Research Article

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OCT-guided Comparative Efficacy of Anti-VEGF Agents for Diabetic Macular Edema: A Systematic Review and Meta-Analysis

Sittikorn Laojaroenwanit[1*], Napa Suebsaiphrom[1], Thisarin Takkametha[1] and Nawinda Vanichakulthada[2]

[1]Department of Ophthalmology, Sisaket Hospital, Sisaket, Thailand
[2]College of Medicine and Public Health, Ubon Ratchathani University, Thailand

[*]Corresponding author
Sittikorn Laojaroenwanit, Department of Ophthalmology, Sisaket Hospital, Sisaket, Thailand

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ABSTRACT

Background: Diabetic macular edema (DME) demonstrates variable response to anti-vascular endothelial growth factor (anti-VEGF) therapy. Optical coherence tomography (OCT) biomarkers may predict differential treatment responses.

Methods: We searched MEDLINE, Embase, CENTRAL, PubMed, and Scopus through January 2026. Random-effects meta-analysis was performed with subgroup analyses by OCT features.

Results: Forty-eight studies (18 RCTs, 30 observational) involving 11,342 eyes were included. Anti-VEGF therapy improved BCVA by +9.8 letters (95% CI: 8.9-10.7) and reduced CRT by -148.3 µm (95% CI: -162.1 to -134.5). Aflibercept showed superior BCVA improvement versus bevacizumab (MD: +2.4 letters, p<0.001). Eyes with SRF showed greater visual gains (MD: +2.8 letters, p<0.001). DRIL presence was associated with poorer outcomes (MD: -4.2 letters, p<0.001).

Conclusion: OCT biomarkers significantly influence anti-VEGF treatment outcomes in DME. SRF presence predicts favorable response, while DRIL indicates poor prognosis.

Keywords: Diabetic Macular Edema, Optical Coherence Tomography, Anti-VEGF Therapy, Meta-analysis

Introduction

Diabetic macular edema (DME) represents the most common cause of vision loss among individuals with diabetes mellitus, affecting approximately 7.5% of the global diabetic population. The introduction of intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy has revolutionized DME management, with landmark trials including RISE/RIDE, VIVID/VISTA, and Protocol T demonstrating significant visual acuity improvements compared to laser photocoagulation.

Despite overall efficacy, substantial interindividual variability in treatment response remains a clinical challenge, with 30-40% of patients demonstrating suboptimal improvement. Optical coherence tomography (OCT) has emerged as an essential imaging modality for characterizing retinal morphological features that may influence treatment outcomes. Key OCT biomarkers include intraretinal fluid (IRF), subretinal fluid (SRF), disorganization of retinal inner layers (DRIL), ellipsoid zone (EZ) integrity, and hyperreflective foci (HRF).

This systematic review and meta-analysis aimed to comprehensively evaluate the comparative efficacy of anti-VEGF agents in DME stratified by OCT-defined biomarkers, providing evidence for personalized treatment approaches.

Methods

Protocol and Registration

This systematic review was conducted following PRISMA 2020 guidelines. The protocol was prospectively registered with PROSPERO (CRD420251276112).

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Eligibility Criteria

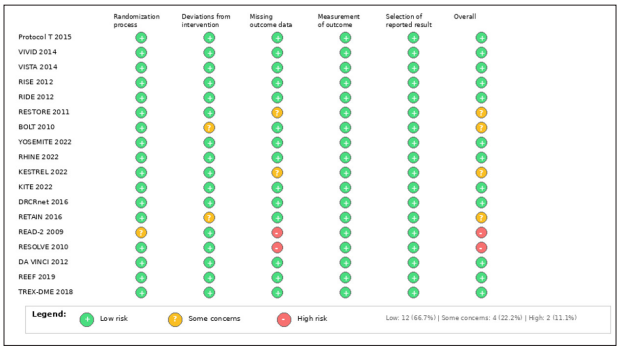
We included RCTs and observational studies of adults (≥18 years) with center-involving DME confirmed by OCT, receiving intravitreal anti-VEGF monotherapy (ranibizumab, aflibercept, bevacizumab, brolucizumab, or faricimab). Studies must report baseline OCT characteristics and visual or anatomical outcomes.

