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Blood Pressure and Glaucomatous Progression in a Large Clinical Population

Alessandro A. Jammal, MD, PhD,[1,2] *Samuel I. Berchuck, PhD,*[1,3] *Eduardo B. Mariottoni, MD,*[1] *Angelo P. Tanna, MD,*[4] *Vital P. Costa, MD, PhD,*[2] *Felipe A. Medeiros, MD, PhD*[1,5]

Purpose: To investigate the effect of systemic arterial blood pressure (BP) on rates of progressive structural damage over time in glaucoma.

Design: Retrospective cohort study.

Participants: A total of 7501 eyes of 3976 subjects with glaucoma or suspected of glaucoma followed over time from the Duke Glaucoma Registry.

Methods: Linear mixed models were used to investigate the effects of BP on the rates of retinal nerve fiber layer (RNFL) loss from spectral-domain OCT (SD-OCT) over time. Models were adjusted for intraocular pressure (IOP), gender, race, diagnosis, central corneal thickness (CCT), follow-up time, and baseline disease severity.

Main Outcome Measure: Effect of mean arterial pressure (MAP), systolic arterial pressure (SAP), and diastolic arterial pressure (DAP) on rates of RNFL loss over time.

Results: A total of 157 291 BP visits, 45 408 IOP visits, and 30 238 SD-OCT visits were included. Mean rate of RNFL change was −0.70 μm/year (95% confidence interval, −0.72 to −0.67 μm/year). In univariable models, MAP, SAP, and DAP during follow-up were not significantly associated with rates of RNFL loss. However, when adjusted for mean IOP during follow-up, each 10 mmHg reduction in mean MAP (−0.06 μm/year; $P = 0.007$) and mean DAP (−0.08 μm/year; $P < 0.001$) but not SAP (−0.01 μm/year; $P = 0.355$) was associated with significantly faster rates of RNFL thickness change over time. The effect of the arterial pressure metrics remained significant after additional adjustment for baseline age, diagnosis, sex, race, follow-up time, disease severity, and corneal thickness.

Conclusions: When adjusted for IOP, lower MAP and DAP during follow-up were significantly associated with faster rates of RNFL loss, suggesting that levels of systemic BP may be a significant factor in glaucoma progression. *Ophthalmology 2021;■:1−10 © 2021 by the American Academy of Ophthalmology*

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Glaucoma is a chronic optic neuropathy and the leading cause of irreversible blindness worldwide.[1] Although a myriad of factors contribute to the disease, intraocular pressure (IOP) remains the only proven modifiable risk factor for both development and progression of glaucoma, which currently limits treatment of the disease to IOP-lowering interventions.[2-7] However, vascular factors affecting the blood supply to the eye have long been suspected of playing a role in the glaucomatous process, which would allow for additional opportunities for therapy.

Major epidemiologic studies have provided evidence on the relationship between ocular perfusion pressure (OPP) and primary open-angle glaucoma (POAG), reporting a risk 2 to 6 times higher of having POAG for lower levels of the diastolic component of OPP.[8-12] However, it is possible that the relationship between low OPP and glaucoma may be secondary to the impact of high IOP,[13] because OPP is simply calculated as the difference between mean systemic blood pressure (BP) and IOP. In an attempt to further adjust OPP for the effects of IOP, previous studies have inappropriately included the latter as a covariate in regression models,[12,14] which leads to IOP ultimately forming part of 2 terms in the same regression model.[15] Additionally, clinical studies to date have not been able to determine the effect of BP levels alone in glaucoma partially due to design limitations, which have mostly included cross-sectional investigations.[8-12,16] The few longitudinal studies investigating this issue have been restricted to a limited number of follow-up time points or small sample sizes.[13,17,18] Also, the effect of BP has often been analyzed on the basis of arbitrary cutoffs or presence or absence of a known diagnosis of systemic hypertension. If vascular factors ultimately increase the susceptibility to glaucoma damage, this relationship may be better captured by evaluating the direct effects of BP on longitudinal rates of progressive optic nerve damage in the disease, while controlling for potential confounding effects of IOP.

In the present study, a large cohort of glaucoma and glaucoma suspect patients extracted from a large electronic health record (EHR) database was used to investigate the hypothesis that BP has an effect on the rate of structural measures of glaucoma progression.

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Methods

This was a retrospective cohort study of patients from the Duke Glaucoma Registry, an EHR database developed by the Vision, Imaging, and Performance Laboratory that houses several million clinical data points for glaucoma patients.[19] The database contains clinical information from baseline and follow-up visits, including patient diagnostic and procedure codes, medical history, best-corrected visual acuity, slit-lamp biomicroscopy, IOP measurement using the Goldmann applanation tonometry (Haag-Streit), central corneal thickness (CCT), gonioscopy, ophthalmoscopy examination, stereoscopic optic disc photographs, and the results of all Spectralis spectral domain OCT (SD-OCT) (Heidelberg Engineering, GmbH) scans from adults 18 years or older with glaucoma or glaucoma suspect diagnoses who were evaluated at the Duke Eye Center or its satellite clinics between January 2009 and September 2019. The Duke University Institutional Review Board approved this study with a waiver of informed consent because of the retrospective nature of this work. All methods adhered to the tenets of the Declaration of Helsinki for research involving human subjects and were conducted in accordance with regulations of the Health Insurance Portability and Accountability Act.

Participant Selection

Patients were included in the study if they had glaucoma or suspicion of glaucoma based on International Classification of Diseases (ICD) codes at baseline. All tests and visits from all available subjects in the Duke Glaucoma Registry at the time of the analysis were used for this study. Eyes had their data censored after the first occurrence of any diagnosis of retinal detachment, retinal or malignant choroidal tumors, nonglaucomatous disorders of the optic nerve and visual pathways, uveitis, and venous or arterial retinal occlusion according to ICD codes. In addition, tests performed after treatment with panretinal photocoagulation according to Current Procedural Terminology (CPT) codes were also excluded. Tests were further censored after any filtration procedure (i.e., trabeculectomy or tube shunt surgery) performed during follow-up. The ICD and CPT codes used for inclusion and exclusion in the study have been described in detail previously.[20] For the present study, subjects were required to have a follow-up period of at least 6 months between the first and last valid SD-OCT scans, during which a minimum of 2 IOP and 2 BP measures were acquired in routine clinical visits. Eligible patients had their medication history extracted from the EHR database. Use of medication for systemic arterial hypertension (SAH) was defined by the record of use of any SAH oral medication class (i.e., diuretics, calcium-channel blockers, angiotensin-converting enzyme and renin inhibitors, angiotensin II receptor antagonists, alpha-2 adrenergic receptor agonists, and beta-blockers) or association at any time in the EHR. Total time of SAH use was defined as the time between the first reported use of any SAH drug in the class in the patient's medications list up to the last reported use of the drug in the EHR or the end of the study follow-up (i.e., last available valid SD-OCT test).

