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Natural History and Predictors of Vision Loss in Eyes with Diabetic Macular Edema and Good Initial Visual Acuity

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Abbreviations:

Diabetic retinopathy (DR), diabetes mellitus (DM), diabetic macular edema (DME), optical coherence tomography (OCT), central subfield thickness (CST), vascular endothelial growth factor (VEGF), best corrected visual acuity (BCVA), spectral-domain (SD), hyperreflective foci (HF), disorganization of retinal inner layers (DRIL), external limiting membrane (ELM) disruption, and ellipsoid zone (EZ), vitreomacular traction (VMT), interdigitation zone (IZ), non-proliferative diabetic retinopathy (NPDR), proliferative diabetic retinopathy (PDR), hemoglobin (Hb), minimal angle of resolution (logMAR), vitreomacular adhesion (VMA), epiretinal membrane (ERM), intraretinal fluid (IRF), inner nuclear layer (INL), outer plexiform layer (OPL), outer nuclear layer (ONL), posterior vitreous detachments (PVD)

ABSTRACT

Purpose: To identify clinical and anatomic factors associated vision loss in eyes with treatment-naïve diabetic macular edema (DME) and good initial visual acuity (VA).

Methods: Retrospective cohort study following long-term history of eyes with untreated center-involving DME and baseline VA ≥ 20/25 seen at the University of California, Davis Eye Center between March 2007-March 2018. We collected characteristics including diabetes type, hemoglobin A1c, presence of visual symptoms, VA, and diabetic retinopathy (DR) severity; and spectral domain-optical coherence tomography (SD-OCT) biomarkers including central subfield thickness (CST), intraretinal cyst size, intraretinal hyperreflective foci, disorganization of retinal inner layers, and outer layer disruptions to determine factors associated with vision loss as defined by DRCR Protocol V as threshold for initiating aflibercept therapy.

Results: 56 eyes (48 patients) with untreated DME and mean baseline VA of logMAR 0.05 ± 0.05 (Snellen 20/22) was followed for an average of 5.1 ± 3.3 years, with a median time to vision loss of 465 days (15 months). Older age (hazard ratio (HR) 1.04/year, P = 0.0195), and eyes with severe NPDR (HR 3.0, P = 0.0353) or proliferative DR (HR 7.7, P = 0.0008) had a higher risk of a vision loss event. None of the SD-OCT biomarkers were associated with vision loss except CST (HR 0.98, P = 0.0470) and cyst diameter (HR 1.0, P = 0.0094).

Conclusions: In eyes with DME and good initial vision, those with older age and worse DR severity should be monitored closely for prompt treatment initiation when vision loss occurs.

Keywords: diabetic macular edema, diabetic retinopathy, optical coherence tomography.

Summary statement:

In eyes with untreated DME and good baseline BCVA, older age and worse DR severity are associated with greater risk of vision loss. Patients with these risk factors should be monitored closely for prompt treatment when vision loss occurs.

INTRODUCTION

Ocular complications of diabetes mellitus are the leading cause of blindness in working-age adults in the U.S.,[1] and diabetic macular edema (DME) is one of the main contributors of central vision loss among diabetic patients.[2, 3] While therapeutic options for DME include laser photocoagulation and intravitreal corticosteroids, intravitreal anti-vascular endothelial growth factor (VEGF) injections have emerged as first-line treatment, with multiple randomized prospective studies supporting their use for the management of DME.[4-10]

While earlier trials included only DME patients with a best corrected visual acuity (BCVA) of 20/32 to 20/40 Snellen equivalent or worse, the DRCR Retinal Network Protocol V study focused on those with good initial BCVA (20/25 or better). The study randomized 702 participants with treatment-naïve center-involving DME and good BCVA into 3 groups: 2.0 mg aflibercept, focal/grid laser photocoagulation, or observation, with the option to receive aflibercept injections in the laser and observation group if visual acuity decreased from baseline by at least 10 letters (2 lines) at any visit or by 5 to 9 letters (1 line) at 2 consecutive visits. After 2 years, the Protocol V study found no significant difference in vision loss between the 3 groups, suggesting that observation alone may be a reasonable strategy for DME with good visual acuity.[11, 12]

Yet, clinical trial participants do not reflect diabetic patients in real-world settings, who follow-up less regularly, receive fewer injections, and experience inferior visual and anatomic outcomes.[13] In a retrospective cohort analysis of 122 eyes with DME and good initial visual acuity in real-world settings, VA declined over a median follow-up of 3 years, with better VA at the time of initial treatment associated with improved long-term vision.[14] Combined with the results of Protocol V, these findings suggest that while initial observation of DME with good BCVA may be appropriate, delay in treatment could be detrimental to long-term outcomes and close observation is necessary to maintain good vision. Therefore, determining the clinical and anatomic factors that can predict the risk of vision loss could help eye care providers to determine the appropriate frequency of monitoring these patients.

