

Continuing Medical Education:

Baseline factors predicting the risk of conversion from ocular hypertension to primary open-angle glaucoma during a 10-year follow-up

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Learning Objectives

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

1. Determine baseline clinical factors that predict conversion to POAG in patients with OHT, based on a single-center, prospective, longitudinal observational study.
2. Determine baseline morphologic factors that predict conversion to POAG in patients with OHT.
3. Identify baseline functional factors that predict conversion to POAG in patients with OHT.

Authors/Editors disclosure information

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Baseline factors predicting the risk of conversion from ocular hypertension to primary open-angle glaucoma during a 10-year follow-up

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Abstract

Purpose To evaluate the ability of baseline clinical, morphological, and functional factors to predict the conversion to primary open-angle glaucoma (POAG) in ocular hypertensive (OHT) patients.

Methods This single-center prospective longitudinal observational study included 116 eyes of 116 OHT patients followed for a 10-year period. All patients had intraocular pressure (IOP) ≥ 24 mm Hg in one eye and > 21 mm Hg in the other eye, normal visual fields (VFs) and normal optic disc (OD) appearance in both eyes at baseline. All OHT patients were untreated at baseline with subsequent treatment upon need according to clinical judgement. Only one eye per subject was randomly selected. Patient age, gender, IOP, central corneal thickness (CCT), and ibopamine test results were collected at baseline. All patients underwent standard automated perimetry, short-wavelength automated perimetry (SWAP), frequency-doubling technology, confocal scanning laser ophthalmoscopy (CSLO), and scanning laser polarimetry (SLP) at baseline and every 6 months thereafter. Main outcome measure was the conversion to POAG, defined as the development of reproducible VF and/or OD abnormalities attributable to glaucoma. Cox proportional hazards models were used to identify the baseline factors predictive of POAG conversion.

Results During the 10-year follow-up, 25% of eyes converted to POAG. In multivariate Cox models, baseline factors that were significant predictors of POAG development

included: older age (hazard ratio (HR) 1.0, 99% confidence intervals (CIs) 1.0–1.2, per 1 year older); SWAP Glaucoma Hemifield test 'outside normal limits' (HR 4.3, 99% CIs 1.2–17.9); greater SLP 'Inter-eye Symmetry' (HR 1.1, 99% CIs 0.4–3.0, per 1 unit lower); lower CSLO Rim Volume (HR 1.1, 99% CIs 0.3–3.2, per 0.1 mm³ lower); and greater CSLO cup-to-disc ratio (HR 6.0, 99% CIs 3.6–16.8, per 0.1 unit greater).

Conclusions The baseline parameters that proved to be useful in assessing the likelihood of an OHT patient to develop POAG included age, functional variables provided by SWAP, and structural variables provided by SLP and CSLO. In this cohort of patients, baseline IOP, CCT, and ibopamine provocative test results were not significant predictors of POAG conversion.

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Introduction

Ocular hypertension (OHT) has been shown to be the most important risk factor in the development of primary open-angle glaucoma (POAG),^{1–5} and intraocular pressure (IOP) reduction has proven to be beneficial in halting or delaying POAG onset⁶ and progression.⁷ The treatment of all OHT patients, however, is not justified because of the high prevalence of OHT;⁸ the low conversion rate to POAG;^{3–5} and the cost and possible adverse effects of treatment.

In order to prevent the onset of POAG in OHT patients, previous large prospective cohort

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studies³⁻⁵ have attempted to identify predictive factors of the conversion of OHT to POAG, in order to identify those OHT patients who might benefit from close observation and early treatment. Older age, higher IOP, larger vertical or horizontal cup-to-disc (C/D) ratio, greater standard automated perimetry (SAP) pattern standard deviation (PSD) and thinner central corneal thickness (CCT) at baseline have all been found to be significant predictors for the onset of POAG in OHT patients in large multicenter long-term clinical trials, such as the Ocular Hypertension Treatment Study (OHTS)³ and the European Glaucoma Prevention Study (EGPS).⁵ The OHTS-EGPS prediction model has been validated in large independent populations showing predictive value.^{9,10} Other risk factors for POAG are age, race, positive family history, and low diastolic perfusion pressure.^{1,2,11-13}

Although SAP and ophthalmoscopic examination of the optic disc (OD) are still considered to be the clinical gold standards in the diagnosis and follow-up of glaucoma,^{14,15} several new instrumental tests have been shown to provide earlier detection of functional or morphological glaucomatous damage,^{16,17} including short-wavelength automated perimetry (SWAP),¹⁸ frequency-doubling technology (FDT),¹⁹ confocal scanning laser ophthalmoscopy (CSLO) with Heidelberg Retina Tomography (HRT),²⁰ and scanning laser polarimetry (SLP).²¹ The ability of predictive models may improve with the inclusion of parameters provided by these new non-conventional perimetric tests and imaging instruments.