Intraocular Pressure and Blood Pressure Metrics

All BP and IOP measures available for each patient in the database were exported and evaluated. For IOP, only those measured with Goldmann applanation tonometry were included in the analysis. For BP, all measurements acquired during clinical hours as part of routine examination in any clinical visit from any clinical specialty were considered. Blood pressure measurements not obtained from the brachial artery or not in a seated position were excluded from the analysis, as indicated in clinical records.

Although true mean arterial pressure (MAP) can only be measured directly by invasive monitoring, estimates of MAP using the systolic arterial pressure (SAP) and diastolic arterial pressure (DAP) from standard BP measures were used to represent the perfusion pressure seen by organs in the body. Mean arterial pressure accounts for the fact that BP changes at each heartbeat, and the diastolic status would represent the majority of the time at normal resting heart rates. Mean arterial pressure was calculated, as follows:

$$MAP = DAP + \frac{1}{3}(SAP - DAP)$$

The mean values over the study period for IOP, MAP, SAP, and DAP were calculated for each patient and eye and used in the analysis.

Assessment of Glaucoma Progression

Rates of glaucoma progression were evaluated by the change in global SD-OCT retinal nerve fiber layer (RNFL) thickness over time. We opted to use a structural metric in this study because attempts to study this relationship with perimetry, an indirect functional measurement of neural damage, could be confounded by the subjective nature of the test and nonlinearities in translating RGC loss to visual sensitivity thresholds.[21-23]

Peripapillary RNFL thickness measurements were obtained from a 12-degree (for single circle scans) or comparable 3.45-mm−diameter circle scan (for scans from the Glaucoma Mode Premium Edition) acquired using the Spectralis SD-OCT, as described in detail previously.[24] The global average was calculated as the average thickness of all 768 points distributed equidistantly around the optic nerve head (ONH). Tests were acquired using the latest available software version at the time of the scan and exported using the latest available version at the time of the analysis (software version 6.8).

Only good-quality scans were included in the analyses. A good-quality scan was defined as a test with a quality score of 15 or greater. Furthermore, because manual review of all tests was impractical, scans that had average global RNFL thickness measurements with implausible values (i.e., <20 and >150 μm) were also considered of low quality and excluded. Those cutoffs represent measurements above the highest (i.e., thickest) values reported for RNFL thickness for normal controls and below the lowest values (i.e., thinnest) for glaucoma subjects[25-27] and may indicate the presence of acquisition or segmentation errors in the presence of otherwise good-quality scores.[28] When more than 1 good-quality test was available for the same date, the mean global RNFL thickness of all tests from that date was used in the analysis. The baseline characteristics and demographics were drawn from the date when the first valid SD-OCT test for each eye was performed.

Data Analyses

Linear mixed models (LMMs) were used to estimate the effect of IOP and BP metrics on rates of RNFL thickness change over time. This standard technique has been described in detail by Laird and Ware.[29] In brief, mixed models take into account the natural correlation of such data over time, as well as the fact that each patient may contribute 2 eyes in the analysis. Differences in rates of change between eyes and subjects are taken into account by introducing random slopes and random intercepts. Best linear unbiased predictions (BLUPs) were used to estimate individual slopes of change for each eye. These estimates are more precise than those obtained by ordinary least squares linear regression,[30,31] notably in the presence of a small number of

tests over time, which may occur with some eyes. As the number of tests increase for an eye, BLUP estimates become essentially identical to those obtained from ordinary least squares regression.

Univariable models were first used to evaluate the effect of BP parameters (i.e., MAP, SAP, and DAP) on rates of RNFL thinning over time, as well as baseline demographics and clinical characteristics. To allow for the interpretation of the effects of BP while taking into account IOP, we subsequently derived separate LMMs for each BP metric including IOP as a covariate. Finally, we built multivariable models for each of the BP parameters that included additional adjustment for age, gender, race, glaucoma diagnosis, CCT, follow-up time, and baseline RNFL thickness. An interaction term of age at baseline and mean IOP during follow-up was also added to the multivariable models, because age has been demonstrated to be a significant modifier of the relationship between IOP and glaucomatous RNFL loss over time.[32]

To summarize the impact of BP metrics on rates of RNFL change, predicted RNFL thickness trajectories are presented across a range of mean MAP, SAP, and DAP levels using estimates from the multivariable LMMs. To calculate the trajectories, mean values were assumed for the remaining clinical characteristics. Trajectories are presented with 95% confidence intervals. To interpret the joint effect of different levels of IOP and MAP, SAP, and DAP on the average rates of RNFL change, we used contour plots. This visualization technique allows for a 3-way relationship to be easily interpreted. The effects of remaining clinical characteristics were fixed at zero, so that the joint effect on the average slope can be interpreted as either protective (green, or slower rates of change) or harmful (warmer colors, or faster rates of change) for the different levels of BP and IOP.

The baseline characteristics and demographics were drawn from the date when the first reliable SD-OCT for each eye was performed. All statistical analyses were completed in Stata (version 16, StataCorp LP) within the Protected Analytics Computing Environment, a highly protected virtual network space developed by Duke University for analysis of identifiable protected health information.

Results

This study included 7501 eyes of 3976 patients with a total of 157 291 clinical visits with BP measurement, 45 408 visits with IOP measurement, and 32 168 SD-OCT tests acquired over 30 238 SD-OCT visits. Average age ± standard deviation of subjects at baseline was 64.5 ± 12.5 years (range, 18–94), and eyes had a mean ± standard deviation follow-up time of 4.0 ± 1.9 (range, 0.5–9.5) years, with a mean number of 4.0 ± 1.8 SD-OCT visits, ranging from 2 to 13. Subjects had an average of 20.7 ± 23.4 (median, 13; interquartile range, 6–27) clinical visits with BP measurement, with 6.1 ± 3.8 IOP visits per eye. Of these patients, 2399 (60.3%) were female and 1255 (31.6%) were self-identified as Black; 57.0% of the eyes were classified as glaucoma suspect, 23.8% as POAG, and 19.2% as "other glaucoma" types, according to ICD codes from the baseline visit. The unadjusted mean rate of change for global RNFL thickness in the overall population was −0.70 μm/year (95% confidence interval, −0.72 to −0.67 μm/year). Table 1 details the demographic and clinical characteristics of the eyes included in the study, and Figure 1 demonstrates the distribution of baseline RNFL thickness, mean IOP, and MAP in the sample.

