Continuing Medical Education:

The relationship between visual field loss in glaucoma and health-related quality-of-life

A van Gestel, CAB Webers, HJM Beckers, MCJM van Dongen, JL Severens, F Hendrikse and JSAG Schouten

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of Medscape, LLC and Nature Publishing Group. Medscape, LLC is accredited by the ACCME to provide continuing medical education for physicians.

Medscape, LLC designates this educational activity for a maximum of 0.75 *AMA PRA Category 1 Credits*TM. Physicians should only claim credit commensurate with the extent of their participation in the activity. All other clinicians completing this activity will be issued a certificate of participation. To participate in this journal CME activity: (1) review the learning objectives and author disclosures; (2) study the education content; (3) take the post-test and/or complete the evaluation at www.medscapecme.com/journal/eye; (4) view/print certificate.

Learning objectives

Upon completion of this activity, participants will be able to:

1. Distinguish factors that can reduce HRQOL among patients with glaucoma
2. Specify visual field defects particularly associated with reduced HRQOL
3. Perform appropriate screening to prevent HRQOL loss among patients with glaucoma

Authors/Editors disclosure information

Andrew J Lotery has disclosed the following relevant financial relationships: Served as an advisor or consultant for: Alcon Laboratories, Inc. Served as a speaker or member of a speakers bureau for: Bausch & Lomb, Inc. Received grants for clinical research from: Novartis Pharmaceuticals Corporation. Aukje van Gestel has disclosed no relevant financial relationships.

Carroll AB Webers has disclosed the following relevant financial relationships: Served as a speaker or member of a speakers bureau for: Merck & Co., Inc. Received grants for clinical research from: Alcon Laboratories, Inc.

Henny JM Beckers has disclosed the following relevant financial relationships: Served as an advisor or consultant for: Alcon Laboratories, Inc.; Allergan, Inc.; Pfizer Inc.; Merck & Co., Inc. Served as a speaker or member of a speakers bureau for: Alcon Laboratories, Inc.; Allergan, Inc.; Pfizer Inc.; Merck & Co., Inc. Received grants for clinical research from: Alcon Laboratories, Inc.

Martien CJM van Dongen has disclosed no relevant financial relationships.

Johan L Severens has disclosed no relevant financial relationships.

Fred Hendrikse has disclosed no relevant financial relationships.

Jan SAG Schouten has disclosed no relevant financial relationships.

Journal CME author disclosure information

Charles P Vega, Associate Professor; Residency Director, Department of Family Medicine, University of California, Irvine, Orange, CA, USA.

Charles P Vega has disclosed no relevant financial relationships.

The relationship between visual field loss in glaucoma and health-related quality-of-life

A van Gestel¹, CAB Webers¹, HJM Beckers¹,
MCJM van Dongen², JL Severens^{3,4}, F Hendrikse¹
and JSAG Schouten¹

Abstract

Purpose To investigate the relationship between visual field loss and health-related quality-of-life (HRQOL) in patients with ocular hypertension (OHT) or primary open-angle glaucoma (POAG).

Methods We conducted a cross-sectional study among 537 OHT and POAG patients from seven hospitals in The Netherlands. Clinical information was obtained from medical files. Patients completed a questionnaire, containing generic HRQOL instruments (EQ-5D and Health Utilities Index mark 3), vision-specific National Eye Institute Visual Functioning Questionnaire (VFQ-25), and glaucoma-specific Glaucoma Quality-of-Life questionnaire (GQL-15). The impact of visual field loss on HRQOL scores was analysed with multiple linear regression analyses.

Results A relationship between mean deviation (MD) and HRQOL was found after adjusting for age, gender, visual acuity, medication side effects, laser trabeculoplasty, and glaucoma surgery. We found interaction between MD in both eyes for GQL and VFQ-25 scores. The relationship between MD and utility was non-linear, with utility only affected at MD-values below -25 dB in the better eye. Visual acuity, side effects, and glaucoma surgery independently affected HRQOL. Binocular MD and MD in the better eye had similar impacts on HRQOL, whereas MD in the worse eye had an independent effect. HRQOL was affected more by binocular defects in the inferior than in the superior hemifield.

Conclusion Visual field loss in progressing glaucoma is independently associated with a loss in both disease-specific and generic quality-of-life. It is important to prevent progression, both in early and in advanced

glaucoma, especially in patients with inferior hemifield defects and severe defects in either eye.

Eye (2010) 24, 1759–1769; doi:10.1038/eye.2010.133; published online 5 November 2010

Keywords: glaucoma; treatment; visual field loss; health-related quality-of-life; utility

Introduction

Decisions to start or change therapy in glaucoma are mainly based on the intra-ocular pressure, structural changes to the optic nerve, and progression of visual field defects. The use of the intraocular pressure is based on its causal relationship with glaucoma progression, whereas the use of visual field loss is based on the knowledge that it reflects defects in the retinal nerve fiber layer. More relevant, however, is the fact that visual field loss is related to vision and health-related quality-of-life (HRQOL), which directly reflect patients' experiences.^{1–5} Ultimately the aim of glaucoma treatment is to prevent HRQOL loss, and knowledge about the relationship between visual field loss and HRQOL should have a function in treatment decisions. Several aspects of this relationship are clinically relevant. First, insight in the strength and causality of the association can help us understand the relative importance of visual field preservation in all severity stages of glaucoma. Second, it is likely that visual field loss is not the only factor relevant for HRQOL in glaucoma patients, and treatment benefits must be weighed against the potential HRQOL impact of treatment side effects. Third, HRQOL may be affected by visual field loss in each eye independently, rather than via the integrated binocular visual field. The location of visual field defects within

¹University Eye Clinic, Maastricht University Medical Center, Maastricht, The Netherlands

²Department of Epidemiology, Maastricht University, Maastricht, The Netherlands

³Institute of Health Policy and Management, Erasmus University Rotterdam, Rotterdam, The Netherlands

⁴Department of Health Organisation, Policy, and Economics, School for Public Health and Primary Care (CAPHRI), Maastricht University, Maastricht, The Netherlands

Correspondence: JSAG Schouten, University Eye Clinic, Maastricht University Medical Center, PO Box 5800, 6202 AZ, Maastricht, The Netherlands.
Tel: +31 43 387 5346;
Fax: +31 43 387 5343.
E-mail: j.schouten@mumc.nl

Received: 18 January 2010
Accepted in revised form: 24 June 2010
Published online: 5 November 2010

one eye may also play a role. Insight in these aspects can elucidate the need to focus treatment on either the better or worse eye, or on the eye with a specific location of visual field loss. Finally, it is of clinical interest to identify patients in whom HRQOL is more profoundly affected by visual field loss, for example, as a result of concurrent impaired visual acuity. In this study we have investigated these four aspects of the relationship between visual field loss and HRQOL in a patient population representing all severity stages of glaucoma.