In a post-hoc analysis of the DRCR Protocol V study, eyes with greater central subfield thickness (CST), worse diabetic retinopathy (DR) severity level, or a fellow eye receiving DME treatment were associated with a higher likelihood of requiring aflibercept for VA loss.[12, 15-18] In this study, we retrospectively identified a cohort of eyes with untreated center-involving DME and good visual acuity (VA $\geq$ 20/25) in real-world settings resembling those enrolled in DRCR Protocol V, and analyzed imaging biomarkers on spectral domain-optical coherence tomography (SD-OCT) and other clinical characteristics which may be associated with vision loss as defined by the threshold for initiating aflibercept therapy in Protocol V.

METHODS

Patient Selection

We reviewed 2262 medical records from the University of California, Davis Health System between March 8, 2007 to March 8, 2018 for patients diagnosed with diabetic

retinopathy (ICD9 code 250.XX or ICD10 codes E11.311, E11.321X, E11.331X, E11.241X, E11.251X, and E11.37XX). To identify eyes resembling those enrolled in the DRCR Retina Network Protocol V study, we included only eyes that met the following criteria: 1) presence of center-involving DME defined as presence of intraretinal fluid and CST ≥250 □m time-domain OCT equivalent,[11] 2) VA of ≥20/25 at diagnosis, 3) no prior treatment for DME, 4) at least 1 year of follow-up with SD-OCT imaging and 5) no treatment in study eye including intraocular injections or lasers during the study period.[11] Eyes were excluded if they had macular edema due to other causes beside DME including 1) vitreomacular interface abnormalities, 2) other ocular conditions that could affect visual acuity such as vein occlusion, uveitis, neovascular or end-stage glaucoma, or visually-significant cataracts, or 3) history of ocular surgery except uncomplicated cataract extraction.[1] Our study was approved by the Institutional Review Board at the University of California, Davis and conducted in accordance with the tenets of the Declaration of Helsinki.

Demographic & Clinical Characteristics

We recorded baseline demographic and clinical characteristics, including age, sex, type of diabetes (type 1 or type 2), presence of visual symptoms, and diabetic retinopathy severity. Severity of diabetic retinopathy was classified as mild non-proliferative diabetic retinopathy (NPDR), moderate NPDR, severe NPDR, non-high-risk or inactive PDR, or high-risk PDR based on physician documentation and billing codes when physician documentation was unavailable. At baseline and at yearly follow-up visits, defined as the nearest visit within 90 days of 12-month intervals from the initial visit, we also collected the best-measured Snellen VA (converted to logarithm of the minimal angle of resolution (logMAR) scale for statistical purposes), hemoglobin A1c (HbA1c) levels, lens status (phakic or pseudophakic), as well as cataract type

(nuclear, cortical, or posterior subcapsular) and grade (1+, 2+, or 3+) based on physician exam documentation (see details below). The documented best-measured visual acuity include the use of pinhole testing and manifest refraction, but due to the retrospective nature of the study, did not follow a standard protocol for best-corrected VA. We also reviewed all documented clinic visits to determine the time to vision loss, defined as a decrease in VA from baseline by ≥2 lines on a Snellen eye chart at any visit or by 1-2 lines at two consecutive visits, with no corresponding worsening in cataract grade, similar to the threshold defined by the DRCR Protocol V for initiating aflibercept treatment in eyes in the observation arm.[11] As this is a retrospective cohort study, the patients did not adhere to regular follow-up intervals as those in the Protocol V clinical trial. Also, while the documented best-measured Snellen VA included pinhole correction and manifest refraction commonly used in real-world settings, the VA data were not captured following standardized protocols using Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity charts. Eyes that underwent any DME treatment including intraocular injections or laser photocoagulation prior to this vision loss event were excluded from the analysis.

