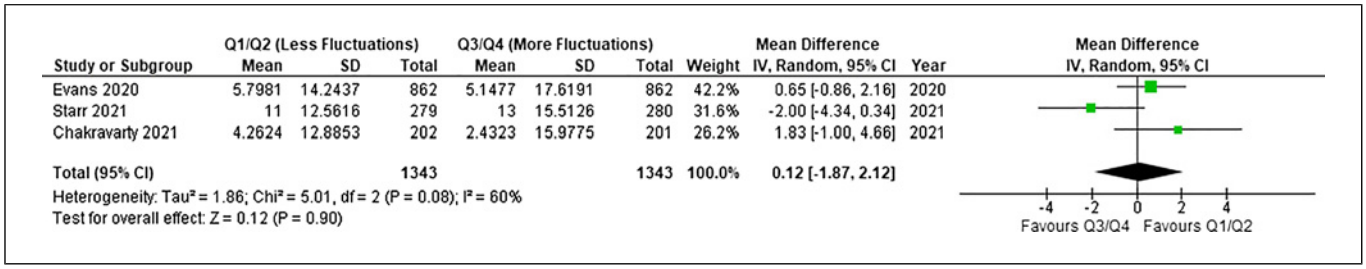

Fig. 5. Forest plot comparing best corrected visual acuity (BCVA) change relative to baseline in Q1/Q2 versus Q3/Q4 eyes, demonstrating no significant differences in mean BCVA changes. Blocks represent point estimates; horizontal lines, 95% confidence intervals; diamond, overall effect estimate of meta-analysis. SD, standard deviation.

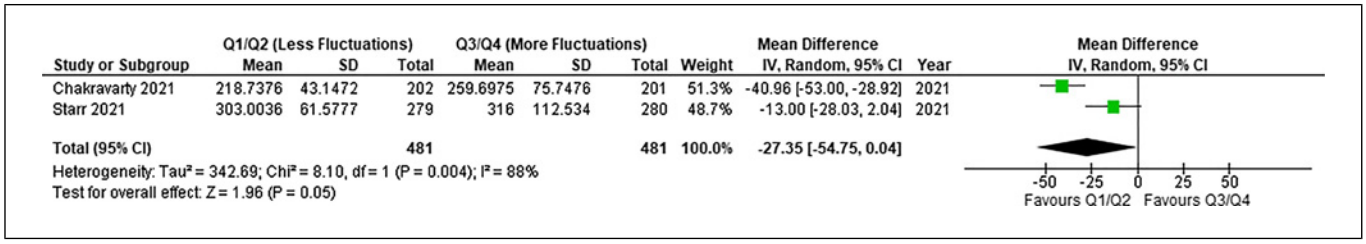

Fig. 6. Forest plot comparing retinal thickness (RT) at final follow-up between Q1/Q2 and Q3/Q4 eyes, demonstrating lower mean final RT in Q1/Q2 (less RT fluctuations). Blocks represent point estimates; horizontal lines, 95% confidence intervals; diamond, overall effect estimate of meta-analysis. SD, standard deviation.

BCVA improvement was also significantly greater in eyes with lower RT fluctuations [16, 18, 19]. Evans et al. [7] found that the likelihood of developing geographic atrophy and fibrosis was greater in eyes with higher RT fluctuations. Chakravarthy et al. [8] demonstrated that IRF fluctuations played a more important role than SRF with respect to final visual outcome. Moreover, Sheth et al. [20] found that SRF fluctuations did not impact final visual outcome. Eyes with lower RT fluctuations had a larger proportion of patient visits who presented with SRF only compared to eyes with moderate and high RT fluctuation [16]. Guo and colleagues [27] demonstrated that increased RT fluctuations over the course of 1 year of anti-VEGF therapy were associated with a greater risk of legal blindness (≤35 ETDRS).