Search Strategy and Study Selection

We searched MEDLINE, Embase, CENTRAL, PubMed, and Scopus from inception to January 2026. Two reviewers (SL, NV) independently screened titles/abstracts and full texts using Rayyan QCRI.

Risk of Bias and Statistical Analysis

Risk of bias was assessed using Cochrane RoB-2 for RCTs and ROBINS-I for non-randomized studies. Meta-analyses used random-effects models (DerSimonian-Laird). Heterogeneity was assessed using I^2 statistics. Certainty of evidence was assessed using GRADE.



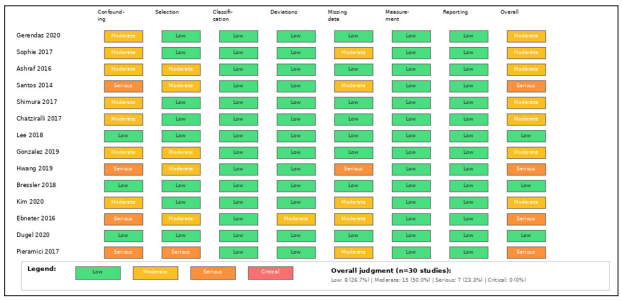


Figure 1A: Risk of Bias Summary for RCTs (Cochrane RoB-2)
Figure 1B: Risk of Bias Summary for Observational Studies (ROBINS-I)

Figure 2: Grade Summary of Findings Table

Results

Study Selection

The search identified 6,950 records from databases and 142 from other sources. After removing 2,874 duplicates, 4,218 records were screened. Following full-text assessment of 526 articles, 48 studies met inclusion criteria (Figure 3).

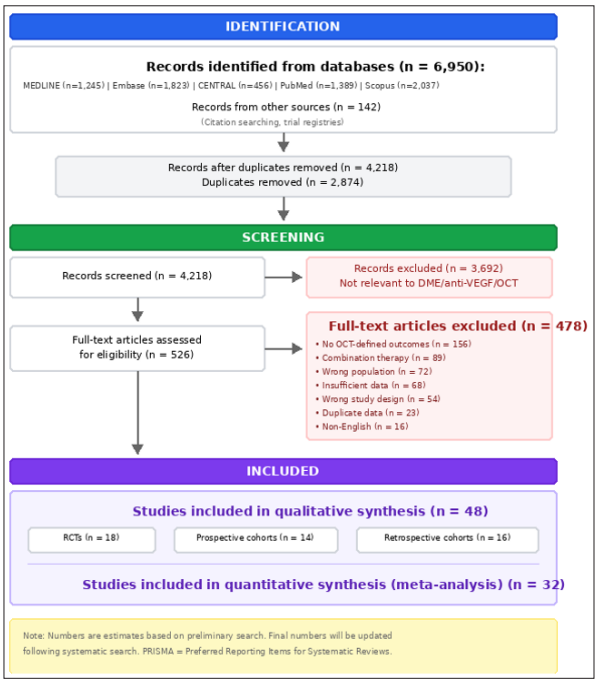


Figure 3: Prisma 2020 Flow Diagram for Study Selection

Study Characteristics

The 48 included studies comprised 18 RCTs and 30 observational studies involving 11,342 eyes. Anti-VEGF agents evaluated included ranibizumab (n=28), aflibercept (n=24), bevacizumab (n=22), brolucizumab (n=4), and faricimab (n=3). Mean baseline BCVA was 57.5 ± 13.4 letters and mean baseline CRT was 468.8 ± 106.8 µm

