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Cardiovascular Disease Predicts Structural and Functional Progression in Early Glaucoma

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Purpose: To investigate the association between cardiovascular disease and baseline structural defects and disease progression in glaucoma.

Design: Prospective, longitudinal study of preperimetric and perimetric glaucoma.

Participants: Two thousand six hundred twenty-eight eyes from 1314 participants recruited to the Progression Risk of Glaucoma: Relevant SNPs with Significant Association (PROGRESSA) study were evaluated for baseline and longitudinal structural thinning using spectral-domain OCT and for visual field progression on Humphrey visual field (HVF) assessment.

Methods: Patients were classified as either predominantly macula ganglion cell–inner plexiform layer (mGCIPL), predominantly peripapillary retinal nerve fiber layer (pRNFL), or both mGCIPL and pRNFL structural change at enrollment, and then evaluated for longitudinal OCT or HVF progression. Cardiovascular disease and medication characteristics of the participants were compared with a reference group of stable patients.

Main Outcome Measures: OCT and HVF baseline status and longitudinal progression.

Results: After accounting for age and cardiovascular characteristics, patients with predominantly mGCIPL thinning at baseline showed a higher prevalence of hypertension (odds ratio [OR], 2.70; 95% confidence interval [CI], 1.66–4.41; $P < 0.001$), antihypertensive use (OR, 2.03; 95% CI, 1.20–3.46; $P = 0.008$), and statin use (OR, 1.98; 95% CI, 1.07–3.66; $P = 0.029$) than reference patients. Patients with predominantly pRNFL thinning exhibited a comparable prevalence of cardiovascular disease or medication with reference patients. Review of longitudinal OCT and HVF data (mean follow-up, 5.34 ± 1.29 years) showed that hypertension was associated with an increased risk of both OCT (OR, 1.79; 95% CI, 1.17–2.75; $P = 0.006$) and HVF progression (OR, 1.92; 95% CI, 1.18–3.15; $P = 0.013$). A 1-standard deviation (approximately 21 mmHg) increase in systolic blood pressure at baseline was associated with a greater risk of OCT progression (OR, 1.27; 95% CI, 1.01–1.63; $P = 0.041$) and HVF progression (OR, 1.32; 95% CI, 1.01–1.73; $P = 0.043$). The association between systolic blood pressure and structural progression was comparable to that observed between intraocular pressure and structural progression (OR, 1.30; 95% CI, 1.01–1.67; $P = 0.039$).

Conclusions: Cardiovascular disease is an important risk factor for glaucoma progression.

Glaucoma is an optic neuropathy in which raised intraocular pressure (IOP) is a major risk factor for retinal ganglion cell degeneration.[1,2] Several large population studies have identified cardiovascular disease also to be a risk factor for the diagnosis of primary open-angle glaucoma.[3–6] Potential shared pathoetiologic mechanisms, including microvascular damage and ocular perfusion pressure abnormalities, have been proposed.[3,7] In this model, retinal vascular hypoperfusion is hypothesized to predispose retinal ganglion cells to injury at an IOP comparable with that of the normal population.[3,8,9]

Retinal ganglion cell degeneration may be monitored clinically using spectral-domain (SD) OCT thickness measurements of the peripapillary retinal nerve fiber layer (pRNFL) and the macula ganglion cell–inner plexiform layer (mGCIPL). Although pRNFL and mGCIPL SD OCT thickness measurements have comparable sensitivity and specificity for glaucoma diagnosis,[2,10–14] emerging evidence suggests that the site of earliest structural defect may hold clinical importance.[15–17] For instance, our group recently demonstrated that mGCIPL loss precedes pRNFL loss in glaucoma with lower average IOP.[18] We therefore hypothesized that alternate pathways, such as vascular dysfunction, may be implicated in patients exhibiting first structural damage in the mGCIPL.

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To test this hypothesis, this study characterized the baseline structural phenotype of patients enrolled into the Progression Risk of Glaucoma: Relevant SNPs [single nucleotide polymorphisms] with Significant Association (PROGRESSA) study. We first compared the prevalence of cardiovascular risk factors within each endophenotype group with a reference group of stable patients, before evaluating the association between these risk factors with both structural and functional progression.

Methods

Study Overview

This study investigated the relationship between systemic cardiovascular risk factors and baseline structural change and longitudinal progression in preperimetric and perimetric glaucoma. Patients studied were selected from the PROGRESSA study, which is an ongoing, longitudinal, prospective, multicenter observational cohort study of patients with early glaucoma and glaucoma suspect patients in Australia; PROGRESSA has been described elsewhere.[19]

Study Group Definitions

We primarily compared patients who exhibited reproducible and detectable thinning on either pRNFL or mGCIPL SD OCT imaging with a reference group of structurally and functionally stable glaucoma suspect patients who did not exhibit any OCT structural thinning. Patients showing structural change at baseline were characterized as demonstrating either (1) predominantly mGCIPL thinning, (2) predominantly pRNFL thinning, (3) equivalent mGCIPL and pRNFL thinning, or (4) no detectable thinning. Predominantly mGCIPL thinning was defined as at least 1 eye showing solely mGCIPL structural change (with the other eye showing either no structural change, solely mGCIPL structural change, or both pRNFL and mGCIPL structural change); predominantly pRNFL thinning was defined as at least 1 eye showing solely pRNFL structural defects (with the other eye showing either no structural change, solely pRNFL structural change, or both pRNFL and mGCIPL structural change). Equivalent mGCIPL and pRNFL thinning was defined as either both eyes showing both pRNFL and mGCIPL defects or one eye showing both pRNFL and mGCIPL defect in the absence of structural change in the other eye. No detectable thinning was defined as neither eye showing a reproducible structural defect of the mGCIPL or pRNFL. We excluded patients who showed solely mGCIPL thinning in one eye and solely pRNFL thinning in the other eye, referred to as a *mixed phenotype*.

The reference group consisted of structurally and functionally stable glaucoma suspect patients. Inclusion into this group required that the patient did not exhibit a structural defect at baseline (i.e., no detectable thinning structural phenotype) and showed no event-based longitudinal SD OCT progression, nor visual field progression in either eye during study involvement. In essence, although these patients were recruited into the PROGRESSA study because of a clinically suspicious disc (i.e., disc damage likelihood scale, $\geq$1 at enrollment), they did not exhibit any structural or functional change over the study period. Herein, they are referred to as *reference patients* or the *reference group*.

This study adhered to the tenets of the Declaration of Helsinki and followed the National Health and Medical Research Council statement of ethical conduct in research involving humans. Informed written consent was obtained from all participants, and the study was approved by the Southern Adelaide Clinical Human Research Ethics Committee.