Ibopamine (3,4 di-isobutyrylester of N-methyldopamine) is a D₁-dopamine and alpha-adrenergic agonist that induces an increased aqueous humor production and a noncycloplegic mydriasis when instilled in the conjunctival sac.²² Previous studies have demonstrated that ibopamine eye drops can cause an IOP increase in subjects having a reduced functioning of the outflow structures, which include patients with: POAG, normal tension glaucoma, positive family history, and hydrodynamic disorders caused by corticosteroids; healthy patients, on the other hand, tend to show no influence on IOP with ibopamine.^{23,24} The ibopamine test has been reported to be an efficient provocative test in the management of glaucoma and patients at risk.²⁵

The purpose of this study was to determine whether higher IOP values, lower CCT measurements, positive ibopamine test results, SAP, SWAP, FDT, CSLO, or SLP alterations at baseline might be associated with an increased risk for development of POAG in OHT patients.

Materials and methods

This single-center prospective longitudinal clinical observational study included 133 OHT patients. Only one eye per subject was randomly selected using a computer-generated randomized number assignment if both eyes met the inclusion criteria.

OHT patients were cases referred by general ophthalmologists sent for further assessment and follow-up to the Department of Ophthalmology Glaucoma Center of the S. Maria della Misericordia Hospital, Udine, Italy, and were prospectively and consecutively evaluated. Eligible OHT patients were consecutive cases of either newly diagnosed or periodically monitored OHT patients in our Glaucoma Center, and were enrolled between 1 January and 30 September 2003.

The study was in compliance with Institutional Review Boards (IRBs) and HIPAA requirements and it was approved by the IRB of the Azienda Ospedaliero-Universitaria 'Santa Maria della Misericordia', Udine, Italy.

The study was in compliance with the tenets of the Declaration of Helsinki Principles. The nature and purpose of the study were explained in detail to all participants, and informed consent (in accordance with the Ethical Review Committee regulations) was obtained from all 133 participants prior to testing.

Inclusion criteria were: IOP (before medication) ≥ 24 mm Hg in one eye and > 21 mm Hg in the other eye, on at least three Goldmann applanation tonometry (GAT) measurements; normal OD and retinal nerve fiber layer (RNFL) appearance in both eyes; two normal and reliable SAP VF test results in both eyes; best-corrected visual acuity better than or equal to 0.7; open anterior chamber angle; absence of ocular pathology other than OHT, mild cataract and rare macular drusen; reliable SAP, SWAP, and FDT test results; good CSLO and SLP image quality; and willingness to provide written informed consent. Normal OD and RNFL appearance were clinically defined as: inter-eye vertical cup-disk asymmetry < 0.2 ; C/D ratio < 0.6 ; and, the absence of diffuse or focal rim thinning, cupping, localized pallor, optic disk hemorrhage, or RNFL defects. The criteria for normal SAP results were defined as not having a cluster of three or more points with *P*-value $< 5\%$ in the pattern deviation probability (PDP) plot, and PSD and glaucoma hemifield test (GHT) results within normal limits.²⁶

Exclusion criteria included: age < 30 years; ocular congenital abnormalities; ametropia $> \pm 5$ diopters; pupil diameter < 2 mm; angle alterations; acquired ocular diseases; secondary causes of high IOP (ie, pseudoexfoliation syndrome, pigment dispersion syndrome, iridocyclitis, trauma, and corticosteroid use); POAG or other primary or secondary glaucoma; systemic

pathologies that could be associated with glaucoma (eg, systemic hypotension, cardiovascular diseases, and diabetes); other diseases that could cause VF loss (eg, neurological disorders, pituitary lesion, and demyelinating diseases); medication that could modify VF results; OD abnormalities; media opacities preventing good image scans; previous intraocular surgery (excluding cataract surgery performed at least 6 months prior); pregnant or nursing women; and debilitating diseases that limit the patient's ability in performing all testing procedures at least twice yearly for 10 years.

All participants enrolled in the study were by definition untreated at baseline. During the follow-up, IOP therapy could be added and modified based on the judgement of the treating clinician. An IOP ≥ 27 mm Hg, a CCT ≤ 500 μm , and the presence of an immediate blood relative affected by glaucoma were strong indicators for adding or modifying the anti-glaucoma medications.

The baseline visit included: demographic and clinical data collection; complete ophthalmologic examination, including IOP and CCT measurements, gonioscopy, and optic disc evaluation using the slit-lamp and a Volk 78-D lens; ibopamine provocative test; functional tests, including SAP, SWAP, and FDT VF testing; and morphological tests, including CSLO and SLP imaging. The follow-up visits were performed at 6 months intervals for 10 years or until a censored event, and included: complete ophthalmologic examination; functional tests, including SAP, SWAP, and FDT VF testing; morphological tests, including CSLO and SLP imaging. Baseline and follow-up visits were performed by a single glaucoma specialist (CT).

Tests and instruments

IOP was taken with GAT. CCT was measured with ultrasonic pachymetry (Altair pachymeter, Optikon 2000, Rome, Italy).

The ibopamine test was performed by instilling 2% ibopamine (3,4 di-isobutyrylester of N-methyldopamine) twice (interval of 5 min between drops) in the conjunctival sac, followed by repeat IOP measurements. The test is considered positive if there is an IOP increase of ≥ 3 mm Hg 45 min after instillation.²⁵

SAP testing was performed using the Humphrey Field Analyzer (HFA) II 750 (Carl Zeiss Meditec, Inc., Dublin, CA, USA) 30–2 test with Standard Swedish Interactive Thresholding Algorithm strategy. Reliability criteria included false-positive $< 15\%$, false-negative $< 33\%$, and fixation losses $< 20\%$.