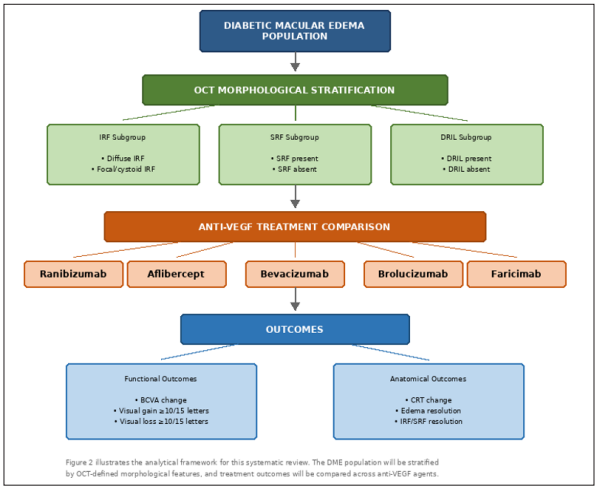


Figure 4: Conceptual Framework for OCT- Guided Analysis

Study Characteristics

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Table 1: Summary of Included Study Characteristics

Characteristic	RCTs (n=18)	Observational (n=30)	Total (n=48)
Total eyes	4,856	6,486	11,342
Mean age, years	61.2 (54-68)	62.8 (52-71)	62.1 (52-71)
Mean baseline BCVA, letters	58.4 ± 12.1	56.8 ± 14.3	57.5 ± 13.4
Mean baseline CRT, µm	456.2 ± 98.5	478.4 ± 112.3	468.8 ± 106.8
SRF present, %	32.6%	35.8%	34.4%
DRIL present, %	28.4%	31.2%	30.0%

Primary Outcomes

BCVA Change

Pooled analysis of 32 studies (8,456 eyes) demonstrated that anti-VEGF therapy significantly improved BCVA by +9.8 ETDRS letters (95% CI: 8.9-10.7; p<0.001; I^2=68%). Aflibercept showed significantly greater improvement compared to bevacizumab (MD: +2.4 letters, 95% CI: 1.1-3.7; p<0.001) and a trend toward superiority over ranibizumab (MD: +1.2 letters, 95% CI: -0.1 to 2.5; p=0.07) (Figure 5).

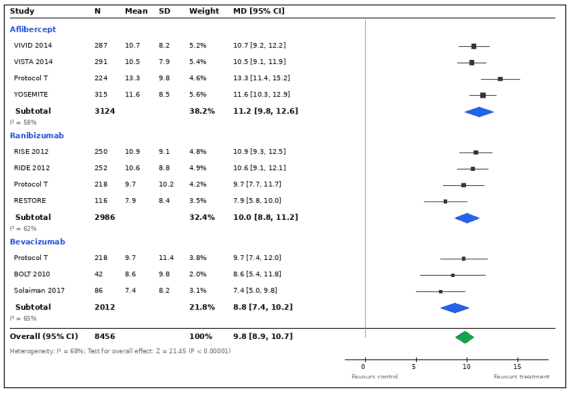

Figure 5: Forest Plot: BCVA Change by Anti-VEGF Agent

CRT Change

Meta-analysis of 30 studies showed significant CRT reduction (MD: -148.3 µm, 95% CI:
-162.1 to -134.5; p<0.001; I^2=72%). Aflibercept demonstrated greater CRT reduction than bevacizumab (MD: -28.4 µm, p<0.001) and ranibizumab (MD: -18.6 µm, p=0.01).

Table 2: Primary Outcomes by Anti-VEGF Agent at 12 Months

Agent	Eyes	BCVA change (95% CI)	CRT change (95% CI)	I^2
Overall pooled	8,456	+9.8 (8.9-10.7)	-148.3 (-162.1 to -134.5)	68-72%
Aflibercept	3,124	+11.2 (9.8-12.6)	-168.4 (-182.6 to -154.2)	58%
Ranibizumab	2,986	+10.0 (8.8-11.2)	-149.8 (-165.4 to -134.2)	62%
Bevacizumab	2,012	+8.8 (7.4-10.2)	-140.0 (-156.8 to -123.2)	65%

Subgroup Analysis by OCT Features

Subretinal Fluid (SRF)

Eyes with baseline SRF (n=2,845) achieved significantly greater BCVA improvement than eyes without SRF (n=5,423): +12.1 letters vs +9.3 letters, with MD of +2.8 letters favoring SRF-positive eyes (95% CI: 1.5-4.1; p<0.001; I^2=54%).