Ocular and Systemic Characteristics of Study Population

Ocular phenotypic data were obtained through 6-month ophthalmologic examinations, as per PROGRESSA study protocol. Clinical ophthalmic data included: best-corrected central visual acuity, IOP measurement (using Goldmann applanation tonometry), and corneal pachymetry, with data from the eye exhibiting the worst mean deviation at baseline used in the analysis. Comprehensive previous ocular and medical history was obtained by the recruiting clinician using a standardized general health questionnaire at the time of study enrollment. This questionnaire specifically addressed the following self-reported cardiovascular risk factors: hypertension, diabetes, myocardial infarction, and clinically diagnosed cerebrovascular events (strokes and transient ischemic attacks). Vascular disease features addressed in the questionnaire include a self-reported history of migraine or history of Raynaud's disease. This questionnaire also asked the patients to "list any regular medications." For the purposes of this study, the presence of the following cardiovascular medications were recorded for each patient: aspirin, clopidogrel, statins, antihypertensives (defined by the presence of either angiotensin converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, or calcium channel blockers), metformin, and insulin. Serum lipid profiles were determined by reviewing hospital and primary care records. The highest recorded total cholesterol and lowest recorded high-density lipoprotein cholesterol within 5 years of study enrollment or during study involvement was used for analysis. Systolic and diastolic blood pressure were measured at enrollment and then annually during follow-up visits using an automated sphygmomanometer.

OCT Imaging

OCT imaging was performed using the Cirrus SD OCT software version 9.5 (Carl Zeiss Meditec, Dublin, CA). Peripapillary retinal nerve fiber layer thickness was measured using the optic disc 200 $\times$ 200 cube scan, and mGCIPL thickness was measured using the macula 512 $\times$ 128 cube scan. Spectral-domain OCT scanning was performed by an experienced operator using Cirrus FastTrac eye-tracking technology with fixation centered on the optic disc and fovea. OCT imaging was performed at the time of enrollment into the PROGRESSA study and at each subsequent 6-month visit. All SD OCT scans were evaluated for image quality before assessment of baseline structural defects by a single investigator (H.M.). Scans with a signal strength of less than 6, a significant acquisition artefact, or a nonglaucomatous pathologic feature were excluded from analyses.

Baseline structural assessment was undertaken by evaluation of the SD OCT 6 $\times$ 6-mm^2 pRNFL and the elliptical mGCIPL thickness deviation maps that were obtained at the patient's enrollment into the PROGRESSA study and at the first follow-up visit. Baseline structural defects were defined by the presence of a reproducible region of 4 $\times$ 4 pixels (>16 contiguous pixels) encoded red on the respective thickness deviation maps. Red pixels indicate that the thickness in this corresponding region of the mGCIPL or pRNFL *en face* image is less than the lower age-adjusted 99th percentile threshold.

Figure 1A below depicts a patient classified as having predominantly pRNFL thinning. Figure 1B depicts a patient classified as having predominantly mGCIPL thinning. We then compared the prevalence of cardiovascular risk factors in each structural phenotype with the reference group of stable patients.

Assessment of longitudinal SD OCT optic nerve head and macula scans was performed using commercially available Cirrus HD-OCT event-based Guided Progression Analysis software. Event-based progression was identified using a replicated likely loss criteria, as described previously.[18,20] In addition, we used longitudinal trend analysis data to evaluate the effect of cardiovascular disease features on the rates of mGCIPL and pRNFL thinning.

Visual Field Assessment

We reviewed the baseline Humphrey visual field (HVF) 24-2 Swedish interactive threshold algorithm standard tests (Humphrey Field Analyzer; Carl Zeiss Meditec, Dublin, CA) for all eyes included in the study to classify patients either as having perimetric glaucoma or as a glaucoma suspect at study enrollment. Perimetric glaucoma patients were defined by the presence of a reproducible glaucomatous visual field defect (as per modified Hodapp-Parrish-Anderson criteria) on consecutive reliable HVF assessments at baseline in at least 1 eye.[21] Reliable HVF results were defined by a fixation loss of less than 33% and a false-positive rate of less than 33%. We defined a glaucomatous visual field defect as abnormal glaucoma hemifield test results or pattern standard deviation (PSD) of less than 5% and 3 contiguous HVF locations with pattern deviation defect of less than a 5% significance level, reproducible in the same HVF zone on 2 successive HVF tests. If the glaucoma hemifield test results and the PSD were normal, then the 3 contiguous HVF locations were required to have a pattern deviation defect at less than a 1% significance level on 2 successive HVF tests. Glaucoma suspect patients did not demonstrate glaucomatous visual field defect at baseline according to the criteria above, albeit having optic disc features of possible or likely glaucoma (disc damage likelihood scale grade, 1−2). Visual field progression for both glaucoma suspects and perimetric glaucoma patients was defined by the presence of a new reproducible visual field defect according to the aforementioned criteria on 2 consecutive reliable visual field tests.

Statistical Analyses

Univariate analyses of ocular and systemic characteristics between the outcome of baseline SD OCT assessment and baseline ocular or systemic features were undertaken using a stepwise protocol. Blood pressure and IOP measurements were adjusted for treatment using censored normal regression.[22] Initially, an analysis of variance was implemented to compare study groups for a given ocular or cardiovascular parameter. The P value threshold was adjusted to 0.002 to account for multiple hypothesis testing (Bonferroni method). We then undertook pairwise comparisons between study groups and reference patients for variables with an analysis of variance P value of less than 0.002 using univariate generalized linear modelling with mixed effects.[23] Generalized linear models with mixed effects were fitted with the glmer function from the lme4 package version 1.1−18−1 in R software version 3.4.1 (RCore Team, Vienna, Austria). The P value threshold was adjusted for family-wise error rate (Bonferroni method; adjusted P value threshold, 0.017). We then undertook a multivariate subanalysis of perimetric glaucoma patients with variable selection using criterion-based procedures to verify the observed association between cardiovascular disease parameters and perimetric glaucoma. We subsequently investigated the influence of those variables predictive of baseline structural phenotype on longitudinal structural and functional progression using SD OCT and HVF assessments. To do so, multivariate logistic and Cox regression survival analyses compared the prevalence of cardiovascular characteristics between reference participants and participants demonstrating the following outcomes: any structural progression (mGCIPL or pRNFL), mGCIPL structural progression, pRNFL structural progression, and visual field progression. The P value threshold for statistical significance in multivariate subanalyses was 0.05.

Tabulated data present mean±standard deviation for continuous variables and prevalence (percent) for discrete variables within each structural phenotype or reference group. Post hoc comparisons between structural phenotype groups (predominantly mGCIPL structural change, equivalent mGCIPL and pRNFL structural change, or predominantly pRNFL structural change) and reference group were undertaken for variables with a P value of less than 0.002 for analysis of variance and are described as mean difference and 95% confidence interval (CI) for continuous variables and odds ratio (OR) and 95% CI for discrete variables.