The FDT N-30 full-threshold procedure was used (Welch Allyn FDT, Skaneateles Falls, NY, USA and Carl Zeiss Meditec, Inc.).¹⁹ The stimulus is a sinusoidal grating of low spatial frequency (0.25 cycles/degree) with high

temporal frequency (25 Hz); a Modified Binary Search strategy is utilized. Reliability criteria included fixation loss, false negative and false positive $< 33\%$.

SWAP¹⁸ was performed using the HFA II (Carl Zeiss Meditec, Inc.). A full-threshold 30–2 test was used with a blue (440 nm) size V (1.72°) 200 msec duration stimulus on yellow background (530 nm). SAP testing reliability criteria were used.

SAP, SWAP, and FDT VF testing were administered in random order, with a rest interval of at least 10 min between tests.

CSLO imaging was performed with the HRT II (Heidelberg Engineering, Heidelberg, Germany, software version 1.4.1.5).²⁰ Exclusion criteria included: acquisition sensitivity $< 90\%$; SD > 40 microns; poor OD centration or image clarity. HRT classification is based on the Moorfields Regression Analysis (MRA) analysis, which includes: 'Within normal limits' (confidence interval (CI) $< 95\%$); 'Borderline' (95–99.9% CI); and, 'Outside normal limits' (CI $> 99.9\%$).

SLP imaging was performed with GDx VCC (Carl Zeiss Meditec, Inc.; software version 5.1.0) equipped with a variable corneal compensator (VCC).²¹ The parameters include mean RNFL thickness average for: the entire 360° (TSNIT average); temporal (335–24°), superior (25–144°), nasal (145–214°), and inferior (215–334°) quadrants. Inclusion criteria included: quality scores > 8 , residual anterior segment retardation ≤ 15 nm, and typical scan score > 25 .

Main outcome measure

The main outcome measure was the conversion from OHT to POAG, defined as the development of reproducible VF abnormalities (functional endpoint) and/or OD or RNFL abnormalities (morphological endpoint) attributable to glaucoma. Morphological endpoint was met if at least one of the following was evident: ONH excavation, that is, undermining of the neural rim; notching involving ≥ 2 clock hours; focal or diffuse thinning of neural rim area involving ≥ 2 clock hours; focal or generalized atrophy of the RNFL. Functional endpoint was reached when at least one of the Anderson and Patella criteria²⁷ was met: (1) a cluster of three points in the PDP plot, located in typical glaucomatous areas, having $P < 5\%$, with at least one point with $P < 1\%$; none of the points could be edge points unless they were located immediately above or below the nasal horizontal meridian; (2) PSD $< 5\%$; (3) GHT result outside normal limits. Confirmed VF defect required three consecutive, abnormal VF test results, with VF damage in the same test locations. The morphological and/or functional endpoint was reached based on masked consensus grading of two expert graders.

Adjudication by a third expert grader was completed in cases of disagreement. The confirmation that the endpoint was attributable to POAG and the exclusion of artifacts as possible causes of VF or OD abnormalities were determined after masked review of the clinical charts by a third masked evaluator.

The endpoint time was defined as the time of development of POAG for patients showing conversion; and as the time of the last visit of the follow-up for non-converters.

Statistical analysis

Data distribution were analyzed using the Kolmogorov–Smirnov test. Comparisons between groups were assessed using the unpaired Student’s *t*-test and the Mann–Whitney test. Differences between proportions were evaluated using the χ^2 -test. Univariate and multivariate Cox proportional hazard models were used to identify the baseline factors that were predictive of POAG conversion.

The variables considered in the univariate models included the following:

Demographic and clinical data: age, sex, CCT; baseline IOP;

Ibopamine test results: (positive *vs* negative; IOP peak 45 min after ibopamine administration and differences in IOP (Δ IOP) in comparison with pre-test IOP value;

SAP: mean deviation (MD), PSD, number of significantly abnormal areas with $P < 5\%$ and $P < 1\%$ in the PDP plot and GHT result. For baseline VF, the second obtained normal and reliable VF was used for the analysis.

SWAP: MD, PSD, number of significantly abnormal areas with $P < 5\%$ and $P < 1\%$ in the PDP plot, and GHT test result;

FDT: MD, PSD, number of significantly abnormal areas with $P < 5\%$ and $P < 1\%$ in the PDP plot. An abnormal FDT examination was defined by the presence of at least two areas with $P < 5\%$ or worse on the PDP plot or by the presence of a PSD with $P < 5\%$ or worse.²⁸

HRT II: all parameters listed on the HRT Stereometric Analysis printout;

GDx VCC: nerve fiber indicator, inter-eye symmetry, TSNIT average, TSNIT-SD, superior average and inferior average.

Variables with $P < 0.1$ in the univariate model were considered in a multivariate model. Cox proportional hazards multivariate model was performed using a backward strategy, with a statistical significance cutoff for variable screening of 0.05. The statistical analysis was performed using SPSS 11.0 for Windows (SPSS, Inc., Chicago, IL, USA). Statistical significance was defined as $P < 0.05$.

