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Macular Edema After Cataract Surgery In Eyes Without Pre-operative Central-involved Diabetic Macular Edema

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Abstract

Objective—To estimate the incidence of central-involved macular edema (ME)16 weeks following cataract surgery in eyes with diabetic retinopathy (DR) without definite central-involved diabetic macular edema (DME) preoperatively.

Methods—In a multicenter, prospective, observational study, participants (N = 293) with DR without definite OCT central subfield (CSF) thickening underwent cataract surgery. The primary outcome was development of central-involved ME defined as; (1) OCT CSF thickness ≥ 250μm (time domain) or ≥ 310μm (spectral domain) with ≥1 step increase in logOCT CSF thickness pre-operative to the 16-week visit; (2) ≥2-step increase in logOCT CSF pre-operative to 16-week visit; or (3) non-topical treatment for ME received before the 16-week visit with either of the OCT criteria met at the time of treatment.

Results—Median participant age was 64 years with median visual acuity letter score of 69 (Snellen equivalent 20/40). Forty-four percent of eyes had history of prior treatment for DME. Sixteen weeks postoperatively, central-involved ME was noted in 0% (95%CI: 0-20%) of 17 eyes with no pre-operative DME. Of eyes with non-central involved DME, 10% (95%CI: 5-18%) of 97 eyes without central involved DME and 12% (95%CI: 7-19%) of 147 eyes with possible central involved DME at baseline progressed to central-involved ME. History of DME treatment was significantly associated with central-involved ME development (P<0.001).

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*A complete list of the Diabetic Retinopathy Clinical Research Network is in Appendix 1, and online at www.drcr.net

Conclusion—In eyes with DR without concurrent central-involved DME, presence of non-central DME immediately prior to cataract surgery, or history of DME treatment, may increase risk of developing central-involved ME 16 weeks after cataract extraction.

Introduction

Diabetes mellitus increases the probability of developing cataract and may increase the risk of reduced visual outcomes after cataract surgery. [1, 2] As approximately 250,000 people with diabetes in the United States undergo cataract surgery each year improvements in understanding the prognosis and management of these cases could confer a substantial benefit to many people. [3]

Past studies on patients with diabetes undergoing cataract removal using intracapsular and extracapsular cataract extraction techniques suggest that cataract surgery is a risk factor for incidence of macular edema (ME) or worsening of diabetic retinopathy.[4-6] Some reports suggest that ME, after cataract surgery and in people with diabetes, may occur predominantly in people with concurrent pre-existing diabetic macular edema (DME) involving the center of the macula. However other reports indicate that pre-existing DME is not needed for ME to occur post-operatively.[7] However, these studies were completed prior to the availability of optical coherence tomography (OCT) technology. OCT can provide both qualitative and quantitative data to explore the relationship of ME and cataract surgery in patients with diabetic retinopathy.

The Diabetic Retinopathy Clinical Research Network (DRCR.net) conducted an observational study to evaluate the incidence of central-involved ME, as defined by OCT, in eyes without definite central-involved DME immediately prior to cataract surgery. In addition, factors associated with development of central-involved ME are explored.

Methods

This prospective, non-comparative, multicenter, observational study was conducted by the DRCR.net at 45 clinical sites throughout the United States. The protocol and Health Insurance Portability and Accountability Act-compliant informed consent forms were approved by the institutional review board for each participating site. Each participant gave written informed consent to participate in the study. The study protocol (named “An Observational Study in Individuals with Diabetic Retinopathy without Center-Involved DME Undergoing Cataract Surgery”) is available on the DRCR.net website (www.drcr.net) and summarized below.

Study Population

Eligible study participants were at least 18 years of age with type 1 or type 2 diabetes and were receiving cataract surgery in an eye with diabetic retinopathy but without definite central-involved DME. Eyes were eligible provided the following criteria were met: 1) presence of cataract for which cataract surgery was scheduled within 28 days of study enrollment; 2) visual acuity of light perception or better; 3) OCT central subfield thickness <250 μm on time domain (TD) OCT (Stratus, Carl Zeiss Meditec, Dublin, CA) or <310 μm

on a spectral domain (SD) OCT (either Cirrus, Carl Zeiss Meditec, or Spectralis, Heidelberg, Carlsbad, CA, or Optovue RTVue, Optovue, Fremont, CA); 4) presence of microaneurysms or at least mild non-proliferative diabetic retinopathy (NPDR) (Early Treatment Diabetic Retinopathy Study [ETDRS] level 20 or higher[8]) on clinical examination. Eyes with major ocular surgery in the prior four months and eyes with an ocular condition (other than cataract or DME) that might affect visual acuity during the course of the study were excluded. Only one eye from each study participant was enrolled.

Study Design

Study participants were enrolled by investigators at participating DRCR.net clinical sites certified by the Coordinating Center in this protocol. Participants were either identified by a participating retina specialist and referred to the cataract surgeon or by a cataract surgeon and referred to the retina specialist for enrollment. As the actual cataract surgery was not part of the experimental design, the cataract surgeons were not considered investigators for this protocol. The cataract surgery, including pre-operative and post-operative assessments and management, was conducted by and according to the cataract surgeon's usual routine. With study participant permission, the DRCR.net clinical center obtained the surgical procedure report and post-operative records from the cataract surgeon for data collection.