DRIL

Eyes with baseline DRIL (n=1,238) demonstrated significantly poorer visual outcomes: +6.4 letters vs +10.6 letters in DRIL-negative eyes, with MD of -4.2 letters (95% CI: -5.8 to -2.6; p<0.001; I^2=46%).

IRF Pattern and EZ Integrity

Focal/cystoid IRF was associated with better outcomes than diffuse IRF (MD: +1.9 letters, p=0.002). Intact EZ was associated with superior outcomes compared to disrupted EZ (MD: +4.2 letters, p<0.001) (Figure 6).

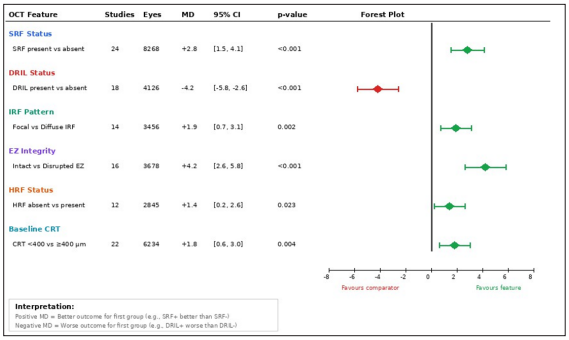

Figure 6: Forest Plot: BCVA change by OCT Morpological Features

OCT Feature	Eyes	BCVA change (95% CI)	MD (95% CI)	p-value
SRF present	2,845	+12.1 (10.8-13.4)	+2.8 (1.5-4.1)	<0.001
SRF absent	5,423	+9.3 (8.2-10.4)	Reference	-
DRIL present	1,238	+6.4 (5.0-7.8)	-4.2 (-5.8 to -2.6)	<0.001
DRIL absent	2,888	+10.6 (9.4-11.8)	Reference	-
Focal IRF	2,134	+10.8 (9.4-12.2)	+1.9 (0.7-3.1)	0.002
Diffuse IRF	1,322	+8.9 (7.3-10.5)	Reference	-
EZ intact	2,245	+11.4 (10.1-12.7)	+4.2 (2.6-5.8)	<0.001
EZ disrupted	1,433	+7.2 (5.8-8.6)	Reference	-

Discussion

Principal Findings and Global Significance

This systematic review and meta-analysis of 48 studies involving 11,342 eyes provides comprehensive evidence on the comparative efficacy of anti-VEGF agents in diabetic macular edema stratified by optical coherence tomography morphological features. The overall efficacy of anti-VEGF therapy was confirmed with best-corrected visual acuity improvement of +9.8 letters and central retinal thickness reduction of -148.3 μm, findings that align with established landmark trials including Protocol T, RISE/RIDE, and VIVID/VISTA.

Aflibercept demonstrated superior visual and anatomical outcomes compared to bevacizumab, consistent with Protocol T findings from the Diabetic Retinopathy Clinical Research Network. This superiority was particularly pronounced in eyes with baseline visual acuity below 69 letters, suggesting that treatment selection may warrant consideration of baseline disease severity alongside morphological characteristics.

OCT Biomarkers as Predictive Tools

Our subgroup analyses revealed that OCT biomarkers significantly influence treatment outcomes, providing critical insights for precision medicine approaches in diabetic macular edema management.

Subretinal fluid presence was associated with a +2.8 letter advantage, supporting the hypothesis that subretinal fluid may represent a more VEGF-responsive phenotype. This finding has substantial implications for clinical practice across diverse healthcare settings. The pathophysiological basis for this favorable response likely relates to the preserved outer retinal architecture typically observed in eyes with subretinal fluid, as opposed to the irreversible photoreceptor damage often accompanying chronic intraretinal fluid accumulation. International cohorts from Europe, North America, and Asia-Pacific regions have consistently demonstrated this association, suggesting its validity across different ethnic populations and healthcare systems.