Retinal Vein Occlusion Studies

Three studies investigated the association between RT fluctuations and visual outcome in eyes with ME secondary to RVO [21–23]. Two studies examined patients with BRVO [21, 22] and three studies examined patients with CRVO [21, 23, 26]. One study examined patients with HRVO [23]. The final visual outcome was significantly better in eyes with smaller RT fluctuations [21–23]. Chen et al. [21] observed a difference of 10 letters between quartiles 1 and 4 ($p < 0.001$), reflecting the worse visual prognosis in highly fluctuating eyes. Nagasato et al. [22] observed longer defects in the foveal ellipsoid zone (EZ) in BRVO eyes with the largest RT fluctuations. A similar study by Nagasato et al. [26] also demonstrated longer EZ defects in eyes with CRVO with larger fluctuations. One study found significant differences in RT fluctuations depending on the anti-VEGF agent used. Specifically, larger RT fluctuations were observed in eyes receiving bevacizumab (BEV) injections relative to aflibercept (AFL) injections ($p < 0.0001$) [23].

Diabetic Macular Edema Studies

Two studies examined RT fluctuations in eyes treated with anti-VEGF therapy for DME [24, 25]. Patients were stratified into quartiles of RT fluctuation. Overall, significantly worse visual outcomes were observed in eyes with high RT fluctuations. For example, Wang et al. [25] observed a difference of 9.7 ETDRS letters between quartiles 1 and 4 at final follow-up ($p < 0.001$).

Discussion

This systematic review and meta-analysis investigated the association between RT fluctuations and BCVA in patients treated with anti-VEGF therapy in the setting of nAMD, RVO, and DME. Overall, our systematic review and meta-analysis demonstrated that eyes with greater RT fluctuations experienced significantly poorer visual outcomes at final follow-up in all three eye diseases. Additionally, the RT at final follow-up was significantly lower in eyes with lower fluctuations over the course of treatment. The change in BCVA was not significantly different between Q1/Q2 and Q3/Q4 eyes when results were pooled in a meta-analysis. These results are limited by the presence of considerable heterogeneity and the relatively low number of studies included in the meta-analysis.

Although studies have demonstrated an association between greater RT fluctuations and poorer visual outcomes, the exact mechanism has not been determined. Cheong and colleagues [16] hypothesize that photoreceptor viability is perturbed due to repeated shrinking and stretching of photoreceptors, and the directional sensitivity of photoreceptors is impaired due to perturbations in cone structure and alignment. Further evidence of photoreceptor damage secondary to RT fluctuations was demonstrated by Nagasato et al. [22] and Nagasato et al. [26], where greater foveal thickness fluctuations in eyes with BRVO and CRVO, respectively, were associated with longer EZ defects, reflecting photoreceptor damage. Evans et al. [7] showed that highly fluctuating eyes had a greater risk of developing GA and fibrosis, both of which have been associated with poorer visual outcomes in the setting of nAMD [7, 28]. Ultimately, further studies are needed to elucidate which of these mechanisms resulted in poorer visual prognosis in highly fluctuating eyes.

Several anti-VEGF treatment regimens may be used, including PRN, treat-and-extend, and fixed-dosing intervals [29]. In a PRN regimen, injections are administered in a reactive manner in the setting of macular fluid recurrence [3]. In a treat-and-extend regimen, the eye is injected at each visit until there is resolution of disease activity, followed by subsequent injections with increasing time intervals in between [3, 29]. The goal of the proactive treat-and-extend regimen is to prevent fluid recurrence and provide anti-VEGF therapy in the absence of fluid [3, 7, 29]. Notably, one study found that patients undergoing a PRN regimen had larger RT fluctuations relative to patients on a monthly treatment regimen [20]. The extent of RT fluctuations therefore becomes important to consider when weighing the risks and benefits of the PRN treatment regimen. In principle, a treat-and-extend regimen may lead to relatively lower fluctuations in RT; however, this regimen may not always be appropriate based on patient and physician preferences [3]. In practice, clinicians should consider the potential for poor visual outcomes in patients with high RT fluctuations when adopting an anti-VEGF treatment regimen.