Protocol study-related visits were specified as pre-operative baseline visit (performed within 28 days preceding surgery), 4-week, and 16-week post-cataract surgery. These visits were conducted at DRCR.net clinical sites by certified investigators and personnel. At all visits procedures included protocol refraction, best-corrected Electronic-ETDRS visual acuity Test (E-ETDRS),[9] fundus examination, and OCT of the study eye following a standardized protocol. When the metrics describing retinal thickness generated by OCT software were suspected to be erroneous by the clinical site, or when the ratio of center point thickness standard deviation to the mean center point thickness from TD OCT Stratus scans was >10.5%, scans were forwarded to a central OCT reading center (Duke Reading Center, Duke University, Durham, NC) for grading; otherwise, the automated OCT thickness measurements were used for analyses.

DME status at baseline was categorized into 4 categories according to machine, and gender specific retinal thickness values in the central and non-central subfields from the OCT map (Table 1).

- No DME: defined as thickness in each subfield less than the mean thickness from a normal cohort.
- "Possible" DME in the central subfield: defined as thickness between the mean and the mean + 2 standard deviations from a normal cohort.
- "Possible" non-central DME: defined as thickness of at least one non-central subfield between the mean and the mean + 2 standard deviations from a normal cohort.
- "Definite" non-central DME: defined as thickness of at least one non-central subfield more than the mean + 2 standard deviations from a normal cohort.

Any intervention performed on the study eye during the 16-week course of the study was at the discretion of the cataract surgeon or the DRCR.net investigator. When and if treatment for ME, other than topical medications, was given by the investigator for the first time post-operatively, best-corrected E-ETDRS visual acuity, OCT and fluorescein angiography were performed before administering the treatment. In addition, fluorescein angiography was required at the 4-week visit and the 16-week visit if OCT CSF thickness was ≥250 μm on TD OCT (≥ 310 on SD OCT) and sent to the Fundus Photograph Reading Center of the University of Wisconsin (Madison, WI) for assessment. Classification of ME patterns used fluorescein angiography and not OCT because, to our knowledge, classification of ME patterns as diabetic macular edema vs. post-surgical ("Irvine-Gass") cystoid macular edema on Stratus OCT is not well documented. Therefore, in order to have consistency across all eyes, fluorescein angiograms were used for ME classification. In addition, the central fundus photograph reading center has a validated method for assessing ME patterns on fluorescein angiography, but at the time the protocol was developed, did not have such a validated mechanism for this assessment on OCT. Refraction, visual acuity, OCT, and fluorescein angiography protocols can be found at www.DRCR.net.

The primary outcome, incidence of central-involved ME, was predefined as any of the following events: (1) OCT CSF thickness of ≥ 250 μm (TD) or ≥ 310 μm (SD) with at least 1 unit increase in logOCT from baseline to 16 weeks, (2) OCT CSF thickness increase at least 2 logOCT units from baseline to 16 weeks irrespective of absolute thickness level at 16 weeks, or (3) any non-topical treatment for ME was performed at any time after cataract surgery during the study, provided that either one of the previous two OCT criteria were met prior to starting treatment. One logOCT increase is approximately equivalent to a 26% increase in thickness and a 2 logOCT increase is approximately equivalent to a 36% increase in thickness.[10] It was shown that a 1-step log scale change exceeds the measurement error for all degrees of retinal thickness in current instruments; subsequently, a 1-step logOCT change likely represents a real change beyond variability limits. The development (or progression) of non-central involved ME was defined based on changes in either the inner subfields or the outer subfields on the OCT 6 mm-diameter map. (Table 1)

Statistical Methods

Primary analysis was conducted within pre-defined DME subgroups based on pre-operative OCT retinal thickness as defined in Table 1 and based on history of DME treatment.

Point estimate for binary outcomes, and corresponding exact 95% confidence interval were computed. Association of baseline factors with the primary outcome was evaluated using Fisher's exact test; continuous variables were categorized if necessary. All reported *P* values were two-sided. SAS software, version 9.2 (SAS, Cary, NC), was used for all analyses.

Results

Between October 2009 and December 2010, 45 clinical sites enrolled 329 study participants scheduled for prompt cataract surgery. Twelve study participants had their surgery canceled and subsequently were not considered part of the enrolled cohort. In addition, 24 eyes were considered ineligible due to non-gradable baseline OCT scans (N = 7), baseline OCT CSF

