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Review article

Anatomic biomarkers as potential endpoints in diabetic macular edema: A systematic literature review with identification of macular volume as a key surrogate for visual acuity

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ABSTRACT

Optimization of diabetic macular edema (DME) treatment pathways can aid in the efficient introduction of new therapies that provide value to patients and healthcare systems. We performed a systematic literature review and multicorrelation analysis to identify and evaluate anatomic biomarkers as potential surrogate endpoints (SEs) for visual acuity (VA) in patients with DME. We performed EMBASE and MEDLINE searches to identify studies reporting on 4 priority biomarkers previously identified by clinical experts: hyperreflective foci, intraretinal cyst, macular volume (MV), and subretinal fluid. Endpoint and treatment effect correlation analyses were performed to establish correlation coefficients between MV and VA using Pearson's correlation. A total of 105 studies reported change from baseline data for VA, and at least 1 biomarker, with MV investigated most often (n = 70 studies). Data extracted from 55 studies focusing on the 6-mm zone for MV were used in statistical analyses. A moderate correlation was observed between MV and VA at the endpoint level ($r = 0.58$; $p < 0.01$); however, a corresponding treatment effect was not found ($r = 0.32$; $p = 0.19$). Our findings suggest MV's potential as an SE for VA in future clinical practice; however, the lack of a significant treatment effect warrants that these findings be interpreted cautiously. Further evidence and improvements in reporting the methods for collecting biomarker data are needed. Analysis of outliers and subanalyses by other optical coherence tomography measures could establish the most meaningful MV values correlating with VA.

1. Introduction

Diabetes mellitus (DM) is a common medical condition that is associated with macrovascular conditions, such as coronary heart disease, and microvascular disorders, including retinopathy.[1,111] The global prevalence of DM continues to increase, estimated at 10.5 % (536.6 million diagnosed) in 2021 and predicted to rise to 12.2 % (783.2 million diagnosed) by the year 2045.[108] This increase has resulted in a substantial impact on patients as well as imposing an economic burden on healthcare systems.[1]

Diabetic macular edema (DME) is caused by excess extravascular fluid accumulation within the macula, leading to increased central retinal thickness and macular volume (MV)[123] and is a leading cause of vision impairment among patients with DM.[24,53] Consequently, patients with DME may experience a gradual progressive loss of vision and washing out of vision in bright sunlight with poor dark-light adaptation,

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resulting in a substantial impact on quality of life.[83] Conversely, patients can be asymptomatic until visual loss occurs.[83]

Treatment for DME generally involves primary management of DM, pharmacotherapeutics targeting the vascular endothelial growth factor (VEGF) pathway, and intravitreal steroid implants;[16] however, multiple factors influence visual outcomes after treatment, and because incomplete response to treatment is common, there remains a large unmet need to develop new pharmacotherapies. There is also a need to better evaluate current treatment effects, improve the efficiency of clinical trials, and expedite health technology assessment (HTA) for novel DME treatments. Using known biomarkers of retinal function as surrogate endpoints (SEs) may help accelerate these processes.

A biomarker is a characteristic that is objectively measured and evaluated as an indication of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. An SE is defined as a biomarker or an intermediate outcome that can substitute for a final patient-relevant outcome, such as mortality and health-related quality of life.[26] In DME, SEs might include both optical coherence tomography (OCT) biomarkers such as disorganization of the inner retinal layers (DRIL), hyperreflective foci (HRF), and MV,[115] and systemic biomarkers such as blood pressure, glycated haemoglobin (HbA_{1c}), and glomerular filtration rate.[2]

We aimed to address the unmet needs in DME treatment by identifying and evaluating OCT biomarkers that can be used as SEs for visual acuity (VA) by conducting a systematic literature review (SLR) and multicorrelation analyses. In addition, we present the potential implications of using SEs in clinical practice.

2. Methods

2.1. Biomarker prioritization for VA

Five clinical experts were consulted to identify OCT biomarkers that could be used and explored as SEs for the clinical outcome of VA in an SLR. During the first stage of biomarker prioritization, discussions focused on outlining several potential SEs and the consistency of reporting selected biomarkers. Clinicians were asked to consider what SEs for VA were clinically plausible to investigate.

In the second stage of biomarker prioritization, a list of all potential SEs discussed in stage 1 was emailed to the clinical specialists. The list presented to the clinical experts consisted of 13 OCT biomarkers that were explored as potential SEs, including subretinal fluid (SRF), HRF, ellipsoid zone alteration, enlarged foveal avascular zone (FAZ), MV, central macular thickness (CMT), DRIL, disorganization of the outer retinal layers (DROL), localization of hard exudates, intraretinal fluid, presence of intraretinal cyst (IC), increased retinal nonperfusion, and external limiting membrane layer. The clinical experts were asked to refine the list to ≤ 5 clinically plausible SEs for VA and inflammation that would most likely fit the following criteria: 1) The endpoint is likely linked or is linked to inflammation; 2) The endpoint is relevant and/or easily identifiable for a clinician in an everyday clinic; 3) No additional tools are required to identify or visualize the SE; 4) There is some evidence or belief that if the candidate SE improves, VA outcomes will also improve; 5) There is a likelihood that the SE will be relatively well reported in the literature. Ultimately, the clinical experts refined this list to include 4 OCT biomarkers of interest (HRF, IC, MV, and SRF).

2.2. Systematic literature review

An SLR was performed per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[95]

To identify potentially relevant studies reporting on the 4 OCT biomarkers that were identified during the biomarker prioritization exercise (HRF, IC, MV, and SRF), searches of Embase, 1974 to present, and MEDLINE, 1946 to present, including MEDLINE Epub Ahead of Print, MEDLINE In-Process & Other Non-Indexed Citations, and MEDLINE Daily were performed via the Ovid platform on March 7, 2023. The search strategy used to interrogate the electronic databases is provided in the Supplementary material (Supplementary Table 1) and Table 1. Due to a paucity of identified evidence, additional hand searches of included publications' reference lists, HTA body websites, and clinical trial registries were performed to identify other relevant evidence. Reference lists of eligible studies (primary studies and relevant reviews) included at full publication screening were reviewed to identify any further relevant publications not identified as part of the electronic database searches. Full eligibility criteria are presented in Table 1.

Citations of interest were identified by 1 reviewer and verified by an independent reviewer based on the title and abstract. Full publications were obtained for all citations of interest and assessed by one reviewer and verified by a second reviewer. Any uncertainties were resolved through discussion. Data were extracted into an Excel spreadsheet by one reviewer and independently checked against the original publication by a second reviewer.

2.3. Quality assessment and risk of bias

For all searches undertaken, the main Embase strategy was independently peer-reviewed by a second analyst, and discrepancies were resolved through discussion or the intervention of a third reviewer. Search strategy peer review was informed by items on the Peer Review of Electronic Search Strategies checklist.[15]

Risk of bias was performed to ensure that the conclusions and findings of the review were based on the best available evidence and that any sources of bias in the data were identified. Assessment of each individual eligible study was conducted using the Joanna Briggs Institute Critical Appraisal Tools considering the type of study.[55] The assessment

Table 1
Eligibility criteria for the SLR.

Criteria	Inclusion criteria	Exclusion criteria
Population	Adult patients (> 18 years old) with DME	-
Intervention & Comparator	Any treatment or surgery, or no treatment	-
Outcomes	Change from baseline (over at least 24 h) for VA* (true endpoint) and the following biomarkers: † • MV • SRF • HRF • IC Comparisons of the biomarkers (MV, SRF, HRF, IC) and VA reporting RR, OR, or MD Biomarkers (MV, SRF, HRF, IC) as risk factors/ predictive for VA improvement	-
Study design	Randomized controlled trials, controlled trials Observational (prospective and retrospective)	Review/editorials Case reports Pharmacokinetic studies Animal or in vitro studies
Geography	No restrictions	-
Date of publication	No restrictions for full texts	Conference abstracts pre-2019
Language of publication	English language only	-

Abbreviations: DME, diabetic macular edema; ETDRS, Early Treatment of Diabetic Retinopathy Study; HRF, hyperreflective foci; IC, intraretinal cyst; logMAR, Logarithm of the Minimum Angle of Resolution; MD, mean difference; MV, macular volume; OR, odds ratio; RR, risk ratio; SLR, systematic literature review; SRF, subretinal fluid; VA, visual acuity.

* Measured by the logMAR scale or ETDRS letters.

† At title and abstract screening stage, all papers reporting the VA and biomarkers were included to map the methods of reporting at later stage.

was performed for randomized controlled trials,[7] cohort studies,[54] and case series.[81]

To evaluate their reporting methods, an extensive assessment of all OCT biomarkers of interest (HRF, IC, MV, and SRF) was performed. The assessment focused on biomarker definition, biomarker unit of measurement, and the total number of studies from which the data could be extracted. The volume and type of available data for each identified OCT biomarker (HRF, IC, MV, and SRF) were assessed to determine their suitability for inclusion in subsequent statistical analyses. MV was chosen for further statistical analysis after assessing all OCT biomarkers. A feasibility assessment was performed for the remaining OCT biomarkers (HRF, IC, and SRF) to determine if the data could be combined. A consensus was reached that no sufficient data could be extracted to perform the statistical analysis for HRF, IC, and SRF.

Results of the full-text screening and overview of the data extraction of studies reporting MV were presented to the clinical experts, during which additional terms were proposed to screen for biomarkers of interest. For context, the Early Treatment Diabetic Retinopathy Study (ETDRS) grid divides the retina into 9 large regions defined by 3 rings: a central foveal ring with 1-mm diameter, an inner macular ring (pericentral) with 3-mm diameter, and an outer macular ring (peripheral) with 6-mm diameter. Based on the MV measurements in the extracted data, the clinical experts agreed to include the assumption that there was a clear distinction between MV values measured at the 1- or 6-mm zone.

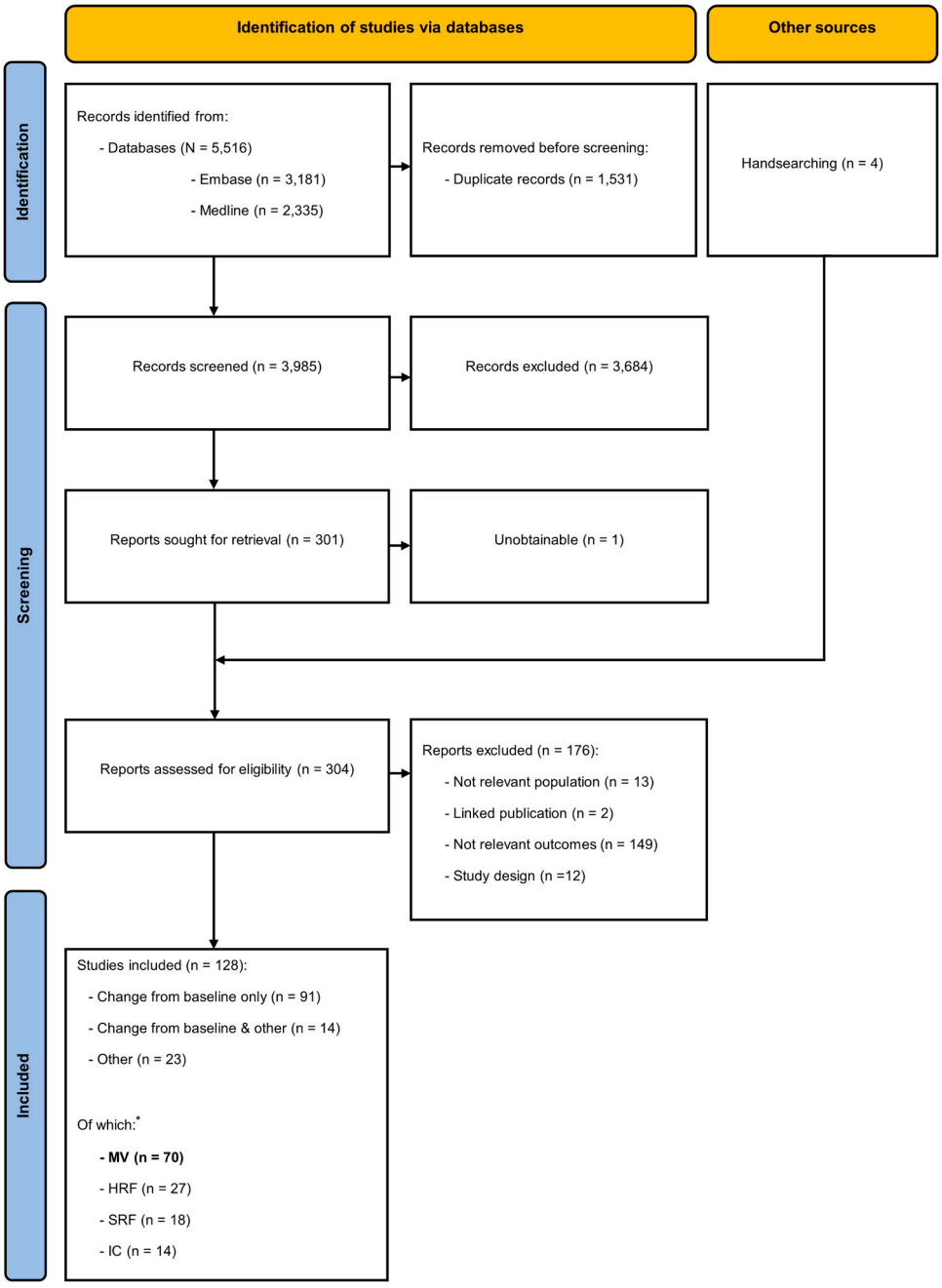


Fig. 1. PRISMA flow diagram. PRISMA flow diagram describing the identification and screening of literature identified from the search strategy, and reasons for exclusion. * An individual study can include more than one biomarker or unit of measurement. Abbreviations: HRF, hyperreflective foci; IC, intraretinal cyst; MV, macular volume; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SRF, subretinal fluid.
Adapted from: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Int J Surg. 2021;88:105906. ⟨https://doi.org/10.1016/j.ijsu.2021.105906⟩.[90]

In addition, after applying eligibility criteria and selecting MV, too few studies reported the 1- or 3-mm measurement zone for analyses to be conducted (n = 7). (Fig. 1).