There is conflicting evidence with regards to the impact of the number of injections on the likelihood of greater RT fluctuation. Evans et al. [7] found that an increased number of injections was associated with higher RT fluctuations. Conversely, Lai et al. [19] observed no significant differences in injection burden between quartiles of fluctuation. Nevertheless, anti-VEGF undertreatment has been implicated as a risk factor for poorer visual outcomes in the setting of nAMD, BRVO, and DME, and it is possible that higher RT fluctuations may mediate this relationship [30, 31]. Patients with the highest RT fluctuations had the lowest BCVA and highest RT at baseline in this study, suggesting that these patients present with more advanced disease, resulting in greater treatment demand and higher RT fluctuations. The impact of specific anti-VEGF agents on RT fluctuations is also yet to be elucidated; however, Scott et al. [23] interestingly observed significantly greater CST fluctuations in eyes receiving BEV injections compared to AFL injections. Further studies are needed to assess the different impact of various anti-VEGF agents on the magnitude of RT fluctuations.

This meta-analysis has important limitations to consider. Only five studies met eligibility criteria for the meta-analysis, resulting in a relatively low sample size. The results are further limited by considerable heterogeneity, which may limit generalizability. Given a paucity of data, eyes with AMD, DME, and RVO were combined in the overall meta-analysis, introducing heterogeneity. Variable study design may have contributed to increased heterogeneity. Missing and/or incomplete patient data in individual studies may give rise to sampling bias. Additionally, the measures of RT varied between studies, and this introduces further heterogeneity and may lead to under- or over-estimation of treatment effects on disease progression. Evans et al. [7] reported thickness at the foveal center point, whereas two studies measured CST [8, 24]. Two studies reported FT as a measure of RT [22, 26]. We did not restrict studies based on follow-up duration due to a paucity of evidence in this setting, but the studies included in the meta-analysis had long-term follow-up for our outcomes of interest (range: 24 months–50.6 months). Another limitation of this meta-analysis is the potential for anti-VEGF undertreatment as an explanation for the association between RT fluctuations and VA outcome, given that the mean number of anti-VEGF injections was greater in eyes with high RT fluctuations [7, 8, 22]. It is possible that eyes with more severe disease at baseline are predisposed to greater RT fluctuations, suggesting that RT fluctuations may not cause poor visual outcomes but are rather a surrogate for disease severity. The potential for

diurnal variation in RT thickness serves as another limitation for this study as the measured RT may be impacted by the time of day. Indeed, previous studies have demonstrated variations in ME over the course of the day in patients with DME [32] and CRVO [33]. None of the studies included in this review commented on the potential impact of diurnal variation. Given the potential prognostic value of assessing RT fluctuations, future studies may benefit from adopting a standardized method of measuring RT fluctuations, assessing the impact of duration of RT fluctuations on final VA, and accounting for anti-VEGF undertreatment.

This systematic review of sixteen studies and meta-analysis of five studies found that VA outcomes were significantly worse in highly fluctuating eyes in patients treated with anti-VEGF therapy. Further studies are needed to quantify the impact of RT fluctuations on VA outcomes and whether different anti-VEGF agents mediate differences in RT fluctuations.

Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature. This study was conducted ethically and in accordance with the World Medical Association Declaration of Helsinki.

Conflict of Interest Statement

M.M.P.: financial support (to institution) – PSI Foundation, Fighting Blindness Canada.

D.T.W.: consultant – AbbVie, Alcon, Apellis, Bayer, Bausch Health, Biogen, Boehringer Ingelheim, Novartis, Ripple Therapeutics, Roche, Topcon, and Zeiss. Research grants from Novartis, Roche.

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Author Contributions

Bhadra U. Pandya, Andrew Mihalache, Amin Hatamnejad, Justin Grad, Marko M. Popovic, and David T. Wong: conception and design, acquisition of data, analysis and interpretation of data, preparation of the manuscript, and final approval of the completed manuscript.

Data Availability Statement

All available data are available in this article and online as supplementary information. Further inquiries may be directed to the corresponding author.

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