Table 1 Ten-year follow-up results

	No. of cases
Included patients	133
Patients that discontinued the follow-up	17
Adverse events	7
Unwillingness to continue the follow-up	10
Patients that completed the follow-up	116
Patients that underwent cataract surgery during the follow-up	15
Non-convertes to POAG	87
Converters to POAG	29
Reaching a functional endpoint	10
Reaching a morphological endpoint	19
Based on optic disc damage	13
Based on retinal nerve fiber layer damage	4
Based on both optic disc and retinal nerve fiber layer damage	2
Patients that underwent anti-glaucoma treatment	92
Non-converters	67
Converters	25
Patients that did not untergo anti-glaucoma treatment	24
Non-converters	20
Converters	4

Abbreviation: POAG, primary open-angle glaucoma.

Results

The 10-year follow-up results are summarized in Table 1. Of the 116 patients that completed the 10-year follow-up, 29 (25%) developed POAG and 87 (75%) did not by the end of the trial (30 September 2013). Mean follow-up time was 85.9 ± 42 months (range 12–120) for converters and 115.3 ± 5.0 months (range 108–120) for non-converters. Median conversion time was 48 ± 20.1 months (range 12–84).

The comparisons of baseline variables for all OHT eyes that either developed PAOG or did not are shown in Table 2. A statistically significant difference was found at baseline between converters and nonconverters for the following parameters: age, SWAP number points with $P < 5\%$ on the PDP plot; number of eyes with SWAP GHT ‘outside normal limits’; GDx VCC inter-eye Symmetry; all HRT II variables with exception to disc area, cup volume, mean cup depth, maximum cup depth, and the number of eyes with MRA ‘outside normal limits’.

Table 3 lists the univariate and multivariate hazard ratios with CIs and *P*-values for the development of POAG among OHT patients for each putative predictive baseline factor. All variables with $P < 0.1$ in the univariate model were entered in a multivariate model. In univariate analysis, baseline variables significantly predictive of the

Table 2 Comparison of baseline variables between converters and non-converters

Variables	Converters (no. of eyes = 29) Mean ± SD ^a	Non-converters (no. of eyes = 87) Mean ± SD ^a	Inter-groups differences P-value
<i>Demographic and clinical data</i>			
<i>Demographic data</i>			
Age (years)	67.8 ± 8.9	63.4 ± 8.2	0.02 ^b
Sex (Male/Female)	16/13	40/47	0.09 ^c
<i>Clinical data</i>			
IOP (mmHg)	25.4 ± 3.6	25.6 ± 3.6	0.82 ^b
CCT (μm)	563.8 ± 41.5	561.5 ± 39.9	0.79 ^b
Anti-glaucoma treatment (yes/no)	25/4	67/20	0.29 ^c
<i>Chemical tests</i>			
<i>Ibopamine test</i>			
Test result (pos/neg)	20/9	51/36	0.23 ^c
Δ IOP (mmHg)	6.2 ± 4.7	5.4 ± 4.9	0.42 ^b
IOP peak (mmHg)	27.0 ± 6.0	27.0 ± 5.0	0.96 ^b
<i>Functional tests</i>			
<i>SAP</i>			
MD (dB)	-0.56 ± 1.3	-0.26 ± 1.1	0.23 ^b
PSD (dB)	1.6 ± 0.3	1.6 ± 0.3	0.79 ^b
Number of points with P < 5%	2.0 ± 2.1	2.0 ± 2.2	0.62 ^d
Number of points with P < 1%	0.0 ± 0.4	0.0 ± 0.5	0.11 ^d
GHT 'outside normal limits' (yes/no)	0/29	0/87	1.0 ^c
<i>SWAP</i>			
MD (dB)	0.81 ± 2.5	0.59 ± 2.5	0.68 ^b
PSD (dB)	3.15 ± 0.8	2.9 ± 0.6	0.11 ^b
Number of points with P < 5%	2.0 ± 3.6	1.0 ± 3.1	0.006 ^d
Number of points with P < 1%	0.0 ± 0.8	0.0 ± 0.6	0.44 ^d
GHT 'outside normal limits' (Yes/No)	5/24	3/84	0.03 ^c
<i>FDT</i>			
MD	1.0 ± 2.3	0.43 ± 2.0	0.20 ^b
PSD	3.8 ± 0.8	3.75 ± 1.3	0.76 ^b
Number of areas with P < 5%	2.0 ± 2.6	2.0 ± 2.2	0.40 ^d
Number of areas with P < 1%	0.0 ± 0.7	0.0 ± 0.9	0.51 ^d
FDT test result (normal/abnormal)	12/17	46/41	0.17 ^c
<i>Structural tests</i>			
<i>GDxVCC</i>			
NFI	19.0 ± 6.5	19.3 ± 6.4	0.81 ^b
TSNIT average (μm)	56.2 ± 5.6	56.6 ± 5.2	0.72 ^b
TSNIT SD	68.1 ± 7.6	68.2 ± 6.8	0.94 ^b
Superior average (μm)	63.6 ± 8.1	64.3 ± 7.5	0.69 ^b
Inferior average (μm)	22.3 ± 4.7	21.5 ± 4.3	0.40 ^b
Inter-eye symmetry	0.83 ± 0.1	0.86 ± 0.1	0.04 ^b
<i>HRT II</i>			
Disc area (mm ²)	1.93 ± 0.4	1.96 ± 0.4	0.75 ^b
Cup area (mm ²)	0.47 ± 0.3	0.35 ± 0.2	0.03 ^b
Rim area (mm ²)	1.46 ± 0.3	1.61 ± 0.3	0.04 ^b
Cup volume (mm ³)	0.09 ± 0.1	0.06 ± 0.1	0.07 ^b
Rim volume (mm ³)	0.36 ± 0.1	0.45 ± 0.1	0.002 ^b
C/D Ratio	0.23 ± 0.1	0.17 ± 0.1	0.01 ^b
Linear C/D Ratio	0.45 ± 0.2	0.39 ± 0.1	0.01 ^b
Mean cup depth (mm)	0.19 ± 0.1	0.18 ± 0.1	0.33 ^b
Maximum cup depth (mm)	0.52 ± 0.2	0.51 ± 0.2	0.91 ^b
Cup shape measure	-0.17 ± 0.1	-0.20 ± 0.1	0.04 ^b
Height variation contour (mm)	0.30 ± 0.1	0.40 ± 0.1	0.004 ^b
Mean RNFL thickness (mm)	0.20 ± 0.1	0.26 ± 0.1	0.004 ^b
RNFL cross sectional area (mm ²)	1.10 ± 0.4	1.30 ± 0.4	0.001 ^b
MRA 'outside normal limits' (yes/no)	0/29	0/87	1.0 ^c