Image Grading

SD-OCT images were captured from the Cirrus HD-OCT (Carl Zeiss Meditec) or Spectralis HRA + OCT instrument (Heidelberg Engineering). CST was automatically determined using the manufacturer's software as the average retinal thickness from the central 1 mm-diameter circle centered on the fovea based on the ETDRS grid,[19] and converted to time-domain OCT equivalent to simulate DRCR Protocol V reporting.[20] Grid centration and accuracy of retina layer segmentation were verified and adjusted where necessary. Additionally, two trained image graders masked to the patients' identity analyzed high-resolution 5-horizontal-line (Cirrus) or 7 horizontal-line raster scans (Spectralis) for SD-OCT biomarkers including vitreomacular

interface abnormalities, intraretinal cyst size, intraretinal hyperreflective foci (HF), disorganization of the retinal inner layers (DRIL), and disruptions in outer retinal layers including the external limiting membrane (ELM), ellipsoid zone (EZ), and interdigitation zone (IZ) within the central macula as defined below (Figure 1).[21]

Vitreomacular interface abnormalities include vitreomacular adhesion (VMA), vitreomacular traction (VMT), and epiretinal membrane (ERM). VMA was defined by attachment of the vitreous cortex within 3 mm of the foveal center with an elevation of the perifoveal vitreous cortex from the retinal surface, while VMT include anatomic changes to the foveal contour, intraretinal pseudocyst formation, and/or elevation of the fovea from the retinal pigment epithelium, as classified by the International Vitreomacular Traction Study Group.[22] The presence, location, and extent of macular fluid was assessed within the central 1-mm wide segment and recorded as intraretinal fluid (IRF) or subretinal fluid (SRF). IRF eyes were classified by fluid location in: 1) the inner nuclear layer (INL) alone, 2) the outer plexiform layer (OPL) and outer nuclear layer (ONL), or 3) both INL and OPL + ONL. The size of the largest intraretinal cyst across all horizontal raster scans was determined by measuring the widest horizontal diameter (µm), and SRF thickness was taken as the linear distance perpendicular to the retinal pigment epithelium (RPE).[23] Eyes were also analyzed for extent of intraretinal HF summed across all horizontal raster scans. Intraretinal HR were defined as discrete, dot-shaped lesions with similar or higher reflectivity than the RPE band on SD-OCT within the central 1-mm wide segment that are at least 20 µm in size to avoid inclusion of noise.[24] DRIL and disruptions in ELM, EZ, and IZ were quantified by measuring the percentage of disruption over the central 1-mm wide segment averaged over the central scans. DRIL was defined by the presence of a region in the inner retinal layers where the boundaries between the ganglion cell

and inner plexiform layer complex and/or INL and OPL could not be distinguished, as previously reported.[23] ELM, EZ, and IZ disruption were defined by discontinuity in the respective bands.[23] Areas obscured by overlying pathologic features were not graded for disruption. All measurements of scale variables were averaged between the two OCT graders, and any discrepancies in categorical variables were adjudicated by a senior retinal specialist grader (G.Y.).

Statistical Analysis

We used a model selection procedure which consisted of univariate analyses to identify potential risk factors for inclusion in a multivariable model. Those variables found to be significant at $P < 0.15$ level were included in the multivariable model. P-values less than 0.05 were considered statistically significant in the multivariable model. Proportional hazard models were fit, accounting for clustering due to some patients contributing both eyes to the study, using the SAS® procedure SURVEYPHREG. We used the proportionality test option in PROC SURVEYPHREG to test the proportional hazards assumption for categorical variables, DR severity. For continuous variables we used the 'assess' option which implements the empirical score process developed by Lin et al that uses a transform of the martingale residuals.[25] Kaplan Meier plots are for visualization only where eyes from the same patient are treated as independent variables. Intergrader reproducibility was measured using intraclass correlation coefficients (ICCs). SAS® software for Windows® version 9.4 was used in all analyses (SAS® Institute Inc., Cary, NC).