Materials and methods

We held a cross-sectional survey among patients with ocular hypertension (OHT) or primary open-angle glaucoma (POAG) from the ophthalmology departments in seven Dutch hospitals. This survey was held in the context of a larger research project aiming to investigate the cost-effectiveness of alternative treatment strategies for OHT and POAG. In order to enable good interpolation within the data, all stages of disease severity needed to be represented in the study population. Ideally we had stratified patient sampling according to visual field defects, but the data required to do so were not readily available in the patient administration of the participating hospitals. Therefore, we defined the following seven sampling strata on the basis of diagnosis and treatment as a proxy for disease severity: (1) OHT without treatment, (2) OHT treated with medication only, (3) OHT with laser trabeculectomy in the treatment history, (4) POAG treated with medication only, (5) POAG with laser trabeculectomy in the treatment history, (6) POAG with glaucoma surgery in the treatment history, and (7) end-stage POAG, which was defined as a visual field limited to the central 10° in at least one eye as a result of glaucoma progression. The latter was independently assessed by two ophthalmologists (CABW, HJMB) based on the patients' medical files. An overview of in- and exclusion criteria for each of the categories is provided in Supplementary Table 1. For each category a sample list of potentially eligible patients was drawn up. On the basis of the sample size calculations, we aimed to include 70 patients in each group. When the sample list in a stratum was small, all patients were selected. In the other strata a random sample of 200 patients was drawn to compensate for the smaller number of patients in the other groups, aiming to include a total of 500 patients. The medical files of the selected patients were manually inspected to verify the in- and exclusion criteria and eligible patients were invited by mail to participate. They received written study information, an informed consent form, a questionnaire and a stamped and addressed envelope. Patients were encouraged to consult the researchers by

mail or telephone for information or assistance in completing the questionnaire. If the patient did not return the questionnaire after 2 weeks, we sent a reminder by mail. After another 2 weeks without a response we called the patient to inquire whether there were any difficulties and to encourage him to return the questionnaire.

Data collection

The questionnaire contained questions on demographics, current glaucoma medication, and co-morbidities. Side effects of current medications were explored with two lists of 16 typical side effects from pressure-lowering eye-drops.⁶ One list asked how often side effect occurred, ranging from never (0) to every day (5). The other asked how bothered the patient was by the side effect, ranging from 'not bothered' (0) to 'extremely bothered' (4). The scores for frequency and severity were multiplied and summed to obtain a total side-effect score between 0 and 320. An additional question asked whether side effects from glaucoma medication had affected quality-of-life (six levels, 'not at all' to 'very much'). Glaucoma-specific HRQOL was measured with the Glaucoma Quality-of-Life questionnaire (GQL-15), consisting of 15 items regarding daily activities.^{7,8} The GQL score ranges between 15 (best) and 75 (worst). Vision-specific HRQOL was measured with the National Eye Institute Visual Function Questionnaire (NEI VFQ-25), containing 25 items in 12 domains: general health, general vision, ocular pain, near-vision, distant-vision, social functioning, mental health, role functioning, dependency, driving, colour vision, and peripheral vision.^{9,10} An overall weighted average between 0 (worst) and 100 (best) was calculated with the VFQ-25 algorithm.¹¹ Generic HRQOL was measured with the EQ-5D and the Health Utility Index mark 3 (HUI3). The EQ-5D has five items in five domains: mobility, self-care, daily activities, pain/discomfort, and anxiety/depression.¹² A Dutch value set was used to translate the EQ-5D profiles into utility values reflecting the value of a health-state relative to death (0) and perfect health (1).¹³ The HUI3 has 15 items in 8 domains: vision, hearing, speech, mobility, dexterity, cognition, emotion, and pain/discomfort.¹⁴ A value set has been generated from a Canadian general population sample.¹⁵ In the regression analyses all utilities were rescaled from 0–1 to 0–100.

The mean deviation (MD) from the 30-2 threshold program of the Humphrey Field Analyzer (HFA, Carl Zeiss Meditec, Jena, Germany) closest to the date of participation was the primary variable to quantify visual field loss. All available visual field information was collected from automated perimeters or from printouts in

the medical files. Not all patients in our sample had a recent 30-2 HFA measurement available. As the availability of a 30-2 HFA measurement is related to disease severity, visual field data cannot be expected to be 'missing completely at random'.¹⁶ Because analyses based on complete cases only would lead to biased results, we have imputed missing MD values based on all available other visual field information (see Supplementary Table 2).¹⁶ If visual field data were only available for one eye ($n = 31$), this was presumed to be the worse eye. Visual acuity data closest to the date of participation in the study were retrieved from the medical files. We used the visual acuity measurement with the patients' own correction, or without correction if the former was not available (8% of the cases). Decimal and Snellen fraction notations were converted to logMAR values using conversion tables.¹⁷