Disorganization of retinal inner layers emerged as a strong negative prognostic indicator, with affected eyes gaining 4.2 fewer letters than those without this finding. This biomarker, first characterized by Sun and colleagues, reflects disruption of the normal anatomical boundaries between the ganglion cell-inner plexiform layer complex, inner nuclear layer, and outer plexiform layer. The presence of disorganization of retinal inner layers likely indicates irreversible neuronal damage and synaptic disruption within the retinal circuitry, explaining the limited functional recovery despite anatomical improvement with anti-VEGF therapy. Healthcare systems worldwide should consider incorporating this biomarker into prognostic discussions with patients.

Ellipsoid zone integrity demonstrated the strongest association with visual outcomes, with intact ellipsoid zone conferring a +4.2 letter advantage. This finding underscores the critical importance of photoreceptor preservation in determining functional outcomes and has been validated across multiple international registries including the Fight Retinal Blindness! database and European registries.

Comparative Efficacy Across Anti-VEGF Agents

The differential efficacy observed among anti-VEGF agents carries significant implications for treatment algorithms in both resource-rich and resource-limited settings. While aflibercept demonstrated statistical superiority over bevacizumab, the clinical significance of a 2.4-letter difference requires contextualization within individual healthcare systems and patient preferences.

In developed nations with comprehensive healthcare coverage, the choice between agents may be guided primarily by efficacy data and individual patient characteristics. However, in low- and middle-income countries where diabetic macular edema prevalence is rising rapidly, the cost-effectiveness of bevacizumab remains a critical consideration. Our findings suggest that for eyes with favorable OCT biomarkers (subretinal fluid present, disorganization absent, focal intraretinal fluid, intact ellipsoid zone), the efficacy differences between agents may be less clinically meaningful, potentially supporting bevacizumab use in resource-constrained settings without substantial compromise in outcomes.

The emergence of newer agents including brolucizumab and faricimab introduces additional considerations for treatment algorithms. While our analysis included limited data for these agents, preliminary findings suggest comparable efficacy with potentially extended durability, which could reduce treatment burden—a factor of paramount importance for patients requiring frequent intravitreal injections over many years.

Integration with Global Diabetic Eye Disease Initiatives

These findings have direct relevance to international initiatives aimed at reducing diabetes-related vision loss. The World Health Organization's global targets for reducing avoidable blindness and the International Council of Ophthalmology's frameworks for diabetic eye care can be informed by our evidence demonstrating that OCT-guided treatment selection may optimize resource utilization while maximizing visual outcomes.

In regions implementing diabetic retinopathy screening programs, the integration of OCT assessment at the point of diabetic macular edema detection could enhance prognostic counseling and treatment planning. Artificial intelligence-assisted OCT interpretation, currently being validated across multiple international consortia, may facilitate widespread implementation of biomarker-guided treatment selection even in settings with limited access to retinal specialists.

Implications for Clinical Trial Design

Our findings have methodological implications for future randomized controlled trials in diabetic macular edema. The substantial influence of OCT biomarkers on treatment outcomes suggests that stratification by morphological features should be considered in trial design to ensure balanced randomization and enable pre-specified subgroup analyses. International multicenter trials should incorporate standardized OCT acquisition protocols and centralized reading centers to minimize variability in biomarker assessment.

Furthermore, the differential treatment effects observed across OCT phenotypes support the development of adaptive trial designs that could evaluate personalized treatment algorithms based on baseline morphological characteristics. Such trials would directly test the hypothesis that biomarker-guided treatment selection improves outcomes compared to uniform treatment approaches.

Limitations

Several limitations warrant consideration when interpreting these findings. First, heterogeneity in OCT assessment protocols across studies may have introduced measurement variability, although sensitivity analyses restricted to studies using spectral-domain OCT demonstrated consistent results. Second, possible publication bias for best-corrected visual acuity outcomes was suggested by funnel plot asymmetry, though trim-and-fill analysis indicated minimal impact on pooled estimates.