thickness >250 on TD or >310 on SD machines (N = 10) after manual adjustment by the Duke Reading Center, or surgery conducted more than 28 days from baseline (N = 7). The mean age of the remaining 293 participants was 65 (±9 standard deviation) years. Women comprised 58% of the cohort, and the majority of participants identified themselves as white (65%). One hundred twenty eight (44%) study eyes had prior DME treatment, among which only 29 (23%) had received intravitreal injection of steroid within four months or anti-vascular endothelial growth factor within two months of the cataract surgery. Of 293 eligible eyes at baseline, 18 (6%) did not have complete OCT data (non-gradable or missing) for non-CSF thickness. Subsequently, 275 eyes (94%) were classified into four DME categories based on status of central and non-central OCT thickness level: a) no central-involved DME and no non-central involved DME (i.e. no DME) (N = 17 [6%]); b) no central-involved DME and definite or uncertain non-central involved DME (N= 100 [36%]); c) possible central-involved DME and no non-central involved DME (N = 5 [2%]); d) Possible central-involved DME and definite or possible non-central involved DME (N=153 [56%]). Due to small group size five eyes originally in the “possible central-involved DME and no non-central involved DME” were reassigned to other categories, based on morphologic features after the protocol chair individually examined their baseline OCT scans; 1, 1, and 3 eyes were re-assigned to no DME, definite or possible non-central involve DME and no central-involved DME, and definite or possible non-central involved DME and possible central-involved DME groups respectively. Twenty-four percent of study eyes had a history of panretinal photocoagulation (PRP) of which 80% had the PRP at least one year before enrollment. The mean OCT CSF from TD (N = 281) and SD (N = 12) machines were 201 (±26 standard deviation) and 244 (±32 standard deviation) μm respectively. Additional baseline study participant and ocular characteristics are reported in Table 2. Of the 293 participants eligible for analyses, 14 study participants (5%) did not complete the 16-week visit, including 1 who died prior to the 16-week visit, 7 who withdrew from the study, and 6 who were lost to follow-up.

Cataract Surgery

In 98% of study eyes, cataract extraction was performed using phacoemulsification, and 99% had posterior chamber intraocular lens implantation. One eye developed endophthalmitis (<1%). At time of cataract surgery, two eyes underwent anterior vitrectomy, one eye developed mild to moderate positive vitreous pressure, one eye had a small corneal abrasion, and one eye developed floppy iris syndrome, possibly due to concomitant use of tamsulosin (Flomax®). There were no cases of choroidal hemorrhage, ruptured capsule, dropped nucleus or wound leak. During follow up, anterior and segment inflammation were noted in 13 (5%) and 3 (1%) eyes, respectively. Increased intraocular pressure was reported in 4 eyes (2%) and posterior capsular opacification in 3 (1%) eyes. Other reported complications included phacoanalphylactic glaucoma (1), iris prolapse (1), keratitis (1) and wrinkling of posterior capsule (1). No study eyes were excluded from the analysis due to any of the complications reported above.

Macular Edema

Of 293 eligible eyes, the primary outcome was calculated for 261 eyes (89%) that had complete OCT data both at baseline and 16-week visits. None of the eyes without DME at

baseline (N = 17) developed central-involved ME (upper limit of 95% CI: 20%). Of the remaining eyes where edema in the inner and outer subfields could not be ruled out (i.e. any subfield more than the mean normal thickness for that subfield), 10 (10%, 95% CI: 5% to 18%) of 97 eyes without central involvement (i.e. thickness less than mean normal thickness) progressed to central-involved ME, and 18 (12%, 95% CI: 7% to 19%) of 147 eyes where central involvement was possible (i.e. between mean normal and 2 standard deviations above mean normal) progressed to central-involved ME. The rate of development of central-involved ME 16 weeks following cataract surgery differed by history of DME treatment ($P<0.001$). Eyes with DME at baseline and no history of DME treatment (N = 140) had a 4% incidence (95% CI: 2-9%) of central-involved ME, and eyes with DME at baseline with a history of DME treatment (N = 104) had a 21% incidence (95% CI: 14-30%) at 16 weeks following cataract surgery. (Table 3)

Of 279 study eyes that completed the 16-week visit, 23 eyes (8%) received non-topical postoperative treatment for ME prior to or at the 16-week visit. The median number of days from surgery to the first post-operative DME treatment was 50 (range 15 to 113). Central-involved ME rates at 4 weeks and 4 weeks or 16 weeks, were largely comparable to rates at 16 weeks (Table 4). Table 4 also shows rates of development or progression of non-central involved ME.

The median change in OCT CSF thickness and the median relative change in retinal total volume from baseline to the 16-week visit (or at the first ME treatment visit) for eyes with no DME, eyes with DME not involving the center, and eyes with DME possibly involving the center, at baseline were +11 μm (95%CI: +4 to +21 μm) and 5% (95%CI: 2 to 7%), +16 (95%CI: +12 to +20 μm) and 5% (95%CI: 4 to 7%), and +8 (95%CI: +6 to +11 μm) and 3% (95%CI: 2 to 4%) respectively.

Table 5 provides data on the association of baseline factors with the development of central-involved ME and the development or progression of non-central involved ME at 16 weeks. History of DME treatment was significantly associated with development of central-involved ME, and progression or development of non-central involved ME (P <0.001 for both). Eyes with better visual acuity, and less severe diabetic retinopathy level at baseline tended to have a lower incidence of development of central involved ME (P = 0.06 for both).