Table 2 shows results of LMM models investigating the effect of each potential predictive factor on rates of global RNFL thickness change. In univariable analyses, higher mean IOP, older age, thicker baseline RNFL, glaucoma diagnosis at baseline, and longer follow-up time were significantly associated with faster rates of global RNFL thickness loss, as well as the interaction term between age and IOP. However, no metric derived from standard BP measures during follow-up (i.e., MAP, SAP, or DAP) showed significant effect on the rates of RNFL thinning over time when evaluated without adjustment for other covariates. We also evaluated the effect of the use and number of medications for SAH and use of diuretics on the rates of change in glaucoma in univariable models. From those, only the number of medication classes for SAH prescribed during follow-up was significantly associated with faster rates of RNFL loss (−0.024 μm/year per class added; $P = 0.025$).

Table 1. Demographics and Clinical Characteristics of Subjects Included in the Study

Characteristic	Overall
Subject-specific	
No. of patients	3976
Age, yrs	
Mean ± SD	64.5 ± 12.5
Median (IQR)	65.8 (57.3–72.9)
Sex, n (%)	
female	2399 (60.3)
Race, n (%)	
Black	1255 (31.6)
Eye-specific	
No. of eyes	7501
Years of follow-up	
Mean ± SD	4.0 ± 1.9
CCT, μm	
Mean ± SD	550.8 ± 41.7
Diagnosis at baseline, n (%)	
Glaucoma suspect	4277 (57.0)
POAG	1784 (23.8)
Other	1440 (19.2)
SD-OCT	
No. of visits	30 238
No. of visits per eye	
Mean ± SD [range]	4.0 ± 1.8 [2–13]
Baseline global RNFL thickness, μm	
Mean ± SD	84.0 ± 16.0
Median (IQR)	86.0 (74.0–95.0)
SD-OCT quality	
Mean ± SD	23.8 ± 4.0
IOP	
No. of visits	45 408
No. of visits per eye	
Mean ± SD [range]	6.1 ± 3.8 [2–34]
Average IOP during follow-up, mmHg	
Mean ± SD	16.0 ± 3.3
BP	
No. of visits	157 291
No. of visits per patient	
Mean ± SD	20.7 ± 23.4
Median (IQR)	13.0 (6.0–27.0)
Average MAP during follow-up, mmHg	
Mean ± SD	93.2 ± 7.5
Average SAP during follow-up, mmHg	
Mean ± SD	129.8 ± 12.5
Average DAP during follow-up, mmHg	
Mean ± SD	74.9 ± 7.0

BP = blood pressure; CCT = central corneal thickness; DAP = diastolic arterial pressure; GS = glaucoma suspect; IOP = intraocular pressure; IQR = interquartile range; MAP = mean arterial pressure; POAG = primary open-angle glaucoma; RNFL = retinal nerve fiber layer; SAP = systolic arterial pressure; SD = standard deviation; SD-OCT = spectral-domain OCT.

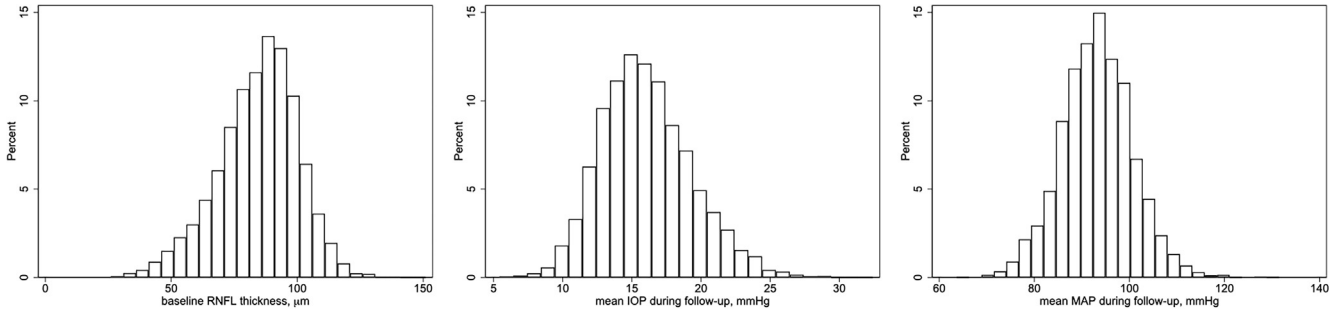

Figure 1. Histograms showing the distribution of spectral-domain OCT (SD-OCT) retinal nerve fiber layer (RNFL) thickness at baseline, mean intraocular pressure (IOP), and mean arterial pressure (MAP) during follow-up.

However, significant effects were seen for MAP and DAP when models were adjusted for IOP. Each 10 mmHg lower mean MAP and DAP during follow-up was associated with a −0.058 µm/year ($P = 0.007$) and −0.083 µm/year ($P < 0.001$) faster rate of RNFL thickness loss, respectively (Table 3). These associations held true even after adjusting for additional demographical and clinical confounding factors of sex, race, age, glaucoma diagnosis, CCT, follow-up time, baseline RNFL thickness, and the interaction term between age and IOP (Table 4). Of note, mean SAP was not associated with significantly faster rates of change over time when adjusted for IOP only (Table 3) but showed a significant effect when adjusted for all covariates in the multivariable model (Table 4). Figure 2 shows expected trajectories of global RNFL thickness across time for different levels of BP, as derived from these multivariable models. All covariates in the model, including IOP, were set to their means in the sample (Table 1). Figure S3 (available at www.aaojournal.org) shows similar trajectory plots for subgroups of patients according to the baseline diagnoses. Patients with POAG, patients with other forms of glaucoma, and glaucoma suspects all showed increasingly faster rates of RNFL loss for lower levels of MAP and DAP.