Results

Study Group Characteristics

The baseline optic disc and macula deviation thickness maps of 2628 eyes from 1314 patients enrolled in the PROGRESSA study between May 2012 and September 2018 were reviewed for evidence of baseline structural thinning. Ninety-two patients (7.0%) were excluded because of poor-quality scans, the presence of significant acquisition artefacts, or nonglaucomatous pathologic features in at least 1 eye. The SD OCT baseline deviation thickness maps of 2444 eyes from 1222 patients were assessed for the presence of structural defects. Two hundred seventy-two patients were classified as showing predominantly mGCIPL thinning, 459 patients were classified as showing equivalent mGCIPL and pRNFL thinning, and 273 patients were classified as showing predominantly pRNFL thinning. Six patients were excluded because of the presence of a mixed phenotype. Two hundred twelve patients did not demonstrate any structural defects on baseline mGCIPL or pRNFL deviation thickness maps in either eye. One hundred eleven of these patients showed SD OCT or HVF deficits during monitoring. The remaining 101 patients demonstrated neither structural nor visual field progression over a minimum of 3 years (mean±standard deviation, 5.34 ± 1.29 years) and were used as an internal reference group. The mean age at baseline was 63.9 years (standard deviation, 11.1 years). Of all nonreference patients, 35.2% (n = 385) were classified as having perimetric glaucoma at baseline and 13.7% (n = 175) did not have reliable visual field results on the baseline test (Fig 2).

Baseline Ocular Characteristics

Univariate analysis of baseline ocular parameters demonstrated that patients with predominantly pRNFL defects demonstrated a higher baseline IOP (mean difference, 1.53 mmHg; 95% CI, 0.41−2.54 mmHg; $P = 0.007$), worse mean deviation (mean difference, −0.83 dB; 95% CI, −0.56 to −1.40 dB; $P < 0.001$), and more myopic spherical equivalent refraction (mean difference, −0.84 diopter [D]; 95% CI, −0.23 to −1.56 D; $P = 0.008$) compared with reference patients (Table 1).

Patients with predominantly mGCIPL thinning also had a worse mean deviation (mean difference, −1.20 dB; 95% CI, −0.56 to −1.74; $P < 0.001$), were older (mean difference, 5.81 years; 95% CI, 3.3−8.24 years; $P < 0.001$), and were more likely to be taking topical glaucoma medication (OR, 6.30; 95% CI, 2.82−14.12; $P < 0.001$) than reference patients (Table 1).

Patients with equivalent mGCIPL and pRNFL defects showed higher baseline IOP (mean difference, 1.62 mmHg; 95% CI, 0.61−2.61 mmHg; $P = 0.002$), showed worse mean deviation

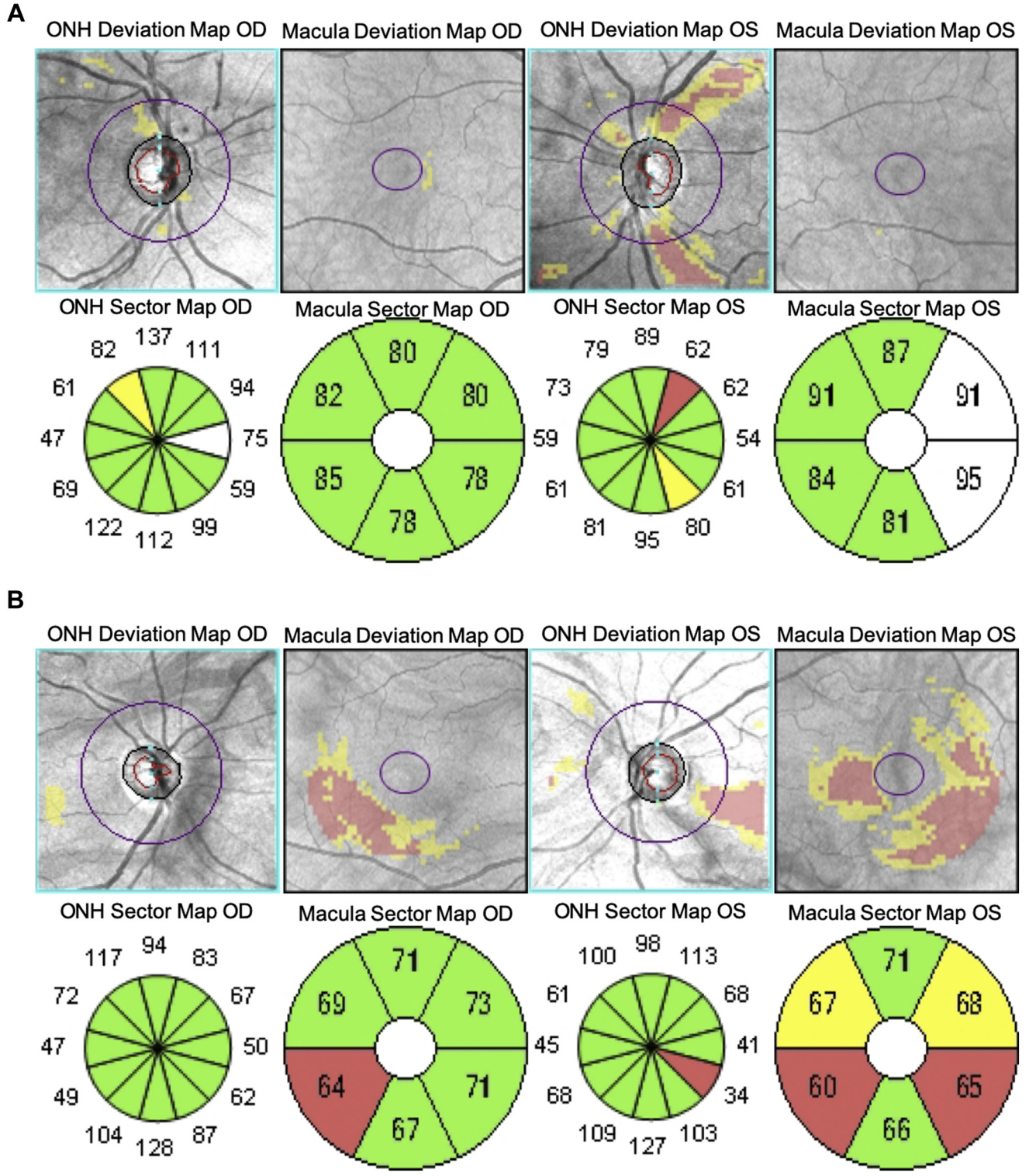

Figure 1. Optic nerve head (ONH) deviation maps, ONH sector thickness diagrams, macula cube deviation maps, and macula cube sector thickness diagrams for both right eye (OD) and left eye (OS) of 2 patients in this study. The optic disc and macula OCT scans for both eyes were performed at the same visit in both patients. **A**, Representative patient with predominantly peripapillary retinal nerve fiber layer (pRNFL) structural change. Although this patient did not exhibit any detectable structural change in the right eye, the presence of solely pRNFL thinning in the left eye leads to the characterization of predominantly pRNFL thinning. **B**, Representative patient with predominantly macula ganglion cell—inner plexiform layer (mGCIPL) structural thinning. Although both the macula and ONH deviation maps for the left eye show structural thinning, the presence of solely mGCIPL thinning in right eye leads to the characterization of predominantly mGCIPL thinning.