RESULTS

Baseline Subject Demographics

We found 107 eyes had DME with good baseline VA, and excluded 50 eyes due to treatments administered prior to vision loss event. Among the 56 eyes from 48 patients (mean age 63.1 ± 11.2 years) with DME and good VA included in our study, 42 eyes (75.0%) underwent visual acuity loss over a mean follow-up period of 4.9 ± 3.3 years (range 0.7 to 11.7 years). There was a predominance of male patients (70.8%), and a majority of patients had type 2 diabetes (89.6%). The mean baseline HbA1c was 8.6 ± 2.0, which remained relatively stable (range 7.4 to 9.2) over the following 4 years. There were similar proportions of right and left eyes. Visual symptoms were only present in 14.6% of eyes, with mean VA of LogMAR 0.05 ± 0.05 (Snellen equivalent 20/22) at baseline. A majority of eyes had mild NPDR (62.5%), followed by moderate NPDR (14.3%), severe NPDR (12.5%), and non-high risk or inactive PDR (10.7%) at baseline, while none exhibited high-risk PDR (Table 1). These clinical characteristics resemble those of patients enrolled in the observation arm of the DRCR Protocol V study (Table 1).

Baseline SD-OCT Biomarkers

Mean baseline time-domain equivalent CST was 291.3 ± 38.8 □m, which is lower than the mean baseline value reported in Protocol V. More than 50% of eyes demonstrated VMA, while no eyes had VMT and 1% had an ERM at baseline. A majority of eyes demonstrated IRF with most located in the OPL/ONL (45.9%) or INL and OPL/ONL (43.2%), while few eyes had SRF (10.8%). The mean diameter of the largest cyst was 278.7 ± 185.0 μm. Most eyes had inner retinal HF (86.0%), with a mean sum of HF of 10.5 ± 12.2 measured per eye. Few eyes showed

significant DRIL or disruption of outer retinal layers. The mean baseline DRIL was 23.2 ± 31.6%, while mean disruption of ELM, EZ, and IZ were 1.0 ± 4.6%, 1.0 ± 5.7%, and 3.5 ± 10.8%, respectively (Table 1). Intergrader reliability was good with ICCs of 0.993 for largest cyst size, 0.983 for sum of HF, 0.969 for DRIL, 0.997 for EZ, and 0.942 for IZ.

Visual Outcomes & Predictors of Vision Loss

Mean Snellen VA declined over the first 4 years of follow-up, from LogMAR 0.05 ± 0.05 (Snellen 20/22) at baseline to LogMAR 0.125 ± 0.194 (Snellen 20/27) at 1 year, LogMAR 0.209 ± 0.165 (Snellen 20/32) at 2 years, LogMAR 0.234 ± 0.201 (Snellen 20/34) at 3 years, and LogMAR 0.260 ± 0.207 (Snellen 20/36) at 4 years (Figure 2A). The median time to vision loss, defined as a decrease in VA of at least 2 Snellen lines from baseline at any visit or 1 line from baseline at 2 consecutive visits, was 442 days (14.5 months) among the 42 eyes that experienced vision loss (Figure 2B). On univariate analysis, older age (P = 0.075) and higher HbA1c (P = 0.031) showed possible associations with vision loss. Eyes with severe NPDR (P = 0.020) and non-high risk or inactive PDR (P = 0.025) also showed a higher risk than mild or moderate NPDR (Table 2). Of the SD-OCT biomarkers, higher baseline CST (P = <0.0001) and larger cyst size (P = 0.0001) were associated with vision loss (Table 2). EZ and IZ could not be analyzed due to the large proportion of eyes with no visible disruption. Multivariate analysis identified that older age (P = 0.020), severe NPDR (P = 0.035), non-high risk PDR (P < 0.001), largest cyst size (P = 0.009), and baseline CST (P = 0.047) were independently associated with vision loss (Table 2). Eyes with severe NPDR and non-high risk or inactive PDR were approximately 3.0 and 7.7-times more likely, respectively, to lose vision with median time to vision loss of 116 days for non-high risk or inactive PDR, 343 days for severe NPDR, 615 days for moderate

NPDR and 520 days for mild NPDR (Figure 2B). There was no evidence of violation of the proportional hazards assumptions.