To illustrate the impact of simultaneous change in BP and IOP on rates of RNFL thickness change, Figure 4 shows contour plots where the *x*-axis represents values for different levels of BP and the *y*-axis represents the average IOP during follow-up. By navigating

Table 2. Univariable Models of the Effect of Each Clinical Characteristic on the Rate of Change of Spectral-Domain OCT Retinal Nerve Fiber Layer Thickness over Time

Characteristic	Individual Effects over Time (Univariable Models)	
	Coefficient	*P*
BP		
Mean MAP, per 10 mmHg lower	−0.013	0.542
Mean SAP, per 10 mmHg lower	0.009	0.518
Mean DAP, per 10 mmHg lower	−0.037	0.116
IOP		
Mean IOP, per 1 mmHg higher	−0.061	**< 0.001**
Medication for SAH		
Use of oral SAH medication at any point during follow-up, yes	−0.046	0.174
No. of classes of oral SAH medications, per 1 more class	−0.024	**0.025**
Duration of treatment with SAH medication, per 10 yrs longer	−0.037	0.369
Diuretics		
Use of diuretics at any point during follow-up, yes	−0.027	0.407
Duration of treatment with diuretics, per 10 yrs longer	−0.001	0.870
Other Characteristics		
Diagnosis, GS	0	**(base)**
POAG	−0.134	**< 0.001**
Other	−0.323	**< 0.001**
Sex, female	0.015	0.636
Race, Black	−0.058	0.091
CCT, per SD µm thinner	−0.002	0.940
Baseline RNFL, per 10 µm thicker	−0.046	**< 0.001**
Follow-up time, per 1 yr longer	0.015	0.083
Age at baseline, per 10 yrs older	−0.077	**< 0.001**
Interaction term of age at baseline and mean IOP	−0.012	**0.002**

The coefficients represent the predicted change in RNFL thickness for a certain change in each characteristic. Boldface indicates statistical significance ($P < 0.05$).
BP = blood pressure; CCT = central corneal thickness; DAP = diastolic arterial pressure; GS = glaucoma suspect; IOP = intraocular pressure; MAP = mean arterial pressure; POAG = primary open-angle glaucoma; RNFL = retinal nerve fiber layer; SAH = systemic arterial hypertension; SAP = systolic arterial pressure; SD = standard deviation; SD-OCT = spectral-domain OCT.

Table 3. Univariable Models Assessing the Effect of Blood Pressure Parameters, Represented by Mean Arterial Pressure, Systolic Arterial Pressure, and Diastolic Arterial Pressure, on the Rate of Change of Retinal Nerve Fiber Layer Thickness over Time, after Adjusting for Intraocular Pressure during Follow-up

	Individual Effects over Time Adjusted for Mean IOP during Follow-up*	
Characteristic	*Coefficient*	*P*
Mean MAP, per 10 mmHg lower	−0.058	**0.007**
Mean SAP, per 10 mmHg lower	−0.012	0.355
Mean DAP, per 10 mmHg lower	−0.083	**< 0.001**

Boldface indicates statistical significance ($P < 0.05$).
DAP = diastolic arterial pressure; IOP = intraocular pressure; MAP = mean arterial pressure; SAP = systolic arterial pressure.
*Coefficients for IOP not shown, all $P < 0.001$.

over the *x*- and *y*-axes, readers can estimate the effect of changing both BP and IOP on the rates of RNFL thickness, with warmer colors representing faster rates of change. These predictions have also been adjusted for the additional confounding factors described previously. One can note that, as expected, increasing IOP shows an important effect on the average rates of change but that this effect is potentiated by lower levels of arterial pressure.

Discussion

In this study, we observed that combined vascular and intraocular factors affecting the blood supply to the eye were significantly associated with rates of RNFL loss in glaucoma suspects and patients with glaucoma. We observed statistically independent effects of systemic arterial pressure parameters on rates of structural loss in glaucoma, suggesting that clinicians should be aware of a patient's BP levels when managing the disease.

Several population-based studies have suggested lower perfusion pressure to the eye as a significant risk factor for glaucoma.[8,10-12] Because the actual pressure at which blood enters the eye cannot be measured in vivo, some authors have argued that a simple weighted subtraction of IOP from MAP (i.e., the OPP) could be used as a surrogate. Using such calculation, the Barbados Eye Study[18] and Rotterdam Study[13] estimated up to a 3-fold higher risk for developing glaucoma for lower levels of diastolic OPP. However, although OPP can be easily calculated, its impact on glaucoma progression may be largely confounded by the effect of IOP, the most important identified risk factor for glaucoma development and progression.[2-4] For example, a difference in diastolic OPP from 60 to 40 mmHg may be caused both by a reduction of 20 mmHg in diastolic BP and an increase of 20 mmHg in IOP. Therefore, it is possible that previous associations between OPP and glaucoma might simply reflect the impact of IOP in the disease outcomes.

In the present investigation, we improved on the design of previous studies by looking closely at the direct impact of BP on glaucoma progression. Using our large database of patients under routine care, we were able to derive precise estimates of the independent effect of BP on rates of structural loss in glaucoma. We observed that, at similar IOP levels, eyes of patients with lower MAP and DAP showed faster rates of RNFL loss. When adjusting for all other covariates, lower SAP was also a significant independent risk factor for faster progression. Such analyses can clarify the effect of BP parameters on glaucoma progression while avoiding misinterpretations from OPP calculations. The contour plots in Figure 4 help illustrate the effects of combinations of a wide range of IOP values and different levels of BP on rates of progression.

Table 4. Multivariable Models Assessing the Effect of Blood Pressure Parameters, Represented by Mean Arterial Pressure, Systolic Arterial Pressure, and Diastolic Arterial Pressure on the Rates of Change of Retinal Nerve Fiber Layer Thickness over Time

	Multivariable Model for MAP		Multivariable Model for SAP		Multivariable Model for DAP	
Characteristic	*Coefficient*	*P*	*Coefficient*	*P*	*Coefficient*	*P*
BP parameter,* per 10 mmHg lower	−0.091	**0.001**	−0.061	**< 0.001**	−0.074	**0.016**
Mean IOP, per 1 mmHg higher	0.009	0.781	0.011	0.732	0.009	0.775
Diagnosis, GS	0	**(base)**	0	**(base)**	0	**(base)**
POAG	−0.196	**< 0.001**	−0.195	**< 0.001**	−0.194	**< 0.001**
Other	−0.296	**< 0.001**	−0.293	**< 0.001**	−0.297	**< 0.001**
Sex, female	0.037	0.346	0.030	0.442	0.035	0.370
Race, Black	−0.057	0.194	−0.058	0.182	−0.047	0.287
CCT, per SD µm thinner	−0.038	0.052	−0.037	0.058	−0.038	0.051
Baseline RNFL, per 10 µm thicker	−0.064	**< 0.001**	−0.064	**< 0.001**	−0.064	**< 0.001**
Follow-up time, per 1 yr longer	−0.002	0.861	−0.003	0.826	−0.001	0.903
Age at baseline, per 10 yrs older	0.085	0.291	0.072	0.371	0.093	0.248
Interaction term of age at baseline and mean IOP	−0.012	**0.021**	−0.012	**0.017**	−0.011	**0.023**