It was assumed that if the zone measured was not reported (n = 35 studies), but MV values were comparable to those reported in other peer-reviewed articles, the 6-mm zone was investigated in the study article/publication. To avoid introducing errors in the analysis, the clinical experts were asked if the assumption regarding the reporting of MV was reasonable, and all agreed that the assumption was plausible. Figs. 2–4 include the results for all papers with a 6 mm zone and the stratification of papers with a confirmed and assumed 6-mm zone. Clinical experts also agreed to include all methods of VA, including both VA and best-corrected VA (BCVA), and highlighted that ETDRS letters could be converted to logarithm of the minimum angle of resolution (logMAR).

2.4. Endpoint (arm-level) correlations

Treatment follow-up time varied depending on each identified study (Table 5). Endpoint (arm-level) correlation was performed for all treatments used to manage DME, including anti-VEGF, steroids, and laser treatment. The correlation between MV and VA could not be determined using a single time point in a patient's treatment protocol.

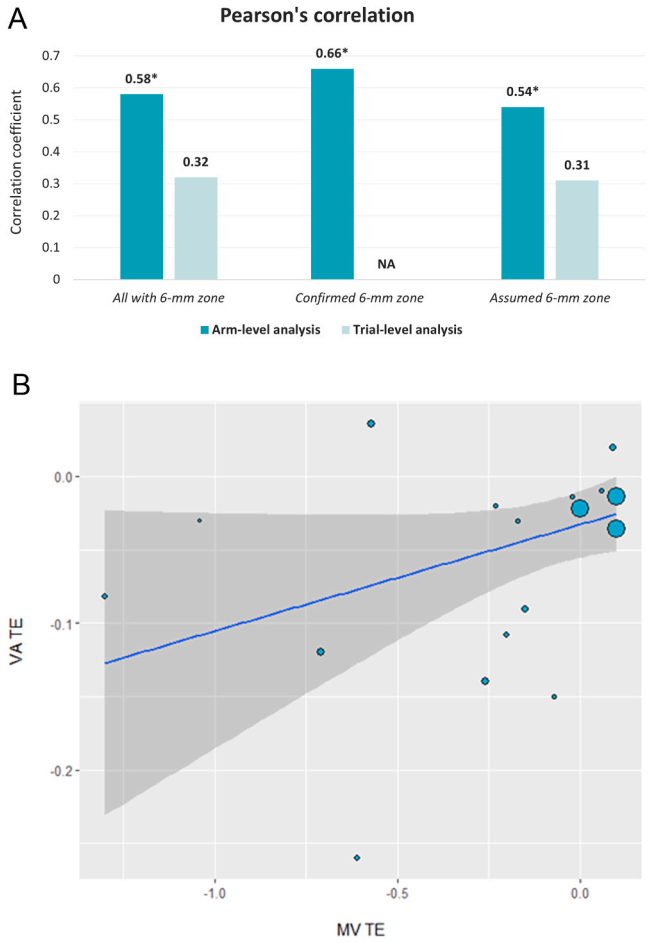


Fig. 2. Arm-level (endpoint) and trial-level (treatment effect) correlation analysis for MV vs VA at the 6 mm zone in the base case. A. Pearson's correlation at the arm-level (endpoint) and trial-level (treatment effect) for MV vs VA for all studies that reported a confirmed and/or assumed 6 mm zone. B. Scatter plot analysis demonstrating the trial-level (treatment effect) correlation between VA and MV for all studies that reported a confirmed and/or assumed 6 mm zone. * Values are statistically significant at the 1 % level ($p < 0.01$). Abbreviations: mm, millimeter; NA, not applicable; MV, macular volume; TE, treatment effect; VA, visual acuity.

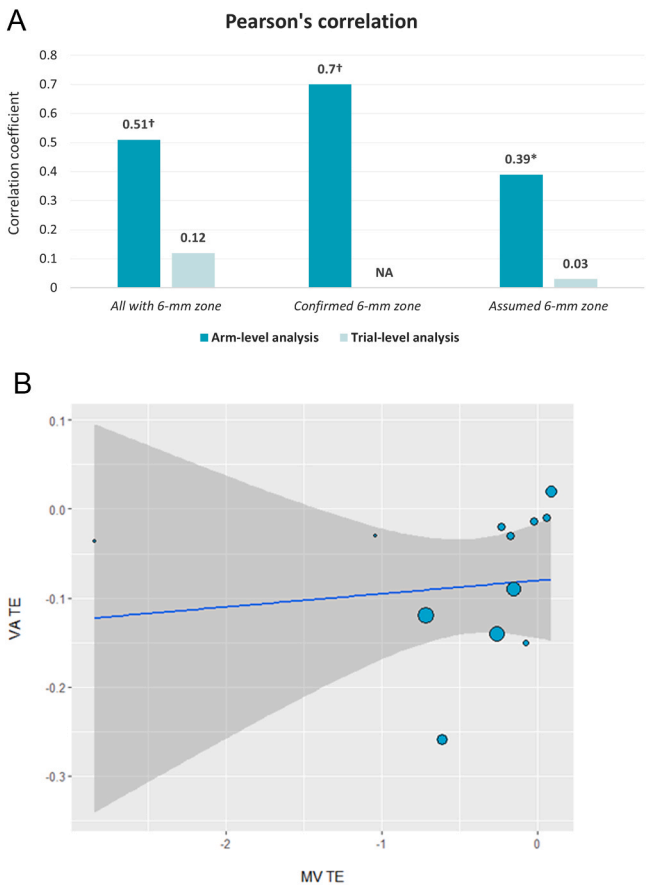


Fig. 3. Arm-level (endpoint) and trial-level (treatment effect) correlation analysis for MV vs VA at the 6-mm zone: Scenario analysis for VA expressed in logMAR. A. Pearson's correlation at the arm-level (endpoint) and trial-level (treatment effect) for MV vs VA for all studies that reported a confirmed and/or assumed 6-mm zone where VA was expressed in logMAR. B. Scatter plot analysis demonstrating the trial-level (treatment effect) correlation between VA and MV for all studies that reported a confirmed and/or assumed 6-mm zone where VA was expressed in logMAR. * Values are statistically significant at the 5 % level ($p < 0.05$). † Values are statistically significant at the 1 % level ($p < 0.01$). Abbreviations: logMAR, Logarithm of the Minimum Angle of Resolution; mm, millimeter; MV, macular volume; NA, not applicable; TE, treatment effect; VA, visual acuity.

Therefore, the change from baseline was used to investigate how changes in MV affect the outcome of VA from the beginning to the end of a treatment protocol. For each study, the change from baseline for MV and VA was either extracted from the literature or calculated directly from available data. A scatter plot of values for change from baseline for MV and VA for each arm of the identified studies was created to estimate endpoint correlation. A regression analysis was then used to fit a trendline and calculate Pearson's correlation. A correlation statistic was calculated if ≥ 10 trial arms were available. The eligible studies were included despite the number of treatment arms. Per the Institute for Quality and Efficiency in Health Care's guidance on the validity of SEs, an endpoint correlation target value of ≥ 0.7 was used to determine if the analysis had a strong justification to progress to treatment effect (trial-level) correlation analysis.[51] A target value of < 0.7 indicated a low to medium association between the changes from baseline in MV and VA.[51]

2.5. Treatment effect (trial-level) correlations

Treatment effect (trial-level) correlation was performed for all types of treatment used to manage DME, including anti-VEGF, corticosteroids,

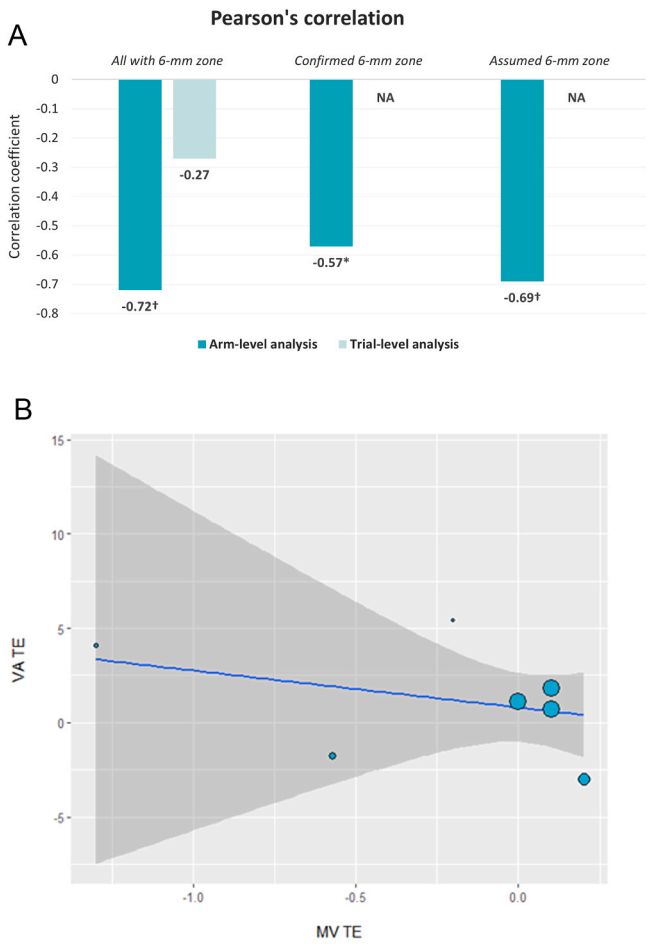


Fig. 4. Arm-level (endpoint) and trial-level (treatment effect) correlation analysis for MV vs VA at the 6-mm zone: Scenario analysis for VA expressed in ETDRS letters. A. Pearson's correlation at the arm-level (endpoint) and trial-level (treatment effect) for MV vs VA for all studies that reported a confirmed and/or assumed 6-mm zone where VA was expressed in ETDRS letters. B. Scatter plot analysis demonstrating the trial-level (treatment effect) correlation between VA and MV for all studies that reported a confirmed and/or assumed 6-mm zone where VA was expressed in ETDRS letters. * Values are statistically significant at the 5 % level ($p < 0.05$). † Values are statistically significant at the 1 % level ($p < 0.01$). Abbreviations: ETDRS, Early Treatment Diabetic Retinopathy Study; mm, millimeter; MV, macular volume; NA, not applicable; TE, treatment effect; VA, visual acuity.

and laser treatment. The differences between changes from baseline for MV and VA were used to calculate the treatment effect for each intervention of interest. The treatment effect correlation between MV and VA was estimated for the trial arms by creating a scatter plot of the treatment effects. A regression analysis was then used to fit a trendline and calculate Pearson's correlation. A correlation statistic was calculated if ≥ 10 trial arm pairs were available, and all eligible studies were included if they reported ≥ 2 treatment arms (Table 5). SE validity was dependent upon correlation strength, with a strong treatment effect correlation of ≥ 0.7 used to indicate a valid SE for VA and < 0.7 used to indicate a low to medium treatment effect correlation.[51]

2.6. Statistical analyses

All statistical analyses were performed using R statistical software.