DISCUSSION

The DRCR Retinal Network Protocol V study demonstrated that patients with DME and good initial visual acuity (Snellen ≤20/25) can be safely observed with no adverse consequences,[11, 12] but patients in real-world settings may not be monitored as closely and can suffer worse outcomes if not treated promptly when vision loss occurs. While some real-world studies suggest that anti-VEGF therapy for DME with good VA do not improve visual outcomes after 1.7 years of follow-up, delayed treatment in these types of patients after a median follow-up of 3 years were linked to poor visual outcomes, with worse VA at the time of treatment initiation associated with poorer long-term visual outcomes.[14] These studies highlight the importance of close monitoring, and the value of identifying factors that may predict the risk of vision loss when observing patients with DME and good initial VA.

In this study, we followed the natural history of 48 patients with treatment-naïve DME and good baseline VA (Snellen equivalent of 20/25 or better) similar to those from DRCR Protocol V's observation arm, and analyzed various baseline clinical and anatomic characteristics that may predict greater risk for a vision loss event, defined as VA loss of ≥2 Snellen lines at any visit or 1-2 lines at two consecutive visits, based on the threshold for initiating aflibercept therapy in Protocol V. We found that the clinical factors most strongly associated with vision loss were age and DR severity. Eyes with severe NPDR and non-high risk or inactive PDR were 3.0 and 7.7-times more likely, respectively, to suffer vision loss requiring

anti-VEGF therapy based on Protocol V recommendations. Our results are consistent with the natural history findings of 350 patients with DME in the MEAD study, where older age and worse baseline DR severity scores were associated with worse BCVA outcomes.[27] We also confirmed the findings from a post hoc analysis of Protocol V, where observed eyes with worse DR severity were also more likely to require anti-VEGF treatment during the 2 year study.[16] While some studies suggest that HbA1c could be used to stratify the monitoring frequency of untreated DME, with eyes with HbA1c ≥8.5% being 5.7 times more likely to develop CST thickening,[28] neither our study or Protocol V found HbA1c to be a useful predictor of vision loss.[16]

Among a large selection of SD-OCT biomarkers we evaluated, including CST, intraretinal fluid, intraretinal HF, DRIL,[23] and outer retinal disruptions, only CST and largest cyst diameter predicted vision loss on univariate analyses, and their relationship were ambiguous (HR = 0.98 = 1.00) in our multivariate model. In the DRCR Protocol V study, eyes with higher baseline CST were more likely to require treatment, and our data suggests that the main driving structural feature may include cyst diameter and baseline CST, although further investigations are needed to clarify this relationship. Because most of the eyes with good VA in our cohort demonstrated minimal DRIL or ELM/EZ/IZ disruptions, which are respective markers of inner and outer neuronal dysfunction, we hypothesize that our cohort study was also not sensitive enough to identify the predictive effects of these biomarkers. Thus, future studies that encompass more severe DME anatomy or longitudinal analysis of OCT biomarkers at later time points may identify additional imaging predictors of visual outcomes.

There are several strengths to this study. First, we performed a comprehensive analysis of major SD-OCT biomarkers using standardized definitions and protocols from reported

literature,[23] with intergrader reproducibility exceeding >0.9 for most measures. We also analyzed all biomarkers as continuous scale variables, compared with some studies where arbitrary binarization of continuous variables may result in multiple hypothesis testing, inaccurate assumption of homogeneous risk across categories, and difficulty in cross-study comparisons.[29] Our study patients exhibited slightly worse HbA1c than the patients enrolled in Protocol V, and the long-term cohort study design reflects follow-up patterns in real-world practice settings.

Weaknesses of our study include its retrospective nature, with variable follow-up frequencies between different individuals and a potential selection bias for eyes with milder DME, since those that received treatment prior to vision loss events were excluded. Because VA change was an important determinant of vision loss as defined in our analysis, this study is also limited by the use of best-measured Snellen VA rather than best-corrected ETDRS VA measurements. However, most clinicians outside of clinical trial settings rely on Snellen VA to decide when to initiate treatments, so our study design may better resemble real-world scenarios. Similarly, we employed physician documentation to determine the severity of retinopathy, which may be considered a weakness, as well as a reflection of real-world settings. Addition of other imaging modalities such as fluorescein or OCT angiography to determine the severity of macular ischemia, for example, would also strengthen our analysis. While there were no significant differences between mean follow-up time amoung the four diabetic retinopathy serverity subgroups, this may be a potential confounder of our study.