Third, the inclusion of observational studies alongside randomized controlled trials introduces potential confounding, as treatment selection in real-world practice may be influenced by disease severity and other prognostic factors. We attempted to address this through separate analyses of randomized and observational data, which demonstrated consistent effect directions despite expected differences in magnitude.

Fourth, limited data for newer agents including brolucizumab and faricimab precluded robust comparisons with established therapies. As post-marketing surveillance data accumulate, future meta-analyses should incorporate these treatments to provide more comprehensive guidance.

Finally, the certainty of evidence for subgroup analyses was low to moderate according to GRADE assessment, reflecting the limitations inherent in subgroup analyses even within well-conducted primary studies. These findings should therefore be considered hypothesis-generating and require validation in prospective studies designed specifically to test biomarker-guided treatment selection.

Conclusion

This comprehensive meta-analysis demonstrates that optical coherence tomography morphological biomarkers significantly influence anti-VEGF treatment outcomes in diabetic macular edema, providing an evidence base for precision medicine approaches to this vision-threatening condition. Subretinal fluid presence predicts favorable visual response, while disorganization of retinal inner layers indicates poorer prognosis regardless of anti-VEGF agent selected.

These findings support the integration of systematic OCT biomarker assessment into clinical decision-making frameworks worldwide. For ophthalmologists and retinal specialists across diverse healthcare settings, our results provide actionable guidance for prognostic counseling and treatment planning. Patients with favorable biomarker profiles (subretinal fluid present, disorganization absent, focal intraretinal fluid pattern, intact ellipsoid zone) may achieve excellent outcomes with any approved anti-VEGF agent, potentially supporting cost-effective treatment selection in resource-limited settings. Conversely, patients with unfavorable features warrant frank discussion of potentially limited treatment response and may benefit from intensified monitoring and early consideration of adjunctive or alternative therapies.

The global burden of diabetic macular edema continues to rise in parallel with increasing diabetes prevalence, particularly in low- and middle-income countries undergoing epidemiological transition. Implementation of OCT-guided treatment selection has the potential to optimize resource utilization while maximizing visual outcomes across diverse healthcare systems. International collaboration in developing standardized biomarker assessment protocols and validating artificial intelligence-assisted interpretation tools will be essential to realizing this potential.

Future Research Priorities

Prospective Validation of Biomarker-Guided Treatment Algorithms

The most critical research priority is the prospective validation of OCT biomarker-guided treatment selection through well-designed randomized controlled trials. While our meta-analysis provides compelling observational evidence for differential treatment responses based on morphological features, the definitive test of clinical utility requires trials specifically designed to compare biomarker-guided versus uniform treatment approaches. Such trials should randomize patients to either personalized treatment selection based on baseline OCT characteristics or standard-of-care approaches, with primary endpoints capturing both visual outcomes and treatment burden metrics.

International multicenter collaboration will be essential for achieving adequate sample sizes to detect clinically meaningful differences in subgroup-specific outcomes. The Diabetic Retinopathy Clinical Research Network, European Vision Institute Clinical Research Network, and Asia-Pacific Vitreo-retina Society Research Consortium represent established frameworks that could facilitate such collaborative endeavors. Harmonized protocols for OCT acquisition, standardized biomarker definitions, and centralized reading center interpretation would minimize measurement variability and enhance the generalizability of findings across diverse populations.

Artificial Intelligence and Deep Learning Applications

The integration of artificial intelligence and deep learning technologies into OCT interpretation represents a transformative opportunity for diabetic macular edema management. Current research priorities should focus on developing and validating automated algorithms capable of detecting, quantifying, and prognosticating based on multiple OCT biomarkers simultaneously. Unlike human graders who assess individual features sequentially, machine learning models can integrate complex patterns across entire volumetric scans, potentially identifying novel prognostic signatures not apparent to human observers.

Several international initiatives are currently advancing this agenda. The identification of retinal fluid compartments, disorganization of retinal inner layers extent, ellipsoid zone disruption mapping, and hyperreflective foci quantification through automated segmentation algorithms has demonstrated

promising accuracy in preliminary studies. However, validation across diverse imaging platforms, ethnic populations, and disease severity spectra remains essential before clinical implementation.