Correlation coefficients were estimated using Pearson's correlation with the number of eyes used as an arm and trial weight. A visual inspection of the data distributions using histograms validated the normality assumption. Multiple analyses were considered to evaluate the correlation between MV and VA: Base case, Scenario 1 (logMAR), and Scenario 2 (ETDRS letters). In the base case, all eligible studies included VA values expressed in logMAR (ETDRS letters were converted to logMAR, and the change from baseline calculated where possible) and included subgroup analyses of studies that reported a confirmed and assumed 6 mm zone. In Scenario 1 (logMAR), all studies reported VA values expressed in logMAR and included subgroup analyses of studies that reported confirmed and assumed 6-mm zone. Finally, in Scenario 2 (ETDRS letters), all studies reported VA values expressed in ETDRS letters and included subgroup analyses of studies that reported a confirmed and assumed 6-mm zone.

3. Results

3.1. Systematic literature review

The electronic database searches identified a total of 5516 publications. Following deduplication, 3985 publications were screened by title and abstract. Of these, 301 were deemed potentially relevant and were screened based on the full publication. One further publication was excluded at this stage. Hand searching yielded an additional 4 citations, giving a total of 304 publications that were screened for eligibility. A further 176 publications were excluded at this stage, leaving a total of 128 unique studies covering the 4 separate OCT biomarkers of interest (HRF, IC, MV, and SRF) for inclusion. The flow of studies through the review is summarized in the PRISMA flow diagram (Fig. 1).

A total of 105 studies reported data for change from baseline for VA and at least one OCT biomarker of interest (HRF, IC, MV, and SRF) (Table 2). MV was investigated most often in studies identified by the SLR with change from baseline measured in mm^3, μm^3, and μm^2 ($n = 70$ studies). Of the remaining OCT biomarkers, change from baseline in HRF was measured by number of HRF and presence/absence of HRF in 26 studies, change from baseline in SRF was measured by presence/absence, µm, mm^3, nL, and score in 17 studies, and change from baseline in IC was measured by µm, mm^3, presence/absence, nL, μm^2, and number of cysts in 11 studies (Table 2).

After the feasibility assessment, MV was chosen as the VA SE as the

Table 2
Summary of how all biomarkers were reported in the literature (N = 105 studies*†).

Biomarker	Unit of measurement	Number of studies	Notes
MV (n = 70)	mm^3	68	Often: total, central MV, within the circle size (3.5- and 5-mm)
	μm^3	3	
	μm^2	1	
SRF (n = 17)	Presence/absence	9	One study had 2 ways of reporting – presence/absence and mm^3 or µm
	µm	3	
	mm^3	4	
	nL	2	
	Score	1	
HRF (n = 26)	Number of HRF	22	Different types of HRF: retina, choroid, inner or outer retina (potentially others) Spots, dots, and foci
	Presence/absence	4	
IC (n = 11)	µm	4	
	mm^3	2	
	Presence/absence	2	
	nL	1	
	μm^2	1	
	Number of cysts	1	

Abbreviations: ETDRS, Early Treatment of Diabetic Retinopathy Study; HRF, hyperreflective foci; IC, intraretinal cyst; logMAR, Logarithm of the Minimum Angle of Resolution; MV, macular volume; SRF, subretinal fluid; VA, visual acuity.

* An individual study can include more than one biomarker or unit of measurement.

† VA (N = 105 studies); ETDRS letters (n = 49 studies); logMAR (n = 56 studies).

data volume was judged sufficient for further statistical analysis. Data extraction and risk of bias assessment were only performed on the studies that investigated and reported MV (n = 70). A total of 63 studies were considered in the statistical analysis, and 7 were discounted as they either reported values in median (n = 3) or used a unit of measurement other than mm^3 (n = 4). A summary of the eligible studies reporting data for MV identified by the SLR is presented in Table 3. A list of studies included in the base case and scenario analyses is presented in the Supplementary materials (Supplementary Table 2). For the remaining biomarkers (HRF, IC, and SRF), a list of studies reporting MV and VA data is presented in the Supplementary material for completeness (Supplementary Table 3).

3.2. Risk of bias of the included studies

Results of the risk of bias are presented in Table 4 for all 70 studies that reported MV. Most studies had an unclear or high risk of bias, and few were well-conducted. Most studies were observational, with approximately 64.3 % being single-arm studies, and many were non-randomized, prospective (35.7 %), or retrospective (45.7 %). Across the studies, patient baseline characteristics were poorly reported, and OCT biomarkers were poorly defined, with a lack of detail regarding their definition or the method of biomarker measurement used. This resulted in assumptions being made regarding the zone in which the OCT biomarker was measured. As previously stated, if the zone measured was not reported (n = 35 studies [Table 5]), but MV values were comparable to those reported in other peer-reviewed articles, it was assumed that the 6-mm zone was investigated.

3.3. Base case for MV vs VA

A summary of all eligible studies (N = 70) reporting data for change from baseline for VA and MV identified by the SLR is presented in Table 3, with a summary of the articles (MV with 6-mm zone; n = 56) used to establish both arm- and trial-level correlation coefficients for MV vs VA in the base case (Table 5). One study was considered an outlier and removed from further analysis. All other outliers were retained as the clinical experts confirmed no clinical justification for excluding them from the analysis.

At the arm-level (endpoint correlation), a moderate and statistically significant correlation coefficient of r = 0.58 ($p < 0.01$) was identified between the change in MV for all studies (n = 52) reporting a confirmed and assumed 6-mm zone and change in VA (Fig. 2). The results suggest that when DME decreases, MV decreases, logMAR decreases, and VA increases. Similar results were reported for studies that included a confirmed (n = 18) or assumed (n = 34) 6-mm zone. A moderate and statistically significant coefficient of r = 0.66 ($p < 0.01$) was identified between MV and VA for studies that included a confirmed 6-mm zone, and a moderate and statistically significant coefficient of r = 0.54 ($p < 0.01$) for studies that included an assumed 6-mm zone (Fig. 2).

At the trial-level (treatment effect correlation), a low and non-significant correlation coefficient of r = 0.32 ($p = 0.19$) was reported between the treatment effects for MV and VA for all studies (n = 14), reporting a confirmed and assumed 6-mm zone (Fig. 2). A similar result was reported for studies (n = 10) reporting an assumed 6-mm zone (r = 0.31; p = nonsignificant [NS]); however, the remaining number of studies (n = 4) that reported a confirmed 6-mm zone was too small to conduct a meaningful analysis (Fig. 2).

3.4. Scenario analysis for MV vs VA (VA expressed in logMAR)

A summary of all eligible studies (N = 70) reporting data for change from baseline for VA and MV identified by the SLR is presented in Table 3, with a summary of the studies (MV with 6-mm zone; n = 28) used to establish both arm- and trial-level correlation coefficients for MV vs VA in the logMAR scenario analysis presented in Table 5.

Consistent with the results in the base case, at the arm-level (endpoint correlation), a moderate and statistically significant correlation coefficient of r = 0.51 ($p < 0.01$) was identified between the change in MV for all studies (n = 28) reporting a confirmed and assumed 6-mm zone and change in VA expressed in logMAR (Fig. 3). The results suggest that when DME decreases, MV decreases, logMAR decreases, and VA increases. Similar results were reported for studies that included a confirmed (n = 11) or assumed (n = 17) 6-mm zone. A high and statistically significant coefficient of r = 0.7 ($p < 0.01$) was identified between MV and VA for studies that included a confirmed 6 mm zone and a low and statistically significant coefficient of r = 0.39 ($p < 0.05$) for studies that included an assumed 6-mm zone (Fig. 3).

At the trial-level (treatment effect correlation), a very low and non-significant correlation coefficient of r = 0.12 (p = NS) was reported between the treatment effects for MV and VA expressed in logMAR for all studies (N = 10) reporting a confirmed and assumed 6-mm zone (Fig. 3). A similar result was reported for studies (n = 7) reporting an assumed 6-mm zone (r = 0.03; p = NS); however, the remaining number of studies (n = 3) that reported a confirmed 6-mm zone was too small to conduct a meaningful analysis (Fig. 3).

3.5. Scenario analysis for MV vs VA (VA expressed in ETDRS letters)

A summary of all eligible studies (N = 70) reporting data for change from baseline for VA and MV identified by the SLR is presented in Table 3, with a summary of the studies (MV with 6-mm zone; n = 27) used to establish both arm- and trial-level correlation coefficients for MV vs VA in the ETDRS letters scenario analysis presented in Table 5.

Consistent with the results in the base case, at the arm-level (endpoint correlation), a high and statistically significant negative correlation coefficient of r = -0.72 ($p < 0.01$) was identified between the change in MV for all studies (n = 27), reporting a confirmed and assumed 6-mm zone and change in VA expressed in ETDRS letters (Fig. 4). The results suggest that when DME decreases, MV decreases, ETDRS letters increase, and VA increases. Similar results were reported for studies that included a confirmed (n = 9) or assumed (n = 18) 6-mm zone. A moderate and statistically significant negative coefficient of r = -0.57 ($p < 0.05$) was identified between MV and VA for studies that included a confirmed 6-mm zone, and a moderate and statistically significant negative coefficient of r = -0.69 ($p < 0.01$) for studies that included an assumed 6-mm zone (Fig. 4).

At the trial-level (treatment effect correlation), a low and non-significant negative correlation coefficient of r = -0.27 (p = NS) was reported between the treatment effects for MV and VA expressed in ETDRS letters for all studies (N = 5) reporting a confirmed and assumed 6-mm zone (Fig. 4); however, the number of studies that reported either a confirmed 6-mm zone (n = 2) or assumed a 6-mm zone (n = 3) was too small to conduct meaningful analyses (Fig. 4).

4. Discussion

This analysis aimed to address the unmet needs in DME by identifying and evaluating OCT biomarkers that can be used as SEs for VA by conducting an SLR and multi-correlation analyses. DME is one of the most common retinal disorders that can lead to visual deterioration in patients with DM,[86] with a prevalence of approximately 30 % for both types 1 and 2 DM after 25 years of disease duration.[13] Intravitreal injections of anti-VEGF agents are recognized as the most effective treatment and considered the standard of care for DME[12,52]; however, current treatment can be suboptimal and is often associated with

Table 3
Summary of eligible studies reporting data for change from baseline for VA and MV*.