Boldface indicates statistical significance ($P < 0.05$).
BP = blood pressure; CCT = central corneal thickness; DAP = diastolic arterial pressure; GS = glaucoma suspect; IOP = intraocular pressure; MAP = mean arterial pressure; POAG = primary open-angle glaucoma; RNFL = retinal nerve fiber layer; SAP = systolic arterial pressure; SD = standard deviation; SD-OCT = spectral-domain OCT.
*MAP, SAP, or DAP.

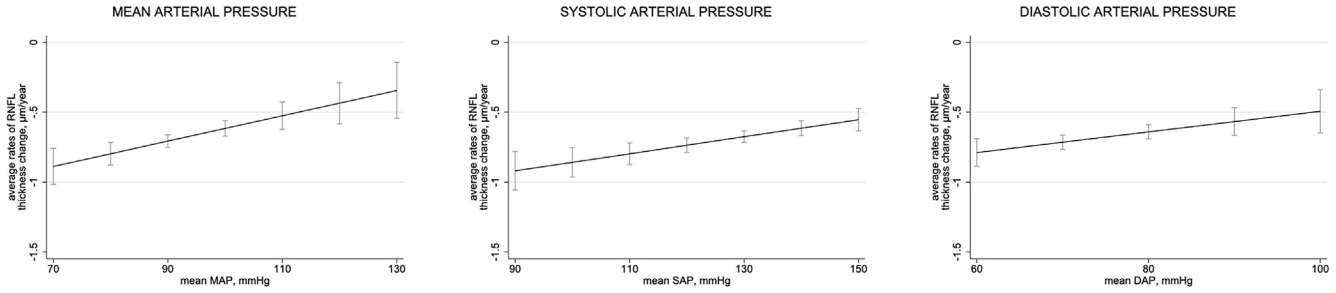

Figure 2. Trajectories of rates of change in retinal nerve fiber layer (RNFL) thickness across levels of systemic blood pressure (BP), represented by mean arterial pressure (MAP) and its systolic arterial pressure (SAP) and diastolic arterial pressure (DAP) components. All covariates were set to their mean values. Capped lines indicate 95% confidence intervals.

Our findings may have particular importance for cases in which glaucoma seems to be progressing despite seemingly well-controlled IOP or cases of so-called normal-tension glaucoma. For these patients, vascular risk factors have been found to be strong predictors of progression. The Low-Pressure Glaucoma Treatment Study identified the use of systemic antihypertensive medication as a risk factor for visual field progression,[33] whereas the Collaborative Normal-Tension Glaucoma Study identified migraine and optic disc hemorrhage as predictive factors for progression.[34] More recently, lowest SAP and DAP were significantly associated with progressive RNFL loss and macular RGC layer thinning in a smaller longitudinal study of patients with normal-tension glaucoma.[17] Although our analysis did not focus on this specific group of patients because of the limitations of using billing and ICD codes for the diagnosis, it is reasonable to suggest that these eyes might benefit from avoiding BP overtreatment, especially if yielding too low DAP values.

Blood pressure is frequently modified in clinical practice with the use of oral medication, which is routinely taken by a large number of glaucoma patients. In fact, many subjects with glaucoma also have SAH as a comorbidity, because both diseases share older age as an important risk factor.[35,36] In a study investigating a large population from the British General Practitioner Research Database, glaucoma patients were 23% to 36% more likely to have systemic hypertension than nonglaucomatous controls.[37] In our sample, 2616 subjects (66%) had records of oral antihypertensive medication use. With increasingly tighter levels of BP control being recommended to reduce the risk of cardiovascular diseases (CVDs), including stroke and myocardial infarction,[38] such a high proportion is not surprising. In fact, by the most recently published guidelines for SAH, it is estimated that 45.6% of the whole U.S. adult population has hypertension, and nonpharmacological intervention alone is advised for only a small fraction of those patients. This translates to more than one-third (36.2%) of all the American adult population being recommended to take at least 1 antihypertensive medication.[39] Therefore, ophthalmologists should work closely with their fellow clinicians to ensure that patients with systemic hypertension and glaucoma are not overmedicated. This can be accomplished by investigating 24-hour BP and avoiding excessive lowering of DAP, a metric that was consistently associated with faster worsening of glaucomatous damage in our analysis. Of note, although higher SAP has been frequently associated with increased CVD risk after adjustment for DAP,[40,41] DAP itself, in contrast, has not been associated with CVD risk, after consideration of SAP through adjustment or stratification.[42,43] Therefore, DAP control could be targeted as a modifiable risk factor for glaucoma without necessarily increasing cardiovascular events. However, as hypertension induces atherosclerosis and impairs vascular autoregulation, some authors propose that high BP may negatively affect blood supply to the optic nerve.[11] The direct association of BP and IOP may also need to be considered. Previous studies have shown that eyes with higher BP may have higher levels of IOP.[10,44] Such association could potentially diminish the beneficial effect of higher BP levels in preventing glaucoma progression. However, the correlation between BP parameters and IOP during follow-up in our sample was low (R^2 lower than 2% for all correlations). By adjusting for IOP in our models, we were able to assess the impact of changes in BP while holding IOP constant, thus revealing the true BP association with progression. However, future prospective longitudinal studies are still necessary to confirm optimum targets of therapeutic value for BP management in avoiding glaucoma progression.