Abbreviations: CCT, central corneal thickness; C/D, cup/disc; CI, confidence interval; FDT, frequency-doubling technology; GDxVCC, scanning laser polarimetry with variable corneal compensator; GHT, glaucoma hemifield test; HRT, Heidelberg retina tomography; IOP, intraocular pressure; MD, mean deviation; MRA, Moorfields regression analysis; NFI, nerve fiber indicator; PSD, pattern standard deviation; RNFL, retinal nerve fiber layer; SAP, standard automated perimetry; SWAP, short-wavelength automated perimetry. ^aMedian ± SE for non-normally distributed variables. ^bUnpaired t-test. ^cχ²-test. ^dMann-Whitney test.

development of POAG included: patient age, SWAP PSD, SWAP number points with P < 5% on the PDP plot, SWAP GHT 'outside normal limits', GDx VCC inter-eye symmetry, HRT II cup area, rim area, cup volume, rim

volume, C/D ratio, linear C/D ratio, cup shape measure, height variation contour, mean RNFL thickness, and RNFL cross sectional area. Baseline variables significantly associated with the development of POAG in both

Table 3 Univariate and Multivariate Cox proportional hazard models for the development of primary open-angle glaucoma among patients with ocular hypertension

Variables	Univariate model			Multivariate model		
	HR	99% CI	P-value	HR	95% CI	P-value
<i>Demographic and clinical data</i>						
<i>Demographic data</i>						
Age (per 1 year older)	1.1	1.0–1.2	0.01	1.0	1.0–1.1	0.047
sex (Male)	1.1	0.8–1.3	0.62	—	—	—
<i>Clinical data</i>						
IOP (per 1 mm Hg higher)	1.0	0.9–1.1	0.85	—	—	—
CCT (per 1 μ m lower)	1.0	0.9–1.0	0.75	—	—	—
Anti-glaucoma treatment (yes)	1.6	0.6–3.5	0.39	—	—	—
<i>Chemical tests</i>						
<i>Ibopamine test</i>						
Test result (positive)	1.5	0.6–2.4	0.28	—	—	—
Δ IOP (per 1 mm Hg higher)	1.0	0.9–1.1	0.45	—	—	—
IOP peak (per 1 mm Hg higher)	1.0	0.9–1.1	0.87	—	—	—
<i>Functional tests</i>						
<i>SAP</i>						
MD (per 0.1 dB lower)	0.8	0.5–1.2	0.18	—	—	—
PSD (per 0.1 dB higher)	0.9	0.2–3.9	0.91	—	—	—
Number of points with $P < 5\%$ (per point abnormal)	1.0	0.8–1.2	0.81	—	—	—
Number of points with $P < 1\%$ (per point abnormal)	1.3	0.6–2.8	0.35	—	—	—
GHT (outside normal limits)	NA	NA	NA	—	—	—
<i>SWAP</i>						
MD (per 0.1 dB lower)	1.0	0.8–1.3	0.71	—	—	—
PSD (per 0.1 dB higher)	1.6	0.8–3.2	0.07	0.7	0.6–2.2	0.48
Number of points with $P < 5\%$ (per point abnormal)	1.5	0.9–3.2	0.03	1.0	0.9–1.2	0.76
Number of points with $P < 1\%$ (per point abnormal)	1.3	0.7–2.2	0.27	—	—	—
GHT (outside normal limits)	3.4	0.8–13.6	0.002	4.3	1.4–13.5	0.01
<i>FDT</i>						
(per 0.1 dB lower)	1.1	0.9–1.4	0.16	—	—	—
(per 0.1 dB higher)	1.0	0.7–1.5	0.71	—	—	—
Number of areas with $P < 5\%$ (per area abnormal)	1.1	0.9–1.3	0.32	—	—	—