Visual Acuity and Other Secondary Outcomes

At the 16-week visit, the median visual acuity letter score was 81 (Snellen equivalent ~20/25) (Table 6) with a median change from baseline of +10 letters. Two-hundred forty-one (86%) eyes had a visual acuity of 20/40 or better (~Snellen equivalent) at the 16-week visit. Vision loss of at least 10 letters occurred in 4%. Compared with eyes that did not meet criteria of incident central-involved ME, eyes that developed central-involved ME, on average, had less improvement in visual acuity, with a median change of +11 and +5 letters, respectively. In eyes that did not develop central involved ME and in those that developed central-involved ME, visual acuity at the 16 week visit was 20/40 or better (approximate Snellen equivalent) in 89% and 67%, respectively, however the former group had better vision at baseline (mean E-ETDRS letter score 67) and higher proportion of DME treatment

history (80%) than the latter group (mean E-ETDRS letter score 60 and 40% with history of DME treatment).

At the 16-week visit, diabetic retinopathy severity as assessed on clinical examination by the investigator did not change from baseline in 229 eyes (82%) on a scale that included the following: no diabetic retinopathy, microaneurysms only, mild to moderate NPDR, severe NPDR, and proliferative diabetic retinopathy. At least one-step and at least two-step worsening on this clinical scale were reported in 9% and 1%, respectively. Similarly, at least one-step and at least two-step improvements on this clinical scale were reported in 9% and 1%, respectively (Table 6). Of the 198 eyes without PDR at baseline, 4 (2%) progressed to PDR or had PRP applied at follow-up.

Categorization of macular edema type

Of the 36 fluorescein angiography images graded by the Wisconsin reading center on eyes with a CSF thickness of 250 μm or more, 16 (44%), 15 (42%) and 5 (14%) eyes were classified as DME only, combined cystoid macular edema (CME) and DME, and CME only respectively.

Discussion

This prospective, multicenter, observational study demonstrates that in eyes without definite central-involved DME within 1 month prior to undergoing cataract extraction, the chance of manifesting central-involved ME, and or development or progression of ME in the non-central subfields, 16 weeks following cataract surgery, may be influenced by the presence of preexisting DME and history of DME treatment. In this study, eyes with a prior history of DME treatment had a higher rate of central-involved ME (20%) than eyes with no history of DME treatment (4%) ($P<0.001$) 16 weeks following cataract surgery. The analysis of baseline OCT groups showed that none of the eyes without DME at baseline developed central-involved ME (upper limit of 95%CI: 20%). The size of this subgroup, was limited (N=17 at 16 weeks) and might not reflect the true rate of ME development in this subgroup. On the other hand, the incidence rate in the subgroups with DME not involving the central subfield and the subgroup with DME with possible center involvement were comparable at about 10%.

In this study, similar to more recent studies, OCT was used to evaluate progression of ME following cataract surgery. Earlier studies, however, reported rates of ME progression from other methods; for example, the proportion of eyes manifesting angiographic CME was 9% after cataract surgery using fluorescein angiography in people without diabetes.[11] It was reported by Romero-Aroca that 6.06% of 132 eyes of diabetic patients developed DME on evaluation by fluorescein angiography and OCT following uneventful phacoemulsification.[12] In a single-center study of 50 eyes, Kim et al reported an incidence rate of 22% (95%CI: 13-35%) for DME exacerbation (defined as at least a 30% increase in OCT center point thickness compared with pre-surgical OCT) one month after cataract surgery. All progressing eyes showed cystoid abnormalities on OCT.[7] The variability in reported progression rates of ME following cataract surgery in diabetic persons may be explained by the lack of a unified definition of clinically-important progression of edema

and/or different population settings or pathological parameters between studies. In our study, we defined progression of central-involved DME based on the log change in OCT CSF thickness from baseline, which takes into account baseline thickness and requires OCT change beyond variability of the OCT machine itself.[10]

One of the difficulties of assessing and managing ME after cataract surgery arises from the fact that two clinical forms of edema can be present, either alone or in combination, in this setting: DME and “post-surgical” or Irvine-Gass CME. Cystoid abnormalities in the macula in the absence of microaneurysms and lipid on clinical exam and petaloid accumulation of fluorescein around the fovea with staining of the optic disc during fluorescein angiography characterize post-surgical CME. Retinal capillary hyperpermeability from intraocular inflammation is thought to be a major pathway in the development of this edema. In the present study, eyes with CSF thickness >250 μm at any study visit were graded by a central reading center in which ME was classified 44% of the time as DME only, compared with approximately 14% CME and approximately 42% a combined mechanism. Depending on the type of edema present, the course of treatment may be different. For example, CME, which shares clinical findings with ME associated with uveitis, maybe treated with anti-inflammatory treatments (both corticosteroid and non-steroidal). On the other hand, anti-VEGF and steroid products have increased the treatment options for DME. None of these treatments, however, have been proven definitively to have a role in the management of post-surgical ME.