Study name, country	Study design	Population	MV: zone measured by OCT (mm)	Interventions	Sample size (patients/eyes)	Baseline characteristics			
						Average age (years)†	% of male/female	Average duration of diabetes (years)†	Average duration of DME (years)†
Baget-Bernaldiz et al. (2017)[3] Spain	Prospective, observational	DME	6 (assumed)	Ranibizumab	35/35	54 (6.2)	42.9/57.1	21.3 (10.7)	NR
Bailey et al. (2021)[4] UK	Retrospective, observational	Chronic DME	6 (assumed)	Fluocinolone acetonide implant	227/256	66.9 (10.6)	51.1/48.9	NR	4.4 (2.9)
Baker et al. (2019)[5] Canada, USA	RCT	CI-DME	6 (assumed)	Aflibercept	226/226	Median (IQR) 59 (52, 65)	58/42	Median (IQR) 15 (10, 21)	NR
				LP	240/240	Median (IQR) 60 (53, 66)	65.8/34.2	Median (IQR) 15 (10, 20)	NR
				Observation	236/236	Median (IQR) 60 (53, 67)	63.1/36.9	Median (IQR) 16 (10, 24)	NR
Best et al. (2019)[8] UK	Retrospective, observational	CI-DME	6 (assumed)	Focal macular LP	69/92	NR	NR/NR	NR	NR
Bezzina et al. (2019)[9] Malta	Retrospective, observational	DME (including refractory)	6	Bevacizumab	65/65	64.26 (8.32)	63.1/36.9	NR	NR
Bonini-Filho et al. (2009)[10] Brazil	Prospective, observational	DME	6	Bevacizumab	10/10	59.8 (4)	30/70	12 (3.2)	NR
Brito et al. (2021)[11] Portugal	Prospective, observational	CI-DME	6 (assumed)	Bevacizumab	67/67	64.09 (13.88)	44.8/55.2	18.22 (9.71)	NR
Cuervo-Lozano et al. (2018)[20] Mexico	RCT	Non-CI-DME	6 (assumed)	Bevacizumab	6/10	56.3 (7.78)	33.3/66.7	NR	NR
				Subthreshold macular photocoagulation	8/12	61.58 (8.51)	37.5/62.5	NR	NR
				Bevacizumab plus subthreshold macular photocoagulation	6/10	59.6 (5.5)	50/50	NR	NR
Curry et al. (2020)[21] Australia	Prospective, observational	DME	6	Aflibercept	26/26	67.4 (10.6)	61.5/38.5	NR	NR
Dehghan et al. (2008)[28‡] UK	RCT	Refractory DME	3.5, 6	Triamcinolone acetonide, placebo	61/88	mean (range) 61.6 (44, 79)	55.7/44.3	Mean (range) 14.7 (2, 40)	NR
Dinah et al. (2021)[29] UK	Retrospective, observational	Naïve DME	6 (assumed)	Aflibercept	221/270	62.8 (12.6)	66.5/33.5	NR	NR
Ehlers et al. (2019)[32] USA	Prospective, comparative	DME	1	Aflibercept every 4 weeks	52/52	62.3 (12)	51.9/48.1	NR	NR
				Aflibercept every 8 weeks	54/54	64.6 (8.7)	42.6/57.4	NR	NR
Elman et al. (2012)[33] USA	RCT	DME	6	Ranibizumab + prompt laser	144/144	NR	NR/NR	NR	NR
				Ranibizumab + deferred laser	147/147	NR	NR/NR	NR	NR
Entezari et al. (2005)[34‡] Iran	RCT	Clinically significant DME	3.5, 6	Triamcinolone acetonide, placebo	38/64	Median (range) 60.1 (26, 81)	26.3/73.7	NR	NR
Escobar-Barranco et al. (2015)[35] Spain	Prospective, comparative	Refractory diffuse DME	6 (assumed)	Dexamethasone (refractory patients)	40/40	Median (range) 65 (53, 85)	52.5/47.5	Mean (range) 21 (14, 30)	NR
				Dexamethasone (naïve patients)	36/36	Median (range) 64 (51, 82)	52.8/47.2	Mean (range) 18 (11, 26)	NR
Faghihi et al. (2017)[36‡] Iran	Prospective, comparative	DME	6 (assumed)	Diclofenac, bevacizumab	26/52	60.1 (6.7)	34.6/65.4	NR	NR
Fazel et al. (2016)[37] Iran	RCT	DME	6 (assumed)	SDM photocoagulation	34/34	52.2 (6.7)	58.8/41.2	18.1 (4.7)	NR
				Conventional LP	34/34	53.7 (7.1)	55.9/44.1	19.8 (4.4)	NR

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Table 3 (*continued*)

Study name, country	Study design	Population	MV: zone measured by OCT (mm)	Interventions	Sample size (patients/eyes)	Baseline characteristics			
						Average age (years)†	% of male/female	Average duration of diabetes (years)†	Average duration of DME (years)†
Fazel et al. (2020a)[38‡] Iran	RCT	DME	6 (assumed)	Bevacizumab plus 2 % topical dorzolamide or placebo	16/32	62 (13)	37.5/62.5	NR	NR
Fazel et al. (2020b)[39‡] Iran	RCT	DME	1 (assumed)	Bevacizumab alone or plus methotrexate	18/36	62.38 (6.2)	NR/NR	NR	NR
Ferrone et al. (2016)[40] USA	RCT	Clinically significant DME	6 (assumed)	Ranibizumab 0.5 mg	23/23	63 (NR)	56.5/43.5	NR	NR
				Ranibizumab 1.0 mg	23/23	61 (NR)	43.5/56.5	NR	NR
Figueiredo et al. (2020)[41] USA	Prospective, observational	DME	6 (assumed)	Aflibercept	14/14	NR	NR/NR	NR	NR
Figueras-Roca et al. (2019)[42] Spain	Prospective, observational	DME	6	Dexamethasone (intravitreal implant)	70/70	71 (9.1)	52.9/47.1	13.5 (8.4)	NR
Gedar Totuk et al. (2020)[43] Turkey	Retrospective, comparative	DME	6	Ranibizumab with vitrectomy	11/11	55 (10)	54.5/45.5	NR	NR
				Ranibizumab without vitrectomy	17/17	62 (9)	47.1/52.9	NR	NR
Ghanbari et al. (2017)[44] Iran	RCT	Naïve DME	6 (assumed)	Bevacizumab plus diclofenac	38/38	60.45 (8.056)	42.1/57.9	NR	NR
				Bevacizumab alone	42/42	62.98 (8.182)	57.1/42.9	NR	NR
Gunay et al. (2021)[47] Turkey	Retrospective, observational	Diffuse DME	5	PPV	37/40	62.4 (8.5)	43.2/56.8	NR	NR
Hernandez-Da Mota et al. (2019)[48] Mexico	Prospective, observational	DME	6	Ziv-aflibercept	20/34	62.2 (6.9)	60/40	NR	NR
Hillier et al. (2018)[49] Canada	Prospective, observational	CI-DME	6	Ranibizumab	48/48	61.9 (7.1)	75/25	NR	NR
Jung et al. (2013)[56] USA	Retrospective, observational	DME	6 (assumed)	Focal laser (NAVILAS)	7/7	Mean (range) 60.8 (48, 85)	57.1/42.9	NR	NR
Kato et al. (2018)[58] Japan	Retrospective, observational	DME	6 (assumed)	LP	21/25	68.3 (9.2)	66.7/33.3	NR	NR
Kawashima et al. (2012)[59] Japan	Retrospective, observational	DME	1	Triamcinolone acetonide sub-tenon injection	43/63	57.4 (14.4)	55.8/44.2	NR	NR
Kern et al. (2020)[60] UK	Retrospective, observational	DME	6	Aflibercept	117/139	62.2 (11.8)	67.5/32.5	NR	NR
Kessler et al. (2021)[61] Germany	Retrospective, observational	Naïve DME	6	Anti-VEGF (ranibizumab, aflibercept or off-label bevacizumab)	37/37	57.54 (8.04)	70.3/29.7	NR	NR
Kim et al. (2009)[62] South Korea	Retrospective, observational	DME	6	Focal LP	45/70	58.76 (13.01)	62.2/37.8	12.04 (8.6)	NR
Kocak Altintas et al. (2020)[63§] Turkey	Retrospective, comparative	DME with/without epiretinal membranes	6	Aflibercept: patients with epiretinal membrane	29/29	63.97 (7.5)	44.8/55.2	NR	NR
				Aflibercept: patients without epiretinal membrane	43/43	61.21 (9.2)	44.2/55.8	NR	NR
Korobelnik et al. (2023)[64] France	Prospective, observational	DME	6 (assumed)	Aflibercept	26/26	64.6 (11.2)	46.2/53.8	NR	NR
Koytak et al. (2013)[66§] Turkey	Retrospective, observational	DME	6 (assumed)	Bevacizumab: diffuse retinal thickening	42/42	57.21 (8.22)	35.7/64.3	NR	NR
				Bevacizumab: cystoid macular edema	31/31	59.29 (11.73)	35.5/64.5	NR	NR
				Bevacizumab: serious retinal detachment	19/19	58.95 (10.99)	42.1/57.9	NR	NR
Kumar et al. (2007)[67] India	RCT	Diffuse DME	6 (assumed)	PPV with dye-enhanced ILM peeling	12/12	57.25 (8.986)	91.7/8.3	NR	NR
				Grid LP	12/12	57.33 (6.84)	83.3/16.7	NR	NR

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Table 3 (*continued*)

Study name, country	Study design	Population	MV: zone measured by OCT (mm)	Interventions	Sample size (patients/eyes)	Baseline characteristics			
						Average age (years)†	% of male/female	Average duration of diabetes (years)†	Average duration of DME (years)†
Lim et al. (2019)[70] UK	Retrospective, observational	Non-CI-DME	3	Subthreshold macular laser treatment	148/185	64.4 (11.9)	NR/NR	NR	NR
Lima Gomez et al. (2015)[71] Mexico	Retrospective, comparative	Diabetes with CSME	6 (assumed)	Focal photocoagulation	89/120	59.5 (8.9)	NR/NR	16.6 (7)	NR
Luis et al. (2021)[72] Portugal	Retrospective, observational	Refractory DME	6 (assumed)	Intravitreal corticosteroid (triamcinolone, dexamethasone or fluocinolone acetonide implant)	101/101	70.69 (8.08)	39.6/60.4	19.87 (8.88)	NR
Lukic et al. (2021a)[74] UK	Retrospective, observational	Fovea-involving DME	6 (assumed)	Aflibercept	67/90	NR	NR/NR	NR	NR
Lukic et al. (2021b)[73] UK	Retrospective, observational	CI-DME	6 (assumed)	Aflibercept	57/64	Mean (range) 54.45 (25, 80)	66.7/33.3	NR	NR
Lukic, et al. (2020)[75] UK	Retrospective, observational	CI-DME	6 (assumed)	Aflibercept	89/99	NR (NR)	NR/NR	NR (NR)	NR
Maia et al. (2009)[77†] Brazil, USA	RCT	Proliferative diabetic retinopathy with CSME	6	LP only or with triamcinolone acetonide	22/44	61.9 (5.3)	45.5/54.5	8.9 (5.4)	NR
Maleita et al. (2021)[78] Portugal	Retrospective, observational	DME	6 (assumed)	Fluocinolone acetonide (intravitreal implant)	11/13	Median (SD) 73 (7.2)	NR/NR	NR	NR
Meyer-Bothling et al. (2021)[79] UK	Prospective, observational	Mild DME	6	Sleep Mask (Noctura 400)	26/26	Median (range) 62.5 (51.5, 73.0)	80.8/19.2	NR	NR
Mian et al. (2015)[80] Bahrain	Retrospective, observational	DME	6	Bevacizumab	71/142	59.5 (NR)	64.8/35.2	12.7 (NR)	NR
Nguyen et al. (2006)[84] USA	Prospective, observational	DME	6	Ranibizumab	10/10	Median (range) 60 (NR)	50/50	NR	NR
Nozaki et al. (2019)[85] Japan	Prospective, observational	DME	6 (assumed)	Focal LP	6/8	66.8 (4.8)	50/50	NR	NR
Ockrim et al. (2008)[87] UK	RCT	Clinically significant DME	6	Triamcinolone acetonide	43/43	62.3 (7.5)	65.1/34.9	NR	NR
				LP	45/45	64.8 (10.1)	71.1/28.9	NR	NR
Ohkoshi et al. (2010)[88] Japan	Prospective, observational	Clinically significant DME	6 (assumed)	SDM LP	36/43	59.6 (7.69)	58.3/41.7	14.3 (8.56)	NR
Patel et al. (2006a)[91] UK	Prospective, observational	Persistent, diffuse, clinically significant DME	6	PPV	12/12	Mean (range) 63 (46, 72)	58.3/41.7	NR	NR
Patel et al. (2006b)[92] UK	Prospective, comparative	Persistent diffuse CSME	6	PPV with ILM peeling	10/10	Mean (range) 73 (31, 72)	80/20	NR	NR
				PPV without ILM peeling	8/8	Mean (range) 57 (46, 72)	50/50	NR	NR
Patrao et al. (2016)[93] UK	Retrospective, observational	CI-DME	6 (assumed)	Ranibizumab	164/200	65.11 (10.83)	63.4/36.6	NR	NR
Plaza-Ramos et al. (2019)[94] USA	Retrospective, observational	DME	6 (assumed)	Ranibizumab	NR/122	69.3 (10.34)	NR/NR	15.89 (9.29)	NR
				Aflibercept	NR/91	68.71 (10.94)	NR/NR	17.86 (8.41)	NR
Robaszkiewicz et al. (2012)[96] Poland	Prospective, observational	Diffuse DME	1, 6	Phacovitrectomy with ILM peeling, retinal endophotocoagulation and bevacizumab	26/29	59 (13.8)	42.3/57.7	NR	NR

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Table 3 (*continued*)

