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Evaluating Objective and Subjective Quantitative Parameters at the Initial Visit to Predict Future Glaucomatous Visual Field Progression

Allison K. Ungar, MD, Gadi Wollstein, MD, Hiroshi Ishikawa, MD, Lindsey S. Folio, BS, Yun Ling, MS, Richard A. Bilonick, PhD, Robert J. Noecker, MD, Juan Xu, PhD, Larry Kagemann, MS, Cynthia Mattox, MD, and Joel S. Schuman, MD

From UPMC Eye Center (AKU, GW, HI, LSF, RAB, RJN, JX, LK, JSS), Eye and Ear Institute, Ophthalmology and Visual Science Research Center, Department of Ophthalmology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; the Department of Bioengineering (AKU, HI, LSF, LK, JSS), Swanson School of Engineering, University of Pittsburgh, Pittsburgh, Pennsylvania; the Department of Biostatistics (YL, RAB), Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania; and New England Eye Center (CM), Tufts University School of Medicine, Boston, Massachusetts

Abstract

BACKGROUND AND OBJECTIVE—To evaluate the ability of structural assessment to predict glaucomatous visual field progression.

PATIENTS AND METHODS—A total of 119 healthy eyes with suspected glaucoma and glaucomatous eyes with 5 or more optic nerve stereophotographs, optical coherence tomography (OCT), and confocal scanning laser ophthalmoscopy (CSLO) all acquired within 6 months of each other were enrolled. Odds ratios to predict progression were determined by generalized estimating equation models.

RESULTS—Median follow-up was 4.0 years (range: 1.5 to 5.7 years). Fifteen eyes progressed by glaucoma progression analysis, 20 by visual field index, and 10 by both. Baseline parameters from stereophotographs (vertical cup-to-disc ratio and Disc Damage Likelihood Scale), OCT (global, superior quadrant, and inferior quadrant retinal nerve fiber layer thickness), and CSLO (cup shape measure and mean cup depth) were significant predictors of progression. Comparing the single best parameter from all models, only the OCT superior quadrant RNFL predicted progression.

CONCLUSION—Baseline stereophotographs, OCT, and CSLO measurements may be clinically useful to predict glaucomatous visual field progression.

INTRODUCTION

Glaucoma is the second leading cause of blindness worldwide.¹ It is characterized by the accelerated death of retinal ganglion cells and presents as progressive functional damage to the visual field.² Decisions in the management of glaucoma remain challenging in part

Address correspondence to Gadi Wollstein, MD, UPMC Eye Center, Eye and Ear Institute, 203 Lothrop St., Pittsburgh, PA 15213. wollsteing@upmc.edu.

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because of inadequate methods to identify those who are likely to develop significant visual loss.

The most widely used clinical method to assess glaucomatous damage is the evaluation of the optic nerve head (ONH) with estimation of the cup-to-disc ratio (CDR). The CDR has been shown to correlate with functional damage³; however, this measure is limited by intraobserver and interobserver variability.⁴ Baseline assessments of CDR have been shown to be predictive of future visual field loss and development of glaucoma in suspected glaucoma.^{5,6} Another staging system that has been shown to strongly correlate with functional damage,⁷ the Disc Damage Likelihood Scale (DDLS),⁸ has demonstrated better reproducibility than CDR.^{9–11} The DDLS is based on the narrowest rim width, the degree of absent rim tissue, and the disc size.

Noninvasive imaging devices have been used to augment the evaluation of glaucoma, with an advantage of being objective and quantitative. Two of the available technologies are optical coherence tomography (OCT) and confocal scanning laser ophthalmoscopy (CSLO). OCT is a noninvasive imaging device based on nonscattered light reflections, which can provide detailed information about tissue layers of the retina. OCT measurements of the retinal nerve fiber layer (RNFL) provide good glaucoma discriminatory ability.^{12–14} CSLO uses confocal optics to provide topographic information about the ONH, and has demonstrated value in distinguishing between healthy and glaucomatous eyes.^{15–17} Baseline measures from OCT and from CSLO have shown to be predictive of future glaucomatous visual field defects in eyes suspect for glaucoma.^{18–22}

The purpose of this study was to evaluate and compare baseline measurements from CDR and DDLS and quantitative objective parameters from OCT and CSLO in predicting future glaucomatous visual field progression. Furthermore, this study was designed to improve the understanding of glaucoma progression prediction by using modeling that combined both subjective and objective structural ONH measures and by including a side-by-side standardized comparison of devices and techniques.