In summary, we found that older age and worse DR severity were associated with risk of vision loss in eyes with DME and good initial VA. Outside of the context of strict adherence to the Protocol V regimen, these features are important factors when deciding on the optimal frequency of follow up visits.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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FIGURE LEGENDS

Figure 1: SD-OCT features in eyes with diabetic macular edema and good visual acuity.

SD-OCT horizontal line B-scans through the fovea of a patient with DME (A-B) , demonstrating the presence of intraretinal hyperreflective foci (HF) in the outer nuclear layer (A, arrowheads) and intraretinal fluid (IRF) measured using the horizontal diameter of the largest cyst (A, horizontal double-arrow). Central 1mm region delineated by dashed lines in A and a magnified view (B) shows boundaries for measuring disorganization of the retinal inner layers (DRIL) defined as loss of distinction between the ganglion cell and inner plexiform layer complex (GCL-IPL), inner nuclear layer (INL), and outer plexiform layer (OPL) (B, solid line) and % disruption of the external limiting membrane (ELM), ellipsoid zone (EZ), and interdigitation zone (IZ) (B, dashed lines). Scale bar 500μm.

Figure 2: Visual outcomes of eyes with DME and good initial visual acuity.

(A) Line graph of the mean BCVA of all eyes with follow-up at 1, 2, 3, and 4 years. **(B)** Kaplan-Meier curve of the probability of vision loss vs. time to VA loss (days) based on DR severity (mild NPDR, moderate NPDR, severe NPDR, and low-risk PDR). *Vision loss defined as a decrease in VA from baseline by ≥2 lines on a Snellen eye chart at any visit or by 1-2 lines at two consecutive visits. Abbreviations: VA, visual acuity; DR, diabetic retinopathy; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

TABLE 1- Clinical and anatomic characteristics of real-world patients and DRCR Protocol V study subjects with diabetic macular edema with good visual acuity

Patient Characteristics	**Current Study All Patients (n = 48)**	**DRCR Protocol V[9] Observation Arm (n=236)**
Mean age, years (IQR)	63.1 (55.0 - 71.0)	60.0 (53.0 - 67.0)
Male sex, no. (%)	34 (70.8)	149 (63.0)
Diabetes type II, no. (%)	43 (89.6)	210 (89.0)
Mean A1c % (IQR)	8.6 (7.4 – 9.2)	7.6 (6.8 - 8.7)
Symptoms present, no. (%)	7 (14.6)	-
Ocular & OCT Characteristics	**All Eyes (n=56)**	**Observation Arm Eyes (n=208)**
Left eye, no. (%)	30 (53.6)	-
Mean baseline VA, logMAR (SD)	0.05 (0.05)	0.1 (0.2)
DR severity, no. (%)		
Mild NPDR (levels 10-20*)	35 (62.5)	7 (3.4)
Moderate NPDR (levels 35, 43*)	8 (14.3)	142 (62.0)
Severe NDPR (levels 47, 53*)	7 (12.5)	62 (27.0)
Inactive or non-high risk PDR (levels 60-65*)	6 (10.7)	7 (3.0)
High risk PDR (levels 71, 75*)	0 (0.0)	9 (4.0)
Mean baseline CST, μm (SD)	291.3 (38.8)	314.0 (64.0)
Mean largest cyst size, μm (SD)	278.7 (185.0)	-
Mean Sum HF, no. (SD)	10.5 (12.2)	-
Mean DRIL, % (SD)	23.2 (31.6)	-
Mean ELM disruption, % (SD)	1.0 (4.6)	-
Mean EZ disruption, % (SD)	1.0 (5.7)	-
Mean IZ disruption, % (SD)	3.5 (10.8)	-

* Equivalent diabetic retinopathy severity scores based on DRCR Retina Protocol V study
Abbreviations: IQR=interquartile range, DR = Diabetic retinopathy, SD = standard deviation, IQR = inter-quartile range, CST = central subfield thickness, OCT = optical coherence tomography, VA = visual acuity, HF = hyper-reflective foci, DRIL = disorganization of retinal inner layers, ELM = external limiting membrane, EZ = ellipsoid zone, IZ = interdigitation zone