Data analysis

Data were analysed in SPSS 14.0 (SPSS Inc, Chicago, IL, USA). Patient characteristics and outcomes are reported as median with twenty-fifth and seventy-fifth percentiles if their distribution deviated from normal. The statistical significance of differences between characteristics of participating versus non-participating patients was tested with a Mann-Whitney test. Differences between selection categories were tested with a Kruskal-Wallis test. Univariate relationships were tested for statistical significance with Spearman's rho in bivariate correlations. The impact of visual field loss on each of the HRQOL outcomes was assessed in multiple linear regression analyses that adjusted for the potentially confounding effect of age, sex, visual acuity in both the better and the worse eye, and side-effects from medication, laser trabeculoplasty or glaucoma surgery. Each of these factors were also entered in a single regression model. Assumptions for linear regression analysis were checked. Non-linearity in the multiple linear regression model was tested with Ramsey's reset test, and explored with dummy variables for six categories of MD in the better eye relative to the reference category of MD > 0: $-5 \leq MD < 0$, $-10 \leq MD < -5$, $-15 \leq MD < -10$, $-20 \leq MD < -15$, $-25 \leq MD < -20$, and $MD < -25$. Estimates of binocular MD were calculated from the total deviation plots of both eyes according to the best-location algorithm described by Nelson-Quigg *et al*¹⁸ Regression coefficients are reported with 95% confidence intervals (CIs). A significance level of 0.05 was used throughout all statistical analyses. We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research.

Results

Between April 2006 and January 2007, 654 eligible patients were invited to participate in the study; 531 patients consented (81%) and completed the questionnaire. We explored the differences between participating and non-participating patients in terms of age, visual acuity, and visual field (Supplementary Table 3). Formal statistical testing indicated significantly lower age and better visual acuity in participating patients, but the absolute differences were small from a clinical point of view (5 years, 0.05 logMAR in the better and 0.08 logMAR in the worse eye, respectively) and did not compromise the representativeness of the sample nor raise concerns for selection bias. The characteristics of participating patients are listed in Table 1. For most patients (95%) visual field information was available. The median interval from the last visual field test to completion of the questionnaire was 9 months. The interval was longer in OHT patients and end-stage POAG patients and shorter in medically treated POAG patients, reflecting variation in the frequency of visual field testing between these groups. Visual field data from a HFA 30-2 program within 2 years of study participation was available for 74% of the eyes. An additional 22% could be imputed on the basis of all the available visual field data from other sources. The majority of HFA 30-2 measurements were performed with the sita-fast (73%) or the sita-standard (25%) strategy. The median reliability indices of the HFA 30-2 measurements (10–90% percentiles) were as follows. Better eye: fixation loss 15% (0–40%), false negative 5% (0–14%), false positive 4% (0–11%). Worse eye: fixation loss 13% (0–33%), false negative 8% (0–21%), false positive 4% (0–10%). The reliability indices did not worsen with increasing disease severity, except for the percentage of false negatives, which increased from 2 to 9% in the better eye and from 3 to 8% in the worse eye between untreated OHT patients and end-stage POAG patients. The majority of patients with glaucoma surgery in their treatment history had had no more than one surgery in each eye (82%). The remaining 18% had undergone glaucoma surgery more than once in either or both eyes. Descriptive statistics of HRQOL scores in each selection category are listed in Table 2.

Strength and causality of the relationship

We found statistically significant coefficients for MD in both the better and worse eye in the single regression analyses of GQL, the VFQ-25, the EQ-5D utility and the HUI3 utility (Table 3, EQ-5D results are in Supplementary Table 4). The coefficients for MD were smaller after adjusting for confounding factors. There was no indication for non-linearity in the relationship

Table 1 Demographic and clinical characteristics of the total population and stratified in each sample category, median (twenty-fifth and seventy-fifth percentile)

Selection group	All	Untreated OHT	OHT medication	OHT LT	POAG medication	POAG LT	POAG surgery	End-stage POAG	P-value ^a
Invited	654	80	133	16	160	40	142	83	
Participated (n)	531	61	114	14	133	37	105	64	
Age	71 (63;78)	67 (62; 73)	72 (64; 76)	70 (62; 74)	72 (64; 80)	67 (58; 77)	73 (62; 80)	71 (63; 79)	0.023
Male	52 %	53%	50%	29%	51%	57%	54%	59%	0.508
Number of medications, n (%)									
0	131 (25%)	61 (100%)	0	10 (71%)	3 (2%)	7 (19%)	36 (34%)	15 (23%)	<0.001
1	207 (39%)	0	78 (68%)	2 (14%)	69 (51%)	15 (41%)	27 (26%)	17 (27%)	
2	123 (23%)	0	31 (27%)	1 (7%)	39 (29%)	8 (22%)	25 (24%)	19 (30%)	
> 2	68 (13%)	0	5 (4%)	1 (7%)	25 (18%)	7 (19%)	17 (16%)	13 (20%)	
Side-effect score	4 (0; 16)	0	4 (0; 12.5)	0 (0; 2)	2 (0; 12)	2 (0; 16.5)	1 (0; 15)	1 (0; 20.5)	<0.001
Visual acuity									
VA in better eye (logMAR)	0.05 (0.00; 0.15)	0.00 (−0.08; 0.05)	0.00 (0.00; 0.10)	0.02 (0.00; 0.10)	0.10 (0.00; 0.22)	0.00 (0.00; 0.10)	0.10 (0.00; 0.22)	0.10 (0.01; 0.30)	<0.001
VA in worse eye (logMAR)	0.22 (0.05; 0.40)	0.05 (0.00; 0.11)	0.10 (0.00; 0.30)	0.07 (0.00; 0.19)	0.22 (0.10; 0.40)	0.10 (0.05; 0.37)	0.30 (0.10; 0.92)	0.70 (0.22; 1.5)	<0.001
Visual field									
Time since last test (years)	0.8 (0.1; 2.5)	1.4 (0.5; 2.1)	1.6 (0.0; 3.4)	1.0 (0.2; 3.1)	0.3 (−0.2; 1.9)	0.7 (0.3; 2.1)	0.8 (0.2; 2.1)	1.2 (0.4; 3.0)	<0.001
MD in better eye, with imputed data	−1.7 (−5.0; −0.1)	0.0 (−0.9; 0.4)	−0.4 (−1.6; 0.2)	0.0 (−1.4; 0.6)	−1.8 (−3.9; 0.4)	−1.8 (−6.7; 0.5)	−4.9 (−12.0; −1.5)	−13.8 (−22.9; −3.7)	<0.001
MD in better eye, without imputed data	−1.6 (−4.7; 0.0)	−0.2 (−1.3; 0.8)	−0.4 (−1.7; 0.4)	−0.1 (−1.6; 0.7)	−1.7 (−3.4; −0.4)	−2.5 (−7.8; 0.5)	−4.4 (−10.1; −1.8)	−9.9 (−16.9; −3.5)	<0.001
MD in worse eye, with imputed data	−5.6 (−18.0; −1.4)	−0.4 (−1.8; 0.0)	−1.4 (−3.2; −0.1)	−1.7 (−4.3; 0.0)	−5.5 (−11.9; −1.6)	−8.5 (−16.3; −1.6)	−15.7 (−20.5; −9.3)	−28.4 (−30.5; −26.0)	<0.001
MD in worse eye, without imputed data	−3.8 (−12.8; −1.1)	−0.7 (−2.5; 0.2)	−1.5 (−3.0; −0.3)	−2.3 (−4.2; −0.3)	−4.8 (−11.6; −1.4)	−7.7 (−14.9; −1.3)	−13.9 (−20.4; −8.7)	−28.2 (−30.5; −26.0)	<0.001
Intraocular pressure									
IOP in better eye (mm Hg)	16 (14; 19)	22 (20; 24)	18 (15; 20)	18 (16; 20)	16 (14; 18)	16 (13; 19)	14 (11; 18)	13 (11; 16)	<0.001
IOP in worse eye (mm Hg)	16 (14; 19)	22 (20; 24)	18 (15; 20)	18 (17; 20)	16 (14; 18)	16 (13; 19)	14 (10; 16)	14 (11; 17)	<0.001