PATIENTS AND METHODS

Data for this study were collected as a retrospective review of the Pittsburgh Imaging Technology Trial, an ongoing prospective longitudinal study at the University of Pittsburgh Medical Center Eye Center and the New England Eye Center.

Inclusion Criteria

Patients included in this study had a best-corrected visual acuity of 20/60 or better and a refractive error of +6.00 to –6.00 diopters. Participants needed at least five reliable visual field tests (Humphrey Field Analyzer, Carl Zeiss Meditec, Inc., Dublin, CA) and good-quality single baseline measures from disc photographs (Nidek 3-Dx; Nidek, Gamagori, Japan), OCT (StratusOCT; Carl Zeiss Meditec, Inc.), and CSLO (Heidelberg Retina Tomography; Heidelberg Engineering, Heidelberg, Germany), all acquired within 6 months of each other.

Exclusion Criteria

Patients were excluded for a history of diabetes mellitus or posterior pole pathology other than glaucoma. Additionally, patients were excluded for use of systemic steroids, any other systemic medication known to affect the retina, and any neurological condition known to affect the visual field. Furthermore, eyes that underwent any intraocular surgery including cataract extraction during the follow-up period were excluded.

Study Protocol

All participants underwent a complete baseline ophthalmic examination by an ophthalmologist, including a full medical history, intraocular pressure measurement, undilated and dilated biomicroscopy, visual field testing, dilated optic disc photographs, and scanning with OCT and CSLO. Participants were scheduled for follow-up assessments every 6 months unless otherwise medically indicated. Follow-up visits included an ophthalmic examination and visual field tests. Glaucomatous eyes were medically treated as deemed appropriate by the clinicians. Both eyes were included in the study whenever possible; single eyes were used if the contralateral eye met exclusion criteria.

Clinical Diagnosis

The study population included patients with clinically diagnosed glaucoma, suspected glaucoma, and healthy eyes. Healthy eyes had full visual fields, intraocular pressures between 8 and 21 mm Hg, and normal-appearing ONH. Eyes were considered to have suspected glaucoma if they had full visual fields but an intraocular pressure greater than 22 mm Hg, asymmetrical cupping (> 0.2 difference in CDR between eyes), increased cupping (> 0.6 CDR), or were the fellow eye of a glaucomatous eye. Glaucomatous eyes were diagnosed based on having a reproducible and characteristic visual field defect of three non-edge points, all of which were depressed on the pattern deviation plot at the P value less than 5% level, along with any of the structural changes present in the suspected glaucoma.

Visual Field Testing

All patients underwent at least five Swedish Interactive Thresholding Algorithm Standard 24-2 perimetry tests. Reliable tests had fewer than 30% fixation losses and false-negative and false-positive responses. Two independent visual field criteria were used to define progression: the instrument provided glaucoma progression analysis (GPA) and visual field index (VFI). GPA is a point-by-point event analysis, whereas the VFI is a regression (trend) analysis using the VFI percentage score for each field. An eye was considered to have glaucomatous progression by GPA with analysis output of either “possible progression” or “likely progression.” An eye was considered to have glaucomatous progression by VFI when the slope of the VFI analysis was negative and significant, as reported by the instrument.

Optic Disc Photographs

All baseline stereoscopic color photographs were taken after pupillary dilation. Good quality photographs were those with proper focus and adequate illumination. The photographs were independently graded by three glaucoma experts masked to the clinical diagnosis. The experts graded each photograph for vertical cup-to-disc ratio and DDLS,⁸ assuming an average disc size (1.5 to 2.0 mm).^{9,10} The data used for the analysis were the average of the three experts.