The ways in which systemic arterial pressure may contribute to the pathogenesis of glaucoma and neuronal loss are likely multifactorial. Low BP may lead to compensatory vasoconstriction of peripheral organs and tissues,[45] whereas vascular modifications, such as atherosclerosis and impaired modulation of blood flow, could further decrease blood supply to the optic nerve head and predispose to glaucoma progression.[46] It is also possible that the mechanism of damage includes the nervous system as a whole, where the visual system could also become more susceptible to ischemia and neural degeneration under conditions of hypoperfusion to the brain.[47] Studies have also indicated that the treatment of systemic hypertension with oral antihypertensive medication may be associated with increased risk for the

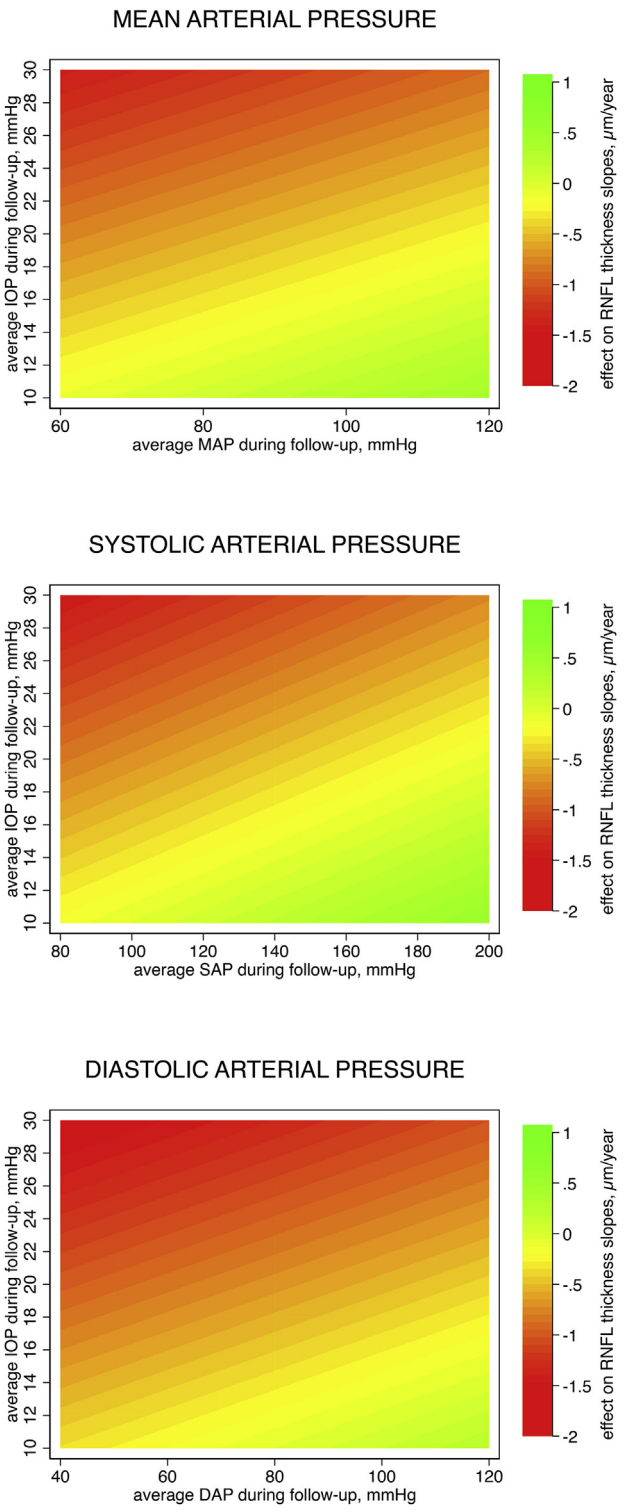

Figure 4. Contour plots showing the estimated effect of different levels of mean intraocular pressure (IOP) and blood pressure (BP) during follow-up on the average rates of retinal nerve fiber layer (RNFL) thickness change over time. Readers can navigate over the *x*-axis to estimate the influence of each systemic arterial pressure metric and a given value of IOP (*y*-axis) on the average rates of RNFL thickness progression. Warmer colors represent faster rates of global RNFL thickness loss in µm/year. DAP = diastolic arterial pressure; MAP = mean arterial pressure; SAP = systolic arterial pressure.

development or progression of glaucoma.[33,48,49] In our sample, although the use and duration of treatment with oral antihypertensives were not significantly associated with faster rates of structural loss, the number of classes of SAH medications prescribed during follow-up was ($P = 0.025$). This could indicate excessive treatment or cases of resistant hypertension. To further test if the significant effect of BP was present only in the group under SAH medication, as indicated in previous studies, we repeated the analysis in the group with no records of use of oral antihypertensives (n = 2591 eyes). A significant effect in RNFL thickness loss was still seen for MAP (−0.092 µm/year per 10 mmHg lower; $P = 0.020$), SAP (−0.057 µm/year per 10 mmHg lower; $P = 0.028$), and DAP (−0.095 µm/year per 10 mmHg lower; $P = 0.037$) in the multivariable models.

Study Limitations

It has also been shown that glaucoma patients may have a significant nocturnal dip in BP[50] and these dips may be associated with increased risk for glaucoma progression.[51] Our study was not able to assess fluctuations in systemic arterial pressure during the day, because BP measures were taken at office hours and averaged over time. Of note, some classes of medications previously associated with nocturnal dips in BP and glaucoma development,[52] such as diuretics, were also not significantly associated with faster progression in our analysis. Additionally, certain topical glaucoma medications such as beta-blockers may be associated with low BP due to systemic absorption of the drug.[53] It is possible that patients who exhibited faster progression may have been treated more often with topical beta-blockers, creating a potential association between faster progression and low BP. Given the large number of therapeutic options, multiple changes in treatment plan during follow-up, adherence issues, and frequent inaccuracies in recording ocular medications in EHR, it would have been largely impossible to obtain reliable estimates of individual ocular drug effects on rates of RNFL change in our study.

Additional limitations should be considered in our analyses. We required a minimum of 2 SD-OCT tests for inclusion, which could suggest that some eyes may not have had enough tests to assess progression over time. However, excluding eyes with fewer tests could potentially bias the results by removing eyes that may have had fast progression over a short period of time. Including all eyes with available follow-up data improves the accuracy and precision of the estimates of the effects of the variables of interest and avoids such unwarranted biases. To support our conclusions, we repeated the analyses using eyes with at least 5 SD-OCT visits, and the results remained essentially unchanged (Table S5, available at www.aaojournal.org). The findings of this study should be examined in light of the population they represent. Because the EHR dataset was drawn from a single institution, care should be exercised when extrapolating the findings to different populations. Future studies with more diverse populations should provide better estimates for other specific groups, including those with more severe disease. Finally, because

BP was obtained by a medical provider in a hospital setting, elevated BP readings may not be representative of an individual's true BP status because of the impact of the "white coat syndrome."[54]

In conclusion, our study indicates that systemic arterial pressure has a significant independent effect on rates of structural loss in glaucoma. Thus, BP can be reasonably regarded as a potentially modifiable risk factor for glaucoma, and clinicians should be mindful of not only the IOP but also the systemic arterial pressure to better assess the risk of faster glaucoma progression.