(mean difference, −1.57 dB; 95% CI, −0.56 to −2.14; $P < 0.001$), were older (mean difference, 3.54 years; 95% CI, 1.18−5.89 years; $P = 0.003$), and were more likely to be taking topical glaucoma medications (OR, 10.23; 95% CI, 5.63−26.93; $P < 0.001$) or to have undergone selective laser trabeculoplasty (OR, 3.71; 95% CI, 1.66−8.29; $P = 0.001$) when compared with reference patients (Table 1).

Baseline Cardiovascular Disease Characteristics

Prevalence of cardiovascular risk factors was compared between patients with structural defects and reference patients. Patients with predominantly mGCIPL thinning demonstrated a higher prevalence of hypertension (OR, 2.70; 95% CI, 1.66−4.41; $P < 0.001$) and a higher prevalence of previous myocardial infarction (OR, 5.14; 95% CI, 1.55−17.12; $P = 0.007$) than reference patients. No differences were observed between patients with predominantly pRNFL thinning and reference patients (Table 2).

Baseline Cardiovascular Medication Characteristics

Participants with predominantly mGCIPL structural defects were more likely to have been prescribed regular antihypertensive medications (OR, 3.02; 95% CI, 1.84−4.89; $P < 0.001$), aspirin (OR, 2.95; 95% CI, 1.35−6.43; $P = 0.006$), and statins (OR, 3.06; 95% CI, 1.72−5.44; $P < 0.001$) than reference patients. Participants showing equivalent mGCIPL and pRNFL structural defects showed a higher prevalence of regular antihypertensive use (OR, 1.620; 95% CI, 1.02−2.58; $P = 0.010$) and statin use (OR, 2.00; 95% CI, 1.14−3.51; $P = 0.015$) than reference patients. The cardiovascular medication profiles of participants with predominantly pRNFL structural change did not differ from those of reference patients (Table 3). Figure 3 summarizes the differences in cardiovascular disease features and medication profiles of each subgroup for each variable for which a statistically significant distribution P value ($P < 0.002$) was observed.

A subanalysis assessed to what extent the age differences between study cohorts and the correlation between cardiovascular traits confounded our primary analysis. Separate multivariate analyses for cardiovascular disease (hypertension and myocardial infarction) and medication (antihypertensives, aspirin, angiotensin-receptor blockers, and statins) characteristics were constructed, and both included age as a covariate. Age squared also was used as a covariate, but this did not change the outcome (data not shown). In the cardiovascular disease model, patients showing predominantly mGCIPL thinning demonstrated a higher prevalence of hypertension (OR, 2.04; 95% CI, 1.22−3.42; $P = 0.006$) than reference patients. Although patients with the predominantly mGCIPL thinning phenotype also showed a higher prevalence of myocardial infarction, this did not demonstrate nominal significance (OR, 3.29; 95% CI, 0.97−11.18; $P = 0.056$). In the cardiovascular medications model, patients with predominantly mGCIPL defects showed a higher prevalence of treatment with antihypertensive medications (OR, 2.03; 95% CI, 1.20−3.46; $P = 0.008$) and statins (OR, 1.98, 95% CI, 1.07−3.66; $P = 0.029$). Treatment with aspirin (OR, 1.78; 95% CI, 0.79−4.06; $P = 0.159$) and angiotensin-receptor blockers (OR, 1.65; 95% CI, 0.72−3.78; $P = 0.236$) were no longer significantly associated with the mGCIPL structural phenotype, although a trend remained.

Subanalysis of Ocular and Systemic Risk factors in Early Manifest Glaucoma Patients

A subanalysis of the 305 patients classified as having early manifest glaucoma on baseline visual field assessment was undertaken to evaluate further our findings in the setting of clearly defined perimetric glaucoma. Seventy-seven patients (25.2%) were classified as demonstrating predominantly mGCIPL thinning, 172 patients (56.4%) were classified as demonstrating both pRNFL and mGCIPL defects, and 56 patients (18.4%) were classified as demonstrating predominantly pRNFL thinning. In this analysis, we compared the prevalence of cardiovascular disease and medications in each structural phenotype with reference patients. Analyses were undertaken using separate multivariate models for cardiovascular disease and for cardiovascular medication, and both included age as a covariate. Multivariate analysis of cardiovascular diseases identified a higher prevalence of hypertension (OR, 2.46; 95% CI, 1.31−4.62; $P = 0.005$) and myocardial infarction (OR, 4.11; 95% CI, 1.10−15.20; $P = 0.034$) in those patients demonstrating predominantly mGCIPL structural change compared with reference patients.

Perimetric glaucoma patients with predominantly mGCIPL defects exhibited a higher prevalence of treatment with antihypertensive medications (OR, 2.34; 95% CI, 1.22−9.56; $P = 0.001$) and statins (OR, 2.96; 95% CI, 1.48−5.90; $P = 0.015$) than reference patients. These patients exhibited a higher prevalence of aspirin use, but this did not reach statistical significance after accounting for other cardiovascular medications and age (OR, 2.24; 95% CI, 0.89−5.59; $P = 0.083$). Perimetric glaucoma patients with predominantly pRNFL structural change were not associated with a higher prevalence of any cardiovascular disease or medication compared with reference patients. However, these patients did exhibit a higher baseline IOP than reference patients (mean difference, 2.05 mmHg; 95% CI, 1.09−3.92; $P < 0.001$). Figure 4 illustrates the prevalence of cardiovascular disease and medication characteristics between structural endophenotypes in perimetric glaucoma patients and reference patients.

Longitudinal Structural and Functional Progression

We reviewed longitudinal SD OCT and HVF data for all PROGRESSA patients with more than 3 years of follow-up (n = 1067 patients; mean duration of monitoring, 5.34 ± 1.29 years). We then assessed the association of cardiovascular disease and medications with structural or functional progression or both. Analyses accounted for age and baseline IOP as covariates.