OCT

All baseline OCT scans used in this study were from Stratus time-domain OCT using the Fast RNFL scanning mode. Good-quality scans were well centered with signal strength of 6 or greater or a signal-to-noise ratio of 30 or greater. Quality scans subjectively had less than 10% continuous or 15% total algorithm failure. Global and sectoral RNFL thickness measurements were used for the analysis after registering all measurements to the right eye orientation. Clock hours 11 to 1 and 5 to 7 were selected because they have been shown to best correlate with glaucomatous damage.²³

CSLO

Baseline CSLO scans used in this study were taken with the Heidelberg Retina Tomography 1, 2, or 3. Good-quality scans were well centered with a topographic standard deviation less than 50. The following instrument-provided topographic measures were collected: rim area, CDR, global mean cup depth, rim volume, and cup shape measure.

Statistical Analysis

Generalized estimating equation models accounting for baseline age²⁴ and the use of both eyes from some of the patients were used to calculate odds ratios of visual field progression as defined by GPA and VFI. Generalized estimating equation is a population-averaged and not subject-specific method for obtaining unbiased estimates when accounting for repeated observations. This provided a population-based risk calculation for glaucoma progression, rather than a particular study patient's risk assessment.

Seven generalized estimating equation models were grouped by device, and one generalized estimating equation model employed only the best performing parameters from each device (Fig. 1). To allow direct comparison between parameters, a secondary analysis standardized the variables within each model by subtracting the mean from each observation and dividing by its corresponding standard deviation. The parameters included in the Best Parameter Model (Model 8) were determined based on the highest standardized point estimate in each category (stereoscopic color photographs, OCT, and CSLO). This model combined both subjective and objective structural ONH data.

All analyses were conducted using the R Language and Environment for Statistical Computing Program.²⁵ For all analyses, a *P* value of less than .05 was considered statistically significant.

RESULTS

Data were collected on 119 eyes of 70 patients; 44 eyes were glaucomatous, 57 eyes were suspected glaucoma, and 18 were healthy. Eighty-two eyes were from females and 37 eyes were from males. Baseline measurements for each group are reported in Table 1. Median length of visual field follow-up was 4.0 years (range: 1.5 to 5.7 years). Twenty eyes (17%) progressed by VFI, 15 (13%) eyes progressed by GPA, and 10 (8%) eyes progressed by both VFI and GPA. The distribution of progression by diagnosis is presented in Table 2.

Odds ratios and confidence intervals for the unstandardized generalized estimating equation models are presented in Table 3. The standardized odds ratios necessary to compare parameters within and between models are presented in Figures 2 and 3 for GPA and VFI prediction, respectively.

In the stereoscopic color photographs models (Models 1 and 2), both vertical CDR and DDLS were significant predictors of visual field progression by GPA and VFI (confidence interval not crossing the value of 1). A 0.1-unit increase in vertical CDR was associated with a 3.2- and 2.2-fold increase in likelihood of progression by GPA and VFI, respectively. A 1-grade increase in DDLS was associated with a 2.2- and 1.8-fold increase in likelihood of progression by GPA and VFI, respectively. Using the standardized analysis, vertical CDR and DDLS had overlapping confidence intervals with a higher point estimate coming from vertical CDR.

In the OCT models (Models 3 to 5) predicting GPA progression, global mean RNFL, temporal quadrant RNFL, and superior quadrant RNFL were significant predictors. In the OCT models predicting VFI progression, global mean RNFL, and all quadrants were

significant predictors. None of the clock hours in Model 5 were predictive of either GPA or VFI progression. Using the standardized data, the superior quadrant RNFL thickness was the most significant predictor of GPA and VFI progression both in the OCT models and in comparison with all parameters from stereoscopic color photographs and CSLO.

In the CSLO model (Model 6), cup shape measure was the only significant predictive parameter for GPA progression and mean cup depth was the only predictive parameter for VFI progression.

In the visual field model (Model 7), pattern standard deviation (PSD) was a significant predictor of VFI progression. Neither mean deviation nor PSD was predictive of GPA progression.

The single best parameters for predicting GPA progression using the stereoscopic color photographs models (Models 1 and 2), OCT models (Models 3 to 5), and CSLO model (Model 6) were OCT superior quadrant RNFL, vertical CDR, and CSLO cup shape measure, in descending order of ability. The single best parameters for predicting VFI progression using the stereoscopic color photographs, OCT, and CSLO models were OCT superior quadrant RNFL, vertical CDR, and CSLO mean cup depth. These parameters were used in the Best Parameter Model (Model 8), which showed only OCT superior quadrant RNFL thickness to be a significant predictor of GPA progression. No parameters were significant predictors of VFI progression in Model 8.