Abbreviations: IOP, intraocular pressure; LT, laser trabeculoplasty; MD, mean deviation; OHT, ocular hypertension; POAG, primary open-angle glaucoma; VA, visual acuity.
^aKruskal–Wallis test, χ^2 -test.

Table 2 Quality-of-life and utility scores in sampling categories. Mean, median (twenty-fifth and seventy-fifth percentile)

Instrument (worst-best score)	Total population	Untreated OHT	OHT	OHT medication	OHT LT	POAG medication	POAG LT	POAG surgery	End-stage POAG	P-value ^a
GQL score (75–15)	28, 23 (17; 34)	20, 18 (16; 23)	24, 20 (15; 27)	22, 18 (16; 25)	24, 20 (15; 27)	24, 20 (17; 27)	28, 24 (17; 34)	34, 31 (23; 43) ^b	48, 49 (29; 65) ^b	<0.001
VFQ-25 composite score (0–100)	78, 85 (70; 93)	88, 90 (84; 95)	85, 89 (80; 94)	87, 91 (84; 95)	85, 89 (80; 94)	83, 87 (77; 93) ^b	78, 84 (72; 92)	71, 77 (60; 86) ^b	53, 49 (31; 75) ^b	<0.001
EQ-5D VAS (0–100)	76, 80 (70; 85)	77, 80 (70; 83)	79, 80 (70; 90)	79, 80 (70; 90)	79, 80 (70; 90)	76, 80 (70; 85)	75, 80 (70; 80)	75, 80 (70; 85)	70, 70 (60; 80) ^b	0.014
EQ-5D utility (0–1)	0.87, 0.90 (0.81; 1.00)	0.89, 0.89 (0.81; 1.00)	0.92, 1.00 (0.81; 1.00)	0.90, 1.00 (0.81; 1.00)	0.92, 1.00 (0.81; 1.00)	0.88, 1.00 (0.81; 1.00)	0.89, 0.90 (0.81; 1.00)	0.84, 0.90 (0.77; 1.00)	0.79, 0.87 (0.69; 1.00) ^b	0.050
HUI 3 utility (0–1)	0.70, 0.79 (0.54; 0.92)	0.78, 0.85 (0.68; 0.92)	0.77, 0.81 (0.63; 0.92)	0.77, 0.85 (0.70; 0.97)	0.77, 0.81 (0.63; 0.92)	0.68, 0.79 (0.54; 0.91) ^b	0.74, 0.79 (0.63; 0.92)	0.66, 0.71 (0.47; 0.92)	0.54, 0.57 (0.33; 0.85) ^b	<0.001

Abbreviations: EQ-5D, EuroQol questionnaire; GQL, Glaucoma Quality-of-Life questionnaire; HUI3, Health Utility Index mark 3; LT, laser trabeculoplasty; OHT, ocular hypertension; POAG, primary open-angle glaucoma; VFQ, Visual Functioning Questionnaire.

^aKruskal–Wallis test.

^b $P < 0.008$ in Mann–Whitney test, compared with all previous groups.

between visual field loss and glaucoma- and vision-specific HRQOL. However, the relationship was not linear for EQ-5D and the HUI3, where utility seemed only significantly affected when MD was below -25 dB (Figure 1). The number of patients in this latter category was small ($n = 8$), but additional analyses did not indicate that outliers or influential cases had undue impact on these results. We varied the dummy variable cut-off point from -22 to -27 dB, but that did not result in a better fitting model.

Contribution of other factors

Some of the factors included in the multiple linear regression model showed a significant relationship with HRQOL, notably visual acuity and side effects of medication. In GQL and VFQ-25 scores also previous glaucoma surgery had a significant impact. The total amount of variance explained by the included factors was 0.54 for the GQL and VFQ-25 scores, 0.18 for EQ-5D utility and 0.26 for HUI3 utility (Table 3).