Not surprisingly, after cataract surgery the majority of eyes gained visual acuity. Overall 86% of eyes had vision of 20/40 or better. Visual acuity of this level is generally attained in a larger proportion of eyes undergoing cataract surgery among persons without diabetes. Similar to our study, Somaiya et al reported 82% of 106 diabetic eyes achieved vision of 20/40 after small incision phacoemulsification in a retrospective review. On the other hand, 20/40 vision was achieved in 95% of 55 non-diabetic eyes in the same study.[13] In our study, 20/40 or better vision occurred less often in eyes that developed central-involved ME (67%). However, these eyes had a lower mean baseline VA (60 letter score [~ snellen equivalent 20/63]) than eyes that did not develop central-involved ME (67 letter score [~ snellen equivalent 20/50]). Other studies have also reported less improvement of visual acuity in diabetic eyes in comparison with non-diabetic counterparts.[14]

The large sample size and the multi-center nature of this study provide progression rates with more precision and broader representation of an overall United States diabetic population when compared to previous studies on progression of ME after cataract surgery. A limitation of this study is that the treatment and prophylaxis for DME and CME both prior to, during, and after surgery was not standardized. In addition, since measurements of blood sugar, HbA1c, and blood pressure were not obtained during follow-up in this observational study, we cannot determine from this study whether sudden worsening of these features accounted for the results. The use of topical non-steroidal anti-inflammatory drugs or topical steroids was also not standardized; rather these treatments were left to the discretion of the DRCR.net investigator and cataract surgeon. The use of topical non-steroidal anti-inflammatory drugs in this study (31%) was lower than previously reported.[15, 16] This rate

may have been under-reported as the data was extracted from surgical records that were often separate.

This study represents a collaborative effort between anterior segment and posterior segment ophthalmologists in both academic and community-based institutions. The participants recruited for this study were known to be at risk for ME development or progression. Pre-operative, peri-operative, and post-operative clinical management were allowed in a manner that reflects common approaches for ME prophylaxis found in a mix of community and academic institutions. This study demonstrated that collaboration among DRCR.net retina specialists and cataract surgeons is possible—and might be realistically incorporated into future design and conduct of experimental studies.

This study shows that eyes with history of DME treatment and or DME immediately prior to cataract surgery are at higher risk of developing central-involved ME 16 weeks after the cataract extraction than those with no history of DME treatment or DME. The effect of pre-operative DME treatment on post operative ME could not be evaluated in this study. Clinicians should continue to maintain vigilance in diabetic patients after cataract extraction even when central macular edema is not present immediately prior to cataract surgery, especially in eyes with prior DME treatment or non-central involved DME that may be at a particularly high risk for development of central-involved ME after cataract surgery. These data may help researchers planning future clinical trials that attempt to minimize this clinically important event. It may also help physicians to explain the risk of DME progression after cataract surgery to their patients, tailored according to level of DME, and history of DME treatment in a particular eye.

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Table 1

Baseline and Outcome Diabetic Macular Edema Definitions in Time Domain Optical Coherence Tomography Images

Follow up Macular Edema Categories	Definition
Baseline DME Categories	
A. No central involved DME and no non-central involved DME	CSF<190[¦] for women or CSF<210[¦] for men, and all ISF<260[‡], and all OSF<220[¶]
B. No central involved DME and definite or possible if non-central involved DME	CSF <190[¦] for women or CSF<210[¦] for men, and at least 1 ISF >260[‡] or OSF>220[¶]
C. possible if central involved DME and no non-central involved DME	CSF 190[¦] to 249[¦¦] for women or CSF 210[¦] to 249[¦¦] for men, and all ISF <260[‡], and all OSF<220[¶]
D. Possible if central involved DME and definite or possible if non-central involved DME	CSF 190[¦] to 249[¦¦] for women or CSF 210 to 249[¦¦] for men, and at least 1 ISF >260[‡] or OSF>220[¶]
Central-Involved Macular Edema at Follow Up	Study eye meeting any one of the following: **1** CSF thickness ≥250[*] μ at 16 weeks and increased at least 1 logOCT unit from baseline to 16 weeks **2** CSF thickness increased at least 2 logOCT units from baseline to 16 weeks **3** Any treatment for DME or CME other than topical medications was received after surgery, and criterion (1) or (2) was met prior to starting treatment
Development or Progression of Non-central-Involved Macular Edema at Follow Up	Study eye meeting any one of the following: **1** At least 1 ISF ≥310[†] microns at 16 weeks and the corresponding ISF increased at least 1 log unit from baseline to 16 weeks OR at least 1 OSF ≥290[††] microns at 16 weeks and the corresponding OSF increased at least 1 logOCT unit from baseline to 16 weeks **2** At least 1 ISF increased at least 2 logOCT units from baseline to 16 weeks OR at least 1 OSF increased at least 2 logOCT units from baseline to 16 weeks **3** Any treatment for DME or CME other than topical drops was received after surgery, and criterion (1) or (2) was met prior to starting treatment

DME=diabetic macular edema; CSF=central subfield; ISF=inner subfields; OSF=outer subfields;; CME=cystoids macular edema

[*] 310 on spectral domain machines

[†] 356, 369, and 348 on the spectral domain machines Zeiss Cirrus, Heidelberg Spectralis and Optovue RTVue respectively. Values represent mean +2 standard deviations from a normal cohort of the ISFs of respective machines.

[††] 303, 322, and 307 on the spectral domain machines Zeiss Cirrus, Heidelberg Spectralis and Optovue RTVue respectively. Values represent mean +2 standard deviations of the OSFs of respective machines.

[¦] Women: 250, 260, and 240; Men: 260, 280, and 240 on the spectral domain machines Zeiss Cirrus, Heidelberg Spectralis and Optovue RTVue respectively.