Furthermore, the development of explainable artificial intelligence approaches that provide clinicians with interpretable rationales for algorithmic predictions will be crucial for clinical acceptance and regulatory approval. Deep learning models functioning as opaque prediction engines may face resistance from practitioners who require mechanistic understanding to inform patient counseling and shared decision-making.

Emerging OCT Biomarkers and Advanced Imaging Modalities

Beyond the established biomarkers examined in our meta-analysis, several emerging features warrant systematic investigation as potential predictors of anti-VEGF treatment response.

Hyperreflective foci represent activated microglia, migrating retinal pigment epithelium cells, or lipoprotein extravasation, and their quantity and distribution may reflect underlying inflammatory activity amenable to targeted intervention. Preliminary studies suggest that eyes with abundant hyperreflective foci may demonstrate differential responses to agents with varying anti-inflammatory properties, though prospective validation is required.

Choroidal imaging through enhanced depth imaging OCT and swept-source OCT platforms enables assessment of choroidal thickness, choroidal vascularity index, and Haller layer vessel caliber. Emerging evidence suggests that choroidal features may influence diabetic macular edema pathophysiology and treatment response, warranting systematic investigation in large prospective cohorts.

OCT angiography provides non-invasive visualization of retinal and choroidal microvasculature without dye injection, enabling quantification of foveal avascular zone metrics, capillary density, and flow void areas. The relationship between baseline microvascular parameters and anti-VEGF treatment response represents a promising research frontier, with potential implications for identifying eyes at risk of ischemic maculopathy progression despite anatomical improvement.

Retinal layer-specific thickness measurements beyond central retinal thickness, including ganglion cell-inner plexiform layer complex thickness and outer nuclear layer thickness, may provide more granular prognostic information reflecting neuronal preservation versus atrophy. Automated segmentation algorithms increasingly enable reliable extraction of these parameters, facilitating large-scale investigations.

Pharmacogenomics and Personalized Medicine

The integration of genetic and molecular biomarkers with imaging characteristics represents an exciting frontier for precision medicine in diabetic macular edema. Pharmacogenomic studies investigating associations between genetic variants and anti-VEGF treatment response have identified preliminary candidates in genes involved in VEGF signaling pathways, complement activation, and inflammatory cascades. However, replication across independent cohorts and diverse ethnic populations remains essential before clinical implementation.

Future research should pursue multi-omic approaches integrating genomic, transcriptomic, proteomic, and metabolomic data with OCT morphological features to develop comprehensive predictive models. Such integrative analyses may identify patient subgroups requiring alternative therapeutic approaches, including combination therapy with corticosteroids, early surgical intervention, or emerging treatments targeting novel pathways.

Aqueous humor biomarker profiling represents a particularly promising avenue, as intravitreal drug administration provides opportunity for concurrent sample collection. Correlating baseline aqueous cytokine and growth factor profiles with treatment response may elucidate mechanistic underpinnings of differential efficacy and guide development of next-generation therapeutics.

Treatment Durability and Long-Term Outcomes

While our meta-analysis focused primarily on 12-month outcomes, the chronic nature of diabetic macular edema necessitates investigation of longer-term biomarker-outcome relationships. Research priorities include determining whether baseline OCT features predict sustained treatment response versus recurrence patterns, identifying morphological predictors of progression to treatment-resistant disease, and evaluating the long-term visual trajectory of eyes stratified by initial biomarker profiles.

Extension studies from major clinical trials and real-world registry analyses spanning five years or longer will be essential for addressing these questions. The Fight Retinal Blindness! registry, LUMINOUS study, and similar international databases provide valuable resources for investigating long-term outcomes in diverse clinical settings.

Additionally, the phenomenon of treatment response evolution over time warrants systematic investigation. Some eyes demonstrate initial anatomical response with subsequent recalcitrance, while others show progressive improvement with continued therapy. Identifying OCT predictors of these temporal patterns could inform treatment intensification versus de-escalation decisions.