Number of areas with $P < 1\%$ (per area abnormal)	0.9	0.4–1.8	0.64	—	—	—
Test result (abnormal)	1.2	0.8–1.5	0.28	—	—	—
<i>Structural tests</i>						
<i>GDxVCC</i>						
NFI (per 1 unit higher)	1.0	0.9–1.1	0.74	—	—	—
TSNIT average (per 10 μ m thinner)	1.0	0.9–1.1	0.80	—	—	—
TSNIT SD (per 10 μ m greater)	1.0	0.9–1.1	1.0	—	—	—
Superior Average (per 10 μ m thinner)	1.0	0.9–1.1	0.67	—	—	—
Inferior Average (per 10 μ m thinner)	1.0	0.9–1.2	0.45	—	—	—
Inter-eye symmetry (per 1 unit lower)	1.2	0.6–3.6	0.03	1.1	0.7–2.7	0.02
<i>HRT II</i>						
Disc area (per 0.1 mm ² greater)	0.8	0.3–2.5	0.76	—	—	—
Cup area (per 0.1 mm ² greater)	4.9	1.4–16.7	0.01	2.0	1.1–6.9	0.48
Rim area (per 0.3 mm ² lower)	0.9	0.2–3.1	0.04	0.7	0.4–1.3	0.25
Cup volume (per 0.1 mm ³ greater)	3.7	1.2–9.8	0.06	1.2	0.8–4.8	0.62
Rim volume (per 0.1 mm ³ lower)	0.8	0.3–2.6	0.002	1.1	0.5–2.8	0.005
C/D ratio (per 0.1 unit greater)	6.2	3.2–17.7	0.008	6.0	3.9–14.9	0.02
Linear C/D ratio (per 0.1 units greater)	4.1	1.8–9.2	0.06	1.4	1.0–2.0	0.10
Mean cup depth (per 0.1 mm greater)	1.3	1.0–1.7	0.51	—	—	—
Maximum cup depth (per 0.1 mm greater)	1.2	0.7–2.7	0.85	—	—	—
Cup shape measure (per 0.1 units greater)	5.3	2.0–19.1	0.05	3.3	1.4–9.8	0.72
Height variation contour (per 0.1 mm greater)	2.7	1.7–4.1	0.003	1.5	1.2–1.7	0.61
Mean RNFL thickness (per 0.2 mm lower)	0.9	0.7–2.0	0.002	0.7	0.6–1.1	0.57
RNFL cross sectional area (per 0.3 mm ² lower)	0.7	0.4–2.1	0.003	0.4	0.3–1.0	0.66
MRA (outside normal limits)	NA	NA	NA	—	—	—

Abbreviations: C/D, cup/disc; CI, confidence interval; FDT, frequency-doubling technology; GDxVCC, scanning laser polarimetry with variable corneal compensator; GHT, glaucoma hemifield test; HR, hazard ratios; HRT, Heidelberg retina tomography; MD, mean deviation; MRA, Moorfields regression analysis NA, not applicable; NFI, nerve fiber indicator; PSD, pattern standard deviation; RNFL, retinal nerve fiber layer; SAP, standard automated perimetry; SWAP, short-wavelength automated perimetry.

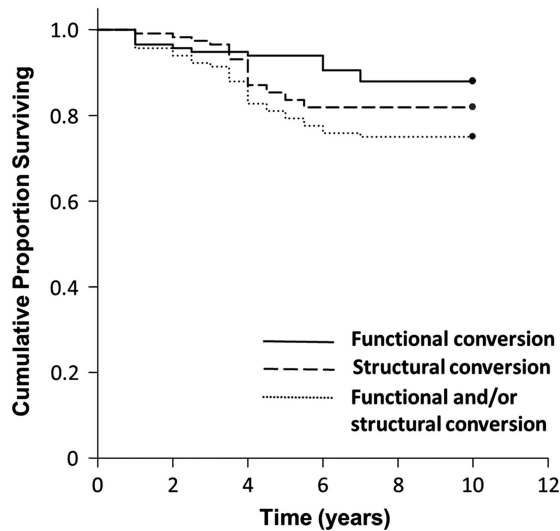


Figure 1 Kaplan–Meier survival curves of our cohort of OHT patients. Cumulative proportion surviving = proportion without POAG conversion. Study endpoint was defined as the development of functional (continuous line), structural (dashed line), or functional and/or structural (dotted line) glaucomatous damage.

uni- and multi-variate models included: patient age, SWAP GHT ‘outside normal limits’, GDx VCC inter-eye symmetry, HRT II rim volume and HRT II C/D ratio.

Figure 1 shows the Kaplan–Meier plots for the cumulative probability of survival from functional, morphological or mixed conversion to POAG. The conversion rate from OHT to POAG found in our study during the 10-year follow-up was 25%.