Study name, country	Study design	Population	MV: zone measured by OCT (mm)	Interventions	Sample size (patients/eyes)	Baseline characteristics			
						Average age (years)†	% of male/female	Average duration of diabetes (years)†	Average duration of DME (years)†
Shalchi et al. (2018)[98] UK	Retrospective, observational	DME	6 (assumed)	Ranibizumab	312/312	NR	NR/NR	NR	NR
Sheth et al. (2011)[101] Australia	Prospective, comparative	CI-DME	6 (assumed)	Triamcinolone acetonide	12/12	65.8 (11.6)	58.3/41.7	10.2 (2)	NR
				Bevacizumab plus dexamethasone	12/12	63.5 (11.1)	66.7/33.3	10.6 (2.2)	NR
Soliman et al. (2008a)[104] Denmark, Egypt	Prospective, observational	DME	6	Bevacizumab	10/10	Mean (range) 59.2 (28, 77)	70/30	Mean (range) 23.7 (15, 38)	NR
Soliman et al. (2008b)[103] Denmark, Egypt	Prospective, observational	DME	6	No treatment	26/28	66.4 (8.8)	NR/NR	15.04 (4.26)	NR
Srinivas et al. (2020)[105] USA	Prospective, observational	CI-DME	6	Ranibizumab injections	24/24	65 (8.55)	41.7/58.3	16.71 (8.52)	NR
Tachi et al. (2017)[109] Japan	Retrospective, observational	Recurrent DME	6 (assumed)	PPV	20/20	64.1 (8.2)	70/30	NR	NR
Tang et al. (2022)[110] China	Retrospective, comparative	DME	5 (assumed)	Triamcinolone acetonide	174/174	62.75 (4.65)	48.9/51.1	NR	NR
				Conbercept	176/176	63.26 (4.87)	53.4/46.6	NR	NR
Tran et al. (2022)[112] France	Prospective, observational	Persistent DME	6 (assumed)	Aflibercept	44/46	Median (IQR) 67.5 (59, 73.5)	59.1/40.9	Median (IQR) 17 (11.8, 26.2)	NR
Turski et al. (2022)[113] USA	Retrospective, observational	DME	6 (assumed)	Bevacizumab	46/52	64.22 (8.12)	58.7/41.3	18.47 (9.92)	NR
Vaz-Pereira et al. (2020)[114] Portugal	Retrospective, observational	DME (persistent or recurrent)	6 (assumed)	Fluocinolone acetonide implant	36/44	69.2 (7.4)	NR/NR	NR	3.3 (1.9)
Vujosevic et al. (2016)[116‡] Italy	Prospective, comparative	CI-DME	6 (assumed)	Anti-VEGF injections, no treatment	20/40	63 (8.2)	80/20	11.3 (10)	NR
Wu et al. (2012)[119] Taiwan	Retrospective, observational	DME	3	Bevacizumab	24/31	63.68 (7.75)	NR/NR	NR	NR
Yoon et al. (2014)[121§] USA	Retrospective, comparative	DME	3	Anti-VEGF (0.3 mg ranibizumab or 1.25 mg bevacizumab): DME only	4/5	56 (8)	75/25	NR	NR
				Anti-VEGF (0.3 mg ranibizumab or 1.25 mg bevacizumab): DME plus vitreomacular interface abnormalities	7/10	67 (5)	71.4/28.6	NR	NR
Yoon et al. (2022)[122] South Korea	Retrospective, comparative	DME	6	Ranibizumab with additional treatment (anti-VEGF or steroid injection)	15/15	66.13 (7.9)	46.7/53.3	21.36 (6.25)	1.91 (1.33)
				Ranibizumab without additional treatment	17/17	68.18 (12.21)	29.4/70.6	21.14 (6.93)	1.03 (0.98)

Abbreviations: anti-VEGF, anti-vascular endothelial growth factor therapy; CI-DME, centre-involving DME; CSME, clinically significant macular edema; DME, diabetic macular edema; ILM, internal limiting membrane; IQR, interquartile range; LP, laser photocoagulation; MV, macular volume; NR, not reported; OCT, optical coherence tomography; PPV, pars plana vitrectomy; RCT, randomized controlled trial; SD, standard deviation; SDM, subthreshold diode micropulse; UK, United Kingdom; USA, United States of America; VEGF, vascular endothelial growth factor VA, visual acuity.

* Of the 70 studies that investigated and reported MV, 63 studies were considered in the statistical analysis and 7 were discounted at this stage due to reporting median values (n = 3; Maleita et al.,[78] Patel et al.,[91,92]), or using a unit of MV measurement other than mm^3 (n = 4; Kessler et al.,[61] Kocak Altintas et al.,[63] Meyer-Bothling et al.,[79] and Tang et al.[110]).

† Values are provided as mean (SD) unless otherwise stated.

‡ All baseline characteristics not available per treatment arm.

§ Baseline characteristics available per subpopulation included in the study rather than full population.

limitations, including a high rate of disease recurrence and frequent injections required to maximize outcomes.[118]

Consequently, there is a need to optimize DME treatment pathways and efficiently bring new therapies to patients. This may be achieved by improving the efficiency of clinical trials, supporting real-world comparative effectiveness research, and predicting real-world outcomes. One approach to achieving these aims is to identify biomarkers that can be used as SEs for DME markers.

Table 4
Risk of bias in the included studies.

Study ID	Question number													Overall bias
	1	2	3	4	5	6	7	8	9	10	11	12	13	
RCTs														
Baker et al. (2019)[5]	ü	ü	ü	û	û	û	ü	ü	ü	ü	ü	ü	ü	Unclear
Cuervo-Lozano et al. (2018)[20]	ü	~	ü	ü	û	ü	ü	ü	ü	ü	ü	ü	ü	Low
Dehghan et al. (2008)[28]	~	~	~	~	~	ü	~	ü	ü	ü	ü	ü	~	Unclear
Elman et al. (2012)[33]	ü	ü	ü	~	~	ü	~	ü	ü	ü	ü	ü	ü	Unclear
Entezari et al. (2005)[34]	~	~	~	ü	û	~	û	ü	ü	û	ü	~	û	High
Fazel et al. (2016)[37]	~	~	~	ü	û	ü	~	ü	ü	~	ü	ü	~	Unclear
Fazel et al. (2020a)[38]	~	~	~	ü	ü	ü	~	ü	ü	ü	ü	ü	~	Unclear

Study ID	Question number													Overall bias
	1	2	3	4	5	6	7	8	9	10	11	12	13	
Fazel et al. (2020b)[39]	~	~	~	~	~	ü	~	ü	ü	~	ü	ü	~	Unclear
Ferrone et al. (2016)[40]	~	~	ü	ü	û	~	~	ü	ü	û	ü	ü	~	High
Ghanbari et al. (2017)[44]	û	~	ü	ü	û	ü	ü	ü	~	ü	ü	ü	~	Unclear
Kumar et al. (2007)[67]	~	ü	~	~	~	~	~	ü	ü	ü	ü	ü	~	Unclear
Ockrim et al. (2008)[87]	ü	ü	ü	ü	~	~	~	ü	ü	ü	ü	ü	~	Unclear
Maia et al. (2009)[77]	~	~	ü	~	û	ü	~	ü	ü	ü	ü	ü	ü	Unclear

Study ID	Question number											Overall bias
	1	2	3	4	5	6	7	8	9	10	11	
Ehlers et al. (2019)[32]	ü	ü	ü	û	~	NA	ü	ü	~	NA	ü	Unclear
Escobar-Barranco et al. (2015)[35]	û	~	~	~	~	NA	~	ü	û	û	ü	High
Faghihi et al. (2017)[36]	ü	ü	~	û	û	NA	~	ü	ü	NA	~	Unclear
Gedar Totuk et al. (2020)[43]	ü	ü	NA	~	~	NA	ü	ü	ü	NA	ü	Low
Kocak Altintas et al. (2020)[63]	ü	ü	ü	~	~	NA	ü	ü	ü	NA	ü	Unclear
Lima Gomez et al. (2015)[71]	ü	ü	ü	~	~	NA	ü	û	ü	NA	ü	Unclear
Lukic et al. (2021a)[74]	ü	ü	~	~	~	NA	~	ü	ü	NA	~	Unclear
Patel et al. (2006b)[92]	ü	~	NA	û	~	NA	~	ü	ü	NA	~	Unclear
Plaza-Ramos et al. (2019)[94]	~	ü	ü	~	~	NA	~	ü	ü	NA	ü	Unclear
Sheth et al. (2011)[101]	û	ü	ü	û	û	NA	ü	~	ü	NA	ü	Unclear
Srinivas et al. (2020)[105]	ü	ü	ü	~	~	NA	ü	ü	ü	NA	ü	Low

Study ID	Question number											Overall bias
	1	2	3	4	5	6	7	8	9	10	11	
Tang et al. (2022)[110]	ü	ü	ü	~	~	NA	~	ü	ü	NA	ü	Unclear
Vujosevic et al. (2016)[116]	ü	ü	~	û	û	NA	~	ü	ü	NA	ü	Unclear
Yoon et al. (2014)[121]	ü	ü	~	û	û	NA	~	ü	ü	NA	~	Unclear
Yoon et al. (2022)[122]	ü	ü	ü	û	û	NA	~	~	û	û	~	High

Study ID	Question number										Overall bias
	1	2	3	4	5	6	7	8	9	10	
Case studies											
Baget-Bernaldiz et al. (2017)[3]	ü	~	~	~	~	ü	ü	ü	ü	ü	Low
Bailey et al. (2021)[4]	ü	~	ü	~	~	ü	~	û	ü	~	High
Best et al. (2019)[8]	~	~	~	û	~	û	û	û	û	~	High
Bezzina et al. (2019)[9]	ü	ü	~	~	ü	ü	ü	ü	ü	ü	Low

Study ID	Question number										Overall bias
	1	2	3	4	5	6	7	8	9	10	
Bonini-Filho et al. (2009)[10]	ü	ü	~	~	~	ü	ü	ü	ü	ü	Low
Brito et al. (2021)[11]	ü	~	~	~	~	ü	ü	~	ü	~	Unclear
Curry et al. (2020)[21]	ü	~	ü	~	~	û	û	ü	ü	ü	Unclear
Dinah et al. (2021)[29]	ü	ü	ü	~	û	ü	ü	~	ü	ü	Unclear
Figueiredo et al. (2020)[41]	ü	~	ü	~	~	~	ü	~	ü	ü	Unclear
Figueras-Roca et al. (2019)[42]	ü	~	~	~	~	ü	ü	ü	û	ü	Unclear
Gunay et al. (2021)[47]	ü	ü	ü	~	~	û	û	ü	ü	ü	Unclear
Hernandez-Da Mota et al. (2019)[48]	û	ü	ü	~	~	ü	ü	ü	ü	~	Unclear
Hillier et al. (2018)[49]	ü	~	~	~	~	ü	ü	û	ü	ü	Unclear
Jung et al. (2013)[56]	ü	ü	~	~	~	~	ü	ü	ü	ü	Unclear
Kato et al. (2018)[58]	û	ü	ü	~	~	ü	ü	ü	ü	ü	Unclear

Study ID	Question number										Overall bias
	1	2	3	4	5	6	7	8	9	10	
Kawashima et al. (2012)[59]	ü	ü	ü	~	~	û	ü	û	ü	ü	Unclear
Kern et al. (2020)[60]	~	ü	ü	û	û	ü	û	û	ü	ü	Unclear
Kessler et al. (2021)[61]	ü	ü	ü	~	~	~	û	ü	~	ü	Unclear
Kim et al. (2009)[62]	ü	ü	ü	~	~	ü	ü	ü	ü	ü	Low
Korobelnik et al. (2023)[64]	ü	ü	ü	~	û	ü	~	ü	ü	ü	Unclear
Koytak et al. (2013)[66]	ü	ü	ü	~	~	ü	ü	ü	ü	ü	Low
Lim et al. (2019)[70]	~	~	~	~	û	ü	~	û	û	~	Unclear
Luis et al. (2021)[72]	ü	~	ü	û	û	ü	ü	ü	û	~	High
Lukic et al. (2021b)[73]	ü	~	~	~	ü	~	û	ü	û	~	Unclear
Lukic, et al. (2020)[75]	ü	ü	~	û	~	û	û	ü	ü	ü	Unclear
Maleita et al. (2021)[78]	~	~	~	ü	ü	û	û	û	ü	~	High

(continued on next page)

Table 4 (*continued*)