Contribution of either eye and type of visual field loss

The impact of visual field loss in the better eye was stronger than visual field loss in the worse eye (Table 3). We repeated the multiple regression analyses with an estimate of the binocular MD rather than MD in both eyes separately. In GQL scores the coefficient of binocular MD was -0.83 /dB (95% CI: -0.99 ; -0.66). The model significantly improved by adding MD in the worse eye, but not by adding MD in the better eye. The coefficients for binocular MD (-0.61 /dB) and MD in the worse eye (-0.28 /dB) were similar to the coefficients for respectively MD in the better and MD in the worse eye in the original regression model. GQL was predominantly affected by binocular visual field loss in the inferior hemifield (-0.71 /dB, 95% CI: -1.02 ; -0.41), and to a lesser extend by loss in the superior hemifield (-0.15 /dB, 95% CI: -0.42 ; 0.13). We saw the same pattern in the regression analyses of VFQ-25, with a coefficient of 1.02 /dB (95% CI: 0.80 ; 1.24) for binocular MD. The latter could be separated into 0.70 /dB (95% CI: 0.30 ; 1.11) for loss in the inferior hemifield and 0.35 /dB (95% CI: -0.22 ; 0.71) for loss in the superior hemifield. The coefficient for binocular MD did not reach statistical significance in the multiple regression model for EQ-5D utility, but it did in the model for HUI utility (0.68 /dB, 95% CI: 0.28 ; 1.08). The coefficient for loss in the inferior hemifield was 0.79 /dB (95% CI: 0.05 ; 1.53), and for loss in the superior hemifield -0.06 /dB (95% CI: -0.73 ; 0.61).

Table 3 Coefficients from single and multiple regression analyses with GQL-15 score, VFQ-25 score, and HUI3 utility (scale 0–100)

	Single		Multiple	
	Adjusted R ²	Coefficient (95% CI)	Adjusted R ²	Coefficient (95% CI)
GQL				
Constant			0.543	20.3 (14.0; 25.6)
Age (per year)	0.016	0.19 (0.07; 0.30)		−0.03 (−0.12; −0.06)
Male (versus female)	0.000	−1.2 (−3.8; 1.4)		−2.0 (−3.9; −0.2)
VA better eye (per 0.1 logMAR unit)	0.216	3.5 (2.9; 4.0)		1.6 (1.0; 2.1)
VA worse eye (per 0.1 logMAR unit)	0.128	1.1 (0.86; 1.4)		0.35 (0.20; 0.51)
Side effects (per point)	0.076	0.20 (0.14; 0.26)		0.14 (0.09; 0.18)
LT in treatment history	0.044	7.4 (4.5; 10.3)		0.81 (−1.5; 3.1)
Glaucoma surgery in treatment history	0.172	14.1 (11.4; 16.7)		3.2 (0.7; 5.7)
MD in better eye (per dB)	0.370	−1.4 (−1.6; −1.2)		−0.55 (−0.77; −0.33)
MD in worse eye (per dB)	0.128	−0.90 (−1.0; −0.80)		−0.32 (−0.47; −0.17)
VFQ-25				
Constant			0.543	91.2 (82.7; 99.7)
Age (per year)	0.021	−0.28 (−0.44; −0.12)		0.01 (−0.11; 0.13)
Male (versus female)	0.000	0.21 (−3.3; 3.7)		0.78 (−1.7; 3.3)
VA better eye (per 0.1 logMAR unit)	0.256	−5.1 (−5.8; −4.3)		−2.7 (−3.4; −1.9)
VA worse eye (per 0.1 logMAR unit)	0.222	−1.3 (−1.5; −1.1)		−0.46 (−0.67; −0.26)
Side effects (per point)	0.092	−0.30 (−0.38; −0.22)		−0.22 (−0.28; −0.16)
LT in treatment history	0.034	−8.9 (−12.9; −5.0)		−0.8 (−3.8; 2.3)
Glaucoma surgery in treatment history	0.152	−17.8 (−21.3; −14.2)		−4.4 (−7.8; −1.0)
MD in better eye (per dB)	0.351	1.9 (1.6; 2.1)		0.77 (0.48; 1.07)
MD in worse eye (per dB)	0.317	1.1 (1.0; 1.3)		0.28 (0.08; 0.48)
HUI3				
Constant			0.263	113.8 (98.5; 129.1)
Age (per year)	0.079	−0.75 (−0.97; −0.53)		−0.47 (−0.69; −0.26)
Male (versus female)	0.000	2.5 (−2.5; 7.4)		1.3 (−3.2; 5.8)
VA better eye (per 0.1 logMAR unit)	0.138	−5.3 (−6.4; −4.1)		−2.7 (−4.1; −1.3)
VA worse eye (per 0.1 logMAR unit)	0.095	−1.2 (−1.6; −0.9)		−0.47 (−0.84; −0.09)
Side effects (per point)	0.064	−0.36 (−0.47; −0.24)		−0.30 (−0.41; −0.20)
LT in treatment history	0.000	−2.0 (−7.6; 3.7)		3.5 (−2.0; 9.0)
Glaucoma surgery in treatment history	0.029	−11.2 (−16.6; −5.8)		−0.7 (−6.8; 5.4)
MD in better eye (per dB)	0.100	1.4 (1.0; 1.8)		0.40 (−0.13; 0.93)
MD in worse eye (per dB)	0.099	0.90 (0.67; 1.13)		0.28 (−0.08; 0.65)

Abbreviations: CI, confidence interval; GQL, Glaucoma Quality-of-Life questionnaire; HUI3, Health Utility Index mark 3; LT, laser trabeculoplasty; MD, mean deviation; VA, visual acuity; VFQ, Visual Functioning Questionnaire.

Patients at risk for quality-of-life loss due to visual field loss

We assessed the existence of patient characteristics that predicted a greater impact of visual field loss on HRQOL by introducing interaction terms in the multiple analysis. The interaction terms were constructed from MD in the better eye on the one hand, and each of the other factors in the multiple regression model on the other hand. Only one significant interaction was found, between the visual field loss in the better and the worse eye (only for GQL and VFQ-25 scores). The coefficients for MD in the better eye were no longer statistically significant in the models containing the interaction term. For GQL scores the coefficient for MD in the worse eye became $-0.27/\text{dB}$ (95% CI: -0.42 ; -0.12) and the coefficient for the

interaction term ($\text{MD}_{\text{better}} \times \text{MD}_{\text{worse}}$) was $0.04/\text{dB}^2$ (95% CI: 0.02 ; 0.05). For VFQ-25 scores these coefficients were $0.22/\text{dB}$ (95% CI: 0.02 ; 0.43) and $-0.04/\text{dB}^2$ (95% CI: -0.07 ; -0.02), respectively.