A past medical history of hypertension was associated with an increased likelihood of any structural progression (OR, 1.79; 95% CI, 1.17−2.75; $P = 0.006$), mGCIPL structural progression (OR, 1.84; 95% CI, 1.27−2.67; $P = 0.001$), and pRNFL structural progression (OR, 1.64; 95% CI, 1.09−2.45; $P = 0.016$) and also was associated with a faster rate of average mGCIPL thinning on trend analysis (estimate, −0.07 μm/year; 95% CI, −0.01 to −0.12 μm/year; $P = 0.011$). Hypertension additionally was associated with a greater likelihood of visual field progression, as determined by Hodapp-Parrish-Anderson criteria (OR, 1.92; 95% CI, 1.18−3.15; $P = 0.013$).

The presence of antihypertensive treatment was associated with an increased risk of any structural progression (OR, 1.83; 95% CI, 1.19−2.08; $P = 0.005$), mGCIPL structural progression (OR, 1.97; 95% CI, 1.28−3.10; $P = 0.002$), and a faster rate of average mGCIPL thinning (estimate, −0.057 μm/year; 95% CI, 0.03−0.08 μm/year; $P = 0.017$). Antihypertensive treatment also was associated with an increased risk of visual field progression during study involvement (OR, 1.91; 95% CI, 1.16−3.13; $P = 0.010$).

Further evaluation of blood pressure explored the relationship between recorded blood pressure at enrollment and longitudinal SD OCT and HVF progression. Systolic and diastolic blood pressure measurements were adjusted for antihypertensive therapy by fitting a censored regression model. A higher systolic blood pressure was associated with a greater risk of structural progression (OR, 1.014/mmHg; 95% CI, 1.003−1.024/mmHg; $P = 0.010$), mGCIPL

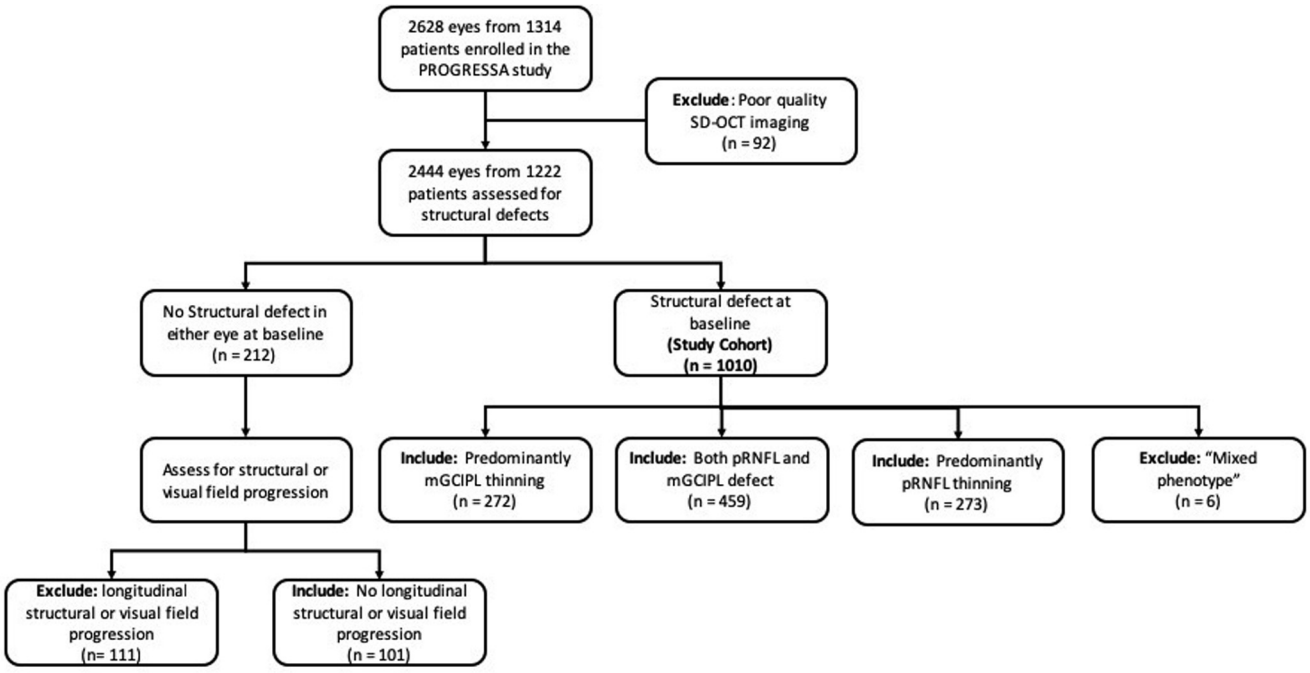

Figure 2. Schematic illustration of study characterization. "Mixed phenotype" refers to patients who showed solely peripapillary retinal nerve fiber layer (pRNFL) thinning in one eye and solely macular ganglion cell–inner plexiform layer (mGCIPL) thinning in the other. PROGRESSA = Progression Risk of Glaucoma: Relevant SNPs with Significant Association; SD = spectral-domain.

structural progression (OR, 1.019/mmHg; 95% CI, 1.008–1.030/mmHg; $P = 0.001$), and a greater risk of visual field progression (OR, 1.01/mmHg; 95% CI, 1.005–1.029/mmHg; $P = 0.006$). A higher systolic blood pressure was associated with pRNFL structural progression, but this did not maintain significance after accounting for age and IOP ($P = 0.102$). Diastolic blood pressure also was associated with a greater risk of any structural progression (OR, 1.02/mmHg; 95% CI, 1.01–1.04/mmHg; $P = 0.010$) and mGCIPL progression (OR, 1.04/mmHg; 95% CI, 1.02–1.06/mmHg; $P < 0.001$). Diastolic blood pressure was not associated with visual field progression ($P = 0.108$).

Comparative analysis between IOP and systolic blood pressure showed that a 1-standard deviation increase in systolic blood pressure showed a similar association with structural progression as a 1-standard deviation increase in IOP (systolic blood pressure: OR, 1.27; 95% CI, 1.01–1.63; $P = 0.041$; IOP: OR, 1.30; 95% CI, 1.01–1.67; $P = 0.039$). However, IOP was associated more strongly with visual field progression than systolic blood pressure (systolic blood pressure: OR, 1.32; 95% CI, 1.01–1.73; $P = 0.043$; IOP: OR, 1.52; 95% CI, 1.10–2.09; $P = 0.010$). Baseline IOP was not associated with mGCIPL structural progression ($P = 0.122$).

Assessment of the relationship between blood pressure and IOP observed that a 10-mmHg increase in baseline systolic blood pressure was associated with a 0.47-mmHg increase in baseline IOP (coefficient, 0.047 mmHg; 95% CI, 0.027–0.061; $P < 0.001$; $R^2 = 2.01\%$). The presence of systemic hypertension additionally was associated with a higher baseline IOP after accounting for age and antihypertensive treatment (mean difference, 2.02 mmHg; 95% CI, 1.32–2.72 mmHg; $P < 0.001$).