DISCUSSION

The ability to predict future glaucoma progression can markedly influence clinical management. In this study, we examined the capability of structural information to predict future functional progression. Selected parameters from stereophotography of the ONH, OCT, and CSLO have demonstrated statistically significant ability to predict future visual field progression. Using a model with the best parameter from each device showed that only RNFL thickness in the superior quadrant was capable of predicting progression.

Seven generalized estimating equation models grouped by device revealed the strongest predictive ability to come from the OCT superior quadrant RNFL thickness. Thinner global mean and inferior quadrant RNFL were also found to be significant predictors. These findings are consistent with Lalezary et al., who reported similar findings in a population with suspected glaucoma.¹⁸ These are also the locations that have been shown in cross-sectional studies to be most affected by glaucomatous damage.^{23,26}

No clock hours were significant predictors of either GPA or VFI progression. This indicates that finer sectoral measurements are not sufficiently robust for progression prediction.

After OCT's superior quadrant RNFL, expert subjective assessment vertical CDR was the next best predictor of visual field progression by GPA and VFI. Both the Ocular Hypertension Treatment Study and the European Glaucoma Prevention Study have previously established vertical CDR as a predictor of glaucomatous visual field progression in a population with suspected glaucoma.^{5,6} The other subjective expert assessment, DDLS, was also a significant predictor of downstream visual field progression. Although the DDLS point estimate odds ratio was lower than that of vertical CDR, its confidence interval was tighter, likely because of better intragrader and intergrader reproducibility than CDR.⁹⁻¹¹

Two CSLO baseline topographic parameters, cup shape measure and mean cup depth, were predictive of GPA and VFI progression, respectively. The standardized odds ratios for these parameters fall below several of the best performing parameters from stereoscopic color

photographs and OCT. The Confocal Scanning Laser Ophthalmoscopy Ancillary study to the Ocular Hypertension Treatment Study found that mean cup depth was a significant predictor of visual field progression, whereas cup shape measure was not.¹⁹

Modeling both subjective and objective data together, with only the single best performing parameters from stereoscopic color photographs, OCT, and CSLO, revealed only the OCT parameter (superior quadrant RNFL) to be a statistically significant predictor. This reflects the strong prediction ability of this parameter, also seen as the highest point estimate for all individual parameters after standardization.

As would be expected, baseline PSD was predictive of VFI progression, but not GPA progression, because VFI is a derivative of PSD.²⁷ Similar to previous studies, we found no significant predictive ability from mean deviation.^{5,6,18}

This study included healthy eyes and glaucomatous eyes in addition to those with suspected glaucoma, whereas previous studies only examined suspected glaucoma. For the purposes of using structural measurements as predictive tools for functional progression, the inclusion of normal patients is advantageous. This served not only to provide a larger range of structural baseline parameters, but also as an internal control, because no healthy eyes were expected to progress. Including normal patients as part of the analysis allowed for the data to be representative of a clinical population and thus more applicable. Another beneficial aspect of this study's design was that visual field progression was defined through the use of two clinically available instrument derived parameters, GPA and VFI, the former being a marker of focal event based progression and the later providing a global progression marker.

Thickening of the nasal and temporal OCT quadrants were each predictive of glaucomatous visual field progression. The OCT nasal quadrant results are likely secondary to using solely visual field parameters to define progression. This leads to unreliable results due to the limited visual field data available in the corresponding area. The OCT temporal quadrant results are likely secondary to severe disease not being highly represented in the data set (average baseline mean deviation in glaucomatous eyes was -5.1 dB). This makes the OCT temporal quadrant RNFL thickness an unreliable predictor because temporal RNFL damage typically appears late in the glaucomatous course. Having a population of eyes without severe disease avoided the potential "floor effect" that could prevent detection of disease progression.

There are several possible limitations to this study. First, explanatory factors that are highly correlated cannot be included in the same model and, therefore, only selective parameters were included in the study. Additionally, patients with glaucoma were treated as deemed medically necessary, with regimen modifications per the treating physician. This was an inevitable source of variation in following glaucomatous eyes longitudinally.