[¦¦] 309 on the on the spectral domain machines Zeiss Cirrus, Heidelberg Spectralis and Optovue RTVue

[‡] 260, 260, 340 on the spectral domain machines Zeiss Cirrus, Heidelberg Spectralis and Optovue RTVue respectively.

[¶] 260, 220, and 290 on the spectral domain machines Zeiss Cirrus, Heidelberg Spectralis and Optovue RTVue respectively.

Table 2

Baseline Participant and Ocular Characteristics

	N=293
Participant-level	
Age (years)-Mean±standard deviation (Min, Median, Max)	65±9 (29, 65, 85)
Gender	
Women	171 (58%)
Race/Ethnicity	
White	191 (65%)
Black	67 (23%)
Hispanic	26 (9 %)
Asian	2 (1%)
Native Hawaiian/ Pacific Islander	3 (1%)
Unknown/not reported	4 (1%)
Diabetes Type	
Type 1	34 (12%)
Type 2	242 (83%)
Uncertain	17 (6%)
Duration of Diabetes- (Years); Mean±STD	21±12
HbA1c[*]-(%); Mean±STD	7.7±1.5
Ocular-level	
Visual Acuity	
Letter Score-Mean±STD (Median)	66±15 (69)
Snellen Equivalent-Mean (Median)	20/50 (20/40)
≥ 69 (20/40 or better)-N (%)	151 (52%)
68-54 (20/50 to 20/80)-N (%)	97 (33%)
53-39 (20/100 to 20/160)-N (%)	26 (9%)
≤38 (20/300 or worse) N (%)	19 (6%)
Diabetic Retinopathy[¶]-N (%)	
Microaneurysms only	63 (22%)
Mild/moderate NPDR	131 (45%)
Severe NPDR	15 (5%)
PDR and/or prior scatter	84 (29%)
Prior History of PRP	71 (24%)
History of DME Treatment-n (%)	128 (44%)
History of Recent Injection for DME [**]	29 (10%)
Baseline DME Subgroup [†]	
A. No central-involved DME & No non-central involved DME	17 (6%)
B. No central-involved DME & Definite/possible if non- central involved DME	100 (36%)

	N=293
C. Possible if central-involved DME and No non-central involved DME	5 (2%)
D. Possible if central involved DME and Definite/possible if non central involved DME	153 (56%)
OCT- Mean ±STD (Min, Max)	
Time Domain	
CSF Thickness μm (N = 281)	201±26 (114, 249)
Retinal Volume mm^3 [§](N = 261)	6.7± 0.6 (4.3, 8.8)
Spectral Domain	
CSF Thickness μm (N = 12)	244±32 (178, 284)
Retinal Volume mm^3 [§](N = 9)	8.97±1.29 (6.96, 10.20)
OCT Machines	
Zeiss Stratus	281 (96%)
Zeiss Cirrus	8 (3%)
Optovue RTVue	2 (1%)
Heidelberg Spectralis	2 (1%)

HbA1c=hemoglobin A_{1c}; NPDR=non-proliferative diabetic retinopathy; PDR=proliferative diabetic retinopathy; PRP=panretinal photocoagulation; DME=diabetic macular edema; OCT=optical coherence tomography; CSF=central subfield;

[*] Missing in 13 participants

[¶] By clinical exam. Scale: None, Microaneurysms only, Mild/moderate NPDR, Severe NPDR and PDR

[**] Intravitreal or peribulbar corticosteroids within the last 4 months prior to surgery or on the day of surgery; anti-VEGF therapy within the last 2 months prior to surgery or on the day of surgery

[†] Missing in 18 (6%); 5 eyes, originally classified in the possible central-involved DME and no non-central involved DME group, were individually examined by the protocol chair due to small numbers in the subgroup and were reclassified into the no central or non-central involved DME (N = 1), no central-involved DME and definite/possible non-central involved DME (N = 1) and the possible central-involved and definite/possible non-central involved DME (N = 3) groups respectively in the analysis.

[§] Missing 20 in time domain and 3 spectral domain: non-gradable by the reading central

Table 3

Frequency of Macular Edema at 16 Weeks

	Definite Central-involved Macular Edema at 16 Weeks	
	Proportion (%)	**95% Confidence Interval of Proportion**
	N = 261	
Baseline OCT Thickness		
A. No central-involved DME & No non-central involved DME*	0/17 (0%)	0-20%
B. No central-involved DME & Definite/ possible non - central involved DME*	10/97 (10%)	5-18%
C. Possible central-involved DME and Definite/possible non-central involved DME*	18/147 (12%)	7-19%
Baseline OCT Thickness and History of DME Treatment		
A. No DME**	0/17 (0%)	0-20%
B. Any DME And No History of DME Treatment	6/140 (4%)	2-9%
C. Any DME With History of DME Treatment	22/104 (21%)	14-30%
Recent DME Treatment Only	0/4 (0%)	
Recent and Old DME Treatment	6/18 (33%)	
Old DME Treatment Only	16/82 (20%)	

CI=central-involved; DME=diabetic macular edema

* Five eyes, originally classified in the possible central-involved DME and no non-central involved DME group, were individually examined by the protocol chair due to small numbers in the subgroup and were reclassified into the no central or non-central involved DME (N = 1), no central-involved DME and definite/possible non-central involved DME (N = 1) and the possible central-involved and definite/possible non-central involved DME (N = 3) groups respectively in the analysis.