Footnotes and Disclosures

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[1] Vision, Imaging and Performance Laboratory, Duke Eye Center and Department of Ophthalmology, Duke University, Durham, North Carolina.

[2] Department of Ophthalmology, Universidade Estadual de Campinas, São Paulo, Brazil.

[3] Department of Statistical Science and Forge, Duke University, Durham, North Carolina.

[4] Department of Ophthalmology, Northwestern University Feinberg School of Medicine, Chicago, Illinois.

[5] Department of Electrical and Computer Engineering, Pratt School of Engineering, Duke University, Durham, North Carolina.

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Author Contributions:

Conception and design: Jammal, Berchuck, Medeiros

Data collection: Jammal, Mariottoni

Analysis and interpretation: Jammal, Berchuck, Tanna, Costa, Medeiros

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Abbreviations and Acronyms:
BLUP = best linear unbiased prediction; **BP** = blood pressure; **CCT** = central corneal thickness; **CVD** = cardiovascular disease; **DAP** = diastolic arterial pressure; **EHR** = electronic health record; **ICD** = International Classification of Diseases; **IOP** = intraocular pressure; **LMM** = linear mixed model; **MAP** = mean arterial pressure; **OPP** = ocular perfusion pressure; **POAG** = primary open-angle glaucoma; **RNFL** = retinal nerve fiber layer; **SAH** = systemic arterial hypertension; **SAP** = systolic arterial pressure; **SD-OCT** = spectral domain OCT.

Keywords:
Glaucoma, Progression, systemic hypertension, blood pressure, ocular perfusion pressure, intraocular pressure, OCT, rates of change, retinal nerve fiber layer.

Correspondence:
Felipe A. Medeiros, MD, PhD, Duke Eye Center, Department of Ophthalmology, Duke University, 2351 Erwin Road, Durham, NC 27705. E-mail: felipe.medeiros@duke.edu.

References

1. Steinmetz JD, Bourne RRA, Briant PS, et al. Causes of blindness and vision impairment in 2020 and trends over 30 years, and prevalence of avoidable blindness in relation to VISION 2020: the Right to Sight: an analysis for the Global Burden of Disease Study. *Lancet Glob Health*. 2021;9:e144−e160.
2. The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. The AGIS Investigators. *Am J Ophthalmol*. 2000;130:429−440.
3. Leske MC, Heijl A, Hussein M, et al. Factors for glaucoma progression and the effect of treatment: the early Manifest Glaucoma Trial. *Arch Ophthalmol*. 2003;121:48−56.
4. Kass MA, Heuer DK, Higginbotham EJ, et al. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Arch Ophthalmol*. 2002;120:701−713. discussion 829-830.
5. Collaborative Normal-Tension Glaucoma Study Group. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. *Am J Ophthalmol*. 1998;126:487−497.
6. Garway-Heath DF, Crabb DP, Bunce C, et al. Latanoprost for open-angle glaucoma (UKGTS): a randomised, multicentre, placebo-controlled trial. *Lancet*. 2015;385:1295−1304.
7. Heijl A, Leske MC, Bengtsson B, et al. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. *Arch Ophthalmol*. 2002;120:1268−1279.