Discussion

This study has shown systemic cardiovascular disease to be an important risk factor for structural and functional progression in early glaucoma. We initially determined that systemic cardiovascular disease characteristics, such as hypertension and myocardial infarction, as well as medications, such as antihypertensives, aspirin, and statins, were predictive of mGCIPL structural defects at baseline. After a review of longitudinal progression data, hypertension, antihypertensive use, and higher systolic blood pressure were associated with an increased risk of structural and functional progression in these patients, the effect sizes of which were comparable with those observed for baseline IOP.

One must consider our findings in conjunction with the existing literature surrounding cardiovascular disease and glaucoma. Several large clinical studies have shown hypertension to be an important risk factor for glaucoma diagnosis and progression.[3–5,24,25] The present study further characterized this risk by identifying associations between hypertension and baseline mGCIPL thinning, longitudinal mGCIPL and pRNFL thinning, and visual field progression. It also identified that a higher systolic blood pressure was associated with an increased risk of visual field progression and mGCIPL progression. The observed relationship between blood pressure and IOP implies that the effects of hypertension on glaucomatous progression may be mediated partly by IOP pathways.[26] The association between mGCIPL progression and blood pressure, but not IOP, suggests that vascular pathways may be particularly important in glaucomatous damage of the macula. These findings provide support for the treatment of poorly controlled hypertension in glaucoma, as proposed by the Blue Mountains Eye Study.[4,25,27–30]

Other major studies also have shown hypotension to be a risk factor for glaucoma.[4,25,27–30] This has led the Los

Table 1. Comparison of Ocular Characteristics between Study Groups

	Patients with Predominantly Macula Ganglion Cell–Inner Plexiform Layer Thinning (n = 272)	Patients Showing Both Phenotypes (n = 459)	Patients with Predominantly Peripapillary Retinal Nerve Fiber Layer Thinning (n = 273)	Reference Patients (n = 101)	Global *P* Value
Baseline ocular parameters					
Baseline IOP (mmHg)	18.42 ± 6.52	19.25 ± 4.74	19.18 ± 4.84	17.63 ± 4.51	**<0.001**
Post hoc comparison	0.79 (−0.26 to 1.89; $P = 0.141$)	1.62 (0.61–2.61; **P = 0.002**)	1.53 (0.41–2.54; **P = 0.007**)		
VCDR	0.69 ± 0.119	0.73 ± 0.10	0.67 ± 0.11	0.64 ± 0.12	<0.001
MD at baseline (dB)	−1.76 ± 2.43	−2.13 ± 2.18	−1.39 ± 2.04	−0.56 ± 1.85	**<0.001**
Post hoc comparison	−1.20 (−0.56 to −1.74; **P <0.001**)	−1.57 (−0.56 to −2.14; **P <.001**)	−0.83 (−0.56 to −1.40; **P <0.001**)		
Central corneal thickness (μm)	550 ± 38.4	543 ± 35.2	549 ± 9.4	551 ± 36.5	0.065
Spherical equivalent (D)	−0.5 ± 2.630	−1.41 ± 2.96	−0.69 ± 2.14	0.24 ± 1.84	**<0.001**
Post hoc comparison	0.74 (−0.02 to −1.46; $P = 0.042$)	−1.65 (−0.96 to −2.31; **P <0.001**)	−0.84 (−0.23 to −1.56; **P = 0.008**)		
Age (yrs)	66.9 ± 9.2	64.6 ± 10.9	61.6 ± 11.0	61.1 ± 10.7	**<0.001**
Post hoc comparison	5.81 (3.3–8.24; **P <0.001**)	3.54 (1.18–5.89; **P = 0.003**)	0.53 (−2.01 to 3.051; $P = 0.681$)		
Gender (% female)	57.69	57.64	51.09	59.3	0.269
Ocular history					
Perimetric glaucoma (%)	37.4	48.4	25.8	0	NA
Topical glaucoma medication (%)	37.7	48.5	32.0	9.6	**<0.001**
Post hoc comparison	6.30 (2.82–14.12; **P <0.001**)	10.23 (5.63–26.93; **P <0.001**)	5.210 (2.32–11.70; **P <0.001**)		
SLT (%)	13.8	24.1	15.1	9.9	<0.001
Post hoc comparison	1.83 (0.78–4.29; $P = 0.165$)	3.71 (1.66–8.29; **P =0.001**)	2.04 (0.87–4.75; $P = 0.099$)		
Trabeculectomy (%)	0	0	0	0	NA
Cataract surgery at baseline (%)	25.52	17.89	14.53	16.2	0.018
Disc hemorrhage (%)	3.7	3.9	3.3	0	0.348
Glaucoma family history (%)	46.34	51.82	54.25	59.61	0.299

D = diopter; IOP = intraocular pressure; MD = mean deviation; NA = not applicable; SLT = selective laser trabeculoplasty; VCDR = vertical cup-to-disc ratio.
Boldface indicates statistical significance following adjustment for multiple hypothesis testing.

Table 2. Comparison of Cardiovascular Comorbidity between Study Groups and Reference Groups

	Patients with Predominantly Macula Ganglion Cell–Inner Plexiform Layer Thinning (n = 272)	Patients Showing Both Phenotypes (n = 459)	Patients with Predominantly Peripapillary Retinal Nerve Fiber Layer Thinning (n = 273)	Reference Patients (n = 101)	Global *P* Value
Past medical history					
Diabetes (%)	18.5	13.5	13.7	10.9	0.176
Hypertension (%)	53.3	40.4	39.1	29.7	**<0.001**
Post hoc comparison	**2.70 (1.66–4.41; *P* < 0.001)**	1.61 (1.11–2.56; *P* = 0.020)	1.51 (0.93–2.47; *P* = 0.098)		
Myocardial infarction (%)	13.6	6.9	5.8	3.2	**<0.001**
Post hoc comparison	**5.14 (1.55–17.1; *P* = 0.007)**	2.41 (0.73–8.04; *P* = 0.151)	2.00 (0.57–7.02; *P* = 0.278)		
Stroke/TIA (%)	6.2	5.2	1.1	1.0	0.003
Raynaud's syndrome (%)	7.4	5.8	5.4	4.2	0.607
Migraine (%)	19.5	18.5	21.7	16.8	0.665
Blood pressure and cholesterol measurements*					
Systolic blood pressure (mmHg)	139.4 ± 24.63	138.28 ± 23.31	134.46 ± 21.33	131.36 ± 24.68	0.013
Diastolic blood pressure (mmHg)	79.11 ± 13.53	78.39 ± 14.40	76.31 ± 13.35	73.59 ± 13.78	0.007
Total cholesterol (mmol/l)	5.05 ± 1.29	4.77 ± 1.13	5.23 ± 1.28	5.37 ± 1.18	0.221
HDL cholesterol (mmol/l)	1.48 ± 0.42	1.37 ± 0.42	1.61 ± 0.28	1.60 ± 0.42	0.250

HDL = high-density lipoprotein; TIA = transient ischemic attack.
Boldface indicates statistical significance.
*Values adjusted for the presence of antihypertensive or lipid-lowering therapy for all eyes.