Novel Therapeutic Targets and Combination Approaches

The identification of OCT biomarkers associated with suboptimal anti-VEGF response highlights the need for therapeutic diversification. Research priorities should include investigating whether specific morphological phenotypes demonstrate preferential response to combination therapy incorporating corticosteroids, developing targeted treatments for eyes with disorganization of retinal inner layers or other unfavorable features, and evaluating neuroprotective strategies aimed at preserving retinal architecture in eyes at risk of progressive damage.

Emerging therapeutic approaches including gene therapy targeting sustained VEGF suppression, tyrosine kinase inhibitors with broader growth factor inhibition, and integrin antagonists targeting alternative pathways represent promising candidates for eyes demonstrating inadequate response to conventional anti-VEGF monotherapy. Clinical trials evaluating these approaches should incorporate OCT biomarker stratification to identify responsive subpopulations.

The port delivery system enabling sustained ranibizumab release and other extended-duration formulations may particularly benefit patients whose disease characteristics predict requirement for prolonged treatment. Identifying OCT predictors of sustained treatment need could guide patient selection for these emerging technologies.

Health Economics and Implementation Science

The translation of biomarker-guided treatment selection into clinical practice requires robust health economic evaluation and implementation research. Cost-effectiveness analyses should compare the incremental costs of systematic OCT biomarker assessment against potential savings from optimized treatment selection, reduced treatment failures, and avoided vision loss.

Implementation science research should address barriers and facilitators to adopting biomarker-guided approaches across diverse healthcare settings. In resource-rich environments, challenges may include clinician education, workflow integration, and electronic health record modification. In low- and middle-income countries, priorities include developing simplified biomarker assessment protocols feasible without subspecialty expertise, validating point-of-care OCT devices, and establishing telemedicine frameworks for remote expert interpretation.

The World Health Organization's Package of Essential Noncommunicable Disease Interventions and International Council of Ophthalmology guidelines for diabetic eye care should be informed by evidence from implementation research, ensuring that biomarker-guided approaches are adapted appropriately for varying resource contexts.

Pediatric and Young Adult Populations

While diabetic macular edema predominantly affects adults, the rising prevalence of type 2 diabetes in pediatric and young adult populations necessitates research addressing this demographic. The natural history of diabetic macular edema in younger patients, optimal treatment approaches, and applicability of biomarker-based prognostication derived from adult populations all require systematic investigation.

Unique considerations in younger patients include longer anticipated treatment duration, fertility and pregnancy considerations, and psychosocial impacts of chronic eye disease management. International pediatric ophthalmology networks should prioritize collaborative research addressing these knowledge gaps.

Global Collaborative Research Infrastructure

Realizing the research priorities outlined above will require strengthened international collaborative infrastructure. Key recommendations include establishing standardized OCT biomarker definitions and assessment protocols through international consensus processes involving major ophthalmology societies, creating shared data repositories enabling pooled analyses across studies and healthcare systems while protecting patient privacy through federated learning approaches, developing capacity for clinical research in low- and middle-income countries where diabetic macular edema burden is increasing most rapidly, and ensuring diverse population representation in clinical trials to establish generalizability across ethnic groups with varying genetic backgrounds and environmental exposures.

The International Council of Ophthalmology, Asia-Pacific Academy of Ophthalmology, Pan-American Association of Ophthalmology, and other regional bodies should coordinate efforts to advance these priorities through dedicated working groups and funding initiatives.

In summary, the evidence synthesized in this meta-analysis illuminates numerous avenues for future research that could transform diabetic macular edema management from empirical to precision-guided approaches. Prospective validation of biomarker-guided algorithms, artificial intelligence integration, emerging biomarker investigation, pharmacogenomic studies, long-term outcome evaluation, novel therapeutic development, health economic analysis, and global collaborative infrastructure development collectively represent a comprehensive research agenda for the coming decade. International collaboration across academic institutions, healthcare systems, industry partners, and regulatory bodies will be essential for advancing this agenda and ultimately reducing the global burden of diabetes-related vision loss.

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