TABLE 2- Clinical and OCT characteristics associated with VA loss

Univariate Analysis				
Clinical or Ocular Characteristic	**Category or Increment**	**Hazard Ratio**	**95% Confidence Interval**	**P-value***
Age	1 year	1.03	1.00, 1.05	0.075*
Sex	Male vs. Female	37.20	0.12, $1.9x10^4$	0.214
DM Type	Type 1 vs. 2	0.39	0.01, 17.50	0.622
Baseline A1c	1%	0.49	0.26, 0.94	0.031*
Laterality	Left vs. Right	1.88	0.10, 35.29	0.667
Symptoms	Present vs. Absent	5.36	0.11, $2.58x10^2$	0.388
Baseline VA	1 logMAR	0.16	0.01, 4.00	0.255
DR severity	1 level			
Mild NPDR		Reference	-	-
Moderate NPDR		0.88	0.26, 2.92	0.825
Severe NPDR		2.46	1.16, 5.22	0.020*
Non-high risk PDR		3.73	1.19, 11.67	0.025*
Baseline CST	1 μm	1.07	1.04, 1.10	<0.0001*
Largest cyst size	1 μm	1.01	1.01, 1.02	0.0001*
Sum of HF	1 HF	0.97	0.840, 1.122	0.680
% DRIL	1%	9.22	0.01, $8.1x10^3$	0.512
% ELM	1%	$9.57x10^2$	0.00, $7.22x10^{15}$	0.642
Multivariate Analysis				
Age	1 year	1.04	1.01, 1.08	0.020*
DR Severity	1 level			
Mild NPDR		Reference	-	-
Moderate NPDR		1.74	0.54, 5.60	0.350
Severe NPDR		3.01	1.08, 8.40	0.035*
Non-high risk PDR		7.72	2.33, 2.63	0.0008*
Baseline A1c	1%	0.97	0.80, 1.18	0.750
Baseline CST	1 μm	0.98	0.96, 1.00	0.047*
Largest cyst size	1 μm	1.00	1.00, 1.01	0.009*

*P-values <0.15 on univariate analysis were included in the multivariate model, where P-value <0.05 are statistically-significant.

Abbreviations: DM = Diabetes mellitus, DR = Diabetic retinopathy, SD = standard deviation, CST = central subfield thickness, VA = visual acuity, HF = hyper-reflective foci, DRIL = disorganization of retinal inner layers, ELM = external limiting membrane, EZ = ellipsoid zone, IZ = interdigitation zone

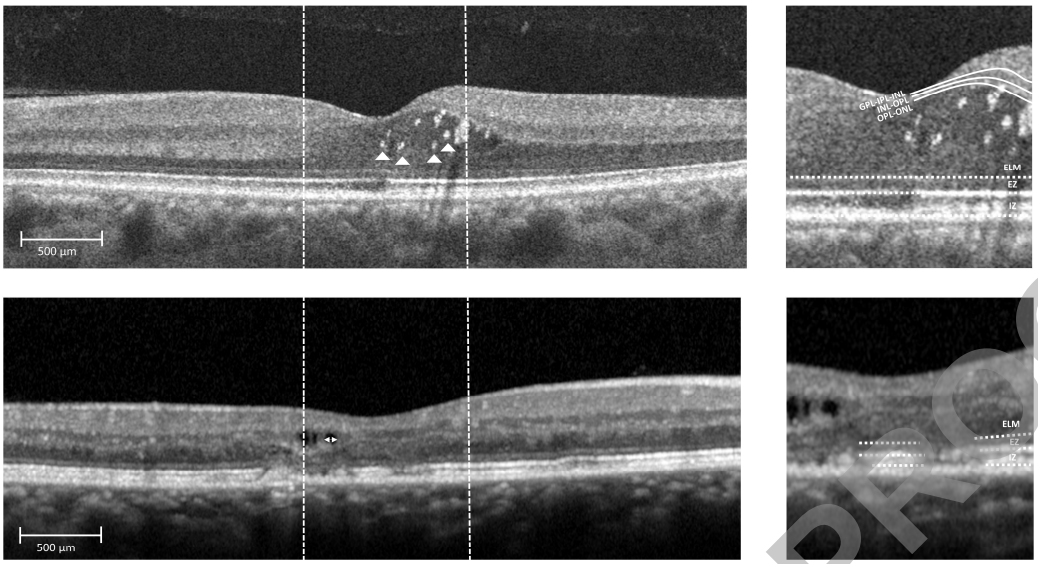

Figure 2 - Overall visual outcomes for patients with DME.