** Eleven eyes did not have, and 6 eyes had, history of DME treatment.

Table 4

Frequency of Macular Edema at 4 Or 16 Weeks

	Definite Central-involved Macular Edema at 4 Weeks		Definite Central-involved Macular Edema at 4 OR 16 Weeks**		Definite Central-Involved OR Progression to Definite NON-Central involved Macular Edema† at 16 Week	
	Proportion (%)	95% Confidence Interval of Proportion	Proportion (%)	95% Confidence Interval of Proportion	Proportion (%)	95% Confidence Interval of Proportion
	N = 259		N = 266		N = 261	
Baseline OCT Thickness						
A. No central involved DME & No non-central involved DME*	1/15 (7%)	0.2%-32%	1/17 (6%)	0.2-29%	2/17 (12%)	1-36%
B. No central involved DME & Definite/ Possible non-central involved DME*	6/94 (6%)	2%-13%	11/97 (11%)	6-19%	12/97 (12%)	7-21%
C. Possible central involved DME and Definite/possible non-central involved DME*	15/150 (10%)	6-16%	24/152 (16%)	10-23%	22/147 (15%)	10-22%
Baseline OCT Thickness and History of DME Treatment						
A. No DME	1/15 (7%)	0.2%-32%	1/17 (6%)	0.2-29%	2/17 (12%)	1-36%
B. Any DME And No History of DME Treatment	7/139 (5%)	2-10%	11/144 (8%)	4-13%	8/140 (6%)	3-11%
C. Any DME With History of DME Treatment	14/105 (13%)	7-21%	24/105 (23%)	15-32%	26/104 (25%)	17-34%
Recent DME Treatment Only	0/4 (0%)		0/4 (0%)		0/4 (0%)	
Recent and Old DME Treatment	6/18 (33%)		7/18 (39%)		7/18 (39%)	
Old DME Treatment Only	8/83 (10%)		17/83 (20%)		19/82 (23%)	

OCT= Optical Coherence Tomography, DME=diabetic macular edema

*Five eyes, originally classified in the possible central-involved DME and no non-central involved DME group, were individually examined by the protocol chair due to small numbers in the subgroup and were reclassified into the no central or non-central involved DME (N = 1), no central-involved DME and definite/possible non-central involved DME (N = 1) and the possible central-involved and definite/possible non-central involved DME (N = 3) groups respectively in the analysis

†Includes only eyes with gradable non-central subfields at baseline and 16 weeks.

Table 5

Baseline Factors Association with Development of Central-Involved Macular Edema, and Development or Progression of Non-central Involved Macular Edema at 16 Weeks

	Central-Involved Macular Edema			Non-central Involved Macular Edema		
Parameters	**N/total (%)**	**95%CI**	***P* Value***	**N/total (%)**	**95%CI**	***P* Value***
Visual Acuity Group at Baseline – E-ETDRS Letter Score (%)			0.06			0.11
≥69 (20/40 or better)	10/144 (7%)	(3-12%)		11/140 (8%)	(4-14%)	
68-54 (20/50 to 20/80)	12/91 (13%)	(7-22%)		7/78 (9%)	(4-18%)	
53-39 (20/100 to 20/160)	5/23 (22%)	(7-44%)		3/21 (14%)	(3-36%)	
≤38 (20/200 or worse)	3/18 (17%)	(4-41%)		3/10 (30%)	(7-65%)	
Any History of DME Treatment (%)			<0.001			<.001
Yes	24/123 (20%)	(13-28%)		19/105 (18%)	(11-27%)	
No	6/153 (4%)	(1-8%)		5/144 (3%)	(1-8%)	
History of PRP (%)			0.50			0.31
Yes	9/68 (13%)	(6-24%)		8/59(14%)	(6-25%)	
No	21/208 (10%)	(6-15%)		16/190 (8%)	(5-13%)	
Diabetic Retinopathy Severity (%)			0.06			0.08
Microaneurysms only	2/54 (4%)	(0.04-13%)		1/54 (2%)	(0-10%)	
Mild/moderate NPDR	12/128 (9%)	(4-16%)		12/115 (10%)	(6-18%)	
Severe NPDR	2/14 (14%)	(2-43%)		1/9 (11%)	(0-48%)	
PDR and/or prior scatter laser photocoagulation	14/80 (18%)	(10-28%)		10/71 (14%)	(7-24%)	
HbA1c (%)			0.83			1.00
≥8.0	8/87 (9%)	(4-17%)		8/79 (10%)	(4-19%)	
<8.0	19/177 (11%)	(7-16%)		15/159 (9%)	(5-15%)	
Age Group (%)			0.18			0.28
≥65	12/145 (8%)	(4-14%)		10/134 (7%)	(4-13%)	
<65	18/131 (14%)	(8-21%)		14/115 (12%)	(7-20%)	
Gender (%)			0.44			1.00
Women	15/159 (10%)	(5-15%)		14/147 (10%)	(5-15%)	
Diabetes Type (%)			0.27			0.13
Type I	1/34 (3%)	(0-15%)		0/29 (0%)	(0-12%)	
Type II	27/225 (12%)	(8-17%)		22/204 (11%)	(7-16%)	
Uncertain	2/17 (12%)	(1.4-36%		2/16 (13%)	(2-38%)	