Study ID	Question number										Overall bias
	1	2	3	4	5	6	7	8	9	10	
Meyer-Bothling et al. (2021)[79]	ü	~	ü	~	û	û	ü	û	û	~	High
Mian et al. (2015)[80]	~	ü	ü	~	~	ü	ü	ü	ü	ü	Low
Nguyen et al. (2006)[84]	ü	ü	ü	~	~	û	û	û	ü	~	High
Nozaki et al. (2019)[85]	ü	~	ü	~	ü	ü	ü	ü	ü	ü	Low
Ohkoshi et al. (2010)[88]	ü	ü	ü	ü	ü	~	~	ü	~	~	Unclear
Patel et al. (2006a)[91]	ü	ü	ü	û	û	û	û	û	ü	ü	High
Patrao et al. (2016)[93]	ü	~	~	ü	ü	ü	ü	ü	ü	ü	Low
Robaszkiewicz et al. (2012)[96]	ü	ü	ü	~	~	ü	ü	ü	ü	ü	Low
Shalchi et al. (2018)[98]	~	~	~	~	~	û	û	ü	ü	ü	High
Soliman et al. (2008a)[104]	ü	ü	ü	ü	ü	ü	û	ü	ü	~	Unclear
Soliman et al. (2008b)[103]	ü	ü	ü	~	~	û	û	û	ü	~	Unclear

Study ID	Question number										Overall bias
	1	2	3	4	5	6	7	8	9	10	
Tachi et al. (2017)[109]	ü	~	~	~	~	û	û	ü	ü	ü	Unclear
Tran et al. (2022)[112]	ü	ü	ü	~	~	ü	ü	û	ü	ü	Unclear
Turski et al. (2022)[113]	ü	ü	ü	û	û	ü	ü	NA	ü	ü	Unclear
Vaz-Pereira et al. (2020)[114]	ü	~	~	û	ü	ü	ü	ü	û	ü	Unclear
Wu et al. (2012)[119]	ü	~	~	~	~	ü	ü	ü	ü	~	Unclear

Abbreviations: ID, identification; RCT, randomized controlled trial.
Questions:
1. Was true randomization used for assignment of participants to treatment groups? 2. Was allocation to treatment groups concealed? 3. Were treatment groups similar at the baseline? 4. Were participants blind to treatment assignment? 5. Were those delivering treatment blind to treatment assignment? 6. Were treatment groups treated identically other than the intervention of interest? 7. Were outcomes assessors blind to treatment assignment? 8. Were outcomes measured in the same way for treatment groups? 9. Were outcomes measured in a reliable way? 10. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed? 11. Were participants analyzed in the groups to which they were randomized? 12. Was appropriate statistical analysis used? 13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?
Abbreviations: NA, not applicable.
Questions:
1. Were the 2 groups similar and recruited from the same population? 2. Were the exposures measured similarly to assign people to both exposed and unexposed groups? 3. Was the exposure measured in a valid and reliable way? 4. Were confounding factors identified? 5. Were strategies to deal with confounding factors stated? 6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)? 7. Were the outcomes measured in a valid and reliable way? 8. Was the follow-up time reported and sufficient to be long enough for outcomes to occur? 9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored? 10. Were strategies to address incomplete follow up utilized? 11. Was appropriate statistical analysis used?
Abbreviations: ID, identification; NA, not applicable.
Questions:
1. Were there clear criteria for inclusion in the case series? 2. Was the condition measured in a standard, reliable way for all participants included in the case series? 3. Were valid methods used for identification of the condition for all participants included in the case series? 4. Did the case series have consecutive inclusion of participants? 5. Did the case series have complete inclusion of participants? 6. Was there clear reporting of the demographics of the participants in the study? 7. Was there clear reporting of clinical information of the participants? 8. Were the outcomes or follow-up results of cases clearly reported? 9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information? 10. Was statistical analysis appropriate?

4.1. Key findings of the analysis

This analysis was supported by clinical experts who provided their expertise in DME by identifying 13 OCT biomarkers that could be explored as potential SEs for VA. A biomarker prioritization exercise identified 4 key OCT biomarkers (HRF, IC, MV, and SRF) that could be further explored in an SLR. Of the 128 unique studies identified by the SLR, 105 reported data for change from baseline for VA and at least one OCT biomarker of interest. MV was investigated most often and was chosen as the lead biomarker to be explored as a potential SE for VA. HRF, IC, and SRF were deemed unfit for analysis due to an insufficient number of studies and/or a lack of a standardized method of reporting across available studies.

Data from 70 studies reporting MV were extracted, of which 55 studies were considered in the multi-correlation statistical analyses. In the base case, at the arm-level (endpoint correlation), a moderate and

Table 5
Base case and scenario analyses (logMAR and ETDRS) summary of articles.

Study name, country	Interventions	Follow-up period	MV				VA			
			Biomarker (description of zone)	Average baseline value (mm^3)*	Average follow-up value (mm^3)*	Change from baseline†	Type, unit of measurement	Average baseline value*	Average follow-up value*†	Change from baseline†
Baget-Bernaldiz et al. (2017)[3] Spain	Ranibizumab	12 months	Total MV (NR)	9.93 (1.56)	9.12 (14.56)	− 0.81	BCVA (ETDRS)	46.7 (16.47)	59.1 (17.2)	− 0.25
Bailey et al. (2021)[4] UK	Fluocinolone acetonide implant	48 months	MV (NR)	9.9 (NR)	8.8 (NR)	− 1.10	BRVA (ETDRS)	52.6 (NR)	57.1 (NR)	− 0.09
Baker et al. (2019)[5] Canada, USA	Aflibercept	2 years	MV (NR)	7.9 (1.1)	NR	− 0.50	VA (ETDRS)	85.2 (3.5)	86 (7.4)	− 0.02
	LP	2 years		8 (1.2)	NR	− 0.60	VA (ETDRS)	85.2 (3.8)	85.3 (7.4)	0.00
	Observation	2 years		8 (1.1)	NR	− 0.60	VA (ETDRS)	85.2 (3.8)	84.2 (10.1)	0.02
Best et al. (2019)[8] UK	Focal macular LP	3 years	MV (NR)	8.42 (NR)	7.85 (NR)	− 0.57	VA (ETDRS)	74.84 (NR)	73.4 (NR)	0.03
Bezzina et al. (2019)[9] Malta	Bevacizumab	6 weeks	MV (taking 6 radial cuts [6-mm diameter] of the macular field)	9.65 (2.03)	8.99 (1.97)	− 0.66	BCVA (logMAR)	0.6 (0.28)	0.53 (0.24)	− 0.07
Bonini-Filho et al. (2009)[10] Brazil	Bevacizumab	54 weeks	Total MV (6 high-density linear 6-mm OCT scans were performed)	10.883 (3.297)	8.751 (1.618)	− 2.13	BCVA (logMAR)	0.786 (0.383)	0.558 (0.38)	− 0.23
Brito et al. (2021)[11] Portugal	Bevacizumab	12 months	MV (NR)	10.9 (1.89)	9.51 (1.32)	− 1.39	VA (logMAR)	0.58 (0.24)	0.4 (0.2)	− 0.18
Cuervo-Lozano et al. (2018)[20] Mexico	Bevacizumab	3 months	Total MV (NR)	7.79 (0.57)	7.5 (0.56)	− 0.30	BCVA (logMAR)	0.28 (0.27)	0.22 (0.2)	− 0.06
	Subthreshold macular photocoagulation	3 months		7.77 (0.76)	7.7 (0.81)	− 0.07	BCVA (logMAR)	0.2 (0.17)	0.16 (0.14)	− 0.04
	Bevacizumab plus subthreshold macular photocoagulation	3 months		7.9 (0.57)	7.65 (0.73)	− 0.24	BCVA (logMAR)	0.19 (0.16)	0.12 (0.14)	− 0.07
Curry et al. (2020)[21] Australia	Aflibercept	2 years	Central MV (within 6-mm of the fovea)	10 (1.6)	8.5 (0.8)	− 1.50	BCVA (ETDRS)	69.7 (6.2)	73.8 (10.7)	− 0.08
Dehghan et al. (2008)[28] UK	Triamcinolone acetonide	4 months	MV (MV of the 6-mm circle)	10.93 (4.3)	10.05 (3.9)	− 0.88	BCVA (logMAR)	0.97 (0.35)	0.9 (0.28)	− 0.07
	Placebo	4 months		10.66 (4)	10.49 (4.2)	− 0.17	BCVA (logMAR)	0.89 (0.31)	0.94 (0.33)	0.05
Dinah et al. (2021)[29] UK	Aflibercept	12 months	MV (NR)	10.3 (1.9)	NR	− 1.05	BCVA (ETDRS)	66.4 (14.6)	70.4 (NR)	− 0.08
Elman et al. (2012)[33] USA	Ranibizumab + prompt laser	3 years	MV (reported as OCT retinal volume on 6-mm scans)	NR	7.2 (1.4)	− 1.60	VA (ETDRS)	NR	NR	ETDRS 7
	Ranibizumab + deferred laser	3 years		NR	7 (0.9)	− 1.80	VA (ETDRS)	NR	NR	ETDRS 10
Entezari et al. (2005)[34§] Iran	Triamcinolone acetonide	4 months	MV (MV at 6-mm)	10.68 (NR)	10.57 (NR)	− 0.11	BCVA (logMAR)	0.75 (0.38)	0.71 (0.42)	− 0.04
	Placebo	4 months		10.92 (NR)	14.45 (NR)	3.53	BCVA (logMAR)	0.93 (0.39)	0.88 (0.48)	− 0.05
Escobar-Barranco et al. (2015)[35] Spain	Dexamethasone (refractory patients)	6 months	Total MV (NR)	11.13 (1.86)	8.7 (1.7)	− 2.43	VA (ETDRS)	51.25 (15.47)	59 (14.7)	− 0.16
	Dexamethasone (naïve patients)	6 months		11.17 (1.75)	9.5 (1.3)	− 1.67	VA (ETDRS)	59.58 (9.09)	71.1 (9.6)	− 0.23
Faghihi et al. (2017)[36] Iran	Diclofenac	6 months	MV (NR)	10.91 (1.41)	10.38 (1.47)	− 0.44	BCVA (logMAR)	0.52 (10)	0.29 (0.07)	− 0.23
	Bevacizumab	6 months		10.8 (1.23)	10.17 (1.04)	− 0.53	BCVA (logMAR)	0.5 (0.13)	0.25 (0.1)	− 0.25
Fazel et al. (2016)[37] Iran	SDM photocoagulation	4 months	Central MV (NR)	8.62 (1.24)	8.42 (1.23)	− 0.20	BCVA (logMAR)	0.59 (0.3)	0.52 (0.29)	− 0.07
	Conventional LP	4 months		8.89 (1.23)	8.84 (1.25)	− 0.05	BCVA (logMAR)	0.58 (0.32)	0.6 (0.33)	0.02
Fazel et al. (2020a)[38] Iran	Bevacizumab plus 2 % topical dorzolamide	2 months	Central MV (NR)	11 (1.02)	10.71 (0.99)	− 0.29	BCVA (logMAR)	0.213 (0.0806)	0.23 (0.0946)	0.02
	Bevacizumab plus placebo	2 months		11.22 (1.27)	10.95 (1.24)	− 0.27	BCVA (logMAR)	0.181 (0.0911)	0.21 (0.0957)	0.03
Ferrone et al. (2016)[40] USA	Ranibizumab 0.5 mg	12 months	MV (NR)	9.75 (NR)	NR	− 0.80	BCVA (ETDRS)	59 (NR)	62.8 (NR)	− 0.08
	Ranibizumab 1.0 mg	12 months		9.88 (NR)	NR	− 2.10	BCVA (ETDRS)	59 (NR)	66.9 (NR)	− 0.16

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Table 5 (*continued*)