Discussion

Our study included one eye of 116 OHT patients, which were representative of our clinical practice and prospectively followed for a 10-year period. Intergroups comparison of the baseline variables and Cox univariate models revealed that some baseline parameters were significantly different between groups and significantly associated with the development of POAG, which included: age, functional abnormalities provided by SWAP, and structural parameters measured with GDxVCC and HRT II. Gender, IOP, CCT, ibopamine test results, SAP, and FDT variables were comparable between groups and were not predictive for glaucoma conversion.

Our results are in disagreement with several previous studies demonstrating that higher IOP,^{3–5,9,10} thinner CCT,^{3,5,9,10,28,29} and greater SAP PSD^{3,5,9,10} at baseline are predictive of the development of POAG among OHT subjects. The differences among results of the various studies could be related to several factors including: number and race of study population; anti-glaucoma

therapy and other intercurrent factors during the follow-up; data collection methods used; VF and OD evaluation methods; definition of OHT and conversion to glaucoma. In particular, our study included only one eye per patient, whereas in the glaucoma predictive models developed by the OHTS,⁶ EGPS,¹³ and Diagnostic Innovation in Glaucoma Study (DIGS)³⁰ studies, both eyes of each participant were included in the study if they met the inclusion criteria; the baseline predictive factors values were calculated by averaging the values of the two eyes of a single participant; and the end point was defined as the development of POAG in one eye per patient.

Differently from previous studies,^{6,13,30} numerous patients in our OHT cohort began IOP-lowering eye drop medication when needed based on the discretion of the attending physician therapy during the follow-up, which included 79.3% treated eyes. This may have reduced the significance of the baseline IOP as predictor, considering that IOP-related intercurrent factors, such as mean follow-up IOP and mean follow-up IOP reduction, have been demonstrated to be significant predictors for the glaucoma conversion in OHT patients.³¹

The mean CCT value of our cohort of patients was lower than that reported by other studies for OHT subjects.^{32,33} Considering that a substantial number of OHT patients tend to have an overestimation of GAT IOP based on a thicker cornea,³⁴ the significance of the CCT value as predictor for POAG development could be related to the proportion of false-positive OHT patients included in the study. Moreover, IOP and CCT values are related and this could have masked the real effect of both parameters in predicting POAG conversion.

As part of the inclusion criteria for our study, all OHT patients were required to have normal SAP results in both eyes. SAP was defined as normal based on the Hoddapp, Parrish and Anderson criteria,²⁶ which tend to be more stringent than those used in previous studies,^{6,13,30} where normal VF test results were defined as a MD and PSD within 95% confidence limits and a GHT result within normal limits.

Our data are in disagreement with previous studies showing that FDT abnormalities^{35,36} at baseline are predictive of the development of POAG among OHT subjects. FDT testing gave rise to a high percentage of abnormal results in our cohort of OHT subjects, which included 47.1% in the nonconverters and 58.6% in the converters subjects, and a low ability in discriminating between the two groups ($P=0.17$). The percentage of OHT subjects with abnormal FDT results found in our study was comparable to that reported by other authors,^{35–38} yet greater than the number that would be expected to convert to glaucoma, suggesting that the high sensitivity of FDT in detecting early glaucomatous damage could be partially related to false positive results.

In agreement with our data, older age has been identified as a baseline risk factor for developing POAG among OHT patients in multiple progression studies.^{3,5,39} Moreover, our findings are in accordance with previous studies showing that the risk of POAG conversion in OHT and glaucoma suspects is significantly associated with the presence of baseline abnormalities in SWAP,^{40,41} SLP,⁴² and CSLO.^{43,44} The significantly higher proportion of SWAP, SLP, and CSLO alterations found in converters in comparison with nonconverters could be considered as a sign of early glaucomatous damage in eyes with normal SAP and OD examination results, rather than true risk factors.

The only SLP parameter showing predictive ability in our study was 'Inter-eye Symmetry'. In agreement with these data, a predictive value of asymmetry between eyes in OHT patients for the development of POAG has been already reported for IOP,⁴⁵ cup-to-disc ratio,⁵ and VF threshold.⁴⁵

Although several HRT II parameters showed predictive ability, rim volume, C/D ratio, and mean RNFL thickness showed the best performance. These results are in accordance with the CSLO ancillary study of the OHTS, demonstrating that several baseline HRT parameters can be used to predict the development of POAG in OHT patients.^{43,44}

To the best of our knowledge, this is the first study evaluating the predictive ability of the ibopamine test for the conversion to glaucoma in OHT patients. The ability of the ibopamine test result in discriminating between converters and non-converters was very poor, with a sensitivity of 69% and a specificity of 41.4%, suggesting that a large proportion of the OHT subjects had a reduced outflow of the aqueous humor. Although several previous authors have demonstrated that the ibopamine test has high accuracy in differentiating glaucomatous eyes from normal⁴⁶ and glaucoma suspect eyes,⁴⁷ our data show that the positivity of the ibopamine test has no predictive value for the development of glaucoma. The results of the present study suggest that the ibopamine provocative test seems to be efficient in indicating the actual health status of the trabecular meshwork, but it seems unable to predict the evolution of the glaucomatous disease.

The results of the multivariate model suggest that patients with older age, SWAP GHT results 'outside normal limits', lower GDx VCC inter-eye symmetry, lower HRT II rim volume, and greater HRT II C/D ratio exhibit an increased risk of glaucoma progression and may need enhanced treatment management. A smaller rim volume at baseline was one of the most consistent predictors of POAG in the multivariate models.