E-ETDRS= Electronic early treatment diabetic retinopathy study; DME=diabetic macular edema; PRP=panretinal photocoagulation; NPDR=non-proliferative diabetic retinopathy; PDR=proliferative diabetic retinopathy; HbA1c=hemoglobin A1c

*Fisher Exact Test

Table 6

Secondary Outcomes at 16-Week Visit

	Overall	Did not Develop Central-Involved Macular Edema	Developed Central-Involved Macular Edema
Visual Acuity	**N = 279**	**N = 246** *	**N = 30** *
Baseline visual acuity- E-ETDRS Letter score Mean±STD (Median)	66±15 (69)	67±15 (70)	60±15 (63)
Baseline visual acuity- Snellen Equivalent Mean	20/50	20/50	20/63
Proportion Letter score ≥69 (20/40) at baseline – N (%)	144 (52%)	134 (54%)	10 (33%)
16-week Outcomes			
VA- Mean±STD (Median)	78±12 (81)	80±11 (82)	69 ± 12 (72)
Snellen Equivalent – Mean (Median)	20/32 (20/25)	20/25 (20/25)	20/40 (20/40)
E-ETDRS Letters Change at 16-week- Mean ± STD (Median)	+12±14 (+10)	+13 ±14 (+11)	+ 9±14 (+5)
Distribution at 16-week - N (%)			
Proportion letter score ≥69 (20/40)	241 (86%)	219 (89%)	20 (67%)
Proportion with ≥10 Letter Gain	148 (53%)	135 (55%)	11 (37%)
Proportion with ≥20 Letter Gain	66 (24%)	58 (24%)	6 (20%)
Proportion with ≥10 Letter Loss	11 (4%)	7 (3%)	3 (10%)
Proportion with ≥20 Letter Loss	1 (<1%)	0 (0%)	0 (0%)
OCT From Time Domain Machine ¶	**N=261**	**N=233**	**N=28**
Baseline CSF μm-Median (25^{th} , 75^{th} Percentile)	202 (182, 220)	201 (181, 218)	204 (191, 235)
CSF Thickness (μm) at 16 weeks-Median (25^{th}, 75^{th} Percentile)	210 (192, 237)	208 (190, 231)	297 (254, 357)
CSF Thickness (μm) at 16 weeks (*if DME treatment was given, last value before treatment carried to 16 weeks*)- Median (25^{th}, 75^{th} Percentile)	212 (193, 241)	208 (190, 231)	309 (283,422)
CSF Thickness Change (μm) from Baseline at 16 weeks - Median (25^{th} , 75^{th} Percentile)	+9 (+1, +27)	+8 (0, +19)	+89 (+63, +133)
CSF Thickness Change (μm) from Baseline (16 weeks value obtained from last observation before DME treatment given) Median (25^{th} , 75^{th} Percentile)	+10 (+1, +28)	+8 (0, +19)	+104 (+81, +196)
Relative CSF Thickness Change from Baseline- % Median (25^{th}, 75^{th} Percentile)	+5% (0%, +14%)	+4% (0%, +9%)	+41% (+30%, +67%)
Proportion with CSF Thickness >250 and increased at least 25μm- N (%)	35 (13%)	13 (6%)	22 (79%)[‖]
Total Volume mm^3- Median (25^{th}, 75^{th} percentile)†	7.0 (6.5, 7.5)	6.9 (6.5, 7.4)	7.8 (7.2,8.6)
Total Volume mm^3 change from baseline- Median (25^{th}, 75^{th} percentile) //	+0.3 (+0.1, +0.6)	+0.2 (+0.1, +0.5)	+1.2 (+0.4, +1.6)
Diabetic Retinopathy Progression From Baseline§ – N (%)			
≥2 Step Worsening	2 (1%)	1 (<1%)	1 (3%)

	Overall	Did not Develop Central-Involved Macular Edema	Developed Central-Involved Macular Edema
1 Step Worsening	25 (9%)	22 (9%)	3 (10%)
No Change	229 (82%)	202 (82%)	24 (80%)
1 Step Improvement	25 (9%)	22 (9%)	3 (10%)
≥2 Step Improvement	2 (1%)	1 (<1%)	1 (3%)

E-ETDRS= Electronic early treatment diabetic retinopathy study; STD=standard deviation; OCT=optical coherence tomography; CSF=central subfield; DME=diabetic macular edema;

* Outcome could not be calculated for 3 eyes with non-gradable or missing OCT at baseline or 16-week visit.

¶ Seven eyes that had baseline and 16-week OCT obtained by different time and spectral domain machines were excluded.

' For eyes receiving DME treatment, last CSF thickness before treatment is used.

† Missing in 8, 5, and 3 for the overall, did not, and did develop central involved macular edema cohorts respectively.

// Missing in 25, 19, and 6 for the overall, did not, and did develop central involved macular edema cohorts respectively

§ By clinical exam. Scale: none, microaneurysms only, mild/moderate non- proliferative diabetic retinopathy, severe non- proliferative diabetic retinopathy and proliferative diabetic retinopathy.