Study name, country	Interventions	Follow-up period	MV				VA			
			Biomarker (description of zone)	Average baseline value (mm^3)*	Average follow-up value (mm^3)*	Change from baseline†	Type, unit of measurement	Average baseline value*	Average follow-up value*†	Change from baseline†
Figueiredo et al. (2020)[41] USA	Aflibercept	12 months	MV (NR)	NR	9.7 (0.5)	− 1.1	BCVA (ETDRS)	NR	NR	ETDRS 5
Figueras-Roca et al. (2019)[42] Spain	Dexamethasone (intravitreal implant)	2 months	MV (OCT performed using a standard macular cube 518 × 128 μm protocol)	12.13 (2.1)	10.76 (1.41)	− 1.37	BCVA (logMAR)	0.61 (0.41)	0.55 (0.42)	− 0.07
Gedar Totuk et al. (2020)[43] Turkey	Ranibizumab with vitrectomy	24 months	Total MV (calculated by summation of all the volumes of the 9 ETDRS subfields)	9.35 (1.52)	8.25 (1.47)	− 1.10	BCVA (logMAR)	0.7 (0.3)	0.44 (0.24)	− 0.26
	Ranibizumab without vitrectomy	24 months		9.04 (1.28)	8.01 (0.79)	− 1.03	BCVA (logMAR)	0.51 (0.26)	0.4 (0.22)	− 0.11
Ghanbari et al. (2017)[44] Iran	Bevacizumab plus diclofenac	4 weeks	MV (NR)	11.58 (2.19)	10.48 (1.53)	− 1.10	BCVA (logMAR)	0.968 (0.458)	0.74 (0.37)	− 0.23
	Bevacizumab alone	4 weeks		12.59 (2.75)	11.75 (2.05)	− 0.84	BCVA (logMAR)	0.812 (0.389)	0.723 (0.41)	− 0.09
Hernandez-Da Mota et al. (2019)[48] Mexico	Ziv-aflibercept	2 months	MV (the scanning protocol according to a macular cube 512 × 128 μm program)	13 (3)	10.8 (1.8)	− 2.20	BCVA (ETDRS)	31.5 (16)	41.2 (15.6)	− 0.19
Hillier et al. (2018)[49] Canada	Ranibizumab	3 months	MV (a 512 × 128 μm macular cube protocol was used; 6-mm diameter with a total of 9 subfields)	13 (2.4)	NR	− 1.57	BCVA (logMAR)	0.6 (0.3)	NR	− 0.20
Jung et al. (2013)[56] USA	Focal laser (NAVILAS)	12 months	Total MV (NR)	7.84 (0.874)	7.44 (0.757)	− 0.40	BCVA (logMAR)	0.695 (0.574)	0.477 (0.57)	− 0.22
Kato et al. (2018)[58] Japan	LP	12.8 months	MV (NR)	12.3 (1.9)	11.3 (1.3)	− 1.00	BCVA (logMAR)	0.21 (0.32)	0.23 (0.33)	0.02
Kern et al. (2020)[60] UK	Aflibercept	2 years	Total MV (Total retinal volume within the 9 macular ETDRS grids)	10.12 (2.05)	9.01 (1.29)	− 1.11	BCVA (ETDRS)	60.1 (14.5)	69.3 (12.1)	− 0.18
Kim et al. (2009)[62] South Korea	Focal LP	6 months	Total MV (OCT examinations of 6 radial 6-mm-long scans)	8.88 (2.01)	8.54 (2.21)	− 0.34	VA (logMAR)	0.46 (0.39)	0.47 (0.42)	0.01
Korobelnik et al. (2023)[64] France	Aflibercept	48 weeks	MV (NR)	11.6 (1.7)	10.1 (0.8)	− 1.50	BCVA (ETDRS)	62.5 (15.2)	72 (10.1)	− 0.19
Koytak et al. (2013)[66] Turkey	Bevacizumab: diffuse retinal thickening	4 weeks	Total MV (NR)	9.35 (2.04)	9.07 (1.82)	− 0.28	BCVA (logMAR)	0.75 (0.48)	0.61 (0.46)	− 0.14
	Bevacizumab: cystoid macular edema	4 weeks		8.79 (1.9)	7.88 (1.56)	− 0.91	BCVA (logMAR)	0.67 (0.47)	0.53 (0.44)	− 0.13
	Bevacizumab: serious retinal detachment	4 weeks		11.03 (2.58)	10.11 (2.54)	− 0.92	BCVA (logMAR)	0.88 (0.57)	0.79 (0.6)	− 0.09
Kumar et al. (2007)[67] India	PPV with dye-enhanced ILM peeling	6 months	MV (NR)	12.4 (3.23)	8.46 (1.46)	− 3.94	VA (logMAR)	1.046 (0.037)	0.932 (0.117)	− 0.12
	Grid LP	6 months		11.1 (1.87)	10 (1.24)	− 1.10	VA (logMAR)	1.043 (0.028)	0.965 (0.1)	− 0.08
Lima Gomez et al. (2015)[71] Mexico	Focal photocoagulation	3 weeks	MV (NR)	7.82 (0.58)	7.7 (0.52)	− 0.12	VA (logMAR)	0.52 (0.27)	0.54 (0.28)	0.02
Luis et al. (2021)[72] Portugal	Intravitreal corticosteroid (triamcinolone, dexamethasone or fluocinolone acetonide implant)	3 months	MV (NR)	9.4 (3.2)	8.3 (2.3)	− 1.20	BCVA (logMAR)	0.65 (0.39)	0.6 (0.36)	− 0.04
Lukic et al. (2021a)[74] UK	Aflibercept (switched to aflibercept >3 months post-ranibizumab)	12 months	MV (NR)	9.69 (2.2)	8.14 (1.31)	− 1.55	VA (ETDRS)	63.65 (17.79)	69.38 (15.96)	− 0.11

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Table 5 (*continued*)

Study name, country	Interventions	Follow-up period	MV				VA			
			Biomarker (description of zone)	Average baseline value (mm^3)*	Average follow-up value (mm^3)*	Change from baseline†	Type, unit of measurement	Average baseline value*	Average follow-up value*†	Change from baseline†
	Aflibercept (switched to aflibercept <3 months post-ranibizumab)	12 months		10.15 (2.6)	8.63 (2.08)	− 1.52	VA (ETDRS)	62.57 (14.37)	65.66 (15.66)	− 0.06
Lukic et al. (2021b)[73] UK	Aflibercept	36 months	MV (NR)	9.51 (2.01)	8.35 (1.62)	− 1.16	VA (ETDRS)	61.45 (16.3)	68.34 (13.66)	− 0.14
Lukic, et al. (2020)[75] UK	Aflibercept	12 months	MV (NR)	9.53 (1.79)	8.43 (1.58)	− 1.08	VA (ETDRS)	59.66 (16.11)	69.56 (15.24)	− 0.20
Maia et al. (2009)[77] Brazil, USA	LP with triamcinolone acetonide	12 months	Total MV (6 linear 6.00-mm scans)	8.59 (1.68)	7.32 (0.6)	− 1.27	BCVA (logMAR)	0.44 (0.17)	0.12 (0.07)	− 0.32
	LP only	12 months	Total MV (6 linear 6.00-mm scans)	8.44 (1.51)	7.78 (0.59)	− 0.66	BCVA (logMAR)	0.38 (0.17)	0.32 (0.16)	− 0.06
Mian et al. (2015)[80] Bahrain	Bevacizumab	6 weeks	Total MV (the 9 macular subfields seen on the OCT)	9.1 (NR)	8.4 (NR)	− 0.70	BCVA (logMAR)	0.47 (NR)	0.48 (NR)	− 0.01
Nguyen et al. (2006)[84] USA	Ranibizumab	7 months	MV (throughout entire 6-mm zone)	9.22 (NR)	7.47 (NR)	− 1.75	VA (ETDRS)	NR	NR	ETDRS 12.30
Nozaki et al. (2019)[85] Japan	Focal LP	6 months	MV (NR)	12.9 (1.9)	11.6 (1.2)	− 1.30	BCVA (logMAR)	0.49 (0.33)	0.39 (0.33)	− 0.10
Ockrim et al. (2008)[87] UK	Triamcinolone acetonide	12 months	MV (The macula was scanned using the 6×6-mm radial line scan protocol)	9.74 (2.41)	8.41 ()	− 1.33	VA (ETDRS)	54.6 (13.3)	54.5 (13.6)	0.00
	LP	12 months		9.42 (2.02)	8.66 ()	− 0.76	VA (ETDRS)	53 (14.2)	54.7 (17.7)	− 0.03
Ohkoshi et al. (2010)[88] Japan	SDM LP	3 months	Total MV (NR)	8.763 (1.605)	8.636 (1.408)	− 0.13	BCVA (logMAR)	0.12 (0.2)	0.12 (0.21)	0.00
Patrao et al. (2016)[93] UK	Ranibizumab	12 months	MV (NR)	10.46 (2.28)	NR	− 1.50	VA (ETDRS)	54.4 (15.26)	61 (NR)	− 0.13
Plaza-Ramos et al. (2019)[94] USA	Ranibizumab or aflibercept	12 months	Central MV (NR)	10.26 (1.96)	9.49 (1.24)	− 0.77	BCVA (logMAR)	0.52 (0.34)	0.4 (0.33)	− 0.12
Robaszkiewicz et al. (2012)[96] Poland	Phacovitrectomy with ILM peeling, retinal endophotocoagulation and bevacizumab	12 months	Central MV (CMV in the 6-mm zone)	11.4 (2.88)	8.35 (1.4)	− 3.05	BCVA (logMAR)	0.74 (0.36)	0.42 (0.29)	− 0.32
Shalchi et al. (2018)[98] UK	Ranibizumab	1 year	MV (NR)	9.99 (1.95)	8.86 (1.52)	− 1.13	VA (ETDRS)	54.9 (16.6)	61.3 (12.4)	− 0.13
Sheth et al. (2011)[101] Australia	Triamcinolone acetonide	6 weeks	MV (NR)	9.11 (1)	7.46 (0.73)	− 1.65	BCVA (logMAR)	0.76 (0.13)	0.65 (0.15)	− 0.11
	Bevacizumab plus dexamethasone	6 weeks		9.03 (0.96)	8.42 (1.18)	− 0.61	BCVA (logMAR)	0.77 (0.14)	0.69 (0.15)	− 0.08
Soliman et al. (2008a)[104] Denmark, Egypt	Bevacizumab	4 months	MV (6-mm scan display map)	9.9 (1.9)	9 (2.4)	− 0.90	BCVA (ETDRS)	51 (17)	58 (20)	− 0.14
Soliman et al. (2008b)[103] Denmark, Egypt	No treatment	6 months	MV (6-mm scan display map)	Mean (95 % CI) 8.29 (8.7, 7.88)	Mean (95 %CI) 7.94 (8.44, 7.45)	− 0.35	BCVA (ETDRS)	Mean (95 %CI) 68.96 (73.89, 64.04)	Mean (95 %C) 69.43 (74.05, 64.81)	− 0.01
Srinivas et al. (2020)[105] USA	Ranibizumab injections (until DME and hard exudates resolved)	12 months	MV (a 512 × 128 μm macular cube protocol (6 × 6-mm) cantered on the fovea)	11.99 (2.07)	10.08 (1.01)	− 1.91	BCVA (ETDRS)	61.33 (9.53)	74.83 (8.32)	− 0.27
	Ranibizumab injections (until DME resolved)	12 months		12.03 (2.01)	10.73 (1.08)	− 1.30	BCVA (ETDRS)	65.42 (5.6)	77.92 (9.61)	− 0.25
Tachi et al. (2017)[109] Japan	PPV	6 months	MV (NR)	10.8 (1.4)	9.7 (1)	− 1.10	BCVA (logMAR)	0.43 (0.31)	0.25 (0.23)	− 0.18
Tran et al. (2022)[112] France	Aflibercept	24 months	MV (NR)	10.1 (2.5)	NR	− 1.00	BCVA (ETDRS)	53.3 (14.7)	58.7 (NR)	− 0.11

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Table 5 (*continued*)

Study name, country	Interventions	Follow-up period	MV				VA			
			Biomarker (description of zone)	Average baseline value (mm^3)*	Average follow-up value (mm^3)*	Change from baseline†	Type, unit of measurement	Average baseline value*	Average follow-up value*†	Change from baseline†
Turski et al. (2022)[113] USA	Bevacizumab	NR	MV (NR)	10.45 (1.8)	9.98 (1.5)	− 0.47	BCVA (ETDRS)	63.9 (NR)	65.9 (NR)	− 0.04
Vaz-Pereira et al. (2020)[114] Portugal	Fluocinolone acetonide implant	8 months	MV (NR)	10.8 (NR)	10.1 (NR)	− 0.69	VA (ETDRS)	41.93 (20.83)	50.82 (NR)	− 0.18
Vujosevic et al. (2016)[116] Italy	Anti-VEGF injections	6 months	MV (NR)	12.1 (2.5)	11.5 (2.3)	− 0.60	BCVA (ETDRS)	64.9 (9.1)	70.4 (10.2)	− 0.11
	No treatment	6 months		11.2 (3)	10.8 (2.3)	− 0.40	BCVA (ETDRS)	77.6 (10)	77.7 (9.2)	0.00
Yoon et al. (2022)[122] South Korea	Ranibizumab with additional treatment (anti-VEGF or steroid injection)	7 years	MV (a 512 × 128 μm scan mode protocol)	11.98 (1.64)	10.01 (1.51)	− 1.97	BCVA (logMAR)	0.5 (0.22)	0.63 (0.5)	0.13
	Ranibizumab without additional treatment	7 years		10.72 (0.88)	9.64 (0.8)	− 1.08	BCVA (logMAR)	0.45 (0.24)	0.29 (0.3)	− 0.16

Abbreviations: anti-VEGF, anti-vascular endothelial growth factor therapy; BCVA, best-corrected visual acuity; CI, confidence interval; DME, diabetic macular edema; ETDRS, Early Treatment Diabetic Retinopathy Study; ILM, internal limiting membrane; logMAR, Logarithm of the Minimum Angle of Resolution; LP, laser photocoagulation; MV, macular volume; NR, not reported; OCT, optical coherence tomography; PPV, pars plana vitrectomy; SD, standard deviation; SDM, subthreshold diode micropulse; UK, United Kingdom; USA, United States of America; VA, visual acuity.