We cannot recommend any single best parameters from stereoscopic color photographs, OCT, or CSLO for predicting future glaucomatous visual field progression. Although parameters from stereoscopic color photographs (vertical CDR, DDLS), OCT (global mean, superior quadrant, inferior quadrant), and CSLO (cup shape measure, mean cup depth) were statistically significant predictors, the side-by-side standardized comparison demonstrates large overlapping confidence intervals between the parameters' odds ratios and suggests that more data are needed to further clarify this topic. When modeling both subjective and objective structural ONH measures together, the objective imaging provided predictive ability. The degree of increased predictive ability provided by objective imaging also merits further investigation.

Baseline parameters from stereoscopic color photographs, OCT, and CSLO scans may be useful clinically to predict future glaucomatous visual field progression in patients with suspected glaucoma and glaucoma.

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Figure 1.

Statistical design using 8 models, each adjusted for baseline age. Model 8, the Best Parameter Model, was constructed based on the best performing parameters from Models 1 to 6. Each model was used to predict progression by guided progression analysis and visual field index. SP = stereophotographs of the optic nerve head; OCT = optical coherence tomography; CSLO = confocal scanning laser ophthalmoscopy; VF = visual field; VCD = vertical cup-to-disc ratio; DDLS = Disc Damage Likelihood Scale; RNFL = retinal nerve fiber layer; C/D = cup-to-disc ratio; MD = mean deviation; PSD = pattern standard deviation.

Figure 2.

Standardized odds ratios and confidence intervals for each guided progression analysis (GPA) model adjusted for baseline age. SD = standard deviation; VCD = vertical cup-to-disc ratio; DDL5 = Disc Damage Likelihood Scale; RNFL = retinal nerve fiber layer.

Figure 3. Standardized odds ratios and confidence intervals for each visual field index (VFI) model adjusted for baseline age. SD = standard deviation; VCD = vertical cup-to-disc ratio; DDLS = Disc Damage Likelihood Scale; RNFL = retinal nerve fiber layer.

TABLE 1

Baseline Characteristics of the Study Population

Baseline Parameter	Healthy (n = 18)	Suspected Glaucoma (n = 57)	Glaucomatous (n = 44)
Age (y)	46.2 ± 4.0	57.0 ± 10.4	63.6 ± 9.1
VF			
Mean deviation (dB)	0.27 ± 0.92	-0.16 ± 1.11	-5.10 ± 5.23
Pattern standard deviation (dB)	1.33 ± 0.18	1.64 ± 0.36	6.51 ± 3.98
Visual field index	99.78 ± 0.55	99.16 ± 0.92	85.66 ± 13.79
SP			
VCD	0.42 ± 0.09	0.65 ± 0.16	0.78 ± 0.14
DDLS	3.38 ± 0.80	4.81 ± 1.07	5.91 ± 1.32
OCT			
Global Mean RNFL (μm)	108.16 ± 10.00	91.59 ± 10.44	70.61 ± 14.95
Temporal (μm)	73.17 ± 9.41	67.37 ± 15.40	56.59 ± 13.86
Superior (μm)	131.56 ± 12.36	116.05 ± 17.31	83.55 ± 22.15
Nasal (μm)	87.44 ± 21.26	70.91 ± 16.64	57.73 ± 13.04
Inferior (μm)	140.50 ± 16.83	112.04 ± 18.05	84.43 ± 24.71
11 o'clock (μm)	144.87 ± 21.01	121.33 ± 26.93	92.86 ± 28.95
12 o'clock (μm)	130.83 ± 19.63	119.90 ± 22.99	81.78 ± 24.29
1 o'clock (μm)	118.89 ± 20.99	106.96 ± 21.63	76.04 ± 24.14
5 o'clock (μm)	131.42 ± 32.84	96.33 ± 22.21	78.31 ± 21.33
6 o'clock (μm)	153.78 ± 27.17	121.61 ± 25.16	90.78 ± 29.75
7 o'clock (μm)	136.55 ± 19.60	118.32 ± 24.85	84.01 ± 32.52
CSLO			
Rim area (mm ²)	1.52 ± 0.29	1.20 ± 0.27	0.92 ± 0.24
Cup-to-disc area ratio	0.17 ± 0.10	0.36 ± 0.14	0.47 ± 0.17
Mean cup depth (mm)	0.18 ± 0.07	0.28 ± 0.11	0.29 ± 0.11
Rim volume (mm ³)	0.42 ± 0.10	0.29 ± 0.10	0.21 ± 0.10
Cup shape measure	-0.22 ± 0.07	-0.13 ± 0.07	-0.07 ± 0.08

VF = visual field; SP = stereophotographs of the optic nerve head; OCT = optical coherence tomography; CSLO = confocal scanning laser ophthalmoscopy; VCD = vertical cup-to-disc ratio; DDLS = Disc Damage Likelihood Scale; RNFL = retinal nerve fiber layer.