8. Quigley HA, West SK, Rodriguez J, et al. The prevalence of glaucoma in a population-based study of Hispanic subjects: Proyecto VER. *Arch Ophthalmol*. 2001;119:1819–1826.
9. Leske MC, Wu SY, Nemesure B, Hennis A. Vascular risk factors for primary open angle glaucoma. *Arch Ophthalmol*. 2002;120:945–959.
10. Bonomi L, Marchini G, Marraffa M, et al. Vascular risk factors for primary open angle glaucoma: the Egna-Neumarkt Study. *Ophthalmology*. 2000;107:1287–1293.
11. Tielsch JM, Katz J, Sommer A, et al. Hypertension, perfusion pressure, and primary open-angle glaucoma. A population-based assessment. *Arch Ophthalmol*. 1995;113:216–221.
12. Memarzadeh F, Ying-Lai M, Chung J, et al. Los Angeles Latino Eye Study Group. Blood pressure, perfusion pressure, and open-angle glaucoma: the Los Angeles Latino Eye Study. *Invest Ophthalmol Vis Sci*. 2010;51:2872–2877.
13. Ramdas WD, Wolfs RC, Hofman A, et al. Ocular perfusion pressure and the incidence of glaucoma: real effect or artifact? The Rotterdam Study. *Invest Ophthalmol Vis Sci*. 2011;52:6875–6881.
14. Zheng Y, Wong TY, Mitchell P, et al. Distribution of ocular perfusion pressure and its relationship with open-angle glaucoma: The Singapore Malay Eye Study. *Invest Ophthalmol Vis Sci*. 2010;51:3399–3404.
15. Khawaja AP, Crabb DP, Jansonius NM. The role of ocular perfusion pressure in glaucoma cannot be studied with multivariable regression analysis applied to surrogates. *Invest Ophthalmol Vis Sci*. 2013;54:4619–4620.
16. Kim H, Choi B. Nonlinear relationship between blood pressure and glaucoma in US adults. *Am J Hypertens*. 2019;32:308–316.
17. Lee K, Yang H, Kim JY, et al. Risk factors associated with structural progression in normal-tension glaucoma: intraocular pressure, systemic blood pressure, and myopia. *Invest Ophthalmol Vis Sci*. 2020;61:35.
18. Leske MC, Wu SY, Nemesure B, Hennis A. Incident open-angle glaucoma and blood pressure. *Arch Ophthalmol*. 2002;120:954–959.
19. Jammal AA, Thompson AC, Mariottoni EB, et al. Rates of glaucomatous structural and functional change from a large clinical population: The Duke Glaucoma Registry Study. *Am J Ophthalmol*. 2021;222:238–247.
20. Jammal AA, Thompson AC, Mariottoni EB, et al. Impact of intraocular pressure control on rates of retinal nerve fiber layer loss in a large clinical population. *Ophthalmology*. 2021;128:48–57.
21. Medeiros FA, Lisboa R, Weinreb RN, et al. A combined index of structure and function for staging glaucomatous damage. *Arch Ophthalmol*. 2012;130:1107–1116.
22. Garway–Heath DF, Caprioli J, Fitzke FW, Hitchings RA. Scaling the hill of vision: the physiological relationship between light sensitivity and ganglion cell numbers. *Invest Ophthalmol Vis Sci*. 2000;41:1774–1782.
23. Abe RY, Diniz-Filho A, Zangwill LM, et al. The relative odds of progressing by structural and functional tests in glaucoma. *Invest Ophthalmol Vis Sci*. 2016;57:421–428. OCT.
24. Leite MT, Rao HL, Zangwill LM, et al. Comparison of the diagnostic accuracies of the Spectralis, Cirrus, and RTVue optical coherence tomography devices in glaucoma. *Ophthalmology*. 2011;118:1334–1339.
25. Varma R, Bazzaz S, Lai M. Optical tomography-measured retinal nerve fiber layer thickness in normal Latinos. *Invest Ophthalmol Vis Sci*. 2003;44:3369–3373.
26. Patel NB, Lim M, Gajjar A, et al. Age-associated changes in the retinal nerve fiber layer and optic nerve head. *Invest Ophthalmol Vis Sci*. 2014;55:5134–5143.
27. Bowd C, Zangwill LM, Weinreb RN, et al. Estimating optical coherence tomography structural measurement floors to improve detection of progression in advanced glaucoma. *Am J Ophthalmol*. 2017;175:37–44.
28. Asrani S, Essaid L, Alder BD, Santiago-Turla C. Artifacts in spectral-domain optical coherence tomography measurements in glaucoma. *JAMA Ophthalmol*. 2014;132:396–402.
29. Laird NM, Ware JH. Random-effects models for longitudinal data. *Biometrics*. 1982;38:963–974.
30. Medeiros FA, Zangwill LM, Weinreb RN. Improved prediction of rates of visual field loss in glaucoma using empirical Bayes estimates of slopes of change. *J Glaucoma*. 2012;21:147–154.
31. Medeiros FA, Zangwill LM, Mansouri K, et al. Incorporating risk factors to improve the assessment of rates of glaucomatous progression. *Invest Ophthalmol Vis Sci*. 2012;53:2199–2207.
32. Jammal AA, Berchuck SI, Thompson AC, et al. The effect of age on increasing susceptibility to retinal nerve fiber layer loss in glaucoma. *Invest Ophthalmol Vis Sci*. 2020;61:8.
33. De Moraes CG, Liebmann JM, Greenfield DS, et al. Risk factors for visual field progression in the low-pressure glaucoma treatment study. *Am J Ophthalmol*. 2012;154:702–711.
34. Drance S, Anderson DR, Schulzer M; Collaborative Normal-Tension Glaucoma Study Group. Risk factors for progression of visual field abnormalities in normal-tension glaucoma. *Am J Ophthalmol*. 2001;131:699–708.
35. Rapsomaniki E, Timmis A, George J, et al. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1.25 million people. *Lancet*. 2014;383:1899–1911.
36. De Moraes CG, Cioffi GA, Weinreb RN, Liebmann JM. New recommendations for the treatment of systemic hypertension and their potential implications for glaucoma management. *J Glaucoma*. 2018;27:567–571.
37. Langman MJ, Lancashire RJ, Cheng KK, Stewart PM. Systemic hypertension and glaucoma: mechanisms in common and co-occurrence. *Br J Ophthalmol*. 2005;89:960–963.
38. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2018;71:e127–e248.
39. Muntner P, Carey RM, Gidding S, et al. Potential U.S. Population Impact of the 2017 ACC/AHA High Blood Pressure Guideline. *J Am Coll Cardiol*. 2018;71:109–118.
40. Rutan GH, Kuller LH, Neaton JD, et al. Mortality associated with diastolic hypertension and isolated systolic hypertension among men screened for the Multiple Risk Factor Intervention Trial. *Circulation*. 1988;77:504–514.
41. Stamler J, Stamler R, Neaton JD. Blood pressure, systolic and diastolic, and cardiovascular risks. US population data. *Arch Intern Med*. 1993;153:598–615.
42. Lindenstrom E, Boysen G, Nyboe J. Influence of systolic and diastolic blood pressure on stroke risk: a prospective observational study. *Am J Epidemiol*. 1995;142:1279–1290.
43. Benetos A, Thomas F, Bean K, et al. Prognostic value of systolic and diastolic blood pressure in treated hypertensive men. *Arch Intern Med*. 2002;162:577–581.
44. Klein BE, Klein R, Knudtson MD. Intraocular pressure and systemic blood pressure: longitudinal perspective: the Beaver Dam Eye Study. *Br J Ophthalmol*. 2005;89:284–287.

45. Wright Jr JT, Williamson JD, Whelton PK, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med*. 2015;373:2103–2116.
46. Flammer J, Orgul S, Costa VP, et al. The impact of ocular blood flow in glaucoma. *Prog Retin Eye Res*. 2002;21:359–393.
47. Yucel YH, Gupta N. Paying attention to the cerebrovascular system in glaucoma. *Can J Ophthalmol*. 2008;43:342–346.
48. Topouzis F, Coleman AL, Harris A, et al. Association of blood pressure status with the optic disk structure in non-glaucoma subjects: the Thessaloniki eye study. *Am J Ophthalmol*. 2006;142:60–67.
49. Harris A, Topouzis F, Wilson MR, et al. Association of the optic disc structure with the use of antihypertensive medications: the Thessaloniki Eye Study. *J Glaucoma*. 2013;22:526–531.
50. Costa VP, Jimenez-Roman J, Carrasco FG, et al. Twenty-four-hour ocular perfusion pressure in primary open-angle glaucoma. *Br J Ophthalmol*. 2010;94:1291–1294.
51. Charlson ME, de Moraes CG, Link A, et al. Nocturnal systemic hypotension increases the risk of glaucoma progression. *Ophthalmology*. 2014;121:2004–2012.
52. Miglior S, Torri V, Zeyen T, et al. Intercurrent factors associated with the development of open-angle glaucoma in the European Glaucoma Prevention study. *Am J Ophthalmol*. 2007;144:266–275.
53. Schuman JS. Effects of systemic β-blocker therapy on the efficacy and safety of topical brimonidine and timolol. Brimonidine Study Groups 1 and 2. *Ophthalmology*. 2000;107:1171–1177.
54. Verdecchia P, Schillaci G, Borgioni C, et al. Prognostic significance of the white coat effect. *Hypertension*. 1997;29:1218–1224.