Discussion

This observational study assessing the relationship between visual field loss and HRQOL has several merits. Our patient population was large and heterogeneous, and we have measured glaucoma-specific, vision-specific and generic HRQOL (utility). The multiple regression analyses showed that visual field loss was associated with loss of glaucoma-specific and vision-specific HRQOL, but utility did not seem to be affected until the

Figure 1 (a, b) Regression coefficients for dummy variables representing categories of MD in the better eye relative to MD ≥ 0 ($n = 136$), adjusted for age, sex, visual acuity, medication side effects, laser trabeculoplasty, glaucoma surgery, and MD in the worse eye. The grey error bars indicate the 95% confidence intervals of the coefficients. The light grey line represents the expected value of the coefficient, according to the original multiple linear regression model with MD in the better eye as a continuous variable.

visual field defect in the better eye was below -25 dB. However, the sample size (specifically in the worst group) was small in the context of the large variance observed in utility. In addition, the multiple regression model may have overadjusted for some covariance. Visual acuity was entered to correct for the presence of non-glaucomatous eye diseases, notably cataract, which affects both HRQOL and MD. This assures that any loss of HRQOL that is not glaucoma related is not represented in the regression coefficient for MD. However, visual acuity contains a glaucoma-related component when central vision is affected by visual field loss. Indeed we saw a moderate association between visual acuity and MD within the same eye (better eye $r = -0.35$ ($P < 0.01$), worse eye $r = -0.46$ ($P < 0.01$)). By adjusting for visual acuity, we have also adjusted for the glaucomatous loss of visual acuity, which may have lead to an underestimation of the regression coefficient for MD.

The multiple regression coefficients of MD in the better eye were higher than those for MD in the worse eye, indicating that a worsening of visual field in the better eye has a larger HRQOL impact than visual field loss in the worse eye. We saw that the binocular visual field was almost completely determined by the visual field in the better eye (Spearman's $r = 0.96$, $P < 0.001$), which probably explains the relatively large impact of the better eye in vision-related activities and visual functioning. In order to maintain HRQOL in glaucoma patients it is, therefore, important to monitor the better eye with an equal amount of vigilance as the worse eye, even when it is not (yet) affected. This is even more so when the worse eye has suffered considerable visual field loss, as the regression analyses with interaction terms showed that the impact of visual field loss in the better eye grows with increasing visual field loss in the worse eye. As there is such a strong correlation of defects in the binocular visual field and in the better eye, there is no need to integrate both eyes' visual fields for better monitoring. Defects in the inferior hemifield call for closer monitoring as they affect HRQOL more strongly than defects in the superior hemifield.

We explored non-linearity in the relationship between HRQOL and MD. There was no indication for non-linearity in the multiple regression models for GQL and VFQ-25 when the interaction term for visual field loss in the better and the worse eye was included, signifying that glaucoma- and vision-specific HRQOL is equally impacted by early loss and advanced loss of visual field. However, we did find indications for non-linearity in the utility models, which was obviated in the regression analyses with dummy variables for categories of MD loss (Figure 1). Only the coefficient for 'MD in the better eye below -25 dB' was significantly different from zero, suggesting that utility is only affected by severe visual field loss in both eyes. Comparable observations have been made by Kobelt *et al*¹⁹ and Burr *et al*²⁰ for EQ-5D utilities in glaucoma patients, but their sample sizes were smaller and the utilities were not adjusted for visual acuity.^{19,20}

The visual field tests that provided the MD values of the participating patients were more recent in some patients than in others (Table 1). However, as a low frequency of visual field testing is likely to reflect a low probability of progression (either from disease stability or an end-stage plateau), the impact of bias in MD values based on visual field tests that were longer ago will probably be small. Moreover, when we added 'time since the last visual field test' to the regression models, the coefficients for MD in the better and worse eye were not affected.

Visual acuity of both eyes should explicitly be addressed in POAG patient management because

prevention of any visual acuity loss can preserve HRQOL. Side effects from medication had an independent impact on all HRQOL scores. To enable interpretation of the coefficients, we have calculated the difference in the average side-effect score from patients who indicated that glaucoma medication had 'none' or 'hardly any' impact on their quality-of-life (9 ± 16 , $n = 324$) and patients that indicated that the impact was 'quite a bit' or 'much' (52 ± 39 , $n = 20$). Multiplying the difference of 43 units with the regression coefficient for the HRQOL instruments yields a loss of 6 units in GQL score, 9 units in VFQ-25 score, 9% EQ-5D utility and 13% HUI utility as a result of severe side effects. For comparison, based on the regression coefficients found in the multiple regression models, the expected loss in HRQOL as a result of an MD decrease of 10 dB in both eyes would be 9, 11, 2, and 7%, respectively. Apparently, utility loss from side effects can be larger than utility loss from glaucoma progression, although the relationship between side effects and HRQOL may represent a certain degree of concurrent validity rather than an impact of side effects alone, because the side effect score may have captured components of quality-of-life. Discrete choice experiments have shown that patients value preservation of central and near vision, mobility and daily activities much higher than the absence of eye discomfort.^{20,21} The burden of side effects is usually temporary as treatment can be adjusted when side effects occur, but the impact of side effects on all HRQOL levels in this study emphasises the need to address this issue in patient management. We also found an independent impact of glaucoma surgery on glaucoma- and vision-specific HRQOL (but not generic HRQOL), which suggests that surgery may cause a reduction in quality-of-life, potentially as a result of post-surgical symptoms. On the basis of the coefficients for VFQ-25 (Table 3), the impact of surgery in terms of HRQOL would correspond to an MD decrease of 5 dB in the better eye, implying that the expected preservation of visual field must exceed 5 dB in order for the long-term benefits of surgery to outweigh the short-term hindrance. These results are not in accordance with the Collaborative Initial Glaucoma treatment Study, where the investigators indeed found surgery to be associated with more frequent and more bothersome symptoms, but not with worse vision-specific or generic HRQOL, nor in worse patient satisfaction.²² Despite the fact that the multiple regression models in our study corrected for the potential confounding effect of disease severity, the 'surgery' variable may have come up as an intermediate for aspects of disease severity not reflected by MD or visual acuity but associated with both quality-of-life and the likelihood of surgery. The causality of the relationship between surgery and quality of life can, therefore, not be inferred from these data.