Figure 1 shows the Kaplan–Meier plots for the cumulative probability of survival from functional, morphological, or mixed conversion to POAG.

The conversion rate from OHT to POAG found in our study was 21.5% during the initial 5-year follow-up and 25% during the entire 10-year follow-up. During the follow-up, our OHT patients were put on IOP-lowering eye drop medication when needed based on the discretion of the attending physician; thus, the study included both treated (79.3%) and untreated eyes (20.7%). The 5-year cumulative probability of developing POAG in large multicenter long-term clinical trials was 9.5% in the untreated group and 4.4% in the treated group in the OHTS;⁶ 13.7% and 16.4%, respectively, in the untreated and treated patients in the EGPS;¹³ and 25% in a group of untreated OHT patients in the DIGS.³⁰

In agreement with the EGPS,¹³ and in disagreement with the OHTS,¹² the conversion rate was comparable between untreated (20.8%) and treated eyes (26.2%; $P=0.11$). Converters were more likely to receive treatment (86.2%) than nonconverters (77%) during the study period, probably because they were deemed at higher risk for glaucoma by the treating clinician. The proportions of converters reaching a morphological, functional, or mixed endpoint, which were 51.7%, 27.6% and 20.7%, respectively, were comparable with those found in previous reports.^{6,30} These results are in agreement with several previous studies, which show that structural damage may often be detected several years before the development of VF defects measured by SAP in early glaucoma.^{48–50}

Our study has several limitations. A number of factors described as predictive for POAG among OHT eyes in previous studies were not evaluated in this study, including: family history of POAG, myopia, diabetes, race, cardiovascular disease, systemic blood hypo- and hypertension, ocular perfusion pressure, and local and systemic therapy.^{1–3,5,11,12} The prediction model developed in our study incorporated only baseline variables. Models incorporating intercurrent risk factors may provide an improved risk assessment.⁴⁸ The exact recruitment process data are not available, thus the precise number of patients that were approached, or considered ineligible or that did not give the consent to the study cannot be reported, which is a limiting factor of our study. Our OHT patients were treated upon need based on the discretion of the attending physician, thus both treated and untreated eyes were included in the study. Moreover, various anti-glaucoma medications were used to treat patients, which may have influenced the rate of glaucoma development in each individual. Another limitation in our study is related to the subjective nature of the OD assessment, even if the OD evaluations were performed in a standardized manner by highly trained graders. Finally, our findings may be not applicable to other clinical settings due to the specific

population included in our cohort, in which certain risk factors may have a more important role than others.

In conclusion, the results of our study showed that, in a cohort of OHT patients which were representatives of our clinical practice, baseline older age, and functional abnormalities provided by SWAP, and structural alterations shown by GDxVCC and HRT II were significantly associated with the risk of future structural or functional glaucomatous damage among OHT patients. These findings may also have significant implications in the detection of early glaucomatous damage in OHT patients. Mean IOP, CCT, SAP PSD, and the ibopamine test results at baseline did not show any predictive value. Our study suggests that the combination of patient age with structural and functional variables provided by various instruments could help the clinician in better managing a general population of OHT patients, even if a predictive model alone cannot replace clinical judgment. Prospective studies based on a greater cohort of patients, longer follow-ups, and additional parameters are required to assess the clinically usefulness of future predictive models.

Summary

What was known before

- Risk factors for OHT patients to develop POAG.

What this study adds

- Combination of various parameters together with ibopamine, GDx, SAP, etc on a single clinic study with a long follow-up.

Conflict of interest

The authors declare no conflict of interest.

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Baseline factors predicting the risk of conversion from ocular hypertension to primary open-angle glaucoma during a 10-year follow-up

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1. Your patient is a 62-year-old man with ocular hypertension (OHT). According to the prospective observational study by Salvetat and colleagues, which of the following clinical factors at baseline is *most* likely to predict conversion to primary open-angle glaucoma (POAG)?

- A Male gender
- B Higher elevation of baseline intraocular pressure (IOP)
- C Positive ipobamine test results
- D Older age

2. According to the prospective observational study by Salvetat and colleagues, which of the following baseline morphologic factors *most* likely predicted conversion to POAG in patients with OHT?

- A Lower scanning laser polarimetry (SLP) 'inter-eye symmetry'
- B Higher confocal scanning laser ophthalmoscopy (CSLO) rim volume
- C Greater CSLO cup-to-disc (C/D) ratio
- D Thicker baseline central corneal thickness (CCT)

3. According to the prospective observational study by Salvetat and colleagues, which of the following statements about baseline functional factors that predict conversion to POAG in patients with OHT is *correct*?

- A Functional abnormalities on the short wavelength automated perimetry (SWAP) Glaucoma Hemifield test (GHT) 'outside normal limits' (HR, 4.3; 99% CI, 1.2–17.9) significantly predicted POAG
- B Greater standard automated perimetry (SAP) pattern standard deviation (PSD) significantly predicted glaucoma conversion
- C Frequency-doubling technology (FDT) variables were significantly predictive for glaucoma conversion
- D This study included patients with abnormal visual fields at baseline

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