Table 3. Comparison of Cardiovascular Medication between Study Groups and Reference Patients

Medication	Patients with Predominantly Macula Ganglion Cell–Inner Plexiform Layer Thinning (n = 272)	Patients Showing Both Phenotypes (n = 459)	Patients with Predominantly Peripapillary Retinal Nerve Fiber Layer Thinning (n = 273)	Reference Patients (n = 101)	Global *P* Value
Aspirin (%)	20.2	13.5	11.2	7.9	**0.003**
Post hoc comparison	**2.95 (1.35–6.43; *P* = 0.006)**	1.82 (0.84–3.93; *P* = 0.127)	1.46 (0.65–3.30; *P* = 0.357)		
Clopidogrel (%)	4.4	2.4	2.5	0	0.107
Statin (%)	38.2	28.8	22.4	16.8	**<0.001**
Post hoc comparison	**3.06 (1.72–5.44; *P* < 0.001)**	**2.00 (1.14–3.51; *P* = 0.015)**	1.42 (0.78–2.58; *P* = 0.242)		
Antihypertensive (%)	55.9	40.6	37.9	29.7	**<0.001**
Post hoc comparison	**3.02 (1.84–4.89; *P* < 0.001)**	1.620 (1.02–2.58; **P = 0.010**)	1.44 (0.88–2.43; *P* = 0.142)		
β-blocker (%)	15.1	7.1	7.6	7.9	**0.002**
Post hoc comparison	2.06 (0.93–4.57; *P* = 0.074)	0.89 (0.39–1.98; *P* = 0.772)	0.95 (0.41–2.23; *P* = 0.913)		
ACE inhibitor (% eyes)	10.3	11.2	10.8	6.9	0.650
Angiotensin receptor blocker (%)	23.2	14	15.2	8.9	**0.001**
Post hoc comparison	**3.08 (1.47–6.46; *P* = 0.002)**	1.66 (0.798,3.46; *P* = 0.175)	1.83 (0.85–3.90; *P* = 0.120)		
Calcium channel blockers (%)	8.5	5.4	5.1	2.0	0.008
Metformin (%)	9.6	7.7	6.1	6.9	0.502
Insulin (%)	3.7	2.4	1.8	0.0	0.178

ACE = angiotensin converting enzyme.
Boldface indicates statistical significance.

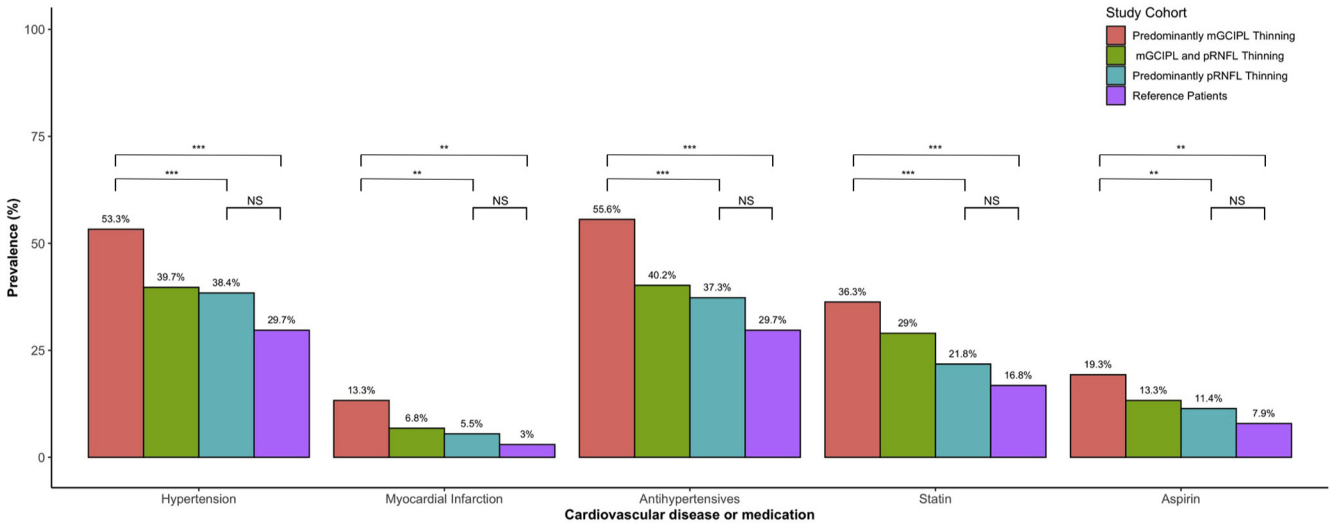

Figure 3. Bar graph summarizing the prevalence of systemic cardiovascular characteristics and medications between study groups. *P* values depicted for comparisons between the predominantly macular ganglion cell–inner plexiform layer (mGCIPL) thinning phenotype and reference patients (top row), the predominantly mGCIPL thinning phenotype and the predominantly peripapillary retinal nerve fiber layer (pRNFL) thinning phenotype (middle row), and the predominantly pRNFL thinning phenotype and reference patients (bottom row). *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. NS = nonsignificant.

Angeles Eye Study to propose a U-shaped relationship between blood pressure and glaucoma. In this model, both hypotension and hypertension are risk factors for glaucoma. Our study identified an increased risk of structural and functional progression in those patients treated with antihypertensive medications. Previous groups have proposed that antihypertensive use may be a risk factor for glaucomatous progression by causing nocturnal hypotension.[31–33] In the absence of ambulatory blood pressure monitoring, it is plausible that these patients were experiencing this phenomenon. Alternatively, antihypertensive therapy simply may be a surrogate marker for hypertension in this study. Further investigation of these possibilities clearly is warranted.