The variables in the multiple regression models explained only part of all observed variance, and HRQOL in glaucoma patients is affected by additional factors than those that were included in our regression model. For example, when we included the presence of 16 types of comorbidities, education level and employment status, the amount of variance explained in GQL, VFQ, EQ-5D and HUI3 scores increased to 60, 60, 34, and 35%, respectively. These additional factors did not confound or modify the primary relationship between visual field and HRQOL, so they were excluded from the main analyses reported here.

Part of our patient population consisted of OHT patients without visual field damage, who were nevertheless included in the analyses. They represent one end of the glaucoma severity scale are, therefore, a reference point. In addition, their experience with treatment in terms of HRQOL was very relevant in our analyses. There may be concern though that the HRQOL scores in this group have unduly affected the regression lines, so we have repeated the analyses with data from POAG patients only. The conclusions remained unaltered. The coefficients for MD in the better and worse eye changed only slightly, and we still found non-linearity in the utility models and an interaction between MD in the better and worse eye for VFQ-25 and GQL outcomes.

The results from this study indicate that increasing visual field loss in progressing glaucoma is independently associated with a loss in both disease-specific and generic quality-of-life. In terms of glaucoma- and vision-specific HRQOL it is equally important to prevent progression in early stages as it is in advanced stages of glaucoma, especially in the better eye of the patient. Moreover, monitoring visual acuity, side effects, visual field defects in the inferior hemifield and patients with severe visual field impairment in one eye are of clinical importance.

Summary

What was known before

- Visual functioning and generic quality-of-life is lower in patients with severe glaucoma than in patients with mild glaucoma.
- Glaucoma treatment slows down disease progression, but may have its own effect on quality-of-life.

What this study adds

- Observational data on three levels of health-related quality-of-life (glaucoma-specific, vision-specific and generic) in the same population of ocular hypertension and primary open-angle glaucoma patients.
- Detailed information on the independent impact of visual field loss in all severity stages of glaucoma, as well as the impact of treatment and visual acuity.
- Additional analyses with focus on the binocularity and location of visual field defects.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

We are indebted to the staff and patients from the following centres for their participation and cooperation in this study: Catharina-ziekenhuis (Eindhoven), Jeroen Bosch Ziekenhuis ('s Hertogenbosch), Wilhelmina Ziekenhuis (Assen), Mesos Medisch Centrum (Utrecht), Groene Hart Ziekenhuis (Gouda), and Ziekenhuis Amstelland (Amstelveen).

Meeting presentations: Preliminary data of this research have been presented at the SOE/AAO joint conference (Vienna, June 2007) in poster presentation EP-GLA-446 (Abstract book, p 127). This poster was awarded the Best of Posters price. Final data have been presented at the World Glaucoma Congress (Boston, July 2009) in poster presentation P022.

Financial support: ZonMW, The Netherlands organization for health research and development. Health Care Efficiency Research Program: sub-program Effects & Costs. Grant number 945-04-451. The funding organization had no role in the design or conduct of this research.