* Values are provided as mean (SD) unless otherwise stated.

† Reported or calculated based on the available data.

‡ Reported in logMAR unless otherwise stated. If change from baseline was only available in ETDRS letters, the study was included in the scenario analysis.

§ At the statistical analysis stage, the study was considered an outlier and removed from the final analysis following the inspection of the plots.

statistically significant correlation coefficient was identified between the MV and VA ($r = 0.58$, $p < 0.01$); however, this was not reflected at the trial-level (treatment effect correlation) where a non-significant correlation coefficient was reported ($r = 0.32$, $p = 0.19$). A similar trend was observed in both scenario analyses when VA was expressed in both logMAR (endpoint correlation 0.51, $p < 0.01$; treatment effect correlation $r = 0.12$, $p =$ NS) and ETDRS letters (endpoint correlation $r = -0.72$, $p < 0.01$; treatment effect correlation $r = -0.27$, $p =$ NS). As the study was considered an exploratory analysis, it progressed to the treatment effect correlation stage despite the endpoint correlation target value of ≥ 0.7 not being achieved at the arm-level.

The results should be interpreted with caution as an endpoint correlation value < 0.7 indicates that there might be a low or moderate association between the changes in MV and VA. This observation could be attributed to the quality of the studies identified by the SLR. In the base case, a relatively small number of studies were included at the trial level, compared with the arm-level (14 studies vs 55 studies). A similar trend was observed for trial-level vs arm-level analyses in the logMAR (10 studies vs 28 studies) and ETDRS letters (5 studies vs 27 studies) scenario analyses. In addition, in the base case, 8/14 studies (57 %) included a small sample size of less than 50 patients with a smaller sample size decreasing the precision in the study estimates. Furthermore, 9/14 studies (64 %) reported outcomes over < 12 months (range 1–6 months), with a shorter follow-up time likely not to capture full treatment effectiveness. Further analysis of the included studies highlighted that outliers were affecting the estimate of the trial-level correlation; however, there was no clinical justification for removing all outliers from the analysis, and most studies were retained. Specifically, the spread of the results was wide and would require guessing to determine which studies should or should not be included. The removal of more studies would have further decreased the robustness of the analysis, which was not advised due to wide confidence intervals.

4.2. Use of biomarkers and SEs in DME

Among patients with DME, the association of VA with retinal thickness, or retinal volume, is incomplete. Once the retina is too thin, potentially due to loss or atrophy of specific structures (ganglion cells, inner plexiform layer synapses, and/or photoreceptors), and the retinal layers become disorganized, VA may decrease. Due to this inconsistent correlation between anatomy and function, different biomarkers and other OCT findings may become more relevant. Several biomarkers of DME have been reported by OCT and are effective for the evaluation and treatment of DME.[107] The external limiting membrane status has been significantly correlated with VA,[82] and ellipsoid zone disruption is a preoperative predictor of VA in patients with DME.[76,120] Furthermore, CMT has been proposed as an endpoint in DME treatment and has been recommended as a guide to decision-making when determining treatment frequency.[118] However, CMT is poorly correlated to VA,[117] illustrating the need for additional SEs that can be used for VA in patients with DME. It is possible that additional SEs may help improve the efficiency of clinical trials, the evaluation of current treatment effects, and future therapies for DME.

The need for faster access to innovative treatments has led to the introduction of regulatory initiatives to accelerate their development.[31] Using SEs allows trials to be conducted less expensively, with fewer patients, and in shorter time.[17] Evidence from SEs can expedite the regulatory approval of new health technologies, with regulatory agencies such as the European Medicines Agency and the Food and Drug Administration having increasingly approved treatments based on SEs.[23,30] Furthermore, SEs can inform reimbursement decisions, with regulatory authorities and payers often basing their decision-making on surrogate outcomes.[30] Descriptive analysis of submissions to the National Institute for Health and Care Excellence, the Pharmaceutical Benefits and Advisory Committee, and the Common Drug Review demonstrated that between 27 % and 50 % of submissions were based

on SEs;[19] however, it is widely recognized that there is an urgent need for better understanding and reporting on the use of SEs.[18] A greater focus on including biomarkers in studies and improvements to help standardize the reporting of the methods of collecting biomarker data is required.

4.3. Limitations of the analysis

A key limitation of the current analysis is related to the quality of studies identified by the SLR. Despite MV being investigated most often in the literature, the SLR identified a paucity of relevant studies and information. Quality assessment of the identified studies highlighted several limitations, including low patient numbers, short follow-up time, and poorly defined biomarkers. Consequently, a low and limited number of studies (and trial arms) were included in the base case analysis.

Further to the quality of the included studies, limitations were associated with the clinical interpretation of the available data. For example, very low MV may reflect a loss of ganglion cells or a thin retinal ganglion cell layer attributed to low visual function.[57] Reduced ganglion cell-inner plexiform layer thickness can indicate impaired ganglion cell integrity and loss of synapses, which causes visual impairment and loss of vision.[57] Furthermore, MV may reflect photoreceptor loss in advanced disease, resulting in vision loss.[69,76,99]

Despite the endpoint correlation target value of ≥ 0.7 not being achieved, the analysis progressed to the treatment effect correlation stage as it was considered exploratory.; however, the results should be interpreted with caution as an endpoint correlation value < 0.7 indicates that there may be a low or moderate association between the changes in MV and VA at the arm-level (endpoint correlation). Other factors that may have contributed to the limited endpoint correlation include macular ischemia and the association between diabetes severity and retinal thickness. Diabetic macular ischemia (DMI) is associated with reduced VA in eyes with moderate to severe ETDRS-DMI grades of ischemia.[102] A thinner inner macula has been observed in patients with diabetic retinopathy, and negative correlations between retinal thickness and VA have been reported in patients with DME and/or retinal vein occlusion.[25,45,46,97,106]

Finally, limited endpoint correlation may relate to the inconsistent relationship between anatomy and function. While this analysis did report an endpoint correlation between MV and VA, instances exist where the relationship between these endpoints is detached. Significant improvements in VA have been observed after cataract surgery despite postoperative increases in MV.[14,50,68] Patients with DME treated with anti-VEGF therapies have experienced improvements in VA without significant change in CMT.[65] Conversely, intravitreal corticosteroid treatment in patients with DME has shown a significant reduction in MV without improvements in VA.[100] These same results for MV and VA were found in patients with multiple sclerosis after treatment with immunosuppressive drugs.[22]

While MV may serve as an interesting and potentially more informative anatomical endpoint compared to CMT for evaluating the efficacy of a molecule in DME, functional outcomes such as VA remain essential for patient care in daily practice. Treatment adherence is a critical issue among diabetic patients, and demonstrating the efficacy of a drug on their VA is crucial for improving compliance. While MV can provide valuable insights, it should complement rather than replace functional assessments.

4.4. Recommendations and future implications

This exploratory study sought to analyze and communicate the current landscape for generating endpoint and outcome data. This study demonstrated that methodology exists to identify a biomarker that can be used as an SE in DME and that MV may have potential as an SE for VA; however, this analysis identified few relevant studies, and further research is required to identify additional evidence and improvements in reporting the methods for collecting biomarker data. A potential solution for future analyses is adopting an artificial intelligence (AI) methodological approach using large databases, which could help identify biomarkers[27] and SE data. This could facilitate new ways of measuring endpoints and outcomes in DME and support patient access to the most appropriate treatments.

While our study demonstrates a correlation between MV and VA, suggesting MV's potential as an SE, it is crucial to acknowledge that MV alone may not capture the nuanced qualitative anatomical changes increasingly recognized as important in clinical practice.

Biomarkers are prognostic of clinical outcomes and predictive of treatment effects in other diseases.[6] Therefore, biomarker profiling through genomic testing and biomarker pattern recognition by AI could be used to predict treatment responses in patients with DME. Identifying which biomarkers are predictive of specific treatment responses could facilitate a personalized medicine approach by identifying the most appropriate treatment based on an individual biomarker profile.[89]

Furthermore, SEs could shift the DME treatment paradigm through earlier diagnosis and treatment. If an increase in MV can be detected early, there is a potential to treat patients sooner and prevent visual loss. Using biomarkers as SEs could help optimize DME treatment pathways and bring new therapies to patients by supporting real-world comparative effectiveness research, predicting real-world outcomes, and improving the efficiency of clinical trials.

5. Conclusions

Findings from this analysis demonstrated a moderate and statistically significant correlation between MV and VA at the arm-level ($r = 0.58$; $p < 0.01$); however, the treatment effect was not visible at the trial level where a low and non-statistically significant correlation was reported ($r = 0.32$; $p = 0.19$). Based on this analysis, there may be potential for MV to be considered as an SE for VA in future clinical practice for patients with DME; however, the lack of a significant treatment effect warrants that these findings be interpreted with caution. More research is required before declaring that MV can serve as an SE for VA in clinical practice. Specifically, further evidence and improvements in reporting the methods for collecting biomarker data are needed. The analysis of outliers in future studies may also help understand at which MV values the correlation with VA is most meaningful. Subanalyses by other OCT measures, such as ganglion cell-inner plexiform layer thickness, may also add insight.

CRediT authorship contribution statement

Peto Tunde: Writing – review & editing, Conceptualization. **Pintard Pierre-Jean:** Writing – review & editing, Conceptualization. **Couturier Aude:** Writing – review & editing, Conceptualization. **Wykoff Charles C.:** Writing – review & editing, Conceptualization. **Lupidi Marco:** Writing – review & editing, Conceptualization. **Udaondo Patricia:** Writing – review & editing, Conceptualization.

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Method of literature search

We searched the electronic databases of Embase, 1974 to present and MEDLINE, 1946 to present, including MEDLINE Epub Ahead of Print, MEDLINE In-Process & Other Non-Indexed Citations, and MEDLINE Daily on March 7, 2023. The search strategy used to interrogate the electronic databases is provided in the Supplementary material. We also performed hand searches of included publications' reference lists, HTA body websites, and clinical trial registries to identify other relevant evidence. Citations of interest were identified by one reviewer and

verified by an independent second reviewer, based on the title and abstract. Full publications were obtained for all citations of interest and were also assessed by one reviewer and verified by a second reviewer. Any uncertainties were resolved through discussion. Data were extracted into an Excel spreadsheet by one reviewer and independently checked against the original publication by a second reviewer.

Declaration of Competing Interest

Aude Couturier is a consultant for AbbVie, Bayer, Horus, Novartis; and reports speaker's fees from Roche, and Zeiss; all outside the submitted work.

Charles C. Wykoff is a consultant for Adverum, Aerie Pharmaceuticals, AbbVie, Apellis, Bausch + Lomb, Bayer, Bionic Vision Technologies, Clearside Biomedical, EyePoint Pharmaceuticals, Genentech/Roche, Gyroscope, Iveric Bio, Kato Pharmaceuticals, Kodiak Sciences, NGM, Novartis, Ocular Therapeutix, ONL Therapeutics, Opthea Limited, Palatin, Regeneron, REGENXBIO, Roche; has received research support from Adverum, Aerie Pharmaceuticals, Alimera Sciences, AbbVie, Apellis, Bayer, Boehringer Ingelheim, Chengdu Kanghong Biotechnologies, Clearside Biomedical, Genentech/Roche, Gyroscope, IONIS Pharmaceuticals, Iveric Bio, Kodiak, Neurotech, NGM, Novartis, Regeneron, REGENXBIO, Roche; and has stock options from ONL Therapeutics, RecensMedical, and Visgenx.

Marco Lupidi reports speaker's fees and advisory board fees from AbbVie, Apellis, Bayer, Heidelberg Engineering, Novartis, Optomed, and Roche.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.survophthal.2025.04.004.

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