Similarly, the interaction between hypercholesterolemia, statin use, and primary open-angle glaucoma is debated in the literature.[34] A meta-analysis by Wang and Bao[35] revealed a 1.37 relative risk of glaucoma in individuals with hypercholesterolemia, but Kang et al[36] more recently pooled 3 large population-based studies and found no association between hypercholesterolemia and glaucoma. Further in this debate, statins have been proposed to be protective against glaucoma, with some studies postulating that the degree of neuroprotection is proportional to the

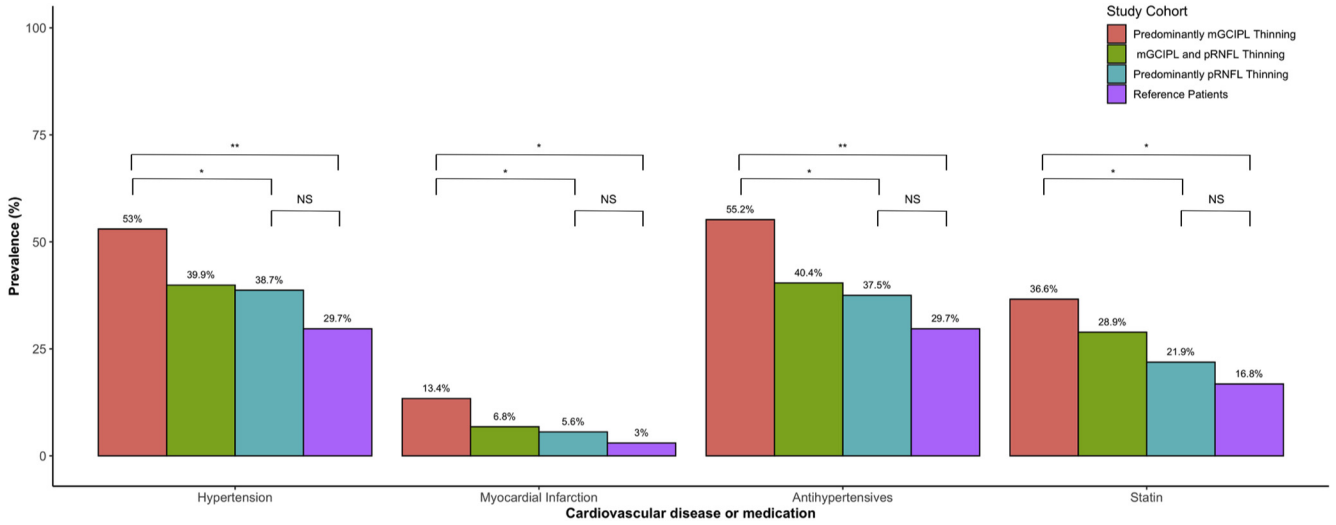

Figure 4. Bar graph comparing prevalence of cardiovascular treatment and disease in perimetric glaucoma patients. *P* values depicted for multivariate comparisons between solely macular ganglion cell–inner plexiform layer (mGCIPL) and reference patients (top row), solely mGCIPL and peripapillary retinal nerve fiber layer (pRNFL; middle row), and solely pRNFL and reference patients (bottom row) after adjustment for age. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. NS = nonsignificant.

duration of statin use.[37,38] In the present study, statin use was predictive of baseline mGCIPL defects. However, we were unable to demonstrate an association between measured cholesterol parameters and structural phenotype, which may be a consequence of the high prevalence of statin use in our study leading to lower cholesterol levels in those receiving treatment. In the absence of historical cholesterol data, we favor the hypothesis that statin use in our study may represent a surrogate marker of hypercholesterolemia in those exhibiting mGCIPL structural change.

Finally, Mondal et al[39] demonstrated that myocardial infarction was associated with a worsening visual field in a prospective study of 62 patients with stable open-angle glaucoma. Our current study developed on this work by illustrating that myocardial infarction is associated with a thinner mGCIPL at baseline in a substantially higher-powered longitudinal prospective study. Further study is required to understand the nature of, and mechanism for, the observed association among ischemic heart disease, baseline structural characteristics, and glaucoma progression.

Although we have identified that cardiovascular phenomena clearly are associated with macular structural defects, we recognize several study limitations. It is unknown if the structural changes observed on macular SD OCT analysis are related to glaucoma, to cardiovascular disease, or to both diseases. However, we did identify that cardiovascular disease was associated with baseline structural phenotypes in perimetric glaucoma patients and with longitudinal visual field progression, which supports the notion that these macula changes truly are glaucomatous defects and are important in considering visual morbidity and progressive visual field loss in glaucoma. Similarly, age-related macular changes (both pathologic and degenerative) may have contributed to the detected structural defects. We mitigated the detection of pathologic artefacts by excluding patients with observable nonglaucomatous defects on SD OCT or reduced visual acuity resulting from nonglaucomatous pathologic features. We also sought to avoid false detection of age-related degeneration by using Cirrus HD-OCT thickness deviation maps. These provide comparisons with the age-matched population and have been shown to have high accuracy for glaucoma diagnosis.[14,40–43] One also may argue that our results may have been confounded by the correlation between cardiovascular disease traits and the age difference between study groups. We subsequently conducted multivariate sensitivity analyses of our preliminary findings to account for these covariates and included age in all subsequent comparisons.

The use of stable glaucoma suspects as reference patients also may draw criticism, because they are not truly representative of the healthy population. However, this study sought to identify the role of cardiovascular disease in glaucoma progression. By fulfilling the same entry criteria (disc damage likelihood scale, >1) and undergoing the same monitoring and treatment protocol as the progressing participants, these study participants are well suited for the clinically controlled progression analyses that were undertaken in this study. Our use of the 24-2 Humphrey visual field test to assess visual field progression may miss up to 50% of macula defects, which typically are deeper and closer to fixation and better detected on 10-2 perimetry.[44,45] The 10-2 field testing was not part of the study protocol, and we might have expected stronger associations between cardiovascular disease and visual field progression if this form of perimetry were available. Finally, the enrollment for this study predated the commercial availability of OCT angiography. In the future, we will evaluate the associations among cardiovascular risk factors, blood vessel phenotypes, and macula thinning.

This study evaluated structural and functional phenotypes of glaucoma. Using a combination of baseline and longitudinal SD OCT imaging of the mGCIPL and the pRNFL and Humphrey visual field assessment, we have highlighted the importance of cardiovascular disease in both structural and functional disease progression. The importance of these parameters far exceeded that of other clinical covariates such as Raynaud's disease, migraine, and diabetes, which often receive more clinical attention in risk stratification. The strong associations observed in this study between cardiovascular parameters and glaucoma phenotype and progression underscore the need for mechanistic research to determine the best way to slow disease progression in ways that do not depend solely on lowering IOP.

Footnotes and Disclosures

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No animal subjects were included in this study.

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Conception and design: Marshall, Mullany, Siggs, Hassall, Ridge, Andrew, Healey, Graham, Mills, Landers, Casson, Craig

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Obtained funding: Craig

Overall responsibility: Marshall, Mullany, Qassim, Siggs, Hassall, MacGregor, Graham, Landers, Casson, Craig

Abbreviations and Acronyms:
CI = confidence interval; **CVD** = cardiovascular disease; **D** = diopter; **HVF** = Humphrey visual field; **IOP** = intraocular pressure; **mGCIPL** = macula ganglion cell–inner plexiform layer; **ONH** = optic nerve head; **OR** = odds ratio; **pRNFL** = peripapillary retinal nerve fiber layer; **PROGRESSA** = Progression Risk of Glaucoma: Relevant SNPs with Significant Association; **SD** = spectral-domain.

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