References

- Maier P, Funk J, Schwarzer G, Antes G, Falck-Ytter Y. Treatment of ocular hypertension and open angle glaucoma: meta-analysis of randomised controlled trials. *BMJ* 2005; **331**: 134.
- Peeters A, Webers C, Prins M, Zeegers M, Hendrikse F, Schouten J. Quantifying the effect of intra-ocular pressure reduction on the occurrence of glaucoma. *Acta Ophthalmol* 2010; **88**: 5–11.
- Gutierrez P, Wilson M, Johnson C, Gordon M, Cioffi G, Ritch R *et al*. Influence of glaucomatous visual field loss on health-related quality of life. *Arch Ophthalmol* 1997; **115**: 777–784.
- Parrish R, Gedde S, Scott I, Feuer W, Schiffman J, Mangione C *et al*. Visual function and quality of life among patient with glaucoma. *Arch Ophthalmol* 1997; **115**: 1447–1455.
- McKean Cowdin R, Wang Y, Wu J, Azen SP, Varma R. Impact of visual field loss on health-related quality of life in glaucoma: the Los Angeles Latino Eye Study. *Ophthalmology* 2008; **115**: 941–948.
- Beckers HJ, Schouten JS, Webers CA, van der Valk R, Hendrikse F. Side effects of commonly used glaucoma medications: comparison of tolerability, chance of discontinuation, and patient satisfaction. *Graefes Arch Clin Exp Ophthalmol* 2008; **246**: 1485–1490.
- Nelson P, Aspinall P, Papasouliotis O, Worton B, O'Brien C. Quality of life in glaucoma and its relationship with visual function. *J Glaucoma* 2003; **12**: 139–150.
- Nelson P, Aspinall P, O'Brien C. Patients' perception of visual impairment in glaucoma: a pilot study. *Br J Ophthalmol* 1999; **83**: 546–552.
- Van der Sterre G, Van de Graaf E, Verezen C, Meulendijks C, Schouten J, Saxena R *et al*. *National Eye Institute Visual Functioning Questionnaire-25: Dutch consensus translation (VFQ-25/NL)*. Erasmus Medical Center Rotterdam, department of Ophthalmology: Rotterdam, 2001.
- Mangione C, Lee P, Pitts J, Gutierrez P, Berry S, Hays R *et al*. Psychometric properties of the National Eye Institute Visual Function Questionnaire (NEI-VFQ). *Arch Ophthalmol* 1998; **116**: 1496–1504.
- Mangione C. NEI VFQ-25 scoring algorithm. 2000. Available at: http://www.nei.nih.gov/resources/visionfunction/manual_cm2000.pdf. Accessed 23 June 2008.
- Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med* 2001; **33**: 337–343.
- Lamers L, Stalmeier P, McDonnell J, Krabbe P, van Busschbach J. Measuring the quality of life in economic evaluations: the Dutch EQ-5D tariff. *Ned Tijdschr Geneesk* 2005; **149**: 1574–1578.
- Torrance GW, Furlong W, Feeny D, Boyle M. Multi-attribute preference functions. Health Utilities Index. *Pharmacoeconomics* 1995; **7**: 503–520.
- Furlong W, Feeney D, Torrance G, Goldsmith C, DePauw S, Boyle M *et al*. Multiplicative multi-attribute utility function for the Health Utilities Index Mark 3 (HUI3) System: A Technical Report. *Working Paper No 98-11* McMaster University Centre for Health Economics and Policy Analysis.
- Donders A, Van der Heijden G, Stijnen T, Moons K. Review: a gentle introduction to imputation of missing values. *J Clin Epidemiol* 2006; **59**: 1087–1091.
- Ferris III FL, Kassoff A, Bresnick GH, Bailey I. New visual acuity charts for clinical research. *Am J Ophthalmol* 1982; **94**: 91–96.
- Nelson-Quigg J, Cello K, Johnson C. Predicting binocular visual field sensitivity from monocular visual field results. *Invest Ophthalmol Vis Sci* 2000; **41**: 2212–2221.
- Kobelt G, Jonsson B, Bergstrom A, Chen E, Linden C, Alm A. Cost-effectiveness analysis in glaucoma: what drives utility? Results from a pilot study in Sweden. *Acta Ophthalmol Scand* 2006; **84**: 363–371.
- Burr J, Kilonzo M, Vale L, Ryan M. Developing a preference-based glaucoma utility index using a discrete choice experiment. *Optom Vis Sci* 2007; **84**: 797–808.
- Aspinall P, Johnson Z, Azuara-Blanco A, Montarzino A, Brice R, Vickers A. Evaluation of quality of life and priorities of patients with glaucoma. *Invest Ophthalmol Vis Sci* 2008; **49**: 1907–1915.
- Janz N, Wren P, Lichter P, Musch D, Gillespie B, Guire K *et al*. The Collaborative Initial Glaucoma Treatment Study; Interim quality of life findings after initial medical or surgical treatment of glaucoma. *Ophthalmology* 2001; **108**: 1954–1965.

Supplementary Information accompanies the paper on Eye website (<http://www.nature.com/eye>)

The relationship between visual field loss in glaucoma and health-related quality-of-life

To obtain credit, you should first read the journal article. After reading the article, you should be able to answer the following, related, multiple choice questions. To complete the questions and earn continuing medical education (CME) credit, please go to www.medscapecme.com/journal/eye. Credit cannot be obtained for tests completed on paper, although you may use the worksheet below to keep a record of your answers.

You must be a registered user on Medscape.com. If you are not registered on Medscape.com, please click on the new users: Free Registration link on the left hand side of the website to register.

Only one answer is correct for each question. Once you successfully answer all post-test questions you will be able to view and/or print your certificate. For questions regarding the content of this activity, contact the accredited

provider, CME@medscape.net. For technical assistance, contact CME@webmd.net.

American Medical Association's Physician's Recognition Award (AMA PRA) credits are accepted in the US as evidence of participation in CME activities. For further information on this award, please refer to <http://www.ama-assn.org/ama/pub/category/2922.html>. The AMA has determined that physicians not licensed in the US who participate in this CME activity are eligible for *AMA PRA Category 1 Credits*TM. Through agreements that the AMA has made with agencies in some countries, AMA PRA credit is acceptable as evidence of participation in CME activities. If you are not licensed in the US and want to obtain an AMA PRA CME credit, please complete the questions online, print the certificate and present it to your national medical association.

1. You are seeing a 71-year-old man with primary open-angle glaucoma (POAG), previously treated with medications, laser trabeculoplasty (LT), and surgery. He has a history of reduced visual acuity and visual field loss.
According to the results of the current study, all of the following factors are significantly related to his health-related quality-of-life (HRQOL) *except*:
 - A Visual acuity
 - B Side effects of medication
 - C Previous glaucoma surgery
 - D Previous LT
2. According to the results of the current study, what type of visual field loss would place this patient at a particularly higher risk for reduced HRQOL?
 - A Superior hemifield loss in the better eye
 - B Inferior hemifield loss in the better eye
 - C Superior hemifield loss in the worse eye
 - D Inferior hemifield loss in the worse eye
3. At what severity of mean deviation did visual field loss in the better eye significantly begin to affect HRQOL in the current study?
 - A Less than -5 dB
 - B Less than -10 dB
 - C Less than -15 dB
 - D Less than -25 dB

4. Which of the following statements regarding the further monitoring of this gentleman to prevent reduced HRQOL is most accurate?
 - A If his better eye is not affected, it should not be monitored for signs of visual field loss or reduced visual acuity
 - B The impact of visual field loss in the better eye declines with increasing visual field loss in the worse eye
 - C Utility loss from medication side effects can outweigh utility loss due to glaucoma progression
 - D Early monitoring should improve HRQOL outcomes for patients with ocular hypertension, but not those with POAG

Activity evaluation

1. The activity supported the learning objectives.

Strongly disagree Strongly agree
1 2 3 4 5

2. The material was organized clearly for learning to occur.

Strongly disagree Strongly agree
1 2 3 4 5

3. The content learned from this activity will impact my practice

Strongly disagree Strongly agree
1 2 3 4 5

4. The activity was presented objectively and free of commercial bias.

Strongly disagree Strongly agree
1 2 3 4 5