TABLE 2

Distribution of Eyes That Progressed by VFI and GPA

Visual Field Progression Parameter	Healthy	Suspected Glaucoma	Glaucomatous
GPA	0	2	13
VFI	0	5	15
GPA and VFI	0	2	8

GPA = glaucoma progression analysis; VFI = visual field index.

TABLE 3
Unstandardized Odds Ratios and Confidence Intervals for Each Model Adjusted for Baseline Age^a

Model Parameter (Scale)		GPA Progression		VFI Progression	
		Odds Ratio	Confidence Interval	Odds Ratio	Confidence Interval
Stereophotographs of Optic Nerve Head					
1	VCD (per 0.1 unit increase)	3.22 ^b	1.02–10.25	2.21 ^b	1.18–4.14
2	DDL _S (per 1 grade increase)	2.23 ^b	1.23–4.04	1.79 ^b	1.05–3.06
OCT RNFL Measurements					
3	Global mean (per 10 μm decrease)	2.51 ^b	1.00–4.26	1.64 ^b	1.19–2.25
4	Temporal quadrant (per 10 μm decrease)	0.60 ^b	0.39–0.91	0.56 ^b	0.39–0.81
4	Superior quadrant (per 10 μm decrease)	2.51 ^b	1.59–3.98	1.86 ^b	1.30–2.65
4	Nasal quadrant (per 10 μm decrease)	0.86	0.53–1.43	0.54 ^b	0.32–0.90
4	Inferior quadrant (per 10 μm decrease)	1.21	0.83–1.78	1.54 ^b	1.11–2.11
5	11 o'clock (per 10 μm decrease)	1.37	1.00–1.88	0.93	0.70–1.22
5	12 o'clock (per 10 μm decrease)	1.12	0.81–1.54	1.22	0.85–1.78
5	1 o'clock (per 10 μm decrease)	1.41	0.91–2.23	1.22	0.89–1.71
5	5 o'clock (per 10 μm decrease)	1.33	0.64–2.74	0.75	0.52–1.10
5	6 o'clock (per 10 μm decrease)	0.95	0.48–1.88	1.41	0.99–2.02
	7 o'clock (per 10 μm decrease)	0.91	0.62–1.36	1.00	0.80–1.26
Confocal Scanning Laser Ophthalmoscopy					
6	Rim area (per 1 mm ² decrease)	5.81	0.04–1,000.00	2.46	0.02–250.00
6	Cup to disc area ratio (per 0.1 unit increase)	0.57	0.27–1.21	0.63	0.26–1.48

Model	Parameter (Scale)	GPA Progression		VFI Progression	
		Odds Ratio	Confidence Interval	Odds Ratio	Confidence Interval
6	Mean cup depth (per 0.1 mm increase)	1.51	0.72–3.17	2.51 ^b	1.18–5.31
6	Rim volume (per 0.1 mm ³ decrease)	0.56	0.16–1.99	0.41	0.14–1.16
6	Cup shape measure (per 0.1 unit increase)	4.35 ^b	1.48–12.82	1.24	0.47–3.22
VF					
7	Mean deviation (per 1 dB decrease)	0.95	0.81–1.12	0.87	0.74–1.03
7	Pattern standard deviation (per 1dB increase)	1.20	0.98–1.47	1.35 ^b	1.07–1.70

GPA = glaucoma progression analysis; VFI = visual field index; VCD = vertical cup-to-disc ratio; DDLS = Disc Damage Likelihood Scale; OCT = optical coherence tomography; RNFL = retinal nerve fiber layer; VF = visual field.

^aThese data cannot be used to compare within or between models.

^bStatistically significant odds ratios.